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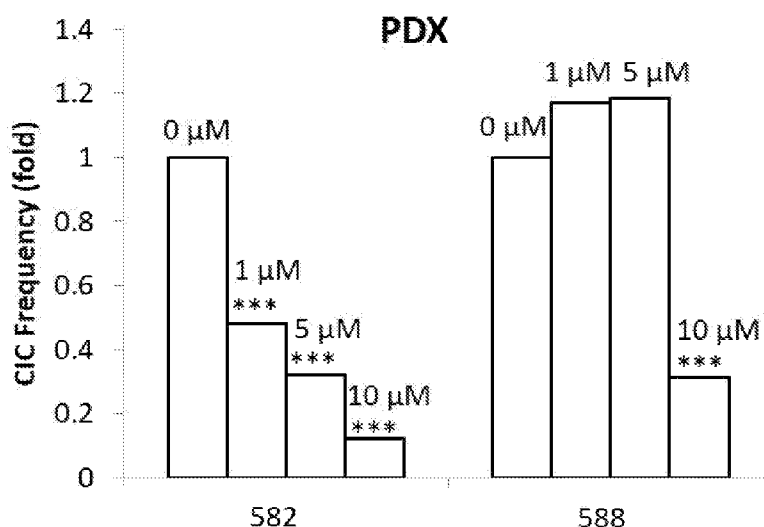
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(54) Title: SUMO INHIBITOR COMPOUNDS AND USES THEREOF

FIG. 1



(57) Abstract: There are disclosed, *inter alia*, methods of inhibiting an E1 enzyme, and compounds useful for inhibiting an E1 enzyme.

SUMO INHIBITOR COMPOUNDS AND USES THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/712,822, filed July 31, 2018, 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

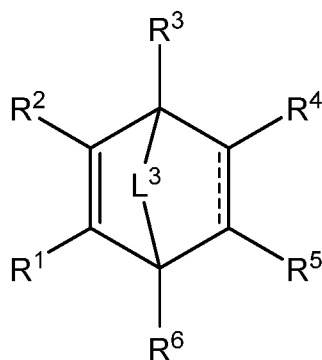
[0002] The Sequence Listing written in file 048440-501001WO_Sequence_Listing_ST25.txt, created July 30, 2019, 7,269 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

BACKGROUND

[0003] Post-translational modifications of cellular proteins by the small ubiquitin-like modifier (SUMO) family of proteins are important epigenetic mechanisms for regulating various cellular functions. Aberrations in post-translational modification of cellular proteins by the small ubiquitin-like modifier (SUMO) family of proteins are associated with the pathogenesis of life-threatening diseases, such as cancer, neurodegenerative disorders, and viral infection. Indeed, the enzymes catalyzing SUMO-modification (e.g., E1 disclosed herein) are present in higher levels in cancer tissues versus normal tissues and in metastasized tumors versus normal cells, and play an important role in cancer proliferation and metastasis. Without wishing to be bound by any theory, it is believed that E1 is a target for the development of therapeutics (e.g., cancer therapeutics). Thus, there are disclosed herein methods of inhibiting an E1 enzyme, and compounds useful for inhibiting an E1 enzyme.

SUMMARY

[0004] In an aspect is provided a method of treating cancer in a subject in need thereof, said method including administering to the subject a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of formula:



[0005]

(I).

[0006] $\equiv$ is a single bond or double bond.[0007] L^3 is $-O-$, $-S-$, $-N-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-N(R^7)-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

5 [0008] R^1 is hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHN R^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHN R^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, $-L^1-E^1$, 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.

15 [0009] R^2 is hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, $-L^2-E^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

20 [0010] R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHN R^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0011] R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHN R^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHN R^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or unsubstituted alkyl,

5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0012] R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHN R^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHN R^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl,

10 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0013] R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHN R^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHN R^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, substituted or unsubstituted alkyl,

15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0014] R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHN R^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHN R^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl,

25 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0015] E^1 and E^2 are independently an electron-withdrawing moiety.

[0016] Each R^{1A} , R^{1B} , R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{6A} , R^{6B} , R^{7A} , and R^{7B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$,

-COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
 -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH,
 -OCX₃, -OCHX₂, -OCH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted
 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

- 5 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form
 a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A}
 and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A}
 10 and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A}
 and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A}
 and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 15 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A}
 and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0017] m₁, m₂, m₃, m₄, m₅, m₆, and m₇ are independently 1 or 2.

[0018] v₁, v₂, v₃, v₄, v₅, v₆, and v₇ are independently 1 or 2.

- 20 [0019] n₁, n₂, n₃, n₄, n₅, n₆, and n₇, are independently an integer from 0 to 4.

[0020] X, X¹, X², X³, X⁴, X⁵, X⁶, and X⁷ are independently -Cl, -Br, -I or -F.

[0021] L¹ and L² are independently a bond, -O-, -S-, -S(O)-, -S(O)₂-, -NH-, -C(O)-,
 -C(O)O-, -C(O)NH-, -C(O)NHNH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-,
 -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted

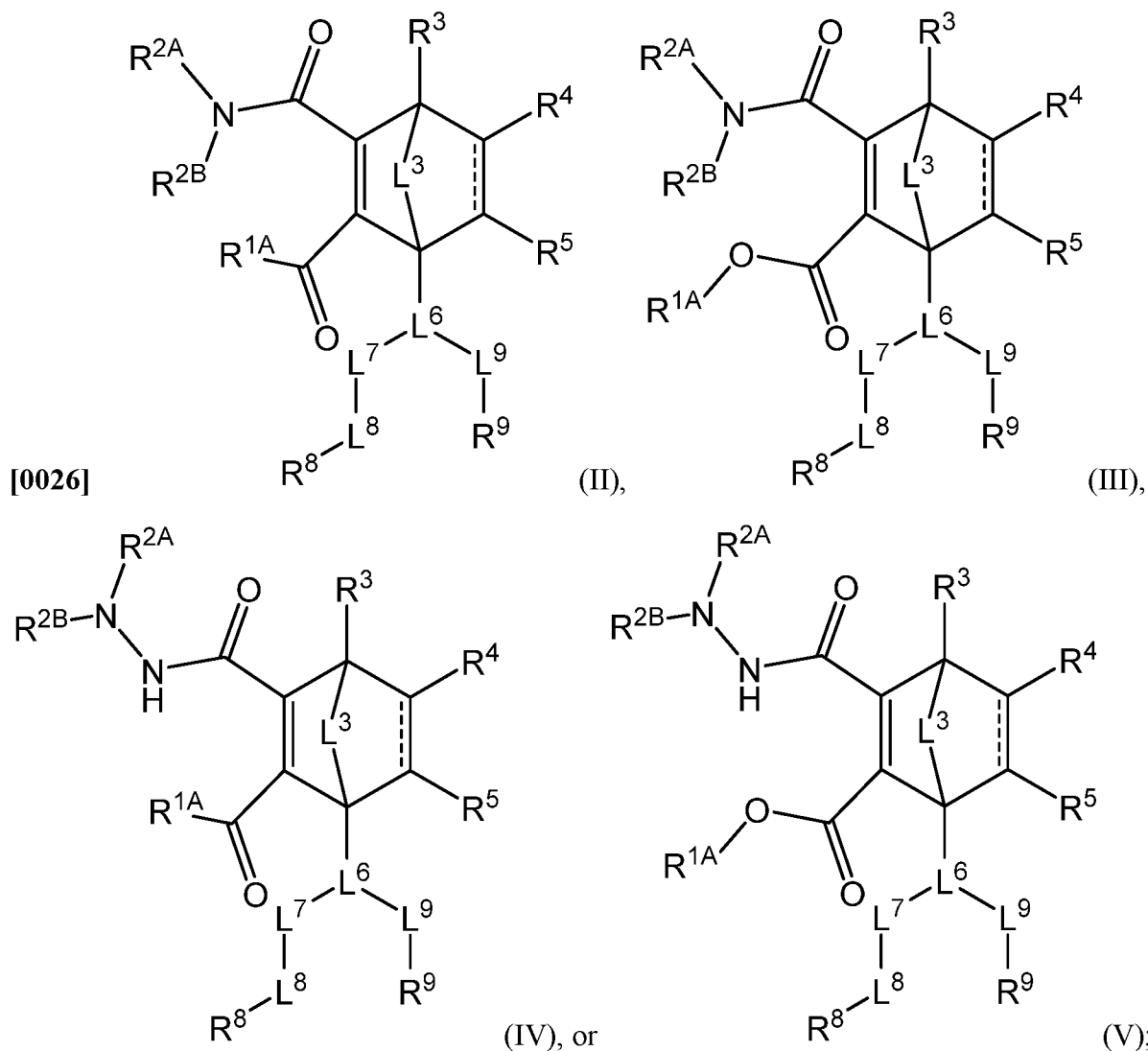
- 25 heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted
 heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted
 heteroarylene.

[0022] R¹ and R² may optionally be joined to form a substituted or unsubstituted
 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 30 substituted or unsubstituted heteroaryl.

[0023] R^4 and R^5 may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0024] Wherein the compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

[0025] In an aspect is provided a compound of Formula:



[0027] L^3 is $-O-$, $-S-$, or $-N(R^7)-$.

10 [0028] L^7 is $-O-$ or $-N(R^{10})-$.

[0029] R^{1A} is hydrogen, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-CN$, $-SO_{n1A}R^{1AA}$, $-SO_{v1A}NR^{1AA}R^{1AB}$, $-NHC(O)NR^{1AA}R^{1AB}$, $-N(O)_{m1A}$, $-NR^{1AA}R^{1AB}$, $-NHNr^{1AA}R^{1AB}$, $-C(O)R^{1AA}$, $-C(O)-OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$,

$-\text{NR}^{1\text{AA}}\text{SO}_2\text{R}^{1\text{AB}}$, $-\text{NR}^{1\text{AA}}\text{C}(\text{O})\text{R}^{1\text{AB}}$, $-\text{NR}^{1\text{AA}}\text{C}(\text{O})\text{OR}^{1\text{AB}}$, $-\text{NR}^{1\text{AA}}\text{OR}^{1\text{AB}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

- 5 **[0030]** $\text{R}^{2\text{A}}$ is hydrogen, halogen, $-\text{CX}^{2\text{A}}_3$, $-\text{CHX}^{2\text{A}}_2$, $-\text{CH}_2\text{X}^{2\text{A}}$, $-\text{OCX}^{2\text{A}}_3$, $-\text{OCH}_2\text{X}^{2\text{A}}$, $-\text{OCHX}^{2\text{A}}_2$, $-\text{CN}$, $-\text{SO}_{n2\text{A}}\text{R}^{2\text{AA}}$, $-\text{SO}_{v2\text{A}}\text{NR}^{2\text{AA}}\text{R}^{2\text{AB}}$, $-\text{NHC}(\text{O})\text{NR}^{2\text{AA}}\text{R}^{2\text{AB}}$, $-\text{N}(\text{O})_{m2\text{A}}$, $-\text{NR}^{2\text{AA}}\text{R}^{2\text{AB}}$, $-\text{NHN}\text{R}^{2\text{AA}}\text{R}^{2\text{AB}}$, $-\text{C}(\text{O})\text{R}^{2\text{AA}}$, $-\text{C}(\text{O})-\text{OR}^{2\text{AA}}$, $-\text{C}(\text{O})\text{NR}^{2\text{AA}}\text{R}^{2\text{AB}}$, $-\text{OR}^{2\text{AA}}$, $-\text{NR}^{2\text{AA}}\text{SO}_2\text{R}^{2\text{AB}}$, $-\text{NR}^{2\text{AA}}\text{C}(\text{O})\text{R}^{2\text{AB}}$, $-\text{NR}^{2\text{AA}}\text{C}(\text{O})\text{OR}^{2\text{AB}}$, $-\text{NR}^{2\text{AA}}\text{OR}^{2\text{AB}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
- 10

- [0031]** $\text{R}^{2\text{B}}$ is hydrogen, halogen, $-\text{CX}^{2\text{B}}_3$, $-\text{CHX}^{2\text{B}}_2$, $-\text{CH}_2\text{X}^{2\text{B}}$, $-\text{OCX}^{2\text{B}}_3$, $-\text{OCH}_2\text{X}^{2\text{B}}$, $-\text{OCHX}^{2\text{B}}_2$, $-\text{CN}$, $-\text{SO}_{n2\text{B}}\text{R}^{2\text{BA}}$, $-\text{SO}_{v2\text{B}}\text{NR}^{2\text{BA}}\text{R}^{2\text{BB}}$, $-\text{NHC}(\text{O})\text{NR}^{2\text{BA}}\text{R}^{2\text{BB}}$, $-\text{N}(\text{O})_{m2\text{B}}$, $-\text{NR}^{2\text{BA}}\text{R}^{2\text{BB}}$, $-\text{NHN}\text{R}^{2\text{BA}}\text{R}^{2\text{BB}}$, $-\text{C}(\text{O})\text{R}^{2\text{BA}}$, $-\text{C}(\text{O})-\text{OR}^{2\text{BA}}$, $-\text{C}(\text{O})\text{NR}^{2\text{BA}}\text{R}^{2\text{BB}}$, $-\text{OR}^{2\text{BA}}$, $-\text{NR}^{2\text{BA}}\text{SO}_2\text{R}^{2\text{BB}}$, $-\text{NR}^{2\text{BA}}\text{C}(\text{O})\text{R}^{2\text{BB}}$, $-\text{NR}^{2\text{BA}}\text{C}(\text{O})\text{OR}^{2\text{BB}}$, $-\text{NR}^{2\text{BA}}\text{OR}^{2\text{BB}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
- 15

- [0032]** R^3 is hydrogen, halogen, $-\text{CX}^3_3$, $-\text{CHX}^3_2$, $-\text{CH}_2\text{X}^3$, $-\text{OCX}^3_3$, $-\text{OCH}_2\text{X}^3$, $-\text{OCHX}^3_2$, $-\text{CN}$, $-\text{SO}_{n3}\text{R}^{3\text{A}}$, $-\text{SO}_{v3}\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{N}(\text{O})_{m3}$, $-\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{NHN}\text{R}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{C}(\text{O})\text{R}^{3\text{A}}$, $-\text{C}(\text{O})-\text{OR}^{3\text{A}}$, $-\text{C}(\text{O})\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{OR}^{3\text{A}}$, $-\text{NR}^{3\text{A}}\text{SO}_2\text{R}^{3\text{B}}$, $-\text{NR}^{3\text{A}}\text{C}(\text{O})\text{R}^{3\text{B}}$, $-\text{NR}^{3\text{A}}\text{C}(\text{O})\text{OR}^{3\text{B}}$, $-\text{NR}^{3\text{A}}\text{OR}^{3\text{B}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
- 20

- [0033]** R^4 is hydrogen, halogen, $-\text{CX}^4_3$, $-\text{CHX}^4_2$, $-\text{CH}_2\text{X}^4$, $-\text{OCX}^4_3$, $-\text{OCH}_2\text{X}^4$, $-\text{OCHX}^4_2$, $-\text{CN}$, $-\text{SO}_{n4}\text{R}^{4\text{A}}$, $-\text{SO}_{v4}\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{N}(\text{O})_{m4}$, $-\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NHN}\text{R}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{C}(\text{O})\text{R}^{4\text{A}}$, $-\text{C}(\text{O})-\text{OR}^{4\text{A}}$, $-\text{C}(\text{O})\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{C}(\text{O})\text{NHN}\text{R}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{OR}^{4\text{A}}$, $-\text{NR}^{4\text{A}}\text{SO}_2\text{R}^{4\text{B}}$, $-\text{NR}^{4\text{A}}\text{C}(\text{O})\text{R}^{4\text{B}}$, $-\text{NR}^{4\text{A}}\text{C}(\text{O})\text{OR}^{4\text{B}}$, $-\text{NR}^{4\text{A}}\text{OR}^{4\text{B}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
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- 30

[0034] R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHN R^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHN R^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl,

5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0035] R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHN R^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHN R^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl,

10 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0036] R^8 is hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-NHN R^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHN R^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, substituted or unsubstituted alkyl,

15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0037] R^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHN R^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHN R^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, substituted or unsubstituted alkyl,

25 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0038] R^{10} is hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHN R^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHN R^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, substituted or

30

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

[0039] Each R^{1AA} , R^{1AB} , R^{2AA} , R^{2AB} , R^{2BA} , R^{2BB} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{7A} , R^{7B} , R^{8A} , R^{8B} , R^{9A} , R^{9B} , R^{10A} , and R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0040] $m1A$, $m2A$, $m2B$, $m3$, $m4$, $m5$, $m7$, $m8$, $m9$, and $m10$ are independently 1 or 2.

[0041] v1A, v2A, v2B, v3, v4, v5, v7, v8, v9, and v10 are independently 1 or 2.

[0042] n1A, n2A, n2B, n3, n4, n5, n7, n8, n9, and n10 are independently an integer from 0 to 4.

[0043] X, X^{1A}, X^{2A}, X^{2B}, X³, X⁴, X⁵, X⁷, X⁸, X⁹, and X¹⁰ are independently -Cl, -Br, -I, or -F.

[0044] L⁶ is 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.

10 [0045] L⁸ is a bond, -C(O)-, -C(O)NH-, -C(O)O-, -S-, -S(O)-, -S(O)₂-, 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.

15 [0046] L⁹ is a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NHC(O)NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

20 [0047] Wherein R^{2A} and R^{2B} may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0048] R⁴ and R⁵ may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

25 [0049] In an aspect is provided a pharmaceutical composition including a compound described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0050] 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 compound described herein.

[0051] In an aspect is provided a method of inhibiting cell proliferation, the method including contacting the cell with a compound described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

5 [0052] FIG. 1. Examination of the effect of compounds 582 and 588 to reduce cancer stem cell (CSC) populations in patient derived xenograft (PDX) models using limited dilution assays. Compound 582 showed dose-dependent inhibition on PDX cancer-initiating-cell (CIC) frequency, even at 1 μ M. Compound 588 only showed inhibition on CIC at high dose 10 μ M.

DETAILED DESCRIPTION

10 I. Definitions

[0053] 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.

15 [0054] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

20 [0055] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals, having the number of carbon atoms designated (i.e., $\text{C}_1\text{-C}_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, 25 n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker ($-\text{O}-$).

[0056] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

5 **[0057]** The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, S, B, As, or Si), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at
 10 any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N(CH}_3\text{)-CH}_3$, $-\text{CH}_2\text{-S-CH}_2\text{-CH}_3$, $-\text{CH}_2\text{-CH}_2$, $-\text{S(O)-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)}_2\text{-CH}_3$, $-\text{CH=CH-O-CH}_3$, $-\text{Si(CH}_3\text{)}_3$, $-\text{CH}_2\text{-CH=N-OCH}_3$, $-\text{CH=CH-N(CH}_3\text{)-CH}_3$, $-\text{O-CH}_3$,
 15 $-\text{O-CH}_2\text{-CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{-NH-OCH}_3$ and $-\text{CH}_2\text{-O-Si(CH}_3\text{)}_3$.

[0058] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2\text{-CH}_2\text{-S-CH}_2\text{-CH}_2-$ and $-\text{CH}_2\text{-S-CH}_2\text{-CH}_2\text{-NH-CH}_2-$. For
 20 heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C(O)}_2\text{R}'$ represents both $-\text{C(O)}_2\text{R}'$ and $-\text{R}'\text{C(O)}_2-$. As described above, heteroalkyl groups, as
 25 used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C(O)R}'$, $-\text{C(O)NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$.

[0059] 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
 30 heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. A “cycloalkylene” and a “heterocycloalkylene,” alone or as

part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0060] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo(C₁-C₄)alkyl” includes, but is not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0061] The term “acyl” means, unless otherwise stated, -C(O)R where R is a substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0062] 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 heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. An “arylene” and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively.

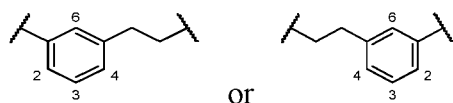
[0063] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other 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.

[0064] The symbol “” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0065] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0066] 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:



[0067] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “cycloalkyl,” “heterocycloalkyl,” “aryl,” and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical.

[0068] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''''R''', -CN, -NO₂, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or

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

[0069] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR'', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''''R''', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''', and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0070] 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.

[0071] 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.

[0072] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), Boron (B), and silicon (Si).

[0073] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H,

-NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂,
 -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -N₃, unsubstituted alkyl (e.g., C₁-C₂₀,
 C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 20 membered,
 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3
 5 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-
 C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3
 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted
 aryl (e.g., 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), and

(B) alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), heteroalkyl (e.g., 2 to 20
 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to
 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-
 C₆), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6
 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl),
 15 or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6
 membered), substituted with at least one substituent selected from:

(i) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl,
 -CH₂Br, -CH₂F, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H,
 -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H,
 20 -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂,
 -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -N₃,
 unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted
 heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6
 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted
 25 cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted
 heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6
 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., 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), and

(ii) alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), heteroalkyl (e.g., 2 to
 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6
 membered, 2 to 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C₃-C₁₀, C₃-C₈,
 C₃-C₆, C₄-C₆, or C₅-C₆), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3

to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), substituted with at least one substituent selected from:

- 5 (a) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I,
- 10 -N₃, unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
- 15 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), and
- (b) alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), substituted
- 20 with at least one substituent selected from: oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -N₃, unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), substituted
- 25 with at least one substituent selected from: oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -N₃, unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), substituted
- 30 with at least one substituent selected from: oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂F, -OCH₂I, -N₃, unsubstituted alkyl (e.g., C₁-C₂₀, C₁-C₁₂, C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 20 membered, 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered), substituted

membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 10 membered, 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., 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).

[0074] 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.

[0075] A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0076] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups

are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0077] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₂₀ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₈ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0078] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₈ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₇ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a

substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

[0079] In embodiments, a substituted or unsubstituted moiety (e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, and/or substituted or unsubstituted heteroarylene) is unsubstituted (e.g., is an unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, unsubstituted alkylene, unsubstituted heteroalkylene, unsubstituted cycloalkylene, unsubstituted heterocycloalkylene, unsubstituted arylene, and/or unsubstituted heteroarylene, respectively). In embodiments, a substituted or unsubstituted moiety (e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, and/or substituted or unsubstituted heteroarylene) is substituted (e.g., is a substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene, respectively).

[0080] 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.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute

stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or (*L*)- for amino acids, and individual isomers are encompassed within the scope of the present 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.

[0085] 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.

[0086] 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.

[0087] 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.

[0088] 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.

[0089] 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 ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0090] 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.

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

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

[0093] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. 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. 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 pharmaceutically 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 pharmaceutically acceptable acid

addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, “Pharmaceutical Salts”, *Journal of Pharmaceutical Science*, 1977, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0094] 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.

[0095] 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.

[0096] 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.

[0097] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of

pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer's, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0098] 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.

[0099] "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.

[0100] 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. 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. 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. The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs.

[0101] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriiform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma

ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhus carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberos carcinoma, verrucous carcinoma, or carcinoma villosum.

[0102] 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.

[0103] “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.

[0104] 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).

[0105] 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.

[0106] 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.

[0107] 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.

[0108] As used herein, the term “about” means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, about means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about includes the specified value.

[0109] 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.*

[0110] "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.

[0111] 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.

[0112] “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).

[0113] 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.

[0114] 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.

[0115] 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) 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.

[0116] 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.

[0117] 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.

[0118] “Anti-cancer agent” and “anticancer agent” are used in accordance with their plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepa, nitrosoureas, nitrogen mustards (e.g., mechlorethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, semustine, streptozocin), triazines (decarbazine)), anti-metabolites (e.g., 5- azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine),

adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplatan; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrididemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziqune; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin

SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin

5 hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon

10 agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine

15 analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor;

20 mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer

25 agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullin; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral

30 cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozone; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors;

picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B;
 plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine
 complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2;
 proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor;
 5 protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine
 nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin
 polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein
 transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium
 Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide;
 10 roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A;
 sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense
 oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain
 antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate; sodium phenylacetate;
 solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D;
 15 spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division
 inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal
 peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans;
 tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur;
 tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide;
 20 tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin;
 thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid
 stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin;
 toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine;
 triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors;
 25 tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor;
 urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene
 therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole;
 zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Adriamycin, Dactinomycin,
 Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine;
 30 adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminogluthetimide;
 amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa;
 azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide
 dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropiramine; busulfan;

cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin
 hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol
 mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride;
 decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziqune; doxorubicin;
 5 doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate;
 duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate;
 epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine;
 estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine;
 fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate;
 10 fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine
 hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iimofosine; interleukin II
 (including recombinant interleukin II, or rIL.sub.2), interferon alfa-2a; interferon alfa-2b;
 interferon alfa-n1; interferon alfa-n3; interferon beta-1a; interferon gamma-1b; iproplatin;
 irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole
 15 hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol;
 maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate;
 melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine;
 meturedapa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin;
 mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole;
 20 nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin
 sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin;
 plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride;
 puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol
 hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium
 25 hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin;
 tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone;
 testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate;
 trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin;
 tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine
 30 sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine 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), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, Auristatin PE (i.e. NSC-654663), Soblidotin (i.e. 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-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, i.e. WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, i.e. ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (i.e. LY-355703), AC-7739 (Ajinomoto, i.e. AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, i.e. AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (i.e. NSC-106969), T-138067 (Tularik, i.e. T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, i.e. DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (i.e. BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, i.e. SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiassterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, i.e. MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (i.e. NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-607 (Tularik, i.e. T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaeyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245

(Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (i.e. NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, i.e. D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (i.e. SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi)), steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (IressaTM), erlotinib (TarcevaTM), cetuximab (ErbixTM), lapatinib (TykerbTM), panitumumab (VectibixTM), vandetanib (CaprelsaTM), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, or the like.

[0119] “Chemotherapeutic” or “chemotherapeutic agent” is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0120] The term “SUMO protein” or “small ubiquitin-like modifier protein” is a family of proteins that are covalently attached to other proteins to modify their function. SUMO proteins are members of the ubiquitin-like protein family. SUMO modification is involved in

various cellular processes, for example, nuclear-cytosolic transport, transcriptional regulation, apoptosis, and protein stability.

[0121] The term “Ubiquitin-activating enzyme” or “E1 enzyme” or “E1” refers to a protein (including homologs, isoforms, and functional fragments thereof) that catalyzes the first step in the ubiquitination reaction, which can target a protein for degradation. E1 enzymes are capable of catalyzing SUMO modification. In embodiments, the E1 enzyme is encoded by UBA1. In embodiments, the E1 enzyme is encoded by UBA2. In embodiments, the E1 enzyme is encoded by UBA3. In embodiments, the E1 enzyme is encoded by UBA4. In embodiments, the E1 enzyme is encoded by UBA5. In embodiments, the E1 enzyme is encoded by UBA6. In embodiments, the E1 enzyme is encoded by UBA7. In embodiments, the E1 enzyme is encoded by ATG7. In embodiments, the E1 enzyme is encoded by NAE1. In embodiments, the E1 enzyme is encoded by SAE1.

[0122] The term “SUMO-activating enzyme subunit 2” or “UBA2” or “UBA2 subunit 2” is a protein involved in SUMO modification. The term “UBA2” refers to the nucleotide sequences or proteins of human UBA2. The term “UBA2” includes both the wild type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, “UBA2” is wild-type UBA2. In some embodiments, “UBA2” is one or more mutant forms. The term “UBA2” XYZ refers to a nucleotide sequence or protein of a mutant UBA2 wherein the Y numbered amino acid of UBA2 has an X amino acid in the wild type instead has a Z amino acid in the mutant. In embodiments, UBA2 is a functional fragment thereof. In embodiments, UBA2 refers to RefSeq (mRNA) NM_005499.2 or RefSeq (Protein) NP_005490.1. In some embodiments, UBA2 refers to UniProt Q9UBT2, having the sequence:

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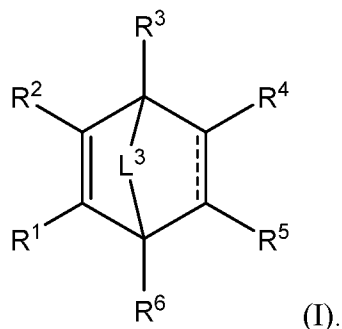
MALSRGLPRELAEAVAGGRVLVVGAGGIGCELLKNLVLTGFSHIDLIDLDTIDVSNLNRQ
FLFQKKHVGRSKAQVAKESVLQFYPKANIVAYHDSIMNPDYNVEFFRQFILVMNALDNRA
ARNHVNRMCLAADVPLIESGTAGYLGQVTTIKKGVTECYECHKPQTQRTFPGCTIRNTPS
EPIHCIVWAKYLFNQLFGCEEDADQEVSPDRADPEAAWEPTAEARARASNEDGDIKRIST
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NEPQLGLKDQQVLDVKSYPARLFSKSIETLRVHLAEKGDGAELIWDKDDPSAMDFVTSAN
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QIEDGKGITILISSEGETEANNHKKLSEFGIRNGSRLQADDFLQDYTLINILHSEDLGK
DVEFEVVGDAPEKVGPKQAEDAASITNGSDDGAQPSTSTAQEQDDVLIVDSDEEDSSNN

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ADVSEEERSRKRKLDEKENLSAKRSRIEQKEELDDVIALD (SEQ ID NO:1).

II. Compounds

[0123] In an aspect is provided a compound having the formula:



5 [0124] --- is a single bond or double bond.

[0125] L^1 and L^2 are independently a bond, -O-, -S-, -S(O)-, -S(O)₂-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -C(O)NHNH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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), substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0126] L^3 is -O-, -S-, -N-, -S(O)-, -S(O)₂-, -C(O)-, -N(R⁷)-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂) or 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).

20 [0127] L^6 is substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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), substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenylene), or substituted or

unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0128] L^7 is $-O-$ or $-N(R^{10})-$.

[0129] L^8 is a bond, $-C(O)-$, $-C(O)NH-$, $-C(O)O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), 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), substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), 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), substituted or unsubstituted arylene (e.g., C_6-C_{12} , C_6-C_{10} , or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0130] L^9 is a bond, $-O-$, $-S-$, $-NH-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)-$, $-NHC(O)-$, $-NHC(O)NH-$, $-OC(O)NH-$, $-NHC(O)O-$, substituted or unsubstituted alkylene (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), 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), substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), 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), substituted or unsubstituted arylene (e.g., C_6-C_{12} , C_6-C_{10} , or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0131] R^1 is hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHN R^{1A}R^{1B}$, $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHN R^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$, $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, $-L^1-E^1$, 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.

[0132] R^2 is hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$,

$-\text{NR}^{2\text{A}}\text{C}(\text{O})\text{R}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{C}(\text{O})\text{OR}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{OR}^{2\text{B}}$, $-\text{N}_3$, $-\text{L}^2\text{-E}^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

- 5 **[0133]** R^1 and R^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.

- [0134]** R^3 is hydrogen, halogen, $-\text{CX}^3$, $-\text{CHX}^3$, $-\text{CH}_2\text{X}^3$, $-\text{OCX}^3$, $-\text{OCH}_2\text{X}^3$, $-\text{OCHX}^3$, $-\text{CN}$, $-\text{SO}_{\text{m}3}\text{R}^{3\text{A}}$, $-\text{SO}_{\text{v}3}\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{N}(\text{O})_{\text{m}3}$, $-\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{NHNR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{C}(\text{O})\text{R}^{3\text{A}}$, $-\text{C}(\text{O})\text{-OR}^{3\text{A}}$, $-\text{C}(\text{O})\text{NR}^{3\text{A}}\text{R}^{3\text{B}}$, $-\text{OR}^{3\text{A}}$, $-\text{NR}^{3\text{A}}\text{SO}_2\text{R}^{3\text{B}}$, $-\text{NR}^{3\text{A}}\text{C}(\text{O})\text{R}^{3\text{B}}$, $-\text{NR}^{3\text{A}}\text{C}(\text{O})\text{OR}^{3\text{B}}$, $-\text{NR}^{3\text{A}}\text{OR}^{3\text{B}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
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- [0135]** R^4 is hydrogen, halogen, $-\text{CX}^4$, $-\text{CHX}^4$, $-\text{CH}_2\text{X}^4$, $-\text{OCX}^4$, $-\text{OCH}_2\text{X}^4$, $-\text{OCHX}^4$, $-\text{CN}$, $-\text{SO}_{\text{m}4}\text{R}^{4\text{A}}$, $-\text{SO}_{\text{v}4}\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{N}(\text{O})_{\text{m}4}$, $-\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NHNR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{C}(\text{O})\text{R}^{4\text{A}}$, $-\text{C}(\text{O})\text{-OR}^{4\text{A}}$, $-\text{C}(\text{O})\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{C}(\text{O})\text{NHNR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{OR}^{4\text{A}}$, $-\text{NR}^{4\text{A}}\text{SO}_2\text{R}^{4\text{B}}$, $-\text{NR}^{4\text{A}}\text{C}(\text{O})\text{R}^{4\text{B}}$, $-\text{NR}^{4\text{A}}\text{C}(\text{O})\text{OR}^{4\text{B}}$, $-\text{NR}^{4\text{A}}\text{OR}^{4\text{B}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
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- [0136]** R^5 is hydrogen, halogen, $-\text{CX}^5$, $-\text{CHX}^5$, $-\text{CH}_2\text{X}^5$, $-\text{OCX}^5$, $-\text{OCH}_2\text{X}^5$, $-\text{OCHX}^5$, $-\text{CN}$, $-\text{SO}_{\text{m}5}\text{R}^{5\text{A}}$, $-\text{SO}_{\text{v}5}\text{NR}^{5\text{A}}\text{R}^{5\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{5\text{A}}\text{R}^{5\text{B}}$, $-\text{N}(\text{O})_{\text{m}5}$, $-\text{NR}^{5\text{A}}\text{R}^{5\text{B}}$, $-\text{NHNR}^{5\text{A}}\text{R}^{5\text{B}}$, $-\text{C}(\text{O})\text{R}^{5\text{A}}$, $-\text{C}(\text{O})\text{-OR}^{5\text{A}}$, $-\text{C}(\text{O})\text{NR}^{5\text{A}}\text{R}^{5\text{B}}$, $-\text{C}(\text{O})\text{NHNR}^{5\text{A}}\text{R}^{5\text{B}}$, $-\text{OR}^{5\text{A}}$, $-\text{NR}^{5\text{A}}\text{SO}_2\text{R}^{5\text{B}}$, $-\text{NR}^{5\text{A}}\text{C}(\text{O})\text{R}^{5\text{B}}$, $-\text{NR}^{5\text{A}}\text{C}(\text{O})\text{OR}^{5\text{B}}$, $-\text{NR}^{5\text{A}}\text{OR}^{5\text{B}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
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- [0137]** R^4 and R^5 may optionally be joined to form a substituted or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), substituted 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., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or substituted or
- 30

unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^4 and R^5 are joined to form a substituted or unsubstituted phenyl. In embodiments, R^4 and R^5 are joined to form an unsubstituted phenyl.

[0138] R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$,
 5 $-CN$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHN R^{6A}R^{6B}$,
 $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHN R^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$,
 $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
 10 heteroaryl, or $-L^6(-L^7-L^8-R^8)(-L^9-R^9)$.

[0139] R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$,
 $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHN R^{7A}R^{7B}$,
 $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHN R^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$,
 $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl,
 15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 unsubstituted heteroaryl.

[0140] R^8 is hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$,
 $-CN$, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-NHN R^{8A}R^{8B}$,
 20 $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHN R^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$,
 $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 unsubstituted heteroaryl.

[0141] R^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$,
 $-CN$, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHN R^{9A}R^{9B}$,
 $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHN R^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$,
 $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, substituted or unsubstituted alkyl,
 25 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 30 unsubstituted heteroaryl.

[0142] R^{10} is hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNr^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNr^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, substituted or
 5 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0143] E^1 and E^2 are independently an electron-withdrawing moiety.

[0144] R^{1A} is hydrogen, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-CN$, $-SO_{n1A}R^{1AA}$, $-SO_{v1A}NR^{1AA}R^{1AB}$, $-NHC(O)NR^{1AA}R^{1AB}$, $-N(O)_{m1A}$,
 10 $-NR^{1AA}R^{1AB}$, $-NHNr^{1AA}R^{1AB}$, $-C(O)R^{1AA}$, $-C(O)-OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$, $-NR^{1AA}SO_2R^{1AB}$, $-NR^{1AA}C(O)R^{1AB}$, $-NR^{1AA}C(O)OR^{1AB}$, $-NR^{1AA}OR^{1AB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 15 substituted or unsubstituted heteroaryl.

[0145] R^{2A} is hydrogen, halogen, $-CX^{2A}_3$, $-CHX^{2A}_2$, $-CH_2X^{2A}$, $-OCX^{2A}_3$, $-OCH_2X^{2A}$, $-OCHX^{2A}_2$, $-CN$, $-SO_{n2A}R^{2AA}$, $-SO_{v2A}NR^{2AA}R^{2AB}$, $-NHC(O)NR^{2AA}R^{2AB}$, $-N(O)_{m2A}$,
 20 $-NR^{2AA}R^{2AB}$, $-NHNr^{2AA}R^{2AB}$, $-C(O)R^{2AA}$, $-C(O)-OR^{2AA}$, $-C(O)NR^{2AA}R^{2AB}$, $-OR^{2AA}$, $-NR^{2AA}SO_2R^{2AB}$, $-NR^{2AA}C(O)R^{2AB}$, $-NR^{2AA}C(O)OR^{2AB}$, $-NR^{2AA}OR^{2AB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0146] R^{2B} is hydrogen, halogen, $-CX^{2B}_3$, $-CHX^{2B}_2$, $-CH_2X^{2B}$, $-OCX^{2B}_3$, $-OCH_2X^{2B}$, $-OCHX^{2B}_2$, $-CN$, $-SO_{n2B}R^{2BA}$, $-SO_{v2B}NR^{2BA}R^{2BB}$, $-NHC(O)NR^{2BA}R^{2BB}$, $-N(O)_{m2B}$,
 25 $-NR^{2BA}R^{2BB}$, $-NHNr^{2BA}R^{2BB}$, $-C(O)R^{2BA}$, $-C(O)-OR^{2BA}$, $-C(O)NR^{2BA}R^{2BB}$, $-OR^{2BA}$, $-NR^{2BA}SO_2R^{2BB}$, $-NR^{2BA}C(O)R^{2BB}$, $-NR^{2BA}C(O)OR^{2BB}$, $-NR^{2BA}OR^{2BB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0147] Each R^{1B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{6A} , R^{6B} , R^{7A} , R^{7B} , R^{1AA} , R^{1AB} , R^{2AA} , R^{2AB} , R^{2BA} , R^{2BB} , R^{8A} , R^{8B} , R^{9A} , R^{9B} , R^{10A} , and R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$,

-CH₂X, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX₃, -OCHX₂, -OCH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,

5 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0148] m1, m2, m3, m4, m5, m6, m7, m8, m9, m10, m1A, m2A, and m2B are independently 1 or 2.

[0149] v1, v2, v3, v4, v5, v6, v7, v8, v9, v10, v1A, v2A, and v2B are independently 1 or 2.

[0150] n1, n2, n3, n4, n5, n6, n7, n8, n9, n10, n1A, n2A, and n2B are independently an integer from 0 to 4.

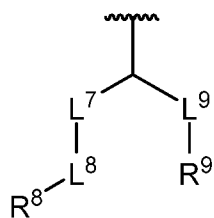
[0151] X, X¹, X², X³, X⁴, X⁵, X⁶, X⁷, X⁸, X⁹, X¹⁰, X^{1A}, X^{2A}, and X^{2B} are independently -Cl, -Br, -I or -F.

[0152] In embodiments, L¹ and L² are independently a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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), substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

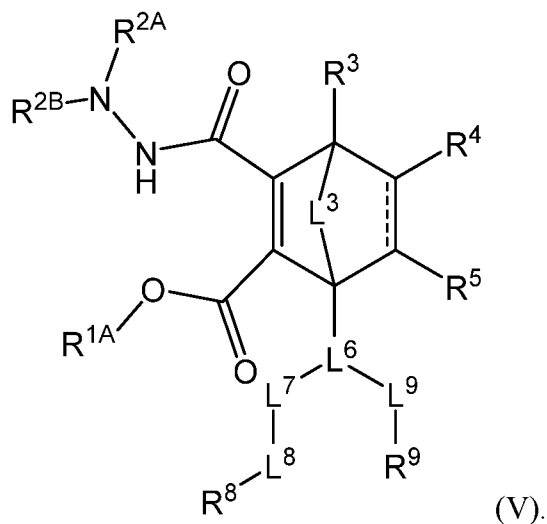
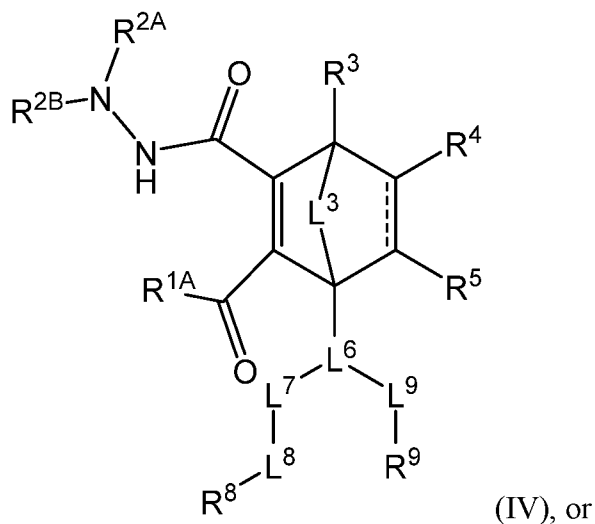
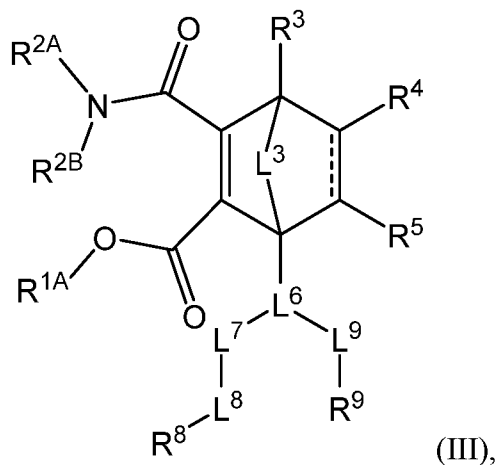
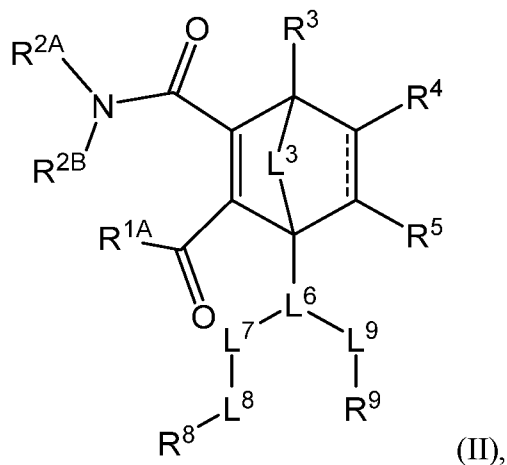
[0153] In embodiments, L⁷ is independently -O-. In embodiments, L⁷ is independently -N(R¹⁰)-.

[0154] In embodiments, L⁸ is a bond, -C(O)-, -C(O)NH-, -C(O)O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), 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), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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), substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L⁸ is independently a bond. In embodiments, L⁸ is independently an unsubstituted phenylene.

[0155] In embodiments, R^6 is independently $-L^6(-L^7-L^8-R^8)(-L^9-R^9)$. In embodiments R^6 is

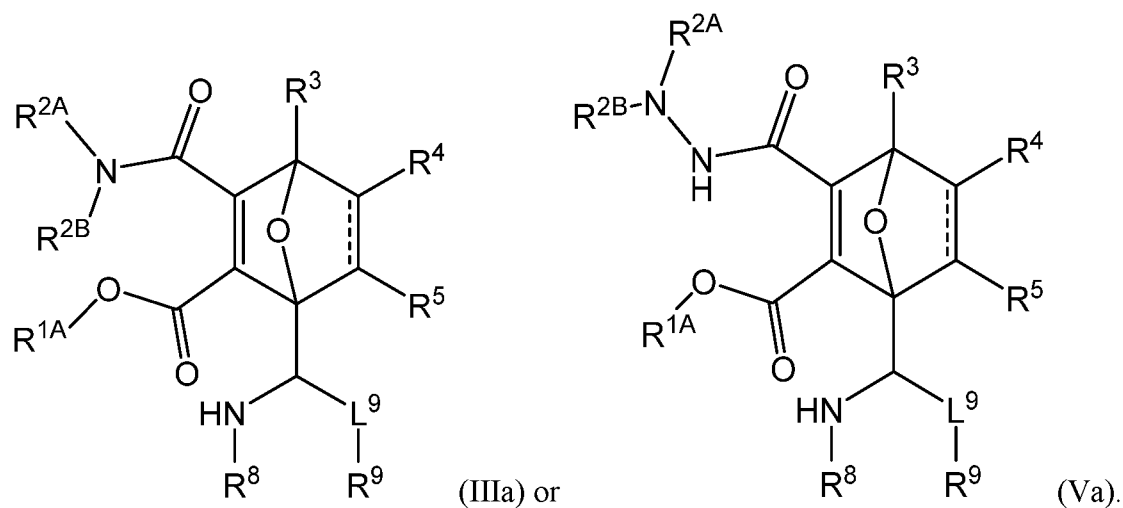


[0156] In an aspect is provided a compound having the formula:



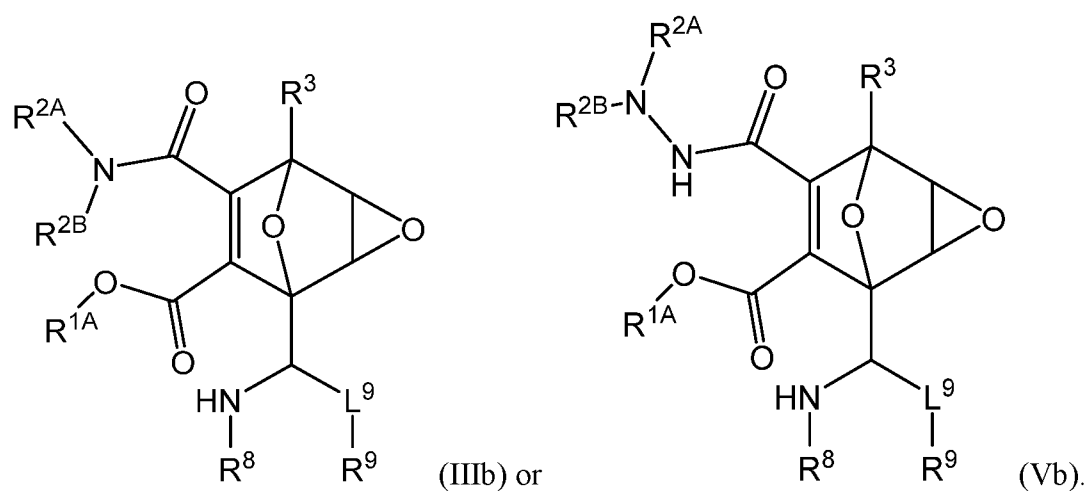
[0157] R^3 , R^4 , R^5 , R^8 , R^9 , R^{1A} , R^{2A} , R^{2B} , L^3 , L^6 , L^7 , L^8 , and L^9 are as described herein. R^8 and R^9 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

[0158] In embodiments, the compound has the formula:



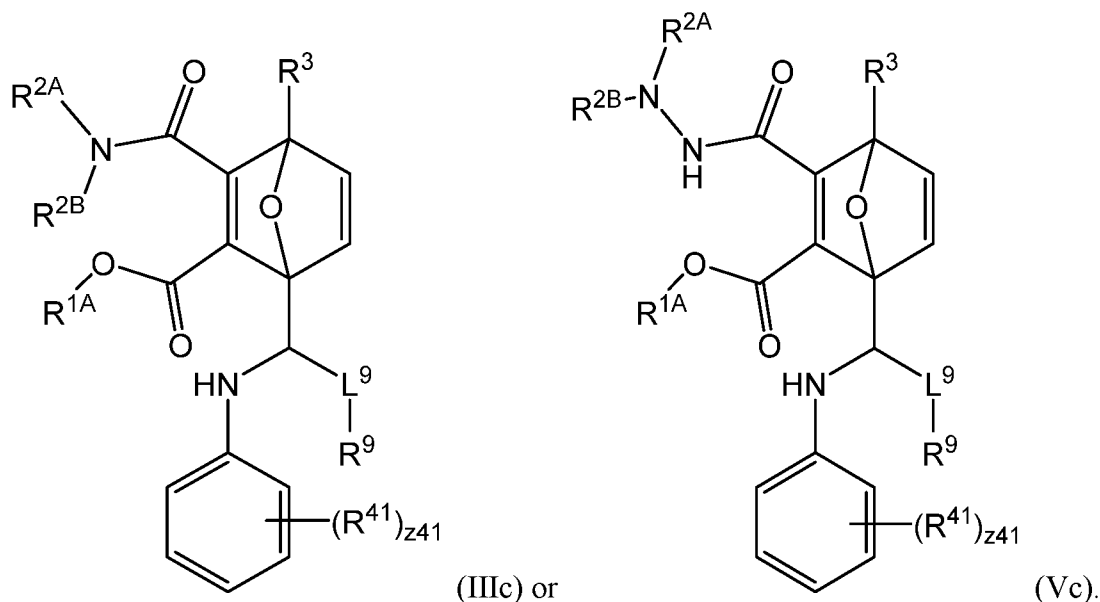
[0159] R^{1A}, R^{2A}, R^{2B}, R³, R⁴, R⁵, R⁸, R⁹, and L⁹ are as described herein. R⁸ and R⁹ substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or a substituted or unsubstituted heteroaryl.

5 [0160] In embodiments, the compound has the formula:



[0161] R^{1A}, R^{2A}, R^{2B}, R³, R⁸, R⁹, and L⁹ are as described herein. R⁸ and R⁹ substituents may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or a substituted or unsubstituted heteroaryl.

10 [0162] In embodiments, the compound has the formula:



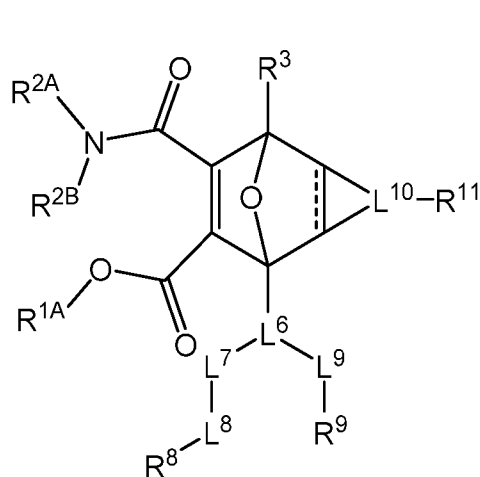
[0163] R^{1A} , R^{2A} , R^{2B} , R^3 , R^9 , and L^9 are as described herein.

[0164] R^{41} is independently halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{41}_3$, $-OCHX^{41}_2$, $-OCH_2X^{41}$, $-OPh$, 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^{41} 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.

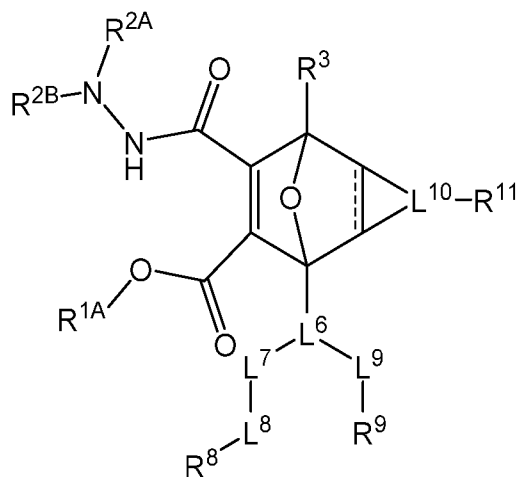
[0165] z_{41} is an integer from 0 to 5.

[0166] X^{41} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0167] In embodiments, the compound has the formula:



(IIIId) or



(Vd).

[0168] R^{1A} , R^{2A} , R^{2B} , R^3 , R^8 , R^9 , L^6 , L^7 , L^8 and L^9 are as described herein. R^8 and R^9 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

[0169] L^{10} is independently a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0170] R^{11} is hydrogen, halogen, 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.

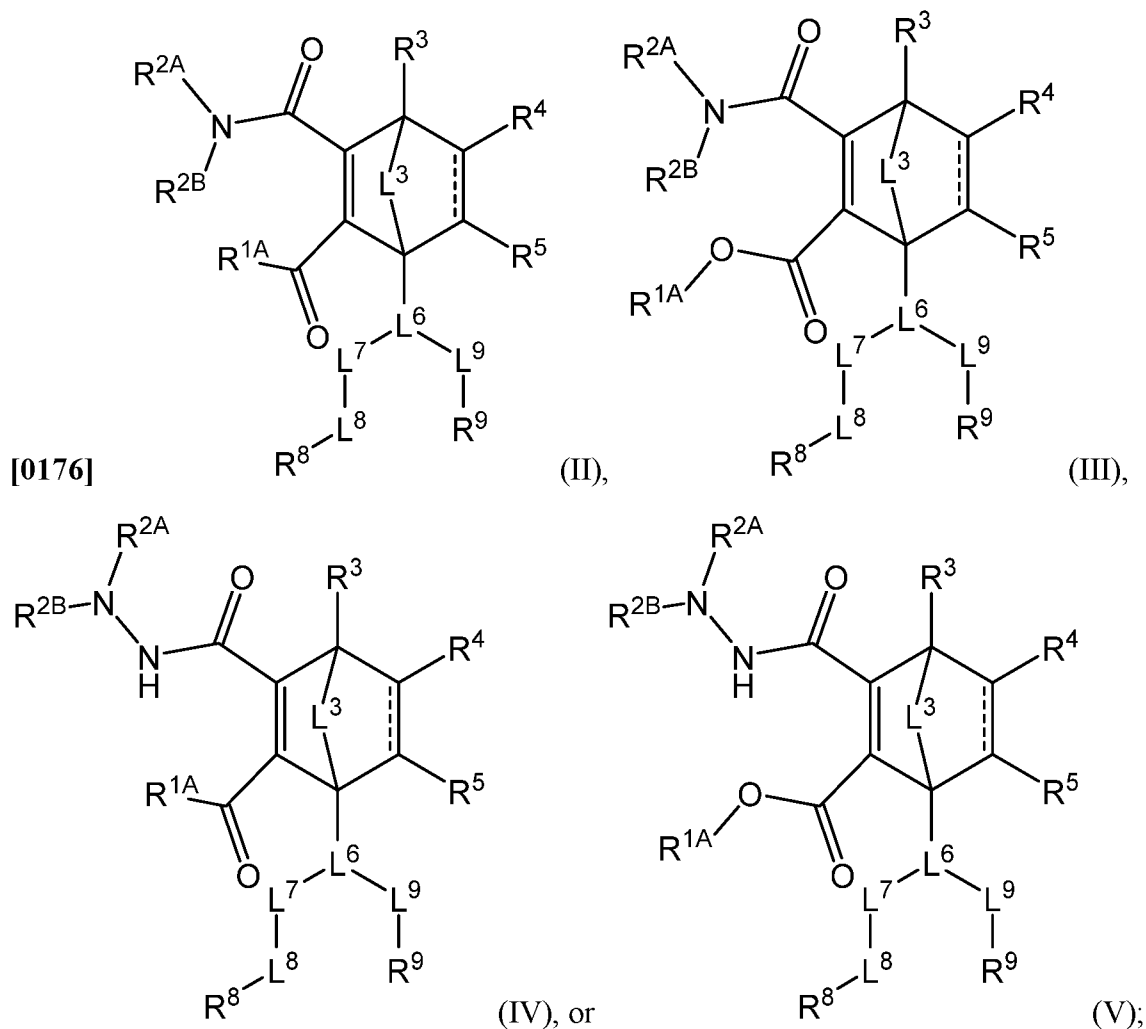
[0171] In embodiments, L^{10} is independently a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), 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), substituted or unsubstituted arylene (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0172] In embodiments, a substituted L^{10} (e.g., 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 L^{10} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when L^{10} is substituted, it is substituted with at least one substituent group. In embodiments, when L^{10} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when L^{10} is substituted, it is substituted with at least one lower substituent group.

[0173] In embodiments, R^{11} is hydrogen, halogen, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , 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).

[0174] In embodiments, a substituted R^{11} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11} is substituted, it is substituted with at least one lower substituent group.

[0175] In an aspect is provided a compound of Formula:



[0177] L^3 is $-O-$, $-S-$, or $-N(R^7)-$.

[0178] L^7 is $-O-$ or $-N(R^{10})-$.

- 5 [0179] R^{1A} is hydrogen, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-CN$, $-SO_{n1A}R^{1AA}$, $-SO_{v1A}NR^{1AA}R^{1AB}$, $-NHC(O)NR^{1AA}R^{1AB}$, $-N(O)_{m1A}$, $-NR^{1AA}R^{1AB}$, $-NHN R^{1AA}R^{1AB}$, $-C(O)R^{1AA}$, $-C(O)-OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$, $-NR^{1AA}SO_2R^{1AB}$, $-NR^{1AA}C(O)R^{1AB}$, $-NR^{1AA}C(O)OR^{1AB}$, $-NR^{1AA}OR^{1AB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
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- [0180] R^{2A} is hydrogen, halogen, $-CX^{2A}_3$, $-CHX^{2A}_2$, $-CH_2X^{2A}$, $-OCX^{2A}_3$, $-OCH_2X^{2A}$, $-OCHX^{2A}_2$, $-CN$, $-SO_{n2A}R^{2AA}$, $-SO_{v2A}NR^{2AA}R^{2AB}$, $-NHC(O)NR^{2AA}R^{2AB}$, $-N(O)_{m2A}$, $-NR^{2AA}R^{2AB}$, $-NHN R^{2AA}R^{2AB}$, $-C(O)R^{2AA}$, $-C(O)-OR^{2AA}$, $-C(O)NR^{2AA}R^{2AB}$, $-OR^{2AA}$, $-NR^{2AA}SO_2R^{2AB}$, $-NR^{2AA}C(O)R^{2AB}$, $-NR^{2AA}C(O)OR^{2AB}$, $-NR^{2AA}OR^{2AB}$, $-N_3$, substituted or
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unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0181] R^{2B} is hydrogen, halogen, $-CX^{2B}_3$, $-CHX^{2B}_2$, $-CH_2X^{2B}$, $-OCX^{2B}_3$, $-OCH_2X^{2B}$, $-OCHX^{2B}_2$, $-CN$, $-SO_{n2B}R^{2BA}$, $-SO_{v2B}NR^{2BA}R^{2BB}$, $-NHC(O)NR^{2BA}R^{2BB}$, $-N(O)_{m2B}$, $-NR^{2BA}R^{2BB}$, $-NHNr^{2BA}R^{2BB}$, $-C(O)R^{2BA}$, $-C(O)-OR^{2BA}$, $-C(O)NR^{2BA}R^{2BB}$, $-OR^{2BA}$, $-NR^{2BA}SO_2R^{2BB}$, $-NR^{2BA}C(O)R^{2BB}$, $-NR^{2BA}C(O)OR^{2BB}$, $-NR^{2BA}OR^{2BB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0182] R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNr^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0183] R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNr^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNr^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0184] R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHNr^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHNr^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0185] R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl,

5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0186] R^8 is hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-SO_{n8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-NHNR^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHNR^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, substituted or unsubstituted alkyl,

10 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0187] R^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-SO_{n9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNR^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, substituted or unsubstituted alkyl,

15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0188] R^8 and R^9 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

[0189] R^{10} is hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNR^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, substituted or

25 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0190] Each R^{1AA} , R^{1AB} , R^{2AA} , R^{2AB} , R^{2BA} , R^{2BB} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{7A} , R^{7B} , R^{8A} , R^{8B} , R^{9A} , R^{9B} , R^{10A} , and R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0191] $m1A$, $m2A$, $m2B$, $m3$, $m4$, $m5$, $m7$, $m8$, $m9$, and $m10$ are independently 1 or 2.

[0192] $v1A$, $v2A$, $v2B$, $v3$, $v4$, $v5$, $v7$, $v8$, $v9$, and $v10$ are independently 1 or 2.

[0193] $n1A$, $n2A$, $n2B$, $n3$, $n4$, $n5$, $n7$, $n8$, $n9$, and $n10$ are independently an integer from 0 to 4.

[0194] X, X^{1A}, X^{2A}, X^{2B}, X³, X⁴, X⁵, X⁷, X⁸, X⁹, and X¹⁰ are independently -Cl, -Br, -I, or -F.

[0195] L⁶ is substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0196] L⁸ is a bond, -C(O)-, -C(O)NH-, -C(O)O-, -S-, -S(O)-, -S(O)₂-, 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.

[0197] In embodiments, L⁸ is a bond, -C(O)-, -C(O)NH-, -C(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. In embodiments, L⁸ is unsubstituted phenylene.

[0198] L⁹ is a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NHC(O)NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0199] Wherein R^{2A} and R^{2B} may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0200] R⁴ and R⁵ 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, R⁴ and R⁵ are joined to form a substituted or unsubstituted phenyl.

[0201] R¹ is hydrogen, halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -SO_{n1}R^{1A}, -SO_{v1}NR^{1A}R^{1B}, -NHC(O)NR^{1A}R^{1B}, -N(O)_{m1}, -NR^{1A}R^{1B}, -NHN^{1A}R^{1B}, -C(O)R^{1A}, -C(O)-OR^{1A}, -C(O)NR^{1A}R^{1B}, -C(O)NHN^{1A}R^{1B}, -OR^{1A}, -NR^{1A}SO₂R^{1B}, -NR^{1A}C(O)R^{1B}, -NR^{1A}C(O)OR^{1B}, -NR^{1A}OR^{1B}, -N₃, -L¹-E¹, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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).

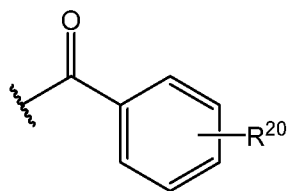
[0202] In embodiments, E¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -SO_{n1}R^{1A}, -SO_{v1}NR^{1A}R^{1B}, -NHC(O)NR^{1A}R^{1B}, -N(O)_{m1}, -NR^{1A}R^{1B}, -NHN^{1A}R^{1B}, -C(O)R^{1A}, -C(O)-OR^{1A}, -C(O)NR^{1A}R^{1B}, -C(O)NHN^{1A}R^{1B}, -OR^{1A}, -NR^{1A}SO₂R^{1B}, -NR^{1A}C(O)R^{1B}, -NR^{1A}C(O)OR^{1B}, -NR^{1A}OR^{1B}, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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).

[0203] In embodiments, E¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -SO_{n1}R^{1A}, -SO_{v1}NR^{1A}R^{1B}, -NHC(O)NR^{1A}R^{1B}, -N(O)_{m1}, -NR^{1A}R^{1B}, -NHN^{1A}R^{1B}, -C(O)R^{1A}, -C(O)-OR^{1A}, -C(O)NR^{1A}R^{1B}, -C(O)NHN^{1A}R^{1B}, -OR^{1A}, -NR^{1A}SO₂R^{1B}, -NR^{1A}C(O)R^{1B}, -NR^{1A}C(O)OR^{1B}, -NR^{1A}OR^{1B}, -N₃, R²⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, 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., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R²⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R²⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

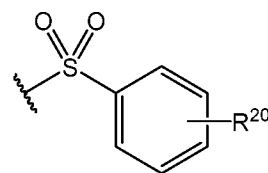
[0204] In embodiments, R¹ is independently hydrogen, halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H,

-NHC(=O)H, -NHC(O)-OH, -NHOH, R²⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, 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., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R²⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or 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, R¹ is independently hydrogen, halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹ is independently -F, -Cl, -Br, or -I.

[0205] In embodiments, R¹ is independently hydrogen. In embodiments, R¹ is independently -COOH. In embodiments, R¹ is independently -C(O)O(C₁-C₄ alkyl). In embodiments, R¹ is independently -CF₃. In embodiments, R¹ is independently -CH₂OH. In embodiments, R¹ is independently -C(O)CH₃. In embodiments, R¹ is independently



. In embodiments, R¹ is independently



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embodiments, R²⁰ is hydrogen, -F, -Cl, or unsubstituted C₁-C₄ alkyl.

[0206] R²⁰ is independently oxo, halogen, -CX²⁰₃, -CHX²⁰₂, -CH₂X²⁰, -OCX²⁰₃, -OCH₂X²⁰, -OCHX²⁰₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, R²¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, 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), R^{21} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{21} -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^{21} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{21} -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^{20} is independently oxo, halogen, $-CX^{20}_3$, $-CHX^{20}_2$, $-CH_2X^{20}$, $-OCX^{20}_3$, $-OCH_2X^{20}$, $-OCHX^{20}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH SO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., 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^{20} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{20} is independently unsubstituted methyl. In embodiments, R^{20} is independently unsubstituted ethyl.

[0207] R^{21} is independently oxo, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH SO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{22} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{22} -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^{22} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{22} -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^{22} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{22} -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^{21} is independently oxo, halogen, $-CX^{21}_3$, $-CHX^{21}_2$, $-CH_2X^{21}$, $-OCX^{21}_3$, $-OCH_2X^{21}$, $-OCHX^{21}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH SO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),

unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²¹ is independently -F, -Cl, -Br, or -I. In embodiments, R²¹ is independently unsubstituted methyl. In embodiments, R²¹ is independently unsubstituted ethyl.

[0208] R²² is independently oxo, halogen, -CX²²₃, -CHX²²₂, -CH₂X²², -OCX²²₃, -OCH₂X²², -OCHX²²₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²² is independently -F, -Cl, -Br, or -I. In embodiments, R²² is independently unsubstituted methyl. In embodiments, R²² is independently unsubstituted ethyl.

[0209] R^{1A} is hydrogen, halogen, -CX^{1A}₃, -CHX^{1A}₂, -CH₂X^{1A}, -OCX^{1A}₃, -OCH₂X^{1A}, -OCHX^{1A}₂, -CN, -SO_{n1A}R^{1AA}, -SO_{v1A}NR^{1AA}R^{1AB}, -NHC(O)NR^{1AA}R^{1AB}, -N(O)_{m1A}, -NR^{1AA}R^{1AB}, -NHNHNR^{1AA}R^{1AB}, -C(O)R^{1AA}, -C(O)-OR^{1AA}, -C(O)NR^{1AA}R^{1AB}, -OR^{1AA}, -NR^{1AA}SO₂R^{1AB}, -NR^{1AA}C(O)R^{1AB}, -NR^{1AA}C(O)OR^{1AB}, -NR^{1AA}OR^{1AB}, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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).

[0210] In embodiments, R^{1A} is independently hydrogen. In embodiments, R^{1A} is independently -CX^{1A}₃. In embodiments, R^{1A} is independently -CHX^{1A}₂. In embodiments, R^{1A} is independently -CH₂X^{1A}. In embodiments, R^{1A} is independently -CN. In

embodiments, R^{1A} is independently $-\text{COOH}$. In embodiments, R^{1A} is independently $-\text{CONH}_2$. In embodiments, X^{1A} is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$.

[0211] In embodiments, R^{1A} is independently hydrogen, $-\text{CX}^{1A}_3$, $-\text{CHX}^{1A}_2$, $-\text{CH}_2\text{X}^{1A}$, $-\text{CN}$, $-\text{COOH}$, $-\text{CONH}_2$, R^{20A} -substituted or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), R^{20A} -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^{20A} -substituted or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), R^{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), R^{20A} -substituted or unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or R^{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^{1A} is independently hydrogen, $-\text{CX}^{1A}_3$, $-\text{CHX}^{1A}_2$, $-\text{CH}_2\text{X}^{1A}$, $-\text{CN}$, $-\text{COOH}$, $-\text{CONH}_2$, 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., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, 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), unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, 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^{1A} is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. In embodiments, R^{1A} is independently hydrogen. In embodiments, R^{1A} is independently unsubstituted methyl. In embodiments, R^{1A} is independently unsubstituted ethyl.

[0212] In embodiments, R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{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^{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^{1A} and R^{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^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{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).

membered). In embodiments, R^{1A} and R^{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).

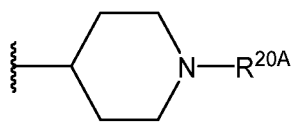
[0213] R^{20A} is independently oxo, halogen, $-CX^{20A}_3$, $-CHX^{20A}_2$, $-CH_2X^{20A}$, $-OCX^{20A}_3$, $-OCH_2X^{20A}$, $-OCHX^{20A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{21A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{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^{21A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{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, $-CX^{20A}_3$, $-CHX^{20A}_2$, $-CH_2X^{20A}$, $-OCX^{20A}_3$, $-OCH_2X^{20A}$, $-OCHX^{20A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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. In embodiments, R^{20A} is independently unsubstituted ethyl.

[0214] R^{21A} is independently oxo, halogen, $-CX^{21A}_3$, $-CHX^{21A}_2$, $-CH_2X^{21A}$, $-OCX^{21A}_3$, $-OCH_2X^{21A}$, $-OCHX^{21A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{22A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - 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., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), 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., C₆-C₁₂, C₆-C₁₀, 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, -CH₂X^{21A}, -OCX^{21A}₃, -OCH₂X^{21A}, -OCHX^{21A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{21A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{21A} is independently unsubstituted methyl. In embodiments, R^{21A} is independently unsubstituted ethyl.

[0215] R^{22A} is independently oxo, halogen, -CX^{22A}₃, -CHX^{22A}₂, -CH₂X^{22A}, -OCX^{22A}₃, -OCH₂X^{22A}, -OCHX^{22A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{22A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{22A} is independently unsubstituted methyl. In embodiments, R^{22A} is independently unsubstituted ethyl.

[0216] In embodiments, R^{1A} is independently hydrogen. In embodiments, R^{1A} is independently -OH. In embodiments, R^{1A} is independently unsubstituted methyl. In embodiments, R^{1A} is independently -OCH₃. In embodiments, R^{1A} is independently



–NH-(C₁-C₄ alkyl). In embodiments, R^{1A} is independently
 In embodiments, R^{1A} is independently –NH-NH-Ph. In embodiments, R^{1A} is independently
 R^{20A}-substituted or unsubstituted 5 membered heteroalkyl. In embodiments, R^{1A} is
 independently R^{20A}-substituted or unsubstituted 6 membered heteroalkyl. In embodiments,
 5 R^{1A} is independently R^{20A}-substituted or unsubstituted 7 membered heteroalkyl. In
 embodiments, R^{20A} is independently –F, –CF₃, or unsubstituted C₁-C₄ alkyl.

[0217] In embodiments, R^{1B} is independently hydrogen, halogen, –CX^{1B}₃, –CHX^{1B}₂,
 –CH₂X^{1B}, –C(O)OH, –C(O)NH₂, –CN, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –SH, –SO₃H,
 –SO₄H, –SO₂NH₂, –NHNH₂, –ONH₂, –NHC(=O)NHNH₂, –NHC(=O)NH₂, –NHSO₂H,
 10 –NHC(=O)H, –NHC(O)OH, –NHOH, –OCX^{1B}₃, –OCHX^{1B}₂, –OCH₂X^{1B}, substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted
 heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4
 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆),
 substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6
 15 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). X^{1B} are independently –Cl, –Br, –I,
 or –F.

[0218] In embodiments, a substituted R^{1B} (e.g., substituted alkyl, substituted heteroalkyl,
 20 substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted
 heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or
 lower substituent group; wherein if the substituted R^{1B} is substituted with a plurality of
 groups selected from substituent groups, size-limited substituent groups, and lower
 substituent groups; each substituent group, size-limited substituent group, and/or lower
 25 substituent group may optionally be different. In embodiments, when R^{1B} is substituted, it is
 substituted with at least one substituent group. In embodiments, when R^{1B} is substituted, it is
 substituted with at least one size-limited substituent group. In embodiments, when R^{1B} is
 substituted, it is substituted with at least one lower substituent group.

[0219] In embodiments, R^{1AA} is independently hydrogen, halogen, –CX^{1AA}₃, –CHX^{1AA}₂,
 30 –CH₂X^{1AA}, –C(O)OH, –C(O)NH₂, –CN, –OH, –NH₂, –COOH, –CONH₂, –NO₂, –SH, –SO₃H,

-SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{1AA}₃, -OCHX^{1AA}₂, -OCH₂X^{1AA}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{1AA} is independently -Cl, -Br, -I, or -F.

[0220] In embodiments, a substituted R^{1AA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1AA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1AA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1AA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1AA} is substituted, it is substituted with at least one lower substituent group.

[0221] In embodiments, R^{1AB} is independently hydrogen, halogen, -CX^{1AB}₃, -CHX^{1AB}₂, -CH₂X^{1AB}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{1AB}₃, -OCHX^{1AB}₂, -OCH₂X^{1AB}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{1AB} is independently -Cl, -Br, -I, or -F.

[0222] In embodiments, a substituted R^{1AB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1AB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1AB} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1AB} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1AB} is substituted, it is substituted with at least one lower substituent group.

[0223] In embodiments, R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, a substituted heterocycloalkyl or substituted heteroaryl formed by the joining of R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a heterocycloalkyl formed by the joining of R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one substituent group. In embodiments, when a heterocycloalkyl formed by the joining of R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a heterocycloalkyl formed by the joining of R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one lower substituent group. In embodiments, when a heteroaryl formed by the joining of R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one substituent group. In embodiments, when a heteroaryl formed by the joining of R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a heteroaryl formed by the joining of R^{1AA} and R^{1AB} substituents bonded

to the same nitrogen atom is substituted, it is substituted with at least one lower substituent group.

[0224] R^2 is hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, $-L^2-E^2$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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).

[0225] In embodiments, E^2 is independently halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v1}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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).

[0226] In embodiments, E^2 is independently halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v1}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, R^{23} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{23} -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^{23} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{23} -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).

membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{23} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{23} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

5 **[0227]** In embodiments, R^2 is independently hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, R^{23} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{23} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 10 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{23} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{23} -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^{23} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{23} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 15 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^2 is independently hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), 20 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^2 is 25 independently $-F$, $-Cl$, $-Br$, or $-I$.

[0228] R^{23} is independently oxo, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{24} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , 30 or C_1 - C_2), R^{24} -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^{24} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{24} -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^{24} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{24} -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^{23} is independently

5 oxo, halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-CH_2X^{23}$, $-OCX^{23}_3$, $-OCH_2X^{23}$, $-OCHX^{23}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NH SO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),

10 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^{23} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{23} is independently unsubstituted

15 methyl. In embodiments, R^{23} is independently unsubstituted ethyl.

[0229] R^{24} is independently oxo, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NH SO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{25} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 ,

20 or C_1 - C_2), R^{25} -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^{25} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{25} -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^{25} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{25} -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^{24} is independently

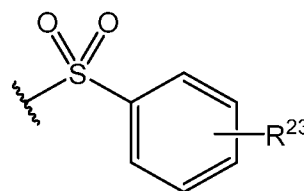
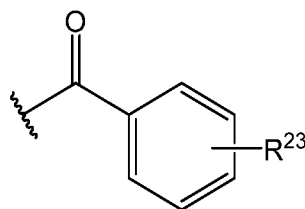
25 oxo, halogen, $-CX^{24}_3$, $-CHX^{24}_2$, $-CH_2X^{24}$, $-OCX^{24}_3$, $-OCH_2X^{24}$, $-OCHX^{24}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NH SO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$,

30 unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6

membered), unsubstituted aryl (e.g., 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). X²⁴ is independently -F, -Cl, -Br, or -I. In embodiments, R²⁴ is independently unsubstituted methyl. In embodiments, R²⁴ is independently unsubstituted ethyl.

- 5 **[0230]** R²⁵ is independently oxo, halogen, -CX²⁵₃, -CHX²⁵₂, -CH₂X²⁵, -OCX²⁵₃, -OCH₂X²⁵, -OCHX²⁵₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NH₂SO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁵ is independently -F, -Cl, -Br, or -I. In embodiments, R²⁵ is independently unsubstituted methyl. In embodiments, R²⁵ is independently unsubstituted ethyl.

- [0231]** In embodiments, R² is independently hydrogen. In embodiments, R² is independently -COOH. In embodiments, R² is independently -C(O)O(C₁-C₄ alkyl). In embodiments, R² is independently -CF₃. In embodiments, R² is independently -CH₂OH. In 20 embodiments, R² is independently -C(O)CH₃. In embodiments, R² is independently



. In embodiments, R¹ is independently
 In embodiments, R²³ is hydrogen, -F, -Cl, or unsubstituted C₁-C₄ alkyl.

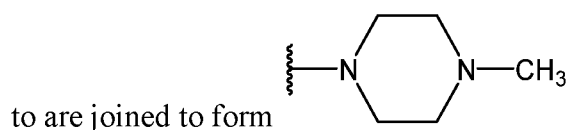
- [0232]** R^{2A} is hydrogen, halogen, -CX^{2A}₃, -CHX^{2A}₂, -CH₂X^{2A}, -OCX^{2A}₃, -OCH₂X^{2A}, -OCHX^{2A}₂, -CN, -SO_{n2A}R^{2AA}, -SO_{v2A}NR^{2AA}R^{2AB}, -NHC(O)NR^{2AA}R^{2AB}, -N(O)_{m2A},
 25 -NR^{2AA}R^{2AB}, -NHNR^{2AA}R^{2AB}, -C(O)R^{2AA}, -C(O)-OR^{2AA}, -C(O)NR^{2AA}R^{2AB}, -OR^{2AA}, -NR^{2AA}SO₂R^{2AB}, -NR^{2AA}C(O)R^{2AB}, -NR^{2AA}C(O)OR^{2AB}, -NR^{2AA}OR^{2AB}, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆),

substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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).

5 **[0233]** In embodiments, R^{2A} is independently hydrogen, -CX^{2A}₃, -CHX^{2A}₂, -CH₂X^{2A}, -CN, -COOH, -CONH₂, R^{23A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{23A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 12 membered, 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{23A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{23A}-substituted or
 10 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^{23A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{23A}-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^{2A} is independently hydrogen, -CX^{2A}₃, -CHX^{2A}₂, -CH₂X^{2A}, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., C₁-
 15 C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
 20 unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{2A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{2A} is independently hydrogen. In embodiments, R^{2A} is independently unsubstituted methyl. In embodiments, R^{2A} is independently unsubstituted ethyl.

[0234] In embodiments, R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may
 25 optionally be joined to form a R^{23A}-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^{23A}-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^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form an unsubstituted heterocycloalkyl (e.g.,
 30 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^{2A} and R^{2B} substituents bonded to the same nitrogen

atom may optionally be joined to form a R^{23A} -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^{2A} and R^{2B} 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^{2A} and R^{2B} substituents bonded to the same nitrogen and the nitrogen they are both bonded



- [0235]** R^{23A} is independently oxo, halogen, $-CX^{23A}_3$, $-CHX^{23A}_2$, $-CH_2X^{23A}$, $-OCX^{23A}_3$, $-OCH_2X^{23A}$, $-OCHX^{23A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, $-OPh$, R^{24A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{24A} -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^{24A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{24A} -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^{24A} -substituted or unsubstituted aryl (e.g., C_6-C_{14} , C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{24A} -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^{23A} is independently oxo, halogen, $-CX^{23A}_3$, $-CHX^{23A}_2$, $-CH_2X^{23A}$, $-OCX^{23A}_3$, $-OCH_2X^{23A}$, $-OCHX^{23A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{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^{23A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{23A} is independently unsubstituted methyl. In embodiments, R^{23A} is independently unsubstituted ethyl. In embodiments, two adjacent R^{23A} substituents may optionally be joined to form an R^{24A} -substituted or unsubstituted cycloalkyl, R^{24A} -substituted or

unsubstituted heterocycloalkyl, R^{24A} -substituted or unsubstituted aryl, or R^{24A} -substituted or unsubstituted heteroaryl.

[0236] R^{24A} is independently oxo, halogen, $-CX^{24A}_3$, $-CHX^{24A}_2$, $-CH_2X^{24A}$, $-OCX^{24A}_3$, $-OCH_2X^{24A}$, $-OCHX^{24A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{25A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{25A} -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^{25A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{25A} -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^{25A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{25A} -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^{24A} is independently oxo, halogen, $-CX^{24A}_3$, $-CHX^{24A}_2$, $-CH_2X^{24A}$, $-OCX^{24A}_3$, $-OCH_2X^{24A}$, $-OCHX^{24A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^{24A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{24A} is independently unsubstituted methyl. In embodiments, R^{24A} is independently unsubstituted ethyl.

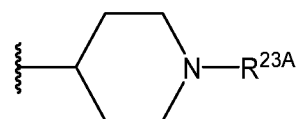
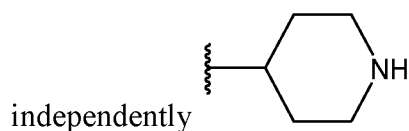
[0237] R^{25A} is independently oxo, halogen, $-CX^{25A}_3$, $-CHX^{25A}_2$, $-CH_2X^{25A}$, $-OCX^{25A}_3$, $-OCH_2X^{25A}$, $-OCHX^{25A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered).

membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{25A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{25A} is independently unsubstituted methyl. In embodiments, R^{25A} is independently

5 unsubstituted ethyl.

[0238] In embodiments, R^{2A} is independently hydrogen. In embodiments, R^{2A} is independently unsubstituted C₁-C₄ alkyl. In embodiments, R^{2A} is independently -CH₂CH₂OH. In embodiments, R^{2A} is independently unsubstituted C₅-C₆ cycloalkyl. In embodiments, R^{2A} is independently R^{23A}-substituted or unsubstituted phenyl. In

10 In embodiments, R^{2A} is independently unsubstituted phenyl. In embodiments, R^{2A} is



is independently -NH-pyridyl. In embodiments, R^{2A} is independently an R^{23A}-substituted or unsubstituted 4 to 9 membered heteroalkyl. In embodiments, R^{2A} is independently an

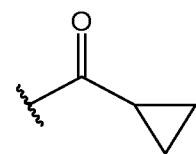
15 unsubstituted 4 to 9 membered heteroalkyl. In embodiments, R^{2A} is independently an R^{23A}-substituted or unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^{2A} is

independently an unsubstituted 5 to 9 membered heteroaryl. In embodiments, R^{23A} is

independently -F or -Cl. In embodiments, R^{23A} is independently -OCH₃. In embodiments,

R^{23A} is independently -OCF₃. In embodiments, R^{23A} is independently -C(O)O-tert-butyl. In

20 In embodiments, R^{23A} is independently -CONH₂. In embodiments, R^{23A} is independently



independently -CH₂CH₂OH. In embodiments, R^{23A} is independently an unsubstituted C₁-C₄ alkyl. In embodiments, R^{23A} is independently an unsubstituted C₂ alkynyl. In embodiments,

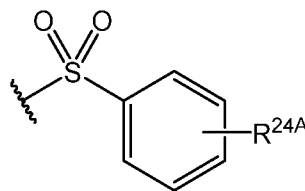
R^{23A} is independently an R^{24A}-substituted or unsubstituted phenyl. In embodiments, R^{23A} is

25 independently an unsubstituted phenyl. In embodiments, R^{23A} is independently an

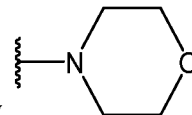
unsubstituted C₁₃ aryl. In embodiments, R^{23A} is independently an R^{24A}-substituted or

unsubstituted pyridyl. In embodiments, R^{23A} is independently an unsubstituted pyridyl. In

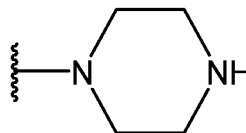
embodiments, R^{23A} is independently -SO₂CH₃. In embodiments, R^{23A} is independently -



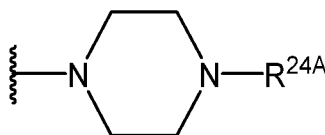
SO₂Ph. In embodiments, R^{23A} is independently . In embodiments,



R^{23A} is independently -OPh. In embodiments, R^{23A} is independently . In
embodiments, R^{23A} is independently an R^{24A}-substituted or unsubstituted 6 membered



heteroalkyl. In embodiments, R^{23A} is independently . In embodiments,



- 5 R^{23A} is independently . In embodiments, R^{23A} is independently an
unsubstituted 6 membered heteroalkyl. In embodiments, R^{24A} is independently oxo. In
embodiments, R^{24A} is independently unsubstituted methyl. In embodiments, R^{24A} is
independently an R^{25A}-substituted or unsubstituted phenyl. In embodiments, R^{24A} is
independently unsubstituted phenyl. In embodiments, R^{24A} is independently an R^{25A}-
10 substituted or unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^{24A} is
independently an unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^{24A} is
independently an R^{25A}-substituted or unsubstituted 5 to 6 membered heteroaryl. In
embodiments, R^{24A} is independently an unsubstituted 5 to 6 membered heteroaryl. In
embodiments, R^{24A} is independently an R^{25A}-substituted thienyl. In embodiments, R^{24A} is
15 independently an unsubstituted thienyl. In embodiments, R^{24A} is independently an R^{25A}-
substituted pyridyl. In embodiments, R^{24A} is independently an unsubstituted pyridyl. In
embodiments, R^{24A} is independently an R^{25A}-substituted pyrimidinyl. In embodiments, R^{24A}
is independently an unsubstituted pyrimidinyl. In embodiments, R^{25A} is independently -
F, -Cl, -CN, or unsubstituted methyl.

- 20 **[0239]** R^{2B} is hydrogen, halogen, -CX^{2B}₃, -CHX^{2B}₂, -CH₂X^{2B}, -OCX^{2B}₃, -OCH₂X^{2B},
-OCHX^{2B}₂, -CN, -SO_{n2B}R^{2BA}, -SO_{v2B}NR^{2BA}R^{2BB}, -NHC(O)NR^{2BA}R^{2BB}, -N(O)_{m2B},
-NR^{2BA}R^{2BB}, -NHNHNR^{2BA}R^{2BB}, -C(O)R^{2BA}, -C(O)-OR^{2BA}, -C(O)NR^{2BA}R^{2BB}, -OR^{2BA},
-NR^{2BA}SO₂R^{2BB}, -NR^{2BA}C(O)R^{2BB}, -NR^{2BA}C(O)OR^{2BB}, -NR^{2BA}OR^{2BB}, -N₃, substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted
25 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).

[0240] In embodiments, R^{2B} is independently hydrogen, -CX^{2B}₃, -CHX^{2B}₂, -CH₂X^{2B}, -CN, -COOH, -CONH₂, R^{23B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{23B}-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^{23B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{23B}-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^{23B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{23B}-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^{2B} is independently hydrogen, -CX^{2B}₃, -CHX^{2B}₂, -CH₂X^{2B}, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{2B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{2B} is independently hydrogen. In embodiments, R^{2B} is independently an unsubstituted methyl. In embodiments, R^{2B} is independently unsubstituted ethyl.

[0241] R^{23B} is independently oxo, halogen, -CX^{23B}₃, -CHX^{23B}₂, -CH₂X^{23B}, -OCX^{23B}₃, -OCH₂X^{23B}, -OCHX^{23B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, -OPh, R^{24B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{24B}-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^{24B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{24B}-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^{24B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{24B} -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^{23B} is independently oxo, halogen, $-CX^{23B}_3$, $-CHX^{23B}_2$, $-CH_2X^{23B}$, $-OCX^{23B}_3$, $-OCH_2X^{23B}$, $-OCHX^{23B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^{23B} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{23B} is independently unsubstituted methyl. In embodiments, R^{23B} is independently unsubstituted ethyl. In embodiments, two adjacent R^{23B} substituents may optionally be joined to form an R^{24B} -substituted or unsubstituted cycloalkyl, R^{24B} -substituted or unsubstituted heterocycloalkyl, R^{24B} -substituted or unsubstituted aryl, or R^{24B} -substituted or unsubstituted heteroaryl.

[0242] R^{24B} is independently oxo, halogen, $-CX^{24B}_3$, $-CHX^{24B}_2$, $-CH_2X^{24B}$, $-OCX^{24B}_3$, $-OCH_2X^{24B}$, $-OCHX^{24B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{25B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{25B} -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^{25B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{25B} -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^{25B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{25B} -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^{24B} is independently oxo, halogen, $-CX^{24B}_3$, $-CHX^{24B}_2$, $-CH_2X^{24B}$, $-OCX^{24B}_3$, $-OCH_2X^{24B}$, $-OCHX^{24B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2),

unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{24B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{24B} is independently unsubstituted methyl. In embodiments, R^{24B} is independently unsubstituted ethyl.

[0243] R^{25B} is independently oxo, halogen, -CX^{25B}₃, -CHX^{25B}₂, -CH₂X^{25B}, -OCX^{25B}₃, -OCH₂X^{25B}, -OCHX^{25B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{25B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{25B} is independently unsubstituted methyl. In embodiments, R^{25B} is independently unsubstituted ethyl.

[0244] In embodiments, R^{2AA} is independently hydrogen, halogen, -CX^{2AA}₃, -CHX^{2AA}₂, -CH₂X^{2AA}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{2AA}₃, -OCHX^{2AA}₂, -OCH₂X^{2AA}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{2AA} is independently -Cl, -Br, -I, or -F.

[0245] In embodiments, a substituted R^{2AA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2AA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2AA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2AA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2AA} is substituted, it is substituted with at least one lower substituent group.

[0246] In embodiments, R^{2AB} is independently hydrogen, halogen, $-CX^{2AB}_3$, $-CHX^{2AB}_2$, $-CH_2X^{2AB}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{2AB}_3$, $-OCHX^{2AB}_2$, $-OCH_2X^{2AB}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). X^{2AB} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0247] In embodiments, a substituted R^{2AB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2AB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2AB} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2AB} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2AB} is substituted, it is substituted with at least one lower substituent group.

[0248] In embodiments, R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, a substituted heterocycloalkyl or substituted heteroaryl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when a heterocycloalkyl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one substituent group. In embodiments, when a heterocycloalkyl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a heterocycloalkyl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one lower substituent group. In embodiments, when a heteroaryl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one substituent group. In embodiments, when a heteroaryl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a heteroaryl formed by the joining of R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one lower substituent group.

[0249] In embodiments, R^{2BA} is independently hydrogen, halogen, $-CX^{2BA}_3$, $-CHX^{2BA}_2$, $-CH_2X^{2BA}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{2BA}_3$, $-OCHX^{2BA}_2$, $-OCH_2X^{2BA}$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6

membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{2BA} is independently -Cl, -Br, -I, or -F.

5 **[0250]** In embodiments, a substituted R^{2BA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2BA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower
10 substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2BA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2BA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2BA} is substituted, it is substituted with at least one lower substituent group.

15 **[0251]** In embodiments, R^{2BB} is independently hydrogen, halogen, -CX^{2BB}₃, -CHX^{2BB}₂, -CH₂X^{2BB}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCX^{2BB}₃, -OCHX^{2BB}₂, -OCH₂X^{2BB}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted
20 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). X^{2BB} is independently -Cl, -Br, -I, or -F.
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[0252] In embodiments, a substituted R^{2BB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or
30 lower substituent group; wherein if the substituted R^{2BB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower

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

- 5 **[0253]** In embodiments, R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, a substituted heterocycloalkyl or
- 10 substituted heteroaryl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted heterocycloalkyl or substituted heteroaryl is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited
- 15 substituent group, and/or lower substituent group may optionally be different. In embodiments, when a heterocycloalkyl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one substituent group. In embodiments, when a heterocycloalkyl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one
- 20 size-limited substituent group. In embodiments, when a heterocycloalkyl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one lower substituent group. In embodiments, when a heteroaryl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one substituent group. In embodiments, when a
- 25 heteroaryl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when a heteroaryl formed by the joining of R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom is substituted, it is substituted with at least one lower substituent group.
- 30 **[0254]** In embodiments, R^3 is independently hydrogen, halogen, $-CX^3$, $-CHX^3$, $-CH_2X^3$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$,

-NHC(O)OH, -NHOH, -OCX³₃, -OCHX³₂, -OCH₂X³, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X³ is independently -Cl, -Br, -I, or -F.

[0255] In embodiments, R³ is independently hydrogen. In embodiments, R³ is independently unsubstituted methyl. In embodiments, R³ is independently -CH₂OH. In embodiments, R³ is independently unsubstituted phenyl.

[0256] In embodiments, a substituted R³ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R³ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R³ is substituted, it is substituted with at least one substituent group. In embodiments, when R³ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R³ is substituted, it is substituted with at least one lower substituent group.

[0257] In embodiments, R^{3A} is independently hydrogen, halogen, -CX^{3A}₃, -CHX^{3A}₂, -CH₂X^{3A}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCX^{3A}₃, -OCHX^{3A}₂, -OCH₂X^{3A}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{3A} is independently -Cl, -Br, -I, or -F.

[0258] In embodiments, a substituted R^{3A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{3A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3A} is substituted, it is substituted with at least one lower substituent group.

[0259] In embodiments, R^{3B} is independently hydrogen, halogen, $-CX^{3B}_3$, $-CHX^{3B}_2$, $-CH_2X^{3B}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{3B}_3$, $-OCHX^{3B}_2$, $-OCH_2X^{3B}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). X^{3B} is independently -Cl, -Br, -I, or -F.

[0260] In embodiments, a substituted R^{3B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{3B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3B} is substituted, it is

substituted with at least one size-limited substituent group. In embodiments, when R^{3B} is substituted, it is substituted with at least one lower substituent group.

[0261] In embodiments, R⁴ is independently hydrogen, halogen, -CX⁴₃, -CHX⁴₂, -CH₂X⁴, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX⁴₃, -OCHX⁴₂, -OCH₂X⁴, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). In embodiments, R⁴ is independently hydrogen. In embodiments, R⁴ is independently -OH. X⁴ is independently -Cl, -Br, -I, or -F.

[0262] In embodiments, a substituted R⁴ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R⁴ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R⁴ is substituted, it is substituted with at least one substituent group. In embodiments, when R⁴ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R⁴ is substituted, it is substituted with at least one lower substituent group.

[0263] In embodiments, R^{4A} is independently hydrogen, halogen, -CX^{4A}₃, -CHX^{4A}₂, -CH₂X^{4A}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{4A}₃, -OCHX^{4A}₂, -OCH₂X^{4A}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆),

substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{4A} is independently -Cl, -Br, -I or, -F.

[0264] In embodiments, a substituted R^{4A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{4A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4A} is substituted, it is substituted with at least one lower substituent group.

[0265] In embodiments, R^{4B} is independently hydrogen, halogen, -CX^{4B}₃, -CHX^{4B}₂, -CH₂X^{4B}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCX^{4B}₃, -OCHX^{4B}₂, -OCH₂X^{4B}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{4B} is independently -Cl, -Br, -I, or -F.

[0266] In embodiments, a substituted R^{4B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower

substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{4B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4B} is substituted, it is substituted with at least one lower substituent group.

[0267] In embodiments, R^5 is independently hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^5_3$, $-OCHX^5_2$, $-OCH_2X^5$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). In embodiments, R^5 is independently hydrogen. In embodiments, R^5 is independently $-OH$. X^5 is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0268] In embodiments, a substituted R^5 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^5 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^5 is substituted, it is substituted with at least one substituent group. In embodiments, when R^5 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^5 is substituted, it is substituted with at least one lower substituent group.

[0269] In embodiments, R^{5A} is independently hydrogen, halogen, $-CX^{5A}_3$, $-CHX^{5A}_2$, $-CH_2X^{5A}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{5A}_3$, $-OCHX^{5A}_2$, $-OCH_2X^{5A}$, substituted or

unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{5A} is independently -Cl, -Br, -I, or -F.

[0270] In embodiments, a substituted R^{5A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{5A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5A} is substituted, it is substituted with at least one lower substituent group.

[0271] In embodiments, R^{5B} is independently hydrogen, halogen, -CX^{5B}₃, -CHX^{5B}₂, -CH₂X^{5B}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCX^{5B}₃, -OCHX^{5B}₂, -OCH₂X^{5B}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{5B} is independently -Cl, -Br, -I, or -F.

[0272] In embodiments, a substituted R^{5B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{5B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5B} is substituted, it is substituted with at least one lower substituent group.

[0273] In embodiments, R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^6_3$, $-OCHX^6_2$, $-OCH_2X^6$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , 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). X^6 is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0274] In embodiments, a substituted R^6 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^6 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^6 is substituted, it is substituted with at least one substituent group. In embodiments, when R^6 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^6 is substituted, it is substituted with at least one lower substituent group.

[0275] In embodiments, R^{6A} is independently hydrogen, halogen, $-CX^{6A}_3$, $-CHX^{6A}_2$, $-CH_2X^{6A}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$,

-SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{6A}₃, -OCHX^{6A}₂, -OCH₂X^{6A}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{6A} is independently -Cl, -Br, -I, or -F.

[0276] In embodiments, a substituted R^{6A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{6A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6A} is substituted, it is substituted with at least one lower substituent group.

[0277] In embodiments, R^{6B} is independently hydrogen, halogen, -CX^{6B}₃, -CHX^{6B}₂, -CH₂X^{6B}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{6B}₃, -OCHX^{6B}₂, -OCH₂X^{6B}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{6B} is independently -Cl, -Br, -I, or -F.

[0278] In embodiments, a substituted R^{6B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{6B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6B} is substituted, it is substituted with at least one lower substituent group.

[0279] In embodiments, R^7 is independently hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^7_3$, $-OCHX^7_2$, $-OCH_2X^7$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , 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). X^7 is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0280] In embodiments, a substituted R^7 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^7 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^7 is substituted, it is substituted with at least one substituent group. In embodiments, when R^7 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^7 is substituted, it is substituted with at least one lower substituent group.

[0281] In embodiments, R^{7A} is independently hydrogen, halogen, $-CX^{7A}_3$, $-CHX^{7A}_2$, $-CH_2X^{7A}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7A}_3$, $-OCHX^{7A}_2$, $-OCH_2X^{7A}$, substituted or
 5 unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). X^{7A} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0282] In embodiments, a substituted R^{7A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted
 15 heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{7A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{7A} is substituted, it is
 20 substituted with at least one substituent group. In embodiments, when R^{7A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{7A} is substituted, it is substituted with at least one lower substituent group.

[0283] In embodiments, R^{7B} is independently hydrogen, halogen, $-CX^{7B}_3$, $-CHX^{7B}_2$, $-CH_2X^{7B}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$,
 25 $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7B}_3$, $-OCHX^{7B}_2$, $-OCH_2X^{7B}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5
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to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{7B} is independently -Cl, -Br, -I, or -F.

[0284] In embodiments, a substituted R^{7B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{7B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{7B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{7B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{7B} is substituted, it is substituted with at least one lower substituent group.

[0285] R^8 is hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-SO_{m8}R^{8A}$, $-SO_{v8}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m8}$, $-NR^{8A}R^{8B}$, $-NHN R^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHN R^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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).

[0286] In embodiments, R^8 is independently hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, R^{41} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{41} -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^{41} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{41} -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^{41} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-

C₁₀, or phenyl), or R⁴¹-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, R⁸ is independently hydrogen, halogen, -CX⁸₃, -CHX⁸₂, -CH₂X⁸, -OCX⁸₃, -OCH₂X⁸, -OCHX⁸₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
 5 -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6
 10 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). X⁸ is independently -F, -Cl, -Br, or -I.

[0287] In embodiments, R⁸ is independently hydrogen. In embodiments, R⁸ is independently unsubstituted methyl. In embodiments, R⁸ is independently -OCH₃. In
 15 embodiments, R⁸ is independently -CN. In embodiments, R⁸ is independently -OPh. In embodiments, R⁸ is independently an R⁴¹-substituted or unsubstituted phenyl. In embodiments, R⁸ is independently an R⁴¹-substituted phenyl. In embodiments, R⁸ is independently an unsubstituted phenyl. In embodiments, R⁴¹ is independently -F, -Cl, -CN, -CH₃, -OCH₃, or -OCH₂CH₃.

[0288] In embodiments, R⁸ and R⁹ substituents may optionally be joined to form a R⁴¹-
 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), or R⁴¹-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, R⁸ and R⁹ substituents may optionally be joined to form an
 25 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, R⁸ and R⁹ substituents may optionally be joined to form a R⁴¹-substituted or unsubstituted
 30 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, R⁸ and R⁹ 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).

[0289] R^{41} is independently oxo, halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-OCX^{41}_3$, $-OCH_2X^{41}$, $-OCHX^{41}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, $-NHPh$, $-OPh$, R^{42} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{42} -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^{42} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{42} -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^{42} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{42} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0290] In embodiments, R^{41} is independently oxo, halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-OCX^{41}_3$, $-OCH_2X^{41}$, $-OCHX^{41}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{42} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{42} -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^{42} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{42} -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^{42} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{42} -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^{41} is independently oxo, halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-OCX^{41}_3$, $-OCH_2X^{41}$, $-OCHX^{41}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^{41} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{41} is independently unsubstituted methyl. In embodiments, R^{41} is independently unsubstituted ethyl.

[0291] R^{42} is independently oxo, halogen, $-CX^{42}_3$, $-CHX^{42}_2$, $-CH_2X^{42}$, $-OCX^{42}_3$, $-OCH_2X^{42}$, $-OCHX^{42}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{43} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{43} -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^{43} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{43} -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^{43} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{43} -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^{42} is independently oxo, halogen, $-CX^{42}_3$, $-CHX^{42}_2$, $-CH_2X^{42}$, $-OCX^{42}_3$, $-OCH_2X^{42}$, $-OCHX^{42}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{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^{42} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{42} is independently unsubstituted methyl. In embodiments, R^{42} is independently unsubstituted ethyl.

[0292] R^{43} is independently oxo, halogen, $-CX^{43}_3$, $-CHX^{43}_2$, $-CH_2X^{43}$, $-OCX^{43}_3$, $-OCH_2X^{43}$, $-OCHX^{43}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{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^{43} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments,

R⁴³ is independently unsubstituted methyl. In embodiments, R⁴³ is independently unsubstituted ethyl.

[0293] R^{8A} is hydrogen, halogen, -CX^{8A}₃, -CHX^{8A}₂, -CH₂X^{8A}, -OCX^{8A}₃, -OCH₂X^{8A}, -OCHX^{8A}₂, -CN, -SO_{n8A}R^{8AA}, -SO_{v8A}NR^{8AA}R^{8AB}, -NHC(O)NR^{8AA}R^{8AB}, -N(O)_{m8A},
 5 -NR^{8AA}R^{8AB}, -NHN^{8AA}R^{8AB}, -C(O)R^{8AA}, -C(O)-OR^{8AA}, -C(O)NR^{8AA}R^{8AB}, -OR^{8AA},
 -NR^{8AA}SO₂R^{8AB}, -NR^{8AA}C(O)R^{8AB}, -NR^{8AA}C(O)OR^{8AB}, -NR^{8AA}OR^{8AB}, -N₃, substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted
 heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4
 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆),
 10 substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6
 membered, 4 to 5 membered, or 5 to 6 membered), 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).

[0294] In embodiments, R^{8A} is independently hydrogen, -CX^{8A}₃, -CHX^{8A}₂, -CH₂X^{8A},
 15 -CN, -COOH, -CONH₂, R^{41A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or
 C₁-C₂), R^{41A}-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^{41A}-substituted or
 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{41A}-substituted or
 unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4
 20 to 5 membered, or 5 to 6 membered), R^{41A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-
 C₁₀, or phenyl), or R^{41A}-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^{8A} is independently
 hydrogen, -CX^{8A}₃, -CHX^{8A}₂, -CH₂X^{8A}, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., C₁-
 C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6
 25 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
 unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12
 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8A} is independently
 30 -F, -Cl, -Br, or -I. In embodiments, R^{8A} is independently hydrogen. In embodiments, R^{8A} is
 independently unsubstituted methyl. In embodiments, R^{8A} is independently unsubstituted
 ethyl.

[0295] In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{41A} -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^{41A} -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^{8A} and R^{8B} 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^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{41A} -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^{8A} and R^{8B} 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).

[0296] In embodiments, R^8 and R^9 substituents may optionally be joined to form a R^{41} -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^{41} -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^8 and R^9 substituents may optionally be joined to form a R^{41} -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^8 and R^9 substituents may optionally be joined to form a R^{41} -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^8 and R^9 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, R^8 and R^9 substituents may optionally be joined to form a R^{41} -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^8 and R^9 substituents may optionally be joined to form a R^{41} -substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^8 and R^9 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).

[0297] R^{41A} is independently oxo, halogen, $-CX^{41A}_3$, $-CHX^{41A}_2$, $-CH_2X^{41A}$, $-OCX^{41A}_3$, $-OCH_2X^{41A}$, $-OCHX^{41A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{42A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{42A} -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^{42A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{42A} -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^{42A} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{42A} -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^{41A} is independently oxo, halogen, $-CX^{41A}_3$, $-CHX^{41A}_2$, $-CH_2X^{41A}$, $-OCX^{41A}_3$, $-OCH_2X^{41A}$, $-OCHX^{41A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{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^{41A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{41A} is independently unsubstituted methyl. In embodiments, R^{41A} is independently unsubstituted ethyl.

[0298] R^{42A} is independently oxo, halogen, $-CX^{42A}_3$, $-CHX^{42A}_2$, $-CH_2X^{42A}$, $-OCX^{42A}_3$, $-OCH_2X^{42A}$, $-OCHX^{42A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{43A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{43A} -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^{43A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{43A} -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^{43A} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{43A} -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^{42A} is independently oxo, halogen, $-CX^{42A}_3$, $-CHX^{42A}_2$, $-CH_2X^{42A}$, $-OCX^{42A}_3$, $-OCH_2X^{42A}$, $-OCHX^{42A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH_2SO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., 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^{42A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{42A} is independently unsubstituted methyl. In embodiments, R^{42A} is independently unsubstituted ethyl.

[0299] R^{43A} is independently oxo, halogen, $-CX^{43A}_3$, $-CHX^{43A}_2$, $-CH_2X^{43A}$, $-OCX^{43A}_3$, $-OCH_2X^{43A}$, $-OCHX^{43A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH_2SO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., 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^{43A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{43A} is independently unsubstituted methyl. In embodiments, R^{43A} is independently unsubstituted ethyl.

[0300] R^{8B} is hydrogen, halogen, $-CX^{8B}_3$, $-CHX^{8B}_2$, $-CH_2X^{8B}$, $-OCX^{8B}_3$, $-OCH_2X^{8B}$, $-OCHX^{8B}_2$, $-CN$, $-SO_{n8B}R^{8BA}$, $-SO_{v8B}NR^{8BA}R^{8BB}$, $-NHC(O)NR^{8BA}R^{8BB}$, $-N(O)_{m8B}$, $-NR^{8BA}R^{8BB}$, $-NHNR^{8BA}R^{8BB}$, $-C(O)R^{8BA}$, $-C(O)-OR^{8BA}$, $-C(O)NR^{8BA}R^{8BB}$, $-OR^{8BA}$, $-NR^{8BA}SO_2R^{8BB}$, $-NR^{8BA}C(O)R^{8BB}$, $-NR^{8BA}C(O)OR^{8BB}$, $-NR^{8BA}OR^{8BB}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6),

substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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).

5 **[0301]** In embodiments, R^{8B} is independently hydrogen, -CX^{8B}₃, -CHX^{8B}₂, -CH₂X^{8B}, -CN, -COOH, -CONH₂, R^{41B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{41B}-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^{41B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{41B}-substituted or unsubstituted
 10 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^{41B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{41B}-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^{8B} is independently hydrogen, -CX^{8B}₃, -CHX^{8B}₂, -CH₂X^{8B}, -CN, -COOH, -CONH₂, unsubstituted alkyl (e.g., C₁-
 15 C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
 20 unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{8B} is independently hydrogen. In embodiments, R^{8B} is independently unsubstituted methyl. In embodiments, R^{8B} is independently unsubstituted ethyl.

[0302] In embodiments, R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may
 25 optionally be joined to form a R^{41B}-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^{41B}-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^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form an unsubstituted heterocycloalkyl (e.g.,
 30 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^{8A} and R^{8B} substituents bonded to the same nitrogen

atom may optionally be joined to form a R^{41B} -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^{8A} and R^{8B} 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).

[0303] R^{41B} is independently oxo, halogen, $-CX^{41B}_3$, $-CHX^{41B}_2$, $-CH_2X^{41B}$, $-OCX^{41B}_3$, $-OCH_2X^{41B}$, $-OCHX^{41B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{42B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{42B} -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^{42B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{42B} -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^{42B} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{42B} -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^{41B} is independently oxo, halogen, $-CX^{41B}_3$, $-CHX^{41B}_2$, $-CH_2X^{41B}$, $-OCX^{41B}_3$, $-OCH_2X^{41B}$, $-OCHX^{41B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6-C_{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^{41B} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{41B} is independently unsubstituted methyl. In embodiments, R^{41B} is independently unsubstituted ethyl.

[0304] R^{42B} is independently oxo, halogen, $-CX^{42B}_3$, $-CHX^{42B}_2$, $-CH_2X^{42B}$, $-OCX^{42B}_3$, $-OCH_2X^{42B}$, $-OCHX^{42B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{43B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{43B} -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^{43B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{43B} -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^{43B} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{43B} -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

- C₄, or C₁-C₂), R^{43B}-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^{43B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{43B}-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^{43B}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{43B}-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^{42B} is independently oxo, halogen, -CX^{42B}₃, -CHX^{42B}₂, -CH₂X^{42B}, -OCX^{42B}₃, -OCH₂X^{42B}, -OCHX^{42B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{42B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{42B} is independently unsubstituted methyl. In embodiments, R^{42B} is independently unsubstituted ethyl.
- [0305]** R^{43B} is independently oxo, halogen, -CX^{43B}₃, -CHX^{43B}₂, -CH₂X^{43B}, -OCX^{43B}₃, -OCH₂X^{43B}, -OCHX^{43B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{43B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{43B} is independently unsubstituted methyl. In embodiments, R^{43B} is independently unsubstituted ethyl.

[0306] R^{8AA} is independently hydrogen, halogen, $-CX^{8AA}_3$, $-CHX^{8AA}_2$, $-CH_2X^{8AA}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8AA}_3$, $-OCHX^{8AA}_2$, $-OCH_2X^{8AA}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl), substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{8AA} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0307] In embodiments, R^{8AA} is independently hydrogen, halogen, $-CX^{8AA}_3$, $-CHX^{8AA}_2$, $-CH_2X^{8AA}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8AA}_3$, $-OCHX^{8AA}_2$, $-OCH_2X^{8AA}$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , 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). X^{8AA} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0308] In embodiments, a substituted R^{8AA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{8AA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{8AA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{8AA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{8AA} is substituted, it is substituted with at least one lower substituent group.

[0309] R^{8AB} is independently hydrogen, halogen, $-CX^{8AB}_3$, $-CHX^{8AB}_2$, $-CH_2X^{8AB}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$,

-NHC(O)OH, -NHOH, -OCX^{8AB}₃, -OCHX^{8AB}₂, -OCH₂X^{8AB}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{8AB} is independently -Cl, -Br, -I, or -F.

- 5 **[0310]** In embodiments, R^{8AB} is independently hydrogen, halogen, -CX^{8AB}₃, -CHX^{8AB}₂, -CH₂X^{8AB}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)OH, -NHOH, -OCX^{8AB}₃, -OCHX^{8AB}₂, -OCH₂X^{8AB}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted
10 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
15 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8AB} is independently -Cl, -Br, -I, or -F.

- [0311]** In embodiments, a substituted R^{8AB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or
20 lower substituent group; wherein if the substituted R^{8AB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{8AB} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{8AB} is substituted, it
25 is substituted with at least one size-limited substituent group. In embodiments, when R^{8AB} is substituted, it is substituted with at least one lower substituent group.

- [0312]** R^{8BA} is independently hydrogen, halogen, -CX^{8BA}₃, -CHX^{8BA}₂, -CH₂X^{8BA}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H,
30 -NHC(O)OH, -NHOH, -OCX^{8BA}₃, -OCHX^{8BA}₂, -OCH₂X^{8BA}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,

substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{8BA} is independently -Cl, -Br, -I, or -F.

[0313] In embodiments, R^{8BA} is independently hydrogen, halogen, $-CX^{8BA}_3$, $-CHX^{8BA}_2$, $-CH_2X^{8BA}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8BA}_3$, $-OCHX^{8BA}_2$, $-OCH_2X^{8BA}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). X^{8BA} is independently -Cl, -Br, -I, or -F.

[0314] In embodiments, a substituted R^{8BA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{8BA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{8BA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{8BA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{8BA} is substituted, it is substituted with at least one lower substituent group.

[0315] R^{8BB} is independently hydrogen, halogen, $-CX^{8BB}_3$, $-CHX^{8BB}_2$, $-CH_2X^{8BB}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8BB}_3$, $-OCHX^{8BB}_2$, $-OCH_2X^{8BB}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{8BB} is independently -Cl, -Br, -I, or -F.

[0316] In embodiments, R^{8BB} is independently hydrogen, halogen, $-CX^{8BB}_3$, $-CHX^{8BB}_2$, $-CH_2X^{8BB}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8BB}_3$, $-OCHX^{8BB}_2$, $-OCH_2X^{8BB}$, substituted or
 5 unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). X^{8BB} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0317] In embodiments, a substituted R^{8BB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted
 15 heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{8BB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{8BB} is substituted, it is
 20 substituted with at least one substituent group. In embodiments, when R^{8BB} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{8BB} is substituted, it is substituted with at least one lower substituent group.

[0318] R^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-SO_{m9}R^{9A}$, $-SO_{v9}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m9}$, $-NR^{9A}R^{9B}$, $-NHNR^{9A}R^{9B}$,
 25 $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNr^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or
 30 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_{12} , C_6-C_{10} ,

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).

[0319] In embodiments, R^9 is independently hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, R^{44} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{44} -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^{44} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{44} -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^{44} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{44} -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^9 is independently hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^9 is independently $-F$, $-Cl$, $-Br$, or $-I$.

[0320] In embodiments, R^8 and R^9 substituents may optionally be joined to form a R^{44} -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^{44} -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^8 and R^9 substituents may optionally be joined to form a R^{44} -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^8 and R^9 substituents may optionally be joined to form a R^{44} -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,

R⁸ and R⁹ 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, R⁸ and R⁹ substituents may optionally be joined to form a R⁴⁴-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, R⁸ and R⁹ substituents may optionally be joined to form a R⁴⁴-substituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R⁸ and R⁹ 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).

- 10 **[0321]** R⁴⁴ is independently oxo, halogen, -CX⁴⁴₃, -CHX⁴⁴₂, -CH₂X⁴⁴, -OCX⁴⁴₃, -OCH₂X⁴⁴, -OCHX⁴⁴₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, -NHPh, -OPh, R⁴⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R⁴⁵-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), R⁴⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R⁴⁵-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), R⁴⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R⁴⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

- 25 **[0322]** In embodiments, R⁴⁴ is independently oxo, halogen, -CX⁴⁴₃, -CHX⁴⁴₂, -CH₂X⁴⁴, -OCX⁴⁴₃, -OCH₂X⁴⁴, -OCHX⁴⁴₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, R⁴⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R⁴⁵-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), R⁴⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R⁴⁵-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), R⁴⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R⁴⁵-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, R⁴⁴ is independently oxo, halogen, -CX⁴⁴₃, -CHX⁴⁴₂, -CH₂X⁴⁴, -OCX⁴⁴₃, -OCH₂X⁴⁴, -OCHX⁴⁴₂, -CN, -OH, -NH₂,

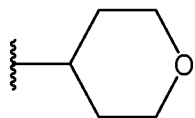
-COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
 -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃,
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to
 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
 5 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). X⁴⁴ is
 independently -F, -Cl, -Br, or -I. In embodiments, R⁴⁴ is independently unsubstituted
 10 methyl. In embodiments, R⁴⁴ is independently unsubstituted ethyl.

[0323] R⁴⁵ is independently oxo, halogen, -CX⁴⁵₃, -CHX⁴⁵₂, -CH₂X⁴⁵, -OCX⁴⁵₃, -OCH₂X⁴⁵,
 -OCHX⁴⁵₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂,
 -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H,
 -NHC(O)-OH, -NHOH, -N₃, R⁴⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄,
 15 or C₁-C₂), R⁴⁶-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), R⁴⁶-substituted or
 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R⁴⁶-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), R⁴⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-
 20 C₁₀, or phenyl), or R⁴⁶-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, R⁴⁵ is independently
 oxo, halogen, -CX⁴⁵₃, -CHX⁴⁵₂, -CH₂X⁴⁵, -OCX⁴⁵₃, -OCH₂X⁴⁵, -OCHX⁴⁵₂, -CN, -OH, -NH₂,
 -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
 -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃,
 25 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to
 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),
 unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl
 (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6
 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl
 30 (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁵ is
 independently -F, -Cl, -Br, or -I. In embodiments, R⁴⁵ is independently unsubstituted
 methyl. In embodiments, R⁴⁵ is independently unsubstituted ethyl.

[0324] R^{46} is independently oxo, halogen, $-CX^{46}_3$, $-CHX^{46}_2$, $-CH_2X^{46}$, $-OCX^{46}_3$, $-OCH_2X^{46}$, $-OCHX^{46}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2),
 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_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
 10 membered, or 5 to 6 membered). X^{46} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{46} is independently unsubstituted methyl. In embodiments, R^{46} is independently unsubstituted ethyl.

[0325] In embodiments, R^9 is independently an R^{44} -substituted or unsubstituted C_1-C_4 alkyl. In embodiments, R^9 is independently an unsubstituted C_1-C_4 alkyl. In embodiments,
 15 R^9 is independently an R^{44} -substituted or unsubstituted C_4-C_6 cycloalkyl. In embodiments, R^9 is independently an unsubstituted C_4-C_6 cycloalkyl. In embodiments, R^9 is independently R^{44} -substituted or unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^9 is independently an unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^9 is independently R^{44} -substituted or unsubstituted phenyl. In embodiments, R^9 is independently
 20 an unsubstituted phenyl. In embodiments, R^9 is independently an R^{44} -substituted or unsubstituted naphthyl. In embodiments, R^9 is independently an unsubstituted naphthyl. In embodiments, R^9 is independently an R^{44} -substituted or unsubstituted pyridyl. In embodiments, R^9 is independently an unsubstituted pyridyl. In embodiments, R^9 is independently an R^{44} -substituted or unsubstituted 10 membered heteroaryl. In embodiments,
 25 R^9 is independently an unsubstituted 10 membered heteroaryl. In embodiments, R^{44} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{44} is independently $-CN$. In embodiments, R^{44} is independently $-O-(C_1-C_4 \text{ alkyl})$. In embodiments, R^{44} is independently $-OCH_3$. In embodiments, R^{44} is independently $-OCH_2CH_3$. In embodiments, R^{44} is independently $-OCF_3$. In embodiments, R^{44} is independently an R^{45} -substituted or
 30 unsubstituted C_1-C_4 alkyl. In embodiments, R^{44} is independently an unsubstituted methyl. In embodiments, R^{44} is independently an R^{45} -substituted or unsubstituted 2 to 5 membered heteroalkyl. In embodiments, R^{44} is independently $-CH_2OH$. In embodiments, R^{44} is independently $-CH_2CH_2OH$. In embodiments, R^{44} is independently an R^{45} -substituted or

unsubstituted phenyl. In embodiments, R^{44} is independently an unsubstituted phenyl. In embodiments, R^{45} is independently oxo. In embodiments, R^{45} is independently an unsubstituted 5 to 6 membered heterocycloalkyl. In embodiments, R^{45} is independently



- 5 **[0326]** R^{9A} is hydrogen, halogen, $-CX^{9A}_3$, $-CHX^{9A}_2$, $-CH_2X^{9A}$, $-OCX^{9A}_3$, $-OCH_2X^{9A}$, $-OCHX^{9A}_2$, $-CN$, $-SO_{n9A}R^{9AA}$, $-SO_{v9A}NR^{9AA}R^{9AB}$, $-NHC(O)NR^{9AA}R^{9AB}$, $-N(O)_{m9A}$, $-NR^{9AA}R^{9AB}$, $-NHN R^{9AA}R^{9AB}$, $-C(O)R^{9AA}$, $-C(O)-OR^{9AA}$, $-C(O)NR^{9AA}R^{9AB}$, $-OR^{9AA}$, $-NR^{9AA}SO_2R^{9AB}$, $-NR^{9AA}C(O)R^{9AB}$, $-NR^{9AA}C(O)OR^{9AB}$, $-NR^{9AA}OR^{9AB}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted
- 10 heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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).

- [0327]** In embodiments, R^{9A} is independently hydrogen, $-CX^{9A}_3$, $-CHX^{9A}_2$, $-CH_2X^{9A}$, $-CN$, $-COOH$, $-CONH_2$, R^{44A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{44A} -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^{44A} -substituted or
- 20 unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{44A} -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^{44A} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{44A} -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^{9A} is independently
- 25 hydrogen, $-CX^{9A}_3$, $-CHX^{9A}_2$, $-CH_2X^{9A}$, $-CN$, $-COOH$, $-CONH_2$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
- 30 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^{9A} is independently

–F, –Cl, –Br, or –I. In embodiments, R^{9A} is independently hydrogen. In embodiments, R^{9A} is independently unsubstituted methyl. In embodiments, R^{9A} is independently unsubstituted ethyl.

[0328] In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{44A} -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^{44A} -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^{9A} and R^{9B} 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^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{44A} -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^{9A} and R^{9B} 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).

[0329] R^{44A} is independently oxo, halogen, $-CX^{44A}_3$, $-CHX^{44A}_2$, $-CH_2X^{44A}$, $-OCX^{44A}_3$, $-OCH_2X^{44A}$, $-OCHX^{44A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{45A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{45A} -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^{45A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{45A} -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^{45A} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{45A} -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^{44A} is independently oxo, halogen, $-CX^{44A}_3$, $-CHX^{44A}_2$, $-CH_2X^{44A}$, $-OCX^{44A}_3$, $-OCH_2X^{44A}$, $-OCHX^{44A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2),

unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{44A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{44A} is independently unsubstituted methyl. In embodiments, R^{44A} is independently unsubstituted ethyl.

[0330] R^{45A} is independently oxo, halogen, -CX^{45A}₃, -CHX^{45A}₂, -CH₂X^{45A}, -OCX^{45A}₃, -OCH₂X^{45A}, -OCHX^{45A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, R^{46A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{46A}-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^{46A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{46A}-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^{46A}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{46A}-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^{45A} is independently oxo, halogen, -CX^{45A}₃, -CHX^{45A}₂, -CH₂X^{45A}, -OCX^{45A}₃, -OCH₂X^{45A}, -OCHX^{45A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{45A} is independently -F, -Cl, -Br, or -I. In embodiments, R^{45A} is independently unsubstituted methyl. In embodiments, R^{45A} is independently unsubstituted ethyl.

[0331] R^{46A} is independently oxo, halogen, $-CX^{46A}_3$, $-CHX^{46A}_2$, $-CH_2X^{46A}$, $-OCX^{46A}_3$, $-OCH_2X^{46A}$, $-OCHX^{46A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2),
 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_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^{46A} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{46A} is independently unsubstituted methyl. In embodiments, R^{46A} is independently unsubstituted ethyl.

[0332] R^{9B} is hydrogen, halogen, $-CX^{9B}_3$, $-CHX^{9B}_2$, $-CH_2X^{9B}$, $-OCX^{9B}_3$, $-OCH_2X^{9B}$, $-OCHX^{9B}_2$, $-CN$, $-SO_{m9B}R^{9BA}$, $-SO_{v9B}NR^{9BA}R^{9BB}$, $-NHC(O)NR^{9BA}R^{9BB}$, $-N(O)_{m9B}$,
 15 $-NR^{9BA}R^{9BB}$, $-NHNR^{9BA}R^{9BB}$, $-C(O)R^{9BA}$, $-C(O)-OR^{9BA}$, $-C(O)NR^{9BA}R^{9BB}$, $-OR^{9BA}$, $-NR^{9BA}SO_2R^{9BB}$, $-NR^{9BA}C(O)R^{9BB}$, $-NR^{9BA}C(O)OR^{9BB}$, $-NR^{9BA}OR^{9BB}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6),
 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), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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).

[0333] In embodiments, R^{9B} is independently hydrogen, $-CX^{9B}_3$, $-CHX^{9B}_2$, $-CH_2X^{9B}$, $-CN$,
 25 $-COOH$, $-CONH_2$, R^{44B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), R^{44B} -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^{44B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), R^{44B} -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^{44B} -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or R^{44B} -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^{9B} is independently

hydrogen, $-CX^{9B}_3$, $-CHX^{9B}_2$, $-CH_2X^{9B}$, $-CN$, $-COOH$, $-CONH_2$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^{9B} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{9B} is independently hydrogen. In embodiments, R^{9B} is independently unsubstituted methyl. In embodiments, R^{9B} is independently unsubstituted ethyl.

[0334] In embodiments, R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{44B} -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^{44B} -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^{9A} and R^{9B} 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^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{44B} -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^{9A} and R^{9B} 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).

[0335] R^{44B} is independently oxo, halogen, $-CX^{44B}_3$, $-CHX^{44B}_2$, $-CH_2X^{44B}$, $-OCX^{44B}_3$, $-OCH_2X^{44B}$, $-OCHX^{44B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{45B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{45B} -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^{45B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{45B} -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^{45B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{45B} -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^{44B} is independently oxo, halogen, $-CX^{44B}_3$, $-CHX^{44B}_2$, $-CH_2X^{44B}$, $-OCX^{44B}_3$, $-OCH_2X^{44B}$, $-OCHX^{44B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^{44B} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{44B} is independently unsubstituted methyl. In embodiments, R^{44B} is independently unsubstituted ethyl.

[0336] R^{45B} is independently oxo, halogen, $-CX^{45B}_3$, $-CHX^{45B}_2$, $-CH_2X^{45B}$, $-OCX^{45B}_3$, $-OCH_2X^{45B}$, $-OCHX^{45B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{46B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{46B} -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^{46B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{46B} -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^{46B} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{46B} -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^{45B} is independently oxo, halogen, $-CX^{45B}_3$, $-CHX^{45B}_2$, $-CH_2X^{45B}$, $-OCX^{45B}_3$, $-OCH_2X^{45B}$, $-OCHX^{45B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered).

membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{45B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{45B} is independently unsubstituted methyl. In embodiments, R^{45B} is independently

5 unsubstituted ethyl.

[0337] R^{46B} is independently oxo, halogen, -CX^{46B}₃, -CHX^{46B}₂, -CH₂X^{46B}, -OCX^{46B}₃, -OCH₂X^{46B}, -OCHX^{46B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂),

10 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

15 membered, or 5 to 6 membered). X^{46B} is independently -F, -Cl, -Br, or -I. In embodiments, R^{46B} is independently unsubstituted methyl. In embodiments, R^{46B} is independently unsubstituted ethyl.

[0338] R^{9AA} is independently hydrogen, halogen, -CX^{9AA}₃, -CHX^{9AA}₂, -CH₂X^{9AA}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{9AA}₃, -OCHX^{9AA}₂, -OCH₂X^{9AA}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{9AA} is independently -Cl, -Br, -I, or -F.

25 **[0339]** In embodiments, R^{9AA} is independently hydrogen, halogen, -CX^{9AA}₃, -CHX^{9AA}₂, -CH₂X^{9AA}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{9AA}₃, -OCHX^{9AA}₂, -OCH₂X^{9AA}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted

30 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). X^{9AA} is independently -Cl, -Br, -I, or -F.

5 **[0340]** In embodiments, a substituted R^{9AA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{9AA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower
10 substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{9AA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{9AA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{9AA} is substituted, it is substituted with at least one lower substituent group.

15 **[0341]** R^{9AB} is independently hydrogen, halogen, -CX^{9AB}₃, -CHX^{9AB}₂, -CH₂X^{9AB}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{9AB}₃, -OCHX^{9AB}₂, -OCH₂X^{9AB}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
20 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{9AB} is independently -Cl, -Br, -I, or -F.

[0342] In embodiments, R^{9AB} is independently hydrogen, halogen, -CX^{9AB}₃, -CHX^{9AB}₂, -CH₂X^{9AB}, -C(O)OH, -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H,
25 -NHC=(O)H, -NHC(O)OH, -NHOH, -OCX^{9AB}₃, -OCHX^{9AB}₂, -OCH₂X^{9AB}, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6
30 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). X^{9AB} is independently -Cl, -Br, -I, or -F.

[0343] In embodiments, a substituted R^{9AB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{9AB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{9AB} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{9AB} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{9AB} is substituted, it is substituted with at least one lower substituent group.

[0344] R^{9BA} is independently hydrogen, halogen, $-CX^{9BA}_3$, $-CHX^{9BA}_2$, $-CH_2X^{9BA}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9BA}_3$, $-OCHX^{9BA}_2$, $-OCH_2X^{9BA}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{9BA} is independently -Cl, -Br, -I, or -F.

[0345] In embodiments, R^{9BA} is independently hydrogen, halogen, $-CX^{9BA}_3$, $-CHX^{9BA}_2$, $-CH_2X^{9BA}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9BA}_3$, $-OCHX^{9BA}_2$, $-OCH_2X^{9BA}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). X^{9BA} is independently -Cl, -Br, -I, or -F.

[0346] In embodiments, a substituted R^{9BA} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{9BA} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{9BA} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{9BA} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{9BA} is substituted, it is substituted with at least one lower substituent group.

[0347] R^{9BB} is independently hydrogen, halogen, $-CX^{9BB}_3$, $-CHX^{9BB}_2$, $-CH_2X^{9BB}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9BB}_3$, $-OCHX^{9BB}_2$, $-OCH_2X^{9BB}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. X^{9BB} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0348] In embodiments, R^{9BB} is independently hydrogen, halogen, $-CX^{9BB}_3$, $-CHX^{9BB}_2$, $-CH_2X^{9BB}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9BB}_3$, $-OCHX^{9BB}_2$, $-OCH_2X^{9BB}$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , 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). X^{9BB} is independently $-Cl$, $-Br$, $-I$, or $-F$.

[0349] In embodiments, a substituted R^{9BB} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted R^{9BB} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{9BB} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{9BB} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{9BB} is substituted, it is substituted with at least one lower substituent group.

[0350] $m8A$, $m8B$, $m9A$, and $m9B$ are independently 1 or 2.

[0351] $v8A$, $v8B$, $v9A$, and $v9B$ are independently 1 or 2.

[0352] $n8A$, $n8B$, $n9A$, and $n9B$ are independently an integer from 0 to 4.

[0353] X^{8A} , X^{8B} , X^{9A} , and X^{9B} are independently -Cl, -Br, -I or -F.

[0354] In embodiments, R^{10} is independently hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10}_3$, $-OCHX^{10}_2$, $-OCH_2X^{10}$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , 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). In embodiments, R^{10} is independently hydrogen or unsubstituted methyl. X^{10} is independently -Cl, -Br, -I, or -F.

[0355] In embodiments, a substituted R^{10} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10} is substituted, it is substituted with at

least one size-limited substituent group. In embodiments, when R^{10} is substituted, it is substituted with at least one lower substituent group.

[0356] In embodiments, R^{10A} is independently hydrogen, halogen, $-CX^{10A}_3$, $-CHX^{10A}_2$, $-CH_2X^{10A}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10A}_3$, $-OCHX^{10A}_2$, $-OCH_2X^{10A}$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , 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). X^{10A} is independently $-Cl$, $-Br$, $-I$, or $-F$.

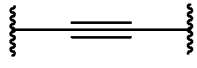
[0357] In embodiments, a substituted R^{10A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10A} is substituted, it is substituted with at least one lower substituent group.

[0358] In embodiments, R^{10B} is independently hydrogen, halogen, $-CX^{10B}_3$, $-CHX^{10B}_2$, $-CH_2X^{10B}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10B}_3$, $-OCHX^{10B}_2$, $-OCH_2X^{10B}$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6

membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-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). X^{10B} is independently -Cl, -Br, -I, or -F.

5 **[0359]** In embodiments, a substituted R^{10B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower
10 substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10B} is substituted, it is substituted with at least one lower substituent group.

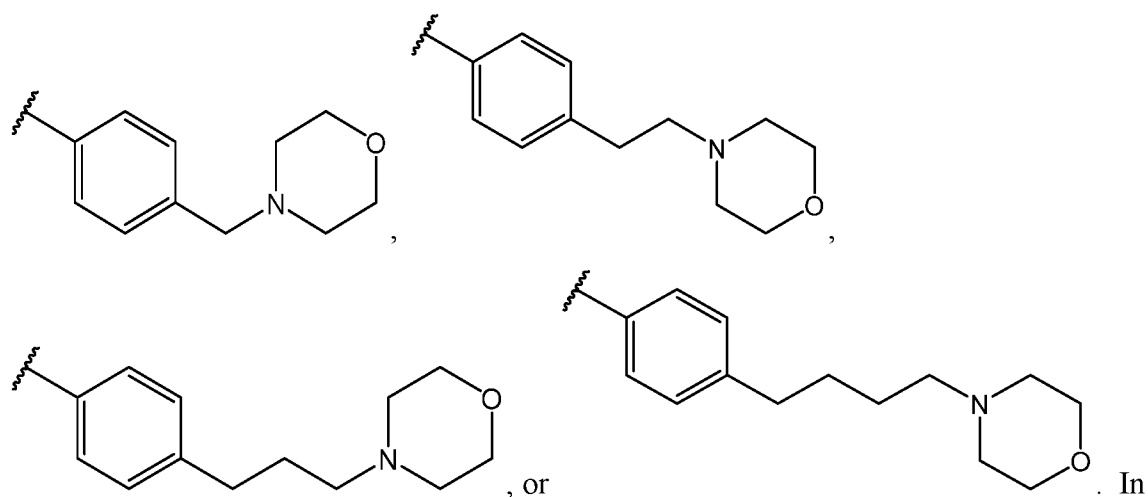
15 **[0360]** In embodiments, a substituted L¹, L², L³, L⁶, L⁸, and/or L⁹ (e.g., substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted L¹, L², L³, L⁶, L⁸, and/or L⁹ is substituted with a plurality of groups
20 selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when L¹, L², L³, L⁶, L⁸, and/or L⁹ is substituted, it is substituted with at least one substituent group. In embodiments, when L¹, L², L³, L⁶, L⁸, and/or L⁹ is substituted, it is substituted with at least one size-limited substituent
25 group. In embodiments, when L¹, L², L³, L⁶, L⁸, and/or L⁹ is substituted, it is substituted with at least one lower substituent group.

[0361] In embodiments, L⁹ is independently a bond. In embodiments, L⁹ is independently -CH₂-. In embodiments, L⁹ is independently . In embodiments, L⁹ is independently unsubstituted C₂-C₄ alkyl. In embodiments, L⁹ is independently a substituted or unsubstituted phenylene. In embodiments, L⁹ is independently a substituted phenylene. In
30 embodiments, L⁹ is independently an unsubstituted phenylene.

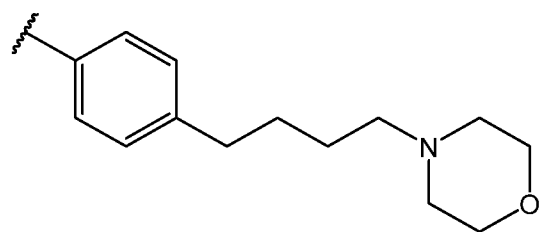
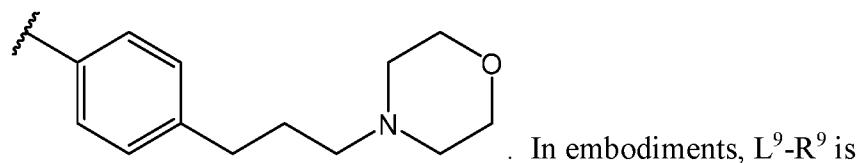
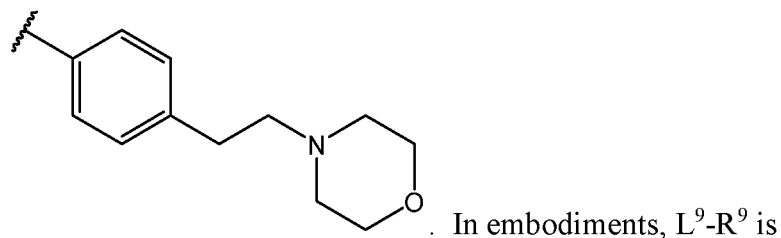
[0362] In embodiments, R^9 is an R^{44} -substituted or unsubstituted C_1 - C_4 alkyl. In
embodiments, R^9 is an R^{44} -substituted C_1 - C_4 alkyl. In embodiments, R^9 is an unsubstituted
 C_1 - C_4 alkyl.

[0363] In embodiments, R^{44} is an R^{45} -substituted or unsubstituted heterocycloalkyl. In
5 embodiments, R^{44} is an R^{45} -substituted heterocycloalkyl. In embodiments, R^{44} is an
unsubstituted heterocycloalkyl. In embodiments, R^{44} is an unsubstituted morpholinyl.

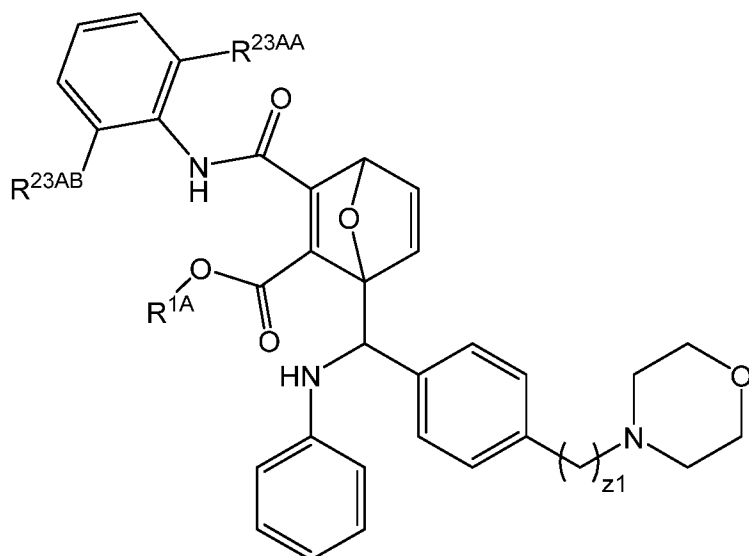
[0364] In embodiments, L^9 - R^9 is



10 embodiments, L^9 - R^9 is . In embodiments, L^9 - R^9 is



[0365] In embodiments, the compound has the formula:



(IIIe). R^{1A} is as described herein,

including in embodiments. The symbol z1 is an integer from 0 to 4.

[0366] R^{23AA} is independently hydrogen, oxo, halogen, -CX^{23AA}₃, -CHX^{23AA}₂, -CH₂X^{23AA},
 5 -OCX^{23AA}₃, -OCH₂X^{23AA}, -OCHX^{23AA}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH,
 -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂,
 -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, -OPh, R^{24AA}-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{24AA}-substituted or unsubstituted
 heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4
 10 to 5 membered), R^{24AA}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or
 C₅-C₆), R^{24AA}-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^{24AA}-substituted or
 unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{24AA}-substituted or unsubstituted
 heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6
 15 membered). In embodiments, R^{23AA} is independently hydrogen, oxo, halogen, -CX^{23AA}₃,
 -CHX^{23AA}₂, -CH₂X^{23AA}, -OCX^{23AA}₃, -OCH₂X^{23AA}, -OCHX^{23AA}₂, -CN, -OH, -NH₂, -COOH,
 -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂,
 -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6
 20 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered),
 unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12

- membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{23AA} is independently -F, -Cl, -Br, or -I. In embodiments, R^{23AA} is independently hydrogen. In embodiments, R^{23AA} is independently unsubstituted methyl. In embodiments, R^{23AA} is independently unsubstituted ethyl. In embodiments, R^{23AA} is independently unsubstituted propyl. In embodiments, R^{23AA} is independently unsubstituted butyl. In embodiments, R^{23AA} is independently unsubstituted tert-butyl. In embodiments, two adjacent R^{23AA} substituents may optionally be joined to form an R^{24AA} -substituted or unsubstituted cycloalkyl, R^{24AA} -substituted or unsubstituted heterocycloalkyl, R^{24AA} -substituted or unsubstituted aryl, or R^{24AA} -substituted or unsubstituted heteroaryl.
- 10 **[0367]** R^{23AB} is independently hydrogen, oxo, halogen, $-CX^{23AB}_3$, $-CHX^{23AB}_2$, $-CH_2X^{23AB}$, $-OCX^{23AB}_3$, $-OCH_2X^{23AB}$, $-OCHX^{23AB}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, -OPh, R^{24AB} -substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{24AB} -substituted or unsubstituted
- 15 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^{24AB} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{24AB} -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^{24AB} -substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{24AB} -substituted or unsubstituted
- 20 heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{23AB} is independently hydrogen, oxo, halogen, $-CX^{23AB}_3$, $-CHX^{23AB}_2$, $-CH_2X^{23AB}$, $-OCX^{23AB}_3$, $-OCH_2X^{23AB}$, $-OCHX^{23AB}_2$, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl
- 25 (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12
- 30 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{23AB} is independently -F, -Cl, -Br, or -I. In embodiments, R^{23AB} is independently hydrogen. In embodiments, R^{23AB} is independently unsubstituted methyl. In embodiments, R^{23AB} is independently unsubstituted ethyl. In embodiments, R^{23AB} is independently unsubstituted

propyl. In embodiments, R^{23AB} is independently unsubstituted butyl. In embodiments, R^{23AB} is independently unsubstituted tert-butyl. In embodiments, two adjacent R^{23AB} substituents may optionally be joined to form an R^{24AB} -substituted or unsubstituted cycloalkyl, R^{24AB} -substituted or unsubstituted heterocycloalkyl, R^{24AB} -substituted or unsubstituted aryl, or R^{24AB} -substituted or unsubstituted heteroaryl.

[0368] R^{24AA} is independently oxo, halogen, $-CX^{24AA}_3$, $-CHX^{24AA}_2$, $-CH_2X^{24AA}$, $-OCX^{24AA}_3$, $-OCH_2X^{24AA}$, $-OCHX^{24AA}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, R^{25AA} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), R^{25AA} -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^{25AA} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), R^{25AA} -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^{25AA} -substituted or unsubstituted aryl (e.g., C_6 - C_{12} , C_6 - C_{10} , or phenyl), or R^{25AA} -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^{24AA} is independently oxo, halogen, $-CX^{24AA}_3$, $-CHX^{24AA}_2$, $-CH_2X^{24AA}$, $-OCX^{24AA}_3$, $-OCH_2X^{24AA}$, $-OCHX^{24AA}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C_6 - C_{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^{24AA} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{24AA} is independently unsubstituted methyl. In embodiments, R^{24AA} is independently unsubstituted ethyl.

[0369] R^{25AA} is independently oxo, halogen, $-CX^{25AA}_3$, $-CHX^{25AA}_2$, $-CH_2X^{25AA}$, $-OCX^{25AA}_3$, $-OCH_2X^{25AA}$, $-OCHX^{25AA}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2),

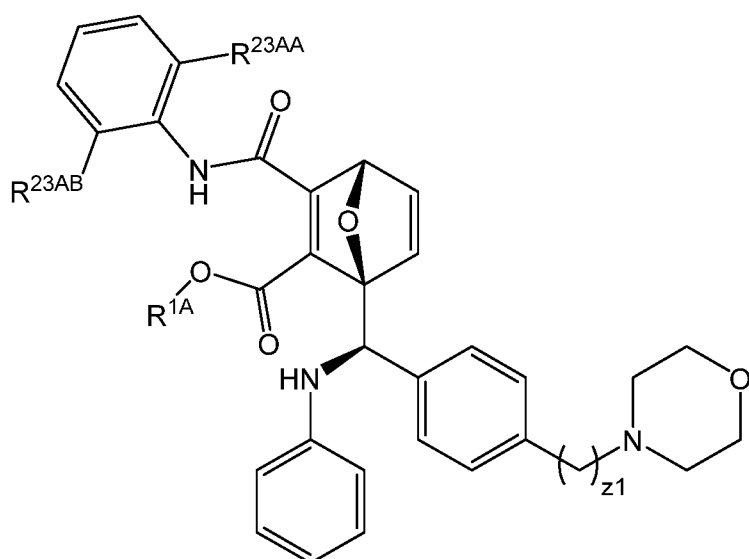
unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{25AA} is independently -F, -Cl, -Br, or -I. In embodiments, R^{25AA} is independently unsubstituted methyl. In embodiments, R^{25AA} is independently unsubstituted ethyl.

[0370] R^{24AB} is independently oxo, halogen, -CX^{24AB}₃, -CHX^{24AB}₂, -CH₂X^{24AB}, -OCX^{24AB}₃, -OCH₂X^{24AB}, -OCHX^{24AB}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, R^{25AB}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{25AB}-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^{25AB}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{25AB}-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^{25AB}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{25AB}-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^{24AB} is independently oxo, halogen, -CX^{24AB}₃, -CHX^{24AB}₂, -CH₂X^{24AB}, -OCX^{24AB}₃, -OCH₂X^{24AB}, -OCHX^{24AB}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{24AB} is independently -F, -Cl, -Br, or -I. In embodiments, R^{24AB} is independently unsubstituted methyl. In embodiments, R^{24AB} is independently unsubstituted ethyl.

[0371] R^{25AB} is independently oxo, halogen, $-CX^{25AB}_3$, $-CHX^{25AB}_2$, $-CH_2X^{25AB}$, $-OCX^{25AB}_3$, $-OCH_2X^{25AB}$, $-OCHX^{25AB}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2),
 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_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
 10 membered, or 5 to 6 membered). X^{25AB} is independently $-F$, $-Cl$, $-Br$, or $-I$. In embodiments, R^{25AB} is independently unsubstituted methyl. In embodiments, R^{25AB} is independently unsubstituted ethyl.

[0372] 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.

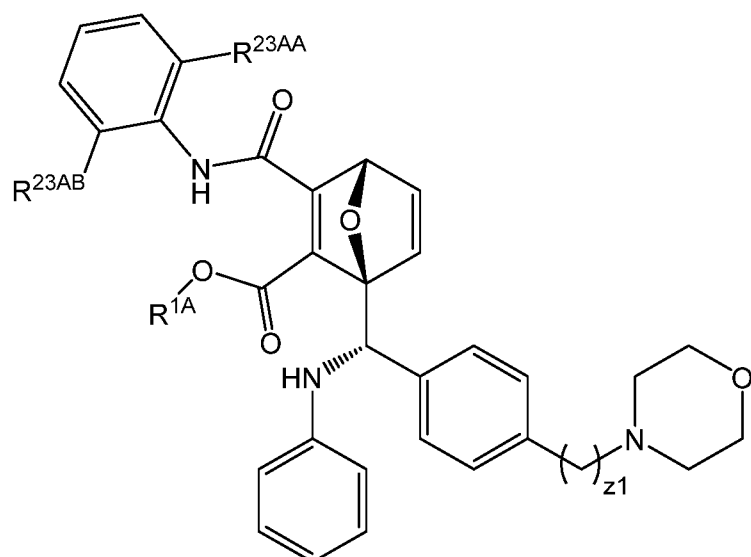
15 [0373] In embodiments, the compound has the formula:



(III f). R^{1A} , R^{23AA} , R^{23AB} , and $z1$

are as described herein, including in embodiments.

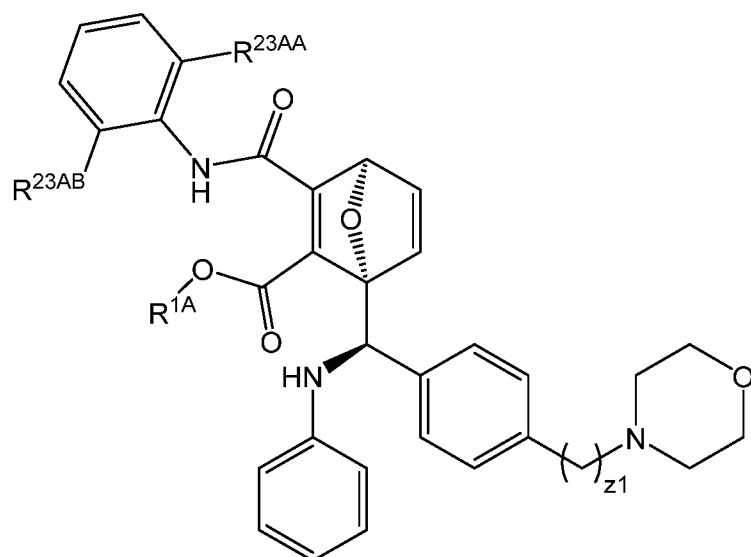
[0374] In embodiments, the compound has the formula:



(IIIg). R^{1A} , R^{23AA} , R^{23AB} , and $z1$

are as described herein, including in embodiments.

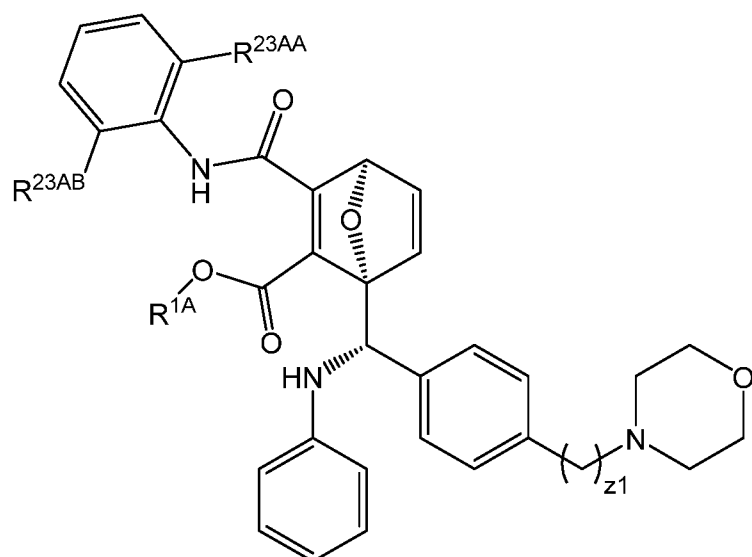
[0375] In embodiments, the compound has the formula:



(IIIh). R^{1A} , R^{23AA} , R^{23AB} , and $z1$

5 are as described herein, including in embodiments.

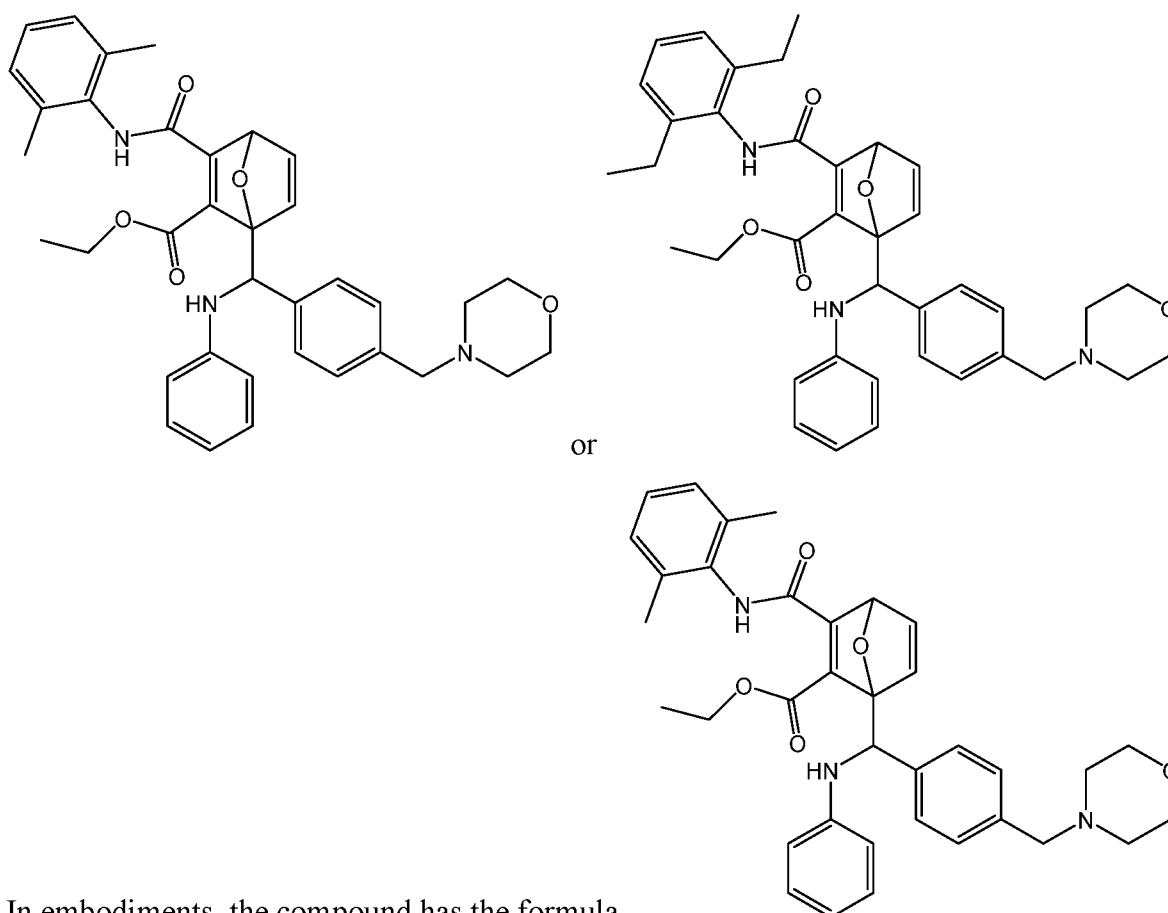
[0376] In embodiments, the compound has the formula:



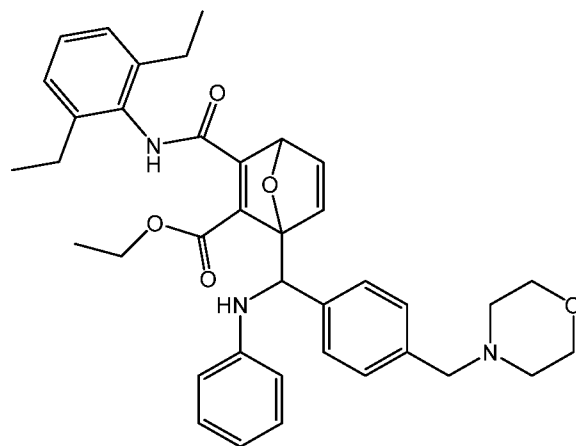
(IIIi). R^{1A} , R^{23AA} , R^{23AB} , and $z1$

are as described herein, including in embodiments.

[0377] In embodiments, the compound has the formula:

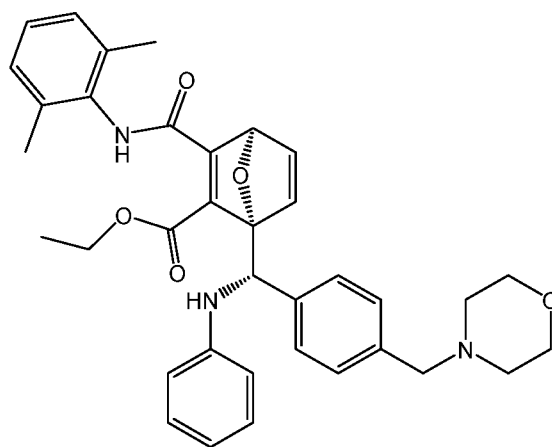
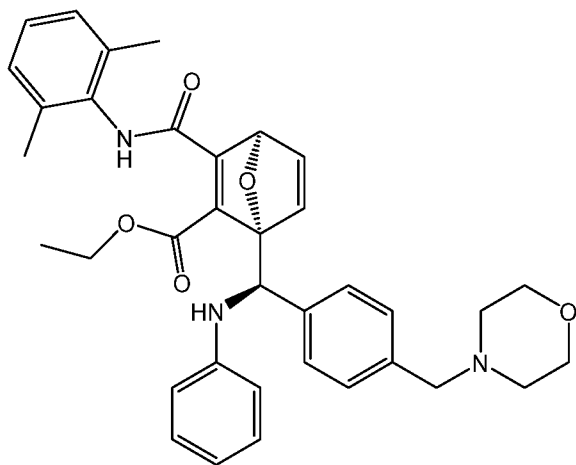
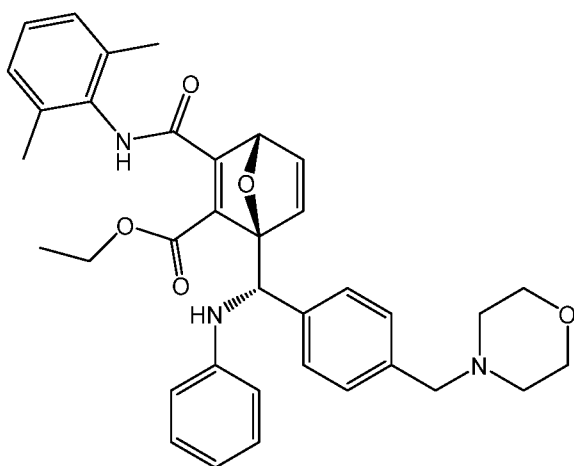
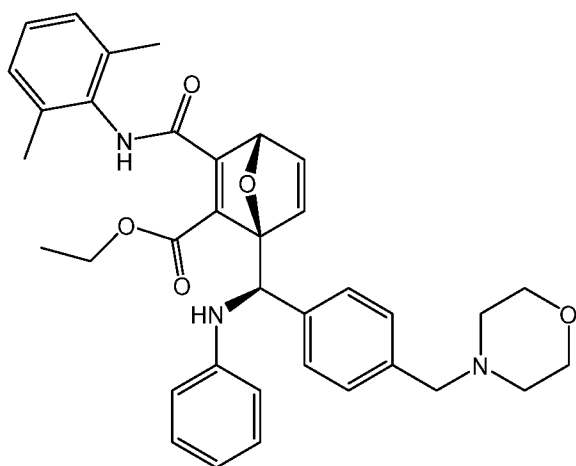


5 In embodiments, the compound has the formula



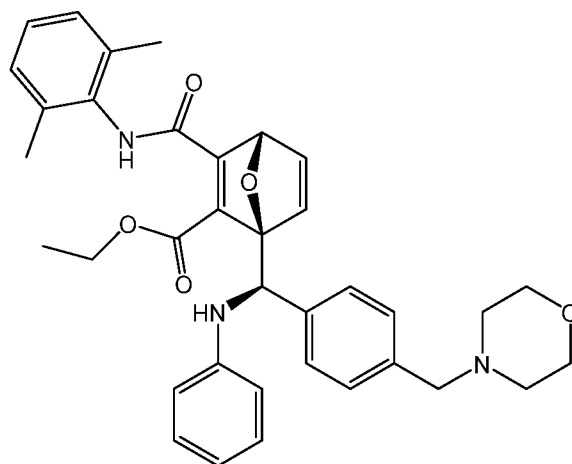
In embodiments, the compound has the formula

[0378] In embodiments, the compound has the formula:



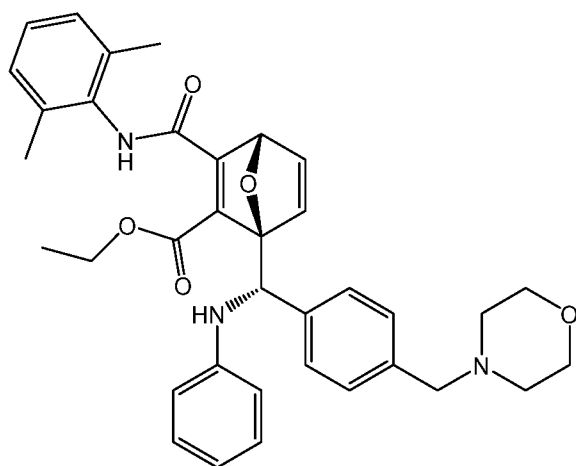
5

, or

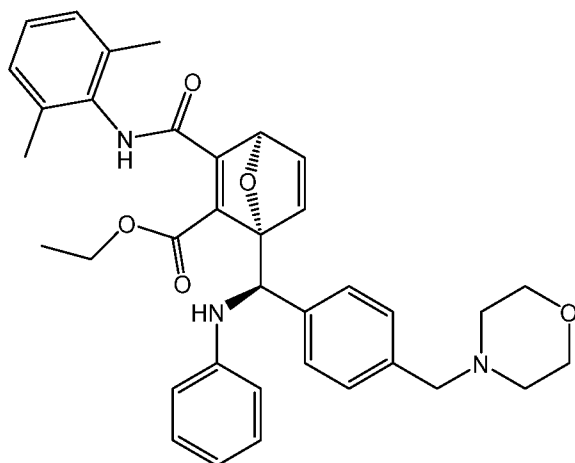


In embodiments, the compound has the formula

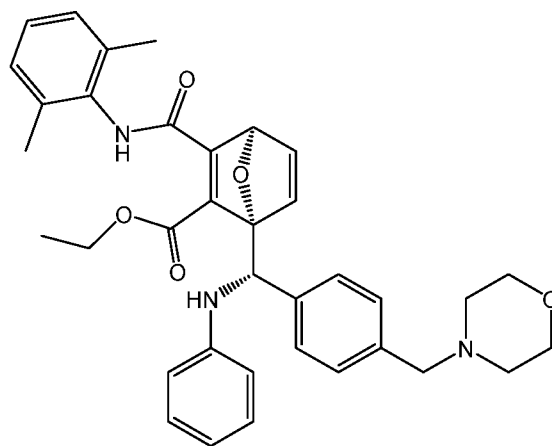
. In embodiments, the compound has the formula



. In embodiments, the compound has the

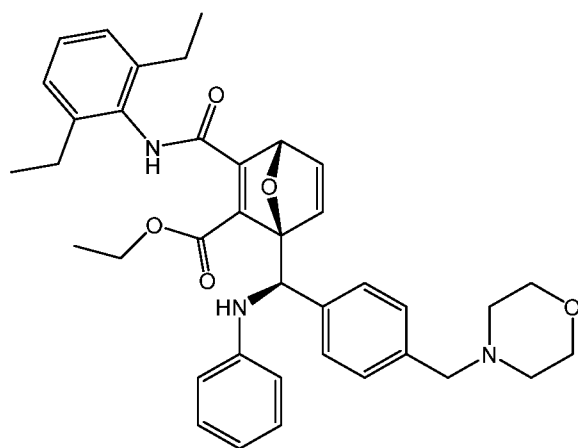


formula

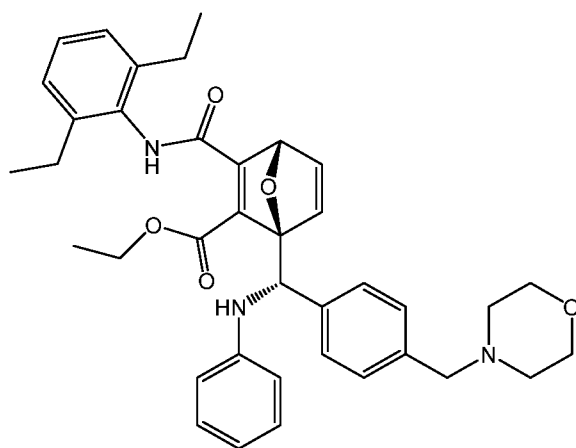


In embodiments, the compound has the formula

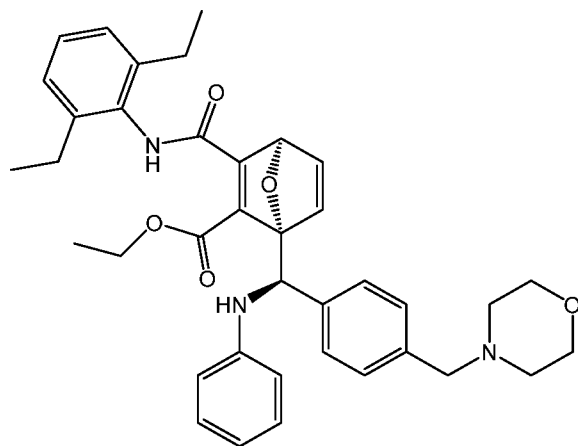
[0379] In embodiments, the compound has the formula:



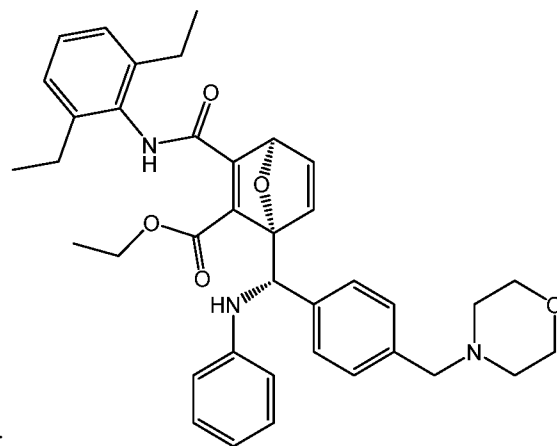
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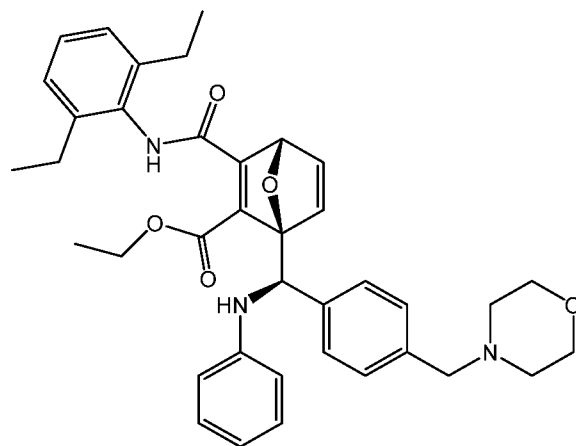


,



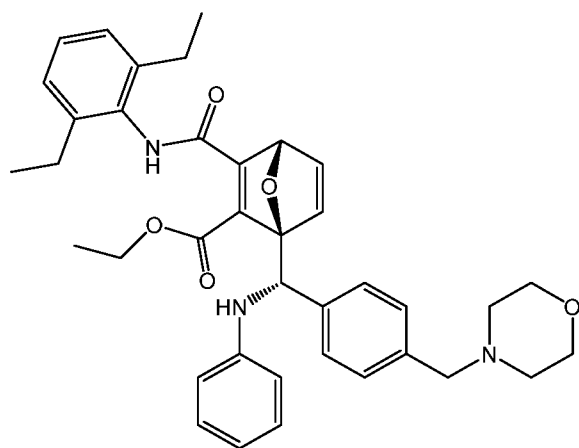
, or



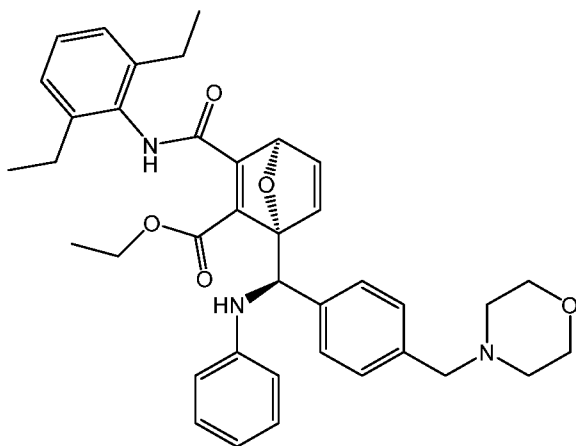


In embodiments, the compound has the formula

. In embodiments, the compound has the formula

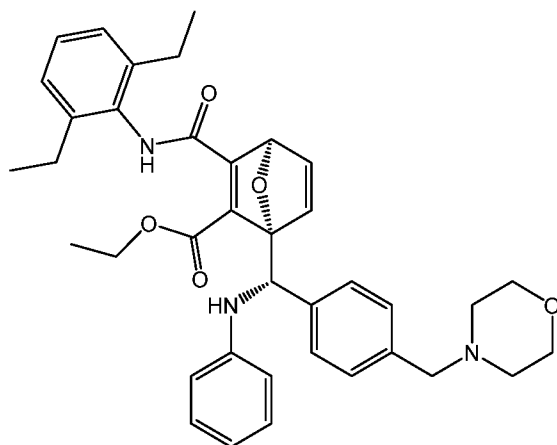


. In embodiments, the compound has the



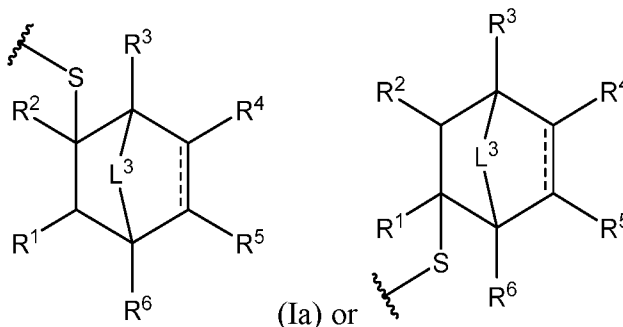
formula

. In embodiments, the compound has



the formula

[0380] In embodiments, the compound is covalently attached to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2. In embodiments, at least one of R^1 or R^2 includes an electron-withdrawing moiety. In embodiments, at least one of R^1 or R^2 are sufficiently electron withdrawing to allow the compound to covalently bind to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2, wherein the E1 cysteine amino acid is bound to ring carbon C_2 attached to R^2 or ring carbon C_1 attached to R^1 . In embodiments, the compound covalently binds to an E1 cysteine amino acid corresponding to Cys30 of Uba2



(Ia) or

subunit 2; and forms a complex of formula:

(Ib). R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and L^3 are as described herein, including in embodiments. In embodiments, R^4 is hydrogen. In embodiments, R^5 is hydrogen. In embodiments, R^8 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,

substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R⁸ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R⁸ is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R⁸ is substituted or unsubstituted phenyl. In

5 embodiments, R⁴¹ is independently halogen or –OPh. In embodiments, z₄₁ is 2. In embodiments, z₄₁ is 1. In embodiments, z₄₁ is 0. In embodiments, L⁹ is a bond or substituted or unsubstituted alkylene. In embodiments, L⁹ is a bond or unsubstituted C₁-C₃ alkylene. In embodiments, L⁹ is an unsubstituted methylene. In embodiments, L⁹ is a bond. In embodiments, R⁹ is substituted or unsubstituted alkyl, substituted or unsubstituted

10 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R⁹ is unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In embodiments, R⁹ is unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl,

15 unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R⁹ is unsubstituted propyl, unsubstituted butyl, unsubstituted pentyl, unsubstituted propenyl, unsubstituted butenyl, unsubstituted pentenyl, unsubstituted propynyl, unsubstituted butynyl, unsubstituted pentynyl, unsubstituted cyclobutyl, unsubstituted cyclopentyl, unsubstituted

20 tetrahydropyranyl, unsubstituted morpholinyl, or unsubstituted phenyl. In embodiments, R⁹ is unsubstituted phenyl. In embodiments, R^{2A} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^{2A} is hydrogen, substituted or unsubstituted C₁-

25 C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted C₃-C₆ aryl, or substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{2A} is hydrogen. In embodiments, R^{2B} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

30 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In embodiments, R^{2B} is hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or

unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted C₃-C₆ aryl, or substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{2B} is hydrogen. In embodiments, R^{2A} and R^{2B} are joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. In embodiments, R^{2A} and R^{2B} are joined to form a substituted or unsubstituted heterocycloalkyl. In embodiments, R^{2A} and R^{2B} are joined to form a substituted or unsubstituted 4 to 6 membered heterocycloalkyl. In embodiments, R^{1A} is hydrogen, -CX^{1A}₃, -CHX^{1A}₂, -CH₂X^{1A}, -OCX^{1A}₃, -OCH₂X^{1A}, -OCHX^{1A}₂, -C(O)R^{1AA}, -C(O)OR^{1AA}, -C(O)NR^{1AA}R^{1AB}, -OR^{1AA}, 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. In embodiments, R^{1A} is hydrogen, -CX^{1A}₃, -CHX^{1A}₂, -CH₂X^{1A}, unsubstituted C₁-C₃ alkyl. In embodiments, R^{1A} is unsubstituted C₁-C₃ alkyl. In embodiments, R^{1A} is hydrogen. In embodiments, R³ is hydrogen, -CX³₃, -CHX³₂, -CH₂X³, substituted or unsubstituted alkyl. In embodiments, R³ is -CH₂OH or -CH₃. In embodiments, R³ is hydrogen. In embodiments, R³ is substituted or unsubstituted phenyl. In embodiments, R³ is unsubstituted phenyl.

[0381] In some embodiments, a compound as described herein may include multiple instances of R¹ 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 R¹ 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}, respectively, wherein the definition of R¹ is assumed by R^{1.1}, R^{1.2}, R^{1.3}, R^{1.4}, R^{1.5}. The variables used within a definition of R¹ and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity.

[0382] In some embodiments, a compound as described herein may include multiple instances of R² 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 R² is different, they may be referred to, for example, as R^{2.1}, R^{2.2}, R^{2.3}, R^{2.4}, R^{2.5}, respectively, wherein the definition of R² is assumed by R^{2.1}, R^{2.2}, R^{2.3}, R^{2.4}, R^{2.5}. The variables used within a definition of R² 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).

[0383] In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a

5 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
10 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).

[0384] In embodiments, the compound is a compound described herein (e.g., in an aspect, embodiment, example, claim, table, scheme, drawing, or figure). In embodiments, a moiety
15 of a compound is a moiety described in a compound of Table I in the Example section below. In embodiments, the moieties of a compound are moieties described in one or a plurality of compounds of Table I in the Example section below.

III. Pharmaceutical compositions

[0385] In an aspect is provided a pharmaceutical composition including a compound
20 described herein, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0386] In embodiments of the pharmaceutical compositions, the compound, or pharmaceutically acceptable salt thereof, is included in a therapeutically effective amount.

[0387] In embodiments of the pharmaceutical compositions, the pharmaceutical
25 composition includes a second agent (e.g., 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
30 embodiments, the second agent is an anti-cancer agent. In embodiments, the second agent is a chemotherapeutic. In embodiments, the administering does not include administration of any active agent other than the recited active agent (e.g., a compound described herein).

IV. Methods of Treatment

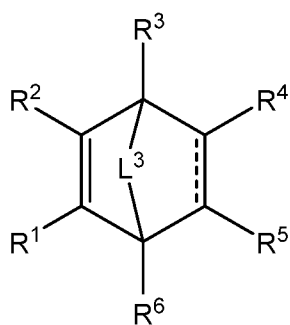
[0388] In an aspect is provided a method of treating cancer, the method including administering to a subject in need thereof an effective amount of a compound described herein. In embodiments, the compound is included in a therapeutically effective amount. In
5 embodiments, the compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

[0389] In embodiments, the half-life of an E1 enzyme is about 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is greater than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26,
10 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is less than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours.

[0390] In an aspect is provided a method of treating a proliferative disease, the method including administering to a subject in need thereof an effective amount of a compound described herein. In embodiments, the compound is included in a therapeutically effective
15 amount. In embodiments, the compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

[0391] In embodiments, the half-life of an E1 enzyme is about 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is greater than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26,
20 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is less than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours.

[0392] In an aspect is provided a method of treating cancer in a subject in need thereof, said method including administering to the subject a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of formula:



[0393] (I). R¹, R², R³, R⁴, R⁵, R⁶, and L³ are as described herein, including in embodiments.

[0394] $\equiv$ is a single bond or double bond.

[0395] L^3 is $-O-$, $-S-$, $-N-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-N(R^7)-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0396] R^1 is hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$,
 5 $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-NHN R^{1A}R^{1B}$,
 $-C(O)R^{1A}$, $-C(O)-OR^{1A}$, $-C(O)NR^{1A}R^{1B}$, $-C(O)NHN R^{1A}R^{1B}$, $-OR^{1A}$, $-NR^{1A}SO_2R^{1B}$,
 $-NR^{1A}C(O)R^{1B}$, $-NR^{1A}C(O)OR^{1B}$, $-NR^{1A}OR^{1B}$, $-N_3$, $-L^1-E^1$, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 10 unsubstituted heteroaryl.

[0397] R^2 is hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$,
 $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$,
 $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$,
 $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, $-L^2-E^2$, substituted or unsubstituted alkyl,
 15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 unsubstituted heteroaryl.

[0398] R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$,
 $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHN R^{3A}R^{3B}$,
 20 $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$,
 $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or
 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0399] R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$,
 25 $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHN R^{4A}R^{4B}$,
 $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHN R^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$,
 $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 30 unsubstituted heteroaryl.

[0400] R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHN R^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHN R^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl,

5 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0401] R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-NHN R^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHN R^{6A}R^{6B}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, substituted or unsubstituted alkyl,

10 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0402] R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$, $-NHN R^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHN R^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl,

15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0403] E^1 and E^2 are independently an electron-withdrawing moiety.

[0404] Each R^{1A} , R^{1B} , R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{6A} , R^{6B} , R^{7A} , and R^{7B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$,

25 $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH SO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

10 [0405] m₁, m₂, m₃, m₄, m₅, m₆, and m₇ are independently 1 or 2.

[0406] v₁, v₂, v₃, v₄, v₅, v₆, and v₇ are independently 1 or 2.

[0407] n₁, n₂, n₃, n₄, n₅, n₆, and n₇, are independently an integer from 0 to 4.

[0408] X, X¹, X², X³, X⁴, X⁵, X⁶, and X⁷ are independently -Cl, -Br, -I or -F.

15 [0409] L¹ and L² are independently a bond, -O-, -S-, -S(O)-, -S(O)₂-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

20 [0410] R¹ and R² may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0411] R⁴ and R⁵ may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

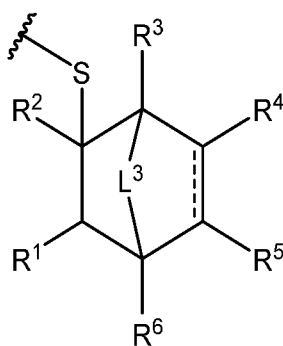
25 [0412] Wherein the compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

[0413] In embodiments, the half-life of an E1 enzyme is about 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is greater than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26,

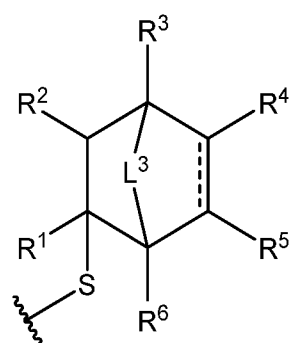
27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is less than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours.

[0414] In embodiments, the cancer is a human cancer, carcinoma, sarcoma, adenocarcinoma, lymphoma, or leukemia. In embodiments, the cancer is a solid cancer, lymphoid cancer, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, or liver cancer. In embodiments, the cancer is hepatocarcinoma or lymphoma. In embodiments, the lymphoma is B-acute lymphoblastic lymphoma, non-Hodgkin's lymphoma (e.g., Burkitt's, Small Cell, and Large Cell lymphomas), Hodgkin's lymphoma, leukemia (e.g., AML, ALL, and CML), or multiple myeloma.

[0415] In embodiments, the compound is covalently attached to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2. In embodiments, at least one of R^1 or R^2 includes an electron-withdrawing moiety. In embodiments, at least one of R^1 or R^2 are sufficiently electron withdrawing to allow the compound to covalently bind to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2, wherein the E1 cysteine amino acid is bound to ring carbon C_2 attached to R^2 or ring carbon C_1 attached to R^1 . In embodiments, the compound covalently binds to an E1 cysteine amino acid corresponding to Cys30 of Uba2



(Ia) or

(Ib). R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and L^3 are as described herein, including

in embodiments.

[0416] In embodiments, the method includes allowing the compound to covalently bind an E1 enzyme. In embodiments, the method includes allowing the compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2. In embodiments, the method includes allowing the E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to ring carbon C₁ attached to R^{1A}. In embodiments, the method includes allowing the E1 cysteine amino acid to bind (e.g., covalently bind) to carbon C₂ attached to R^{2A} and R^{2B} or to carbon C₁ attached to R^{1A}.

[0417] It will be understood that the carbon C₁ is adjacent (e.g., bonded) to an R¹ or R^{1A} group as appropriate for the specified embodiment. It will be understood that the carbon C₂ is adjacent (e.g., bonded) to an R² or R^{2A} or R^{2B} group as appropriate for the specified embodiment.

V. Methods of Inhibition

[0418] In an aspect is provided a method of inhibiting cell proliferation, the method including contacting the cell with a compound described herein. In embodiments, the method includes contacting the cell with an effective amount of the compound. In embodiments, the compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

[0419] In embodiments, the half-life of an E1 enzyme is about 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is greater than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours. In embodiments, the half-life of an E1 enzyme is less than 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 34, or 36 hours.

[0420] In an aspect is provided a method of inhibiting an E1 enzyme, the method including contacting an E1 enzyme with a compound described herein, thereby inhibiting the E1 enzyme. In embodiments, the method includes allowing the compound to covalently bind the E1 enzyme. In embodiments, the method includes allowing the compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2. In embodiments, the method includes allowing the E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to ring carbon C₁ attached to R^{1A}. In embodiments, the method includes allowing the E1 cysteine amino acid to bind (e.g., covalently bind) to carbon C₂ attached to R^{2A} and R^{2B} or to carbon C₁ attached to R^{1A}.

VI. Methods of Screening

[0421] Also provided are methods of identifying ligands (e.g., therapeutic target proteins, druggable hotspots) capable of covalently binding a compound provided herein including embodiments thereof. The methods include combining a ligand and a compound provided
5 herein in a reaction vessel, allowing the ligand and the compound to form a covalent ligand-compound complex, and detecting the covalent ligand-compound complex thereby identifying the ligand as target protein or druggable hotspot. A “reaction vessel” as provided herein refers to a vial, tube, flask, bottle, syringe or other container means, into which the ligand and the compound are combined to allow the formation of a covalent ligand-
10 compound complex. Optionally, one or more of the ligands or compounds are labeled. Optionally, the label is a fluorescent label. Optionally, the compound includes a fluorescent label.

[0422] Provided herein are methods of detecting a ligand capable of covalently binding a compound provided herein including embodiments thereof. The method includes contacting
15 a ligand with a compound provided herein and allowing the compound to covalently bind to the ligand, thereby forming a covalent compound-ligand complex; and detecting the covalent compound-ligand complex by nuclear magnetic resonance (NMR). The ligand may be a protein, for example, any cellular or extracellular protein including without limitation, an enzyme, a structural protein, a cytoplasmic protein and a nuclear protein.

[0423] In one aspect, a method of detecting covalent binding of a ligand to a compound provided herein is provided. The method includes: (i) contacting a ligand with a compound provided herein; (ii) allowing the compound to covalently bind to the ligand, thereby forming a covalent ligand-compound complex; and (iii) detecting the covalent ligand-compound complex using nuclear magnetic resonance, thereby detecting covalent binding of the ligand
20 to the compound. In embodiments, the contacting is performed in a reaction vessel. In embodiments, the ligand is a cysteine bearing polypeptide. In embodiments, the detecting includes determining a chemical shift for an amino acid in the ligand. In embodiments, the detecting includes producing an NMR spectra of the covalent ligand-compound complex and identifying a change in the NMR spectra relative to the absence of the compound. In
25 embodiments, a cysteine residue of the ligand is covalently bound to the compound. A sulfhydryl functional group of a cysteine amino acid of the ligand may form a covalent bond with a compound provided herein including embodiments thereof. Thus, in embodiments,
30

the covalent bond between the ligand and the compound may be formed by a cysteine of the ligand and an electrophilic moiety (e.g., E¹ or E²) of the compound. In embodiments, the covalent bond between the ligand and the compound may be formed by a cysteine of the ligand and an atom adjacent to an electrophilic moiety (e.g., E¹ or E²) of the compound. In
5 embodiments, the covalent bond between the ligand and the compound may be formed by a cysteine of the ligand and an atom adjacent to L¹ or L² of the compound. In embodiments, the ligand is a Uba2 enzyme and the amino acid corresponds to Cys30 of Uba2 subunit 2.

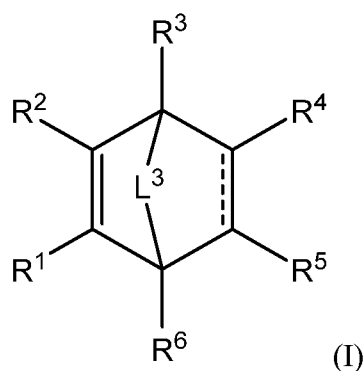
[0424] Provided herein are methods of detecting a ligand capable of covalently binding a compound provided herein including embodiments thereof. The method includes contacting
10 a ligand with a compound provided herein and allowing the compound to covalently bind to the ligand, thereby forming a covalent compound-ligand complex; and detecting the covalent compound-ligand complex by quantitative mass spectrometry. The ligand may be a protein, for example, any cellular or extracellular protein including without limitation, an enzyme, a structural protein, a cytoplasmic protein and a nuclear protein.

[0425] In another aspect, a method of detecting covalent binding of a ligand to a compound provided herein is provided. The method includes: (i) contacting a ligand with a compound provided herein; (ii) allowing the compound to covalently bind to the ligand, thereby forming a covalent ligand-compound complex; and (iii) detecting the covalent ligand-compound
15 complex using quantitative mass spectrometry, thereby detecting covalent binding of the ligand to the compound. In embodiments, the contacting is performed in a reaction vessel. In embodiments, the ligand is a cysteine bearing polypeptide. In embodiments, the detecting includes determining a molecular weight for the covalent ligand-compound complex. In
20 embodiments, the detecting includes producing a quantitative mass spectrometry spectrum of the covalent ligand-compound complex and identifying a change in the quantitative mass spectrometry spectrum relative to the absence of the compound. In embodiments, a cysteine
25 residue of the ligand is covalently bound to the compound. A sulfhydryl functional group of a cysteine amino acid of the ligand may form a covalent bond with a compound provided herein including embodiments thereof. Thus, in embodiments, the covalent bond between the ligand and the compound may be formed by a cysteine of the ligand and an electrophilic
30 moiety (e.g., E¹ or E²) of the compound. In embodiments, the covalent bond between the ligand and the compound may be formed by a cysteine of the ligand and an atom adjacent to an electrophilic moiety (e.g., E¹ or E²) of the compound. In embodiments, the covalent bond

between the ligand and the compound may be formed by a cysteine of the ligand and an atom adjacent to L^1 or L^2 of the compound. In embodiments, the ligand is a Uba2 enzyme and the amino acid corresponds to Cys30 of Uba2 subunit 2.

VII. Embodiments

- 5 [0426] Embodiment P1. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of formula:



wherein:

- 10 --- is a single bond or double bond;

L^3 is $-\text{O}-$, $-\text{S}-$, $-\text{N}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{C}(\text{O})-$, $-\text{N}(\text{R}^7)-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

- R^1 is hydrogen, halogen, $-\text{CX}^1_3$, $-\text{CHX}^1_2$, $-\text{CH}_2\text{X}^1$, $-\text{OCX}^1_3$, $-\text{OCH}_2\text{X}^1$, $-\text{OCHX}^1_2$, $-\text{CN}$, $-\text{SO}_{\text{nl}}\text{R}^{1\text{A}}$, $-\text{SO}_{\text{v1}}\text{NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{N}(\text{O})_{\text{ml}}$, $-\text{NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{NHN}\text{R}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{C}(\text{O})\text{R}^{1\text{A}}$,
 15 $-\text{C}(\text{O})-\text{OR}^{1\text{A}}$, $-\text{C}(\text{O})\text{NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{C}(\text{O})\text{NHN}\text{R}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{OR}^{1\text{A}}$, $-\text{NR}^{1\text{A}}\text{SO}_2\text{R}^{1\text{B}}$, $-\text{NR}^{1\text{A}}\text{C}(\text{O})\text{R}^{1\text{B}}$, $-\text{NR}^{1\text{A}}\text{C}(\text{O})\text{OR}^{1\text{B}}$, $-\text{NR}^{1\text{A}}\text{OR}^{1\text{B}}$, $-\text{N}_3$, $-\text{L}^1-\text{E}^1$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- R^2 is hydrogen, halogen, $-\text{CX}^2_3$, $-\text{CHX}^2_2$, $-\text{CH}_2\text{X}^2$, $-\text{OCX}^2_3$, $-\text{OCH}_2\text{X}^2$, $-\text{OCHX}^2_2$, $-\text{CN}$, $-\text{SO}_{\text{n2}}\text{R}^{2\text{A}}$, $-\text{SO}_{\text{v2}}\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{NHC}(\text{O})\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{N}(\text{O})_{\text{m2}}$, $-\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{NHN}\text{R}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{C}(\text{O})\text{R}^{2\text{A}}$,
 20 $-\text{C}(\text{O})-\text{OR}^{2\text{A}}$, $-\text{C}(\text{O})\text{NR}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{C}(\text{O})\text{NHN}\text{R}^{2\text{A}}\text{R}^{2\text{B}}$, $-\text{OR}^{2\text{A}}$, $-\text{NR}^{2\text{A}}\text{SO}_2\text{R}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{C}(\text{O})\text{R}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{C}(\text{O})\text{OR}^{2\text{B}}$, $-\text{NR}^{2\text{A}}\text{OR}^{2\text{B}}$, $-\text{N}_3$, $-\text{L}^2-\text{E}^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, $-CX^3$, $-CHX^3$, $-CH_2X^3$, $-OCX^3$, $-OCH_2X^3$, $-OCHX^3$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3AR^{3B}}$, $-NHC(O)NR^{3AR^{3B}}$, $-N(O)_{m3}$, $-NR^{3AR^{3B}}$, $-NHN R^{3AR^{3B}}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3AR^{3B}}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 is hydrogen, halogen, $-CX^4$, $-CHX^4$, $-CH_2X^4$, $-OCX^4$, $-OCH_2X^4$, $-OCHX^4$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4AR^{4B}}$, $-NHC(O)NR^{4AR^{4B}}$, $-N(O)_{m4}$, $-NR^{4AR^{4B}}$, $-NHN R^{4AR^{4B}}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4AR^{4B}}$, $-C(O)NHN R^{4AR^{4B}}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^5 is hydrogen, halogen, $-CX^5$, $-CHX^5$, $-CH_2X^5$, $-OCX^5$, $-OCH_2X^5$, $-OCHX^5$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5AR^{5B}}$, $-NHC(O)NR^{5AR^{5B}}$, $-N(O)_{m5}$, $-NR^{5AR^{5B}}$, $-NHN R^{5AR^{5B}}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5AR^{5B}}$, $-C(O)NHN R^{5AR^{5B}}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^6 is hydrogen, halogen, $-CX^6$, $-CHX^6$, $-CH_2X^6$, $-OCX^6$, $-OCH_2X^6$, $-OCHX^6$, $-CN$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6AR^{6B}}$, $-NHC(O)NR^{6AR^{6B}}$, $-N(O)_{m6}$, $-NR^{6AR^{6B}}$, $-NHN R^{6AR^{6B}}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6AR^{6B}}$, $-C(O)NHN R^{6AR^{6B}}$, $-OR^{6A}$, $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^7 is hydrogen, halogen, $-CX^7$, $-CHX^7$, $-CH_2X^7$, $-OCX^7$, $-OCH_2X^7$, $-OCHX^7$, $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7AR^{7B}}$, $-NHC(O)NR^{7AR^{7B}}$, $-N(O)_{m7}$, $-NR^{7AR^{7B}}$, $-NHN R^{7AR^{7B}}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7AR^{7B}}$, $-C(O)NHN R^{7AR^{7B}}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

E^1 and E^2 are independently an electron-withdrawing moiety;

Each R^{1A} , R^{1B} , R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{6A} , R^{6B} , R^{7A} , and R^{7B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , and m_7 are independently 1 or 2;

v_1 , v_2 , v_3 , v_4 , v_5 , v_6 , and v_7 are independently 1 or 2;

n_1 , n_2 , n_3 , n_4 , n_5 , n_6 , and n_7 , are independently an integer from 0 to 4;

X , X^1 , X^2 , X^3 , X^4 , X^5 , X^6 , and X^7 are independently $-Cl$, $-Br$, $-I$ or $-F$;

L^1 and L^2 are independently a bond, $-O-$, $-S-$, $-NH-$, $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-OC(O)-$, $-NHC(O)-$, $-NH-C(O)-NH-$, $-OC(O)NH-$, $-NHC(O)O-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 and R^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;

R^4 and R^5 may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

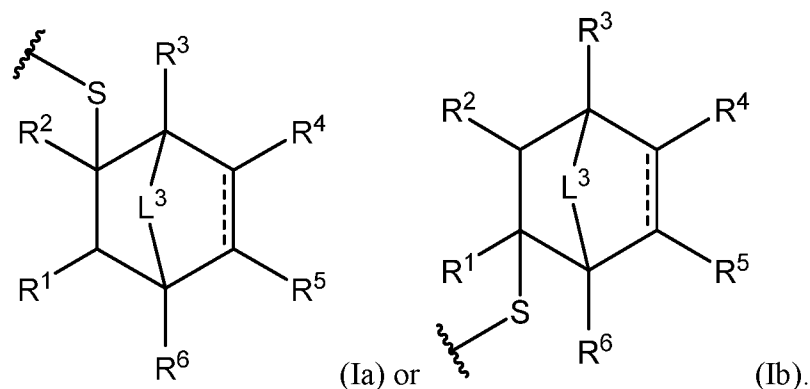
wherein said compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

[0427] Embodiment P2. The method of embodiment P1, wherein said compound is covalently attached to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

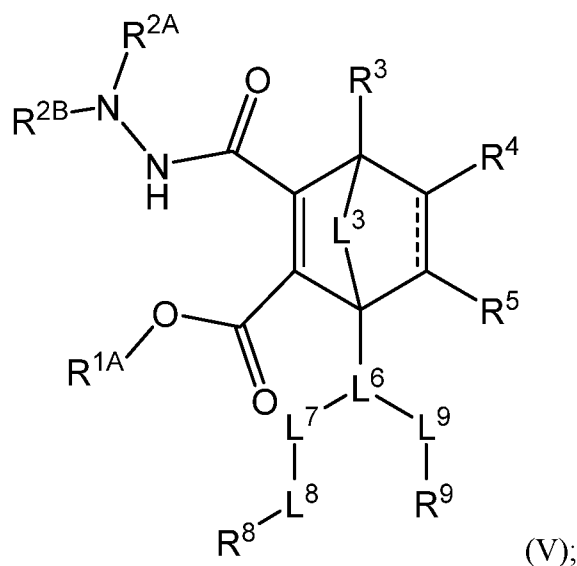
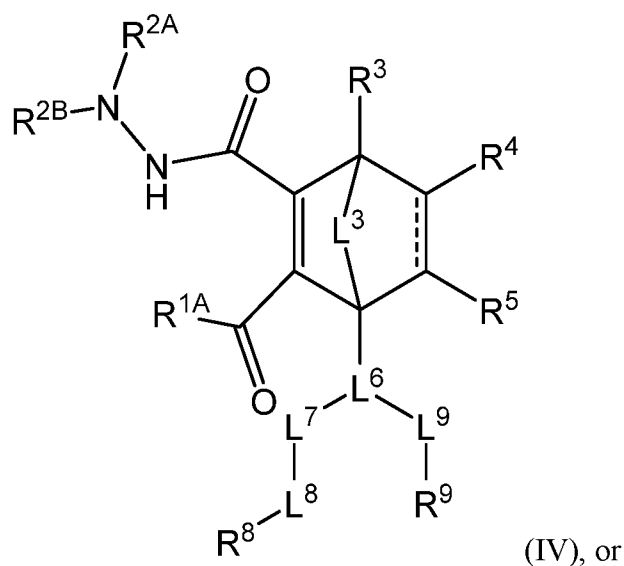
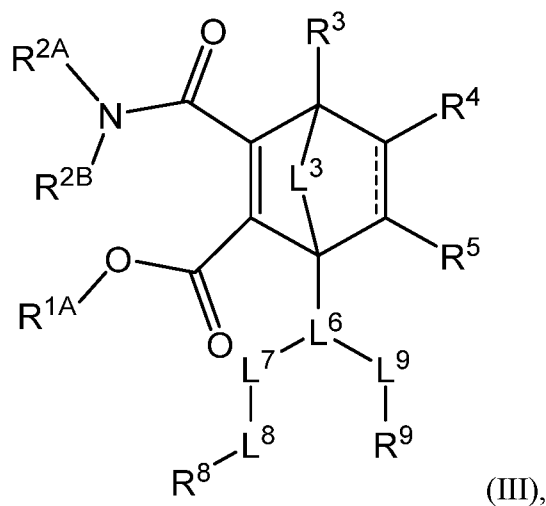
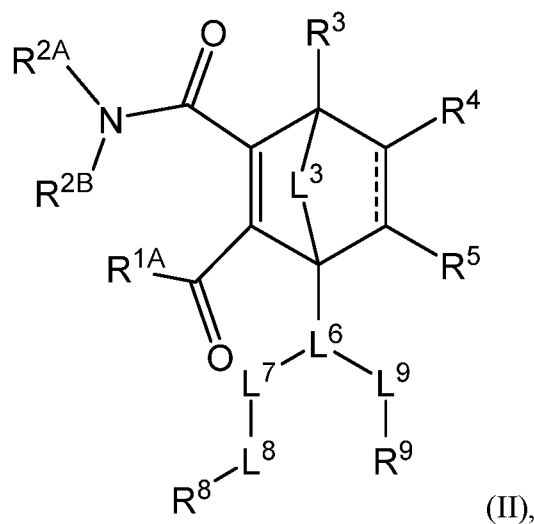
[0428] Embodiment P3. The method of one of embodiments P1 to P2, wherein at least one of R^1 or R^2 comprises an electron-withdrawing moiety.

10 **[0429]** Embodiment P4. The method of one of embodiments P1 to P3, wherein at least one of R^1 or R^2 are sufficiently electron withdrawing to allow said compound to covalently bind to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2, wherein said E1 cysteine amino acid is bound to ring carbon C_2 attached to R^2 or ring carbon C_1 attached to R^1 .

15 **[0430]** Embodiment P5. The method of one of embodiments P1 to P3, wherein said compound covalently binds to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2; and forms a complex of formula:



[0431] Embodiment P6. A compound of Formula:



wherein:

L^3 is $-O-$, $-S-$, or $-N(R^7)-$;

5 L^7 is $-O-$ or $-N(R^{10})-$;

R^{1A} is hydrogen, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-CN$, $-SO_{n1A}R^{1AA}$, $-SO_{v1A}NR^{1AA}R^{1AB}$, $-NHC(O)NR^{1AA}R^{1AB}$, $-N(O)_{m1A}$, $-NR^{1AA}R^{1AB}$, $-NHNr^{1AA}R^{1AB}$, $-C(O)R^{1AA}$, $-C(O)-OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$, $-NR^{1AA}SO_2R^{1AB}$, $-NR^{1AA}C(O)R^{1AB}$, $-NR^{1AA}C(O)OR^{1AB}$, $-NR^{1AA}OR^{1AB}$, $-N_3$, substituted or unsubstituted alkyl,

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

R^{2A} is hydrogen, halogen, $-CX^{2A}_3$, $-CHX^{2A}_2$, $-CH_2X^{2A}$, $-OCX^{2A}_3$, $-OCH_2X^{2A}$, $-OCHX^{2A}_2$, $-CN$, $-SO_{n2A}R^{2AA}$, $-SO_{v2A}NR^{2AA}R^{2AB}$, $-NHC(O)NR^{2AA}R^{2AB}$, $-N(O)_{m2A}$, $-NR^{2AA}R^{2AB}$, $-NHNr^{2AA}R^{2AB}$, $-C(O)R^{2AA}$, $-C(O)-OR^{2AA}$, $-C(O)NR^{2AA}R^{2AB}$, $-OR^{2AA}$, $-NR^{2AA}SO_2R^{2AB}$, $-NR^{2AA}C(O)R^{2AB}$, $-NR^{2AA}C(O)OR^{2AB}$, $-NR^{2AA}OR^{2AB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{2B} is hydrogen, halogen, $-CX^{2B}_3$, $-CHX^{2B}_2$, $-CH_2X^{2B}$, $-OCX^{2B}_3$, $-OCH_2X^{2B}$, $-OCHX^{2B}_2$, $-CN$, $-SO_{n2B}R^{2BA}$, $-SO_{v2B}NR^{2BA}R^{2BB}$, $-NHC(O)NR^{2BA}R^{2BB}$, $-N(O)_{m2B}$, $-NR^{2BA}R^{2BB}$, $-NHNr^{2BA}R^{2BB}$, $-C(O)R^{2BA}$, $-C(O)-OR^{2BA}$, $-C(O)NR^{2BA}R^{2BB}$, $-OR^{2BA}$, $-NR^{2BA}SO_2R^{2BB}$, $-NR^{2BA}C(O)R^{2BB}$, $-NR^{2BA}C(O)OR^{2BB}$, $-NR^{2BA}OR^{2BB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHNr^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHNr^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNr^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHNr^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHNr^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

- R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$, $-OCHX^7_2$, $-CN$, $-SO_{m5}R^{7A}$, $-SO_{v5}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m5}$, $-NR^{7A}R^{7B}$, $-NHNr^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNr^{7A}R^{7B}$, $-OR^{7A}$, $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- R^8 is hydrogen, halogen, $-CX^8_3$, $-CHX^8_2$, $-CH_2X^8$, $-OCX^8_3$, $-OCH_2X^8$, $-OCHX^8_2$, $-CN$, $-SO_{m5}R^{8A}$, $-SO_{v5}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m5}$, $-NR^{8A}R^{8B}$, $-NHNr^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHNr^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- R^9 is hydrogen, halogen, $-CX^9_3$, $-CHX^9_2$, $-CH_2X^9$, $-OCX^9_3$, $-OCH_2X^9$, $-OCHX^9_2$, $-CN$, $-SO_{m5}R^{9A}$, $-SO_{v5}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m5}$, $-NR^{9A}R^{9B}$, $-NHNr^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHNr^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- R^{10} is hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{m10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNr^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNr^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- Each R^{1AA} , R^{1AB} , R^{2AA} , R^{2AB} , R^{2BA} , R^{2BB} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{7A} , R^{7B} , R^{8A} , R^{8B} , R^{9A} , R^{9B} , R^{10A} , and R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

unsubstituted heteroaryl; R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

$m1A$, $m2A$, $m2B$, $m3$, $m4$, $m5$, $m7$, $m8$, $m9$, and $m10$ are independently 1 or 2;

$v1A$, $v2A$, $v2B$, $v3$, $v4$, $v5$, $v7$, $v8$, $v9$, and $v10$ are independently 1 or 2;

$n1A$, $n2A$, $n2B$, $n3$, $n4$, $n5$, $n7$, $n8$, $n9$, and $n10$ are independently an integer from 0 to 4;

X , X^{1A} , X^{2A} , X^{2B} , X^3 , X^4 , X^5 , X^7 , X^8 , X^9 , and X^{10} are independently -Cl, -Br, -I or, -F;

L^6 is 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;

L^8 is a bond, -C(O)-, -C(O)NH-, -C(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or

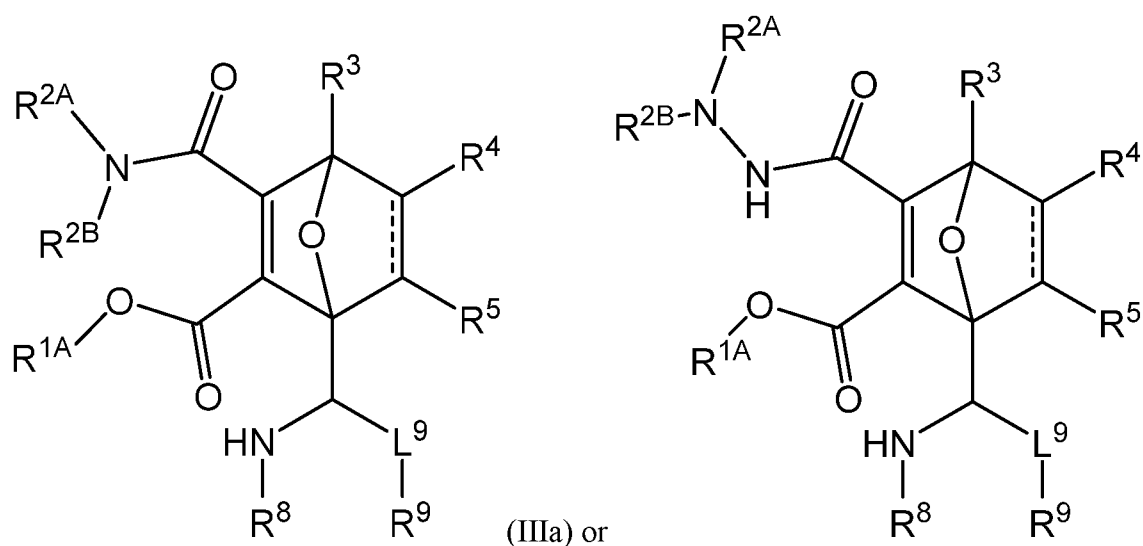
unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

L^9 is a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NHC(O)NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

wherein R^{2A} and R^{2B} may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and.

R^4 and R^5 may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0432] Embodiment P7. The compound of embodiment P6, having the formula:

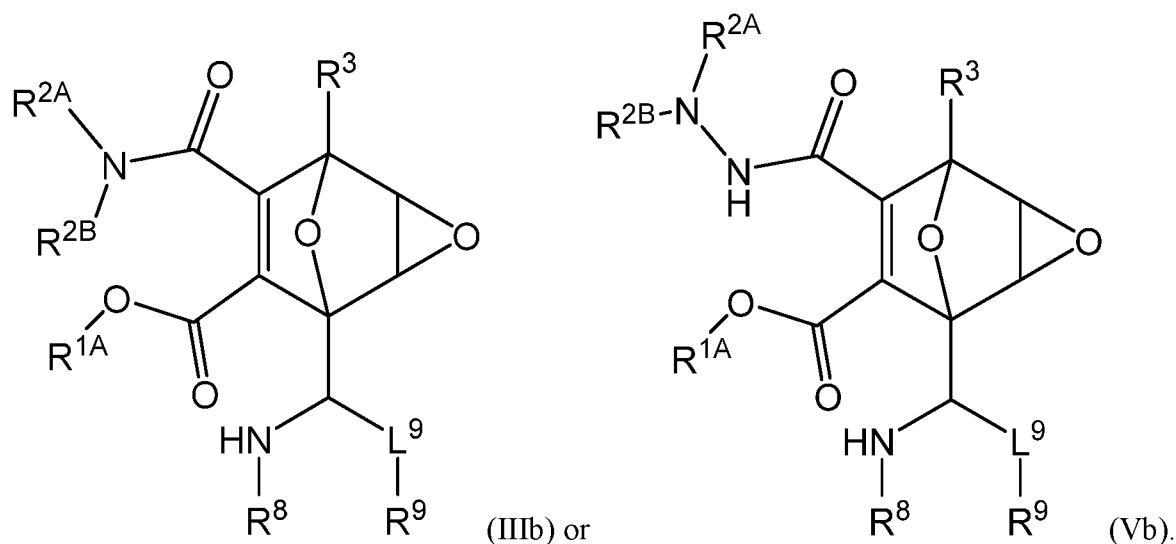


(Va).

[0433] Embodiment P8. The compound of one of embodiments P6 to P7, wherein R^4 is hydrogen.

[0434] Embodiment P9. The compound of one of embodiments P6 to P7, wherein R^5 is hydrogen.

[0435] Embodiment P10. The compound of one of embodiments P6 to P7, having the formula:



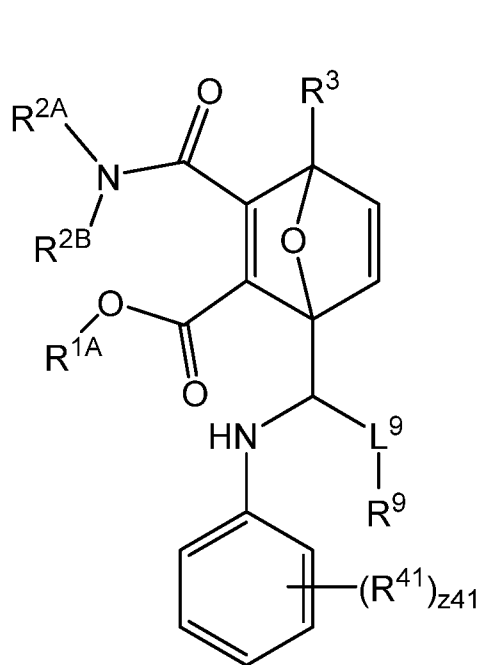
[0436] Embodiment P11. The compound of one of embodiments P6 to P10, wherein R⁸ is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

- 5 **[0437]** Embodiment P12. The compound of one of embodiments P6 to P10, wherein R⁸ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

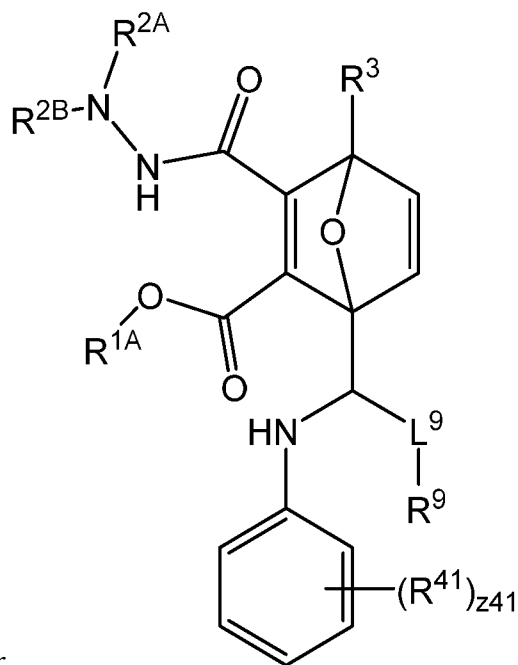
[0438] Embodiment P13. The compound of one of embodiments P6 to P10, wherein R⁸ is substituted or unsubstituted phenyl or substituted or unsubstituted 5 to 6 membered heteroaryl.

- 10 **[0439]** Embodiment P14. The compound of one of embodiments P6 to P10, wherein R⁸ is substituted or unsubstituted phenyl.

[0440] Embodiment P15. The compound of one of embodiments P6 to P7, having the formula:



(IIIc) or



(Vc);

R^{41} is independently halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$,

- 5 $-OCX^{41}_3$, $-OCHX^{41}_2$, $-OCH_2X^{41}$, $-OPh$, 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^{41} substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 10

z_{41} is an integer from 0 to 5;

X^{41} is independently $-Cl$, $-Br$, $-I$ or, $-F$.

[0441] Embodiment P16. The compound of embodiment P15, wherein R^{41} is independently halogen or $-OPh$.

- 15 **[0442]** Embodiment P17. The compound of one of embodiments P15 to P16, wherein z_{41} is 2.

[0443] Embodiment P18. The compound of one of embodiments P15 to P16, wherein z_{41} is 1.

[0444] Embodiment P19. The compound of one of embodiments P15 to P16, wherein z₄₁ is 0.

[0445] Embodiment P20. The compound of one of embodiments P6 to P19, wherein L⁹ is a bond or substituted or unsubstituted alkylene.

5 [0446] Embodiment P21. The compound of one of embodiments P6 to P19, wherein L⁹ is a bond or unsubstituted C₁-C₃ alkylene.

[0447] Embodiment P22. The compound of one of embodiments P6 to P19, wherein L⁹ is an unsubstituted methylene.

10 [0448] Embodiment P23. The compound of one of embodiments P6 to P19, wherein L⁹ is a bond.

[0449] Embodiment P24. The compound of one of embodiments P6 to P23, wherein R⁹ is 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.

15 [0450] Embodiment P25. The compound of one of embodiments P6 to P23, wherein R⁹ is unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

20 [0451] Embodiment P26. The compound of one of embodiments P6 to P23, wherein R⁹ is unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

25 [0452] Embodiment P27. The compound of one of embodiments P6 to P23, wherein R⁹ is unsubstituted propyl, unsubstituted butyl, unsubstituted pentyl, unsubstituted propenyl, unsubstituted butenyl, unsubstituted pentenyl, unsubstituted propynyl, unsubstituted butynyl, unsubstituted pentynyl, unsubstituted cyclobutyl, unsubstituted cyclopentyl, unsubstituted tetrahydropyranyl, unsubstituted morpholinyl, or unsubstituted phenyl.

[0453] Embodiment P28. The compound of one of embodiments P6 to P23, wherein R⁹ is unsubstituted phenyl.

[0454] Embodiment P29. The compound of one of embodiments P6 to P28, wherein R^{2A} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

5 **[0455]** Embodiment P30. The compound of one of embodiments P6 to P28, wherein R^{2A} is hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted C_3 - C_6 aryl, or substituted or unsubstituted 5 to 10 membered heteroaryl.

10 **[0456]** Embodiment P31. The compound of one of embodiments P6 to P28, wherein R^{2A} is hydrogen.

[0457] Embodiment P32. The compound of one of embodiments P6 to P31, wherein R^{2B} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
15 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0458] Embodiment P33. The compound of one of embodiments P6 to P31, wherein R^{2B} is hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted C_3 - C_6 aryl, or
20 substituted or unsubstituted 5 to 10 membered heteroaryl.

[0459] Embodiment P34. The compound of one of embodiments P6 to P31, wherein R^{2B} is hydrogen.

[0460] Embodiment P35. The compound of one of embodiments P6 to P28, wherein R^{2A} and R^{2B} are joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
25 unsubstituted heteroaryl.

[0461] Embodiment P36. The compound of one of embodiments P6 to P28, wherein R^{2A} and R^{2B} are joined to form a substituted or unsubstituted heterocycloalkyl.

[0462] Embodiment P37. The compound of one of embodiments P6 to P28, wherein R^{2A} and R^{2B} are joined to form a substituted or unsubstituted 4 to 6 membered heterocycloalkyl.

[0463] Embodiment P38. The compound of one of embodiments P6 to P37, wherein R^{1A} is hydrogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-C(O)R^{1AA}$, $-C(O)OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$, 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.

[0464] Embodiment P39. The compound of one of embodiments P6 to P37, wherein R^{1A} is hydrogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, unsubstituted C_1 - C_3 alkyl.

[0465] Embodiment P40. The compound of one of embodiments P6 to P37, wherein R^{1A} is unsubstituted C_1 - C_3 alkyl.

[0466] Embodiment P41. The compound of one of embodiments P6 to P37, wherein R^{1A} is hydrogen.

[0467] Embodiment P42. The compound of one of embodiments P6 to P41, wherein R^3 is hydrogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, substituted or unsubstituted alkyl.

[0468] Embodiment P43. The compound of one of embodiments P6 to P41, wherein R^3 is $-CH_2OH$ or $-CH_3$.

[0469] Embodiment P44. The compound of one of embodiments P6 to P41, wherein R^3 is hydrogen.

[0470] Embodiment P45. A method of inhibiting an E1 enzyme, said method comprising contacting an E1 enzyme with a compound of one of embodiments P6 to P44, thereby inhibiting said E1 enzyme.

[0471] Embodiment P46. The method of embodiment P45, wherein said method comprises allowing said compound to covalently bind said E1 enzyme.

[0472] Embodiment P47. The method of embodiment P45 or P46, wherein said method comprises allowing said compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

[0473] Embodiment P48. The method of embodiment P47, wherein said method comprises allowing said E1 cysteine amino acid to bind to carbon C_2 attached to R^{2A} and R^{2B} or to ring carbon C_1 attached to R^{1A} .

[0474] Embodiment P49. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject a compound of one of embodiments P6 to P44.

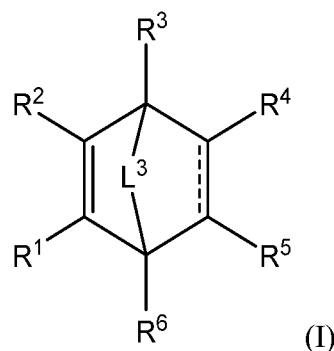
[0475] Embodiment P50. The method of embodiment P49, wherein said method comprises allowing said compound to covalently bind an E1 enzyme.

[0476] Embodiment P51. The method of embodiment P49 or P50, wherein said method comprises allowing said compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

[0477] Embodiment P52. The method of embodiment P51, wherein said method comprises allowing said E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to ring carbon C₁ attached to R^{1A}.

VIII. Additional embodiments

[0478] Embodiment 1. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of formula:



wherein:

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

L³ is -O-, -S-, -N-, -S(O)-, -S(O)₂-, -C(O)-, -N(R⁷)-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R¹ is hydrogen, halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OCX¹₃, -OCH₂X¹, -OCHX¹₂, -CN, -SO_{n1}R^{1A}, -SO_{v1}NR^{1A}R^{1B}, -NHC(O)NR^{1A}R^{1B}, -N(O)_{m1}, -NR^{1A}R^{1B}, -NHN^{1A}R^{1B}, -C(O)R^{1A}, -C(O)-OR^{1A}, -C(O)NR^{1A}R^{1B}, -C(O)NHN^{1A}R^{1B}, -OR^{1A}, -NR^{1A}SO₂R^{1B}, -NR^{1A}C(O)R^{1B}, -NR^{1A}C(O)OR^{1B}, -NR^{1A}OR^{1B}, -N₃, -L¹-E¹, substituted or

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

R^2 is hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$,

- 5 $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, $-L^2-E^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 10

R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$,

- $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHN R^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 15

R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$,

- $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHN R^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHN R^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, 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;
- 20

R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$,

- $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHN R^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHN R^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 25
- 30

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

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

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

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

- 15 E^1 and E^2 are independently an electron-withdrawing moiety;

each R^{1A} , R^{1B} , R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{6A} , R^{6B} , R^{7A} , and R^{7B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NH SO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$,

- 20 $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

- 25 and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A}
- 30 and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A}

and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

m1, m2, m3, m4, m5, m6, and m7 are independently 1 or 2;

v1, v2, v3, v4, v5, v6, and v7 are independently 1 or 2;

5 n1, n2, n3, n4, n5, n6, and n7 are independently an integer from 0 to 4;

X, X¹, X², X³, X⁴, X⁵, X⁶, and X⁷ are independently -Cl, -Br, -I, or -F;

L¹ and L² are independently a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-,
-C(O)NH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or
unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or

10 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R¹ and R² may optionally be joined to form a substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl;

15 R⁴ and R⁵ may optionally be joined to form a substituted or unsubstituted cycloalkyl,
substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
or unsubstituted heteroaryl; and

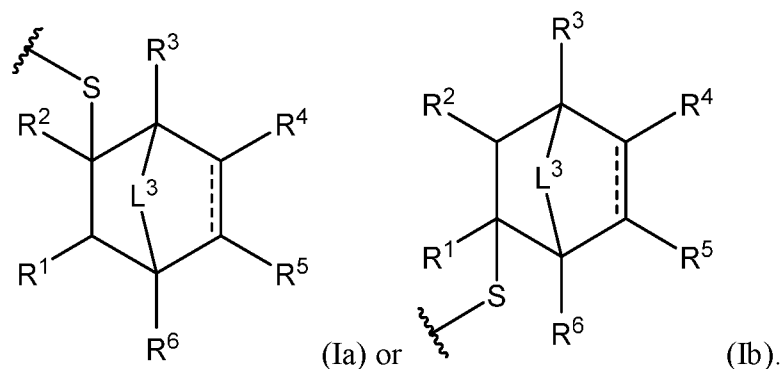
wherein said compound is administered at a rate approximately equal to the half-life of an E1
enzyme.

20 **[0479]** Embodiment 2. The method of embodiment 1, wherein said compound is
covalently attached to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

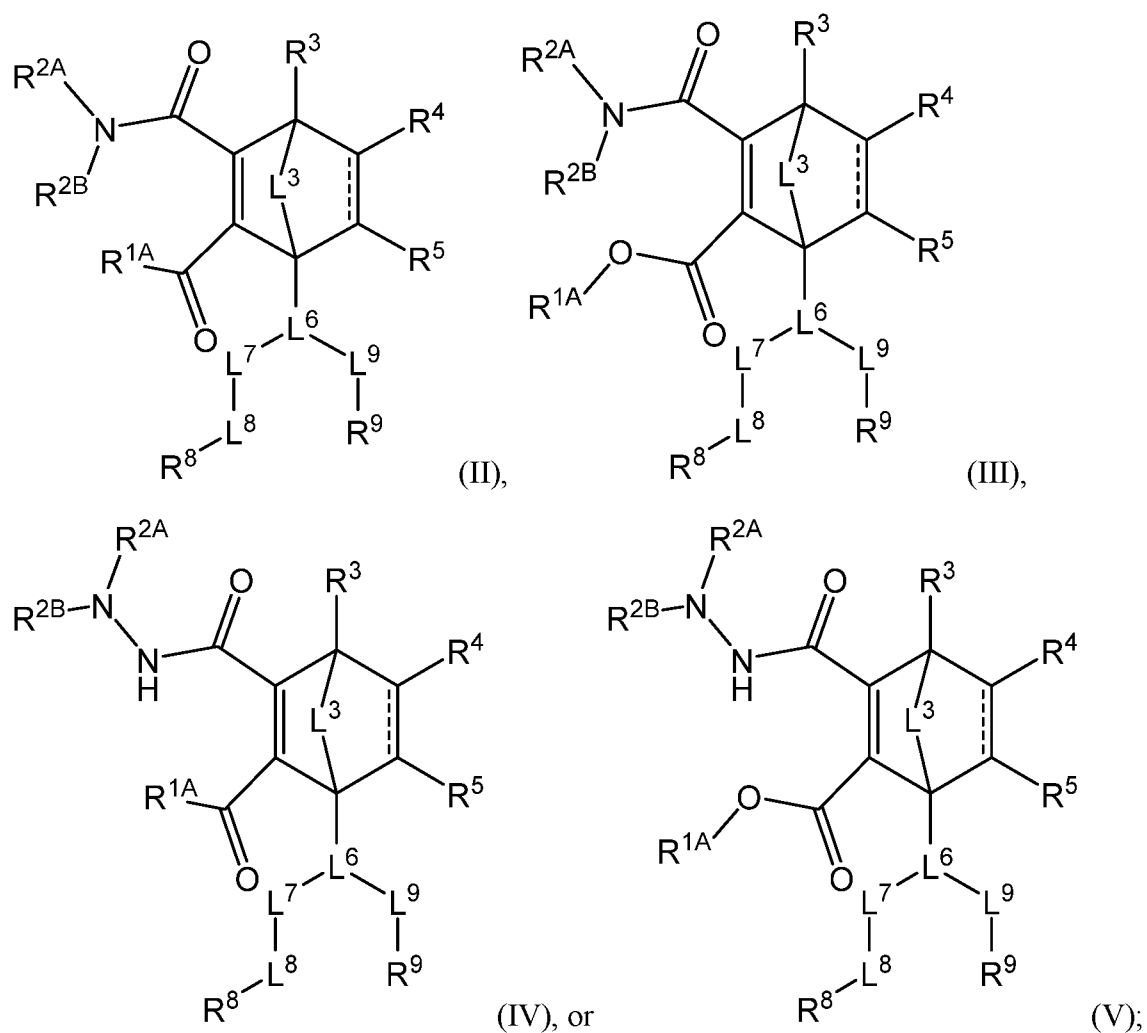
[0480] Embodiment 3. The method of one of embodiments 1 to 2, wherein at least one
of R¹ or R² comprises an electron-withdrawing moiety.

[0481] Embodiment 4. The method of one of embodiments 1 to 3, wherein at least one
25 of R¹ or R² are sufficiently electron withdrawing to allow said compound to covalently bind
to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2, wherein said E1
cysteine amino acid is bound to ring carbon C₂ attached to R² or ring carbon C₁ attached to
R¹.

[0482] Embodiment 5. The method of one of embodiments 1 to 3, wherein said compound covalently binds to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2; and forms a complex of formula:



5 **[0483]** Embodiment 6. A compound of formula:



wherein

L^3 is $-O-$, $-S-$, or $-N(R^7)-$;

L^7 is $-O-$ or $-N(R^{10})-$;

R^{1A} is hydrogen, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$,

$-OCHX^{1A}_2$, $-CN$, $-SO_{n1A}R^{1AA}$, $-SO_{v1A}NR^{1AA}R^{1AB}$, $-NHC(O)NR^{1AA}R^{1AB}$, $-N(O)_{m1A}$,

5 $-NR^{1AA}R^{1AB}$, $-NHN R^{1AA}R^{1AB}$, $-C(O)R^{1AA}$, $-C(O)-OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$,

$-NR^{1AA}SO_2R^{1AB}$, $-NR^{1AA}C(O)R^{1AB}$, $-NR^{1AA}C(O)OR^{1AB}$, $-NR^{1AA}OR^{1AB}$, $-N_3$, substituted or

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or

substituted or unsubstituted heteroaryl;

10 R^{2A} is hydrogen, halogen, $-CX^{2A}_3$, $-CHX^{2A}_2$, $-CH_2X^{2A}$, $-OCX^{2A}_3$, $-OCH_2X^{2A}$,

$-OCHX^{2A}_2$, $-CN$, $-SO_{n2A}R^{2AA}$, $-SO_{v2A}NR^{2AA}R^{2AB}$, $-NHC(O)NR^{2AA}R^{2AB}$, $-N(O)_{m2A}$,

$-NR^{2AA}R^{2AB}$, $-NHN R^{2AA}R^{2AB}$, $-C(O)R^{2AA}$, $-C(O)-OR^{2AA}$, $-C(O)NR^{2AA}R^{2AB}$, $-OR^{2AA}$,

$-NR^{2AA}SO_2R^{2AB}$, $-NR^{2AA}C(O)R^{2AB}$, $-NR^{2AA}C(O)OR^{2AB}$, $-NR^{2AA}OR^{2AB}$, $-N_3$, substituted or

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

15 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or

substituted or unsubstituted heteroaryl;

R^{2B} is hydrogen, halogen, $-CX^{2B}_3$, $-CHX^{2B}_2$, $-CH_2X^{2B}$, $-OCX^{2B}_3$, $-OCH_2X^{2B}$,

$-OCHX^{2B}_2$, $-CN$, $-SO_{n2B}R^{2BA}$, $-SO_{v2B}NR^{2BA}R^{2BB}$, $-NHC(O)NR^{2BA}R^{2BB}$, $-N(O)_{m2B}$,

$-NR^{2BA}R^{2BB}$, $-NHN R^{2BA}R^{2BB}$, $-C(O)R^{2BA}$, $-C(O)-OR^{2BA}$, $-C(O)NR^{2BA}R^{2BB}$, $-OR^{2BA}$,

20 $-NR^{2BA}SO_2R^{2BB}$, $-NR^{2BA}C(O)R^{2BB}$, $-NR^{2BA}C(O)OR^{2BB}$, $-NR^{2BA}OR^{2BB}$, $-N_3$, substituted or

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or

substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$,

25 $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$,

$-NHN R^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$,

$-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl,

substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or

30 unsubstituted heteroaryl;

R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHN R^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHN R^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or

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

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

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

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

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

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

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

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

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

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

R^{10} is hydrogen, halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$,

5 $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHNR^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHNr^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^{1AA} , R^{1AB} , R^{2AA} , R^{2AB} , R^{2BA} , R^{2BB} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{7A} , R^{7B} , R^{8A} , R^{8B} , R^{9A} , R^{9B} , R^{10A} , and R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$,

$-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$,

15 $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may

optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

m1A, m2A, m2B, m3, m4, m5, m7, m8, m9, and m10 are independently 1 or 2;

v1A, v2A, v2B, v3, v4, v5, v7, v8, v9, and v10 are independently 1 or 2;

n1A, n2A, n2B, n3, n4, n5, n7, n8, n9, and n10 are independently an integer from 0 to 4;

X, X^{1A}, X^{2A}, X^{2B}, X³, X⁴, X⁵, X⁷, X⁸, X⁹, and X¹⁰ are independently -Cl, -Br, -I, or -F;

L⁶ is 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;

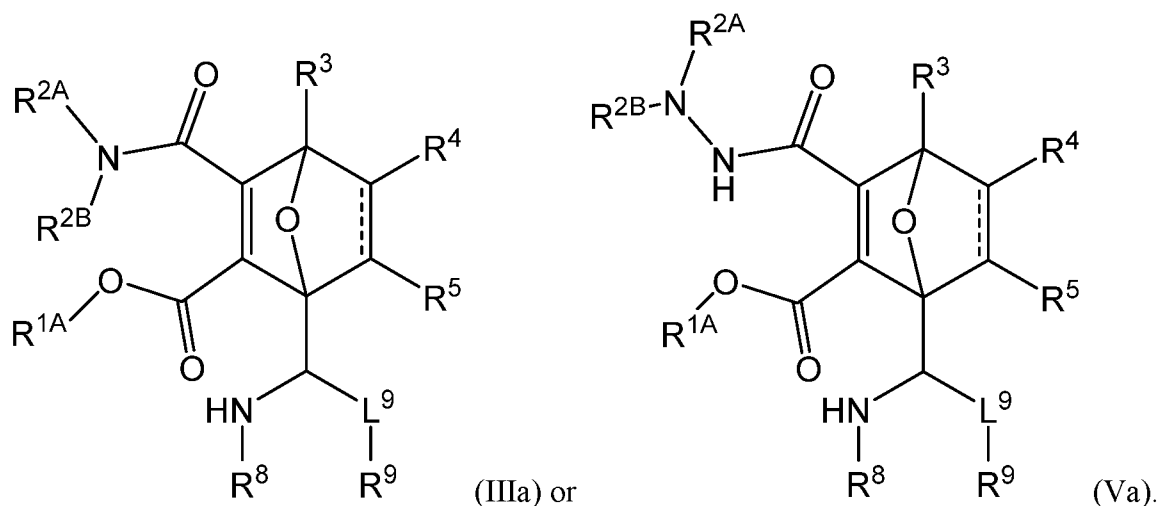
L⁸ is a bond, -C(O)-, -C(O)NH-, -C(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

L⁹ is a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NHC(O)NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

wherein R^{2A} and R^{2B} may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl; and

R⁴ and R⁵ may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

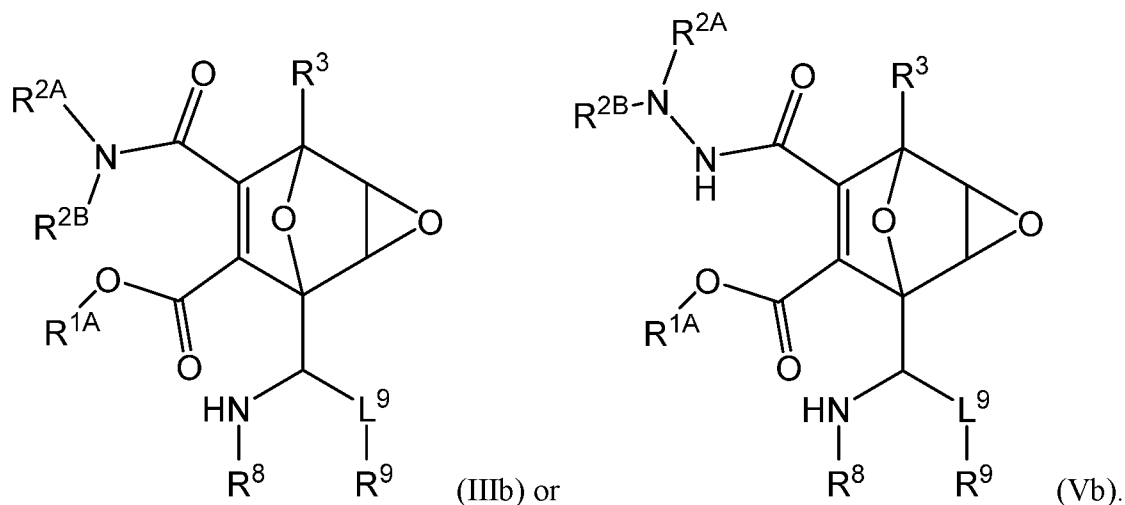
[0484] Embodiment 7. The compound of embodiment 6, having the formula:



[0485] Embodiment 8. The compound of one of embodiments 6 to 7, wherein R^4 is hydrogen.

[0486] Embodiment 9. The compound of one of embodiments 6 to 7, wherein R^5 is hydrogen.

[0487] Embodiment 10. The compound of one of embodiments 6 to 7, having the formula:



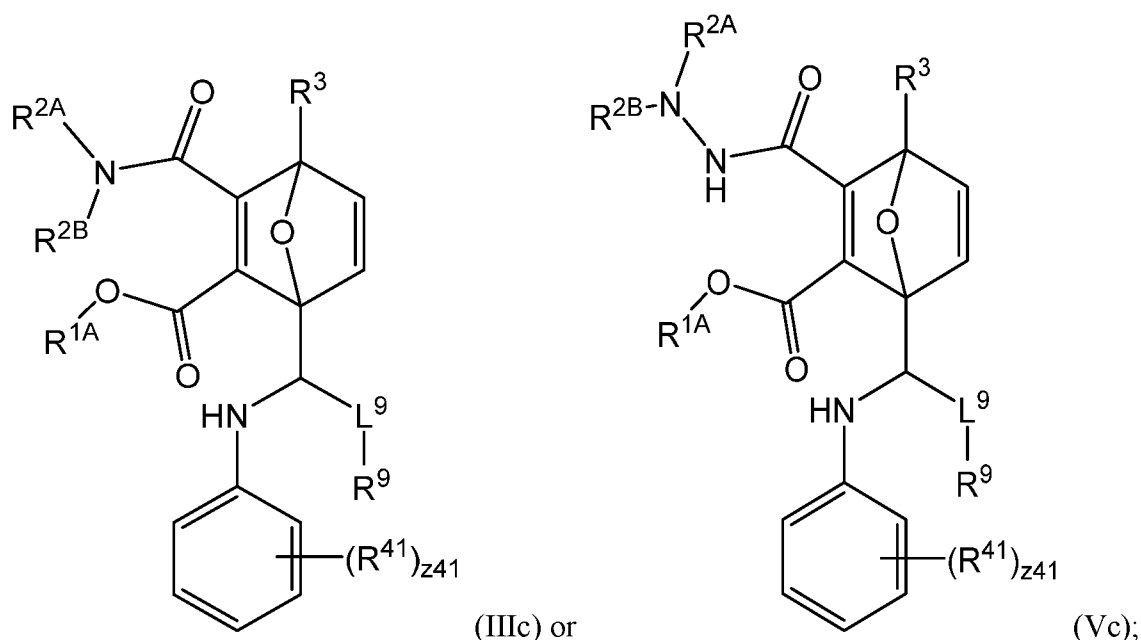
[0488] Embodiment 11. The compound of one of embodiments 6 to 10, wherein R^8 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0489] Embodiment 12. The compound of one of embodiments 6 to 10, wherein R^8 is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0490] Embodiment 13. The compound of one of embodiments 6 to 10, wherein R⁸ is substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0491] Embodiment 14. The compound of one of embodiments 6 to 10, wherein R⁸ is substituted or unsubstituted phenyl.

[0492] Embodiment 15. The compound of one of embodiments 6 to 7, having the formula:



R⁴¹ is independently halogen, -CX⁴¹₃, -CHX⁴¹₂, -CH₂X⁴¹, -C(O)OH,

10 -C(O)NH₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂,
 -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H,
 -NHC(O)OH, -NHOH, -OCX⁴¹₃, -OCHX⁴¹₂, -OCH₂X⁴¹, -OPh, substituted or unsubstituted
 alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
 15 or unsubstituted heteroaryl; two adjacent R⁴¹ 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;

z₄₁ is an integer from 0 to 5; and

X⁴¹ is independently -Cl, -Br, -I, or -F.

[0493] Embodiment 16. The compound of embodiment 15, wherein R⁴¹ is independently halogen or –OPh.

[0494] Embodiment 17. The compound of one of embodiments 15 to 16, wherein z₄₁ is 2.

5 [0495] Embodiment 18. The compound of one of embodiments 15 to 16, wherein z₄₁ is 1.

[0496] Embodiment 19. The compound of one of embodiments 15 to 16, wherein z₄₁ is 0.

10 [0497] Embodiment 20. The compound of one of embodiments 6 to 19, wherein L⁹ is a bond, or substituted or unsubstituted alkylene.

[0498] Embodiment 21. The compound of one of embodiments 6 to 19, wherein L⁹ is a bond or unsubstituted C₁-C₃ alkylene.

[0499] Embodiment 22. The compound of one of embodiments 6 to 19, wherein L⁹ is an unsubstituted methylene.

15 [0500] Embodiment 23. The compound of one of embodiments 6 to 19, wherein L⁹ is a bond.

[0501] Embodiment 24. The compound of one of embodiments 6 to 23, wherein R⁹ is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
20 unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0502] Embodiment 25. The compound of one of embodiments 6 to 23, wherein R⁹ is unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

25 [0503] Embodiment 26. The compound of one of embodiments 6 to 23, wherein R⁹ is unsubstituted C₁-C₆ alkyl, unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered heteroaryl.

[0504] Embodiment 27. The compound of one of embodiments 6 to 23, wherein R⁹ is unsubstituted propyl, unsubstituted butyl, unsubstituted pentyl, unsubstituted propenyl,

unsubstituted butenyl, unsubstituted pentenyl, unsubstituted propynyl, unsubstituted butynyl, unsubstituted pentynyl, unsubstituted cyclobutyl, unsubstituted cyclopentyl, unsubstituted tetrahydropyranyl, unsubstituted morpholinyl, or unsubstituted phenyl.

[0505] Embodiment 28. The compound of one of embodiments 6 to 23, wherein R⁹ is unsubstituted phenyl.

[0506] Embodiment 29. The compound of one of embodiments 6 to 28, wherein R^{2A} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0507] Embodiment 30. The compound of one of embodiments 6 to 28, wherein R^{2A} is hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted C₃-C₆ aryl, or substituted or unsubstituted 5 to 10 membered heteroaryl.

[0508] Embodiment 31. The compound of one of embodiments 6 to 28, wherein R^{2A} is hydrogen.

[0509] Embodiment 32. The compound of one of embodiments 6 to 31, wherein R^{2B} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0510] Embodiment 33. The compound of one of embodiments 6 to 31, wherein R^{2B} is hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted C₃-C₆ aryl, or substituted or unsubstituted 5 to 10 membered heteroaryl.

[0511] Embodiment 34. The compound of one of embodiments 6 to 31, wherein R^{2B} is hydrogen.

[0512] Embodiment 35. The compound of one of embodiments 6 to 28, wherein R^{2A} and R^{2B} are joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

- [0513] Embodiment 36. The compound of one of embodiments 6 to 28, wherein R^{2A} and R^{2B} are joined to form a substituted or unsubstituted heterocycloalkyl.
- [0514] Embodiment 37. The compound of one of embodiments 6 to 28, wherein R^{2A} and R^{2B} are joined to form a substituted or unsubstituted 4 to 6 membered heterocycloalkyl.
- 5 [0515] Embodiment 38. The compound of one of embodiments 6 to 37, wherein R^{1A} is hydrogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$, $-OCHX^{1A}_2$, $-C(O)R^{1AA}$, $-C(O)OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.
- 10 [0516] Embodiment 39. The compound of one of embodiments 6 to 37, wherein R^{1A} is hydrogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, or unsubstituted C_1 - C_3 alkyl.
- [0517] Embodiment 40. The compound of one of embodiments 6 to 37, wherein R^{1A} is unsubstituted C_1 - C_3 alkyl.
- [0518] Embodiment 41. The compound of one of embodiments 6 to 37, wherein R^{1A} is
15 hydrogen.
- [0519] Embodiment 42. The compound of one of embodiments 6 to 41, wherein R^3 is hydrogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, or substituted or unsubstituted alkyl.
- [0520] Embodiment 43. The compound of one of embodiments 6 to 41, wherein R^3 is $-CH_2OH$ or $-CH_3$.
- 20 [0521] Embodiment 44. The compound of one of embodiments 6 to 41, wherein R^3 is hydrogen.
- [0522] Embodiment 45. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, of one of embodiments 6 to 44 and a pharmaceutically acceptable excipient.
- 25 [0523] Embodiment 46. A method of inhibiting an E1 enzyme, said method comprising contacting an E1 enzyme with a compound of one of embodiments 6 to 44, thereby inhibiting said E1 enzyme.
- [0524] Embodiment 47. The method of embodiment 46, wherein said method comprises allowing said compound to covalently bind said E1 enzyme.

[0525] Embodiment 48. The method of embodiment 46 or 47, wherein said method comprises allowing said compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

[0526] Embodiment 49. The method of embodiment 48, wherein said method comprises allowing said E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to ring carbon C₁ attached to R^{1A}.

[0527] Embodiment 50. A method of treating cancer in a subject in need thereof, said method comprising administering to said subject a compound of one of embodiments 6 to 44.

[0528] Embodiment 51. The method of embodiment 50, wherein said method comprises allowing said compound to covalently bind an E1 enzyme.

[0529] Embodiment 52. The method of embodiment 50 or 51, wherein said method comprises allowing said compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

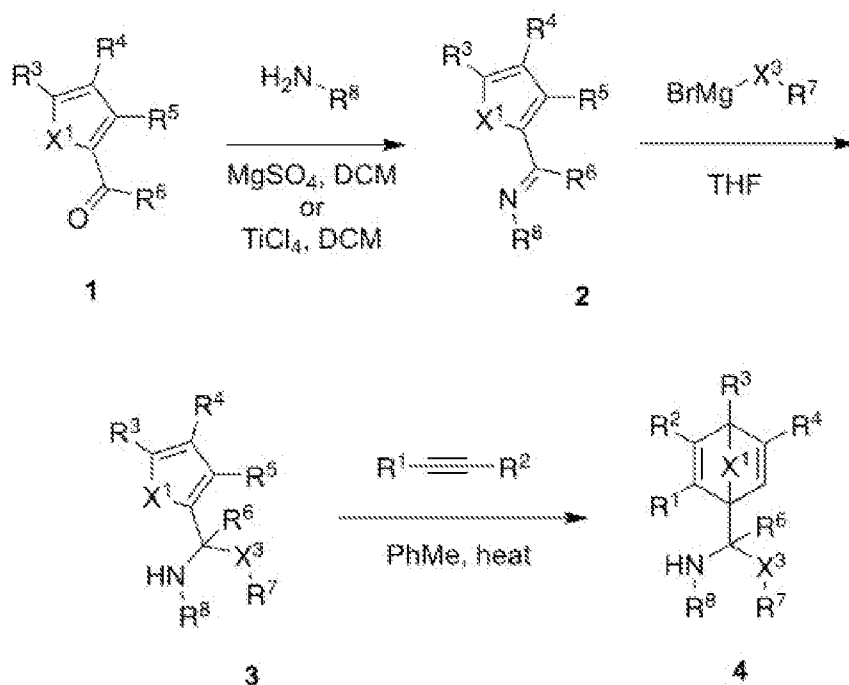
[0530] Embodiment 53. The method of embodiment 52, wherein said method comprises allowing said E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to carbon C₁ attached to R^{1A}.

EXAMPLES

A. Example 1. General synthetic procedures

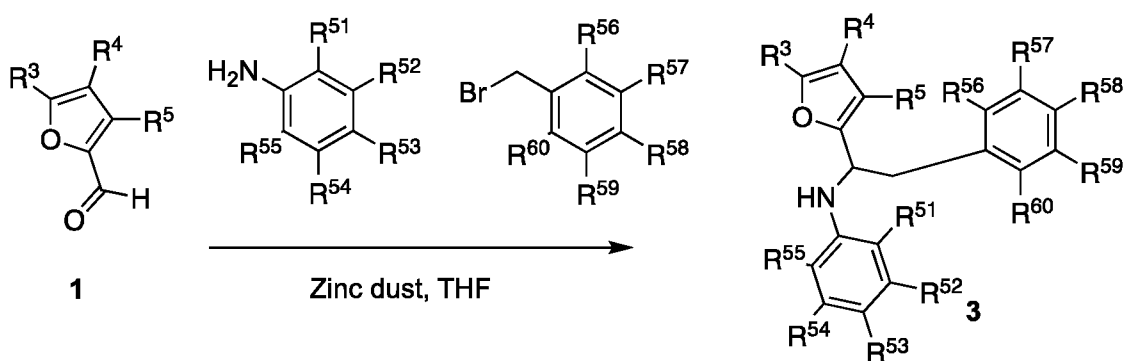
[0531] The compounds of this invention can be synthesized according to the following Schemes.

[0532] Scheme I:



[0533] The compounds of Formula I can be synthesized according to Scheme I. In step 1, carbonyl compound 1 can react with an amine to form imine intermediate 2, which will further react with a Grignard reagent to give compound 3. Compound 3 will undergo Diels-Alder reaction with an alkyne dienophile (at least one of R^1 or R^2 is an electron withdrawing group) to yield compound 4 (Formula I, wherein $X^2 = NH$).

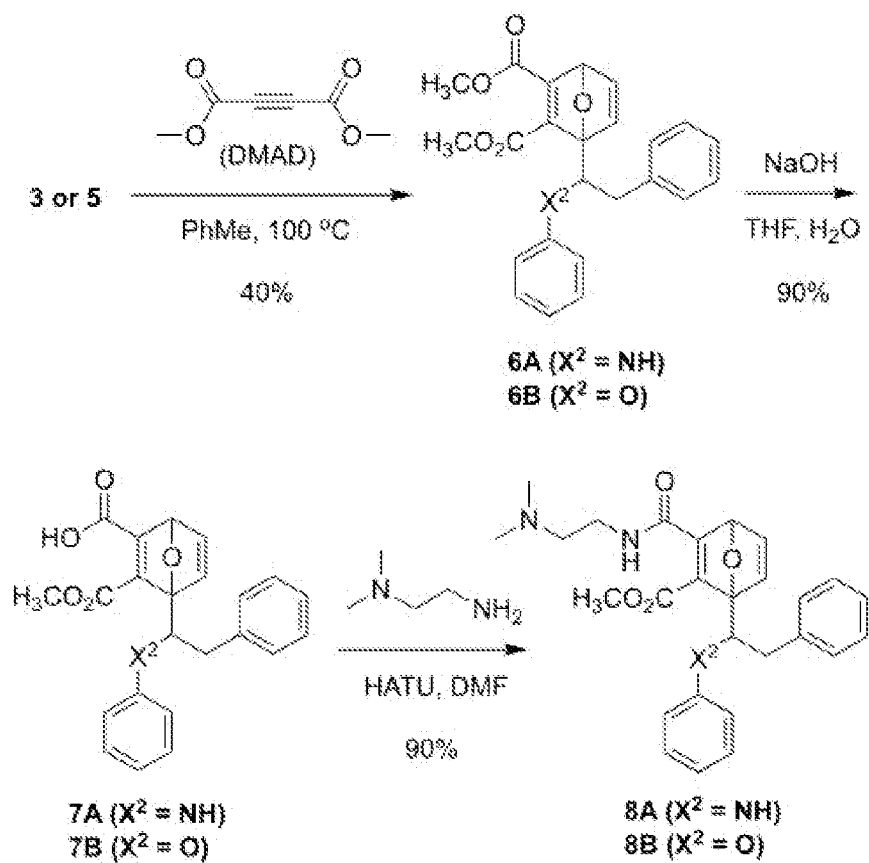
[0534] Scheme II:



[0535] In certain cases, compound 3 can be synthesized directly by mixing 2-furaldehyde 1, aniline and benzyl bromide with Zinc dust in THF as shown in Scheme II, where in $R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}$, is independently hydrogen, deuterium, amino, nitro, cyano, hydroxyl, halo, alkyl, haloalkyl, haloalkyl, alkoxy, haloalkoxy, carboxyalkyl,

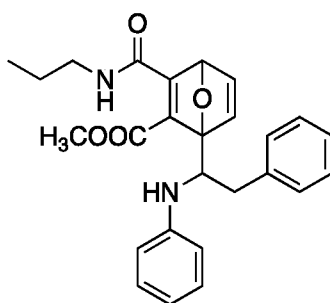
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0536] Scheme III:

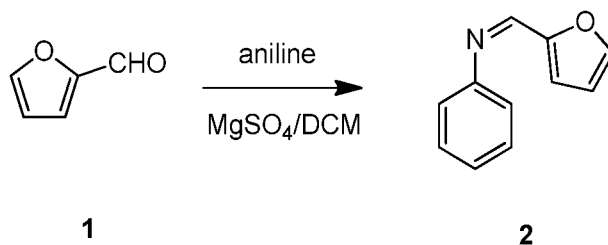


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[0537] Example I:



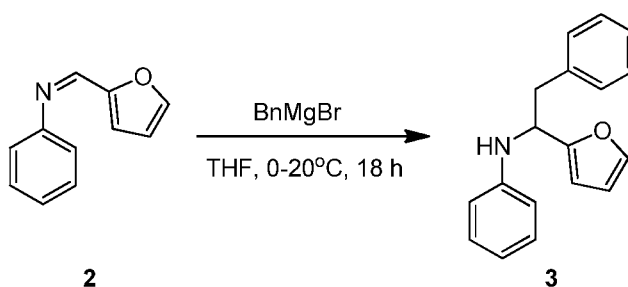
[0538] Step A (Scheme I):



[0539] A mixture of aniline (50 g, 536 mmol), compound **1** (furfural, 47 g, 488 mmol) and MgSO_4 (118 g, 976 mmol) in anhydrous DCM (800 mL) was stirred at 45°C for 18 hours.

5 The mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column (Petroleum ether/ EtOAc = 50:1) to give compound **2** (50 g, 292 mmol, 60% yield) as a yellow oil. ^1H NMR (CDCl_3): δ 8.37 (s, 1H), 7.66 (s, 1H), 7.45 - 7.41 (m, 2H), 7.30 - 7.26 (m, 3H), 7.01 - 7.00 (m, 1H), 6.61 - 6.60 (m, 1H).

[0540] Step B (Scheme I):



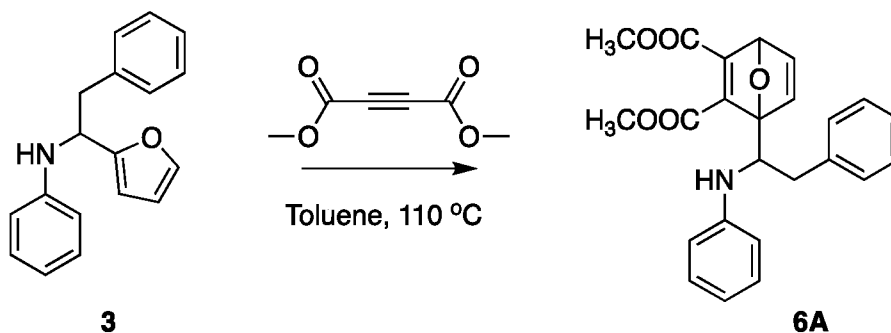
10

To a solution of compound **2** (100 g, 585 mmol) in THF (1 L) was added benzylmagnesium bromide (1 M, 1.05 L, 1.05 mol) dropwise with stirring at 0°C. Then the mixture was stirred at 20°C for 18 hours. The reaction mixture was quenched by saturated NH_4Cl aqueous solution (1 L) and extracted with EtOAc (300 mL x 3), the organic layer was washed with

15 brine (300 mL x 2), dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel chromatography eluted with petroleum ether/ethyl acetate = 30:1 to give compound **3** (20 g, 9.8% yield, 75% purity) as yellow oil. ^1H NMR: (CDCl_3) δ 7.38 (s, 1H), 7.26 - 7.23 (m, 3H), 7.16 - 7.12 (m, 2H), 7.07 - 7.05 (m, 2H), 6.71 - 6.70 (m, 1H), 6.61 - 6.59 (m, 2H), 6.27 - 6.26 (m, 1H), 6.05 - 6.04 (m, 1H), 4.76 (t, J = 6.4 Hz, 1H), 3.96 (s, 1H), 3.22 - 3.19 (m,

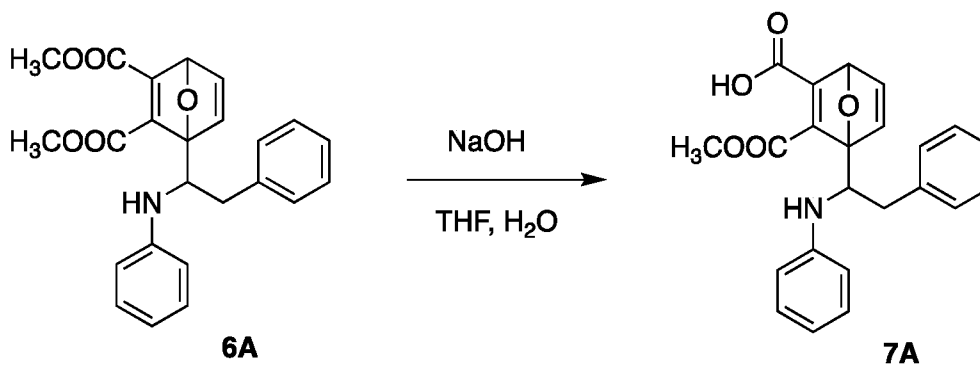
20 2H).

[0541] Step C (Scheme III):



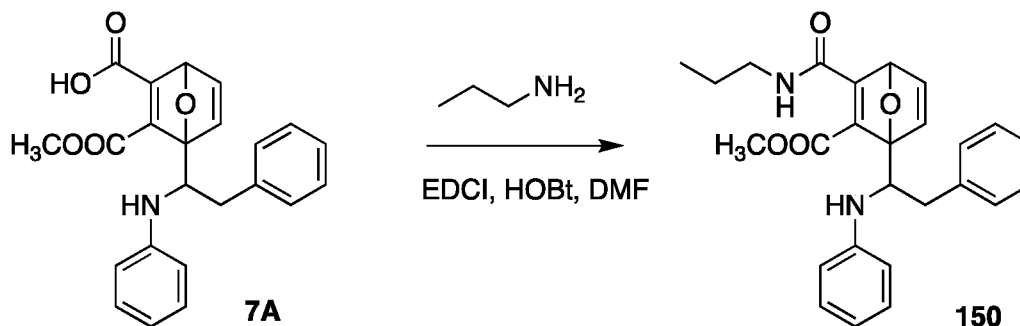
Compound **3** (4.8 g, 18.25 mmol) in 100 mL anhydrous toluene was heated to 110 °C, then dimethyl acetylenedicarboxylate (5.18 g, 36.5 mmol) was added and the mixture was
 5 refluxed overnight. TLC (hexanes/EtOAc = 3:1) and LC-MS of a small pre-TLC indicated the formation of two adjacent spots with the same molecular weight. The solvents were evaporated *in vacuo*, and the crude product was sequentially recrystallized from methanol to give two portions: T and B. T. Bright yellow solid (2.75 g), less polar; LC/MS (M+1) 406.1; ¹H NMR (d₆-DMSO): δ 7.05-7.30 (m, 6H), 6.90 (m, 3H), 6.40 (m, 3H), 5.80 (d, 1H), 5.55
 10 (m, 1H), 4.50 (m, 1H), 3.67 (s, 3H), 3.20 (s, 3H), 2.85 (m, 1H), 2.75 (m, 1H). B. Pale yellow solid (2.16 g), more polar; LC/MS (M+1) 406.1; ¹H NMR (d₆-DMSO): δ 7.25 (m, 1H), 7.21-7.12 (m, 5H), 7.10-7.05 (m, 1H), 6.97-6.90 (m, 2H), 6.50-6.42 (m, 2H), 6.40 (m, 1H), 5.80 (d, 1H), 5.68 (s, 1H), 4.50 (m, 1H), 3.65 (s, 3H), 3.55 (s, 3H), 2.85 (m, 1H), 2.75 (m, 1H).

[0542] Step D (Scheme III):



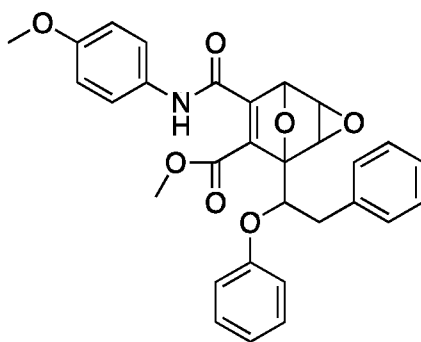
Compound **6A** portion T (910 mg, 2.25 mmol) was dissolved in 22.5 mL THF and the mixture was cooled to 0 °C, then 11.25 mL 0.2 M sodium hydroxide was added and the mixture was stirred at 0 °C for 1 hour. Then another portion of NaOH solution was added (11.25 mL, 0.2 M). After another hour, 20% HCl was added dropwise to neutralize the
 20 reaction mixture. The organic solvents were then evaporated *in vacuo*, and the remaining

aqueous layer were acidified to pH ~3 with 20% HCl then extracted with CHCl₃. The organic layer was dried over anhydrous MgSO₄ and then concentrated to give a crude oil. The crude product was purified by silica gel chromatography eluted with methanol/ethyl acetate = 1:9 to give compound **7A** (810 mg) as yellow solid. LC/MS (M+1): 392.1; (M-1): 390.1. ¹H NMR (d₆-DMSO): δ 7.25 (m, 2H), 7.15 (m, 2H), 7.10 (m, 1H), 6.90 (m, 2H), 6.82 (m, 1H), 6.43 (m, 2H), 6.39 (m, 1H), 5.60 (m, 1H), 5.40 (m, 1H), 4.50 (m, 1H), 3.20 (s, 3H), 2.87 (m, 1H), 2.74 (m, 1H).

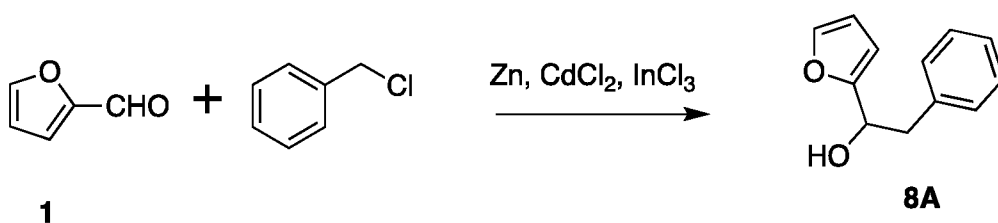


[0543] Compound **7A** (190 mg, 0.486 mmol), EDCI (113 mg, 0.73 mmol) and HOBT (112 mg, 0.73 mmol) were mixed in 5 mL of anhydrous DMF at 0 °C in a ice water bath. Propylamine (28.6 mg, 0.485 mmol) was added to the cold mixture and stirred at 0 °C for 3 hours. The reaction was then allowed to warm up to ambient temperature and stirred overnight. Next morning, the reaction mixture was extracted between ethyl acetate and brine. The organic layer was dried over anhydrous MgSO₄ and then concentrated to give a crude oil. The crude product was purified by silica gel chromatography eluted with hexanes/ethyl acetate = (4:1 to 2:1) to give compound **150** (110 mg) as yellow gum. LC/MS (M+1): 433.1; (M-1): 431.1. ¹H NMR (d₆-DMSO): δ 8.08 (t, 1H), 7.26 (m, 2H), 7.18-7.13 (m, 3H), 7.11-7.07 (m, 1H), 6.90 (t, 2H), 6.75 (d, 1H), 6.47 (d, 2H), 6.41 (t, 1H), 5.68 (d, 1H), 5.42 (d, 1H), 4.70 (m, 1H), 3.31 (s, 3H), 2.06 (m, 2H), 2.88 (m, 1H), 2.76 (m, 1H), 1.40 (m, 2H), 0.81 (m, 3H).

[0544] Example II:

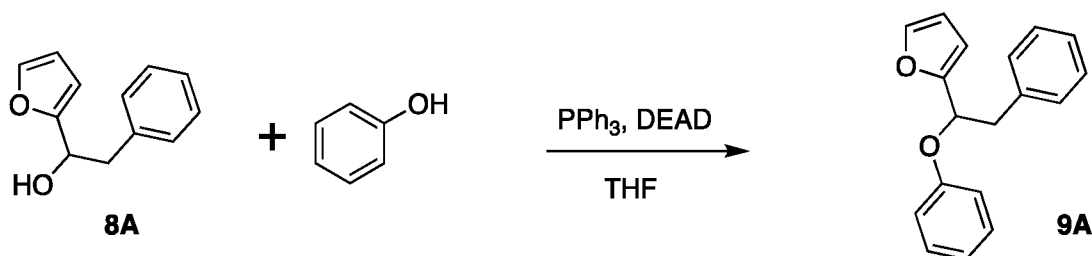


[0545] Step A:



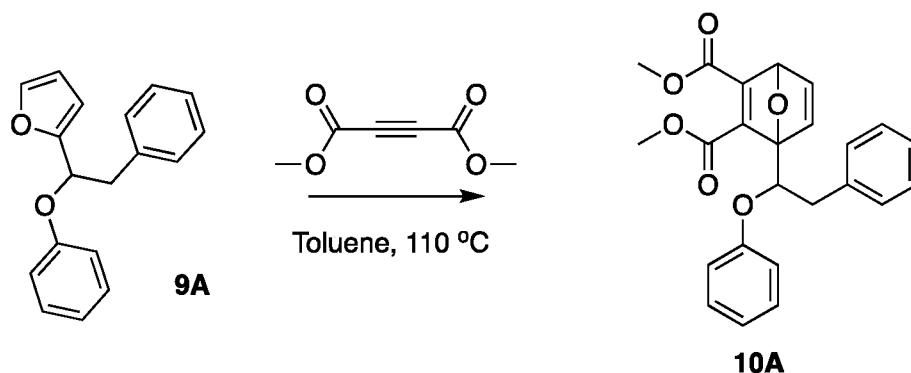
5 [0546] A mixture of 2-Furaldehyde **1** (19.2 g, 200 mmol), benzyl chloride (37.8 g, 300 mmol), zinc dust (19.5 g, 300 mmol), cadmium chloride (36.6 g, 200 mmol), indium chloride (2.2 g, 10 mmol) in distilled water (500 mL) was stirred at room temperature overnight. The mixture was filtered and the filtrate was concentrated, the residue was purified by silica gel column (Hexanes/ EtOAc = 8:1) to give compound **8A** (15 g, 80 mmol, 40% yield) as a
 10 yellow oil.

[0547] Step B:



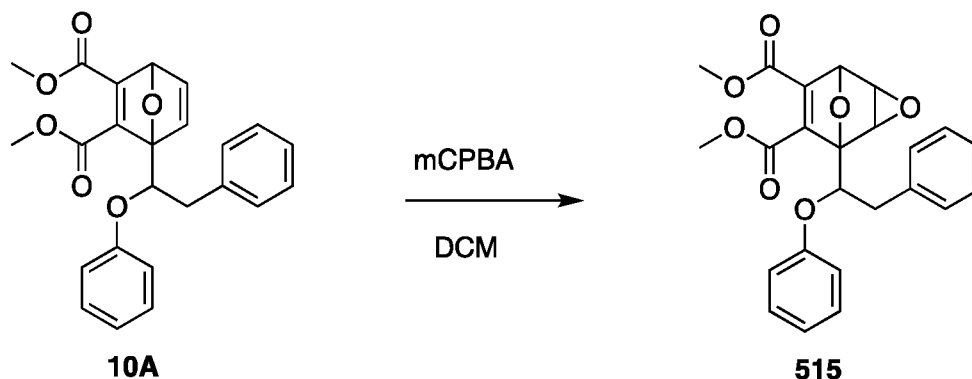
[0548] A solution of compound **8A** (15 g, 80 mmol), phenol (7.5 g, 80 mmol), triphenylphosphine (23 g, 88 mmol) in anhydrous THF (300 mL) was cooled 0°C, then
 15 diethyl azodicarboxylate (16.7 g, 96 mmol) was added slowly to the mixture. The reaction mixture was stirred at room temperature overnight and then concentrated. The product was purified by silica gel chromatography eluted with hexanes/ethyl acetate = 9:1 to 6:1 give compound **9A** (15.5 g, 73% yield) as yellow oil.

[0549] Step C:



[0550] Compound **9A** (15 g, 56.8 mmol) in 100 mL anhydrous toluene was heated to 110 °C, then dimethyl acetylenedicarboxylate (12 g, 85.2 mmol) was added and the mixture was
 5 refluxed overnight. The solvents were evaporated *in vacuo*, and the crude product was purified by silica gel chromatography eluted with hexanes/ethyl acetate = 5:1 to give a yellow oil, which was sequentially recrystallized from methanol to give **10A** as a white solid (4.3 g, 19% yield). ¹H NMR (d₆-DMSO): δ 7.4-6.6 (m, 12H), 5.7 (m, 1H), 5.4 (m, 1H), 3.7 (s, 3H), 3.55 (s, 3H), 3.1 (m, 2H).

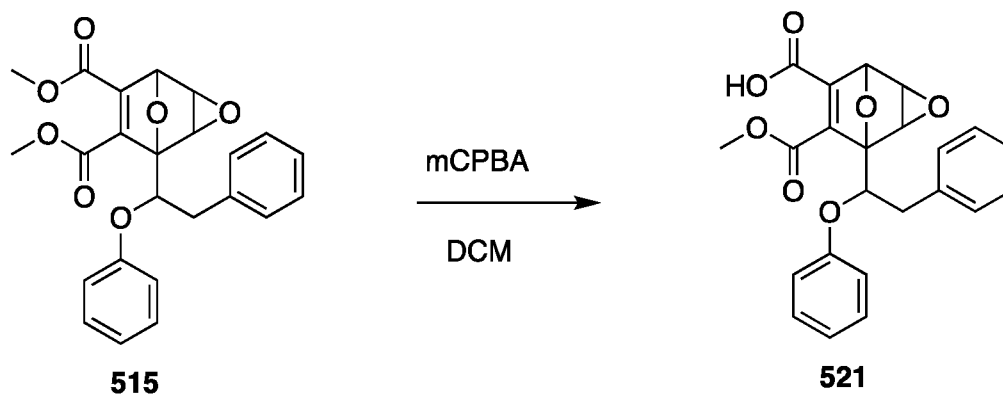
10 [0551] Step D:



[0552] Compound **10A** (4.3 g, 10.6 mmol) was dissolved in 100 mL anhydrous dichloromethane and the mixture was cooled to 0 °C, then *meta*-Chloroperoxybenzoic acid (3.1 g) was added and the mixture was then stirred at room temperature overnight. The
 15 organic solvents were then evaporated *in vacuo*, and the remaining mixture was dissolved in ethyl acetate (50 mL) and then washed with saturated sodium bicarbonate (5 x 50 mL). The organic layer was dried over anhydrous MgSO₄ and then concentrated to give a crude oil. The crude product was purified by silica gel chromatography eluted with hexanes/ethyl acetate/triethylamine = 5:1:0.01 to give compound **515** (1.9 g, 42% yield) as white solid. ¹H

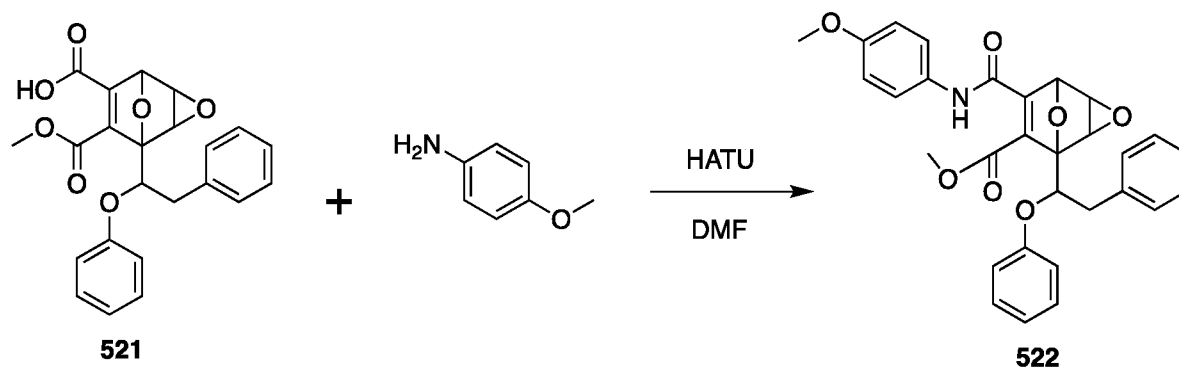
NMR (CDCl₃): δ 7.4-6.7 (m, 10H), 5.3 (m, 1H), 5.2 (m, 1H), 3.80 (s, 3H), 3.75 (m, 1H), 3.65 (m, 1H), 3.55 (s, 3H), 3.2 (m, 2H).

[0553] Step E:



5 [0554] Compound **515** (1.9 g, 4.5 mmol) was dissolved in THF (50 mL) and cooled to 0 °C, then NaOH (198 mg, 4.95 mmol) in distilled water (50 mL) was added. The reaction was then allowed to warm up to ambient temperature and stirred for 1 hour. The mixture was neutralized with 1 M HCl, and the THF was evaporated. The remaining aqueous layer was acidified to pH 4, then extracted with ethyl acetate (50 mL). The organic layer was washed with brine (50 mL), then dried over anhydrous MgSO₄ and then concentrated to give a crude oil. The crude product was purified by silica gel chromatography eluted with ethyl acetate/methanol/acetic acid = 9:1:0.5 to give compound **521** (1.5 g, 82%) as orange solid. LC/MS (M-1): 407.2.

[0555] Step E:



15 [0556] Compound **521** (23 mg, 0.056 mmol), HATU (28 mg, 0.073 mmol) and p-anisidine (8 mg, 0.062 mmol) were mixed at 0 °C in DMF (2 mL), then the mixture was stirred at room temperature for 1 hour. The mixture was extracted between ethyl acetate (20 mL) and brine

(20 mL), the organic layer was dried over MgSO₄ and was then concentrated, the residue was purified by silica gel column (Hexanes/ EtOAc = 3:1) to give compound **8A** (17 mg, 59% yield) as a yellow solid. LC/MS (M+1): 515.1. ¹H NMR (d₆-DMSO): δ 10.3 (s, 1H), 7.6-6.5 (m, 14H), 5.5 (m, 1H), 5.4 (s, 1H), 4.1 (m, 1H), 3.9 (m, 1H), 3.5 (s, 3H), 3.2 (s, 3H), 3.2-3.0 (m, 2H).

[0557] When incubating such compounds with the activating enzymes (E1) of ubiquitin, SUMO, Nedd8, Urm1, ISG15 or Atg7, it forms covalent adducts with the specific Cys residue (e.g., an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2, or an amino acid corresponding to the Cys residue highlighted and in bold in SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7) as depicted herein.

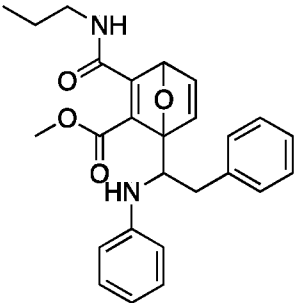
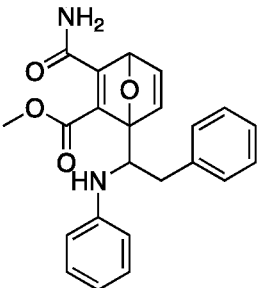
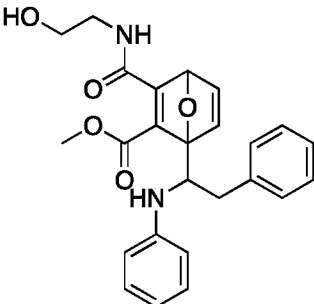
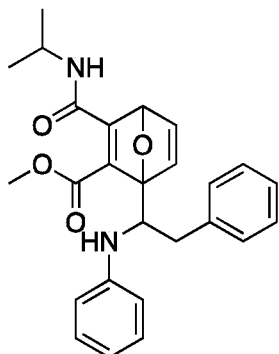
[0558] For the compounds provided herein including embodiments thereof, a covalent adduct may be formed with a cysteine amino acid corresponding to a Cys residue highlighted and in bold from Uba1, Uba2, Uba3, Uba4, Uba7 or Atg7 as shown in the sequence alignment below.

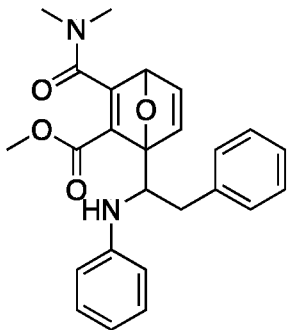
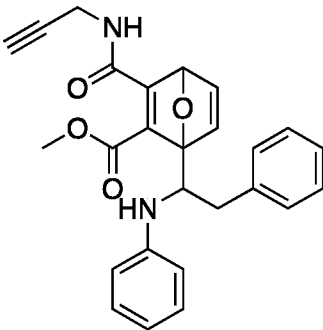
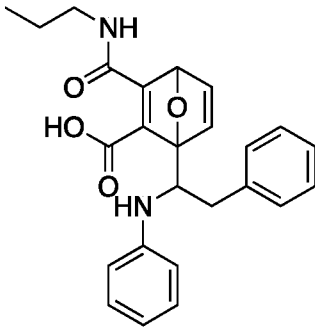
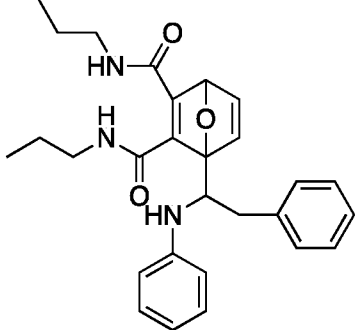
Uba1 (ubiquitin)	LVGAGAI G CELLK	(SEQ ID NO:2)
Uba2 (SUMO)	VVGAGGI G CELLK	(SEQ ID NO:3)
Uba3 (Nedd8)	VIGAGGL G CELLK	(SEQ ID NO:4)
Uba4 (Urm1)	IVGCGGL G CPLAQ	(SEQ ID NO:5)
Uba7 (ISG15)	LVGAGAI G CELLK	(SEQ ID NO:6)
Atg7 (Atg8, Atg12)	LLGAGTL G CNVAR	(SEQ ID NO:7)

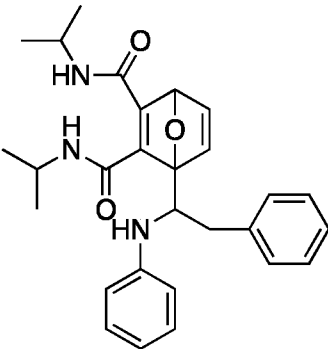
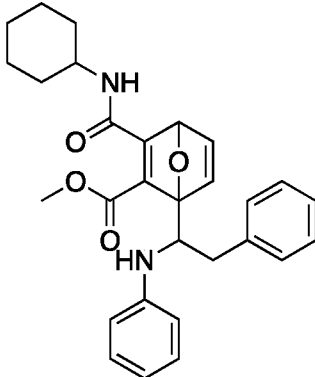
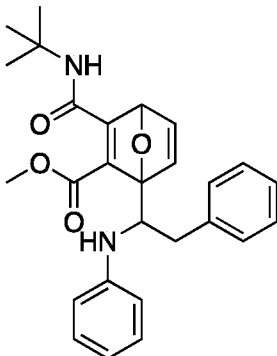
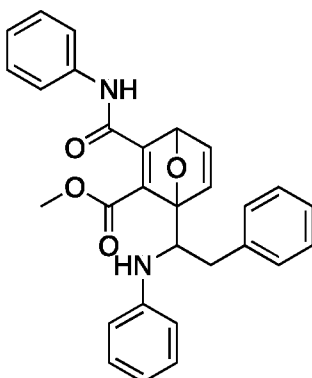
B. Example 2. Compounds

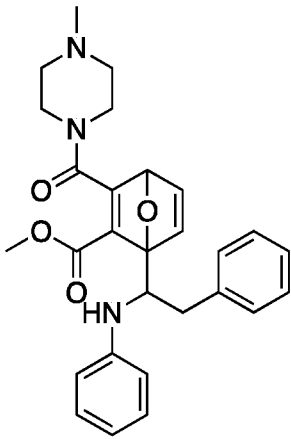
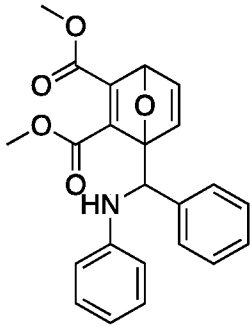
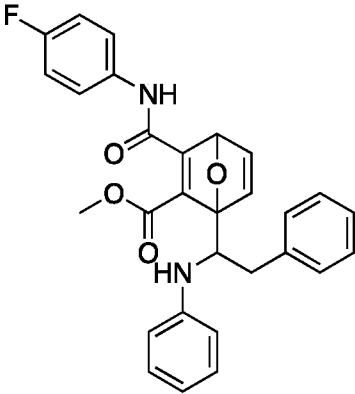
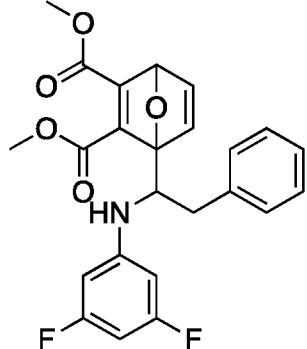
[0559] Table I: compounds synthesized and biological activities.

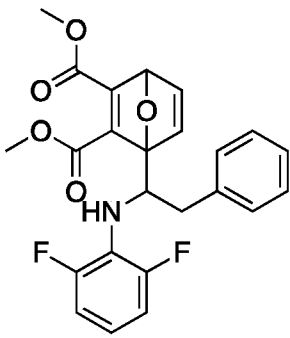
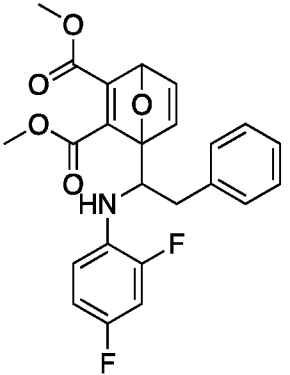
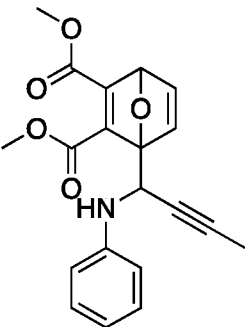
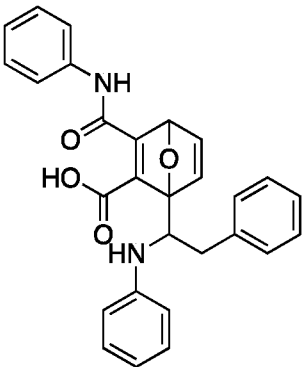
[0560] Activities are listed as + (less active), ++ (active), +++ (most active)

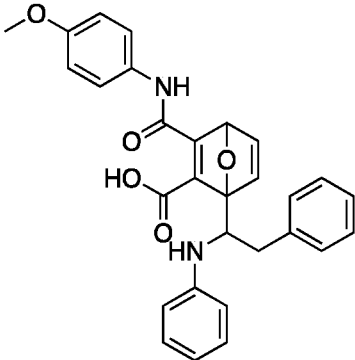
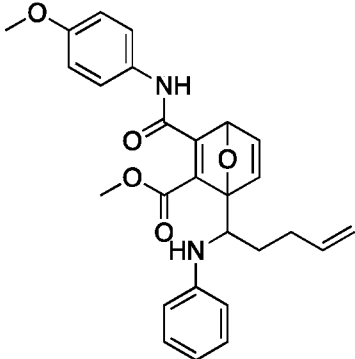
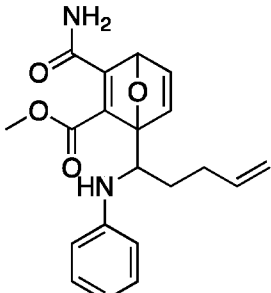
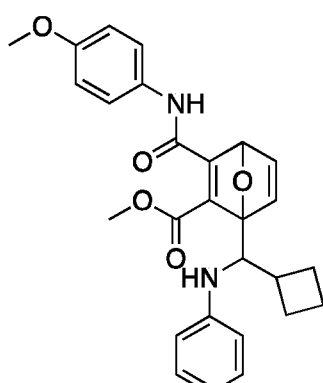
Compound number	Structure	SUMO	Nedd8	Atg7	Ubiquitin	c-Myc
150		++				
151		++				+
152		++				
153		++				

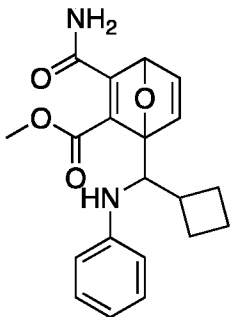
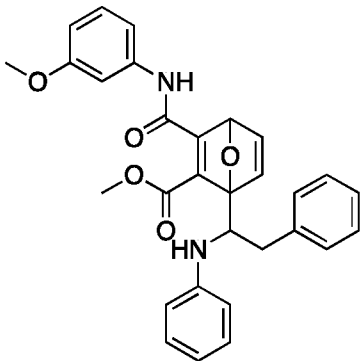
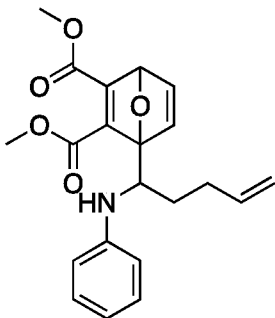
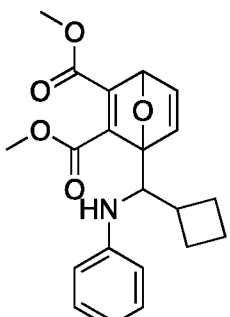
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155		++				
156						
157		+				

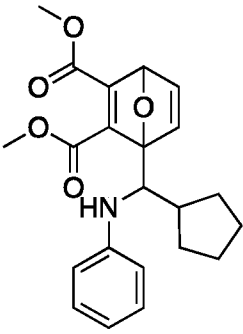
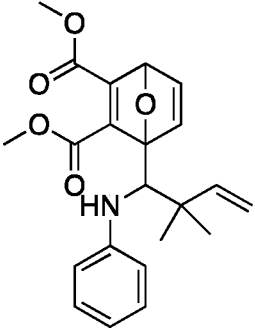
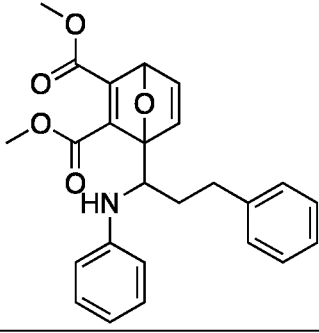
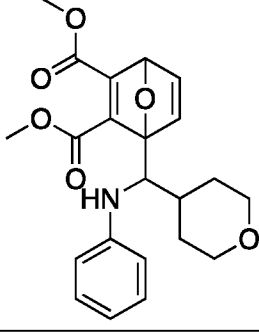
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160		+				+
161		+				+
163		++				+

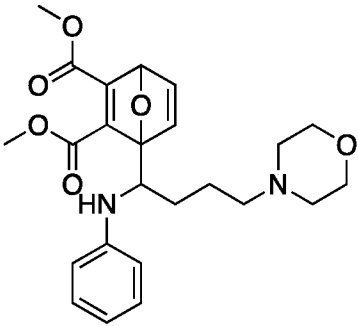
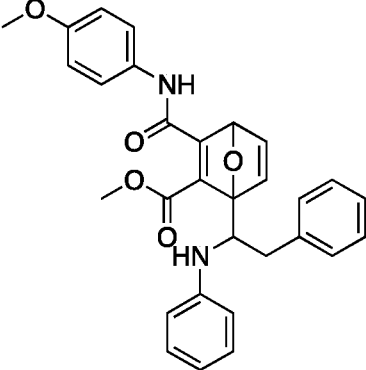
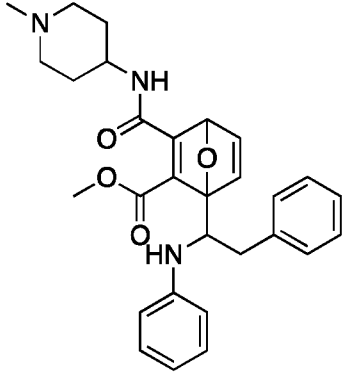
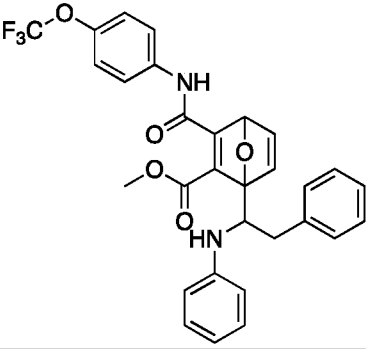
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167		++				+

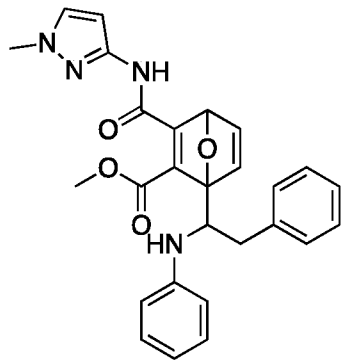
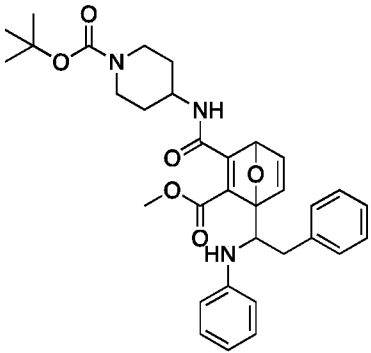
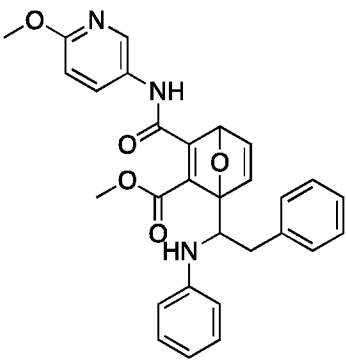
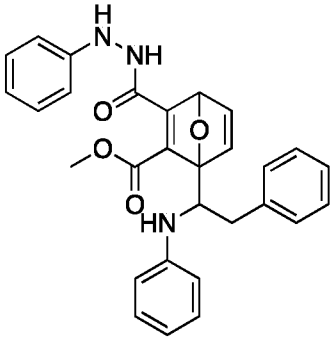
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172		++				++
174		+				

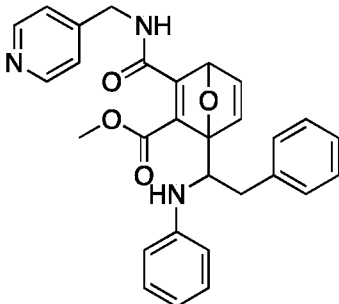
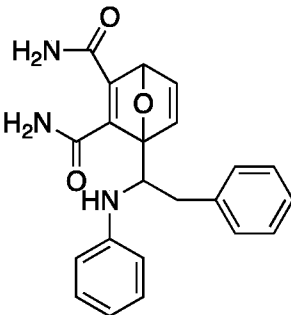
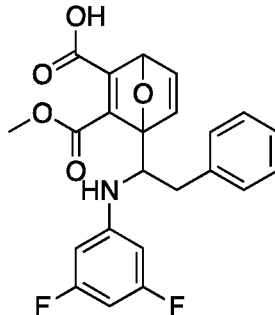
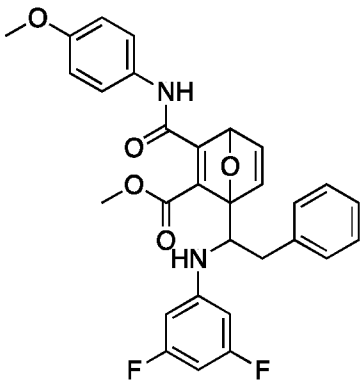
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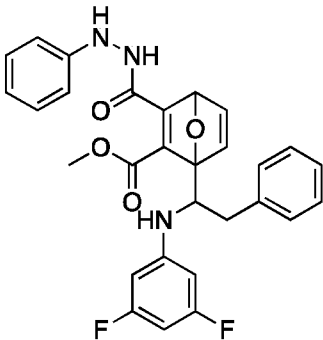
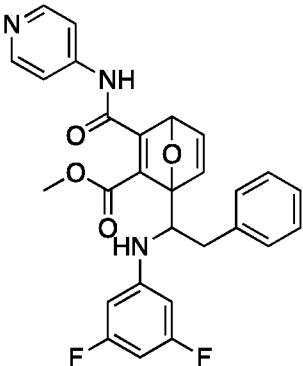
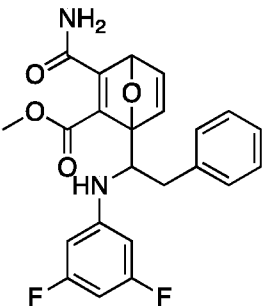
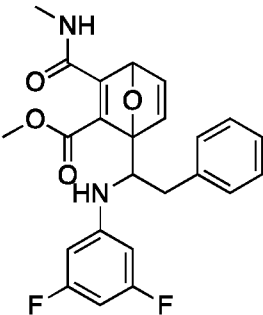
179		+				+
180		+				+
181		++				+
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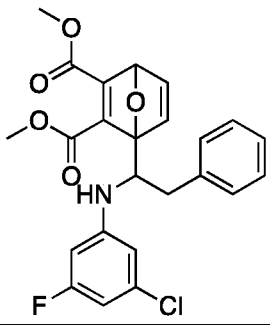
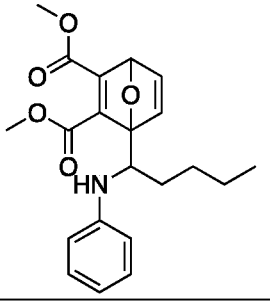
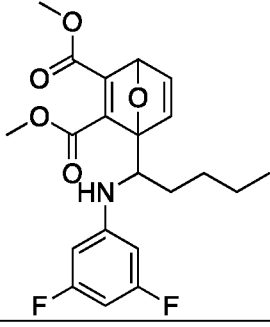
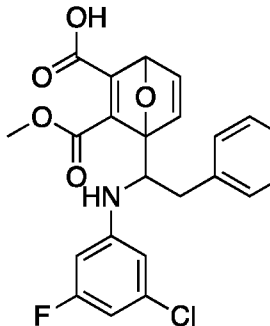
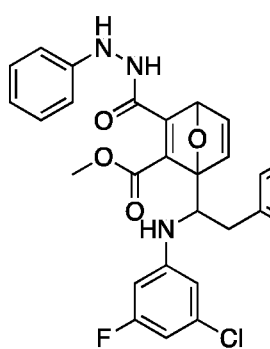
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192		++				

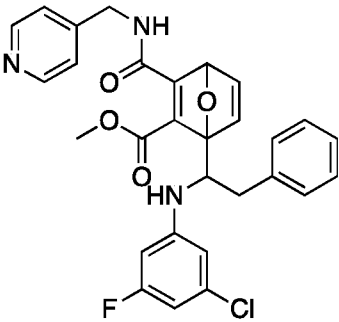
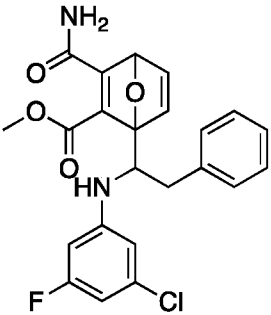
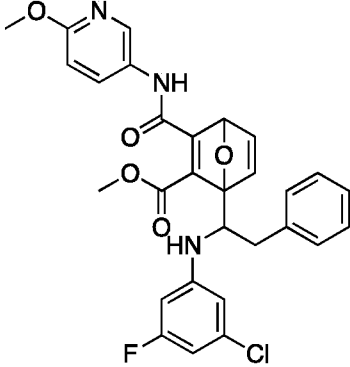
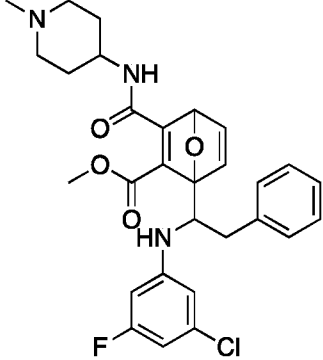
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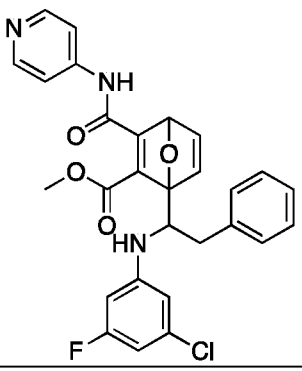
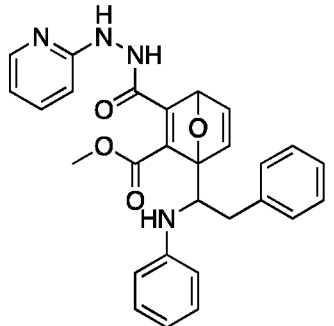
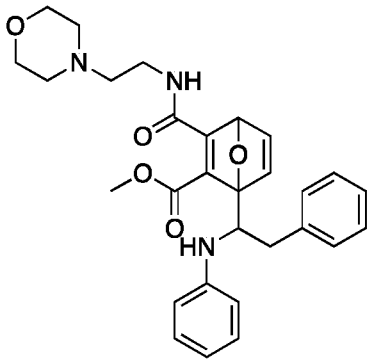
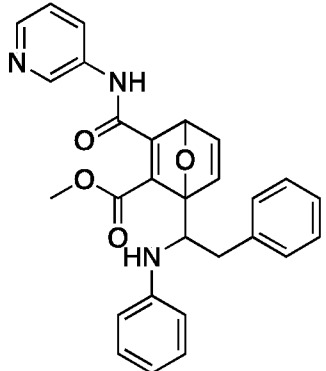
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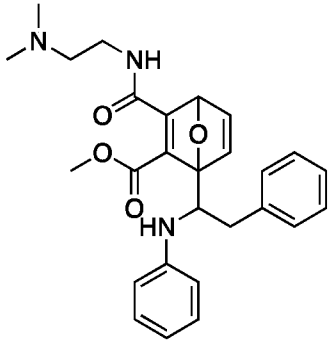
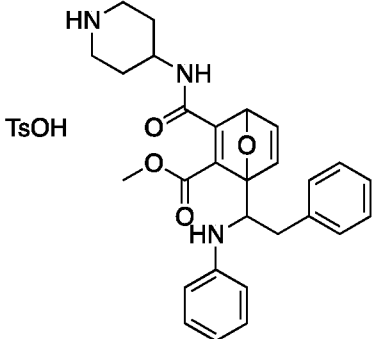
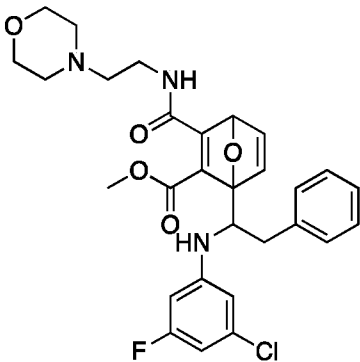
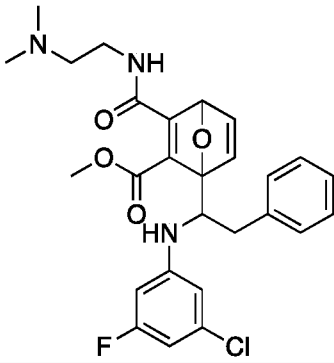
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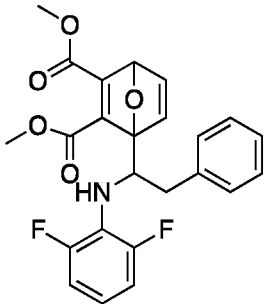
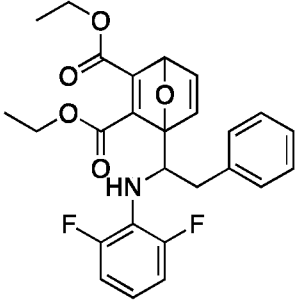
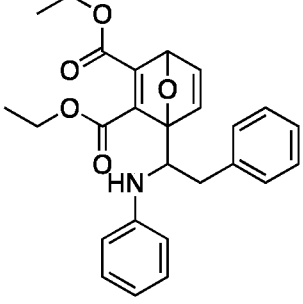
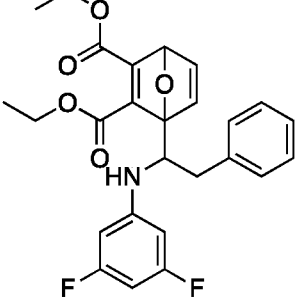
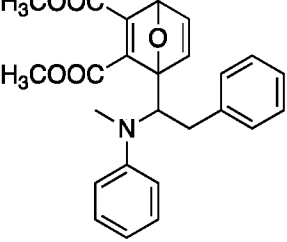
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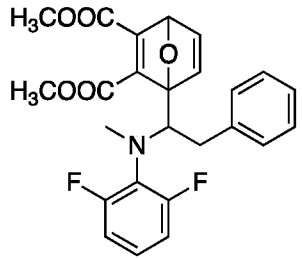
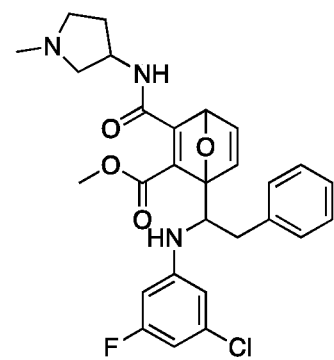
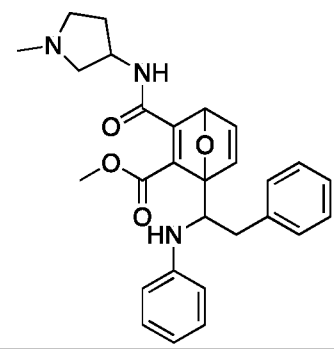
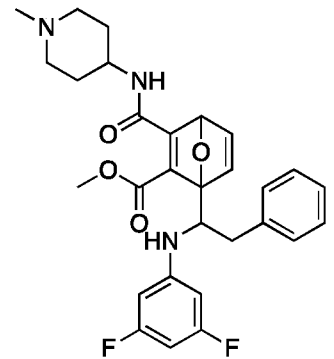
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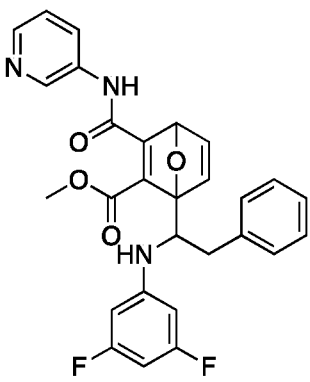
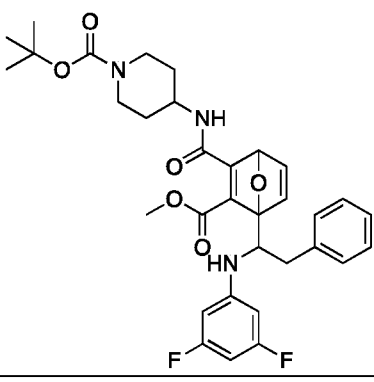
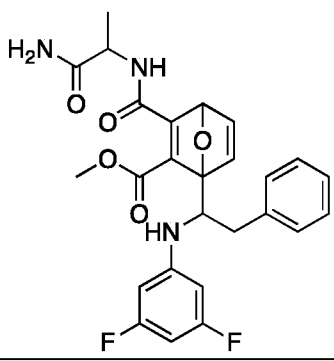
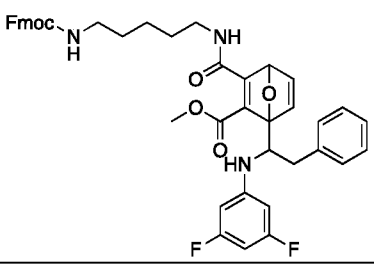
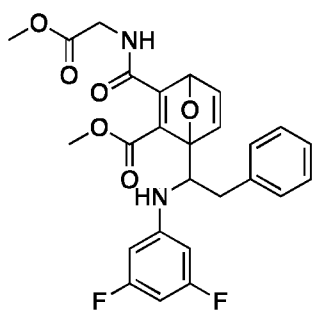
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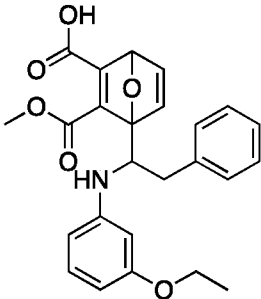
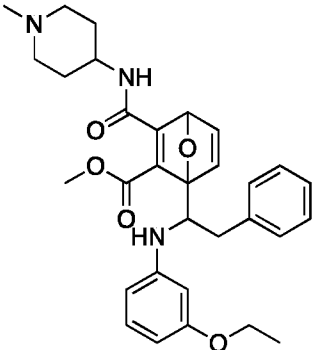
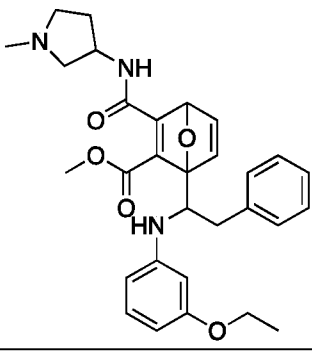
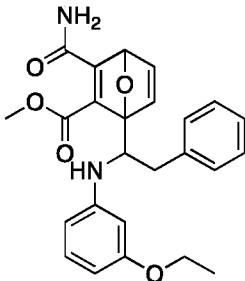
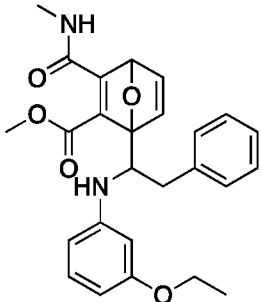
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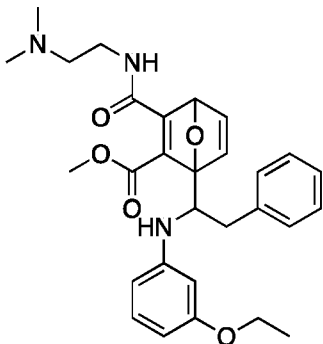
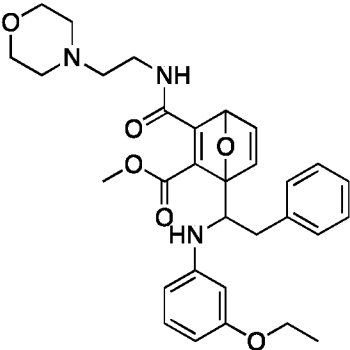
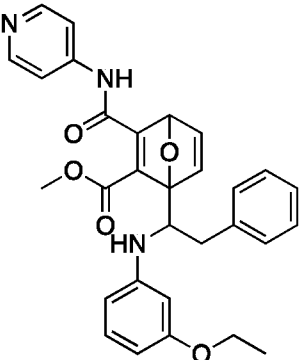
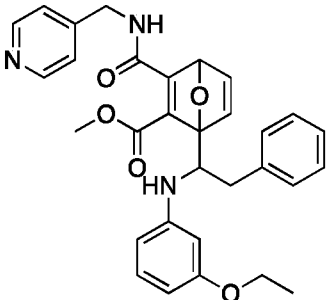
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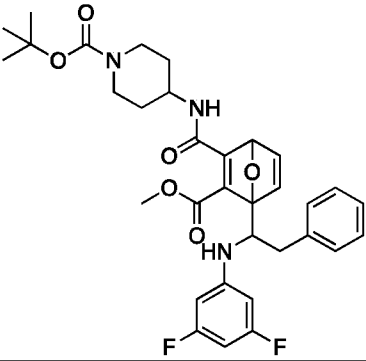
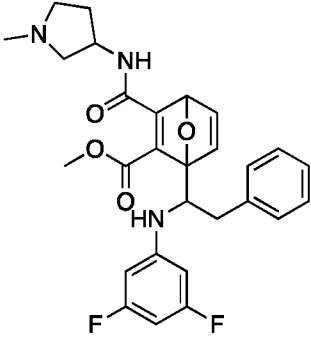
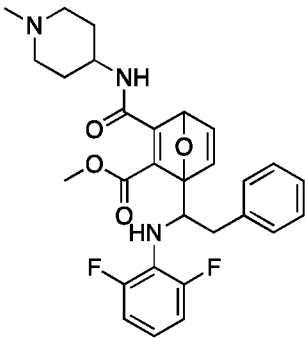
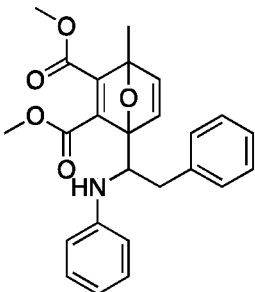
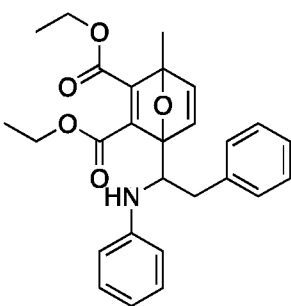
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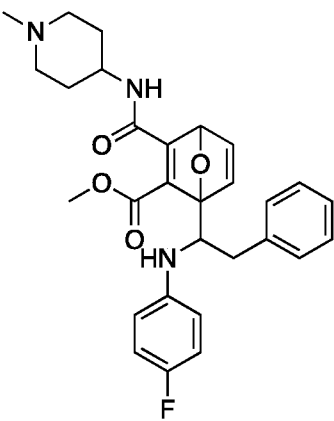
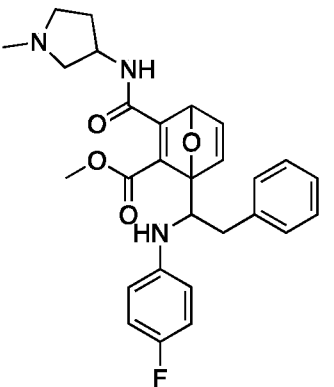
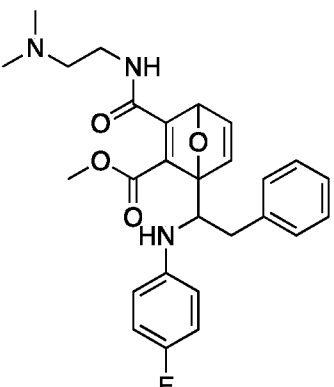
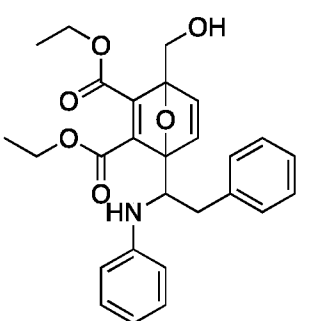
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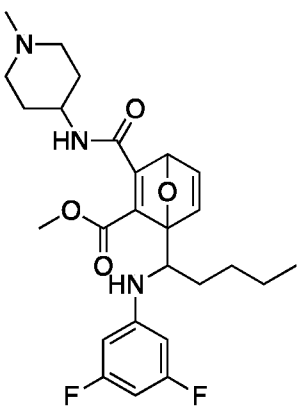
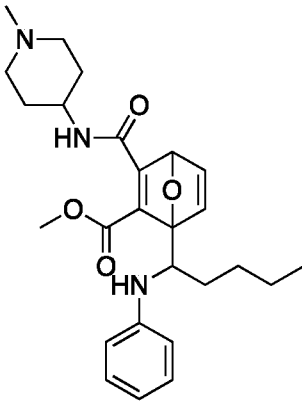
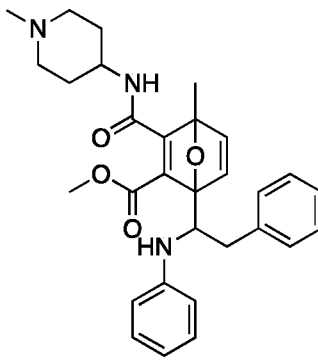
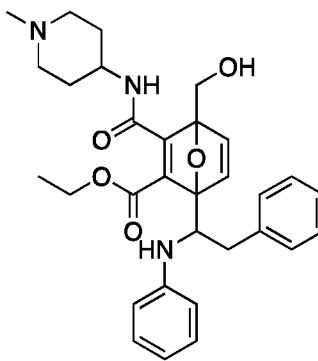
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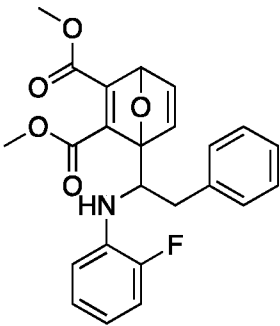
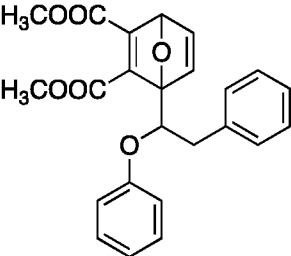
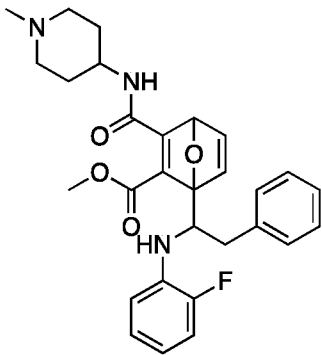
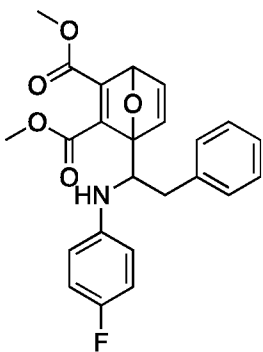
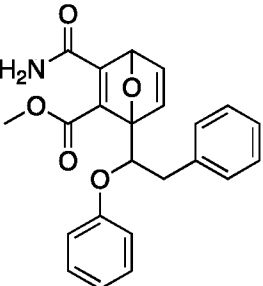
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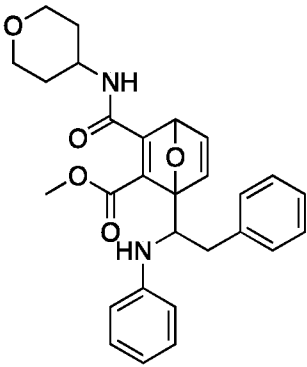
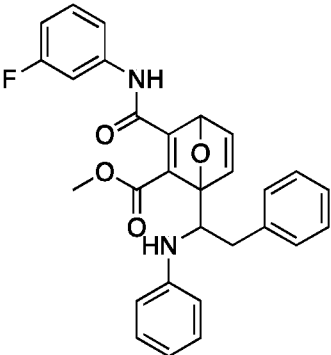
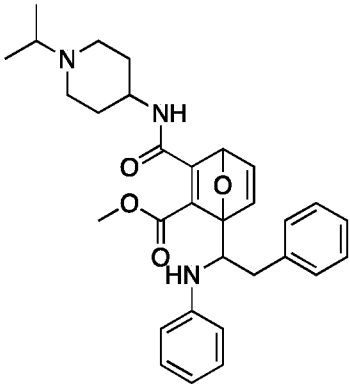
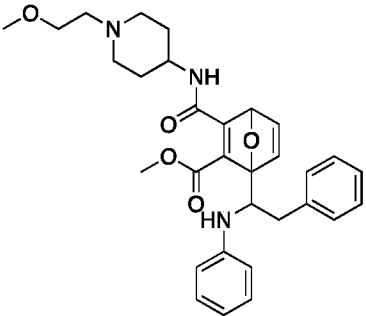
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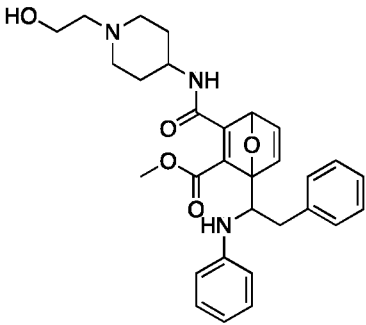
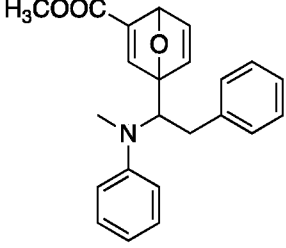
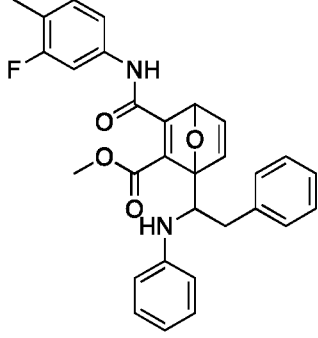
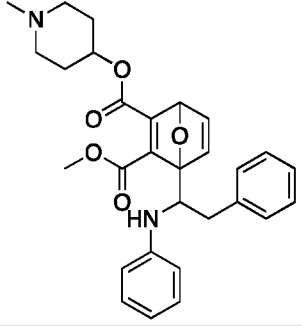
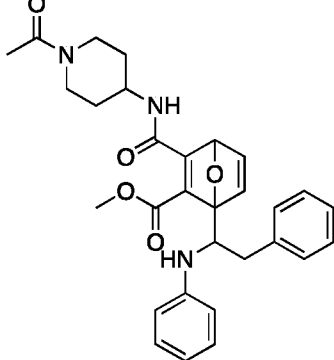
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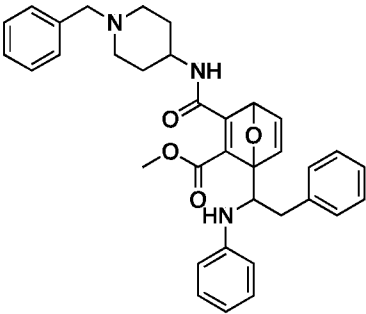
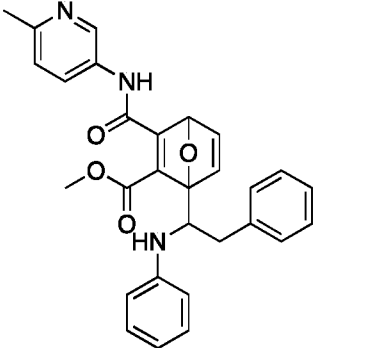
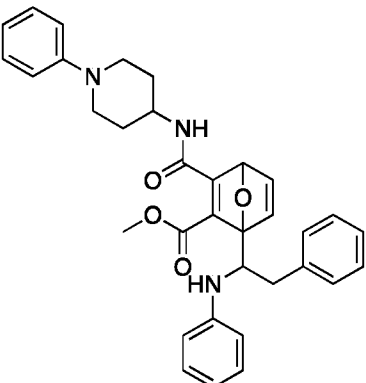
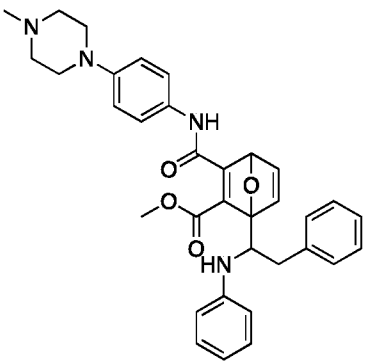
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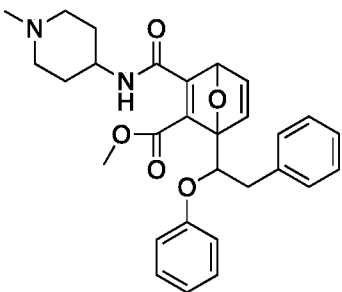
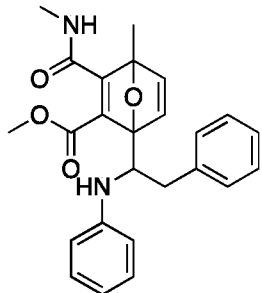
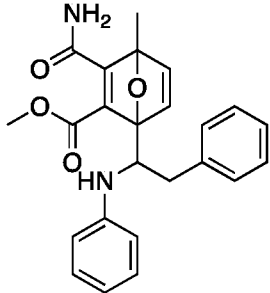
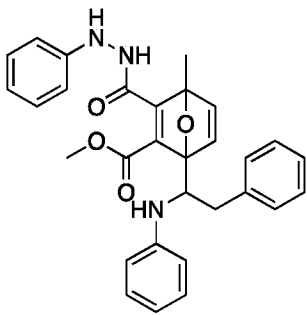
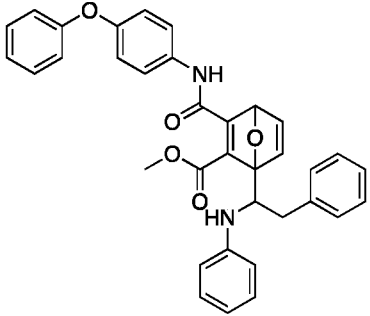
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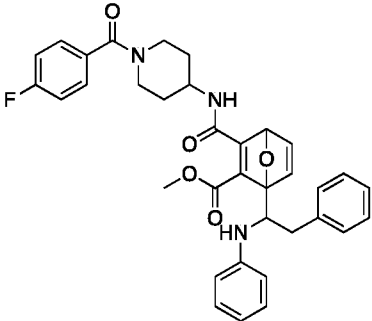
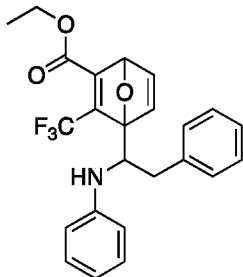
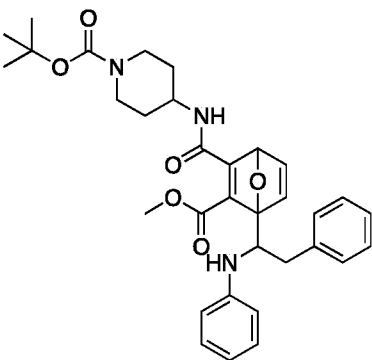
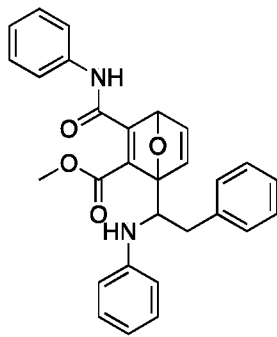
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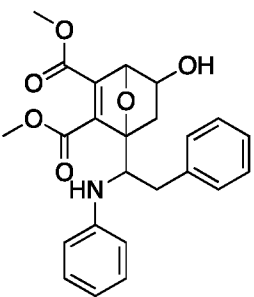
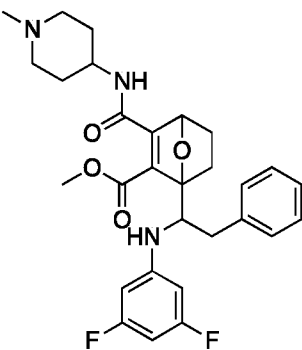
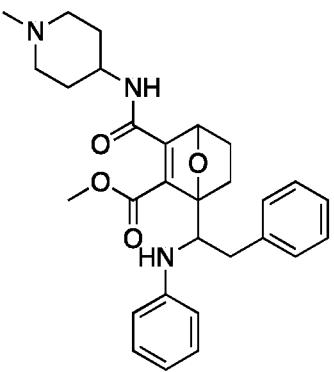
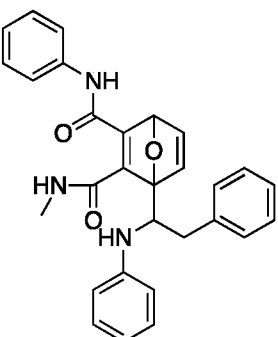
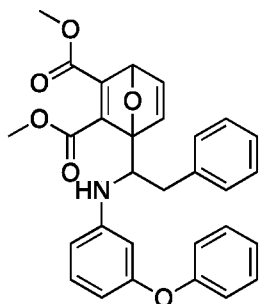
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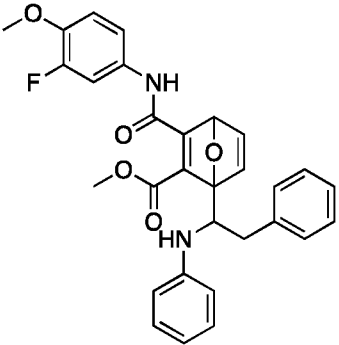
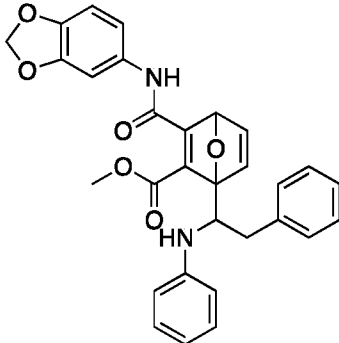
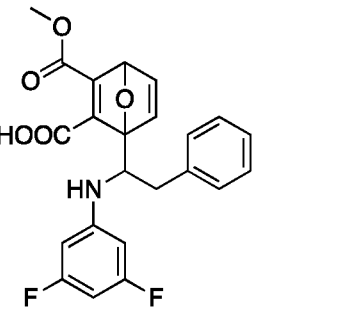
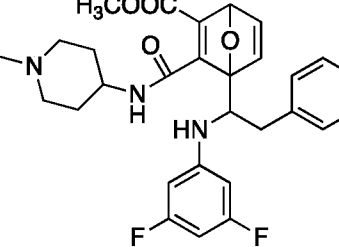
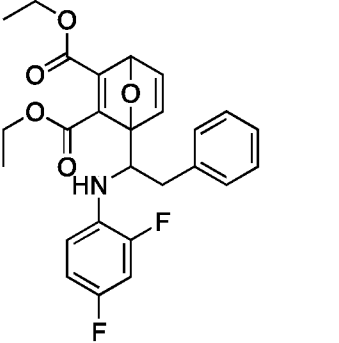
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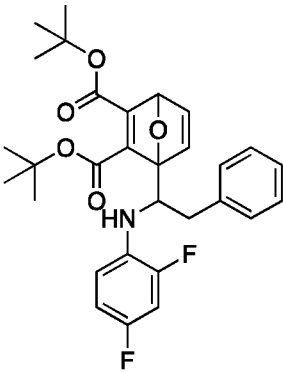
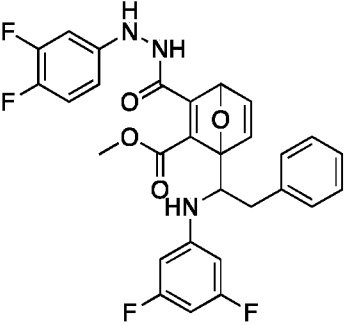
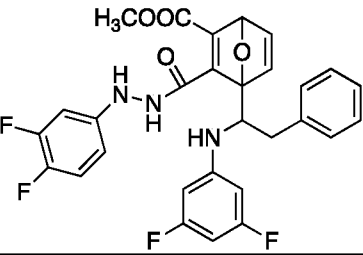
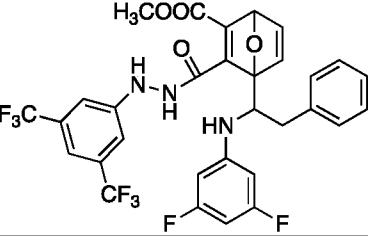
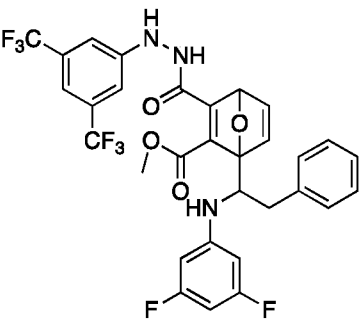
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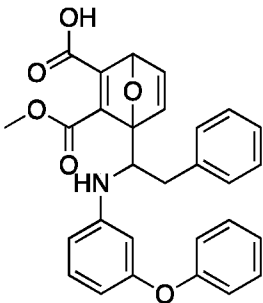
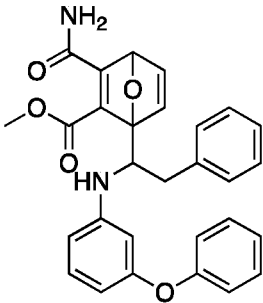
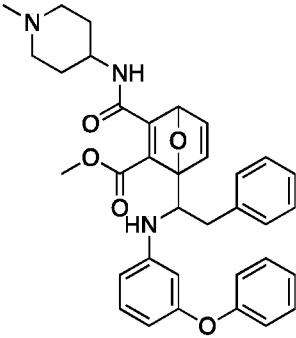
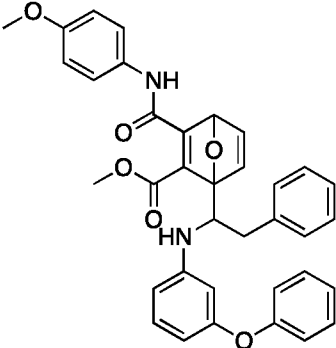
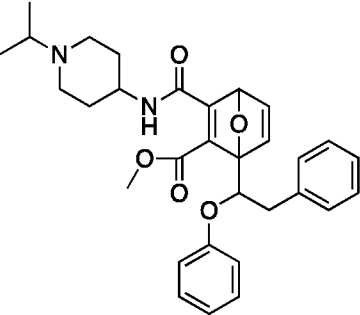
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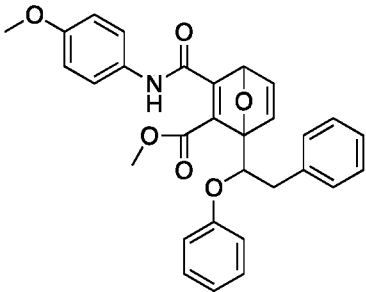
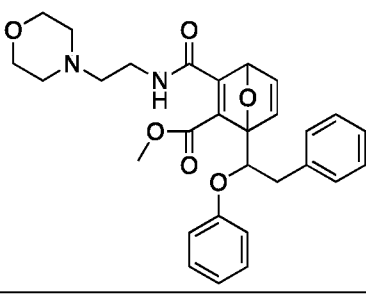
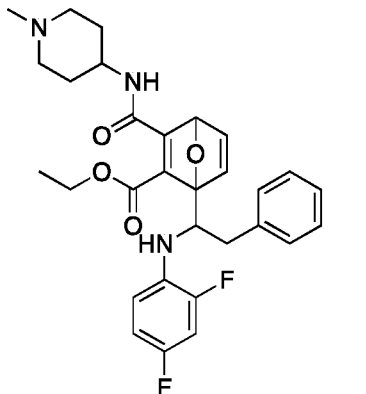
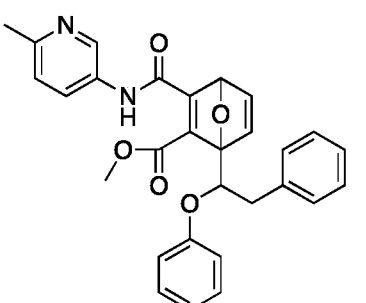
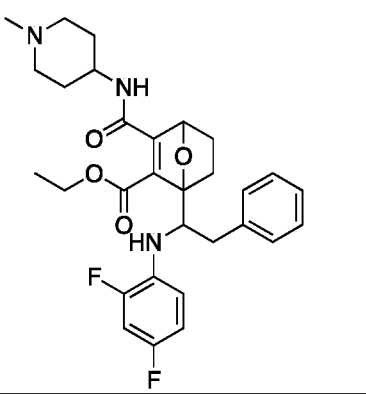
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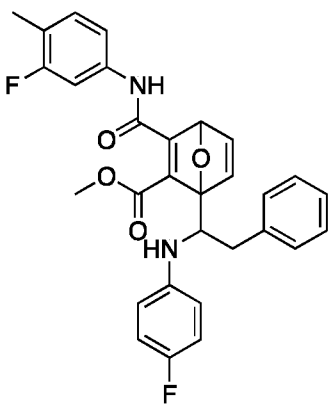
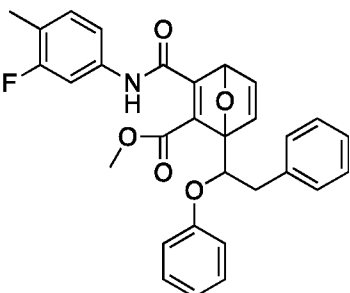
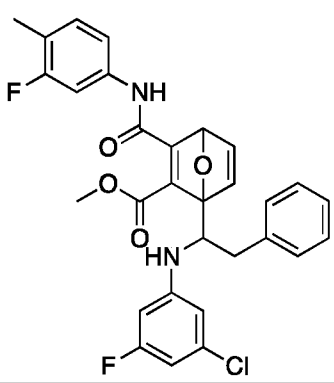
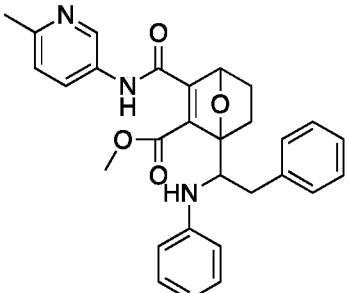
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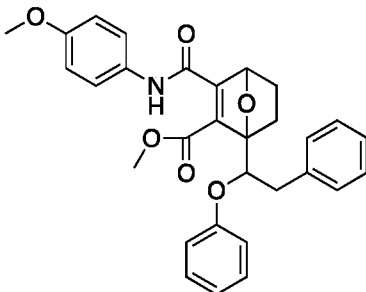
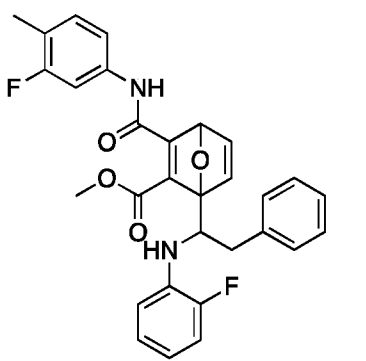
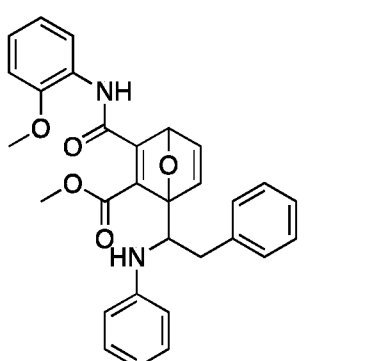
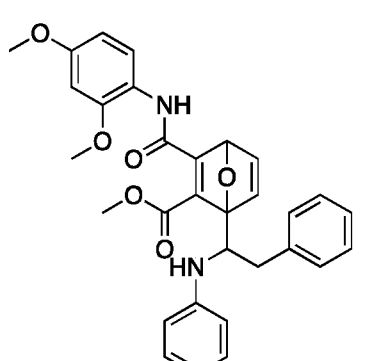
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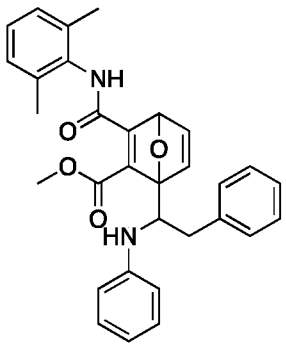
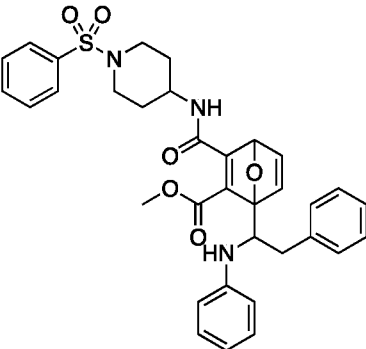
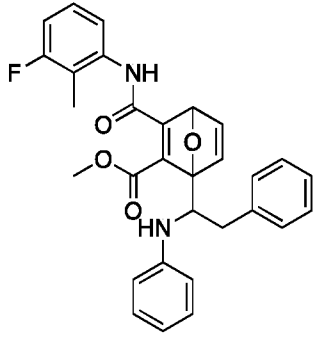
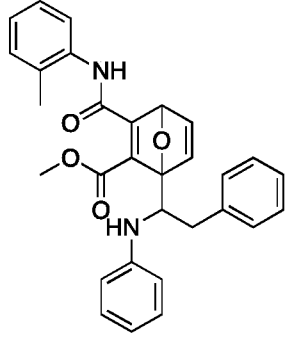
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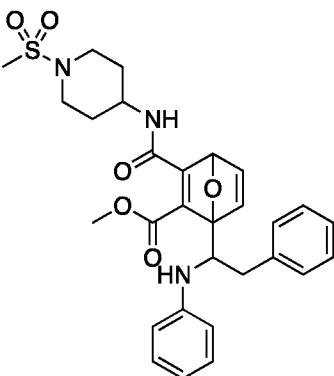
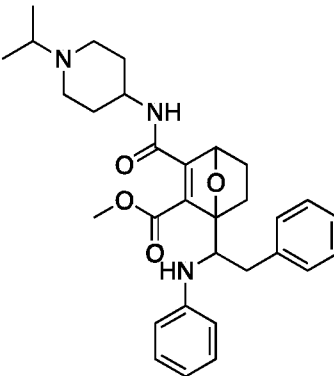
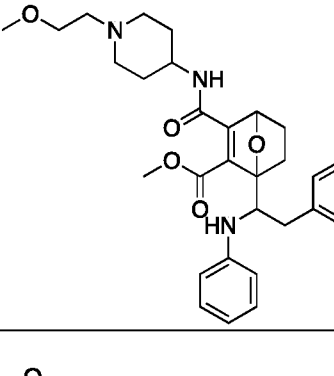
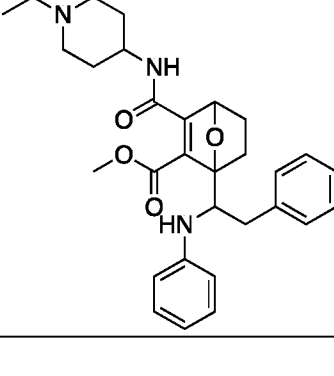
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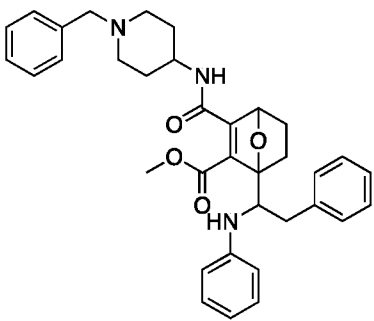
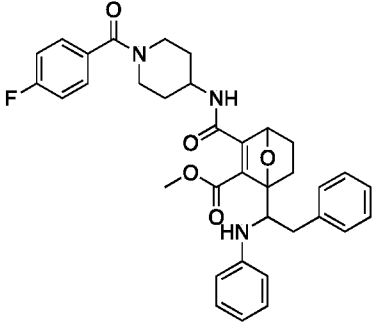
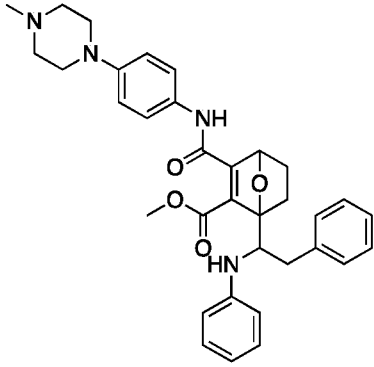
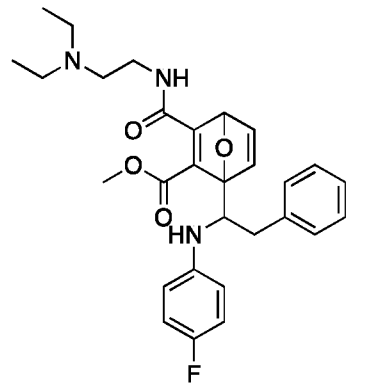
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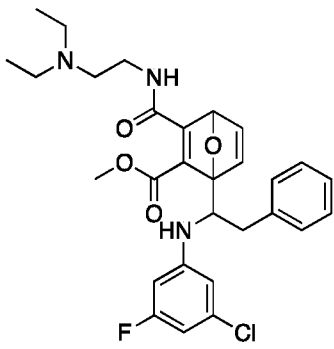
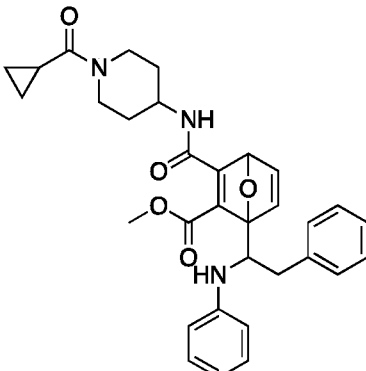
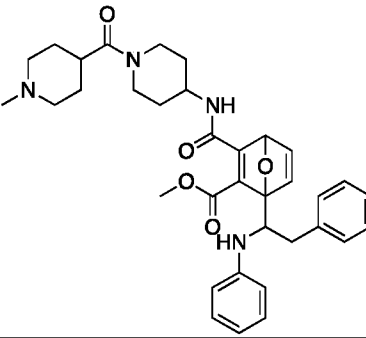
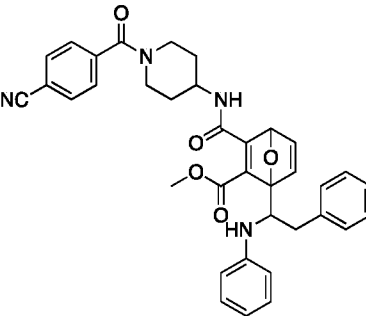
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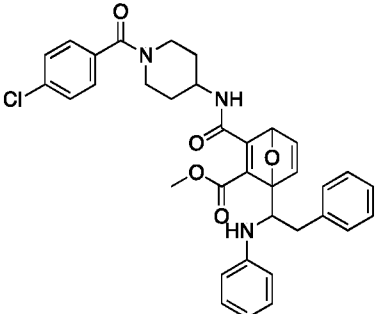
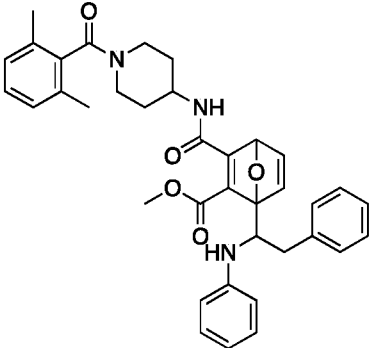
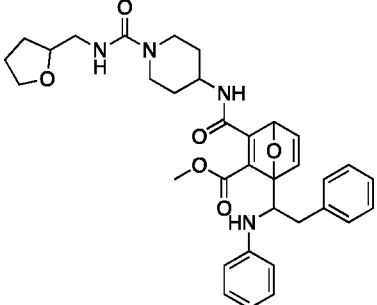
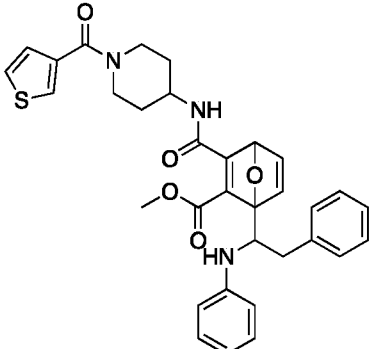
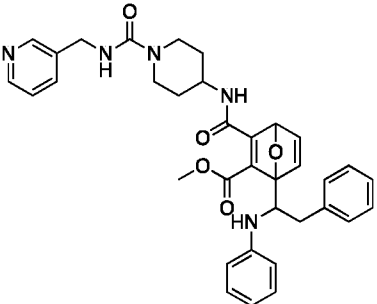
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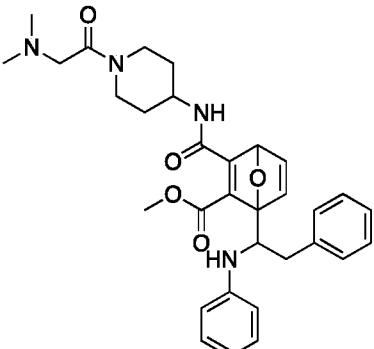
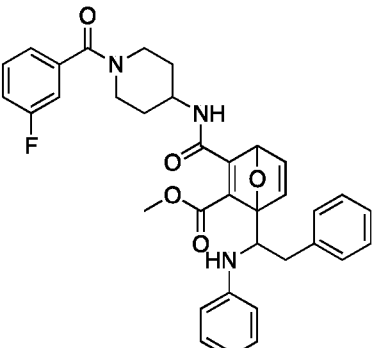
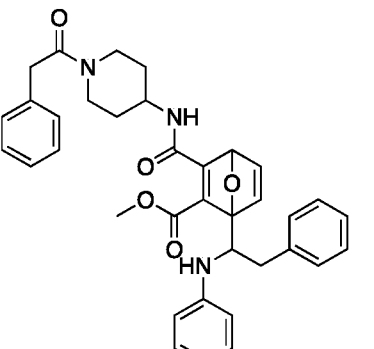
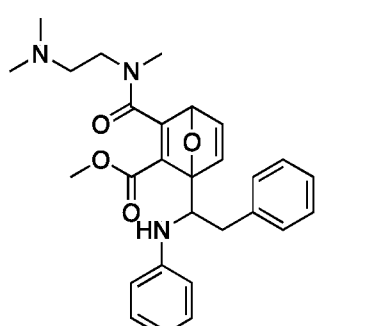
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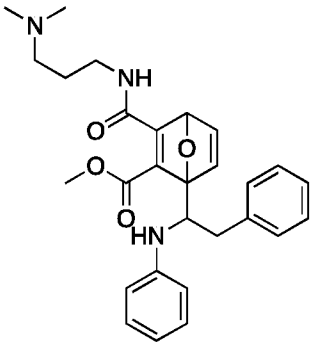
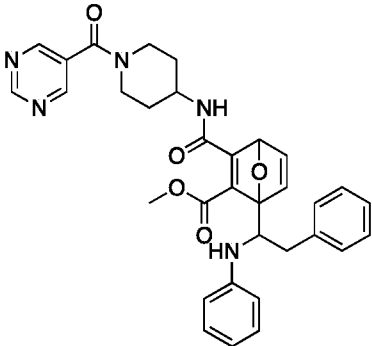
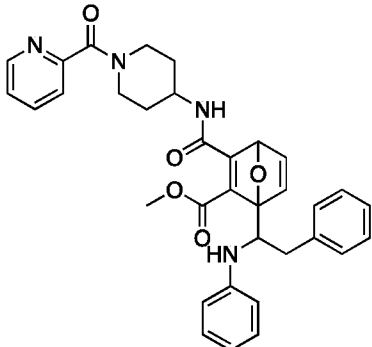
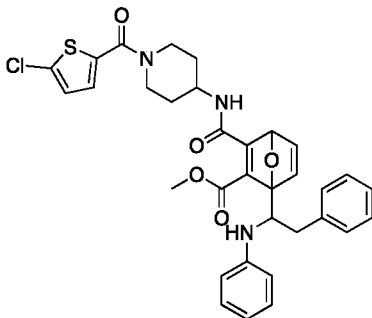
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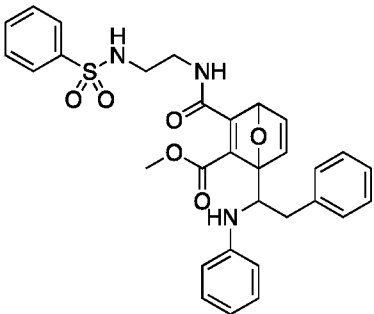
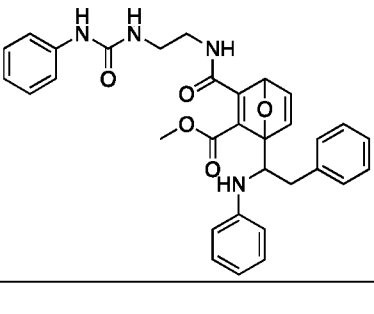
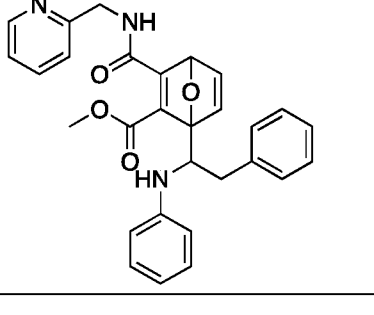
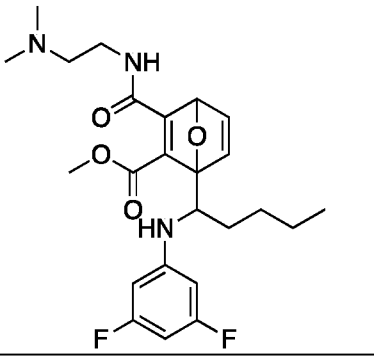
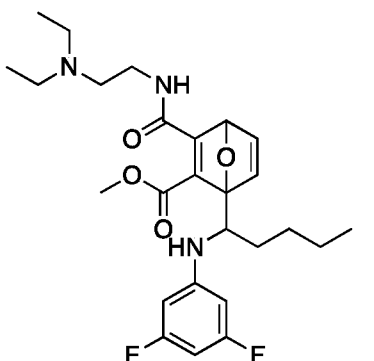
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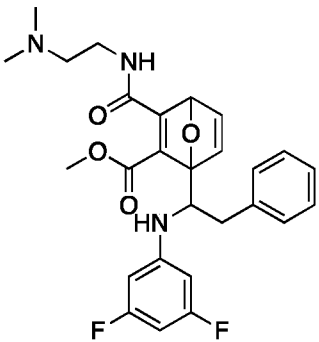
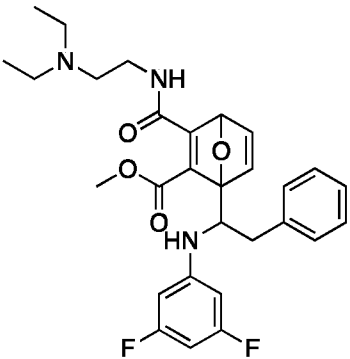
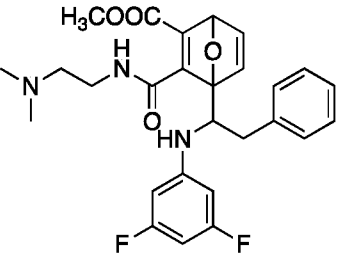
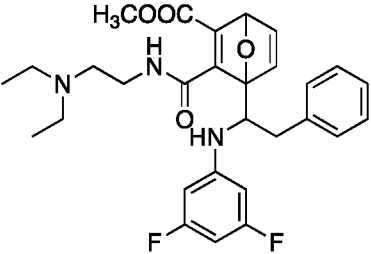
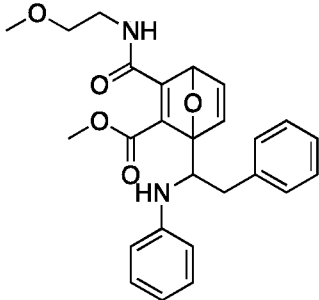
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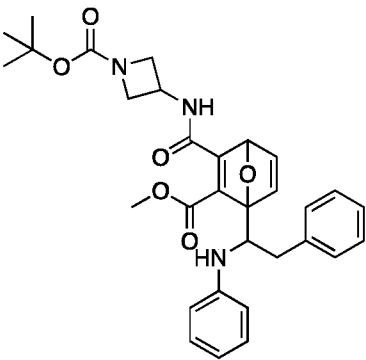
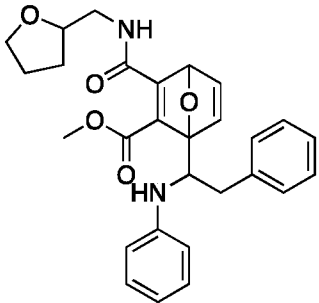
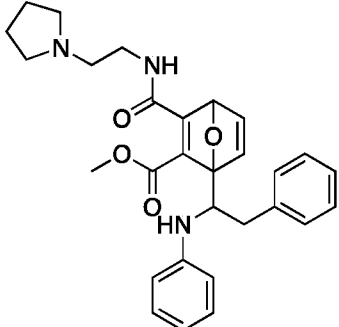
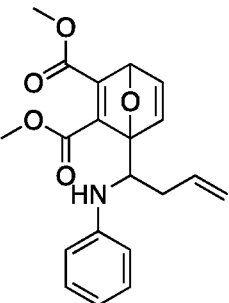
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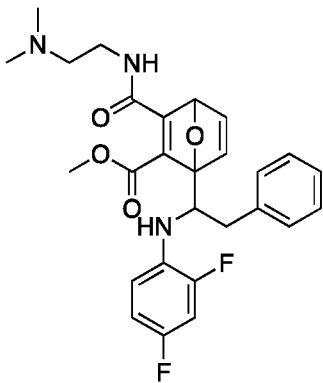
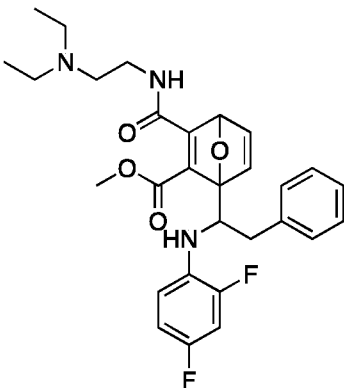
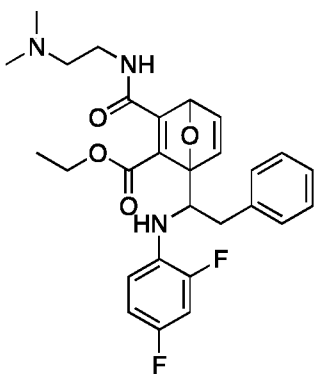
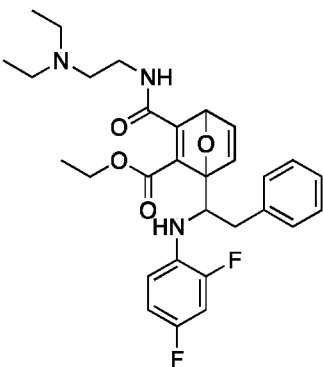
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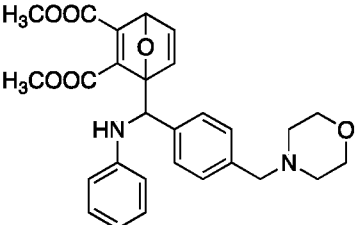
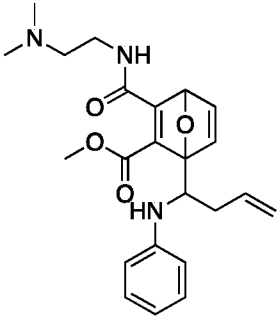
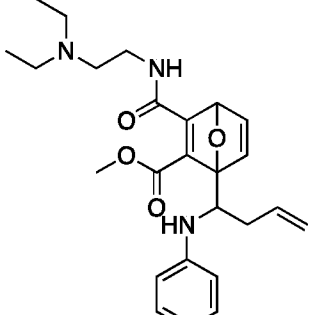
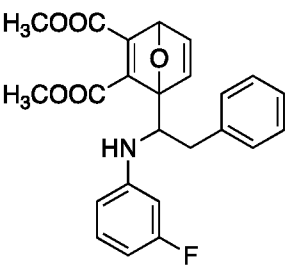
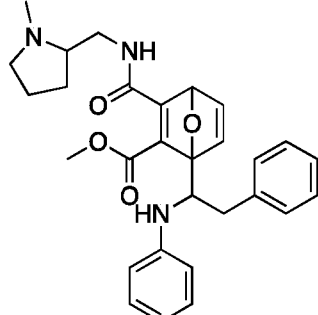
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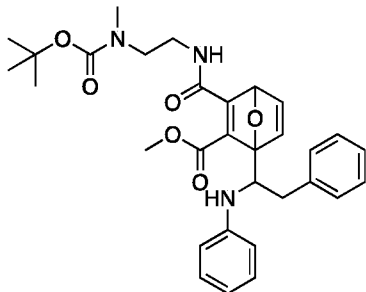
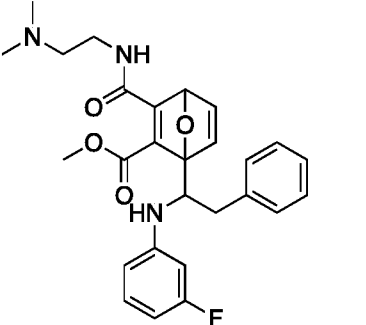
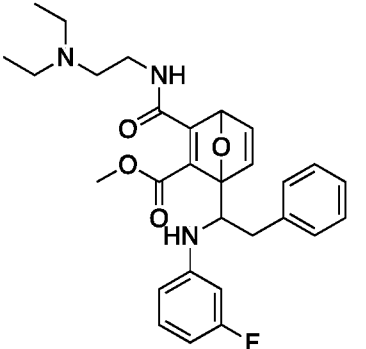
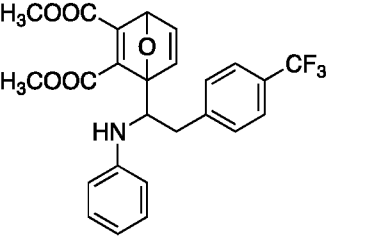
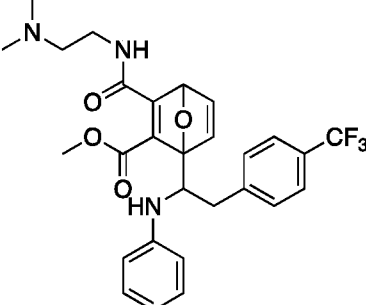
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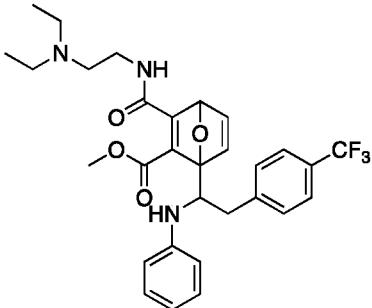
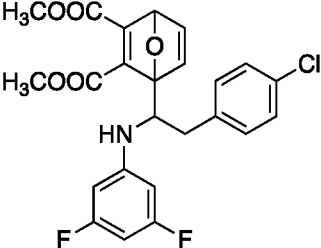
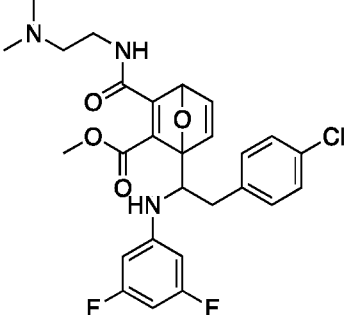
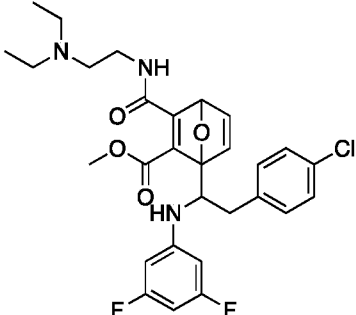
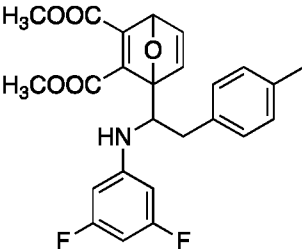
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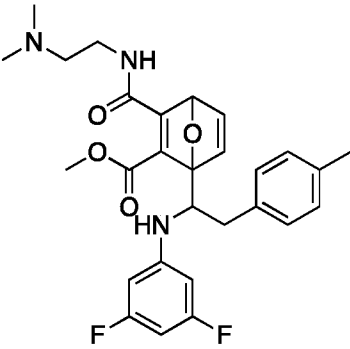
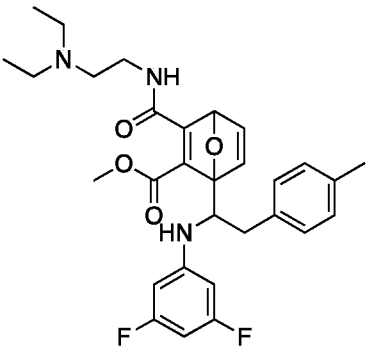
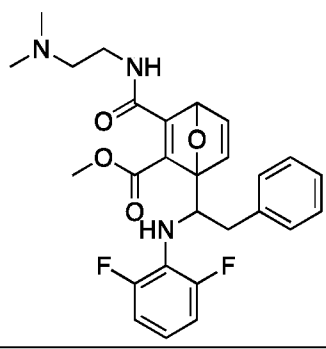
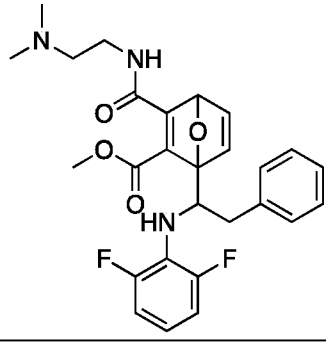
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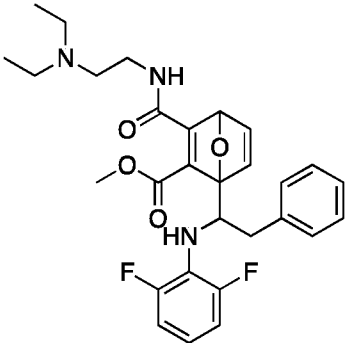
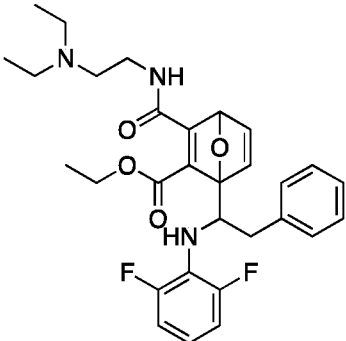
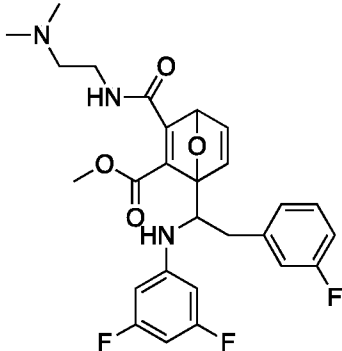
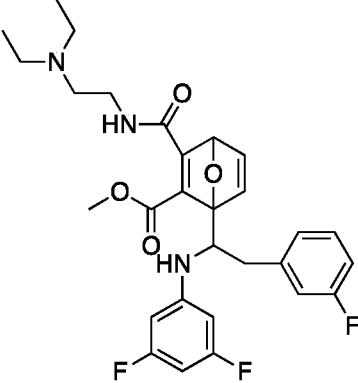
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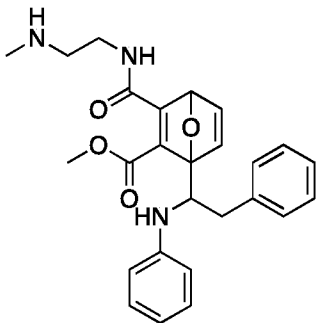
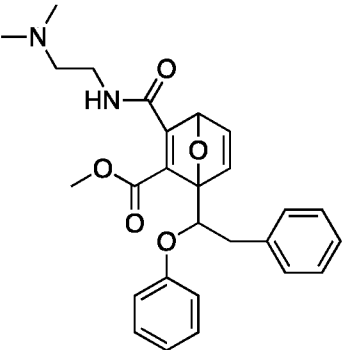
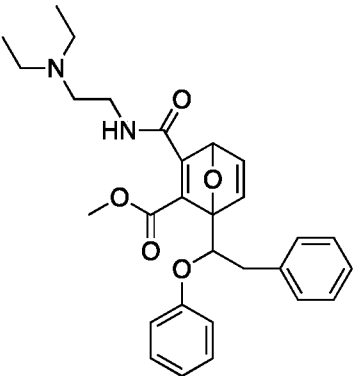
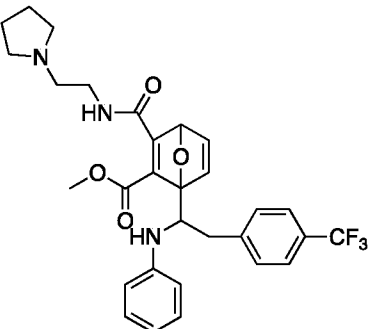
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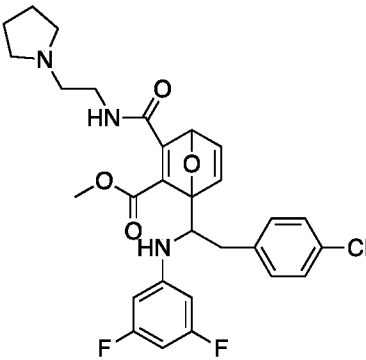
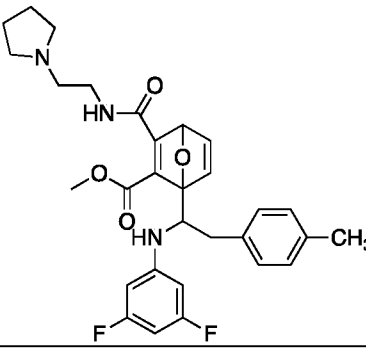
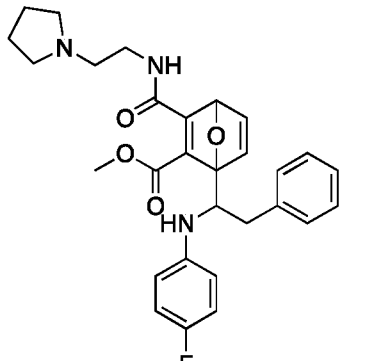
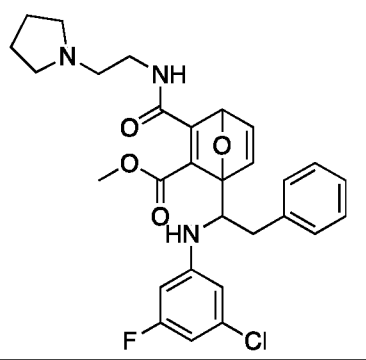
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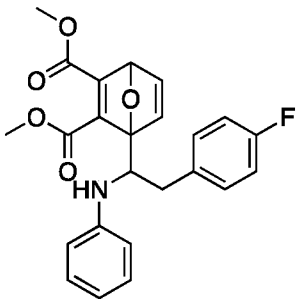
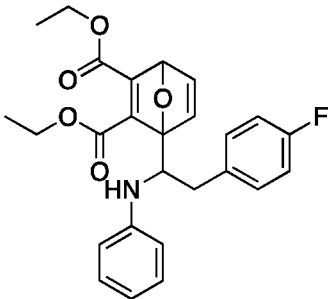
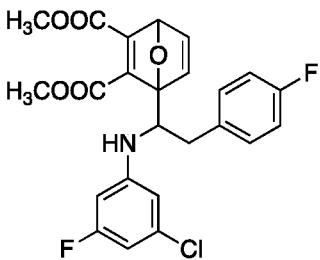
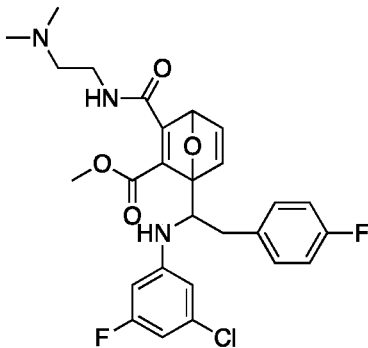
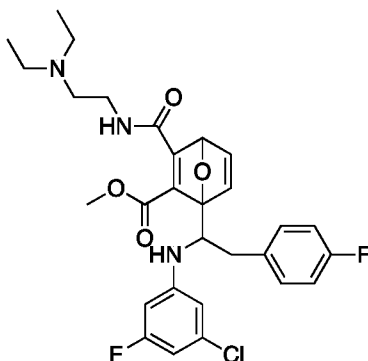
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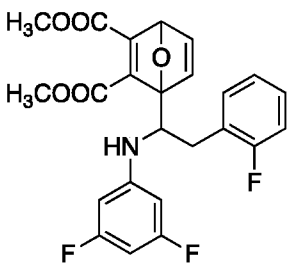
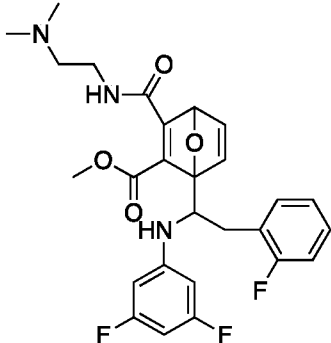
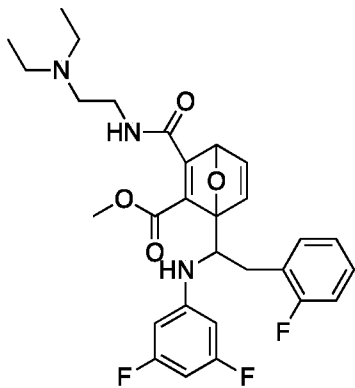
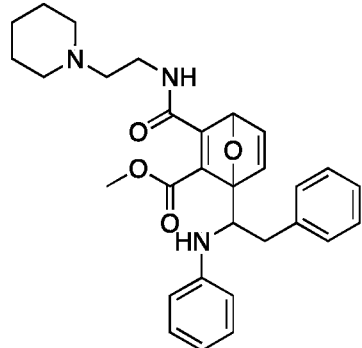
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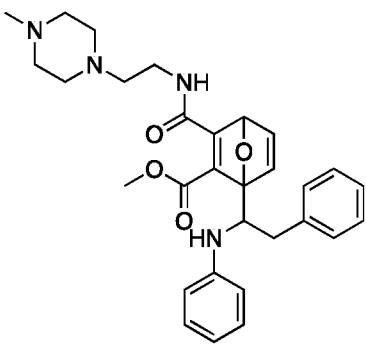
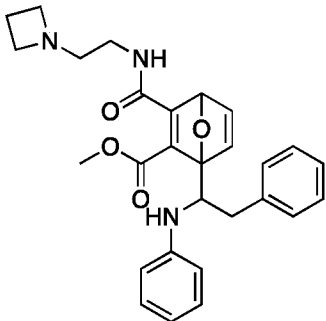
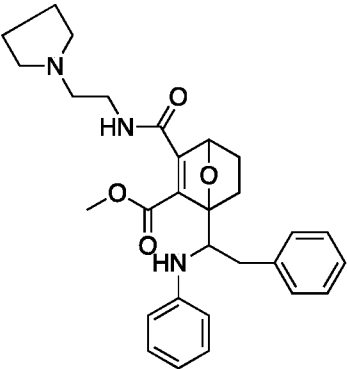
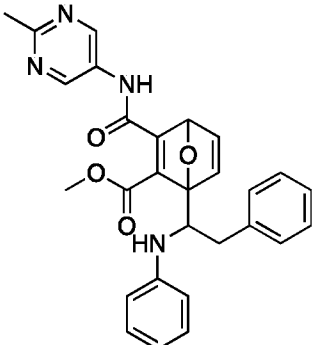
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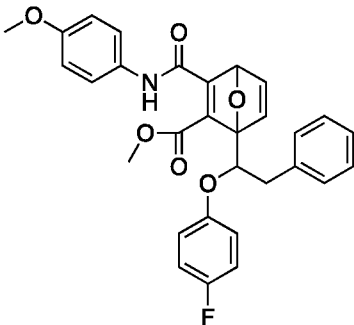
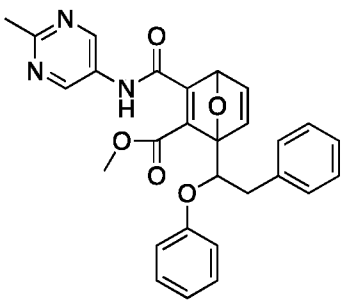
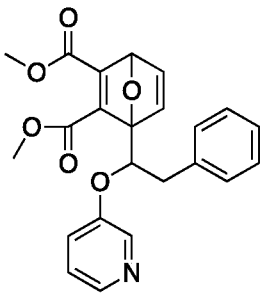
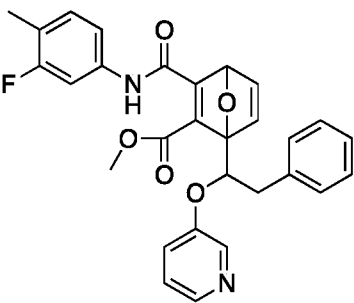
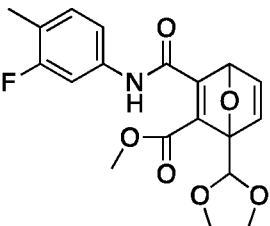
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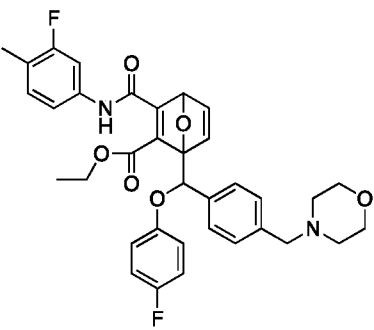
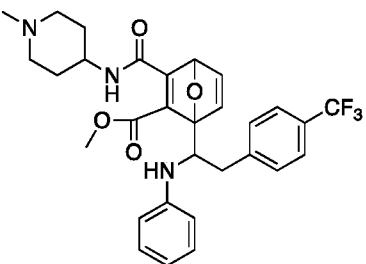
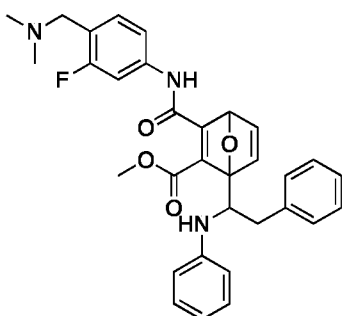
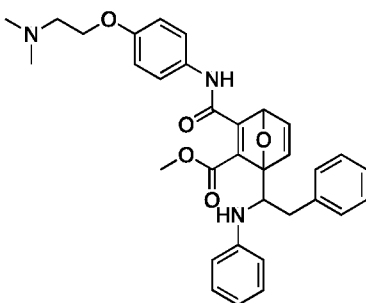
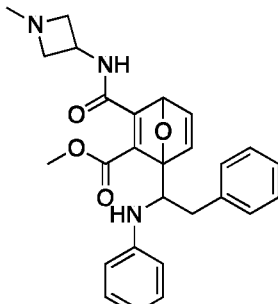
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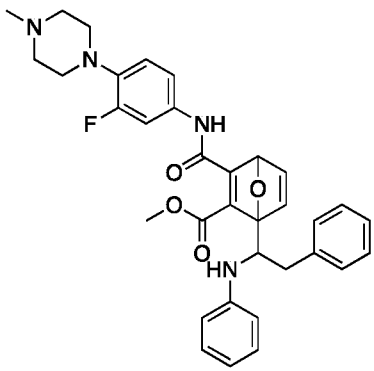
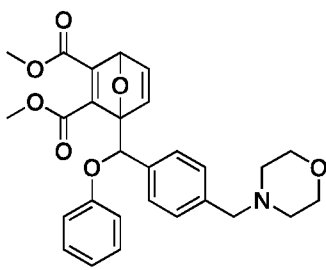
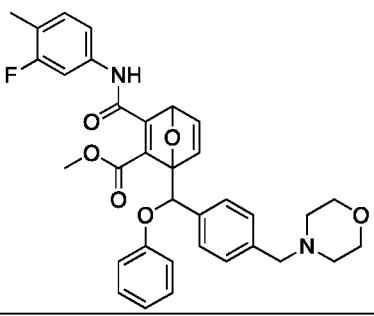
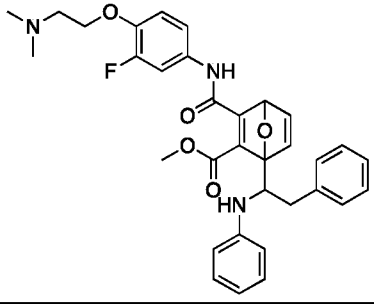
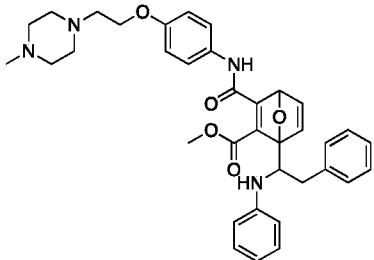
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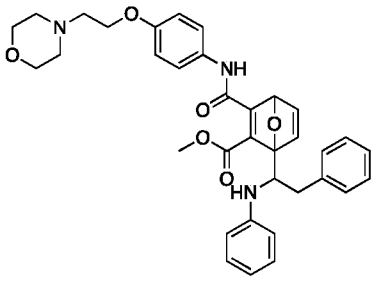
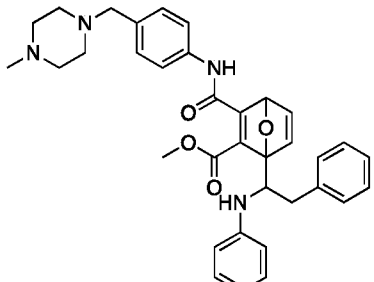
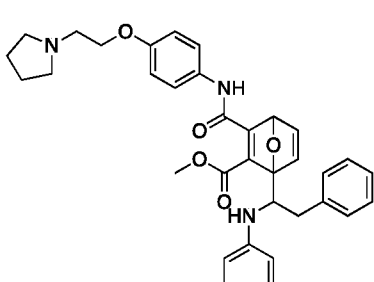
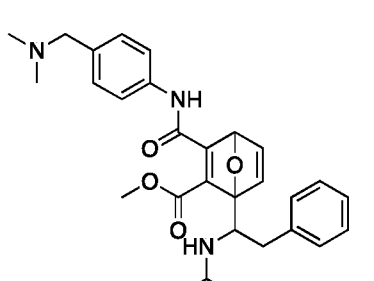
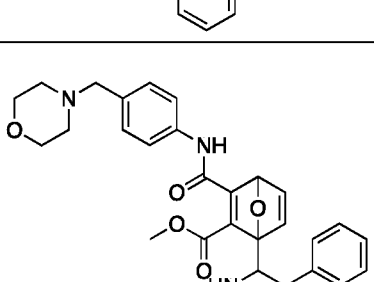
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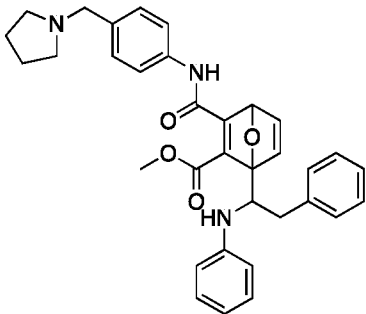
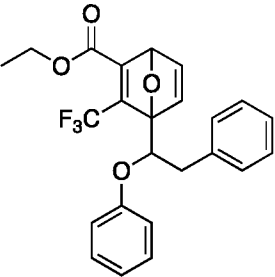
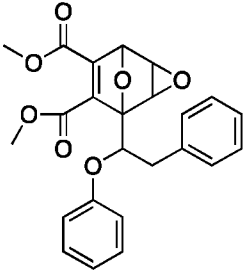
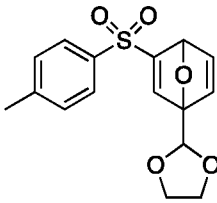
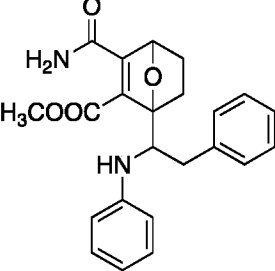
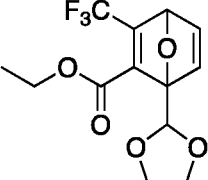
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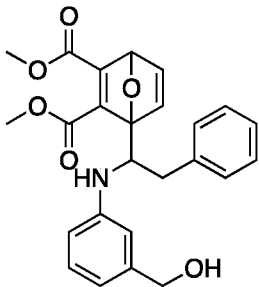
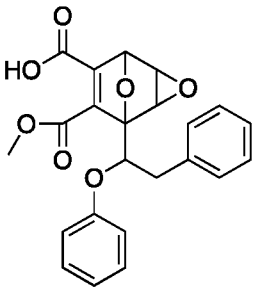
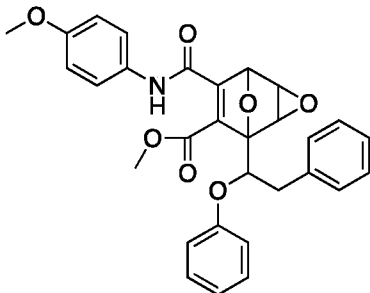
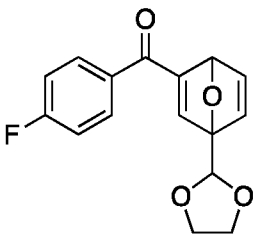
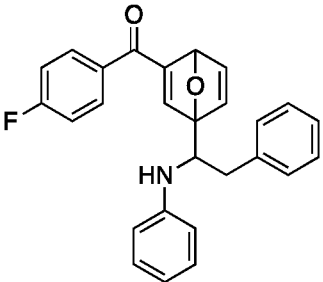
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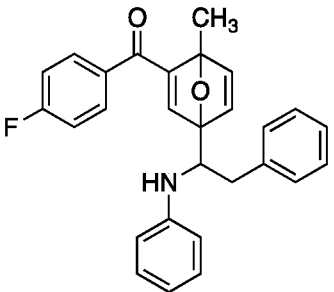
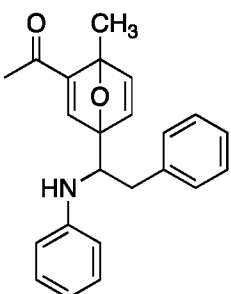
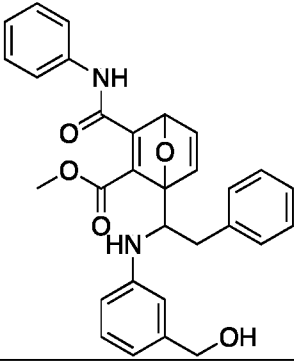
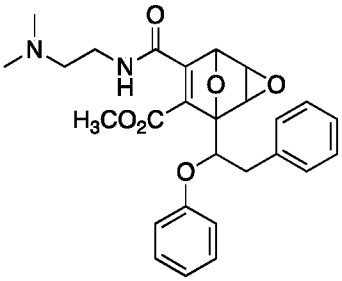
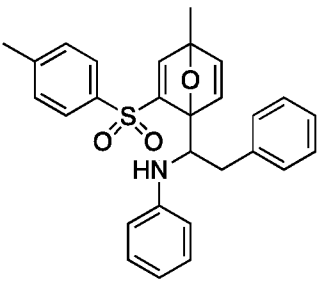
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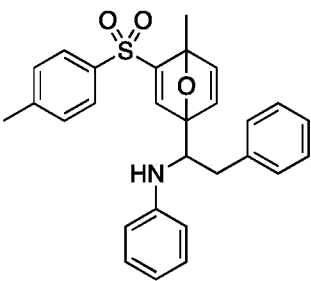
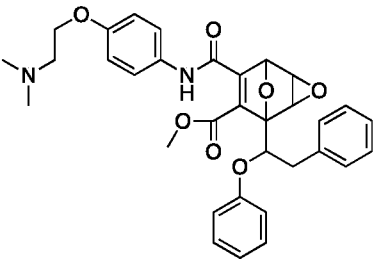
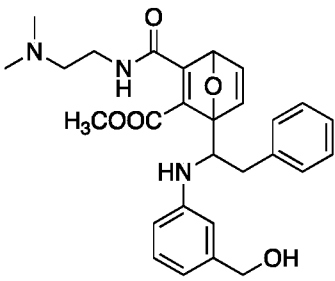
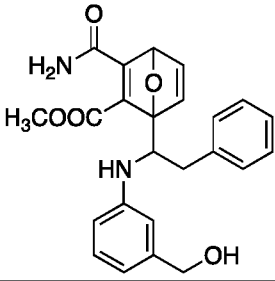
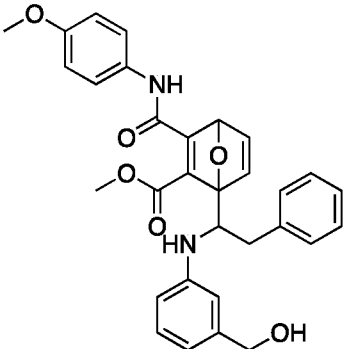
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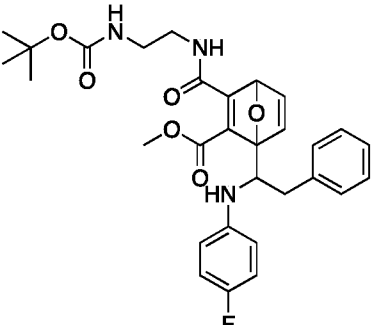
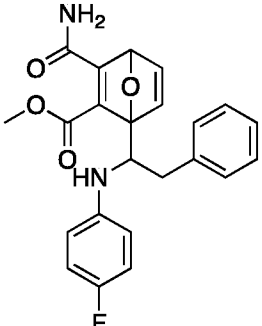
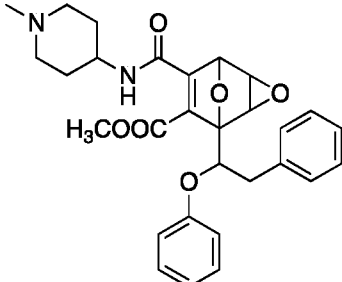
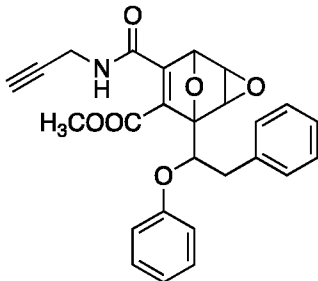
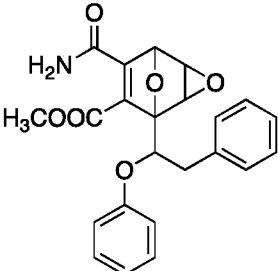
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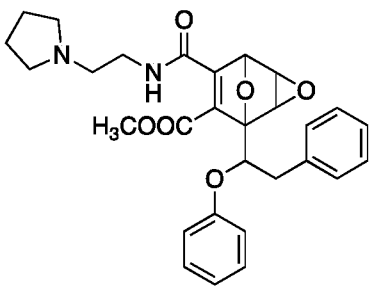
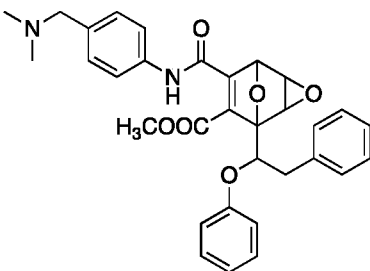
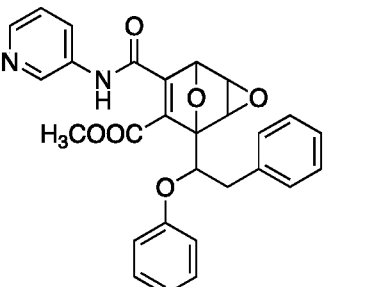
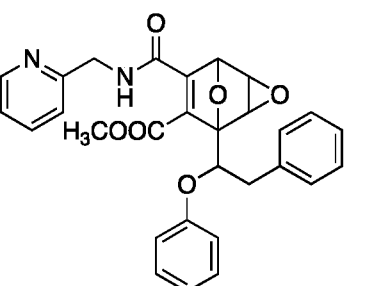
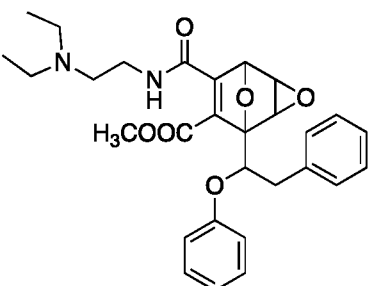
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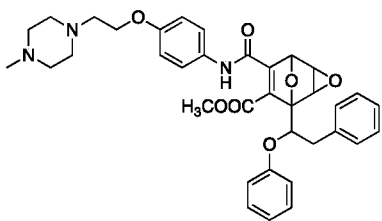
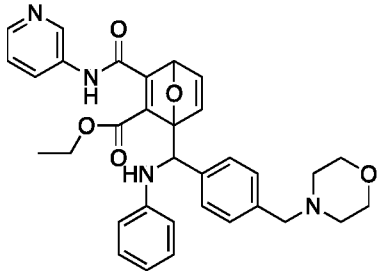
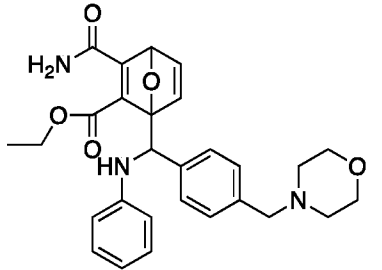
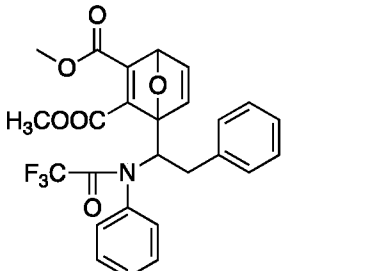
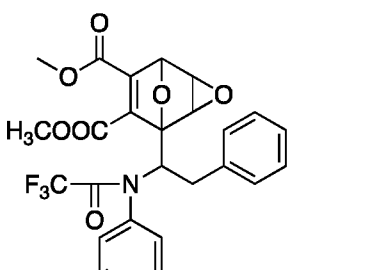
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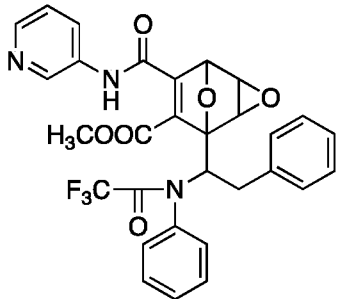
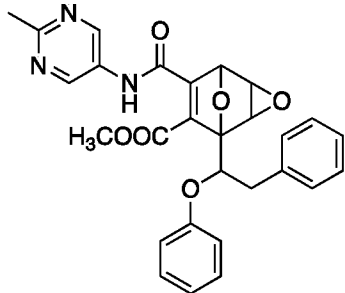
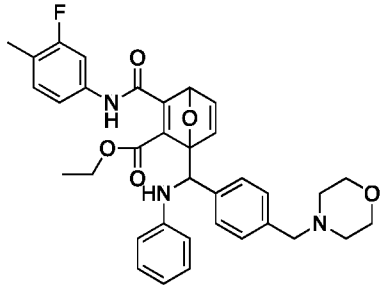
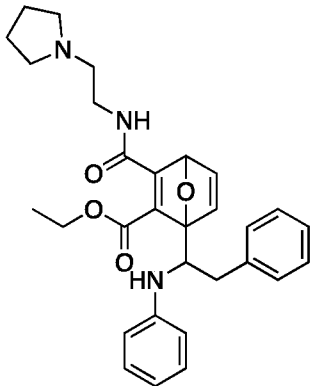
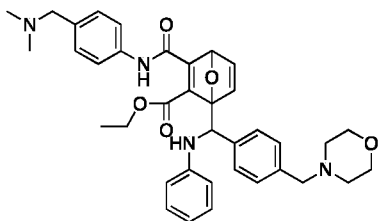
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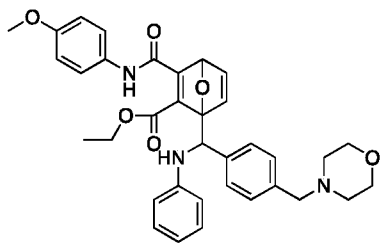
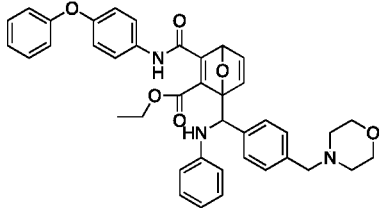
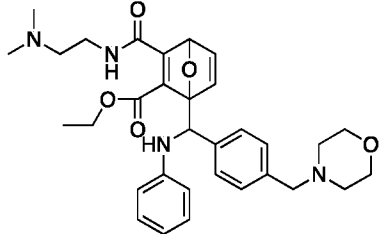
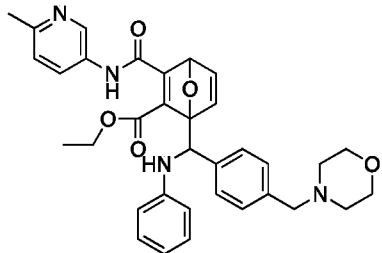
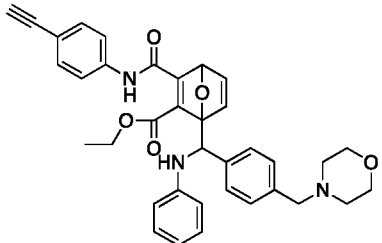
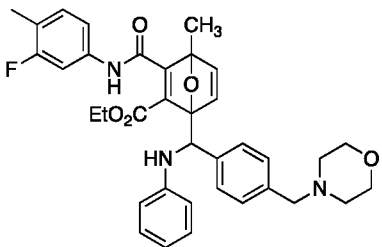
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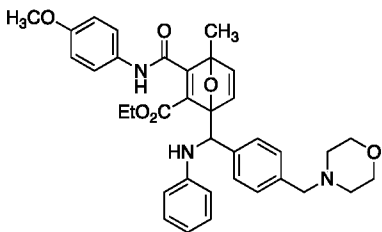
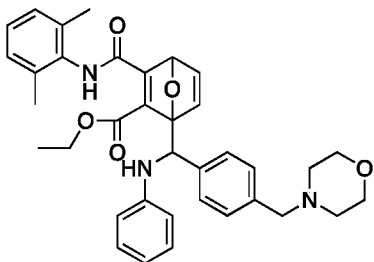
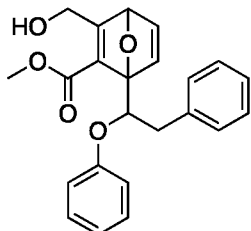
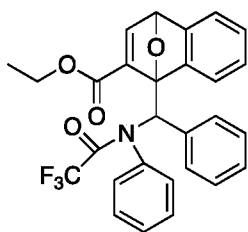
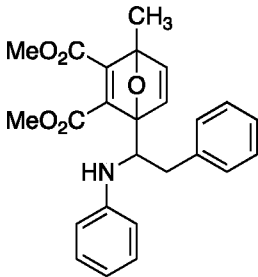
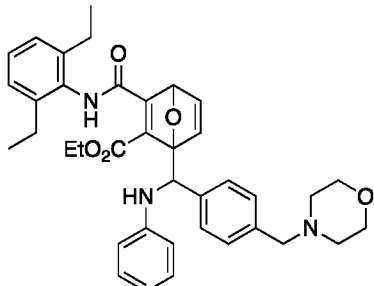
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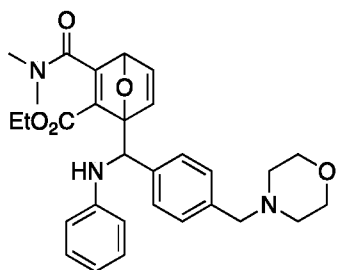
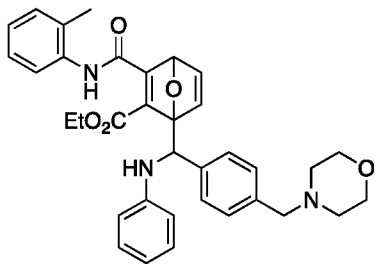
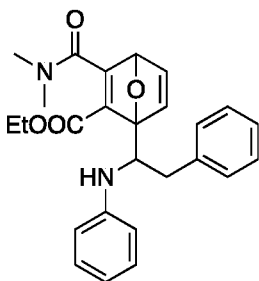
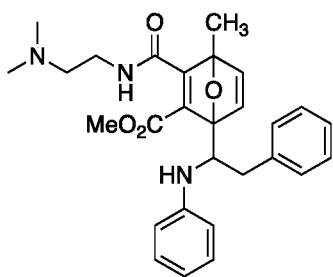
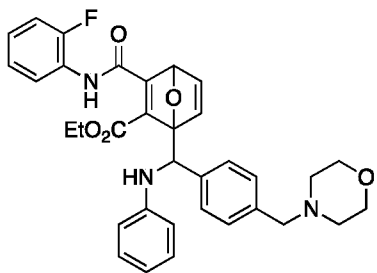
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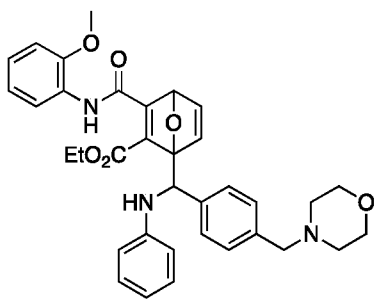
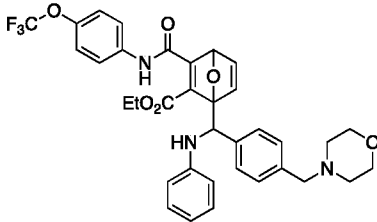
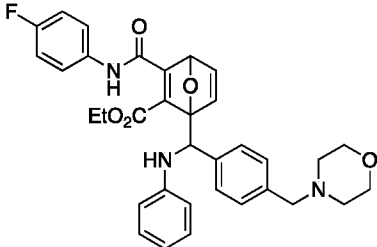
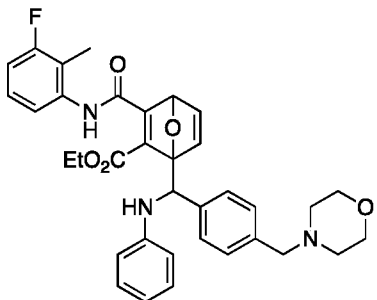
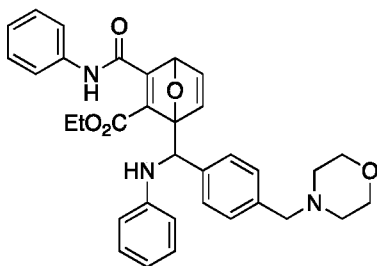
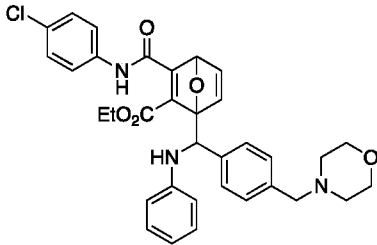
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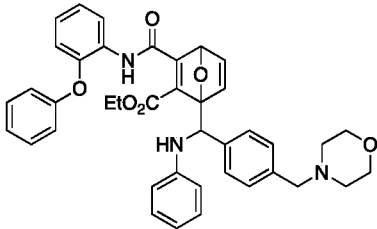
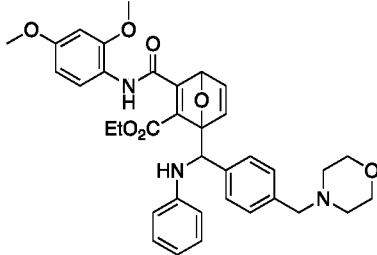
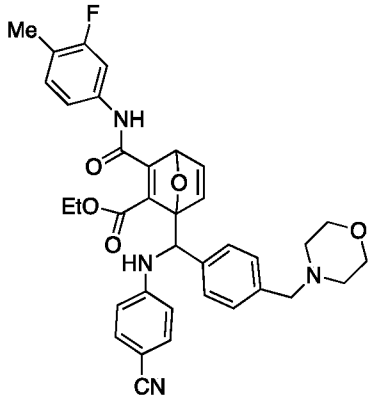
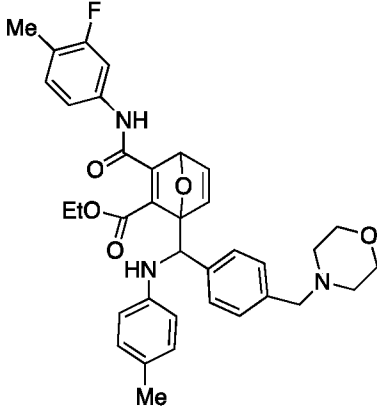
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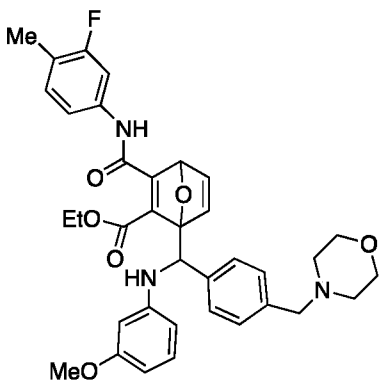
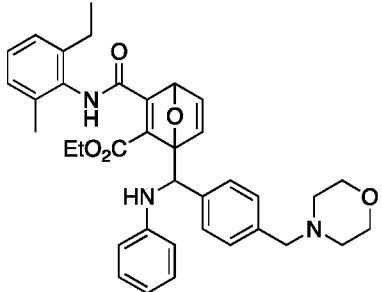
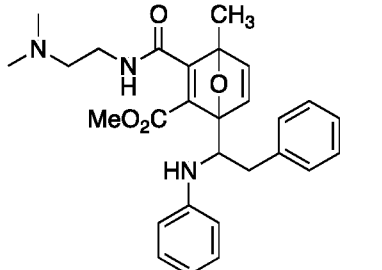
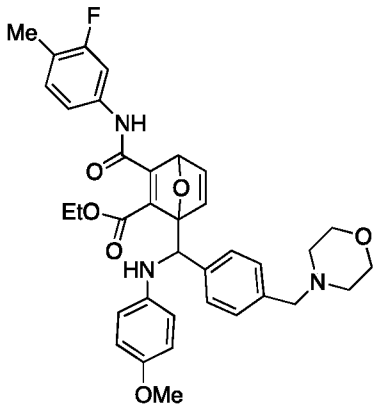
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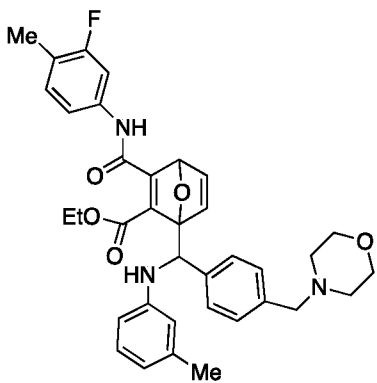
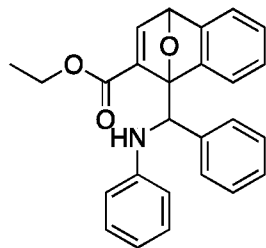
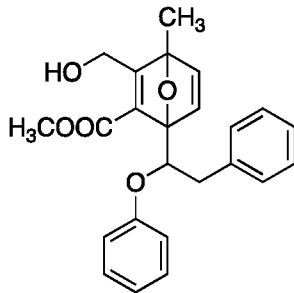
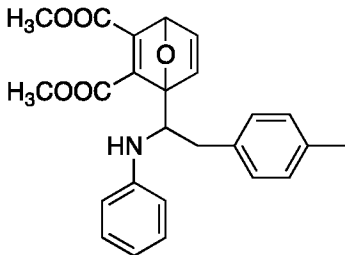
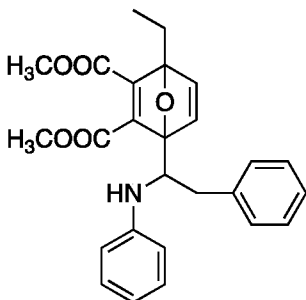
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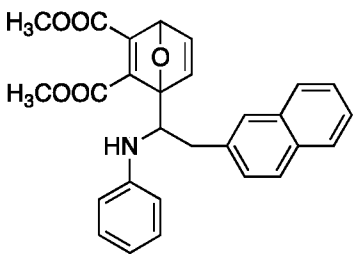
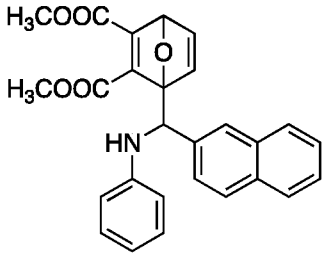
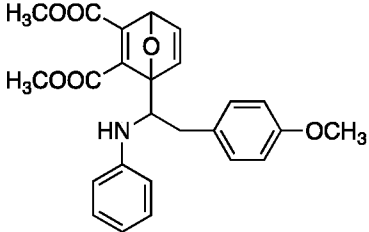
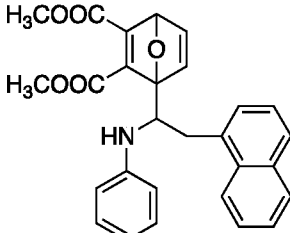
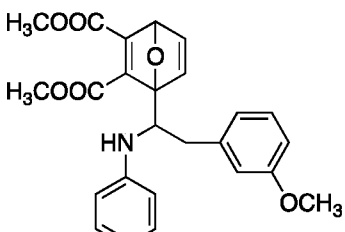
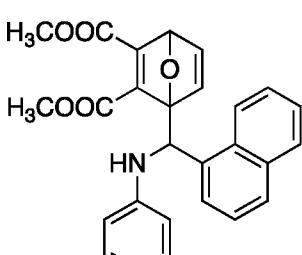
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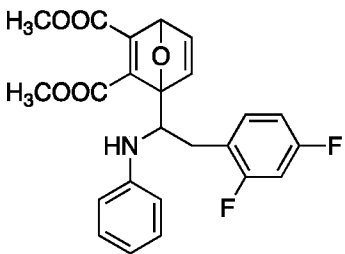
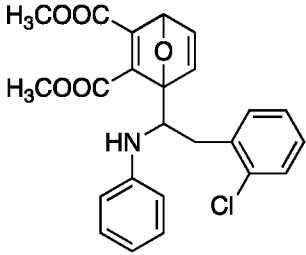
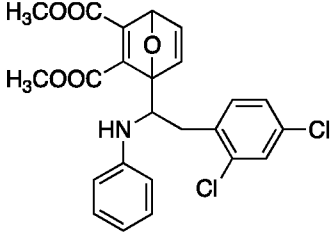
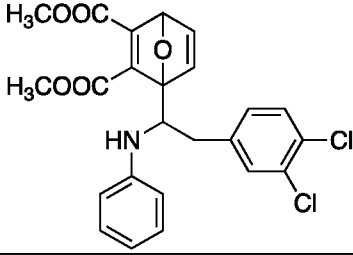
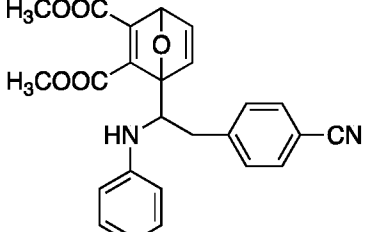
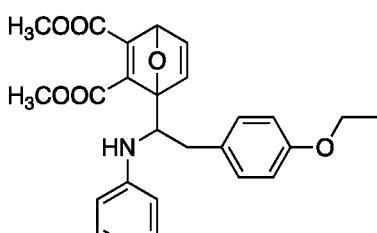
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606		++				+

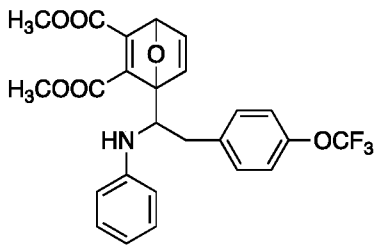
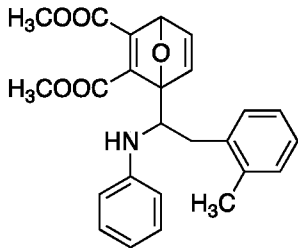
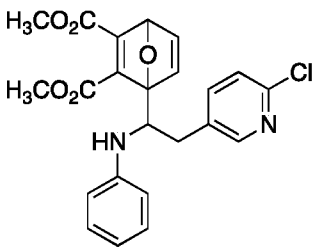
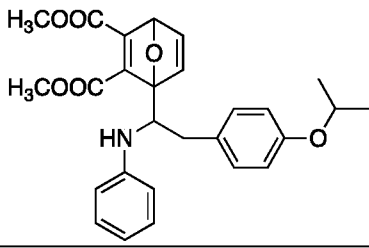
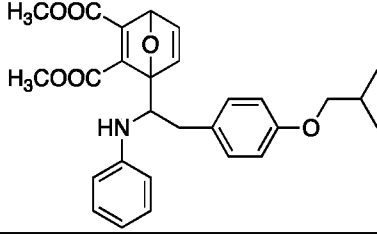
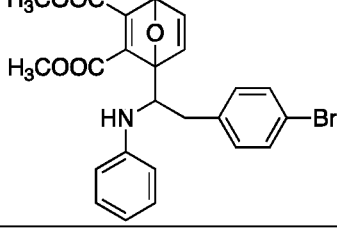
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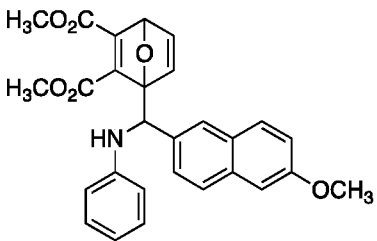
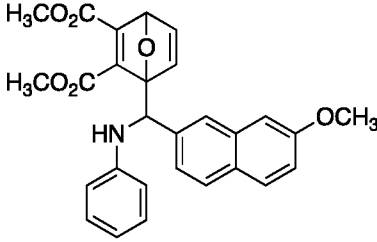
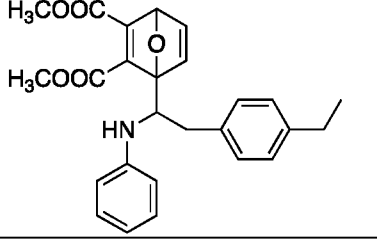
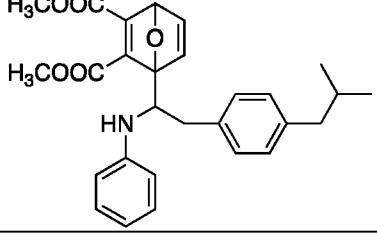
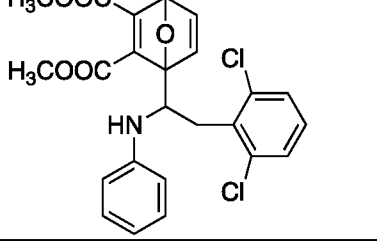
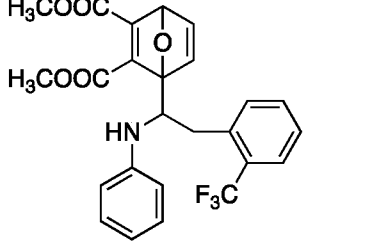
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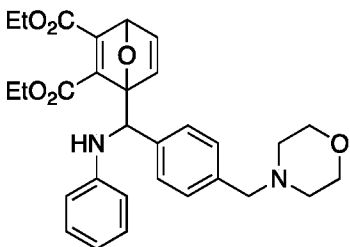
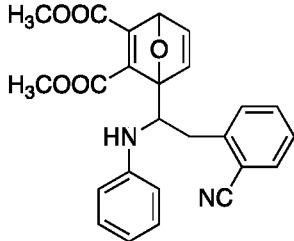
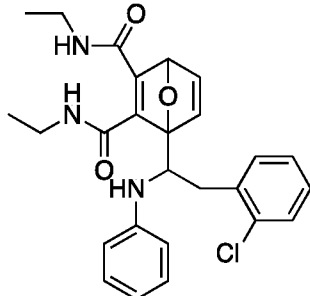
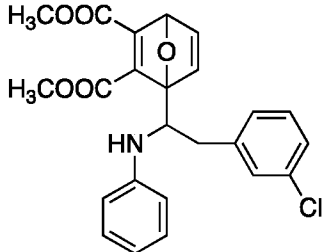
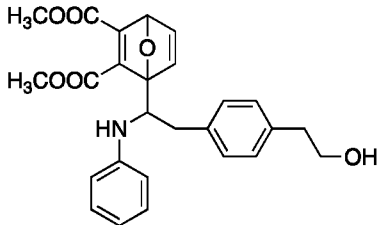
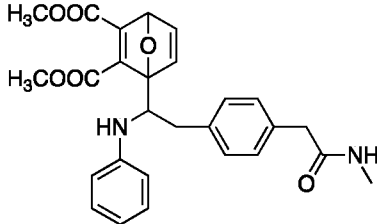
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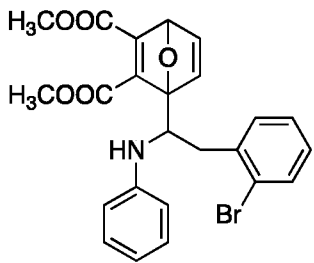
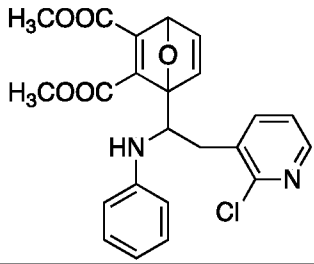
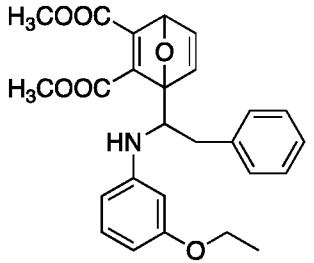
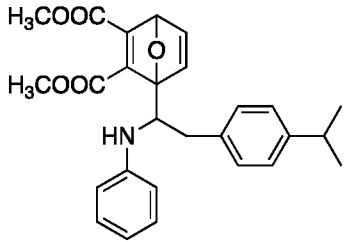
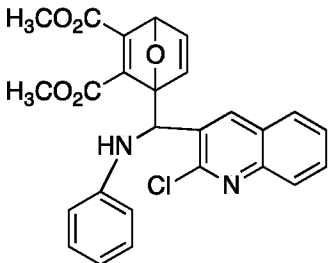
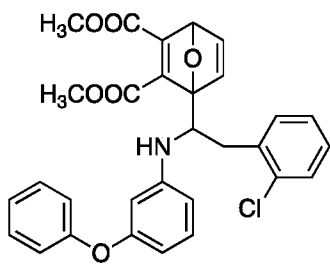
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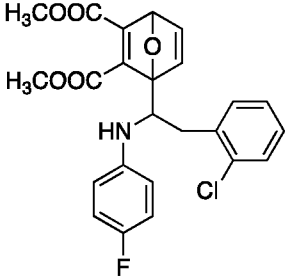
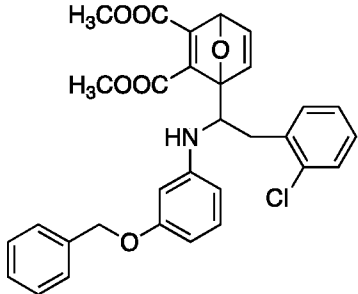
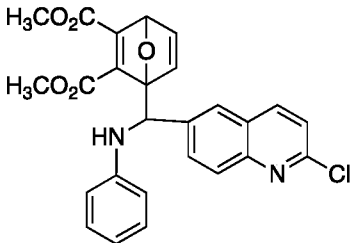
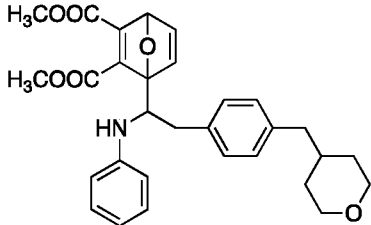
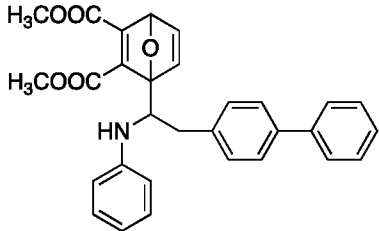
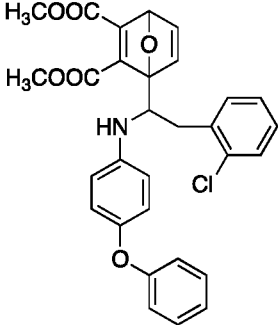
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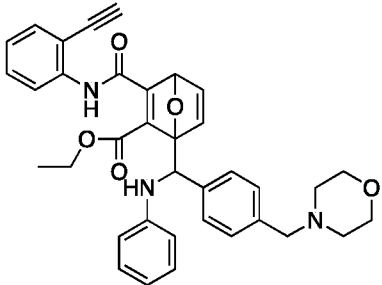
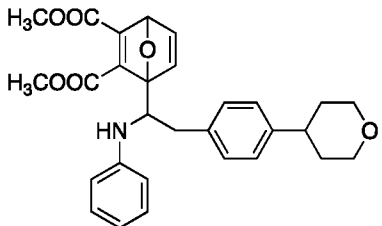
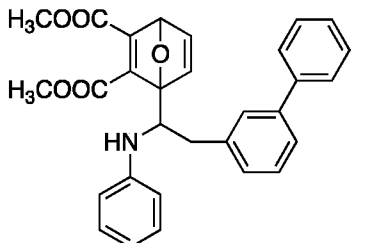
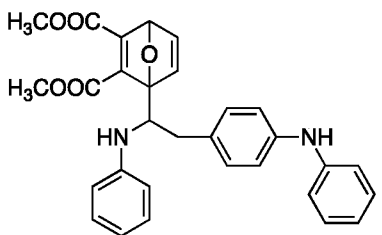
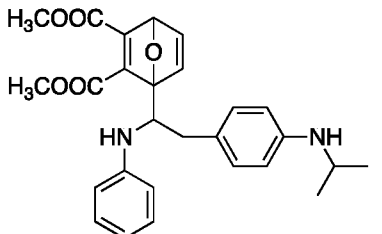
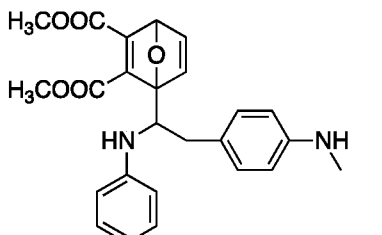
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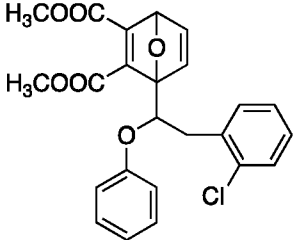
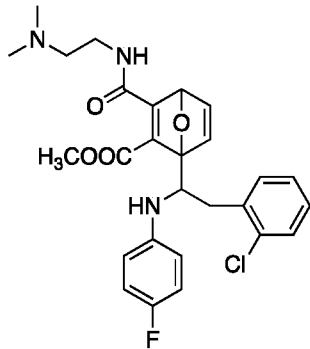
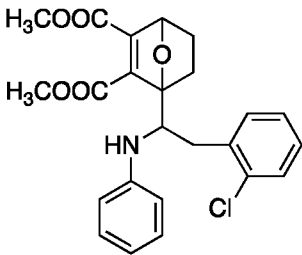
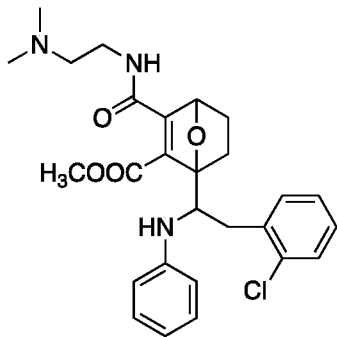
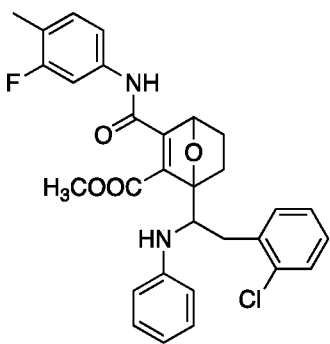
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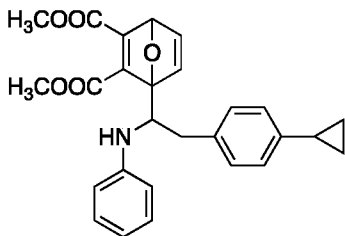
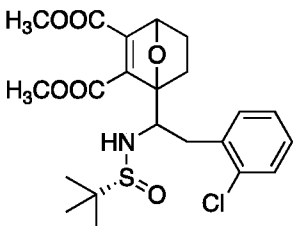
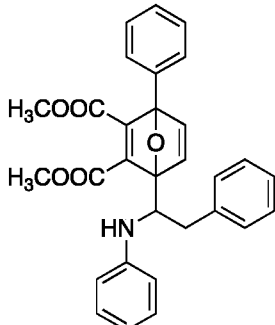
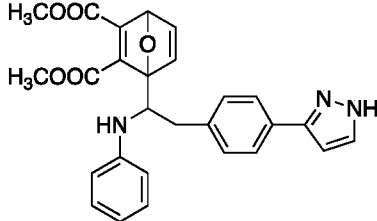
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681		++				
682		+				
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688		+++				
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692		+				

693		++				
694		++				
696		+				
698		+++				

C. Example 3. Methods of screening

[0561] More than 97% of the human proteome have not been addressed by FDA approved drugs of all diseases. An approach to accelerate the discovery of druggable sites and novel targets is by using compound libraries that can form covalent adducts with proteins in the proteome. Such a compound library can be used to screen a cellular disease model and compare with a non-disease model to identify compounds that have potential therapeutic benefit for the disease. Then, quantitative mass spectrometry approaches will be used to identify the specific site(s) in specific target(s) in the cells that the hit(s) covalently bind to through competition with an affinity labeled tool compound.

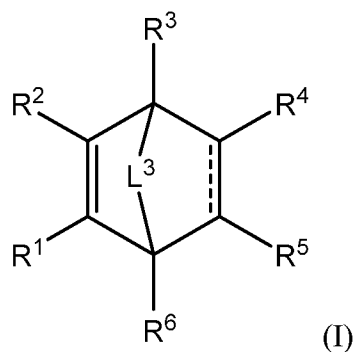
[0562] Such novel target and druggable site identification outcome is affected by the functional groups that form covalent bonds with proteins, known as “warhead” in these libraries. The warhead in the compound library provided herein is different from others used for such studies, and thus is unique. It led to the discovery of Cys30 of the SAE2/Uba2 as a novel druggable site in this novel target.

[0563] Ref: Counihan JL*, Wiggenhorn A*, Anderson KE, Nomura DK. (2018) Chemoproteomics-enabled covalent ligand screening reveals ALDH3A1 as a lung cancer target. ACS Chemical Biology doi:10.1021/acscchembio.8b00381.

[0564] 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 in a subject in need thereof, said method comprising administering to said subject a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound of formula:



wherein:

--- is a single bond or double bond;

L^3 is $-O-$, $-S-$, $-N-$, $-S(O)-$, $-S(O)_2-$, $-C(O)-$, $-N(R^7)-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

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

R^2 is hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-NHN R^{2A}R^{2B}$, $-C(O)R^{2A}$, $-C(O)-OR^{2A}$, $-C(O)NR^{2A}R^{2B}$, $-C(O)NHN R^{2A}R^{2B}$, $-OR^{2A}$, $-NR^{2A}SO_2R^{2B}$, $-NR^{2A}C(O)R^{2B}$, $-NR^{2A}C(O)OR^{2B}$, $-NR^{2A}OR^{2B}$, $-N_3$, $-L^2-E^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHN R^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or

- 28 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 29 unsubstituted heteroaryl;
- 30 R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$,
 31 $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$,
 32 $-NHNR^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHNR^{4A}R^{4B}$, $-OR^{4A}$,
 33 $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or
 34 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 35 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 36 substituted or unsubstituted heteroaryl;
- 37 R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$,
 38 $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$,
 39 $-NHNR^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHNR^{5A}R^{5B}$, $-OR^{5A}$,
 40 $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or
 41 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 42 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 43 substituted or unsubstituted heteroaryl;
- 44 R^6 is hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$,
 45 $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6A}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$,
 46 $-NHNR^{6A}R^{6B}$, $-C(O)R^{6A}$, $-C(O)-OR^{6A}$, $-C(O)NR^{6A}R^{6B}$, $-C(O)NHNR^{6A}R^{6B}$, $-OR^{6A}$,
 47 $-NR^{6A}SO_2R^{6B}$, $-NR^{6A}C(O)R^{6B}$, $-NR^{6A}C(O)OR^{6B}$, $-NR^{6A}OR^{6B}$, $-N_3$, substituted or
 48 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 49 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 50 substituted or unsubstituted heteroaryl;
- 51 R^7 is hydrogen, halogen, $-CX^7_3$, $-CHX^7_2$, $-CH_2X^7$, $-OCX^7_3$, $-OCH_2X^7$,
 52 $-OCHX^7_2$, $-CN$, $-SO_{n7}R^{7A}$, $-SO_{v7}NR^{7A}R^{7B}$, $-NHC(O)NR^{7A}R^{7B}$, $-N(O)_{m7}$, $-NR^{7A}R^{7B}$,
 53 $-NHNR^{7A}R^{7B}$, $-C(O)R^{7A}$, $-C(O)-OR^{7A}$, $-C(O)NR^{7A}R^{7B}$, $-C(O)NHNR^{7A}R^{7B}$, $-OR^{7A}$,
 54 $-NR^{7A}SO_2R^{7B}$, $-NR^{7A}C(O)R^{7B}$, $-NR^{7A}C(O)OR^{7B}$, $-NR^{7A}OR^{7B}$, $-N_3$, substituted or
 55 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 56 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 57 substituted or unsubstituted heteroaryl;
- 58 E^1 and E^2 are independently an electron-withdrawing moiety;
 59 each R^{1A} , R^{1B} , R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{6A} , R^{6B} , R^{7A} , and R^{7B}
 60 is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$,

61 -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,
 62 -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NH₂SO₂H, -NHC=(O)H, -NHC(O)OH, -NHOH,
 63 -OCX₃, -OCHX₂, -OCH₂X, substituted or unsubstituted alkyl, substituted or unsubstituted
 64 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 65 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 66 R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form
 67 a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A}
 68 and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 69 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A}
 70 and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 71 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A}
 72 and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 73 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{6A}
 74 and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 75 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A}
 76 and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a
 77 substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;
 78 m₁, m₂, m₃, m₄, m₅, m₆, and m₇ are independently 1 or 2;
 79 v₁, v₂, v₃, v₄, v₅, v₆, and v₇ are independently 1 or 2;
 80 n₁, n₂, n₃, n₄, n₅, n₆, and n₇ are independently an integer from 0 to 4;
 81 X, X¹, X², X³, X⁴, X⁵, X⁶, and X⁷ are independently -Cl, -Br, -I, or -F;
 82 L¹ and L² are independently a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-,
 83 -C(O)NH-, -OC(O)-, -NHC(O)-, -NH-C(O)-NH-, -OC(O)NH-, -NHC(O)O-, substituted or
 84 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or
 85 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
 86 unsubstituted arylene, or substituted or unsubstituted heteroarylene;
 87 R¹ and R² may optionally be joined to form a substituted or unsubstituted
 88 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 89 substituted or unsubstituted heteroaryl;
 90 R⁴ and R⁵ may optionally be joined to form a substituted or unsubstituted
 91 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 92 substituted or unsubstituted heteroaryl; and

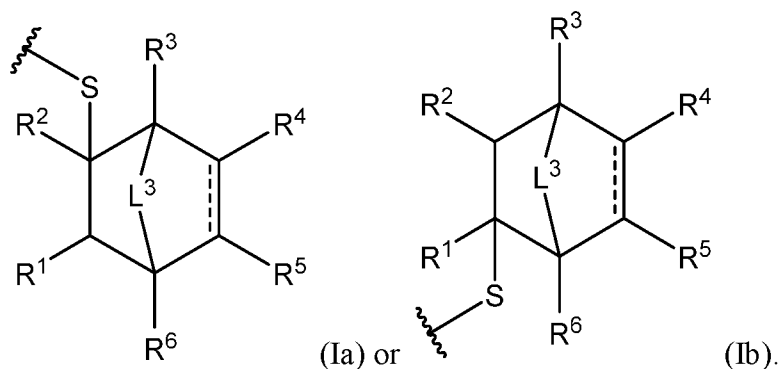
wherein said compound is administered at a rate approximately equal to the half-life of an E1 enzyme.

2. The method of claim 1, wherein said compound is covalently attached to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2.

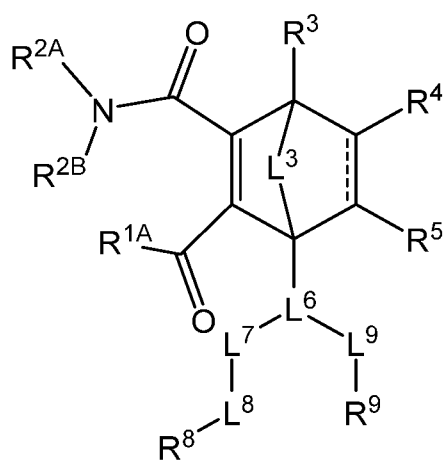
3. The method of claim 1, wherein at least one of R^1 or R^2 comprises an electron-withdrawing moiety.

4. The method of one of claims 1 to 3, wherein at least one of R^1 or R^2 are sufficiently electron withdrawing to allow said compound to covalently bind to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2, wherein said E1 cysteine amino acid is bound to ring carbon C_2 attached to R^2 or ring carbon C_1 attached to R^1 .

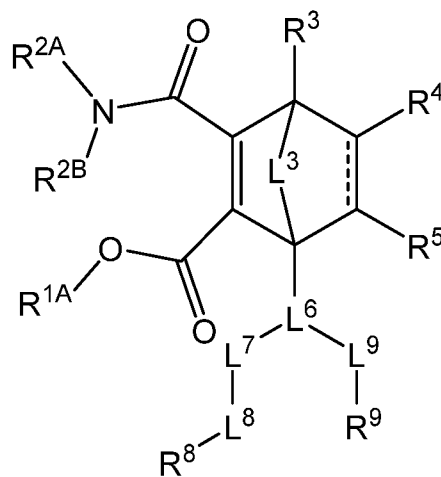
5. The method of one of claims 1 to 3, wherein said compound covalently binds to an E1 cysteine amino acid corresponding to Cys30 of Uba2 subunit 2; and forms a complex of formula:



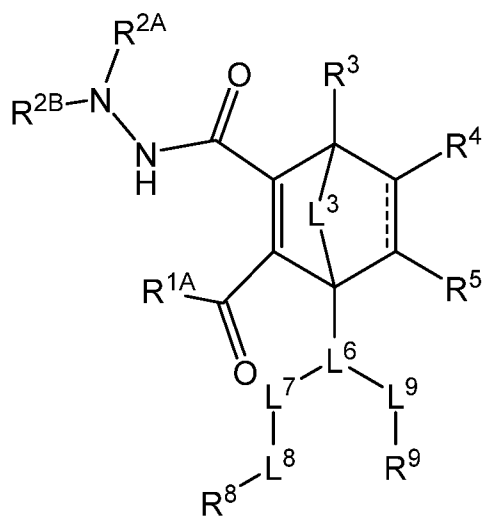
6. A compound of formula:



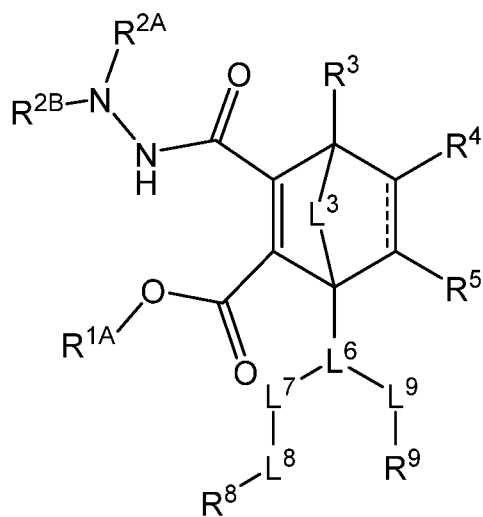
(II),



(III),



(IV), or



(V);

wherein

L^3 is $-O-$, $-S-$, or $-N(R^7)-$;

L^7 is $-O-$ or $-N(R^{10})-$;

R^{1A} is hydrogen, halogen, $-CX^{1A}_3$, $-CHX^{1A}_2$, $-CH_2X^{1A}$, $-OCX^{1A}_3$, $-OCH_2X^{1A}$,

$-OCHX^{1A}_2$, $-CN$, $-SO_{n1A}R^{1AA}$, $-SO_{v1A}NR^{1AA}R^{1AB}$, $-NHC(O)NR^{1AA}R^{1AB}$, $-N(O)_{m1A}$,

$-NR^{1AA}R^{1AB}$, $-NHNR^{1AA}R^{1AB}$, $-C(O)R^{1AA}$, $-C(O)-OR^{1AA}$, $-C(O)NR^{1AA}R^{1AB}$, $-OR^{1AA}$,

$-NR^{1AA}SO_2R^{1AB}$, $-NR^{1AA}C(O)R^{1AB}$, $-NR^{1AA}C(O)OR^{1AB}$, $-NR^{1AA}OR^{1AB}$, $-N_3$, substituted or

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or

substituted or unsubstituted heteroaryl;

R^{2A} is hydrogen, halogen, $-CX^{2A}_3$, $-CHX^{2A}_2$, $-CH_2X^{2A}$, $-OCX^{2A}_3$, $-OCH_2X^{2A}$,

$-OCHX^{2A}_2$, $-CN$, $-SO_{n2A}R^{2AA}$, $-SO_{v2A}NR^{2AA}R^{2AB}$, $-NHC(O)NR^{2AA}R^{2AB}$, $-N(O)_{m2A}$,

$-NR^{2AA}R^{2AB}$, $-NHNR^{2AA}R^{2AB}$, $-C(O)R^{2AA}$, $-C(O)-OR^{2AA}$, $-C(O)NR^{2AA}R^{2AB}$, $-OR^{2AA}$,

$-NR^{2AA}SO_2R^{2AB}$, $-NR^{2AA}C(O)R^{2AB}$, $-NR^{2AA}C(O)OR^{2AB}$, $-NR^{2AA}OR^{2AB}$, $-N_3$, substituted or

unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

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

R^{2B} is hydrogen, halogen, $-CX^{2B}_3$, $-CHX^{2B}_2$, $-CH_2X^{2B}$, $-OCX^{2B}_3$, $-OCH_2X^{2B}$, $-OCHX^{2B}_2$, $-CN$, $-SO_{n2B}R^{2BA}$, $-SO_{v2B}NR^{2BA}R^{2BB}$, $-NHC(O)NR^{2BA}R^{2BB}$, $-N(O)_{m2B}$, $-NR^{2BA}R^{2BB}$, $-NHN R^{2BA}R^{2BB}$, $-C(O)R^{2BA}$, $-C(O)-OR^{2BA}$, $-C(O)NR^{2BA}R^{2BB}$, $-OR^{2BA}$, $-NR^{2BA}SO_2R^{2BB}$, $-NR^{2BA}C(O)R^{2BB}$, $-NR^{2BA}C(O)OR^{2BB}$, $-NR^{2BA}OR^{2BB}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-NHN R^{3A}R^{3B}$, $-C(O)R^{3A}$, $-C(O)-OR^{3A}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3A}$, $-NR^{3A}SO_2R^{3B}$, $-NR^{3A}C(O)R^{3B}$, $-NR^{3A}C(O)OR^{3B}$, $-NR^{3A}OR^{3B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^4 is hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-NHN R^{4A}R^{4B}$, $-C(O)R^{4A}$, $-C(O)-OR^{4A}$, $-C(O)NR^{4A}R^{4B}$, $-C(O)NHN R^{4A}R^{4B}$, $-OR^{4A}$, $-NR^{4A}SO_2R^{4B}$, $-NR^{4A}C(O)R^{4B}$, $-NR^{4A}C(O)OR^{4B}$, $-NR^{4A}OR^{4B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^5 is hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5A}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-NHN R^{5A}R^{5B}$, $-C(O)R^{5A}$, $-C(O)-OR^{5A}$, $-C(O)NR^{5A}R^{5B}$, $-C(O)NHN R^{5A}R^{5B}$, $-OR^{5A}$, $-NR^{5A}SO_2R^{5B}$, $-NR^{5A}C(O)R^{5B}$, $-NR^{5A}C(O)OR^{5B}$, $-NR^{5A}OR^{5B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

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

R^8 is hydrogen, halogen, $-CX^8$, $-CHX^8$, $-CH_2X^8$, $-OCX^8$, $-OCH_2X^8$, $-OCHX^8$, $-CN$, $-SO_{n5}R^{8A}$, $-SO_{v5}NR^{8A}R^{8B}$, $-NHC(O)NR^{8A}R^{8B}$, $-N(O)_{m5}$, $-NR^{8A}R^{8B}$, $-NHN R^{8A}R^{8B}$, $-C(O)R^{8A}$, $-C(O)-OR^{8A}$, $-C(O)NR^{8A}R^{8B}$, $-C(O)NHN R^{8A}R^{8B}$, $-OR^{8A}$, $-NR^{8A}SO_2R^{8B}$, $-NR^{8A}C(O)R^{8B}$, $-NR^{8A}C(O)OR^{8B}$, $-NR^{8A}OR^{8B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^9 is hydrogen, halogen, $-CX^9$, $-CHX^9$, $-CH_2X^9$, $-OCX^9$, $-OCH_2X^9$, $-OCHX^9$, $-CN$, $-SO_{n5}R^{9A}$, $-SO_{v5}NR^{9A}R^{9B}$, $-NHC(O)NR^{9A}R^{9B}$, $-N(O)_{m5}$, $-NR^{9A}R^{9B}$, $-NHN R^{9A}R^{9B}$, $-C(O)R^{9A}$, $-C(O)-OR^{9A}$, $-C(O)NR^{9A}R^{9B}$, $-C(O)NHN R^{9A}R^{9B}$, $-OR^{9A}$, $-NR^{9A}SO_2R^{9B}$, $-NR^{9A}C(O)R^{9B}$, $-NR^{9A}C(O)OR^{9B}$, $-NR^{9A}OR^{9B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{10} is hydrogen, halogen, $-CX^{10}$, $-CHX^{10}$, $-CH_2X^{10}$, $-OCX^{10}$, $-OCH_2X^{10}$, $-OCHX^{10}$, $-CN$, $-SO_{n10}R^{10A}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-NHN R^{10A}R^{10B}$, $-C(O)R^{10A}$, $-C(O)-OR^{10A}$, $-C(O)NR^{10A}R^{10B}$, $-C(O)NHN R^{10A}R^{10B}$, $-OR^{10A}$, $-NR^{10A}SO_2R^{10B}$, $-NR^{10A}C(O)R^{10B}$, $-NR^{10A}C(O)OR^{10B}$, $-NR^{10A}OR^{10B}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^{1AA} , R^{1AB} , R^{2AA} , R^{2AB} , R^{2BA} , R^{2BB} , R^{3A} , R^{3B} , R^{4A} , R^{4B} , R^{5A} , R^{5B} , R^{7A} , R^{7B} , R^{8A} , R^{8B} , R^{9A} , R^{9B} , R^{10A} , and R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1AA} and R^{1AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or

unsubstituted heteroaryl; R^{2AA} and R^{2AB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2BA} and R^{2BB} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{7A} and R^{7B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{8A} and R^{8B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{9A} and R^{9B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

$m1A$, $m2A$, $m2B$, $m3$, $m4$, $m5$, $m7$, $m8$, $m9$, and $m10$ are independently 1 or 2;

$v1A$, $v2A$, $v2B$, $v3$, $v4$, $v5$, $v7$, $v8$, $v9$, and $v10$ are independently 1 or 2;

$n1A$, $n2A$, $n2B$, $n3$, $n4$, $n5$, $n7$, $n8$, $n9$, and $n10$ are independently an integer from 0 to 4;

X , X^{1A} , X^{2A} , X^{2B} , X^3 , X^4 , X^5 , X^7 , X^8 , X^9 , and X^{10} are independently -Cl, -Br, -I, or -F;

L^6 is 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;

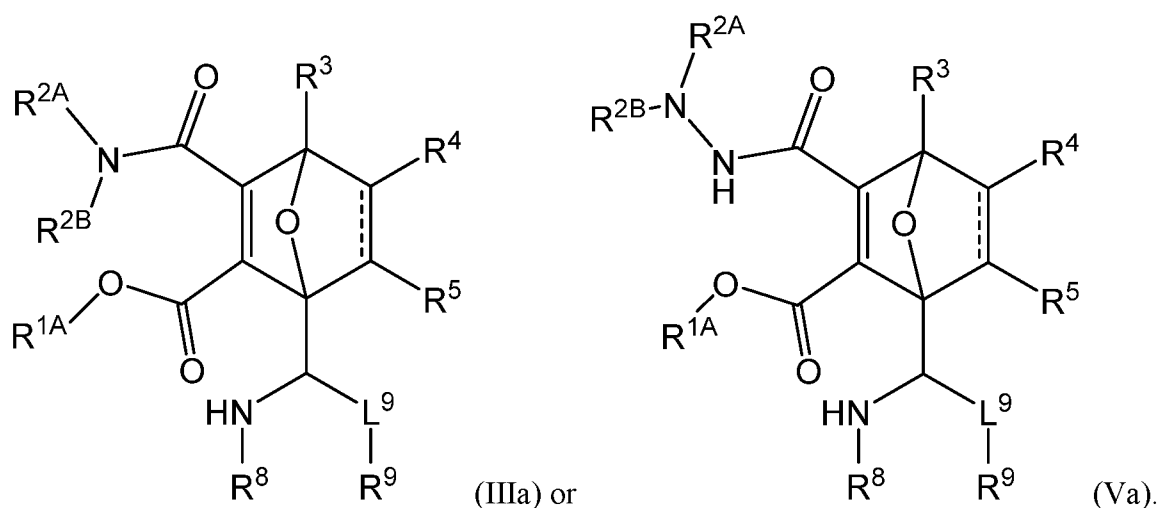
L^8 is a bond, -C(O)-, -C(O)NH-, -C(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

L^9 is a bond, -O-, -S-, -NH-, -C(O)-, -C(O)O-, -C(O)NH-, -OC(O)-, -NHC(O)-, -NHC(O)NH-, -OC(O)NH-, -NHC(O)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

wherein R^{2A} and R^{2B} may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and

R^4 and R^5 may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

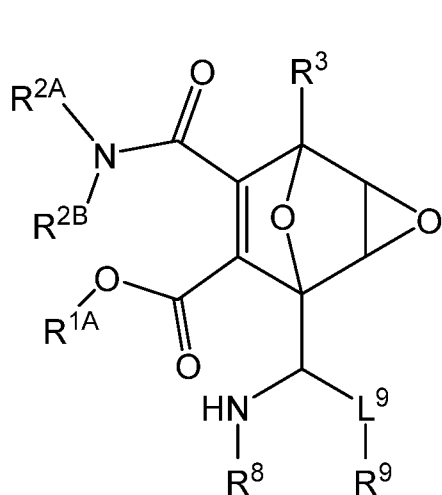
7. The compound of claim 6, having the formula:



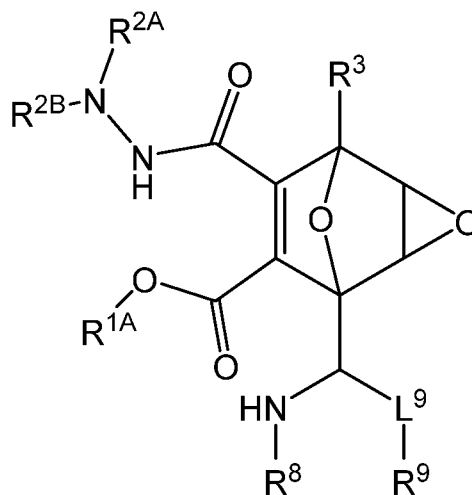
8. The compound of claim 6, wherein R^4 is hydrogen.

9. The compound of claim 6, wherein R^5 is hydrogen.

10. The compound of claim 6, having the formula:



(IIIb) or



(Vb).

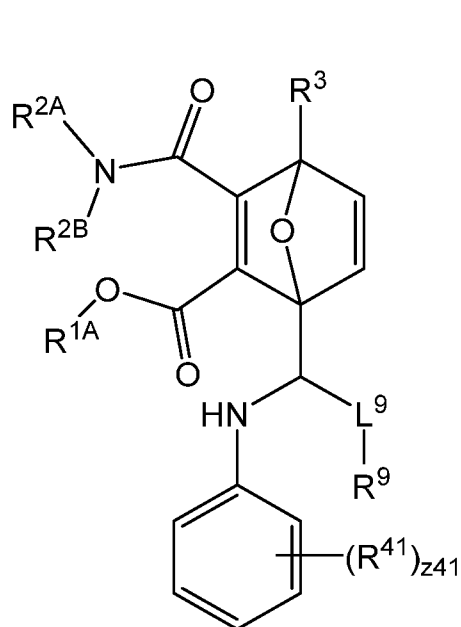
11. The compound of claim 6, wherein R⁸ is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

12. The compound of claim 6, wherein R⁸ is substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

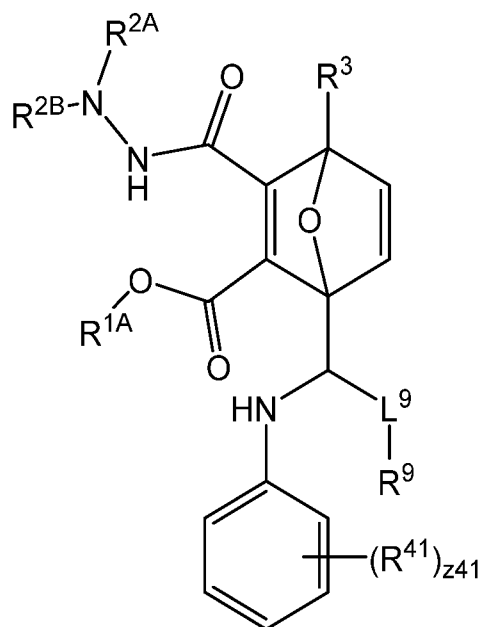
13. The compound of claim 6, wherein R⁸ is substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

14. The compound of claim 6, wherein R⁸ is substituted or unsubstituted phenyl.

15. The compound of claim 6, having the formula:



(IIIc) or



(Vc);

R^{41} is independently halogen, $-CX^{41}_3$, $-CHX^{41}_2$, $-CH_2X^{41}$, $-C(O)OH$, $-C(O)NH_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{41}_3$, $-OCHX^{41}_2$, $-OCH_2X^{41}$, $-OPh$, 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^{41} 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_{41} is an integer from 0 to 5; and

X^{41} is independently $-Cl$, $-Br$, $-I$, or $-F$.

16. The compound of claim 15, wherein R^{41} is independently halogen or $-OPh$.

17. The compound of claim 15, wherein z_{41} is 2.

18. The compound of claim 15, wherein z_{41} is 1.

19. The compound of claim 15, wherein z_{41} is 0.

20. The compound of claim 6, wherein L^9 is a bond, or substituted or unsubstituted alkylene.

- 1 21. The compound of claim 6, wherein L⁹ is a bond, or unsubstituted C₁-C₃
2 alkylene.
- 1 22. The compound of claim 6, wherein L⁹ is an unsubstituted methylene.
- 1 23. The compound of claim 6, wherein L⁹ is a bond.
- 1 24. The compound of claim 6, wherein R⁹ is substituted or unsubstituted
2 alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
3 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted
4 or unsubstituted heteroaryl.
- 1 25. The compound of claim 6, wherein R⁹ is unsubstituted alkyl,
2 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl,
3 unsubstituted aryl, or unsubstituted heteroaryl.
- 1 26. The compound of claim 6, wherein R⁹ is unsubstituted C₁-C₆ alkyl,
2 unsubstituted 2 to 6 membered heteroalkyl, unsubstituted C₃-C₆ cycloalkyl, unsubstituted 3 to
3 6 membered heterocycloalkyl, unsubstituted phenyl, or unsubstituted 5 to 6 membered
4 heteroaryl.
- 1 27. The compound of claim 6, wherein R⁹ is unsubstituted propyl,
2 unsubstituted butyl, unsubstituted pentyl, unsubstituted propenyl, unsubstituted butenyl,
3 unsubstituted pentenyl, unsubstituted propynyl, unsubstituted butynyl, unsubstituted
4 pentynyl, unsubstituted cyclobutyl, unsubstituted cyclopentyl, unsubstituted
5 tetrahydropyranyl, unsubstituted morpholinyl, or unsubstituted phenyl.
- 1 28. The compound of claim 6, wherein R⁹ is unsubstituted phenyl.
- 1 29. The compound of claim 6, wherein R^{2A} is hydrogen, substituted or
2 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
3 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
4 substituted or unsubstituted heteroaryl.
- 1 30. The compound of claim 6, wherein R^{2A} is hydrogen, substituted or
2 unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl,
3 substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered

4 heterocycloalkyl, substituted or unsubstituted C₃-C₆ aryl, or substituted or unsubstituted 5 to
5 10 membered heteroaryl.

1 31. The compound of claim 6, wherein R^{2A} is hydrogen.

1 32. The compound of claim 6, wherein R^{2B} is hydrogen, substituted or
2 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
3 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
4 substituted or unsubstituted heteroaryl.

1 33. The compound of claim 6, wherein R^{2B} is hydrogen, substituted or
2 unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl,
3 substituted or unsubstituted C₃-C₆ cycloalkyl, substituted or unsubstituted 3 to 6 membered
4 heterocycloalkyl, substituted or unsubstituted C₃-C₆ aryl, or substituted or unsubstituted 5 to
5 10 membered heteroaryl.

1 34. The compound of claim 6, wherein R^{2B} is hydrogen.

1 35. The compound of claim 6, wherein R^{2A} and R^{2B} are joined to form a
2 substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

1 36. The compound of claim 6, wherein R^{2A} and R^{2B} are joined to form a
2 substituted or unsubstituted heterocycloalkyl.

1 37. The compound of claim 6, wherein R^{2A} and R^{2B} are joined to form a
2 substituted or unsubstituted 4 to 6 membered heterocycloalkyl.

1 38. The compound of claim 6, wherein R^{1A} is hydrogen, -CX^{1A}₃, -CHX^{1A}₂,
2 -CH₂X^{1A}, -OCX^{1A}₃, -OCH₂X^{1A}, -OCHX^{1A}₂, -C(O)R^{1AA}, -C(O)OR^{1AA}, -C(O)NR^{1AA}R^{1AB},
3 -OR^{1AA}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
4 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
5 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

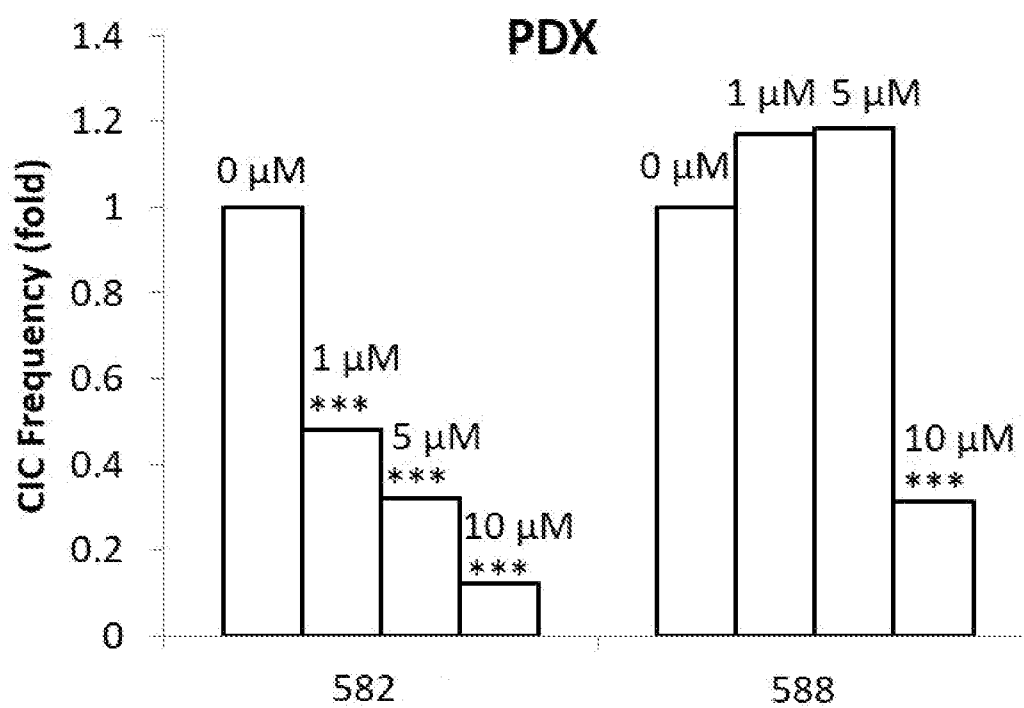
1 39. The compound of claim 6, wherein R^{1A} is hydrogen, -CX^{1A}₃, -CHX^{1A}₂,
2 -CH₂X^{1A}, or unsubstituted C₁-C₃ alkyl.

1 40. The compound of claim 6, wherein R^{1A} is unsubstituted C₁-C₃ alkyl.

- 1 41. The compound of claim 6, wherein R^{1A} is hydrogen.
- 1 42. The compound of claim 6, wherein R³ is hydrogen, -CX³₃, -CHX³₂,
2 -CH₂X³, or substituted or unsubstituted alkyl.
- 1 43. The compound of claim 6, wherein R³ is -CH₂OH or -CH₃.
- 1 44. The compound of claim 6, wherein R³ is hydrogen.
- 1 45. A pharmaceutical composition comprising a compound, or a
2 pharmaceutically acceptable salt thereof, of one of claims 6 to 44 and a pharmaceutically
3 acceptable excipient.
- 1 46. A method of inhibiting an E1 enzyme, said method comprising
2 contacting an E1 enzyme with a compound of one of claims 6 to 44, thereby inhibiting said
3 E1 enzyme.
- 1 47. The method of claim 46, wherein said method comprises allowing said
2 compound to covalently bind said E1 enzyme.
- 1 48. The method of claim 46, wherein said method comprises allowing said
2 compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2
3 subunit 2.
- 1 49. The method of claim 48, wherein said method comprises allowing said
2 E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to ring carbon C₁
3 attached to R^{1A}.
- 1 50. A method of treating cancer in a subject in need thereof, said method
2 comprising administering to said subject a compound of one of claims 6 to 44.
- 1 51. The method of claim 50, wherein said method comprises allowing said
2 compound to covalently bind an E1 enzyme.
- 1 52. The method of claim 50, wherein said method comprises allowing said
2 compound to covalently bind an E1 cysteine amino acid corresponding to Cys30 of Uba2
3 subunit 2.

- 1 53. The method of claim 52, wherein said method comprises allowing said
2 E1 cysteine amino acid to bind to carbon C₂ attached to R^{2A} and R^{2B} or to carbon C₁ attached
3 to R^{1A}.

FIG. 1



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/44404

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/34; C07D 493/08; A61P 35/00 (2019.01)

CPC - A61K 31/34; C07D 493/08

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y --- A	US 9,238,654 B2 (CITY OF HOPE et al.) 19 January 2016 (19.01.2016) Col 3, In 15-25; Col 3, In 47-48; Col 3, In 51-52; Col 8, In 37-33; Col 8, In 41-43; Col 24, In 35-38; Figure 5a; Figure 5b; Figure 13	6-9; 11-34; 38-42; 44, (45-47;50-51)/(6-9,11-34,38-42,44) ----- 1-5; (48;49;52-53)/(6-9,11-34,38-42,44) ----- 10; 35-37; 43; (45-53)/(10,35-37,43)
Y -- A	Xu et al. Targeting the Ubiquitin E1 as a Novel Anti-Cancer Strategy in Current Pharmaceutical Design, 2013, Vol. 19, pp. 3201-3209. pg. 3202, Col 2, para 1; Figure 1; pg. 3205, Table.	1-5; (48;49;52-53)/(6-9,11-34,38-42,44) ----- 10; 35-37; 43; (45-53)/(10,35-37,43)
A	US 2017/0360940 A1 (GEORGIA TECH RESEARCH CORPORATION) 21 December 2017 (21.12.2017) para [0137]	10; 35-37; 43; (45-53)/(10,35-37,43)
A	US 9,447,240 B2 (SUZUKI et al.) 20 September 2016 (20.09.2016) Col 4, In 25-37	10; 35-37; 43; (45-53)/(10,35-37,43)
A	US 2016/0355504 A1 (MILLENNIUM PHARMACEUTICALS, INC.) 08 December 2016 (08.12.2016) ENTIRE DOCUMENT	1-53

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 SEPTEMBER 2019

Date of mailing of the international search report

25 OCT 2019

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/44404

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

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.25 text file.

☐ on paper or in the form of an image file.

b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 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.25 text file (Rule 13ter.1(a)).

☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

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: