



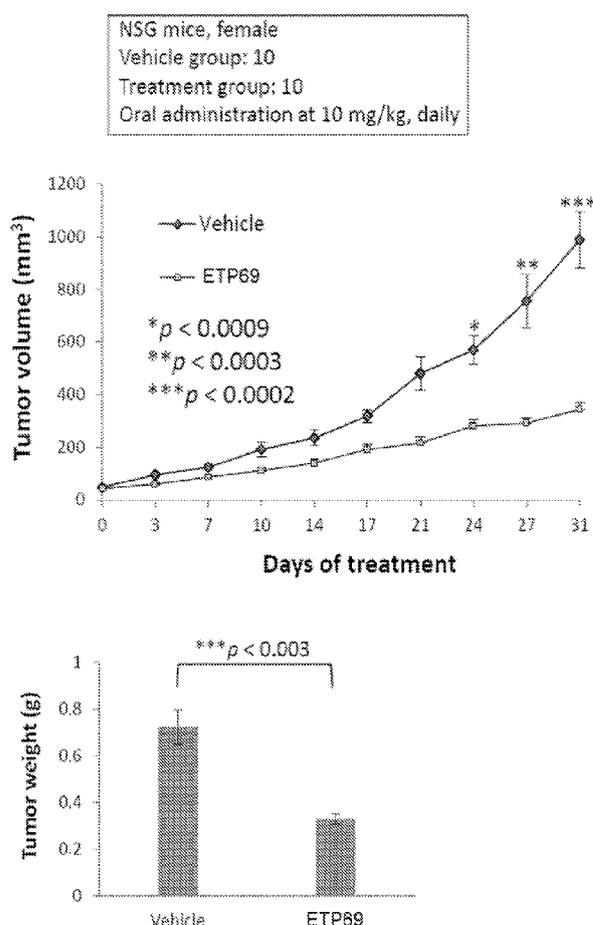
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[Continued on next page]

(54) Title: ETP DERIVATIVES

Figure 15



(57) Abstract: Provided herein, inter alia, is the synthesis of ETP derivatives. The uses of the ETP derivatives described herein include treatment of cancer.

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(81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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ETP DERIVATIVES

5 CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/716,803 filed October 22, 2012 and to U.S. Provisional Application No. 61/799,160 filed March 15, 2013.

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

[0002] This invention was made with government support under grant 2R01-GM030859 and 5F32GM090473 awarded by the NIH National Institute of General Medical Sciences. The government has certain rights in the invention.

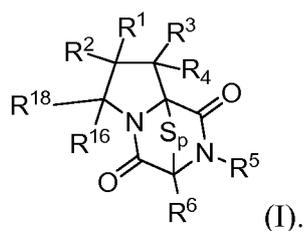
BACKGROUND OF THE INVENTION

15 [0003] ETP natural products represent an intriguing class of (typically) fungal secondary metabolites with a large variety of biological activities ranging from antibiotic to antiviral to antimalarial properties. High levels of toxicity, however, has so far prevented any clinical studies of known ETP structures. No detailed SAR studies of ETPs and their analogues have been reported to date. Furthermore, introduction and elaboration of functional groups for ETP
20 structures has not been previously reported thereby preventing modification of crucial properties such as water solubility, membrane permeability or metabolic stability in biological systems. Accordingly a synthetic route to synthesize ETP analogues for medicinal purposes is crucial and has significant value. Provided herein are solutions to these and other problems in the art.

BRIEF SUMMARY OF THE INVENTION

25 [0004] Provided herein, *inter alia*, are synthetic analogues of ETP compounds. The analogues may be used in the treatment of cancer and may be effective as synergistically combined with other cancer treating compounds. Methods of synthesizing and use are also provided.

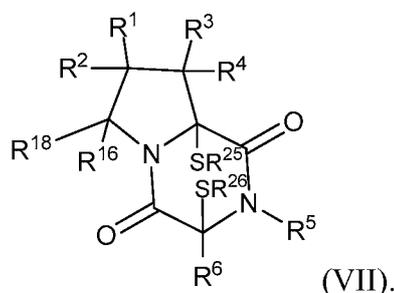
[0005] In a first aspect is a compound having the formula:



[0006] The symbol p is 2, 3 or 4. R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A}, -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A}, -SO_{n1}NR^{34A}R^{35A}, -NHN^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHN^{34A}R^{35A}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33B}, -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -SO_{n2}R^{34b}, -SO_{n2}OR^{34B}, -SO_{n2}NR^{34B}R^{35B}, -NHN^{34B}R^{35B}, -ONR^{34B}R^{35B}, -NHC(O)NHN^{34B}R^{35B}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R³ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33C}, -NR^{34C}R^{35C}, -COOR^{33C}, -CONR^{34C}R^{35C}, -NO₂, -SR^{36C}, -SO_{n3}R^{34C}, -SO_{n3}OR^{34C}, -SO_{n3}NR^{34C}R^{35C}, -NHN^{34C}R^{35C}, -ONR^{34C}R^{35C}, -NHC(O)NHN^{34C}R^{35C}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁴ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33D}, -NR^{34D}R^{35D}, -COOR^{33D}, -CONR^{34D}R^{35D}, -NO₂, -SR^{36D}, -SO_{n4}R^{34D}, -SO_{n4}OR^{34D}, -SO_{n4}NR^{34D}R^{35D}, -NHN^{34D}R^{35D}, -ONR^{34D}R^{35D}, -NHC(O)NHN^{34D}R^{35D}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁵ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33E}, -NR^{34E}R^{35E}, -COOR^{33E}, -CONR^{34E}R^{35E}, -NO₂, -SR^{36E}, -SO_{n5}R^{34E}, -SO_{n5}OR^{34E}, -SO_{n5}NR^{34E}R^{35E}, -NHN^{34E}R^{35E}, -ONR^{34E}R^{35E}, -NHC(O)NHN^{34E}R^{35E}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁶

is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33F}$, $-NR^{34F}R^{35F}$, $-COOR^{33F}$,
 $-CONR^{34F}R^{35F}$, $-NO_2$, $-SR^{36F}$, $-SO_{n6}R^{34F}$, $-SO_{n6}OR^{34F}$, $-SO_{n6}NR^{34F}R^{35F}$, $-NHNr^{34F}R^{35F}$,
 $-ONR^{34F}R^{35F}$, $-NHC(O)NHNr^{34F}R^{35F}$, substituted or unsubstituted alkyl, substituted or
5 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{16}
is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33G}$, $-NR^{34G}R^{35G}$,
 $-COOR^{33G}$, $-CONR^{34G}R^{35G}$, $-NO_2$, $-SR^{36G}$, $-SO_{n7}R^{34G}$, $-SO_{n7}OR^{34G}$, $-SO_{n7}NR^{34G}R^{35G}$,
 $-NHNr^{34G}R^{35G}$, $-ONR^{34G}R^{35G}$, $-NHC(O)NHNr^{34G}R^{35G}$, 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^{18} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33H}$,
 $-NR^{34H}R^{35H}$, $-COOR^{33H}$, $-CONR^{34H}R^{35H}$, $-NO_2$, $-SR^{36H}$, $-SO_{n8}R^{34H}$, $-SO_{n8}OR^{34H}$,
 $-SO_{n8}NR^{34H}R^{35H}$, $-NHNr^{34H}R^{35H}$, $-ONR^{34H}R^{35H}$, $-NHC(O)NHNr^{34H}R^{35H}$, 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^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} ,
 R^{35C} , R^{36C} , R^{33D} , R^{34D} , R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} ,
 R^{36G} , R^{33H} , R^{34H} , R^{35H} , and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
20 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
heteroaryl. The symbol n1, n2, n3, n4, n5, n6, n7, and n8 are independently 1 or 2.

[0007] In another aspect is a compound having the formula:



[0008] R^1 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33A}$,
25 $-NR^{34A}R^{35A}$, $-COOR^{33A}$, $-CONR^{34A}R^{35A}$, $-NO_2$, $-SR^{36A}$, $-SO_{n1}R^{34A}$, $-SO_{n1}OR^{34A}$,

$-\text{SO}_{n1}\text{NR}^{34A}\text{R}^{35A}$, $-\text{NHR}^{34A}\text{R}^{35A}$, $-\text{ONR}^{34A}\text{R}^{35A}$, $-\text{NHC(O)NHR}^{34A}\text{R}^{35A}$, substituted 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, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$,

5 $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33B}$, $-\text{NR}^{34B}\text{R}^{35B}$, $-\text{COOR}^{33B}$, $-\text{CONR}^{34B}\text{R}^{35B}$, $-\text{NO}_2$, $-\text{SR}^{36B}$, $-\text{SO}_{n2}\text{R}^{34b}$, $-\text{SO}_{n2}\text{OR}^{34B}$, $-\text{SO}_{n2}\text{NR}^{34B}\text{R}^{35B}$, $-\text{NHR}^{34B}\text{R}^{35B}$, $-\text{ONR}^{34B}\text{R}^{35B}$, $-\text{NHC(O)NHR}^{34B}\text{R}^{35B}$, substituted 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, $-\text{N}_3$, $-\text{CF}_3$,

10 $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33C}$, $-\text{NR}^{34C}\text{R}^{35C}$, $-\text{COOR}^{33C}$, $-\text{CONR}^{34C}\text{R}^{35C}$, $-\text{NO}_2$, $-\text{SR}^{36C}$, $-\text{SO}_{n3}\text{R}^{34C}$, $-\text{SO}_{n3}\text{OR}^{34C}$, $-\text{SO}_{n3}\text{NR}^{34C}\text{R}^{35C}$, $-\text{NHR}^{34C}\text{R}^{35C}$, $-\text{ONR}^{34C}\text{R}^{35C}$, $-\text{NHC(O)NHR}^{34C}\text{R}^{35C}$, substituted 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

15 is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33D}$, $-\text{NR}^{34D}\text{R}^{35D}$, $-\text{COOR}^{33D}$, $-\text{CONR}^{34D}\text{R}^{35D}$, $-\text{NO}_2$, $-\text{SR}^{36D}$, $-\text{SO}_{n4}\text{R}^{34D}$, $-\text{SO}_{n4}\text{OR}^{34D}$, $-\text{SO}_{n4}\text{NR}^{34D}\text{R}^{35D}$, $-\text{NHR}^{34D}\text{R}^{35D}$, $-\text{ONR}^{34D}\text{R}^{35D}$, $-\text{NHC(O)NHR}^{34D}\text{R}^{35D}$, substituted 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

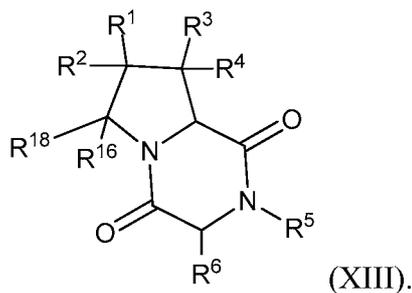
20 is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33E}$, $-\text{NR}^{34E}\text{R}^{35E}$, $-\text{COOR}^{33E}$, $-\text{CONR}^{34E}\text{R}^{35E}$, $-\text{NO}_2$, $-\text{SR}^{36E}$, $-\text{SO}_{n5}\text{R}^{34E}$, $-\text{SO}_{n5}\text{OR}^{34E}$, $-\text{SO}_{n5}\text{NR}^{34E}\text{R}^{35E}$, $-\text{NHR}^{34E}\text{R}^{35E}$, $-\text{ONR}^{34E}\text{R}^{35E}$, $-\text{NHC(O)NHR}^{34E}\text{R}^{35E}$, substituted 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

25 is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33F}$, $-\text{NR}^{34F}\text{R}^{35F}$, $-\text{COOR}^{33F}$, $-\text{CONR}^{34F}\text{R}^{35F}$, $-\text{NO}_2$, $-\text{SR}^{36F}$, $-\text{SO}_{n6}\text{R}^{34F}$, $-\text{SO}_{n6}\text{OR}^{34F}$, $-\text{SO}_{n6}\text{NR}^{34F}\text{R}^{35F}$, $-\text{NHR}^{34F}\text{R}^{35F}$, $-\text{ONR}^{34F}\text{R}^{35F}$, $-\text{NHC(O)NHR}^{34F}\text{R}^{35F}$, substituted 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^{16}

30 is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33G}$, $-\text{NR}^{34G}\text{R}^{35G}$, $-\text{COOR}^{33G}$, $-\text{CONR}^{34G}\text{R}^{35G}$, $-\text{NO}_2$, $-\text{SR}^{36G}$, $-\text{SO}_{n7}\text{R}^{34G}$, $-\text{SO}_{n7}\text{OR}^{34G}$, $-\text{SO}_{n7}\text{NR}^{34G}\text{R}^{35G}$,

-NHN^{34G}R^{35G}, -ONR^{34G}R^{35G}, -NHC(O)NHN^{34G}R^{35G}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R¹⁸ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33H},
 5 -NR^{34H}R^{35H}, -COOR^{33H}, -CONR^{34H}R^{35H}, -NO₂, -SR^{36H}, -SO_{n8}R^{34H}, -SO_{n8}OR^{34H},
 -SO_{n8}NR^{34H}R^{35H}, -NHN^{34H}R^{35H}, -ONR^{34H}R^{35H}, -NHC(O)NHN^{34H}R^{35H}, substituted 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^{33A}, R^{34A}, R^{35A}, R^{36A}, R^{33B}, R^{34B}, R^{35B}, R^{36B}, R^{33C}, R^{34C},
 10 R^{35C}, R^{36C}, R^{33D}, R^{34D}, R^{35D}, R^{36D}, R^{33E}, R^{34E}, R^{35E}, R^{36E}, R^{33F}, R^{34F}, R^{35F}, R^{36F}, R^{33G}, R^{34G}, R^{35G}, R^{36G}, R^{33H}, R^{34H}, R^{35H}, and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol n1, n2, n3, n4, n5, n6, n7, and n8 are independently 1 or 2. R²⁵ and R²⁶
 15 are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0009] In another aspect is a compound having formula:



[0010] R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A},
 20 -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A},
 -SO_{n1}NR^{34A}R^{35A}, -NHN^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHN^{34A}R^{35A}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃,
 25 -Cl₃, -CN, -CHO, -OR^{33B}, -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -SO_{n2}R^{34b},

-SO_{n8}NR^{34H}R^{35H}, -NHN^{34H}R^{35H}, -ONR^{34H}R^{35H}, -NHC(O)NHN^{34H}R^{35H}, substituted 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^{33A}, R^{34A}, R^{35A}, R^{36A}, R^{33B}, R^{34B}, R^{35B}, R^{36B}, R^{33C}, R^{34C}, R^{35C}, R^{36C}, R^{33D}, R^{34D}, R^{35D}, R^{36D}, R^{33E}, R^{34E}, R^{35E}, R^{36E}, R^{33F}, R^{34F}, R^{35F}, R^{36F}, R^{33G}, R^{34G}, R^{35G}, R^{36G}, R^{33H}, R^{34H}, R^{35H}, and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol n1, n2, n3, n4, n5, n6, n7, and n8 are independently 1 or 2.

10 **[0011]** In another aspect a pharmaceutical composition is provided. The pharmaceutical composition includes a compound as provided herein (e.g. of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)) and a pharmaceutically acceptable excipient.

15 **[0012]** In another aspect, a pharmaceutical composition is provided including a compound as provided herein (e.g. of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), a pharmaceutically acceptable excipient, and at least one additional anticancer agent.

20 **[0013]** In another aspect a method of treating cancer is provided. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), including embodiments thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **Figure 1:** Synthesis of racemic ETP derivatives herein: the three step synthesis results in a 5:1 ratio of epimeric derivatives 3 and 4.

25 **[0015]** **Figure 2:** Synthesis of ETP69: installation of the disulfide bridge results in compounds 5 (e.g. ETP69) and compound 6 with an overall 10% yield.

[0016] **Figure 3:** Enantioselective synthetic route for ETP derivatives: enantiomerically pure (S) and (R) derivatives of ETP derivatives may be synthesized from racemic starting material 1.

[0017] **Figure 4:** Comparison of ETP69 enantiomeric activity on MOLM-13 AML cells. The (S) enantiomer of ETP69 shows about a 4x fold increase in inhibitory capacity when compared to the (R) enantiomer.

5 [0018] **Figure 5:** Testing of enantiomerically pure ETP69 shows the (S) enantiomer to be slightly more active than the racemic mixture or the (R) enantiomer; compounds were tested in 10-dose IC₅₀ mode with 3-fold serial dilution starting at 10 μM; curve fits were performed with the activities at the highest concentration of compounds were less than 65%.

10 [0019] **Figure 6:** Testing of ETP analogues described herein against various cancer cell lines: A) shows viability inhibition on DU145 prostate cancer cells, A2058 melanoma cells, and SKOV3 ovarian cancer cells by ETP analogues described herein; B) shows viability inhibition on HCC38, HCC1937, MDA-MB-231, and MDA-MB-468 triple negative breast cancer cells after administration of ETP69; C) shows inhibition of H3K9 trimethylation by ETP69 in A2058 melanoma cells.

15 [0020] **Figure 7:** ETP69 selectively inhibits SUV39H1 and G9a *in vitro*. Comparison of inhibition of ETP69 and known HMT inhibitor Chaetocin shows SUV39H1 and G9a selectivity inhibited by ETP69.

[0021] **Figure 8:** ETP derivatives induce p16 tumor suppressor. ETP69 induces p16 tumor suppressor in DU145 prostate cancer cells and A2058 melanoma cells. *SKOV3 ovarian cancer cells and A549 non-small cell lung cancer cells are p16-null.

20 [0022] **Figure 9:** ETP derivatives induce p53 tumor suppressor, p21WAF1 cyclin-dependent kinase inhibitor 1 and Cyclin-dependent kinase inhibitor 1B p27(Kip1): ETP69 induces p53, p21WAF1 and p27(Kip1) in A2058 melanoma cells, DU145 prostate cancer cells, A549 lung cancer cells, and SKOV3 ovarian cancer cells. *SKOV3 cells do not express p53 protein.

25 [0023] **Figure 10:** FLT3 assays with ETP derivative ETP69: Fms-like tyrosine kinase 3 (FLT3) expressed in AMLs is not directly inhibited by ETP69 (S) enantiomer showing antitumor activities from ETP derivatives is not a result of FLT3 inhibition. MV4-11 and MOLM-13 AML cells have internal tandem duplications of FLT3 (FLT-ITD) – these mutations result in a low outcome with a higher relapse rate.

[0024] **Figure 11:** Effect of ETP69 on SKOV3 ovarian cancer cells: ETP69 induces apoptosis of SKOV3 ovarian cancer cells.

[0025] **Figure 12:** Synergistic effect of ETP and epigenetic inhibitors. ETP69 and azacitidine exhibit a greater effect on reducing viabilities of SKOV3 ovarian cells than when administered
5 alone.

[0026] **Figure 13:** Synergistic effect of ETP and epigenetic inhibitors. ETP69 and decitabine exhibit a greater effect on reducing viabilities of SKOV3 ovarian cells than when administered alone.

[0027] **Figure 14:** Synergistic effect of ETP derivatives and multi-kinase inhibitors. ETP 69 and sorafenib exhibit a greater effect on reducing viabilities of A549 non-small cell lung cancer cells than when administer alone.
10

[0028] **Figure 15:** Efficacy of ETP69 on A549 lung cancer SQ xenografts. Treatment with ETP69 results in decreased tumor volume and tumor weight of mice with no observable toxicity symptoms.

[0029] **Figure 16:** Efficacy of ETP69 on A2058 melanoma SQ xenografts. Treatment with ETP69 results in decreased tumor volume and tumor weight of mice with no observable toxicity symptoms.
15

[0030] **Figure 17:** Efficacy of ETP69 on SKOV3 xenografts. Treatment with ETP69 results in decreased tumor volume and tumor weight of mice with no observable toxicity symptoms.

[0031] **Figure 18:** Efficacy of ETP417 on MV4-11 AML SQ xenografts: Treatment with ETP417 results in decreased tumor volume and tumor weight of mice with no observable toxicity symptoms.
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[0032] **Figure 19:** Pharmacokinetic parameters for intraperitoneal administration of ETP69 in male CD-1 mice: C_0 : Maximum plasma concentration extrapolated to $t=0$; t_{max} : Time of maximum plasma concentration; $t_{1/2}$: half-life, data points used for half-life determination are in bold; AUC_{last} : Area Under the Curve, calculated to the last observable time point; AUC_{∞} : Area Under the Curve, extrapolated to infinity; ND: Not Determined; BLOQ: Below the limit of
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quantitation (2.5 ng/mL); ^aValues are estimates because the correlation coefficient for the half-life determination was <0.85 (actual value was 0.838).

[0033] Figure 20: Pharmacokinetic parameters for oral administration of ETP69 in male CD-1 mice: C₀:Maximum plasma concentration extrapolated to t=0; t_{max}: Time of maximum plasma concentration; t_{1/2}: half-life, data points used for half-life determination are in bold; AUC_{last}: Area Under the Curve, calculated to the last observable time point; AUC_∞: Area Under the Curve, extrapolated to infinity; ND: Not Determined; BLOQ: Below the limit of quantitation (2.5 ng/mL)

[0034] Figure 21: Effect of ETP69 on A549 lung cancer cells: ETP69 displays antitumor activities with IC₅₀ of 0.1 μM against A549 non-small cell lung cancer cells.

[0035] Figure 22: Effect of ETP69 on liver cancer cells: ETP69 displays IC₅₀ values of 3.3 nM and 13.8 nM against Huh-7 and HepG2 hepatocellular carcinoma cells respectively.

[0036] Figure 23: Effect of ETP69 on pancreatic cancer cells: ETP69 displays IC₅₀ values of 86 nM, 210 nM and 824 nM against Su.86.86, BxPC3, and Panc1 pancreatic cancer cell lines respectively.

[0037] Figure 24: Effect of ETP69 on MV4-11 AML, KCL-22 CML and T315I mutant KCL-22 CML cells: ETP69 displays IC₅₀ values of 1.8 nM, 180 nM, and 170 nM against MV4-11 AML, KCL-22 CML and T315I mutant KCL-22 CML cells respectively.

[0038] Figure 25: Effect of ETP enantiomers on activity against AML cells: ETP417 (e.g. S enantiomer) has significantly greater activity than its corresponding R enantiomer (ETP422).

[0039] Figure 26: SUV39H1 expression levels in normal pancreas and Panc1 cancer cells: normal pancreas cells express less SUV39H1 than the Panc1 cancer cell line.

[0040] Figure 27: Stable SUV39H1 Knockdown in Pancreatic Cancer Cells: SUV39H1 expression levels of BxPC3, SU.86.86 and Panc1 cells expressing SUV39H1 shRNA are reduced by 73%, 77% and 90%, respectively, compared to unmodified cells. Cell lines expressing a non-targeting control shRNA (NT) were generated as controls.

[0041] **Figure 28:** p53 Up-Regulation Following SUV39H1 Knockdown or Treatment with ETP69 in Panc1 cells: Treatment with increasing concentrations (100 nM-500 nM) of ETP69 or shRNA-mediated knockdown of SUV39H1 leads to ≥ 3 -fold up-regulation of p53 in Panc1 cells.

[0042] **Figure 29:** SUV39H1 knockdown increases senescence in pancreatic cancer cells

5 -Senescence-associated b-galactosidase activity: SU.86.86 and Panc1 cells expressing SUV39H1shRNA show increased senescence-associated beta-galactosidase activity, as evidenced by the blue stain. No senescence-associated beta-galactosidase activity was detected in the control cells expressing a non-targeting (NT) shRNA.

[0043] **Figure 30:** SUV39H1 Knockdown Increases Senescence in SU.86.86: SU.86.86 cells

10 expressing SUV39H1shRNA show increased senescence-associated beta-galactosidase activity, as evidenced by the blue stain. No senescence-associated beta-galactosidase activity was detected in the control cells expressing a non-targeting (NT) shRNA.

[0044] **Figure 31:** ETP69 induces senescence in Panc1 cancer cells in senescence-associated

15 beta-galactosidase activity: Panc1 pancreatic cancer cells treated with ETP69 for 5 days show increased senescence-associated beta-galactosidase activity (blue stain) compared to Panc1 cells treated with DMSO (vehicle control).

[0045] **Figure 32:** SUV31H1 knockdown assay decreases cell mobility in wound healing

20 assay. BxPC3 cells expressing (shRNA-mediated) low levels of SUV39H1 migrate into denuded areas (between the arrows) in cell monolayers at a lower rate than unmodified BxPC3 cells, failing to close the "wound" within 24h.

[0046] **Figure 33:** Viability of normal pancreatic epithelial cells after treatment with ETP69:

treatment of normal pancreatic epithelial cells with ETP69 at doses from 100 nM to 1000 nM shows little destruction of normal pancreatic cells but significant killing of cells from BxPC3 and SU86.86 pancreatic cancer cell lines.

25 [0047] **Figure 34:** Effect of racemic and enantiomers on colon cancer cells: ETP417 displays greater viability inhibition on HCT116 colon cancer cells than ETP422 and the ETP69.

[0048] **Figure 35** Inhibition of various HMTs, histone acetyltransferases (HAT) and DNMTs:

ETP69 shows specific inhibition of HMT SUV31H1 and G9a, but not HAT p300 and DNMT1.

[0049] **Figure 36:** CD Data for the two enantiomers of ETP69: (3*S*,6*S*,7*S*,8*aS*): $t_{\text{ret}} = 1.40$ min (red); (3*R*,6*R*,7*R*,8*aR*): $t_{\text{ret}} = 2.11$ min (blue) in EtOH ($c \approx 10^{-4}$ M). See text for details.

DETAILED DESCRIPTION

5 I. Definitions

[0050] 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.

[0051] Where substituent groups are specified by their conventional chemical formulae,
10 written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0052] 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
15 multivalent radicals, having the number of carbon atoms designated (i.e., $\text{C}_1\text{-C}_{10}$ means one to ten carbons). 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, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds.
20 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-butynyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker ($-\text{O}-$).

[0053] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise
25 stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group,

generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0054] 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 selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, B, As, and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to: $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$, $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$, $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$, $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$, $-\text{O}-\text{CH}_3$, $-\text{O}-\text{CH}_2-\text{CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ and $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$.

[0055] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'-$ represents both $-\text{C}(\text{O})_2\text{R}'-$ and $-\text{R}'\text{C}(\text{O})_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like.

[0056] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl,”

respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

10 **[0057]** 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.

15 **[0058]** 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.

[0059] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-

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fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene” and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be a -O- bonded to a ring heteroatom nitrogen.

[0060] A “fused ring aryl-heterocycloalkyl” is an aryl fused to a heterocycloalkyl. A “fused ring heteroaryl-heterocycloalkyl” is a heteroaryl fused to a heterocycloalkyl. A “fused ring heterocycloalkyl-cycloalkyl” is a heterocycloalkyl fused to a cycloalkyl. A “fused ring heterocycloalkyl-heterocycloalkyl” is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring aryl-heterocycloalkyl, fused ring heteroaryl-heterocycloalkyl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substituents described herein. Fused ring aryl-heterocycloalkyl, fused ring heteroaryl-heterocycloalkyl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be named according to the size of each of the fused rings. Thus, for example, 6,5 aryl-heterocycloalkyl fused ring describes a 6 membered aryl moiety fused to a 5 membered heterocycloalkyl. 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.

[0061] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0062] The term “thio,” as used herein, means a sulfur that is single bonded to carbon or to another sulfur.

[0063] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “aryl,” and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0064] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, $-OR'$, $=O$, $=NR'$, $=N-OR'$, $-NR'R''$, $-SR'$, $-halogen$, $-SiR'R''R'''$, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, $-NR''C(O)R'$, $-NR'-C(O)NR''R'''$, $-NR''C(O)_2R'$, $-NR-C(NR'R''R''')=NR''''$, $-NR-C(NR'R'')=NR''''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, $-NR'NR''R'''$, $-ONR'R''$, $-NR'C(O)NR''NR''''R''''$, $-CN$, $-NO_2$, $-NR'SO_2R''$, $-NR'C(O)R''$, $-NR'C(O)-OR''$, $-NR'OR''$, in a number ranging from zero to $(2m'+1)$, where m' is the total number of carbon atoms in such radical. R , R' , R'' , R''' , and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound of the invention 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).

[0065] 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''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 of the invention 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.

[0066] 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 or 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.

[0067] 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.

[0068] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally form a ring of the formula $-T-C(O)-(CRR')_q-U-$, wherein T and U are independently $-NR-$, $-O-$, $-CRR'-$, or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently $-CRR'-$, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'-$, or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be

replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R''R''')_d-$, where s and d are independently integers of from 0 to 3, and X' is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R , R' , R'' , and R''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0069] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include, oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), Boron (B), Arsenic (As), and silicon (Si).

10 **[0070]** A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, $-CF_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(i) oxo, halogen, $-CF_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCHF_2$, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

(a) oxo, halogen, $-CF_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCF_3$, $-OCHF_2$, unsubstituted

alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

(b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from: oxo,

5 halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

10 **[0071]** 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
15 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl.

[0072] 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
20 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, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl.

[0073] In some embodiments, each substituted group described in the compounds herein is
25 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
30 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.

[0074] 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, and/or each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. 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, and/or each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene.

[0075] 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, and/or each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl. 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, and/or each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene.

[0076] Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which 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.

5 [0077] 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.

[0078] 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.

10 [0079] 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.

[0080] 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, generally recognized as stable by those skilled in the art, are within the scope of the invention.

[0081] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0082] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

[0083] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0084] “S_p”, “S_t”, or “S_n” refers to a sulfide bridge having p, t, or n sulfurs (e.g. S₂ is -S-S-, S₃ is -S-S-S-, S₄ is -S-S-S-S-).

5 [0085] 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
10 one or more unsubstituted 2 to 20 membered heteroalkyls.

[0086] 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
15 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.

[0087] Description of compounds of the present invention is limited by principles of chemical
20 bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a
25 heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0088] The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular

substituents found on the compounds described herein. When compounds of the present 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 galacturonic 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.

[0089] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

[0090] 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 differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0091] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein include those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0092] 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.

[0093] As used herein, the term "salt" refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[0094] The terms "treating", or "treatment" refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. The term "treating" and conjugations thereof, include prevention of an injury, pathology, condition, or disease.

[0095] A "therapeutically effective amount" or "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
5 grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). 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
10 *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0096] “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
15 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).

[0097] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference
20 to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein relative to the activity or function of the protein in the absence of the inhibitor. In some embodiments inhibition refers to reduction of a disease or symptoms of disease. In some embodiments, inhibition refers to a reduction in the activity of a particular protein or nucleic acid target. Thus, inhibition includes, at least in part, partially or totally
25 blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein.

[0098] “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
30 biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It

should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

5 [0099] 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.

10 [0100] “Patient,” “subject,” “patient in need thereof,” and “subject in need thereof” are herein used interchangeably and refer to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals. In some embodiments, a patient is human.

15 [0101] “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.

[0102] “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
20 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
25 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.

[0103] 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.

5 Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0104] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including

10 parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.*

15 [0105] By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example epigenetic inhibitors or multi-kinase inhibitors. The compound of the invention can be administered alone or can be co-administered to the patient. Co-administration is meant to include simultaneous or sequential administration of the compound individually or in

20 combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.* to reduce metabolic degradation).

[0106] The compositions disclosed herein can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder,

25 dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, *etc.*, suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained

30 release and/or comfort. Such components include high molecular weight, anionic mucomimetic

polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions disclosed herein can also be delivered as microspheres for slow
5 release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the
10 compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the
15 delivery of the compositions of the present invention into the target cells *in vivo*. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions can also be delivered as nanoparticles.

[0107] Pharmaceutical compositions may include compositions wherein the active ingredient
20 (e.g. compounds described herein, including embodiments or examples) is contained in a therapeutically effective amount, *i.e.*, in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia*, on the condition being treated. When administered in methods to treat a disease, such compositions will contain an amount of active ingredient effective to achieve the desired result, e.g., modulating the
25 activity of a target molecule, and/or reducing, eliminating, or slowing the progression of disease symptoms.

[0108] The dosage and frequency (single or multiple doses) administered to a mammal can vary depending upon a variety of factors, for example, whether the mammal suffers from another disease, and its route of administration; size, age, sex, health, body weight, body mass index, and
30 diet of the recipient; nature and extent of symptoms of the disease being treated, kind of

concurrent treatment, complications from the disease being treated or other health-related problems. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of Applicants' invention. Adjustment and manipulation of established dosages (e.g., frequency and duration) are well within the ability of those skilled in the art.

5 [0109] 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.

10 [0110] 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
15 ordinarily skilled artisan.

[0111] 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
20 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
25 clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0112] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease means that the disease is caused by (in whole or in part), a symptom of the disease is caused by (in whole or in part) the substance or substance

activity or function, or a side-effect of the compound (e.g. toxicity) is caused by (in whole or in part) the substance or substance activity or function.

[0113] As used herein, the term "cancer" refers to all types of cancer, neoplasm, or malignant tumors found in mammals, including leukemia, carcinomas and sarcomas. Exemplary cancers include acute myeloid leukemia ("AML"), chronic myelogenous leukemia ("CML"), and cancer of the brain, breast, pancreas, colon, liver, kidney, lung, non-small cell lung, melanoma, ovary, sarcoma, and prostate. Additional examples include, cervix cancers, stomach cancers, head & neck cancers, uterus cancers, mesothelioma, metastatic bone cancer, Medulloblastoma, Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine and exocrine pancreas, and prostate cancer

[0114] The term "leukemia" refers broadly to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic (subleukemic). The murine leukemia model is widely accepted as being predictive of in vivo anti-leukemic activity. It is believed that a compound that tests positive in the P388 cell assay will generally exhibit some level of anti-leukemic activity regardless of the type of leukemia being treated. Accordingly, the present invention includes a method of treating leukemia, including treating acute myeloid leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemmic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute monocytic leukemia, leukopenic

leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocytic leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblastic leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, and undifferentiated cell leukemia.

[0115] The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas which can be treated with a combination of antineoplastic thiol-binding mitochondrial oxidant and an anticancer agent include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, and telangiectaltic sarcoma.

[0116] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas which can be treated with a combination of antineoplastic thiol-binding mitochondrial oxidant and an anticancer agent include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungal melanoma, and superficial spreading melanoma.

[0117] 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

which can be treated with a combination of antineoplastic thiol-binding mitochondrial oxidant and an anticancer agent include, for example, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epiermoid carcinoma, carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypemephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucozellulare, 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, scirrhous carcinoma, carcinoma scroti, signet-ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell carcinoma, carcinoma spongiosum, squamous carcinoma, squamous cell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tuberous carcinoma, verrucous carcinoma, and carcinoma villosum.

[0118] Cancer model organism, as used herein, is an organism exhibiting a phenotype indicative of cancer, or the activity of cancer causing elements, within the organism. The term cancer is defined above. A wide variety of organisms may serve as cancer model organisms, and

include for example, cancer cells and mammalian organisms such as rodents (e.g. mouse or rat) and primates (such as humans). Cancer cell lines are widely understood by those skilled in the art as cells exhibiting phenotypes or genotypes similar to in vivo cancers. Cancer cell lines as used herein includes cell lines from animals (e.g. mice) and from humans.

- 5 **[0119]** An “anticancer agent” as used herein refers to a molecule (e.g. compound, peptide, protein, nucleic acid, antibody) used to treat cancer through destruction or inhibition of cancer cells or tissues. Anticancer agents may be selective for certain cancers or certain tissues. In embodiments, anticancer agents herein may include epigenetic inhibitors and multi-kinase inhibitors.
- 10 **[0120]** An “epigenetic inhibitor” as used herein, refers to an inhibitor of an epigenetic process, such as DNA methylation (a DNA methylation Inhibitor) or modification of histones (a Histone Modification Inhibitor). An epigenetic inhibitor may be a histone-deacetylase (HDAC) inhibitor, a DNA methyltransferase (DNMT) inhibitor, a histone methyltransferase (HMT) inhibitor, a histone demethylase (HDM) inhibitor, or a histone acetyltransferase (HAT). Examples of
15 HDAC inhibitors include Vorinostat, romidepsin, CI-994, Belinostat, Panobinostat, Givinostat, Entinostat, Mocetinostat, SRT501, CUDC-101, JNJ-26481585, or PCI24781. Examples of DNMT inhibitors include azacitidine and decitabine. Examples of HMT inhibitors include EPZ-5676. Examples of HDM inhibitors include pargyline and tranlycypromine. Examples of HAT inhibitors include CCT077791 and garcinol.
- 20 **[0121]** A “multi-kinase inhibitor” is a small molecule inhibitor of at least one protein kinase, including tyrosine protein kinases and serine/threonine kinases. A multi-kinase inhibitor may include a single kinase inhibitor. Multi-kinase inhibitors may block phosphorylation. Multi-kinases inhibitors may act as covalent modifiers of protein kinases. Multi-kinase inhibitors may bind to the kinase active site or to a secondary or tertiary site inhibiting protein kinase activity.
25 A multi-kinase inhibitor may be an anti-cancer multi-kinase inhibitor. Exemplary anti-cancer multi-kinase inhibitors include dasatinib, sunitinib, erlotinib, bevacizumab, vatalanib, vemurafenib, vandetanib, cabozantinib, poatinib, axitinib, ruxolitinib, regorafenib, crizotinib, bosutinib, cetuximab, gefitinib, imatinib, lapatinib, lenvatinib, mubritinib, nilotinib, panitumumab, pazopanib, trastuzumab, or sorafenib.

[0122] “Selective” or “selectivity” or the like of a compound refers to the compound’s ability to discriminate between molecular targets (e.g. a compound having selectivity toward HMT SUV39H1 and/or HMT G9a).

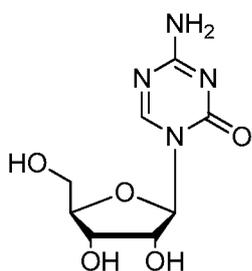
5 [0123] “Specific”, “specifically”, “specificity”, or the like of a compound refers to the compound’s ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell (e.g. a compound having specificity towards HMT SUV39H1 and/or HMT G9a displays inhibition of the activity of those HMTs whereas the same compound displays little-to-no inhibition of other HMTs such as DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR,
10 SMYD2, SUV39H2).

[0124] “HMT SUV39H1,” “SUV39H1,” or “suppressor of varigation 3-9 homolog 1” is a histone methyltransferase protein that trimethylates H3K9 (NCBI GI No. 49456451). HMT SUV39H1 may methylate H3K9.

15 [0125] “HMT G9a” or “G9a” is a histone methyltransferase that dimethylates H3K9 (NCBI GI No. 287865). HMT G9a may dimethylate H3K9.

[0126] “H3K9 trimethylation” refers to tri-methylation of lysine 9 of Histone H3. H3K9 trimethylation may be performed by histone methyl transferases such as SUV39H1.

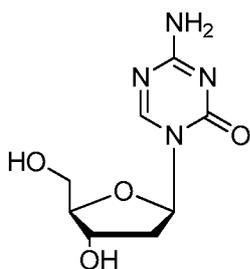
[0127] Azacitidine is an epigenetic inhibitor having the formula:



, including pharmaceutically acceptable salts thereof.

20 [0128] Azacitidine is an anti-cancer epigenetic inhibitor.

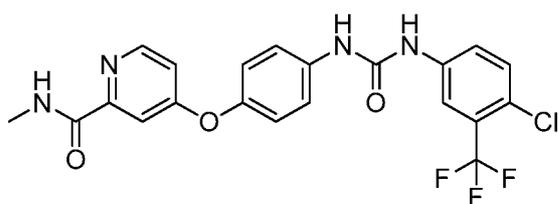
[0129] Decitadine is an epigenetic inhibitor having the formula:



including pharmaceutically acceptable salts thereof.

[0130] Decitadine is an anti-cancer epigenetic inhibitor.

[0131] Sorafenib is a multi-kinase inhibitor having the formula:



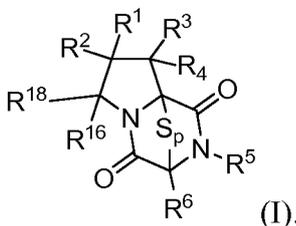
including pharmaceutically acceptable salts thereof.

5 [0132] Sorafenib is an anti-cancer multi-kinase inhibitor.

[0133] The terms “synergy”, “synergism”, “synergistic” and “synergistic therapeutic effect” are used herein interchangeably and refer to a measured effect of compounds administered in combination where the measured effect is greater than the sum of the individual effects of each of the compounds administered alone as a single agent.

10 II. Compositions

[0134] In a first aspect is a compound having the formula:



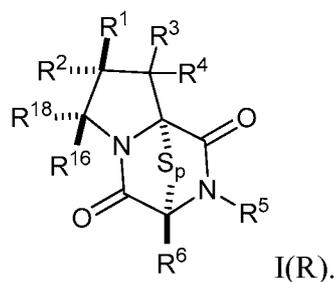
[0135] The symbol p is 2, 3 or 4. R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A}, -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A}, -SO_{n1}NR^{34A}R^{35A}, -NHN^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHN^{34A}R^{35A}, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33B}$, $-NR^{34B}R^{35B}$, $-COOR^{33B}$, $-CONR^{34B}R^{35B}$, $-NO_2$, $-SR^{36B}$, $-SO_{n2}R^{34b}$, $-SO_{n2}OR^{34B}$, $-SO_{n2}NR^{34B}R^{35B}$, $-NHNr^{34B}R^{35B}$, $-ONR^{34B}R^{35B}$, $-NHC(O)NHNr^{34B}R^{35B}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33C}$, $-NR^{34C}R^{35C}$, $-COOR^{33C}$, $-CONR^{34C}R^{35C}$, $-NO_2$, $-SR^{36C}$, $-SO_{n3}R^{34C}$, $-SO_{n3}OR^{34C}$, $-SO_{n3}NR^{34C}R^{35C}$, $-NHNr^{34C}R^{35C}$, $-ONR^{34C}R^{35C}$, $-NHC(O)NHNr^{34C}R^{35C}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33D}$, $-NR^{34D}R^{35D}$, $-COOR^{33D}$, $-CONR^{34D}R^{35D}$, $-NO_2$, $-SR^{36D}$, $-SO_{n4}R^{34D}$, $-SO_{n4}OR^{34D}$, $-SO_{n4}NR^{34D}R^{35D}$, $-NHNr^{34D}R^{35D}$, $-ONR^{34D}R^{35D}$, $-NHC(O)NHNr^{34D}R^{35D}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33E}$, $-NR^{34E}R^{35E}$, $-COOR^{33E}$, $-CONR^{34E}R^{35E}$, $-NO_2$, $-SR^{36E}$, $-SO_{n5}R^{34E}$, $-SO_{n5}OR^{34E}$, $-SO_{n5}NR^{34E}R^{35E}$, $-NHNr^{34E}R^{35E}$, $-ONR^{34E}R^{35E}$, $-NHC(O)NHNr^{34E}R^{35E}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33F}$, $-NR^{34F}R^{35F}$, $-COOR^{33F}$, $-CONR^{34F}R^{35F}$, $-NO_2$, $-SR^{36F}$, $-SO_{n6}R^{34F}$, $-SO_{n6}OR^{34F}$, $-SO_{n6}NR^{34F}R^{35F}$, $-NHNr^{34F}R^{35F}$, $-ONR^{34F}R^{35F}$, $-NHC(O)NHNr^{34F}R^{35F}$, substituted 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^{16} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33G}$, $-NR^{34G}R^{35G}$, $-COOR^{33G}$, $-CONR^{34G}R^{35G}$, $-NO_2$, $-SR^{36G}$, $-SO_{n7}R^{34G}$, $-SO_{n7}OR^{34G}$, $-SO_{n7}NR^{34G}R^{35G}$, $-NHNr^{34G}R^{35G}$, $-ONR^{34G}R^{35G}$, $-NHC(O)NHNr^{34G}R^{35G}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted

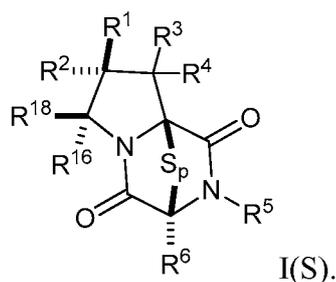
heteroaryl. R^{18} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33H}$, $-NR^{34H}R^{35H}$, $-COOR^{33H}$, $-CONR^{34H}R^{35H}$, $-NO_2$, $-SR^{36H}$, $-SO_{n8}R^{34H}$, $-SO_{n8}OR^{34H}$, $-SO_{n8}NR^{34H}R^{35H}$, $-NHNR^{34H}R^{35H}$, $-ONR^{34H}R^{35H}$, $-NHC(O)NHNR^{34H}R^{35H}$, substituted 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^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} , R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} , and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbols $n1$, $n2$, $n3$, $n4$, $n5$, $n6$, $n7$, and $n8$ are independently 1 or 2.

[0136] R^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} , R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} , and R^{36H} may independently be hydrogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0137] In embodiments, the compound may have the formula:



[0138] In embodiments, the compound may have the formula:



[0139] The symbol p may be 2. The symbol p may be 3. The symbol p may be 4.

[0140] R¹ may be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂,

5 -NHC(O)NHNH₂, substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), or substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl). R¹ may be halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R¹ may be -CN, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R¹ may be -CN or substituted or unsubstituted alkyl. R¹ may be -CN or unsubstituted alkyl. R¹ may be -CN, or unsubstituted heteroalkyl.

10 [0141] R¹ may be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R¹ may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, or unsubstituted membered heteroaryl.

15 [0142] R¹ may be substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 or 8 membered heteroaryl. R¹ may be unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 or 8 membered heteroaryl.

25 [0143] R¹ may be substituted or unsubstituted C₁-C₅ alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. R¹ may be unsubstituted C₁-C₅ alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3-6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0144] R¹ may be substituted or unsubstituted C₁-C₃ alkyl, substituted or unsubstituted 2 to 3 membered heteroalkyl. R¹ may be substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R¹ may be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, or substituted or unsubstituted 6 membered heterocycloalkyl. R¹ may be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, or substituted or unsubstituted 6 membered heteroaryl. R¹ may be unsubstituted C₁-C₃ alkyl or unsubstituted 2 to 3 membered heteroalkyl. R¹ may be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R¹ may be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, or unsubstituted 6 membered heterocycloalkyl. R¹ may be unsubstituted 5 membered aryl, unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, or unsubstituted 6 membered heteroaryl.

[0145] R¹ may be R^{1a}-substituted or unsubstituted alkyl, R^{1a}-substituted or unsubstituted heteroalkyl, R^{1a}-substituted or unsubstituted cycloalkyl, R^{1a}-substituted or unsubstituted heterocycloalkyl, R^{1a}-substituted or unsubstituted aryl, or R^{1a}-substituted or unsubstituted heteroaryl. R¹ may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0146] R¹ may be R^{1a}-substituted or unsubstituted C₁-C₈ alkyl, R^{1a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{1a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{1a}-substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{1a}-substituted or unsubstituted 5 to 8 membered aryl, or R^{1a}-substituted or unsubstituted 5 to 8 membered heteroaryl. R¹ may be unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 to 8 membered heteroaryl.

[0147] R¹ may be R^{1a}-substituted or unsubstituted C₁-C₅ alkyl, R^{1a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{1a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{1a}-substituted or unsubstituted 3-6 membered heterocycloalkyl, R^{1a}-substituted or unsubstituted 5 to 6 membered aryl, or R^{1a}-substituted or unsubstituted 5 to 6 membered heteroaryl. R¹ may be unsubstituted C₁-C₅ alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5

membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, or unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl. .

[0148] R¹ may be R^{1a}-substituted or unsubstituted C₁-C₃ alkyl or R^{1a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R¹ may be R^{1a}-substituted or unsubstituted 3 membered cycloalkyl, R^{1a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{1a}-substituted or unsubstituted 5 membered cycloalkyl. R¹ may be R^{1a}-substituted or unsubstituted 5 membered heterocycloalkyl, R^{1a}-substituted or unsubstituted 6 membered heterocycloalkyl, R^{1a}-substituted or unsubstituted 5 membered aryl, R^{1a}-substituted or unsubstituted 6 membered aryl, R^{1a}-substituted or unsubstituted 5 membered heteroaryl, or R^{1a}-substituted or unsubstituted 6 membered heteroaryl. R¹ may be unsubstituted C₁-C₃ alkyl or unsubstituted 2 to 3 membered heteroalkyl. R¹ may be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl, unsubstituted 5 membered cycloalkyl, unsubstituted 5 membered heterocycloalkyl, unsubstituted 6 membered heterocycloalkyl, unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, unsubstituted 5 membered heteroaryl, or unsubstituted 6 membered heteroaryl.

[0149] R¹ may be R^{1a}-substituted or unsubstituted methyl, R^{1a}-substituted or unsubstituted ethyl, or R^{1a}-substituted or unsubstituted propyl. R¹ may be methyl, ethyl, or propyl.

[0150] R¹ may be halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, NO₂, or -COOR^{33A}. R^{33A} may be hydrogen, C₁-C₃ unsubstituted alkyl, 2 to 5 membered unsubstituted heteroalkyl, or 5 or 6 membered unsubstituted aryl. In embodiments, R¹ is -COOR^{33A}, wherein R^{33A} is C₁-C₃ unsubstituted alkyl. R³³ may be unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl. R¹ may be -COOCH₃. R¹ may be halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -NH₂, or NO₂. R¹ may be -CN. R¹ may be unsubstituted 2 to 5 membered heteroalkyl.

[0151] R^{1a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{1b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{1b}-substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{1b}-substituted or unsubstituted cycloalkyl (e.g. C₃-C₈ cycloalkyl), R^{1b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{1b}-substituted or unsubstituted aryl (e.g. 5 or 6 membered aryl), or R^{1b}-substituted or unsubstituted heteroaryl (e.g. 5 or 6 membered heteroaryl).

[0152] R^{1b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alkyl (e.g. C₁-C₈ alkyl), heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. C₃-C₈ cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 or 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 or 6 membered heteroaryl).

[0153] R¹ may be an electron withdrawing group (EWG) (e.g. halogen, -N₃, -NO₂, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -CONH₂, or substituted or unsubstituted 2 to 8 membered heteroalkyl). An "electron withdrawing group" is used herein according to its common meaning in the art and refers to a chemical moiety that tends to remove electrons (electron density) from a portion of the compound to which it is attached (e.g. a deactivating group). R¹ may be -CN. R¹ may be -NO₂. R¹ may be -CF₃, -CCl₃, -CBr₃, or -Cl₃. R¹ may be substituted or unsubstituted 2 to 8 membered heteroalkyl. R¹ may be -COOCH₃.

[0154] R² may be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), or substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), or substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl). R² may be halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R² may be -CN, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R² may be -CN or substituted or unsubstituted alkyl. R² may be -CN or unsubstituted methyl. R² may be -CN, or unsubstituted heteroalkyl. R² may be substituted alkyl or substituted heteroalkyl.

[0155] R² may be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R² may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0156] R^2 may be substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 or 8 membered aryl, or substituted or unsubstituted 5 or 8 membered heteroaryl. R^2 may be unsubstituted C_1 - C_8 alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 or 8 membered aryl, or unsubstituted 5 or 8 membered heteroaryl.

[0157] R^2 may be substituted or unsubstituted C_1 - C_5 alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 or 6 membered aryl, or substituted or unsubstituted 5 or 6 membered heteroaryl. R^2 may be unsubstituted C_1 - C_5 alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, or unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 or 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl. R^2 may be unsubstituted C_1 - C_5 alkyl or unsubstituted 2 to 5 membered heteroalkyl.

[0158] R^2 may be substituted or unsubstituted C_1 - C_3 alkyl or substituted or unsubstituted 2 to 3 membered heteroalkyl. R^2 may be substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R^2 may be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, substituted or unsubstituted 6 membered heterocycloalkyl, substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, substituted or unsubstituted 5 membered heteroaryl, or substituted or unsubstituted 6 membered heteroaryl. R^2 may be unsubstituted C_1 - C_3 alkyl or unsubstituted 2 to 3 membered heteroalkyl. R^2 may be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R^2 may be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, unsubstituted 6 membered heterocycloalkyl, unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, unsubstituted 5 membered heteroaryl, or unsubstituted 6 membered heteroaryl.

[0159] R^2 may be R^{2a} -substituted or unsubstituted alkyl, R^{2a} -substituted or unsubstituted heteroalkyl, R^{2a} -substituted or unsubstituted cycloalkyl, R^{2a} -substituted or unsubstituted

heterocycloalkyl, R^{2a}-substituted or unsubstituted aryl, or R^{2a}-substituted or unsubstituted heteroaryl. R² may be R^{2a}-substituted or unsubstituted alkyl or R^{2a}-substituted or unsubstituted heteroalkyl.

[0160] R² may be R^{2a}-substituted or unsubstituted C₁-C₈ alkyl, R^{2a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{2a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{2a}-substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 5 or 8 membered aryl, or R^{2a}-substituted or unsubstituted 5 or 8 membered heteroaryl. R² may be R^{2a}-substituted or unsubstituted C₁-C₈ alkyl or R^{2a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{2a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{2a}-substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 5 to 8 membered aryl, or R^{2a}-substituted or unsubstituted 5 to 8 membered heteroaryl.

[0161] R² may be R^{2a}-substituted or unsubstituted C₁-C₅ alkyl, R^{2a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{2a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{2a}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 5 or 6 membered aryl, or R^{2a}-substituted or unsubstituted 5 to 6 membered heteroaryl. R² may be R^{2a}-substituted or unsubstituted C₁-C₅ alkyl or R^{2a}-substituted or unsubstituted 2 to 5 membered heteroalkyl.

[0162] R² may be R^{2a}-substituted or unsubstituted C₁-C₃ alkyl or R^{2a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R² may be R^{2a}-substituted or unsubstituted 3 membered cycloalkyl, R^{2a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{2a}-substituted or unsubstituted 5 membered cycloalkyl. R² may be R^{2a}-substituted or unsubstituted 4 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 5 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 6 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 5 membered aryl, R^{2a}-substituted or unsubstituted 6 membered aryl, R^{2a}-substituted or unsubstituted 5 membered heteroaryl, or R^{2a}-substituted or unsubstituted 6 membered heteroaryl.

[0163] R^{2a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{2b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{2b}-substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{2b}-substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{2b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6

5 membered heterocycloalkyl), R^{2b} -substituted or unsubstituted aryl (e.g. 5 or 6 membered aryl), or R^{2b} -substituted or unsubstituted heteroaryl (e.g. 5 or 6 membered heteroaryl). R^{2a} may be 3 to 6 membered heterocycloalkyl, R^{2b} -substituted or unsubstituted 5 or 6 membered aryl, or R^{2b} -substituted or unsubstituted 5 or 6 membered heteroaryl. R^{2a} may be unsubstituted pyridine. R^{2a} may be unsubstituted morpholino. R^{2a} may be unsubstituted methyl.

10 **[0164]** R^{2b} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, unsubstituted alkyl (e.g. C_1 - C_8 alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 or 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 or 6 membered heteroaryl).

15 **[0165]** R^2 may be hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, R^{2a} -substituted or unsubstituted C_1 - C_8 alkyl, R^{2a} -substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{2a} -substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{2a} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2a} -substituted or unsubstituted 5 or 6 membered aryl, or R^{2a} -substituted or unsubstituted 5 or 6 membered heteroaryl. R^2 may be $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2Ph$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, R^{2a} -substituted or unsubstituted C_1 - C_3 alkyl, or 1 to 3 membered R^{2a} -substituted or unsubstituted heteroalkyl. In embodiments R^2 is unsubstituted C_1 - C_5 alkyl or unsubstituted 2 to 5 membered heteroalkyl. In embodiments R^2 is unsubstituted methyl. In embodiments R^2 is unsubstituted methoxy (e.g. $-OCH_3$).

25 **[0166]** R^2 may be R^{2a} -substituted or unsubstituted C_1 - C_5 alkyl (e.g. R^{2a} -substituted or unsubstituted methylene). R^2 may be R^{2a} -substituted C_1 - C_5 alkyl. When R^2 is substituted or unsubstituted C_1 - C_5 alkyl, R^{2a} may be unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl. R^{2a} may be unsubstituted or unsubstituted morpholino (e.g. R^{2b} -substituted or unsubstituted morpholino). R^2 may be R^{2a} -substituted or unsubstituted 2 to 5 membered heteroalkyl. When R^2 is substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{2a} may be may be unsubstituted C_1 - C_5 alkyl, unsubstituted heterocycloalkyl, unsubstituted aryl,

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or unsubstituted heteroaryl. R² may be -OCH₃. R² may be unsubstituted methyl. R² may be -CN.

[0167] In embodiments, R¹ is halogen, -N₃, -NO₂, -CF₃, CCl₃, CBr₃, Cl₃, -CN, -CHO, -CONH₂, or substituted or unsubstituted 2 to 8 membered heteroalkyl and R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{2a}-substituted or unsubstituted C₁-C₈ alkyl, R^{2a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{2a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{2a}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2a}-substituted or unsubstituted 5 or 6 membered aryl, or R^{2a}-substituted or unsubstituted 5 or 6 membered heteroaryl heteroaryl. In embodiments, at least one of R¹ and R² is an electron withdrawing group (EWG) (e.g. halogen, -N₃, -NO₂, -CF₃, CCl₃, CBr₃, Cl₃, -CN, -CHO, -CONH₂, or substituted or unsubstituted 3 to 8 membered heteroalkyl. When R¹ is CN, R² may be -CN. When R¹ is halogen, R² may be halogen. When R¹ is -CN, R² may be unsubstituted C₁-C₅ alkyl. When R¹ is -CN, R² may be unsubstituted methyl. When R¹ is unsubstituted 2 to 8 membered heteroalkyl (e.g. -COOCH₃), R² may be may be unsubstituted C₁-C₅ alkyl. When R¹ is -CN, R² may be R^{2a}-substituted or unsubstituted C₁-C₅ alkyl. When R¹ is -CN, R² may be R^{2a}-substituted or unsubstituted C₁-C₅ heteroalkyl. R^{2a} may be unsubstituted alkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0168] In embodiments, R² is a polar substituent and provides polarity to the compounds provided herein (e.g. where R² is a substituted or unsubstituted 2 to 8 membered heteroalkyl). A “polar substituent” is understood by one skilled in the art to be a moiety that creates a dipole moment, thereby forming a positive or negative charge on a molecule. R² may be an aqueous solubility enhancing substituent (e.g. a moiety that increases the water solubility of the compound), where germinal substitution at R² with a substituent other than methyl improves the solubility of the compound in an aqueous medium. Solubility enhancing substituents may include basic substituents or groups that add polarity.

[0169] R³ and R⁴ may independently be substituted or unsubstituted heteroalkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 2 to 3 membered heteroalkyl, R^{30a}-substituted or

5 unsubstituted heteroalkyl, R^{30a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{30a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, or R^{30a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R³ and R⁴ may independently be unsubstituted heteroalkyl, unsubstituted 2 to 8 membered heteroalkyl, or unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 2 to 3 membered heteroalkyl.

10 **[0170]** R³ and R⁴ may independently be substituted or unsubstituted cycloalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, substituted or unsubstituted 5 membered cycloalkyl. R³ and R⁴ may independently be R^{30a}-substituted or unsubstituted cycloalkyl, R^{30a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{30a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{30a}-substituted or unsubstituted 3 membered cycloalkyl, R^{30a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{30a}-substituted or unsubstituted 5 membered cycloalkyl.

15 **[0171]** R³ and R⁴ may independently be substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, substituted or unsubstituted 6 membered heterocycloalkyl. R³ and R⁴ may independently be R^{30a}-substituted or unsubstituted heterocycloalkyl, R^{30a}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{30a}-substituted or unsubstituted 4 membered heterocycloalkyl, 20 R^{30a}-substituted or unsubstituted 5 membered heterocycloalkyl, or R^{30a}-substituted or unsubstituted 6 membered heterocycloalkyl.

25 **[0172]** R³ and R⁴ may independently be substituted or unsubstituted aryl, substituted or unsubstituted 5 to 6 membered aryl, substituted or unsubstituted 5 membered aryl, or substituted or unsubstituted 6 membered aryl. R³ and R⁴ may independently be R^{30a}-substituted or unsubstituted aryl, R^{30a}-substituted or unsubstituted 5 to 6 membered aryl, R^{30a}-substituted or unsubstituted 5 membered aryl, or R^{30a}-substituted or unsubstituted 6 membered aryl. R³ and R⁴ may independently be substituted or unsubstituted heteroaryl, substituted or unsubstituted 5 to 6 membered heteroaryl, substituted or unsubstituted 5 membered heteroaryl, or substituted or unsubstituted 6 membered heteroaryl. R³ and R⁴ may independently be R^{30a}-substituted or 30 unsubstituted heteroaryl, R^{30a}-substituted or unsubstituted 5 to 6 membered heteroaryl, R^{30a}-

substituted or unsubstituted 5 membered heteroaryl, or R^{30a}-substituted or unsubstituted 6 membered heteroaryl.

[0173] R³ may be hydrogen, halogen, or R^{30a}-substituted or unsubstituted C₁-C₈ alkyl. R³ may be hydrogen. R³ may be unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl.

5 [0174] R⁴ may be hydrogen, halogen, or R^{30a}-substituted or unsubstituted C₁-C₈ alkyl. R⁴ may be hydrogen. R⁴ may be unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl. In embodiments, R³ and R⁴ are hydrogen.

[0175] R^{30a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
 10 R^{30b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{30b}-substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{30b}-substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{30b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{30b}-substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{30b}-substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

15 [0176] R^{30b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alkyl (e.g. C₁-C₈ alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6
 20 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0177] R⁵ may be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂. R⁵ may be halogen, -CHO, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted alkyl (e.g. C₁-C₅ alkyl), or substituted or
 25 unsubstituted heteroalkyl (e.g. 2 to 6 membered heteroalkyl). R⁵ may be halogen, -CHO, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{5a}-substituted or unsubstituted alkyl (e.g. C₁-C₅ alkyl), or R^{5a}-substituted or unsubstituted heteroalkyl (e.g. 2 to 6 membered heteroalkyl).

[0178] R⁵ may be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁵ may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0179] R⁵ may be substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, or substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 to 8 membered heteroaryl. R⁵ may be unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, or unsubstituted 5 to 8 membered aryl, or unsubstituted 5 to 8 membered heteroaryl.

[0180] R⁵ may be substituted or unsubstituted C₁-C₅ alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, or be substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. R⁵ may be unsubstituted C₁-C₅ alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0181] R⁵ may be substituted or unsubstituted C₁-C₃ alkyl or substituted or unsubstituted 2 to 3 membered heteroalkyl. R⁵ may be substituted or unsubstituted 3 membered cycloalkyl. R⁵ may be substituted or unsubstituted 4 membered cycloalkyl or substituted or unsubstituted 5 membered cycloalkyl. R⁵ may be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, substituted or unsubstituted 6 membered heterocycloalkyl. R⁵ may be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, substituted or unsubstituted 5 membered heteroaryl, or substituted or unsubstituted 6 membered heteroaryl. R⁵ may be unsubstituted C₁-C₃ alkyl or unsubstituted 2 to 3 membered heteroalkyl. R⁵ may be unsubstituted 3 membered cycloalkyl. R⁵ may be unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R⁵ may be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered

heterocycloalkyl, unsubstituted 6 membered heterocycloalkyl. R⁵ may be unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, unsubstituted 5 membered heteroaryl, or unsubstituted 6 membered heteroaryl.

5 [0182] R⁵ may be R^{5a}-substituted or unsubstituted alkyl, R^{5a}-substituted or unsubstituted heteroalkyl, R^{5a}-substituted or unsubstituted cycloalkyl, R^{5a}-substituted or unsubstituted heterocycloalkyl, R^{5a}-substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁵ may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or substituted or unsubstituted heteroaryl.

10 [0183] R⁵ may be R^{5a}-substituted or unsubstituted C₁-C₈ alkyl, R^{5a}-substituted or unsubstituted 3 to 8 membered heteroalkyl, R^{5a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{5a}-substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{5a}-substituted or unsubstituted 5 to 8 membered aryl, or R^{5a}-substituted or unsubstituted 5 to 8 membered heteroaryl. R⁵ may be unsubstituted C₁-C₈ alkyl, unsubstituted 3 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 to 8 membered heteroaryl.

20 [0184] R⁵ may be R^{5a}-substituted or unsubstituted C₁-C₅ alkyl, R^{5a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{5a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{5a}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{5a}-substituted or unsubstituted 5 to 6 membered aryl, or R^{5a}-substituted or unsubstituted 5 to 6 membered heteroaryl. R⁵ may be unsubstituted C₁-C₅ alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or or unsubstituted 5 to 6 membered heteroaryl.

25 [0185] R⁵ may be R^{5a}-substituted or unsubstituted C₁-C₃ alkyl or R^{5a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R⁵ may be R^{5a}-substituted or unsubstituted 3 membered cycloalkyl, R^{5a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{5a}-substituted or unsubstituted 5 membered cycloalkyl. R⁵ may be R^{5a}-substituted or unsubstituted 4 membered heterocycloalkyl, R^{5a}-substituted or unsubstituted 5 membered heterocycloalkyl, or R^{5a}-substituted or unsubstituted 6 membered heterocycloalkyl. R⁵ may be R^{5a}-substituted or unsubstituted 5 membered aryl, R^{5a}-substituted or unsubstituted 6 membered aryl, R^{5a}-substituted or unsubstituted 5 membered heteroaryl, or R^{5a}-substituted or unsubstituted 6 membered

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heteroaryl. R^5 may be unsubstituted C_1 - C_3 alkyl or or unsubstituted 2 to 3 membered heteroalkyl. R^5 may be or unsubstituted 3 membered cycloalkyl, or unsubstituted 4 membered cycloalkyl, or or unsubstituted 5 membered cycloalkyl. R^5 may be or unsubstituted 4 membered heterocycloalkyl, or unsubstituted 5 membered heterocycloalkyl, or or unsubstituted 6 membered heterocycloalkyl. R^5 may be or unsubstituted 5 membered aryl, or unsubstituted 6 membered aryl, or unsubstituted 5 membered heteroaryl, or or unsubstituted 6 membered heteroaryl.

[0186] R^{5a} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, R^{5b} -substituted or unsubstituted alkyl (e.g. C_1 - C_8 alkyl), R^{5b} -substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{5b} -substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{5b} -substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{5b} -substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{5b} -substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0187] R^{5b} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, unsubstituted alkyl (e.g. C_1 - C_8 alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0188] R^5 may be R^{5a} -substituted or unsubstituted C_1 - C_8 alkyl, R^{5a} -substituted or unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, or unsubstituted 3 to 5 membered heterocycloalkyl. R^5 may be unsubstituted C_1 - C_8 alkyl. R^5 may be unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl. R^5 may be methyl, ethyl, or propyl. R^5 may be unsubstituted methyl. R^5 may be unsubstituted ethyl. R^5 may be unsubstituted propyl. R^5 may be unsubstituted allyl. R^5 may be R^{5a} -substituted alkyl. R^{5a} may be unsubstituted 5 or 6 membered heterocycloalkyl. R^{5a} may be unsubstituted morpholino. In embodiments, R^5 is substituted or unsubstituted 2 to 8 membered heteroalkyl. R^5 may be $-(CH_2)_3N(CH_3)_3$. R^5 may be unsubstituted 3 to 5 membered cycloalkyl. In embodiments, R^5 is unsubstituted cyclopropane.

[0189] R⁶ may be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂. R⁶ may be hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, or substituted or unsubstituted alkyl (e.g. C₁-C₅ alkyl),
5 or substituted or unsubstituted heteroalkyl (e.g. 2 to 6 membered heteroalkyl). R⁶ may be halogen, -CHO, -COOH, -CONH₂, -SH, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{6a}-substituted or unsubstituted alkyl (e.g. C₁-C₅ alkyl), or R^{6a}-substituted or unsubstituted heteroalkyl (e.g. 2 to 6 membered heteroalkyl).

[0190] R⁶ may be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
10 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁶ may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0191] R⁶ may be substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted 2 to 8
15 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, or substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 to 8 membered heteroaryl. R⁶ may be unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, or unsubstituted 5 to 8 membered aryl, or
20 unsubstituted 5 to 8 membered heteroaryl.

[0192] R⁶ may be substituted or unsubstituted C₁-C₅ alkyl, substituted or unsubstituted 2 to 5
membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, or be substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. R⁶ may be unsubstituted C₁-C₅
25 alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, or be unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0193] R⁶ may be substituted or unsubstituted C₁-C₃ alkyl or substituted or unsubstituted 2 to 3
membered heteroalkyl. R⁶ may be substituted or unsubstituted 3 membered cycloalkyl,

substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R^6 may be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, substituted or unsubstituted 6 membered heterocycloalkyl. R^6 may be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, substituted or unsubstituted 5 membered heteroaryl, or substituted or unsubstituted 6 membered heteroaryl. R^6 may be unsubstituted C_1 - C_3 alkyl or unsubstituted 2 to 3 membered heteroalkyl. R^6 may be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl, or unsubstituted 5 membered cycloalkyl. R^6 may be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, unsubstituted 6 membered heterocycloalkyl. R^6 may be unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, unsubstituted 5 membered heteroaryl, or unsubstituted 6 membered heteroaryl.

[0194] R^6 may be R^{6a} -substituted or unsubstituted alkyl, R^{6a} -substituted or unsubstituted heteroalkyl, R^{6a} -substituted or unsubstituted cycloalkyl, R^{6a} -substituted or unsubstituted heterocycloalkyl, R^{6a} -substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^6 may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0195] R^6 may be R^{6a} -substituted or unsubstituted C_1 - C_8 alkyl, R^{6a} -substituted or unsubstituted 3 to 8 membered heteroalkyl, R^{6a} -substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{6a} -substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{6a} -substituted or unsubstituted 5 to 8 membered aryl, or R^{6a} -substituted or unsubstituted 5 to 8 membered heteroaryl. R^6 may be unsubstituted C_1 - C_8 alkyl, unsubstituted 3 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 to 8 membered heteroaryl.

[0196] R^6 may be R^{6a} -substituted or unsubstituted C_1 - C_5 alkyl, R^{6a} -substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{6a} -substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{6a} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{6a} -substituted or unsubstituted 5 to 6 membered aryl, or R^{6a} -substituted or unsubstituted 5 to 6 membered heteroaryl. R^6 may be unsubstituted C_1 - C_5 alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5

membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or or unsubstituted 5 to 6 membered heteroaryl.

[0197] R^6 may be R^{6a} -substituted or unsubstituted C_1 - C_3 alkyl or R^{6a} -substituted or unsubstituted 2 to 3 membered heteroalkyl. R^6 may be R^{6a} -substituted or unsubstituted 3 membered cycloalkyl, R^{6a} -substituted or unsubstituted 4 membered cycloalkyl, or R^{6a} -substituted or unsubstituted 5 membered cycloalkyl. R^6 may be R^{6a} -substituted or unsubstituted 4 membered heterocycloalkyl, R^{6a} -substituted or unsubstituted 5 membered heterocycloalkyl, or R^{6a} -substituted or unsubstituted 6 membered heterocycloalkyl. R^6 may be R^{6a} -substituted or unsubstituted 5 membered aryl, R^{6a} -substituted or unsubstituted 6 membered aryl, R^{6a} -substituted or unsubstituted 5 membered heteroaryl, or R^{6a} -substituted or unsubstituted 6 membered heteroaryl. R^6 may be unsubstituted C_1 - C_3 alkyl or or unsubstituted 2 to 3 membered heteroalkyl. R^6 may be or unsubstituted 3 membered cycloalkyl, or unsubstituted 4 membered cycloalkyl, or or unsubstituted 5 membered cycloalkyl. R^6 may be or unsubstituted 4 membered heterocycloalkyl, or unsubstituted 5 membered heterocycloalkyl, or or unsubstituted 6 membered heterocycloalkyl. R^6 may be or unsubstituted 5 membered aryl, or unsubstituted 6 membered aryl, or unsubstituted 5 membered heteroaryl, or or unsubstituted 6 membered heteroaryl.

[0198] R^{6a} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, R^{6b} -substituted or unsubstituted alkyl (e.g. C_1 - C_8 alkyl), R^{6b} -substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{6b} -substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{6b} -substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{6b} -substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{6b} -substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0199] R^{6b} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, unsubstituted alkyl (e.g. C_1 - C_8 alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0200] R⁶ may be hydrogen, halogen, R^{6a}-substituted or unsubstituted C₁-C₈ alkyl, or unsubstituted 5 or 6 membered aryl. R⁶ may be hydrogen. R⁶ may be halogen. R⁶ may be R^{6a}-substituted or unsubstituted C₁-C₈ alkyl. R⁶ may be R^{6a}-substituted or unsubstituted C₁-C₅ alkyl. R⁶ may be unsubstituted C₁-C₈ alkyl. R⁶ may be unsubstituted methyl. R⁶ may be unsubstituted ethyl. R⁶ may be unsubstituted propyl. R⁶ may be unsubstituted allyl. R⁶ may be unsubstituted aryl. R⁶ may be unsubstituted phenyl.

[0201] R⁵ and R⁶ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, unsubstituted alkyl, or unsubstituted cycloalkyl. R⁵ and R⁶ are independently hydrogen, C₁-C₃ unsubstituted alkyl or 3 to 5 membered cycloalkyl. R⁵ and R⁶ are independently hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted allyl, or unsubstituted cyclopropyl. R⁵ and R⁶ may independently be hydrogen or halogen. R⁵ and R⁶ may independently be C₁-C₃ substituted or unsubstituted alkyl. R⁵ and R⁶ may be unsubstituted methyl. R⁵ and R⁶ may independently be unsubstituted methyl or unsubstituted ethyl.

[0202] R¹⁶ may be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂. R¹⁶ may be substituted or unsubstituted alkyl. R¹⁶ may be substituted or unsubstituted C₁-C₈ alkyl. R¹⁶ may be substituted or unsubstituted C₁-C₅ alkyl. R¹⁶ may be substituted or unsubstituted C₁-C₃ alkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted alkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted C₁-C₈ alkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted C₁-C₅ alkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted C₁-C₃ alkyl.

[0203] R¹⁶ may be substituted or unsubstituted heteroalkyl. R¹⁶ may be substituted or unsubstituted 2 to 8 membered heteroalkyl. R¹⁶ may be substituted or unsubstituted 2 to 5 membered heteroalkyl. R¹⁶ may be substituted or unsubstituted 2 to 3 membered heteroalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted heteroalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 2 to 8 membered heteroalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 2 to 5 membered heteroalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 2 to 3 membered heteroalkyl.

- [0204] R¹⁶ may be substituted or unsubstituted cycloalkyl. R¹⁶ may be substituted or unsubstituted 3 to 8 membered cycloalkyl. R¹⁶ may be substituted or unsubstituted 3 to 5 membered cycloalkyl. R¹⁶ may be substituted or unsubstituted 3 membered cycloalkyl. R¹⁶ may be substituted or unsubstituted 4 membered cycloalkyl. R¹⁶ may be substituted or unsubstituted 5 membered cycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted cycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 3 to 8 membered cycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 3 to 5 membered cycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 3 membered cycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 4 membered cycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 5 membered cycloalkyl.
- 10 [0205] R¹⁶ may be substituted or unsubstituted heterocycloalkyl. R¹⁶ may be substituted or unsubstituted 3 to 6 membered heterocycloalkyl. R¹⁶ may be substituted or unsubstituted 4 membered heterocycloalkyl. R¹⁶ may be substituted or unsubstituted 5 membered heterocycloalkyl. R¹⁶ may be substituted or unsubstituted 6 membered heterocycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted heterocycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 4 membered heterocycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 5 membered heterocycloalkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted 6 membered heterocycloalkyl.
- 15 [0206] R¹⁶ may be substituted or unsubstituted aryl. R¹⁶ may be substituted or unsubstituted 5 to 6 membered aryl. R¹⁶ may be substituted or unsubstituted 5 membered aryl. R¹⁶ may be substituted or unsubstituted 6 membered aryl. R¹⁶ may be R^{16a}-substituted or unsubstituted aryl. R¹⁶ may be R^{16a}-substituted or unsubstituted 5 to 6 membered aryl. R¹⁶ may be R^{16a}-substituted or unsubstituted 5 membered aryl. R¹⁶ may be R^{16a}-substituted or unsubstituted 6 membered aryl. R¹⁶ may be substituted or unsubstituted heteroaryl. R¹⁶ may be substituted or unsubstituted 5 to 6 membered heteroaryl. R¹⁶ may be substituted or unsubstituted 5 membered heteroaryl. R¹⁶ may be substituted or unsubstituted 6 membered heteroaryl. R¹⁶ may be R^{16a}-substituted or unsubstituted heteroaryl. R¹⁶ may be R^{16a}-substituted or unsubstituted 5 to 6 membered heteroaryl. R¹⁶ may be R^{16a}-substituted or unsubstituted 5 membered heteroaryl. R¹⁶ may be R^{16a}-substituted or unsubstituted 6 membered heteroaryl.
- 25 [0207] R^{16a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
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R^{16b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{16b}-substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{16b}-substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{16b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{16b}-substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl),
 5 or R^{16b}-substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0208] R^{16b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alkyl (e.g. C₁-C₈ alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted
 10 heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0209] R¹⁶ may be hydrogen, halogen or substituted or unsubstituted alkyl. R¹⁶ may be hydrogen. R¹⁶ may be halogen. R¹⁶ may be substituted or unsubstituted alkyl. R¹⁶ may be substituted or unsubstituted C₁-C₅ alkyl. R¹⁶ may be R^{16a}-substituted or unsubstituted alkyl. R¹⁶
 15 may be R^{16a}-substituted or unsubstituted C₁-C₅ alkyl. In embodiments, R³, R⁴, and R¹⁶ are hydrogen.

[0210] R¹⁸ may be 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.

[0211] R¹⁸ may be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R¹⁸ may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, or unsubstituted membered heteroaryl.

[0212] R¹⁸ may be substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 or 8 membered heteroaryl. R¹⁸ may be unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl,

unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 or 8 membered heteroaryl.

[0213] R^{18} may be substituted or unsubstituted C_1 - C_5 alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 or 6 membered heteroaryl. R^{18} may be unsubstituted C_1 - C_5 alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.

10 [0214] R^{18} may be substituted or unsubstituted C_1 - C_3 alkyl, substituted or unsubstituted 2 to 3 membered heteroalkyl. R^{18} may be substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R^{18} may be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, or substituted or unsubstituted 6 membered heterocycloalkyl. R^{18} may be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, substituted or unsubstituted 6 membered heteroaryl, or substituted or unsubstituted 6 membered heteroaryl. R^{18} may be unsubstituted C_1 - C_3 alkyl or unsubstituted 2 to 3 membered heteroalkyl. R^{18} may be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R^{18} may be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, or unsubstituted 6 membered heterocycloalkyl. R^{18} may be unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, unsubstituted 5 membered heteroaryl, or unsubstituted 6 membered heteroaryl.

25 [0215] R^{18} may be R^{18a} -substituted or unsubstituted alkyl, R^{18a} -substituted or unsubstituted heteroalkyl, R^{18a} -substituted or unsubstituted cycloalkyl, R^{18a} -substituted or unsubstituted heterocycloalkyl, R^{18a} -substituted or unsubstituted aryl, or R^{18a} -substituted or unsubstituted heteroaryl.

[0216] R^{18} may be R^{18a} -substituted or unsubstituted C_1 - C_8 alkyl, R^{18a} -substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{18a} -substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{18a} -substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{18a} -substituted

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or unsubstituted 5 to 8 membered aryl, or R^{18a}-substituted or unsubstituted 5 to 8 membered heteroaryl.

[0217] R¹⁸ may be R^{18a}-substituted or unsubstituted C₁-C₅ alkyl, R^{18a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{18a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{18a}-substituted or unsubstituted 3-6 membered heterocycloalkyl, R^{18a}-substituted or unsubstituted 5 to 6 membered aryl, or R^{18a}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0218] R¹⁸ may be R^{18a}-substituted or unsubstituted C₁-C₃ alkyl or R^{18a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R¹⁸ may be R^{18a}-substituted or unsubstituted 3 membered cycloalkyl, R^{18a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{18a}-substituted or unsubstituted 5 membered cycloalkyl. R¹⁸ may be R^{18a}-substituted or unsubstituted 5 membered heterocycloalkyl, R^{18a}-substituted or unsubstituted 6 membered heterocycloalkyl, R^{18a}-substituted or unsubstituted 5 membered aryl, R^{18a}-substituted or unsubstituted 6 membered aryl, R^{18a}-substituted or unsubstituted 5 membered heteroaryl, or R^{18a}-substituted or unsubstituted 6 membered heteroaryl.

[0219] R^{18a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{18b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{18b}-substituted or unsubstituted alkyl (e.g. 2 to 8 membered heteroalkyl), R^{18b}-substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{18b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{18b}-substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{18b}-substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0220] R^{18b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alkyl (e.g. C₁-C₈ alkyl), unsubstituted heterocycloalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0221] R^{18} may be substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{18} may be R^{18a} -substituted or unsubstituted 5 membered heterocycloalkyl, R^{18a} -substituted or unsubstituted 6 membered aryl, R^{18a} -substituted or unsubstituted 6 membered heteroaryl, R^{18a} -substituted or unsubstituted 6,6 fused ring aryl-heterocycloalkyl, R^{18a} -substituted or unsubstituted 6,5 fused ring aryl-heterocycloalkyl, R^{18a} -substituted or unsubstituted 5,6 fused ring aryl-heterocycloalkyl, where R^{18a} and R^{18b} are as described herein, including embodiments thereof.

[0222] R^{18} may be R^{18a} -substituted or unsubstituted 5 membered heterocycloalkyl, R^{18a} -substituted or unsubstituted 6 membered aryl, R^{18a} -substituted or unsubstituted 6 membered heteroaryl, R^{18a} -substituted or unsubstituted 6,6 fused ring aryl, R^{18a} -substituted or unsubstituted 6,6 fused ring heteroaryl, R^{18a} -substituted or unsubstituted 6,5 fused ring aryl, R^{18a} -substituted or unsubstituted 6,5 fused ring heteroaryl, R^{18a} -substituted or unsubstituted 5,6 fused ring aryl, R^{18a} -substituted 5,6 fused ring heteroaryl, R^{18a} -substituted or unsubstituted 6,6 fused ring aryl-heterocycloalkyl, R^{18a} -substituted or unsubstituted 6,5 fused ring aryl-heterocycloalkyl, or R^{18a} -substituted or unsubstituted 5,6 fused ring aryl-heterocycloalkyl.

[0223] R^{18} may be R^{18a} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl. The R^{18a} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl may be R^{18a} -substituted or unsubstituted thiophenyl, R^{18a} -substituted or unsubstituted thiazolyl, R^{18a} -substituted or unsubstituted oxazolyl, R^{18a} -substituted or unsubstituted imidazolyl, or derivatives thereof. R^{18} may be R^{18a} -substituted or unsubstituted 6 membered aryl. R^{18} may be R^{18a} -substituted or unsubstituted 6 membered heteroaryl. R^{18} may be R^{18a} -substituted or unsubstituted 6,6 fused ring aryl-heterocycloalkyl. The R^{18a} -substituted or unsubstituted 6,6 fused ring aryl-heteroaryl may be R^{18a} -substituted or unsubstituted dihydrobenzo[1,4]dioxinyl. R^{18} may be R^{18a} -substituted or unsubstituted 6,5 fused ring aryl-heterocycloalkyl or R^{18a} -substituted or unsubstituted 5,6 fused ring aryl-heterocycloalkyl. The R^{18a} -substituted or unsubstituted 6,5 or 5,6 fused ring aryl-heterocycloalkyl may be dihydro-indenyl, benzo[1,3]dioxolyl, or indolyl. R^{18a} may be halogen, SO_2Ph , C_1-C_5 R^{18b} -substituted or unsubstituted alkyl, or 2 to 5 membered R^{18b} -substituted or unsubstituted heteroalkyl.

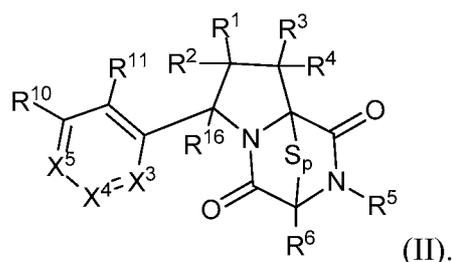
[0224] In one embodiment, R^1 and R^{18} are not joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl

(including fused cycloalkyl-aryl, heterocycloalkyl-aryl and aryl rings) or substituted or unsubstituted heteroaryl (including fused cycloalkyl-heteroaryl, heterocycloalkyl-heteroaryl and heteroaryl rings). In one embodiment, R¹ and R¹⁶ are not joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (including fused cycloalkyl-aryl, heterocycloalkyl-aryl and aryl rings) or substituted or unsubstituted heteroaryl (including fused cycloalkyl-heteroaryl, heterocycloalkyl-heteroaryl and heteroaryl rings).

[0225] In one embodiment, R² and R¹⁸ are not joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (including fused cycloalkyl-aryl, heterocycloalkyl-aryl and aryl rings) or substituted or unsubstituted heteroaryl (including fused cycloalkyl-heteroaryl, heterocycloalkyl-heteroaryl and heteroaryl rings). In one embodiment, R² and R¹⁶ are not joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (including fused cycloalkyl-aryl, heterocycloalkyl-aryl and aryl rings) or substituted or unsubstituted heteroaryl (including fused cycloalkyl-heteroaryl, heterocycloalkyl-heteroaryl and heteroaryl rings).

[0226] In one embodiment, R¹ and R¹⁸ are not hydrogen. In one embodiment the compound of formula (I) does not have the formula (3R,8S,8aR)-8-hydroxy-2-methyltetrahydro-1H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-1,4(6H)-dione. In one embodiment, the compound of formula (I) does not have the formula (3R,8S,8aR)-2-methyl-1,4-dioxohexahydro-1H-3,8a-epidithiopyrrolo[1,2-a]pyrazin-8-yl acetate. In one embodiment the compound of formula (I) does not have the formula (3R,6R,8S,8aR)-6-(((tert-butyl)diphenylsilyl)oxy)methyl)-8-hydroxy-2-methyltetrahydro-1H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-1,4(6H)-dione. In one embodiment, the compound does not have the formula 2,3-dimethyltetrahydro-1H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-1,4(6H)-dione. In one embodiment, the compound does not have the formula 3-(hydroxymethyl)-2-methyltetrahydro-1H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-1,4(6H)-dione.

[0227] The compound of formula (I) may have the formula:



[0228] p , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^{16} are as described herein.

[0229] X^3 is N or CR^7 . X^4 is N or CR^8 . X^5 is N or CR^9 . R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHR^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHR^{34I}R^{35I}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33J}$, $-NR^{34J}R^{35J}$, $-COOR^{33J}$, $-CONR^{34J}R^{35J}$, $-NO_2$, $-SR^{36J}$, $-SO_{n10}R^{34J}$, $-SO_{n10}OR^{34J}$, $-SO_{n10}NR^{34J}R^{35J}$, $-NHR^{34J}R^{35J}$, $-ONR^{34J}R^{35J}$, $-NHC(O)NHR^{34J}R^{35J}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33K}$, $-NR^{34K}R^{35K}$, $-COOR^{33K}$, $-CONR^{34K}R^{35K}$, $-NO_2$, $-SR^{36K}$, $-SO_{n11}R^{34K}$, $-SO_{n11}OR^{34K}$, $-SO_{n11}NR^{34K}R^{35K}$, $-NHR^{34K}R^{35K}$, $-ONR^{34K}R^{35K}$, $-NHC(O)NHR^{34K}R^{35K}$, substituted 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} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHR^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHR^{34L}R^{35L}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} ,

R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} , and R^{36L} , are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbols n9, n10, n11, and n12 are independently 1 or 2.

[0230] R^{10} and R^{11} are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. R^7 and R^8 are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. R^8 and R^9 are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. R^9 and R^{10} are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. p may be 2, 3, or 4.

[0231] When X^3 is N, X^4 may be CR^8 and X^5 may be CR^9 . When X^4 is N, X^3 may be CR^7 and X^5 may be CR^9 . When X^5 is N, X^3 may be CR^7 and X^4 may be CR^8 . X^3 , X^4 , and X^5 may be CR^7 , CR^8 , and CR^9 respectively.

[0232] R^7 may be hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted alkyl (e.g. C_1 - C_8 alkyl), or substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl). R^7 may be halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R^7 may be halogen, substituted or unsubstituted alkyl, or substituted or unsubstituted heteroalkyl. R^7 may be halogen or substituted or unsubstituted alkyl. R^7 may be halogen or unsubstituted alkyl. R^7 may be halogen, or unsubstituted heteroalkyl. R^7 may be halogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, or $-Cl_3$.

[0233] R^7 may be substituted 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 may be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted membered heteroaryl.

[0234] R^7 may be substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 or 8 membered heteroaryl. R^7 may be unsubstituted C_1 - C_8 alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 or 8 membered heteroaryl.

[0235] R^7 may be substituted or unsubstituted C_1 - C_5 alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. R^7 may be unsubstituted C_1 - C_5 alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0236] R^7 may be substituted or unsubstituted C_1 - C_3 alkyl, substituted or unsubstituted 2 to 3 membered heteroalkyl. R^7 may be substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R^7 may be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, or substituted or unsubstituted 6 membered heterocycloalkyl. R^7 may be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, substituted or unsubstituted 5 membered heteroaryl, or substituted or unsubstituted 6 membered heteroaryl. R^7 may be unsubstituted C_1 - C_3 alkyl or unsubstituted 2 to 3 membered heteroalkyl. R^7 may be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R^7 may be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, or unsubstituted 6 membered heterocycloalkyl. R^7 may be unsubstituted 5 membered aryl,

unsubstituted 6 membered aryl, unsubstituted 5 membered aryl, or unsubstituted 6 membered heteroaryl.

[0237] R^7 may be R^{7a} -substituted or unsubstituted alkyl, R^{7a} -substituted or unsubstituted heteroalkyl, R^{7a} -substituted or unsubstituted cycloalkyl, R^{7a} -substituted or unsubstituted heterocycloalkyl, R^{7a} -substituted or unsubstituted aryl, or R^{7a} -substituted or unsubstituted heteroaryl.

[0238] R^7 may be R^{7a} -substituted or unsubstituted C_1 - C_8 alkyl, R^{7a} -substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{7a} -substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{7a} -substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{7a} -substituted or unsubstituted 5 to 8 membered aryl, or R^{7a} -substituted or unsubstituted 5 to 8 membered heteroaryl.

[0239] R^7 may be R^{7a} -substituted or unsubstituted C_1 - C_5 alkyl, R^{7a} -substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{7a} -substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{7a} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{7a} -substituted or unsubstituted 5 to 6 membered aryl, or R^{7a} -substituted or unsubstituted 5 to 6 membered heteroaryl.

[0240] R^7 may be R^{7a} -substituted or unsubstituted C_1 - C_3 alkyl or R^{7a} -substituted or unsubstituted 2 to 3 membered heteroalkyl. R^7 may be R^{7a} -substituted or unsubstituted 3 membered cycloalkyl, R^{7a} -substituted or unsubstituted 4 membered cycloalkyl, or R^{7a} -substituted or unsubstituted 5 membered cycloalkyl. R^7 may be R^{7a} -substituted or unsubstituted 5 membered heterocycloalkyl, R^{7a} -substituted or unsubstituted 6 membered heterocycloalkyl, R^{7a} -substituted or unsubstituted 5 membered aryl, R^{7a} -substituted or unsubstituted 6 membered aryl, R^{7a} -substituted or unsubstituted 5 membered heteroaryl, or R^{7a} -substituted or unsubstituted 6 membered heteroaryl.

[0241] R^{7a} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, R^{7b} -substituted or unsubstituted alky (e.g. C_1 - C_8 alkyl, R^{7b} -substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{7b} -substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{7b} -substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{7b} -substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{7b} -substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0242] R^{7b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alkyl (e.g. C₁-C₈ alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0243] R⁸ and R⁹ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂. R⁸ and R⁹ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, or -SO₂. R⁸ and R⁹ may independently be hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, or -NH₂.

[0244] R⁸ and R⁹ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), or substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl).

[0245] R⁸ and R⁹ may independently be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R⁸ and R⁹ may independently be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, or unsubstituted membered heteroaryl.

[0246] R⁸ and R⁹ may independently be substituted or unsubstituted C₁-C₈ alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 or 8 membered heteroaryl. R⁸ and R⁹ may independently be unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 or 8 membered heteroaryl.

[0247] R⁸ and R⁹ may independently be substituted or unsubstituted C₁-C₅ alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 or 6 membered heteroaryl.

5 R⁸ and R⁹ may independently be unsubstituted C₁-C₅ alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.

[0248] R⁸ and R⁹ may independently be substituted or unsubstituted C₁-C₃ alkyl, substituted or unsubstituted 2 to 3 membered heteroalkyl. R⁸ and R⁹ may independently be substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R⁸ and R⁹ may independently be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, or substituted or unsubstituted 6 membered heterocycloalkyl. R⁸ and R⁹ may independently be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, or substituted or unsubstituted 6 membered heteroaryl. R⁸ and R⁹ may independently be unsubstituted C₁-C₃ alkyl or unsubstituted 2 to 3 membered heteroalkyl. R⁸ and R⁹ may independently be unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R⁸ and R⁹ may independently be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, or unsubstituted 6 membered heterocycloalkyl. R⁸ and R⁹ may independently be be unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, unsubstituted 5 membered aryl, or unsubstituted 6 membered heteroaryl.

[0249] R⁸ and R⁹ may independently be R^{31a}-substituted or unsubstituted alkyl, R^{31a}-substituted or unsubstituted heteroalkyl, R^{31a}-substituted or unsubstituted cycloalkyl, R^{31a}-substituted or unsubstituted heterocycloalkyl, R^{31a}-substituted or unsubstituted aryl, or R^{31a}-substituted or unsubstituted heteroaryl.

[0250] R⁸ and R⁹ may independently be R^{31a}-substituted or unsubstituted C₁-C₈ alkyl, R^{31a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{31a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{31a}-substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{31a}-

substituted or unsubstituted 5 to 8 membered aryl, or R^{31a}-substituted or unsubstituted 5 to 8 membered heteroaryl.

[0251] R⁸ and R⁹ may independently be R^{31a}-substituted or unsubstituted C₁-C₅ alkyl, R^{31a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{31a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{31a}-substituted or unsubstituted 3-6 membered heterocycloalkyl, R^{31a}-substituted or unsubstituted 5 to 6 membered aryl, or R^{31a}-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0252] R⁸ and R⁹ may independently be R^{31a}-substituted or unsubstituted C₁-C₃ alkyl or R^{31a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R⁸ and R⁹ may independently be R^{31a}-substituted or unsubstituted 3 membered cycloalkyl, R^{31a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{31a}-substituted or unsubstituted 5 membered cycloalkyl. R⁸ and R⁹ may independently be R^{31a}-substituted or unsubstituted 5 membered heterocycloalkyl, R^{31a}-substituted or unsubstituted 6 membered heterocycloalkyl, R^{31a}-substituted or unsubstituted 5 membered aryl, R^{31a}-substituted or unsubstituted 6 membered aryl, R^{31a}-substituted or unsubstituted 5 membered heteroaryl, or R^{31a}-substituted or unsubstituted 6 membered heteroaryl.

[0253] R⁸ may be hydrogen, halogen or substituted or unsubstituted alkyl. R⁸ may be hydrogen. R⁸ may be halogen. R⁸ may be substituted or unsubstituted alkyl. R⁸ may be substituted or unsubstituted C₁-C₅ alkyl. R⁸ may be R^{31a}-substituted alkyl. R⁸ may be hydrogen or -OR^{33j} and R⁹, R¹⁰, and R¹¹ may independently be hydrogen or halogen. R^{33j} may be hydrogen, or unsubstituted alkyl. R⁸ may be R^{31a}-substituted C₁-C₅ alkyl. R⁹ may be hydrogen, halogen substituted or unsubstituted alkyl, or unsubstituted or unsubstituted heteroalkyl. R⁹ may be substituted or unsubstituted C₁-C₅ alkyl. R⁹ may be R^{8a}-substituted or unsubstituted alkyl. R⁹ may be R^{31a}-substituted C₁-C₅ or unsubstituted alkyl. R⁹ may be R^{31a}-substituted or unsubstituted heteroalkyl. R⁹ may be R^{31a}-substituted or unsubstituted 2 to 6 membered heteroalkyl.

[0254] R^{31a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{31b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{31b}-substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{31b}-substituted or unsubstituted cycloalkyl (e.g.

3 to 8 membered cycloalkyl), R^{31b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{31b}-substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{31b}-substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0255] R^{31b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alky (e.g. C₁-C₈ alky), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

10 [0256] R⁸ and R⁹ may be joined together to form a substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl). R⁸ and R⁹ may be joined together to form a substituted or unsubstituted heterocycloalkyl (e.g. 3 to 8 membered heterocycloalkyl). R⁸ and R⁹ may be joined together to form a substituted or unsubstituted aryl (e.g. 3 to 8 membered aryl). R⁸ and R⁹ may be joined together to form a substituted or unsubstituted heteroaryl (e.g. 3 to 8 membered heteroaryl).

[0257] R⁷ and R⁸ may be joined together to form a substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl). R⁷ and R⁸ may be joined together to form a substituted or unsubstituted heterocycloalkyl (e.g. 3 to 8 membered heterocycloalkyl). R⁷ and R⁸ may be joined together to form a substituted or unsubstituted aryl (e.g. 3 to 8 membered aryl). R⁷ and R⁸ may be joined together to form a substituted or unsubstituted heteroaryl (e.g. 3 to 8 membered heteroaryl).

[0258] R¹⁰ and R¹¹ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂. R¹⁰ and R¹¹ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, or -SO₂. R¹⁰ and R¹¹ may independently be hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -Cl₃, -OH, or -NH₂.

[0259] R¹⁰ and R¹¹ may independently be hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂,

–NHNH₂, –ONH₂, –NHC(O)NHNH₂, substituted or unsubstituted alkyl (e.g. C₁–C₈ alkyl), or substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl).

[0260] R¹⁰ and R¹¹ may independently be substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R¹⁰ and R¹¹ may independently be unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, or unsubstituted membered heteroaryl.

[0261] R¹⁰ and R¹¹ may independently be substituted or unsubstituted C₁–C₈ alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 8 membered cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted 5 to 8 membered aryl, or substituted or unsubstituted 5 or 8 membered heteroaryl. R¹⁰ and R¹¹ may independently be unsubstituted C₁–C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 8 membered heterocycloalkyl, unsubstituted 5 to 8 membered aryl, or unsubstituted 5 or 8 membered heteroaryl.

[0262] R¹⁰ and R¹¹ may independently be substituted or unsubstituted C₁–C₅ alkyl, substituted or unsubstituted 2 to 5 membered heteroalkyl, substituted or unsubstituted 3 to 5 membered cycloalkyl, substituted or unsubstituted 3–6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 or 6 membered heteroaryl. R¹⁰ and R¹¹ may independently be unsubstituted C₁–C₅ alkyl, unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 3 to 5 membered cycloalkyl, unsubstituted 3–6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.

[0263] R¹⁰ and R¹¹ may independently be substituted or unsubstituted C₁–C₃ alkyl, substituted or unsubstituted 2 to 3 membered heteroalkyl. R¹⁰ and R¹¹ may independently be substituted or unsubstituted 3 membered cycloalkyl, substituted or unsubstituted 4 membered cycloalkyl, or substituted or unsubstituted 5 membered cycloalkyl. R¹⁰ and R¹¹ may independently be substituted or unsubstituted 4 membered heterocycloalkyl, substituted or unsubstituted 5 membered heterocycloalkyl, or substituted or unsubstituted 6 membered heterocycloalkyl. R¹⁰

and R¹¹ may independently be substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 5 membered aryl, substituted or unsubstituted 6 membered aryl, or substituted or unsubstituted 6 membered heteroaryl. R¹⁰ and R¹¹ may independently be unsubstituted C₁-C₃ alkyl or unsubstituted 2 to 3 membered heteroalkyl. R¹⁰ and R¹¹ may independently be
5 unsubstituted 3 membered cycloalkyl, unsubstituted 4 membered cycloalkyl or unsubstituted 5 membered cycloalkyl. R¹⁰ and R¹¹ may independently be unsubstituted 4 membered heterocycloalkyl, unsubstituted 5 membered heterocycloalkyl, or unsubstituted 6 membered heterocycloalkyl. R¹⁰ and R¹¹ may independently be be unsubstituted 5 membered aryl, unsubstituted 5 membered aryl, unsubstituted 6 membered aryl, or unsubstituted 6 membered
10 heteroaryl.

[0264] R¹⁰ and R¹¹ may independently be R^{32a}-substituted or unsubstituted alkyl, R^{32a}-substituted or unsubstituted heteroalkyl, R^{32a}-substituted or unsubstituted cycloalkyl, R^{32a}-substituted or unsubstituted heterocycloalkyl, R^{32a}-substituted or unsubstituted aryl, or R^{32a}-substituted or unsubstituted heteroaryl.

15 **[0265]** R¹⁰ and R¹¹ may independently be R^{32a}-substituted or unsubstituted C₁-C₈ alkyl, R^{32a}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{32a}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{32a}-substituted or unsubstituted 3 to 8 membered heterocycloalkyl, R^{32a}-substituted or unsubstituted 5 to 8 membered aryl, or R^{32a}-substituted or unsubstituted 5 to 8 membered heteroaryl.

20 **[0266]** R¹⁰ and R¹¹ may independently be R^{32a}-substituted or unsubstituted C₁-C₅ alkyl, R^{32a}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{32a}-substituted or unsubstituted 3 to 5 membered cycloalkyl, R^{32a}-substituted or unsubstituted 3-6 membered heterocycloalkyl, R^{32a}-substituted or unsubstituted 5 to 6 membered aryl, or R^{32a}-substituted or unsubstituted 5 to 6 membered heteroaryl

25 **[0267]** R¹⁰ and R¹¹ may independently be R^{32a}-substituted or unsubstituted C₁-C₃ alkyl or R^{32a}-substituted or unsubstituted 2 to 3 membered heteroalkyl. R¹⁰ and R¹¹ may independently be R^{32a}-substituted or unsubstituted 3 membered cycloalkyl, R^{32a}-substituted or unsubstituted 4 membered cycloalkyl, or R^{32a}-substituted or unsubstituted 5 membered cycloalkyl. R¹⁰ and R¹¹ may independently be R^{32a}-substituted or unsubstituted 5 membered heterocycloalkyl, R^{32a}-
30 substituted or unsubstituted 6 membered heterocycloalkyl, R^{32a}-substituted or unsubstituted 5

membered aryl, R^{32a}-substituted or unsubstituted 6 membered aryl, R^{32a}-substituted or unsubstituted 5 membered heteroaryl, or R^{32a}-substituted or unsubstituted 6 membered heteroaryl.

[0268] R^{32a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{32b}-substituted or unsubstituted alkyl (e.g. C₁-C₈ alkyl), R^{32b}-substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{32b}-substituted or unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), R^{32b}-substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{32b}-substituted or unsubstituted aryl (e.g. 5 to 6 membered aryl), or R^{32b}-substituted or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

[0269] R^{32b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted alky (e.g. C₁-C₈ alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. 3 to 8 membered cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 to 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 to 6 membered heteroaryl).

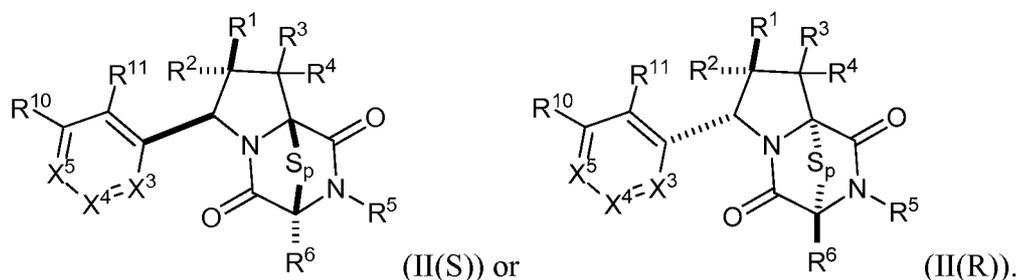
[0270] R⁹ and R¹⁰ may be joined together to form a substituted or unsubstituted 3 to 8 membered cycloalkyl. R⁹ and R¹⁰ may be joined together to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. R⁹ and R¹⁰ may be joined together to form a substituted or unsubstituted 3 to 8 membered aryl. R⁹ and R¹⁰ may be joined together to form a substituted or unsubstituted 3 to 8 membered heteroaryl.

[0271] R¹⁰ and R¹¹ may be joined together to form a substituted or unsubstituted 3 to 8 membered cycloalkyl. R¹⁰ and R¹¹ may be joined together to form a substituted or unsubstituted 3 to 8 membered heterocycloalkyl. R¹⁰ and R¹¹ may be joined together to form a substituted or unsubstituted 3 to 8 membered aryl. R¹⁰ and R¹¹ may be joined together to form a substituted or unsubstituted 3 to 8 membered heteroaryl.

[0272] In embodiments, R⁷, R⁸, R⁹, R¹⁰ and R¹¹ are independently hydrogen, halogen, C₁-C₅ unsubstituted alkyl, 2 to 5 membered unsubstituted heteroalkyl. R⁷, R⁸, R⁹, R¹⁰ and R¹¹ may

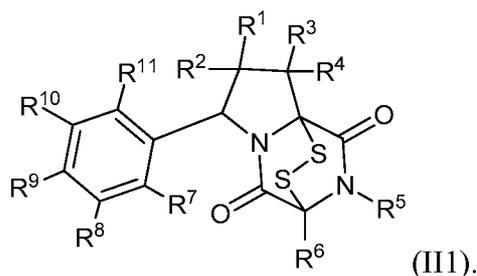
independently be hydrogen, halogen, unsubstituted methyl, $-\text{OCH}_3$ or $-\text{O}(\text{CH}_2)_2=\text{CH}_2$. R^{10} and R^{11} may be hydrogen.

[0273] The compound of formula (II) may have the formula:



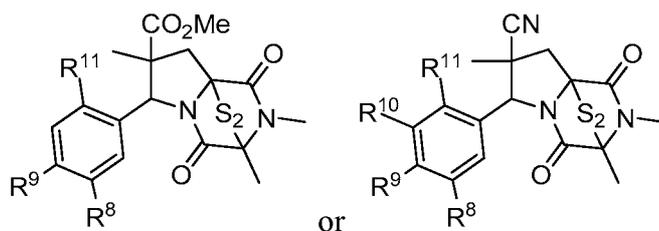
- 5 [0274] The symbol p , X^3 , X^4 , X^5 , p , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , and R^{11} are as described herein, including embodiments thereof. R^5 and R^6 may independently be unsubstituted C_1 - C_3 alkyl or unsubstituted 3 to 5 membered cycloalkyl. R^7 , R^8 , R^9 , and R^{10} may independently be hydrogen, halogen, unsubstituted methyl, $-\text{OCH}_3$ or $-\text{O}(\text{CH}_2)_2=\text{CH}_2$. R^1 may be $-\text{CN}$ or unsubstituted 2 to 5 membered heteroalkyl. R^1 may be $-\text{CN}$. R^1 may be $-\text{COOCH}_3$. R^1 may be
 10 unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-\text{CN}$, R^2 may be unsubstituted methyl. R^3 and R^4 may be hydrogen. R^{10} and R^{11} may be hydrogen.

[0275] The compound of formula (II) may have the formula:



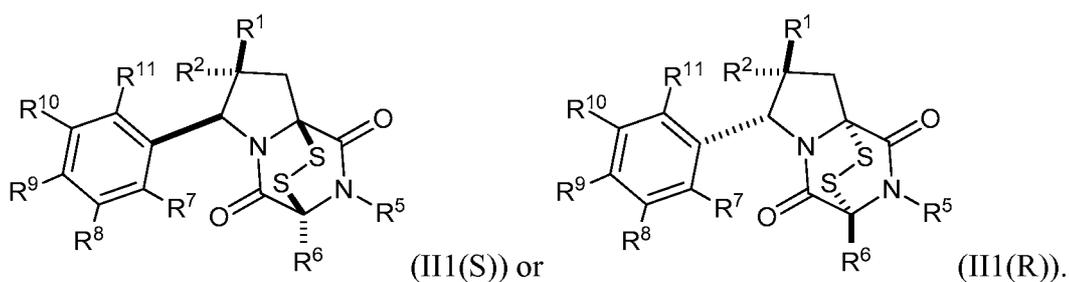
- [0276] In embodiments, R^8 is hydrogen or $-\text{OR}^{33\text{J}}$. R^9 , R^{10} , and R^{11} may independently be
 15 hydrogen or halogen. $\text{R}^{33\text{J}}$ may be hydrogen, or unsubstituted alkyl (e.g. unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl).

[0277] The compound of formula (II) may have the formula:



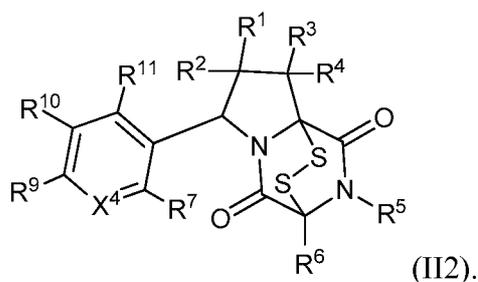
[0278] R⁸ may be hydrogen or -OR^{33J}. R⁹, R¹⁰, and R¹¹ may independently be hydrogen or halogen. R^{33J} may be hydrogen, or unsubstituted alkyl

[0279] The compound of formula (II1) may have the formula:

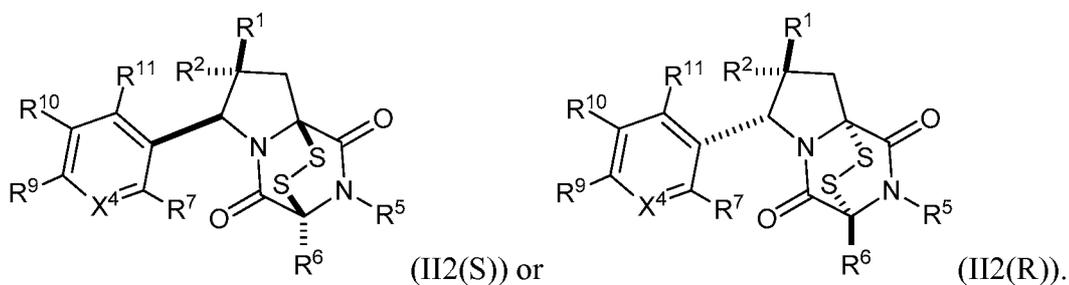


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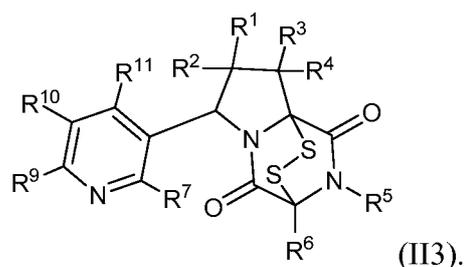
[0280] The compound of formula (II) may have the formula:



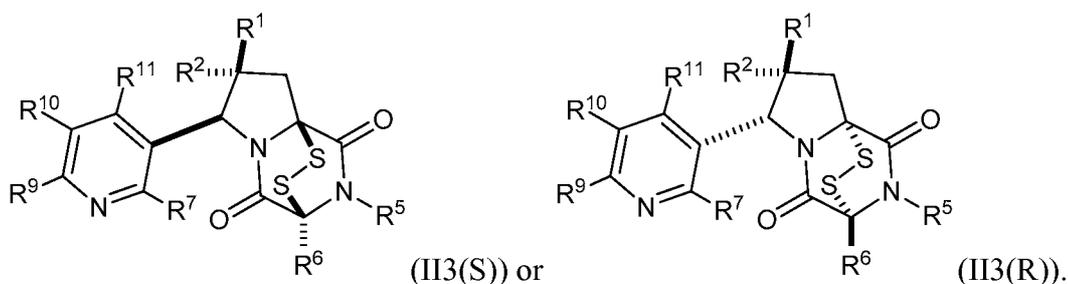
[0281] The compound of formula (II2) may have the formula:



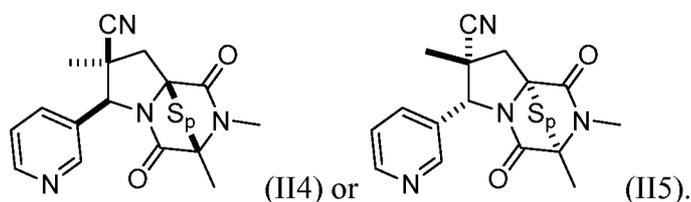
10 [0282] The compound of formula (II) may have the formula:



[0283] The compound of formula (II3) may have the formula:

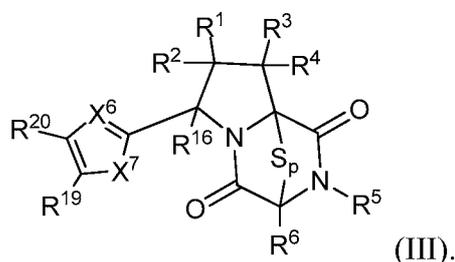


[0284] The compound of formula (II) may have the formula:



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[0285] The compound of formula (I) may have the formula:



[0286] The symbol p, R¹, R², R³, R⁴, R⁵, R⁶, and R¹⁶ are as described herein, including embodiments thereof. R⁵ and R⁶ may independently be unsubstituted C₁-C₃ alkyl or
 10 unsubstituted 3 to 5 membered cycloalkyl. R⁷, R⁸, R⁹, and R¹⁰ may independently be hydrogen, halogen, unsubstituted methyl, -OCH₃ or -O(CH₂)₂=CH₂. R¹ may be -CN or unsubstituted 2 to 5 membered heteroalkyl. R¹ may be -CN. R¹ may be -COOCH₃. R¹ may be unsubstituted

methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^3 and R^4 may be hydrogen. R^{10} and R^{11} may be hydrogen.

[0287] X^6 is CR^{21} or N. X^7 is $CR^{22}R^{23}$, S, O, or NR^{23} . R^{19} , R^{20} , R^{21} , R^{22} and R^{23} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHN R^{34M}R^{35M}$, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; The symbol n13 is 1 or 2.

[0288] R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, substituted or unsubstituted 5 to 6 membered heteroaryl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may be fused to form a substituted or unsubstituted 5 or 6 membered heterocycloalkyl, a substituted or unsubstituted 5 or 6 membered aryl, or a substituted or unsubstituted 5 or 6 membered heteroaryl.

[0289] R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be substituted or unsubstituted alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be substituted or unsubstituted C_1 - C_8 alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be substituted or unsubstituted C_1 - C_5 alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be substituted or unsubstituted C_1 - C_3 alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be R^{37a} -substituted or unsubstituted alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be R^{37a} -substituted or unsubstituted C_1 - C_8 alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be R^{37a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{19} , R^{20} , R^{21} , R^{22} and R^{23} may independently be R^{37a} -substituted or unsubstituted C_1 - C_3 alkyl.

and R²³ may independently be R^{37a}-substituted or unsubstituted heterocycloalkyl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 4 membered heterocycloalkyl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 5 membered heterocycloalkyl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 6 membered heterocycloalkyl.

[0293] R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted 5 to 6 membered aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted 5 membered aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted 6 membered aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 5 to 6 membered aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 5 membered aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 6 membered aryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted 5 to 6 membered heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted 5 membered heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be substituted or unsubstituted 6 membered heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 5 to 6 membered heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 5 membered heteroaryl. R¹⁹, R²⁰, R²¹, R²² and R²³ may independently be R^{37a}-substituted or unsubstituted 6 membered heteroaryl. R^{37a} is as described herein, including embodiments thereof.

[0294] R¹⁹ and R²⁰ may optionally be bonded together to form a substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

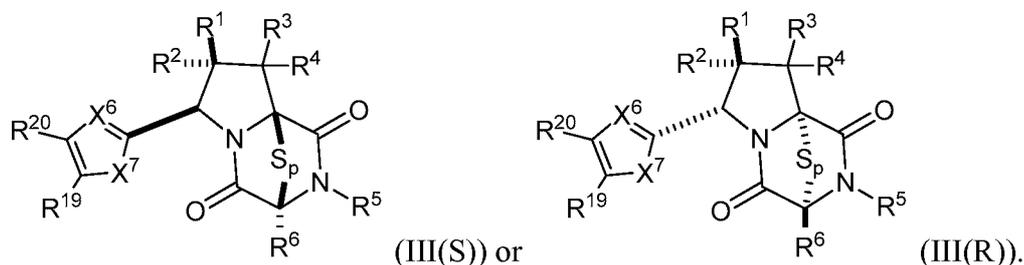
[0295] R¹⁹ and R²² may optionally be bonded together to form a substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl,

substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

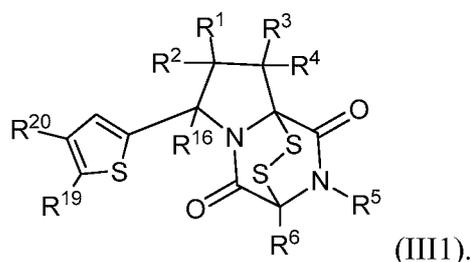
[0296] R^{20} and R^{21} may optionally be bonded together to form a substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0297] When X^7 is S, X^6 may be N or CR^{21} . When X^7 is NH, X^6 may be N or CR^{21} . When X^7 is NR^{23} , X^6 may CR^{21} or N. When X^7 is O, X^6 may be N, CH, or CR^{21} . In certain embodiments, X^7 is S and X^6 is CH. p may be 2, 3, or 4. In certain embodiments p is 2.

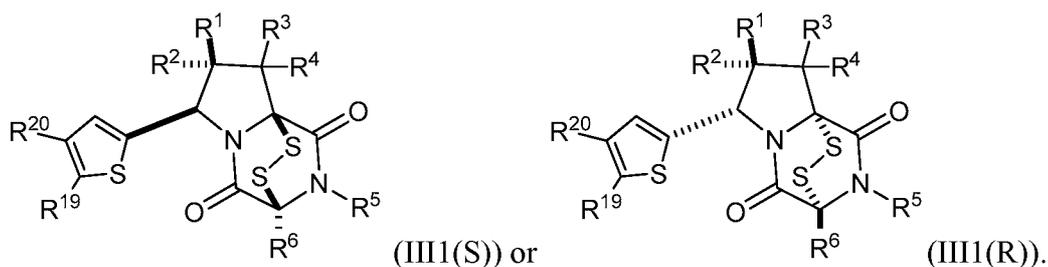
10 [0298] The compound of formula (III) may have the formula:



[0299] The compound of formula (III) may have the formula:

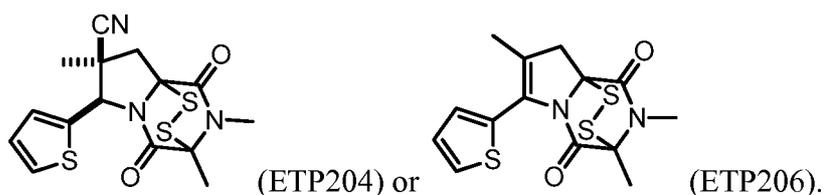


[0300] The compound of formula (III1) may have the formula:

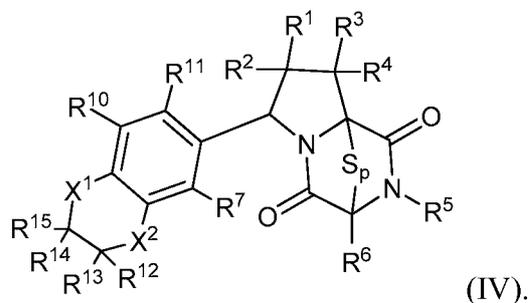


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[0301] The compound of formula (III) may have the formula:



[0302] The compound of formula (I) may have the formula:



[0303] The symbol p , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , and R^{16} are as described herein, including embodiments thereof. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHN R^{34M}R^{35M}$, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbol n_{13} is 1 or 2.

[0304] X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S. X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S. R^5 and R^6 may independently be unsubstituted C_1 - C_3 alkyl or unsubstituted 3 to 5 membered cycloalkyl. R^7 , R^8 , R^9 , and R^{10} may independently be hydrogen, halogen, unsubstituted methyl, $-OCH_3$ or $-O(CH_2)_2=CH_2$. R^1 may be $-CN$ or unsubstituted 2 to 5 membered heteroalkyl. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^3 and R^4 may be hydrogen. R^{10} and R^{11} may be hydrogen. R^{12} , R^{13} , R^{14} , and R^{15} may be hydrogen.

[0305] R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted C_1 - C_8 alkyl, substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted 3 to 6 membered cycloalkyl, substituted or unsubstituted 3 to 6 membered heterocycloalkyl, substituted or unsubstituted 5 to 6 membered aryl, substituted or unsubstituted 5 to 6 membered heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may be fused to form a substituted or unsubstituted 5 or 6 membered heterocycloalkyl, a substituted or unsubstituted 5 or 6 membered aryl, or a substituted or unsubstituted 5 or 6 membered heteroaryl.

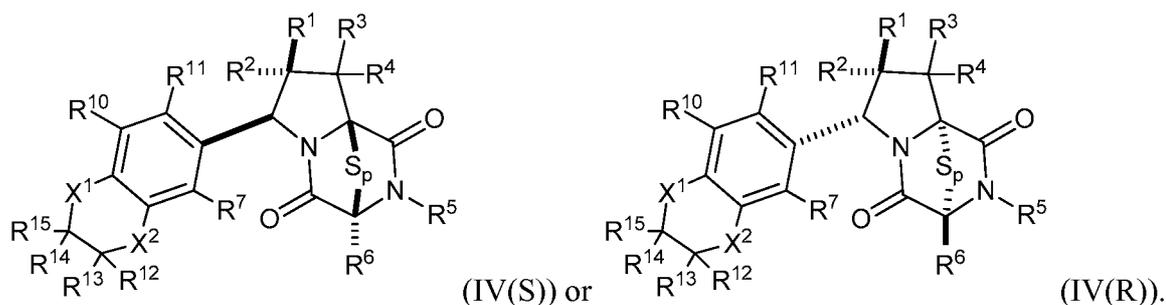
[0306] R^{12} , R^{13} , R^{14} , and R^{15} may independently be substituted or unsubstituted alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted C_1 - C_8 alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted C_1 - C_5 alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted C_1 - C_3 alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted C_1 - C_8 alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted C_1 - C_3 alkyl.

[0307] R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted heteroalkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 2 to 8 membered heteroalkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 2 to 5 membered heteroalkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 2 to 3 membered heteroalkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted heteroalkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 2 to 8 membered heteroalkyl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 2 to 5

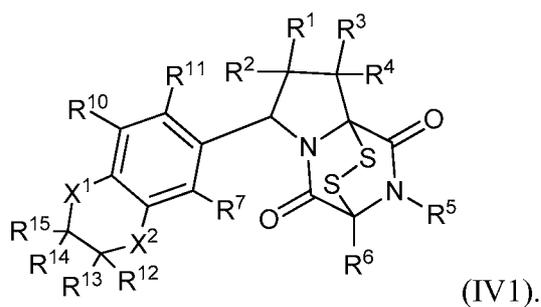
R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 6 membered heterocycloalkyl.

[0310] R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 5 to 6 membered aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 5 membered aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 6 membered aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 5 to 6 membered aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 5 membered aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 6 membered aryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 5 to 6 membered heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 5 membered heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be substituted or unsubstituted 6 membered heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 5 to 6 membered heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 5 membered heteroaryl. R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} may independently be R^{37a} -substituted or unsubstituted 6 membered heteroaryl.

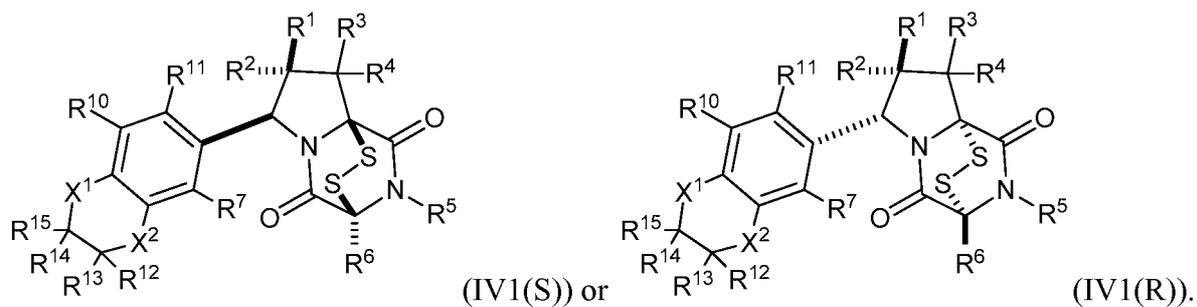
[0311] The compound of formula (IV) may have the formula:



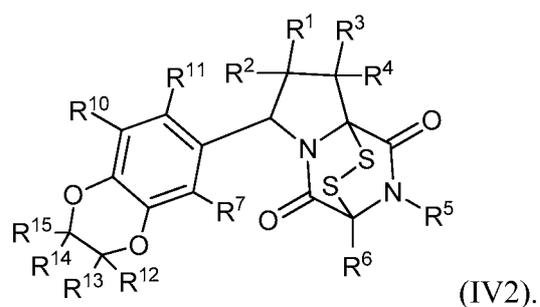
[0312] The compound of formula (IV) may have the formula:



[0313] The compound of formula (IV1) may have the formula:

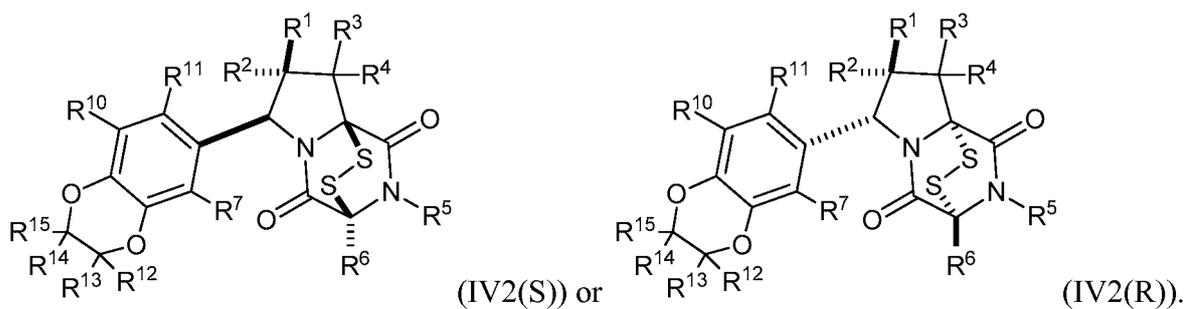


[0314] The compound of formula (IV1) may have the formula:

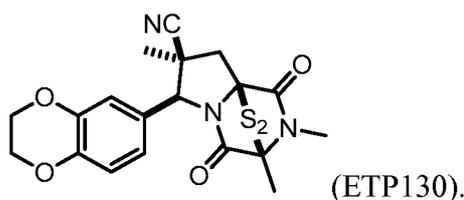


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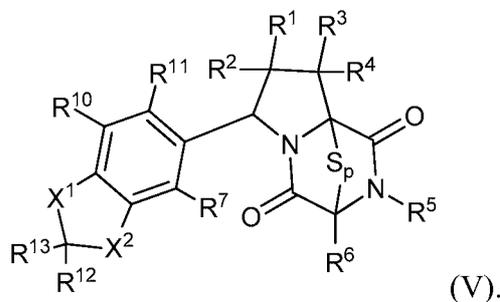
[0315] The compound of formula (IV2) may have the formula:



[0316] The compound of formula (IV2) may have the formula:



[0317] The compound of formula (I) may have the formula:



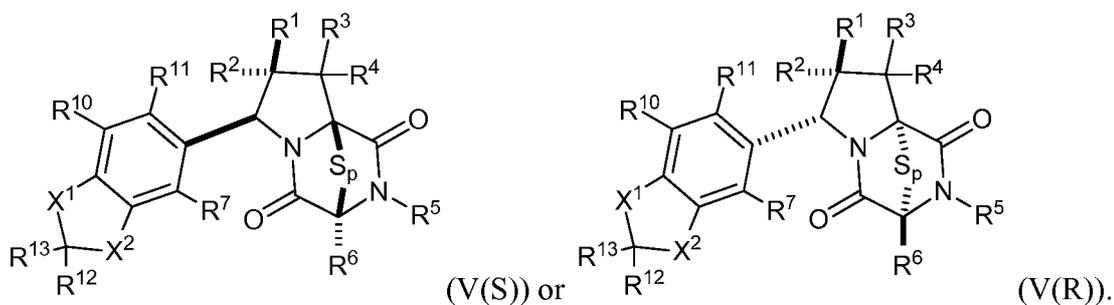
[0318] X^1 , X^2 , p , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , R^{13} , and R^{16} are as described herein,
5 including embodiments thereof.

[0319] In embodiments R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNR^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNR^{34I}R^{35I}$, substituted or unsubstituted
10 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^{10} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNR^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNR^{34L}R^{35L}$, substituted or unsubstituted
15 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. In embodiments, R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} and R^{22A} are independently
20 hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNR^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNR^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or

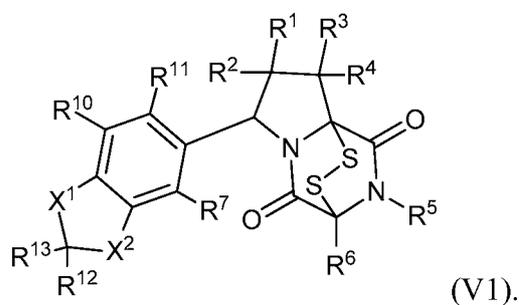
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbols n_9 , n_{11} , and n_{13} may independently be 1 or 2.

[0320] R^5 and R^6 may independently be unsubstituted C_1 - C_3 alkyl or unsubstituted 3 to 5 membered cycloalkyl. R^7 , R^{10} , and R^{11} may independently be hydrogen, halogen, unsubstituted methyl, $-OCH_3$ or $-O(CH_2)_2=CH_2$. R^1 may be $-CN$ or unsubstituted 2 to 5 membered heteroalkyl. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^3 and R^4 may be hydrogen. R^{10} and R^{11} may be hydrogen. R^{12} and R^{13} may be hydrogen.

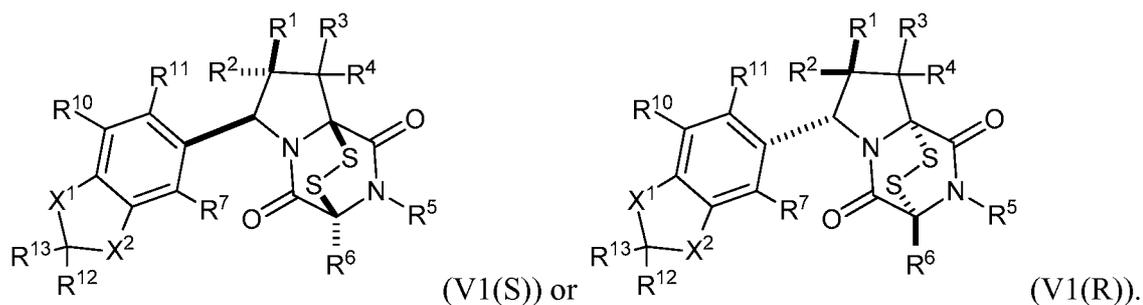
[0321] The compound of formula (V) may have the formula:



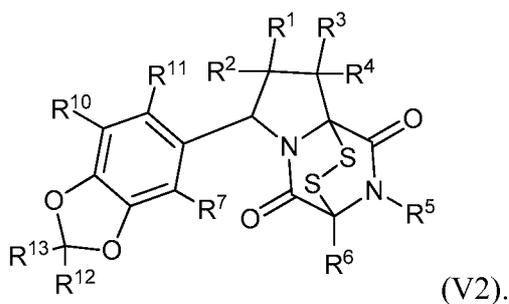
15 [0322] The compound of formula (V) may have the formula:



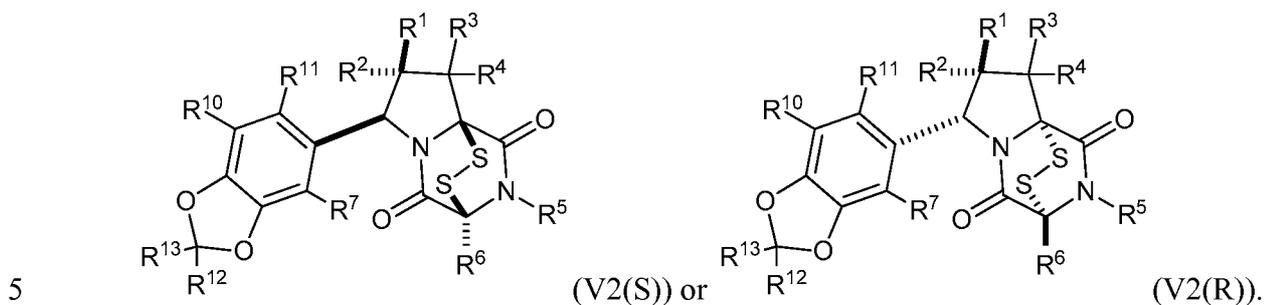
[0323] The compound of formula (V1) may have the formula:



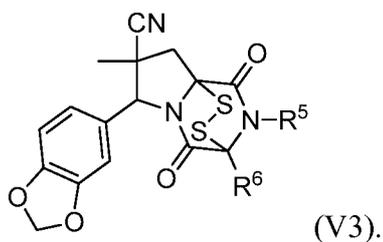
[0324] The compound of formula (V1) may have the formula:



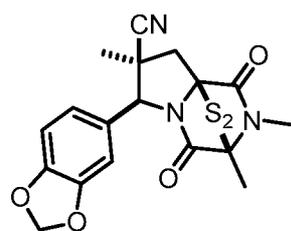
[0325] The compound of formula (V2) may have the formula:



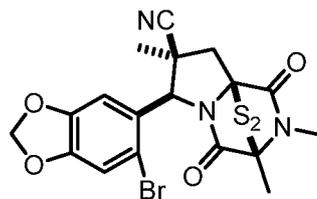
[0326] The compound of formula (V) may have the formula:



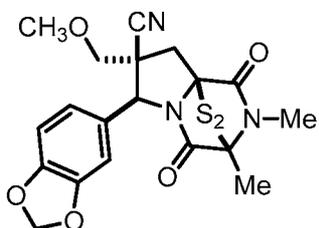
[0327] The compound of formula (V2) may have the formula:



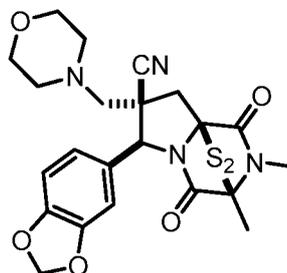
(ETP69),



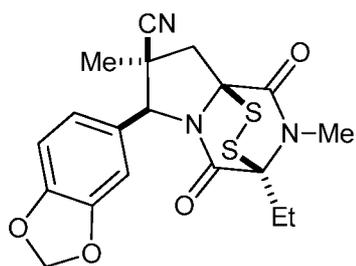
(ETP128),



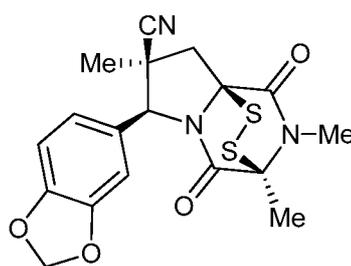
(ETP344),



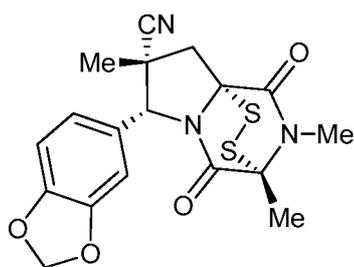
(ETP382),



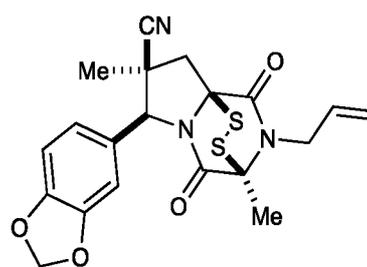
(ETP406),



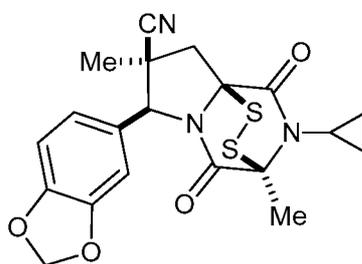
(ETP417),



(ETP422),



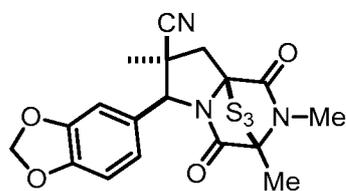
(ETP425), or



(ETP452).

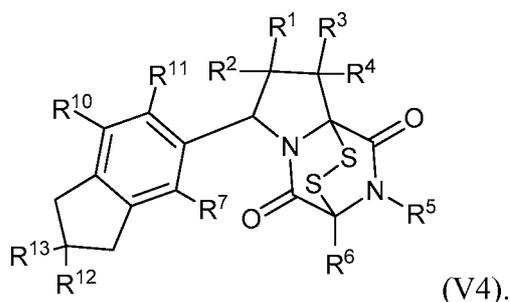
5

[0328] The compound of formula (V) may have the formula:

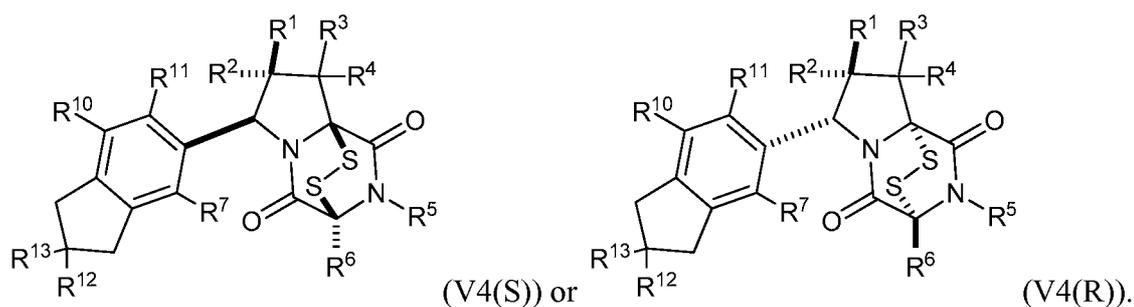


(ETP341).

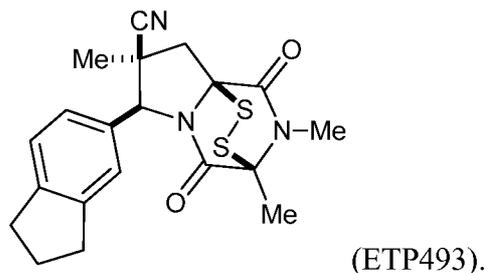
[0329] The compound of formula (V1) may have the formula:



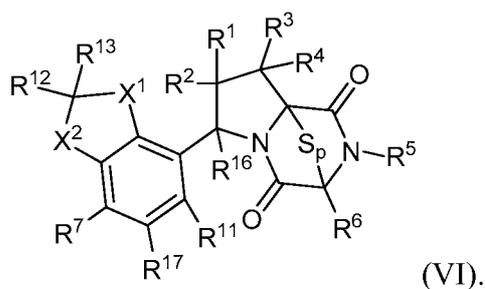
[0330] The compound of formula (V3) may have the formula:



5 [0331] The compound of formula (V4) may have the formula:



[0332] The compound of formula (I) may have the formula:



10 X^1 , X^2 , p , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{11} , R^{12} , R^{13} , and R^{16} are as described herein, including embodiments thereof. R^{17} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$,

$-OR^{33P}$, $-NR^{34P}R^{35P}$, $-COOR^{33P}$, $-CONR^{34P}R^{35P}$, $-NO_2$, $-SR^{36P}$, $-SO_{n15}R^{34P}$, $-SO_{n15}OR^{34P}$,
 $-SO_{n15}NR^{34P}R^{35P}$, $-NHNR^{34P}R^{35P}$, $-ONR^{34P}R^{35P}$, $-NHC(O)NHNR^{34P}R^{35P}$, 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, or are optionally bonded together to form a substituted or
 unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or
 unsubstituted aryl, or a substituted or unsubstituted heteroaryl. R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33L} , R^{34L} ,
 R^{35L} , R^{36L} , R^{33M} , R^{34M} , R^{35M} , R^{36M} , R^{33P} , R^{34P} , R^{35P} , and R^{36P} are independently hydrogen,
 10 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl. The symbols n9, n12, n13 and n15
 are independently 1 or 2.

[0333] In embodiments X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S. In embodiments X^2 is $CR^{22}R^{22A}$, O,
 NR^{22A} , or S. In embodiments R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$,
 15 $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$,
 $-SO_{n9}NR^{34I}R^{35I}$, $-NHNR^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNR^{34I}R^{35I}$, substituted 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^{11} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 20 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$,
 $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNR^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNR^{34L}R^{35L}$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to
 25 form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a
 substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl. In embodiments,
 R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$,
 $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNR^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNR^{34M}R^{35M}$,
 30 substituted 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 [0334] R^5 and R^6 may independently be unsubstituted C_1 - C_3 alkyl or unsubstituted 3 to 5 membered cycloalkyl. R^7 , R^{10} , and R^{11} may independently be hydrogen, halogen, unsubstituted methyl, $-OCH_3$ or $-O(CH_2)_2=CH_2$. R^1 may be $-CN$ or unsubstituted 2 to 5 membered heteroalkyl. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^3 and R^4 may be hydrogen. R^{10} and R^{11} may be hydrogen. R^{12} and R^{13} may be hydrogen. R^7 , R^{10} , and R^{17} may be hydrogen.

10 [0335] R^{17} may be hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$. R^{17} may be substituted or unsubstituted alkyl. R^{17} may be substituted or unsubstituted C_1 - C_8 alkyl. R^{17} may be substituted or unsubstituted C_1 - C_5 alkyl. R^{17} may be substituted or unsubstituted C_1 - C_3 alkyl. R^1 may be R^{17a} -substituted or unsubstituted alkyl. R^{17} may be R^{17a} -substituted or unsubstituted C_1 - C_8 alkyl. R^1 may be R^{17a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{17} may be R^{17a} -substituted or unsubstituted C_1 - C_3 alkyl.

[0336] R^{17} may be substituted or unsubstituted heteroalkyl. R^{17} may be substituted or unsubstituted 2 to 8 membered heteroalkyl. R^{17} may be substituted or unsubstituted 2 to 5 membered heteroalkyl. R^{17} may be substituted or unsubstituted 2 to 3 membered heteroalkyl.
 20 R^{17} may be R^{17a} -substituted or unsubstituted heteroalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 2 to 8 membered heteroalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 2 to 5 membered heteroalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 2 to 3 membered heteroalkyl.

[0337] R^{17} may be substituted or unsubstituted cycloalkyl. R^{17} may be substituted or
 25 unsubstituted 3 to 8 membered cycloalkyl. R^{17} may be substituted or unsubstituted 3 to 5 membered cycloalkyl. R^{17} may be substituted or unsubstituted 3 membered cycloalkyl. R^{17} may be substituted or unsubstituted 4 membered cycloalkyl. R^{17} may be substituted or unsubstituted 5 membered cycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted cycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 3 to 8 membered cycloalkyl. R^{17} may be R^{17a} -substituted or

unsubstituted 3 to 5 membered cycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 3 membered cycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 4 membered cycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 5 membered cycloalkyl.

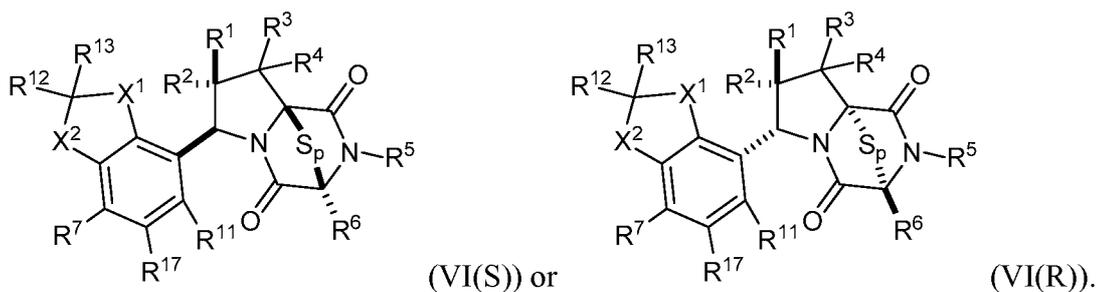
[0338] R^{17} may be substituted or unsubstituted heterocycloalkyl. R^{17} may be substituted or unsubstituted 3 to 6 membered heterocycloalkyl. R^{17} may be substituted or unsubstituted 4 membered heterocycloalkyl. R^{17} may be substituted or unsubstituted 5 membered heterocycloalkyl. R^{17} may be substituted or unsubstituted 6 membered heterocycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted heterocycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 4 membered heterocycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 5 membered heterocycloalkyl. R^{17} may be R^{17a} -substituted or unsubstituted 6 membered heterocycloalkyl.

[0339] R^{17} may be substituted or unsubstituted aryl. R^{17} may be substituted or unsubstituted 5 to 6 membered aryl. R^{17} may be substituted or unsubstituted 5 membered aryl. R^{17} may be substituted or unsubstituted 6 membered aryl. R^{17} may be R^{17a} -substituted or unsubstituted aryl. R^{17} may be R^{17a} -substituted or unsubstituted 5 to 6 membered aryl. R^{17} may be R^{17a} -substituted or unsubstituted 5 membered aryl. R^{17} may be R^{17a} -substituted or unsubstituted 6 membered aryl. R^{17} may be substituted or unsubstituted heteroaryl. R^{17} may be substituted or unsubstituted 5 to 6 membered heteroaryl. R^{17} may be substituted or unsubstituted 5 membered heteroaryl. R^{17} may be substituted or unsubstituted 6 membered heteroaryl. R^{17} may be R^{17a} -substituted or unsubstituted heteroaryl. R^{17} may be R^{17a} -substituted or unsubstituted 5 to 6 membered heteroaryl. R^{17} may be R^{17a} -substituted or unsubstituted 5 membered heteroaryl. R^{17} may be R^{17a} -substituted or unsubstituted 6 membered heteroaryl.

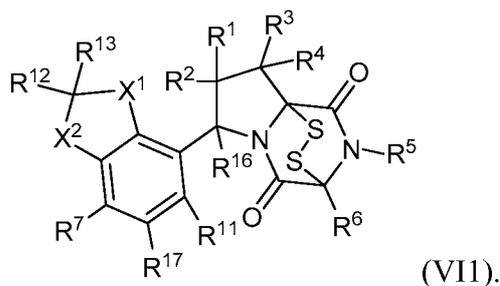
[0340] R^{17a} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, R^{17b} -substituted or unsubstituted alkyl (e.g. C_1 - C_8 alkyl), R^{17b} -substituted or unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), R^{17b} -substituted or unsubstituted cycloalkyl (e.g. C_3 - C_8 cycloalkyl), R^{17b} -substituted or unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), R^{17b} -substituted or unsubstituted aryl (e.g. 5 or 6 membered aryl), or R^{17b} -substituted or unsubstituted heteroaryl (e.g. 5 or 6 membered heteroaryl).

[0341] R^{17b} is halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, unsubstituted alkyl (e.g. C_1 - C_8 alkyl), unsubstituted heteroalkyl (e.g. 2 to 8 membered heteroalkyl), unsubstituted cycloalkyl (e.g. C_3 - C_8 cycloalkyl), unsubstituted heterocycloalkyl (e.g. 3 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g. 5 or 6 membered aryl), or unsubstituted heteroaryl (e.g. 5 or 6 membered heteroaryl).

[0342] The compound of formula (VI) may have the formula:

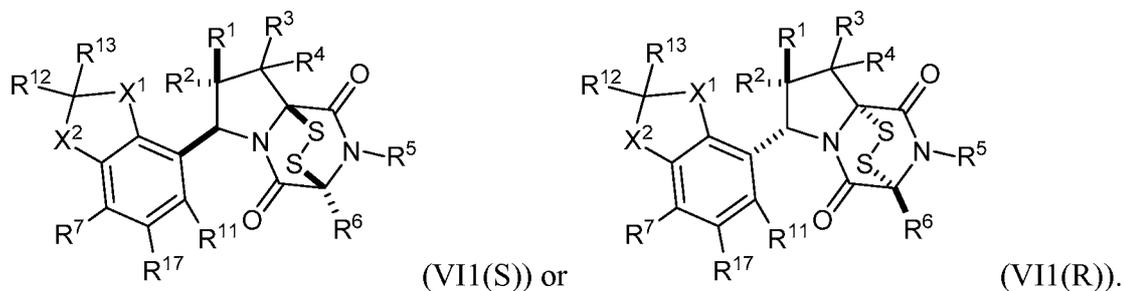


[0343] The compound formula (VI) may have the formula:

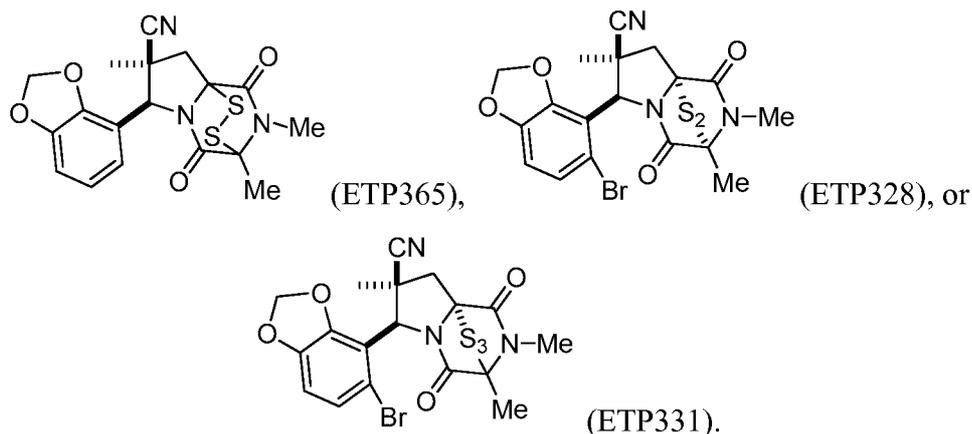


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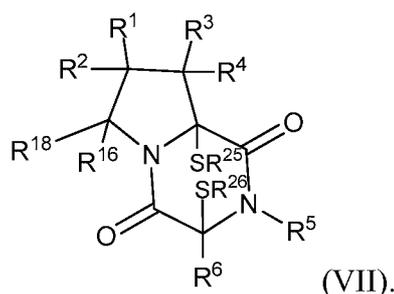
[0344] The compound of formula (VII) may have the formula:



[0345] The compound of formula (VI) may have the formula:



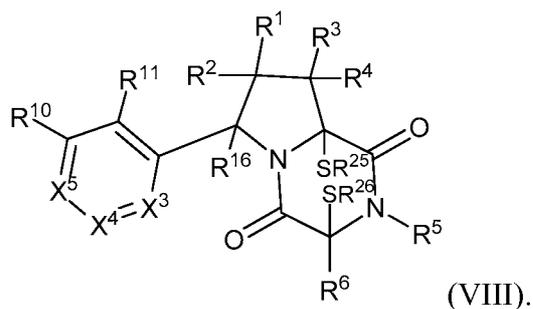
[0346] In another aspect is a compound having the formula:



5 [0347] $R^1, R^2, R^3, R^4, R^5, R^6, R^{16}$ and R^{18} are as described herein, including embodiments thereof. R^{25} and R^{26} are independently hydrogen substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

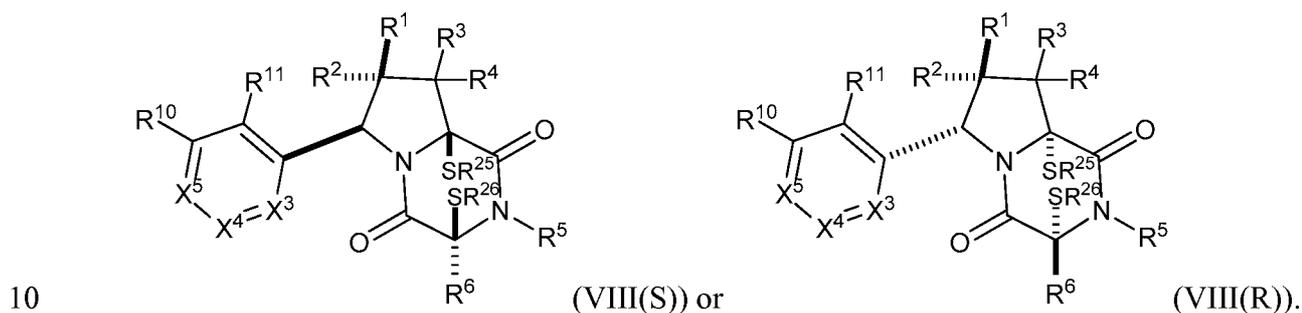
10 [0348] In embodiments, R^{25} and R^{26} are independently, hydrogen, trityl, para-methoxybenzyl, para-methylbenzyl, acetamidomethyl, tert-butyl, tert-butyl thiol, unsubstituted benzyl, unsubstituted methyl, phenylacetyl, or unsubstituted benzyloxycarbonyl.

[0349] The compound of formula (VII) may have the formula:

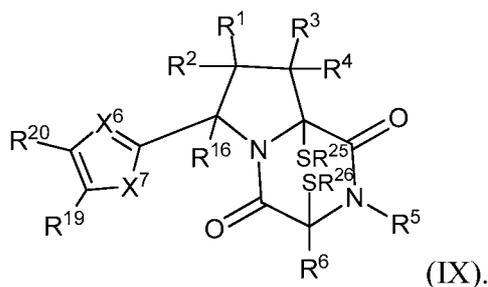


[0350] X^3, X^4, X^5 and $R^1, R^2, R^3, R^4, R^5, R^6, R^{10}, R^{11}, R^{16}, R^{25}$, and R^{26} are as described herein, including embodiments thereof. R^8 and R^9 may be bound together to form an unsubstituted or R^{31a} -substituted 5 or 6 membered heterocycloalkyl. R^8 and R^9 may be oxo. R^5 and R^6 may independently be hydrogen, unsubstituted 3 to 5 membered cycloalkyl, or R^{5a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{5a} may be unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered heterocycloalkyl. R^{5a} may be $-N(CH_3)_2$ or unsubstituted morpholino. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^{11} may be hydrogen or halogen.

[0351] The compound of formula (VIII) may have the formula:



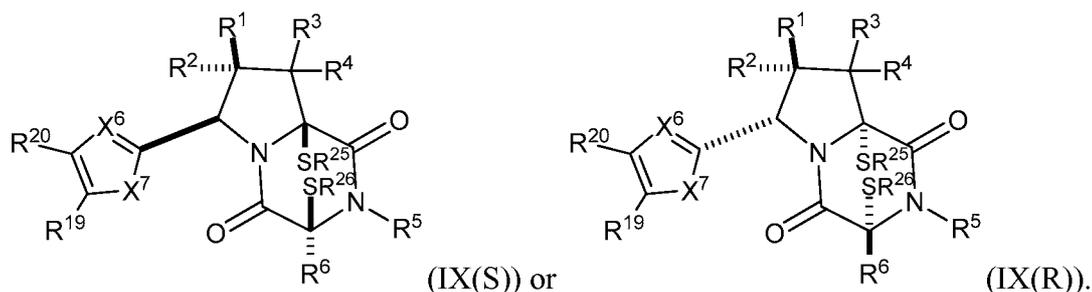
[0352] The compound of formula (VII) may have the formula:



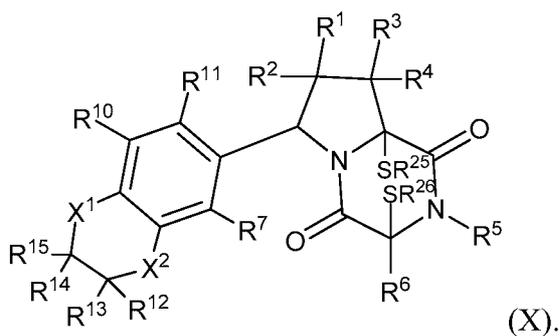
[0353] $X^6, X^7, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{19}, R^{20}, R^{25}$, and R^{26} are as described herein, including embodiments thereof. R^5 and R^6 may independently be unsubstituted 3 to 5 membered cycloalkyl or R^{5a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{5a} may be unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered heterocycloalkyl. R^{5a} may be $-N(CH_3)_2$ or unsubstituted morpholino. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^{11} may be hydrogen or halogen.

15

[0354] The compound of formula (IX) may have the formula:

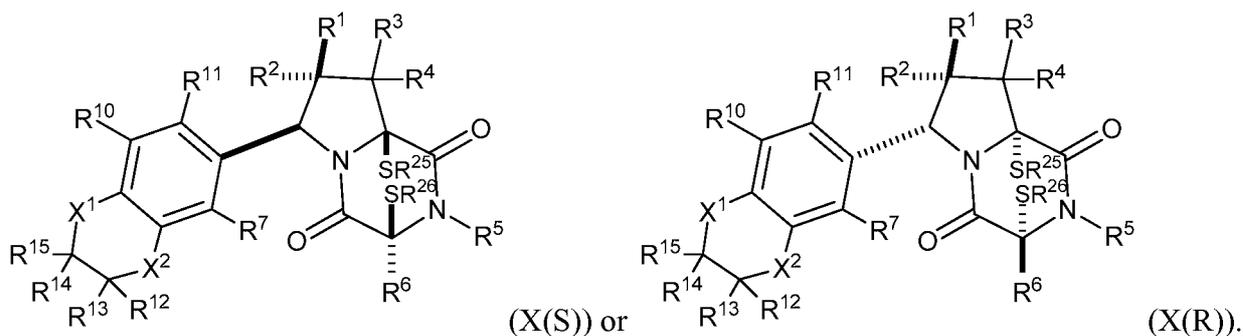


[0355] The compound of formula (VII) may have the formula:

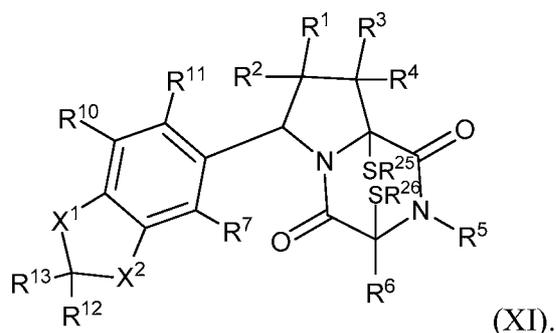


- 5 [0356] $X^1, X^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{25}$, and R^{26} are as described herein, including embodiments thereof. R^5 and R^6 may independently be unsubstituted 3 to 5 membered cycloalkyl or R^{5a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{5a} may be unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered heterocycloalkyl. R^{5a} may be - $N(CH_3)_2$ or unsubstituted morpholino. R^1 may be -CN. R^1 may be - $COOCH_3$. R^1 may be
- 10 unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is -CN, R^2 may be unsubstituted methyl. R^{11} may be hydrogen or halogen.

[0357] The compound of formula (X) may have the formula:

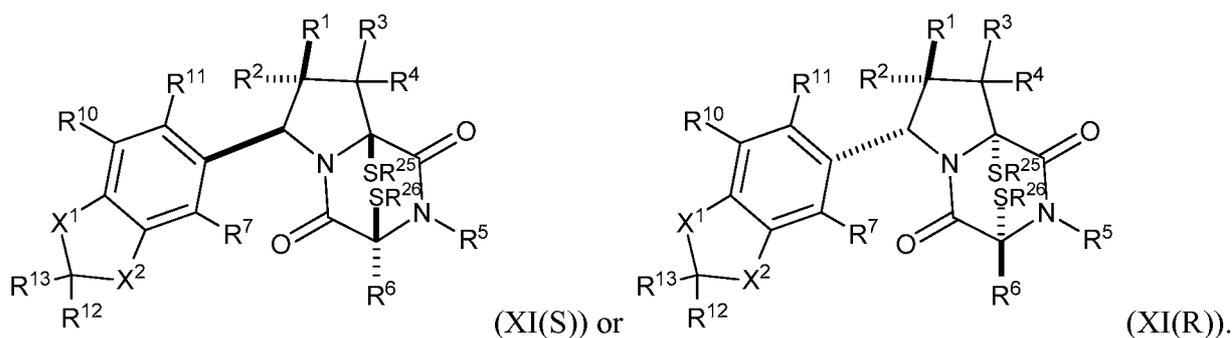


[0358] The compound of formula (VII) may have the formula:

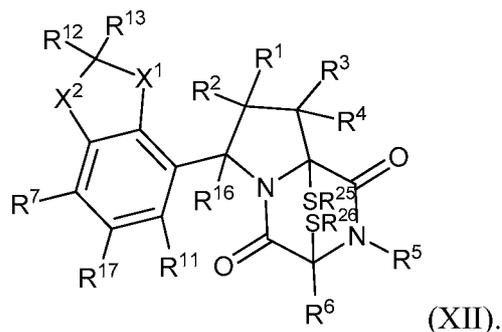


[0359] X^1 , X^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , R^{13} , R^{25} , and R^{26} are as described herein, including embodiments thereof. R^5 and R^6 may independently be unsubstituted 3 to 5 membered cycloalkyl or R^{5a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{5a} may be unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered heterocycloalkyl. R^{5a} may be $-N(CH_3)_2$ or unsubstituted morpholino. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^{11} may be hydrogen or halogen.

10 [0360] The compound of formula (XI) may have the formula:

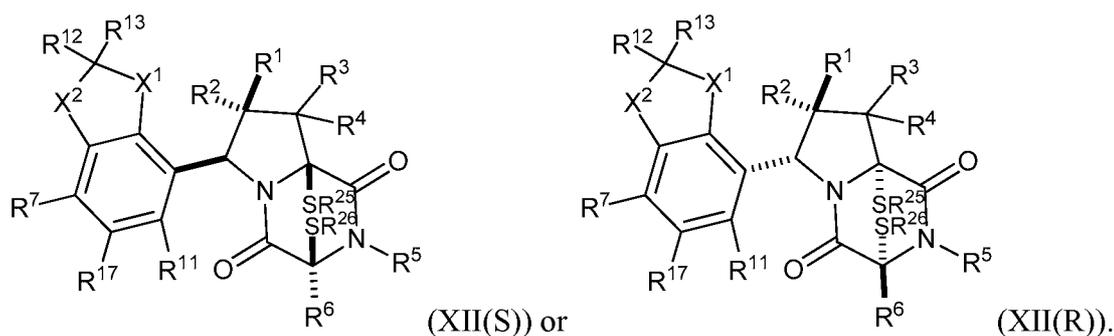


[0361] The compound of formula (VII) may have the formula:

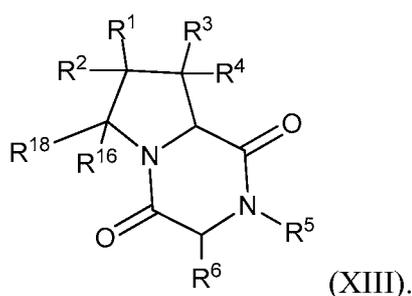


[0362] X^1 , X^2 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{10} , R^{11} , R^{12} , R^{13} , R^{25} , and R^{26} are as described herein, including embodiments thereof. R^5 and R^6 may independently be unsubstituted 3 to 5 membered cycloalkyl or R^{5a} -substituted or unsubstituted C_1 - C_5 alkyl. R^{5a} may be unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered heterocycloalkyl. R^{5a} may be $-N(CH_3)_2$ or unsubstituted morpholino. R^1 may be $-CN$. R^1 may be $-COOCH_3$. R^1 may be unsubstituted methyl. R^2 may be C_1 - C_3 unsubstituted alkyl. When R^1 is $-CN$, R^2 may be unsubstituted methyl. R^{11} may be hydrogen or halogen.

[0363] The compound of formula (XII) may have the formula:

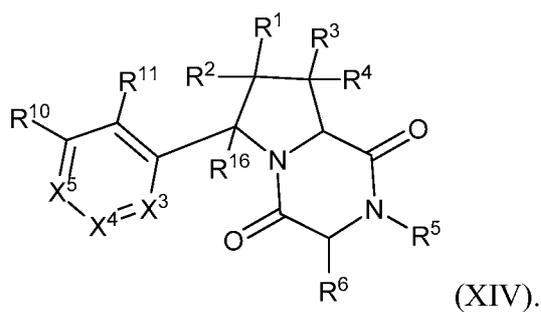


10 **[0364]** In another aspect is a compound having formula:

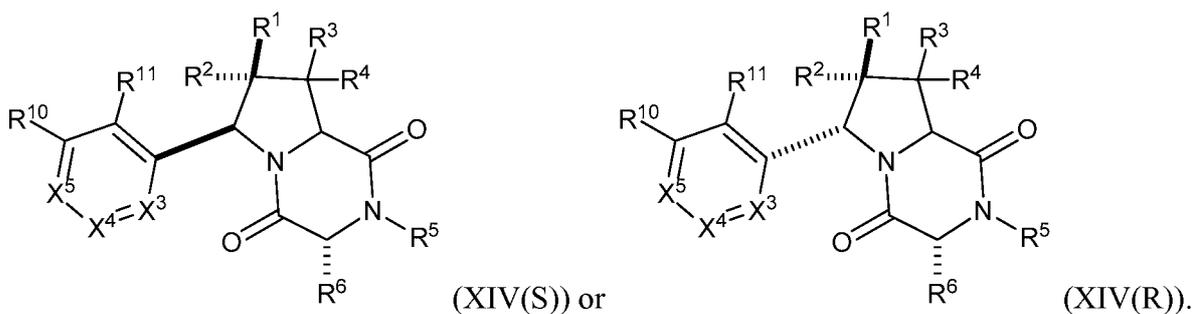


[0365] R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{16} , and R^{18} are as described herein, including embodiments thereof.

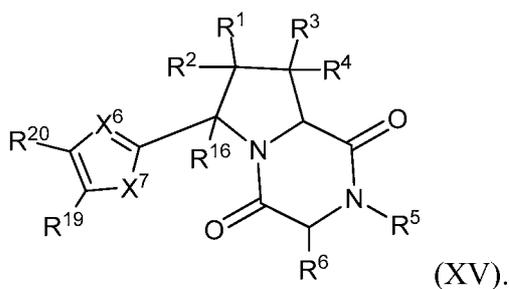
[0366] The compound of formula (XIII) may have the formula:



[0367] The compound of formula (XIV) may have the formula:

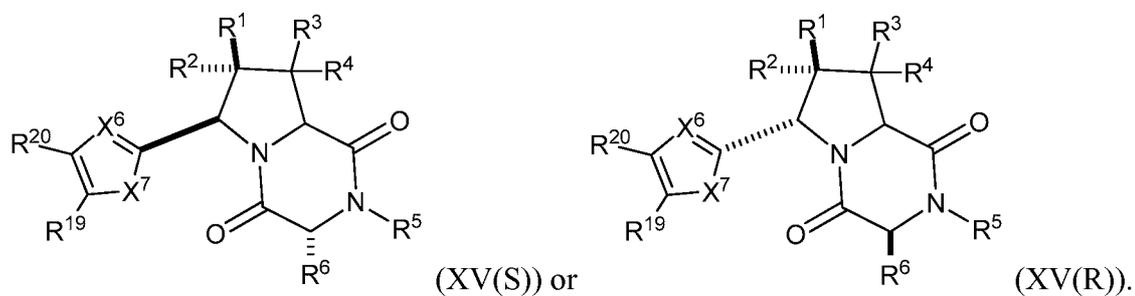


[0368] The compound of formula (XIII) may have the formula:

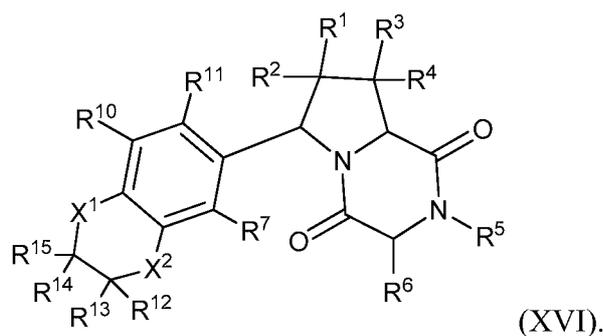


5

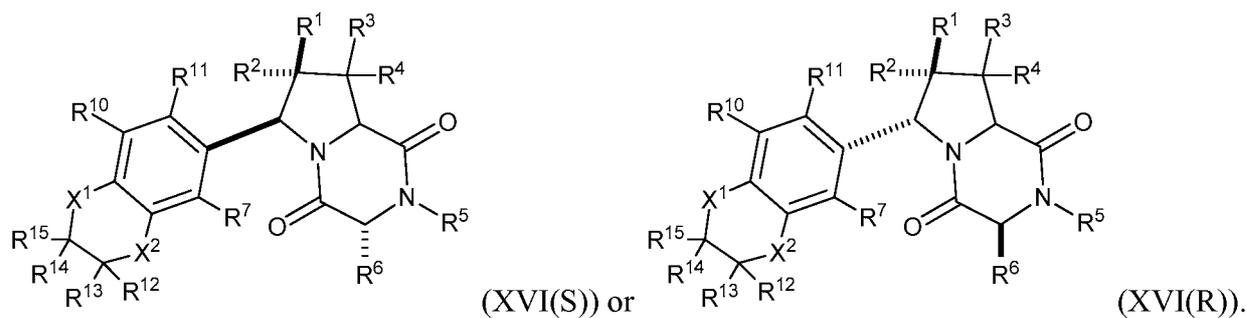
[0369] The compound of formula (XV) may have the formula:



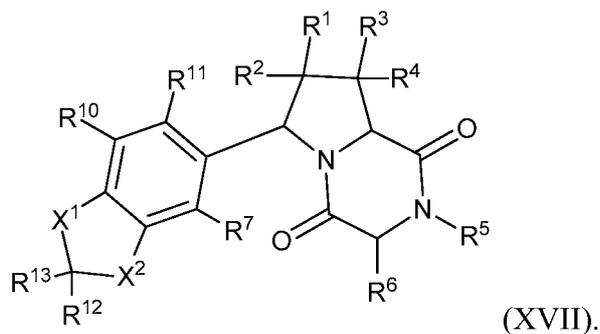
[0370] The compound of formula (XIII) may have the formula:



[0371] The compound of formula (XVI) may have the formula:

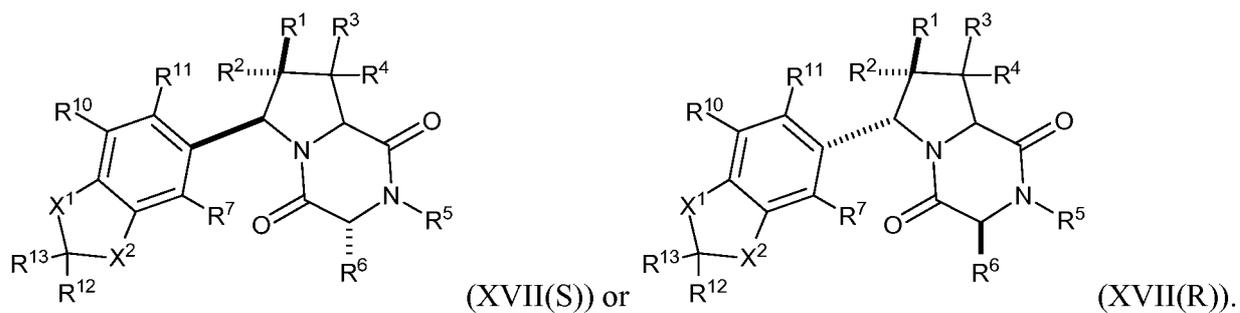


[0372] The compound of formula (XIII) may have the formula:

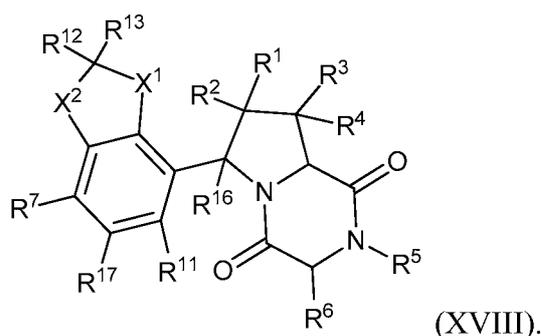


5

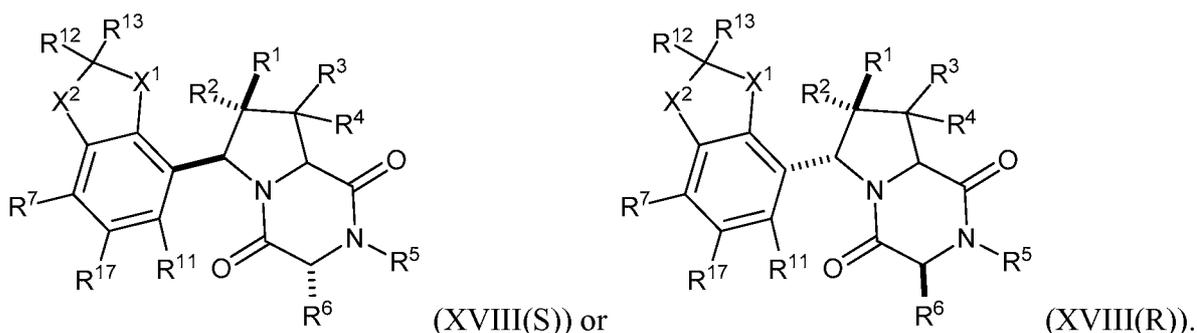
[0373] The compound of formula (XVII) may have the formula:



[0374] The compound of formula (XIII) may have the formula:



[0375] The compound of formula (XVIII) may have the formula:



[0376] In embodiments, R^2 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII), including embodiments thereof) is a polar substituent. In embodiments, R^2 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII), including embodiments thereof) is N_3 , $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2Ph$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, R^{2a} -substituted or unsubstituted C_1 - C_3 alkyl, or 1 to 3 membered R^{2a} -substituted or unsubstituted heteroalkyl. R^{2a} may be $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2Ph$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, R^{2b} -substituted or unsubstituted C_1 - C_5 alkyl, R^{2b} -substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{2b} -substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2b} -substituted or unsubstituted 5 or 6 membered aryl, or R^{2b} -substituted or unsubstituted 5 or 6 membered heteroaryl. R^{2b} may be halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, unsubstituted C_1 - C_8 alkyl, unsubstituted 2 to 8 membered heteroalkyl,

unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0377] In embodiments, R^2 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) is R^{2a} -substituted or unsubstituted C_1 - C_3 alkyl, or 1 to 3 membered R^{2a} -substituted or unsubstituted heteroalkyl, where R^{2a} is unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 or 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl. In embodiments, R^2 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) is unsubstituted methyl or unsubstituted methoxy. In embodiments, R^{2a} of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) is unsubstituted pyridine

[0378] In embodiments, R^5 and R^6 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, unsubstituted alkyl, or unsubstituted cycloalkyl. In embodiments, R^5 and R^6 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) are independently hydrogen, C_1 - C_3 unsubstituted alkyl or 3 to 5 membered cycloalkyl. In embodiments, R^5 and R^6 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) are independently hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted allyl, or unsubstituted cyclopropyl.

[0379] In embodiments, R^1 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) is $-CN$ or unsubstituted heteroalkyl. In embodiments, R^1 of the compounds provided herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVII), including embodiments thereof) is $-CN$.

[0380] In embodiments, the compounds provided herein are prodrugs as described herein, including embodiments thereof. Such prodrugs may take the form of formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII), including embodiments thereof. In embodiments, the prodrugs described herein exist in an inactive form whereupon the compound may be converted to an active form *in vivo*. Prodrugs may also be converted to an active form *ex-vivo* prior to administration (e.g. by chemical modification of the prodrug prior to delivery).

[0381] In embodiments, the compounds provided herein inhibit HMT SUV39H1 activity. In embodiments, the compounds provided herein specifically inhibit HMT SUV39H1 activity (e.g. relative to other HMT's such as one or more of G9a, DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR, SMYD2, SUV39H2). The inhibition may be at least about 2, 3, 4, 5, 10, 100, or 1000 fold greater inhibition relative to inhibition of other HMT's such as one or more of G9a, DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR, SMYD2, SUV39H2. In embodiments, the inhibition of SUV39H1 may be at least 2 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 3 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 4 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 5 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 6 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 7 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 8 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 9 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 10 fold greater than the inhibition of other HMTs described herein.

[0382] In embodiments, the inhibition of SUV39H1 may be at least 10 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 20 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 30 fold greater than the inhibition of other HMTs

described herein. In embodiments, the inhibition of SUV39H1 may be at least 40 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 50 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 60 fold greater than the inhibition of other HMTs described herein. In 5 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 70 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 80 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 90 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 may be at least 100 10 fold greater than the inhibition of other HMTs described herein.

[0383] The compounds provided herein may inhibit HMT G9a activity. The compounds provided herein may specifically inhibiting HMT G9a activity (e.g. relative to other HMT's such as one or more of SUV39H1, DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR, SMYD2, SUV39H2). The inhibition may be at least about 2, 3, 4, 5, 10, 100, or 1000 fold greater inhibition relative to inhibition of other HMT's such as one 15 or more of SUV39H1, DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR, SMYD2, SUV39H2. In embodiments, the inhibition of G9A may be at least 2 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 3 fold greater than the inhibition of other HMTs described 20 herein. In embodiments, the inhibition of G9A may be at least 4 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 5 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 6 fold greater than the inhibition of other HMTs described herein. In 25 embodiments, the inhibition of G9A may be at least 7 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 8 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 9 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 10 fold greater than the inhibition of other HMTs described herein.

[0384] In embodiments, the inhibition of G9A may be at least 10 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 20 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 30 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 40 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 50 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 60 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 70 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 80 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 90 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of G9A may be at least 100 fold greater than the inhibition of other HMTs described herein.

[0385] The compounds provided herein may also inhibiting both HMT SUV39H1 and the activity of HMT G9a. The compounds provided herein may specifically inhibiting both HMT SUV39H1 and the activity of HMT G9a (e.g. relative to other HMT's such as one or more of DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR, SMYD2, SUV39H2). The inhibition may be at least about 2, 3, 4, 5, 10, 100, or 1000 fold greater inhibition relative to inhibition of other HMT's such as one or more of DOT1, EZH1, EZH2, GLP, MLL1, MLL2, MLL3, MLL4, NSD2, SET1b, SET7/9, SET8, SETMAR, SMYD2, SUV39H2. Thus, in embodiments, the compounds provided herein are capable of specifically inhibiting H3K9 dimethylation or trimethylation (e.g. relative to other epigenetic events). The compounds provided herein may be capable of specifically inhibiting H3K9 dimethylation. The compounds provided herein may be capable of specifically inhibiting trimethylation. The compounds provided herein may be capable of specifically inhibiting both H3K9 dimethylation and H3K9 trimethylation.

[0386] In embodiments, the inhibition of SUV39H1 and G9a may be at least 2 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 3 fold greater than the inhibition of other HMTs described

herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 4 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 5 fold greater than the inhibition of other HMTs described herein. In
5 embodiments, the inhibition of SUV39H1 and G9a may be at least 6 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 7 fold greater than the inhibition of other HMTs described herein. In
10 embodiments, the inhibition of SUV39H1 and G9a may be at least 8 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 9 fold greater than the inhibition of other HMTs described herein. In
15 embodiments, the inhibition of SUV39H1 and G9a may be at least 10 fold greater than the inhibition of other HMTs described herein.

[0387] In embodiments, the inhibition of SUV39H1 and G9a may be at least 10 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 20 fold greater than the inhibition of other HMTs described
15 herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 30 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 40 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 50 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of
20 SUV39H1 and G9a may be at least 60 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 70 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 80 fold greater than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 90 fold greater
25 than the inhibition of other HMTs described herein. In embodiments, the inhibition of SUV39H1 and G9a may be at least 100 fold greater than the inhibition of other HMTs described herein.

[0388] In embodiments, a compound herein (e.g. formula (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII), including embodiments thereof) is an epigenetic
30 inhibitor. In embodiments, the compound inhibits H3K9 trimethylation or dimethylation.

[0389] In certain embodiments the compound is a compound as set forth in Table 1.

Table 1: Exemplary embodiments of compounds provided herein.

Structure	Reference	Structure	Reference	Structure	Reference	Structure	Reference
	ETP6		ETP128		ETP303		ETP390
	ETP8		ETP130		ETP309 3:1 mix epimers		ETP406
	ETP12		ETP154		ETP313 3:1 mix epimers		ETP417
	ETP14		ETP167		ETP328		ETP422
	ETP27		ETP178		ETP331		ETP425
	ETP49		ETP195		ETP341		ETP442
	ETP56		ETP204		ETP344		ETP450
	ETP69		ETP206		ETP356		ETP452
	ETP95		ETP214		ETP359		ETP469
	ETP100		ETP218		ETP365		ETP484
	ETP120		ETP223		ETP382		ETP493
	ETP125		ETP229		ETP384		

III. Pharmaceutical Compositions

[0390] In another aspect a pharmaceutical composition is provided. The pharmaceutical composition includes a compound as provided herein (e.g. of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)) and a pharmaceutically acceptable excipient. The compound may be provided in a therapeutically effective amount (e.g. for treating cancer as described herein). The compound may be provided as a prodrug, as described herein, including embodiments thereof. When provided as a prodrug, the prodrug be converted to an active form *in-vivo* or *ex-vivo* according to the methods described herein.

10 [0391] In another aspect, a pharmaceutical composition is provided including a compound as provided herein (e.g. of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), a pharmaceutically acceptable excipient, and an additional anticancer agent. The anticancer agent may be an epigenetic inhibitor or a multi-kinase inhibitor. The epigenetic inhibitor may be a DNA methyltransferase (DNMT) inhibitor.

15 The epigenetic inhibitor may be azacitidine or decitabine. The multi-kinase inhibitor may include a single kinase inhibitor. The multi-kinase inhibitor may be sorafenib. In embodiments the pharmaceutical composition includes more than one multi-kinase inhibitor or more than one epigenetic inhibitor and a compound as provided herein (e.g. of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)). In

20 embodiments the pharmaceutical composition includes a compound as provided herein (e.g. of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), a pharmaceutically acceptable excipient, at least one multi-kinase inhibitor (e.g. a single kinase inhibitor), and at least one epigenetic inhibitor. In embodiments, the epigenetic inhibitor, DNMT inhibitor, multi-kinase inhibitor and single kinase inhibitor are

25 anti-cancer agents. The anti-cancer agents include those described herein and embodiments thereof.

[0392] The pharmaceutical composition may include a first amount of a compound as described herein, including embodiments thereof, and a second amount of the multi-kinase inhibitor. The first amount and second amount may be together an effective amount to provide a synergistic therapeutic effect (e.g. the measured effect of compounds administered in

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combination is greater than the sum of the individual effects of each of the compounds administered alone as a single agent). The multi-kinase inhibitor may be sorafenib. The pharmaceutical composition of may include a first amount of a compound as described herein, including embodiments thereof, and a second amount of the epigenetic inhibitor, wherein the first amount and second amount are together an effective amount to provide a synergistic therapeutic effect. The epigenetic inhibitor may be azacitidine or decitabine.

[0393] The multi-kinase inhibitor of pharmaceutical composition may be dasatinib, sunitinib, erlotinib, bevacizumab, vatalanib, vemurafenib, vandetanib, cabozantinib, poatinib, axitinib, ruxolitinib, regorafenib, crizotinib, bosutinib, cetuximab, gefitinib, imatinib, lapatinib, lenvatinib, mubritinib, nilotinib, panitumumab, pazopanib, trastuzumab, or sorafenib. The multi-kinase inhibitor of the pharmaceutical composition may be sorafenib. The epigenetic inhibitor may be azacitidine or decitabine. The epigenetic inhibitor may be azacitidine. The epigenetic inhibitor may be decitabine. In some dosage forms, the compound and the multi-kinase inhibitor or the epigenetic inhibitor may be co-administered as a single dosage form.

[0394] The pharmaceutical compositions described herein, including embodiments thereof may be used in the treatment of cancers. The pharmaceutical compositions described herein, including embodiments thereof may be used in the treatment of solid and blood tumors, including ovarian cancer, breast cancer, lung cancer, leukemia (e.g. AML or CML), lymphoma, pancreatic cancer, kidney cancer, melanoma, liver cancer, colon cancer, sarcoma, multiple myeloma, brain cancer or prostate cancer. The pharmaceutical compositions described herein, including embodiments thereof may be used in the treatment of non-small cell lung cancer. The pharmaceutical composition of may be used in the treatment of colon cancer. The pharmaceutical composition of may be used in the treatment of AML. The pharmaceutical composition of may be used in the treatment of CML. The pharmaceutical composition of may be used in the treatment of ovarian cancer. The pharmaceutical composition of may be used in the treatment of melanoma. The pharmaceutical composition of may be used in the treatment of breast cancer. The pharmaceutical composition of may be used in the treatment of prostate cancer. The pharmaceutical composition of may be used in the treatment of pancreatic cancer. The pharmaceutical composition of may be used in the treatment of liver cancer.

IV. Methods

[0395] In another aspect a method of treating cancer is provided. The method includes administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), including embodiments thereof. In embodiments, the therapeutically effective amount is of a compound having formula (I), (II), (III), (IV), (V), (VI), or (VII), including embodiments thereof. The compound may have formula (I). The compound may have formula (II). The compound may have formula (III). The compound may have formula (IV). The compound may have formula (V). The compound may have formula (VI). The compound may have formula (VII). The compound may be a compound as set forth in Table 1. In embodiments, the compound is formulated as a pharmaceutical composition as described herein, including embodiments thereof.

[0396] The cancer may be a solid and blood tumor, including ovarian cancer, breast cancer, lung cancer, leukemia (e.g. AML or CML), lymphoma, pancreatic cancer, kidney cancer, melanoma, liver cancer, colon cancer, sarcoma, multiple myeloma, brain cancer or prostate cancer. The cancer may be ovarian cancer. The cancer may be lung cancer. The lung cancer may be non-small cell lung cancer. The cancer may be pancreatic cancer. The cancer may be kidney cancer. The cancer may be melanoma. The cancer may be liver cancer. The cancer may be colon cancer. The cancer may be brain cancer. The cancer may be prostate cancer. The cancer may be a sarcoma. The cancer may be a leukemia. The leukemia may be CML. The cancer may be AML. In embodiments the cancer being treated is AML, wherein the AML expresses Flt3 kinase protein.

[0397] In embodiments, the cancer is caused by misregulation of a histone methyltransferase (HMT). The misregulation may be overexpression, downregulation, intragenic mutation, translocation or promotor DNA methylation. The HMT may be SUV39H1/2 (KMT1A/B), G9a (KMT1C), MLL1 (KMT2A), MLL4 (KMT2D), SMYD3, DOT1L (KMT4), SET8/PR-SET7 (KMT5A) or EZH2 (KMT6). In embodiments, the HMT is SUV39H1/2 (KMT1A/B). In embodiments, the HMT is SUV39H1.

[0398] The method may also include administering an additional anticancer agent. The anticancer agent may be an epigenetic inhibitor or a multi-kinase inhibitor. The administration

may include a first amount of the compound and a second amount of the epigenetic inhibitor, wherein the first amount and second amount are together an effective amount to provide a synergistic therapeutic effect. The epigenetic inhibitor may be azacitidine or decitadine. The compound and the epigenetic inhibitor may be co-administered as a pharmaceutical composition.

5 In certain embodiments the epigenetic inhibitor is a DNMT inhibitor. The administration of the pharmaceutical compound may be useful in treating ovarian cancer. The administration of the pharmaceutical compound may be useful in treating lung cancer. The lung cancer may be non-small cell lung cancer.

[0399] The method may include administering a first amount of the compound and a second
10 amount of the multi-kinase inhibitor, wherein the first amount and second amount are together an effective amount to provide a synergistic therapeutic effect. The multi-kinase inhibitor may be sorafenib. The compound and the multi-kinase inhibitor may be co-administered as a pharmaceutical composition. The administration of the pharmaceutical compound may be useful in treating ovarian cancer. The administration of the pharmaceutical compound may be useful in
15 treating lung cancer. The lung cancer may be non-small cell lung cancer.

[0400] In embodiments, the methods of treatment described herein yield a suppression of tumor growth. The suppressed tumor growth may indicate the absence of toxicity symptoms (e.g. body weight loss). Those skilled in the art understand that body weight loss observed during many cancer treatments is a result of toxicity associated with the treatment (e.g. killing of
20 healthy tissue). Accordingly, the compounds described herein may provide effective therapeutic value without toxicity issues normally associated with cancer treatments.

[0401] Compounds described herein, including embodiments thereof, may be administered in as a therapeutically effective amount. The compound may be administered in any effective size dose or effect dosage regimen (e.g. one dose daily). A therapeutically effective dose may be
25 determined by one of skill in the art using methods described herein and those known in the art.

[0402] In another aspect, a method of inhibiting a histone methyltransferase (HMT) is provided. The method includes contacting a methyltransferase with a compound provided herein (a compound of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), including embodiments thereof). In
30 embodiments, the histone methyltransferase is a lysine-specific HMT. In embodiments, the

histone methyltransferase is an arginine-specific HMT. The HMT may be SUV39H1/2 (KMT1A/B), G9a (KMT1C), MLL1 (KMT2A), MLL4 (KMT2D), SMYD3, DOT1L (KMT4), SET8/PR-SET7 (KMT5A) or EZH2 (KMT6). In embodiments, the HMT is SUV39H1/2 (KMT1A/B). In embodiments, the HMT is SUV39H1. In embodiments, the method of
5 inhibiting is performed *in vitro*.

[0403] In embodiments, the HMT is within a cell. Thus, in embodiments, the cell is within an organism.

[0404] In another aspect, a method of inhibiting growth of a cancer cell *in vivo* is provided. The method includes contacting a cancer cell with a compound provided herein (a compound of
10 formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), or (XVIII)), including embodiments thereof). The cancer cell may be derived from a solid and blood tumor, including ovarian cancer, breast cancer, lung cancer, leukemia (e.g. AML or CML), lymphoma, pancreatic cancer, kidney cancer, melanoma, liver cancer, colon cancer, sarcoma, multiple myeloma, brain cancer or prostate cancer. The cancer cell may be an
15 ovarian cancer cell. The cancer cell may be a lung cancer cell. The lung cancer cell may be a non-small cell lung cancer cell. The cancer cell may be pancreatic cancer cell. The cancer cell may be a kidney cancer cell. The cancer cell may be a melanoma cell. The cancer cell may be a liver cancer cell. The cancer cell may be a colon cancer cell. The cancer cell may be a brain cancer cell. The cancer cell may be a prostate cancer cell. The cancer cell may be a sarcoma
20 cell. The cancer cell may be a leukemia cell. The leukemia cell may be a CML cell. The cancer cell may be an AML cell. In embodiments the cancer cell is an AML cell, wherein the AML cell expresses Flt3 kinase protein.

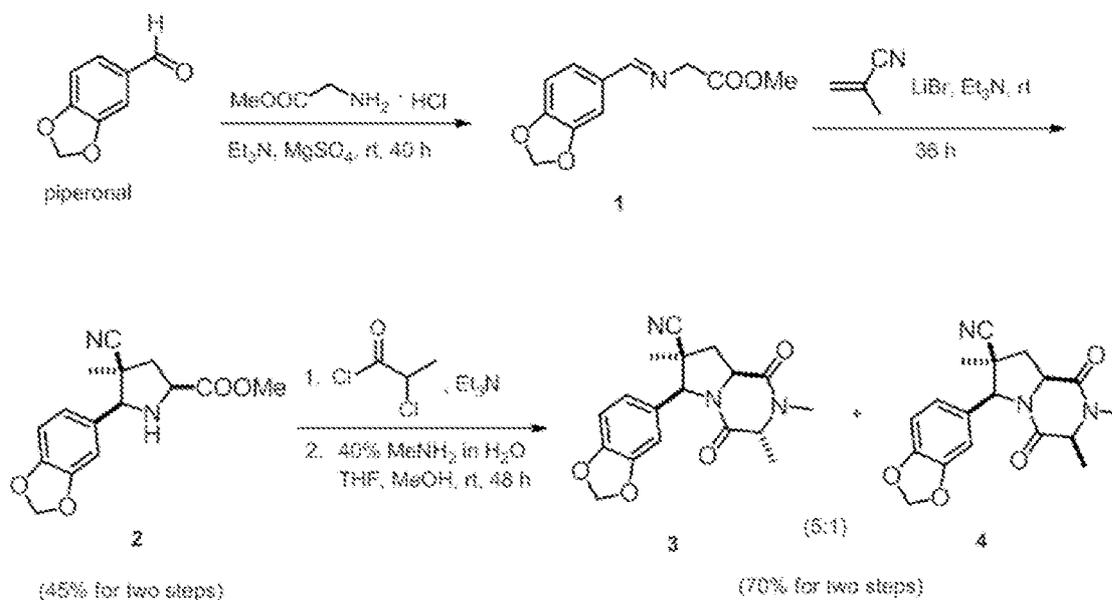
V. Examples

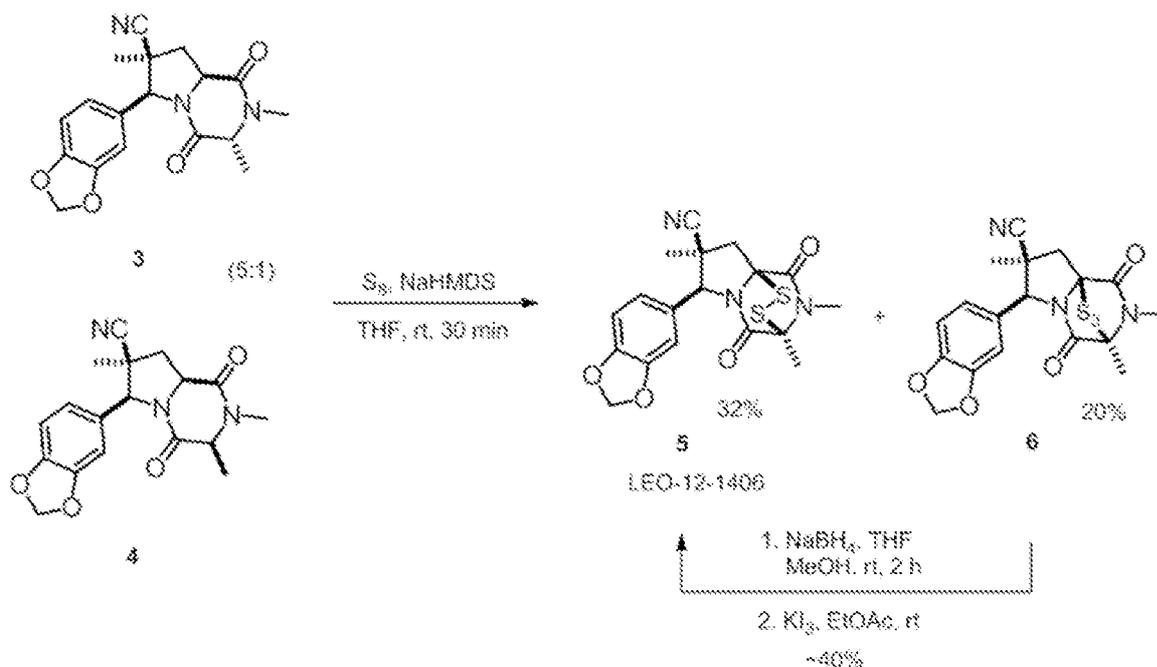
25 Example 1

[0405] The compounds of Formulae I–XVIII can be prepared in a number of ways well known to those skilled in the art, including both solid phase and solution phase techniques. The compounds can be synthesized, for example, by the methods described below, or variations thereof as appreciated by the skilled artisan. Although these syntheses are illustrated for

preparation of ETPs having substituted aryl substituents at C6, identical sequences can be employed to prepare ETPs with substituted heteroaryl substituents at C6. See e.g. Martins, M. M.; Carvalho *Tetrahedron* **2007**, *63*, 9923–9932; Borthwick, A. D. *Chem Rev* **2012**, *112*, 3641–3716; Iwasa, E.; Hamashima, Y.; Sodeoka, M. *Isr. J. Chem.* **2011**, *51*, 420–433; Nicolaou, K. C.; Lu, M.; Totokotsopoulos, S.; Heretsch, P.; Giguère, D.; Sun, Y.-P.; Sarlah, D.; Nguyen, T. H.; Wolf, I. C.; Smee, D. F.; Day, C. W.; Bopp, S.; Winzeler, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 17320–17332. All processes disclosed in association with the present invention are contemplated to be practiced on any scale, including milligram, gram, multigram, kilogram, multikilogram or commercial industrial scale.

10 [0406] **Scheme 1:** Synthesis of racemic ETP derivatives described herein.

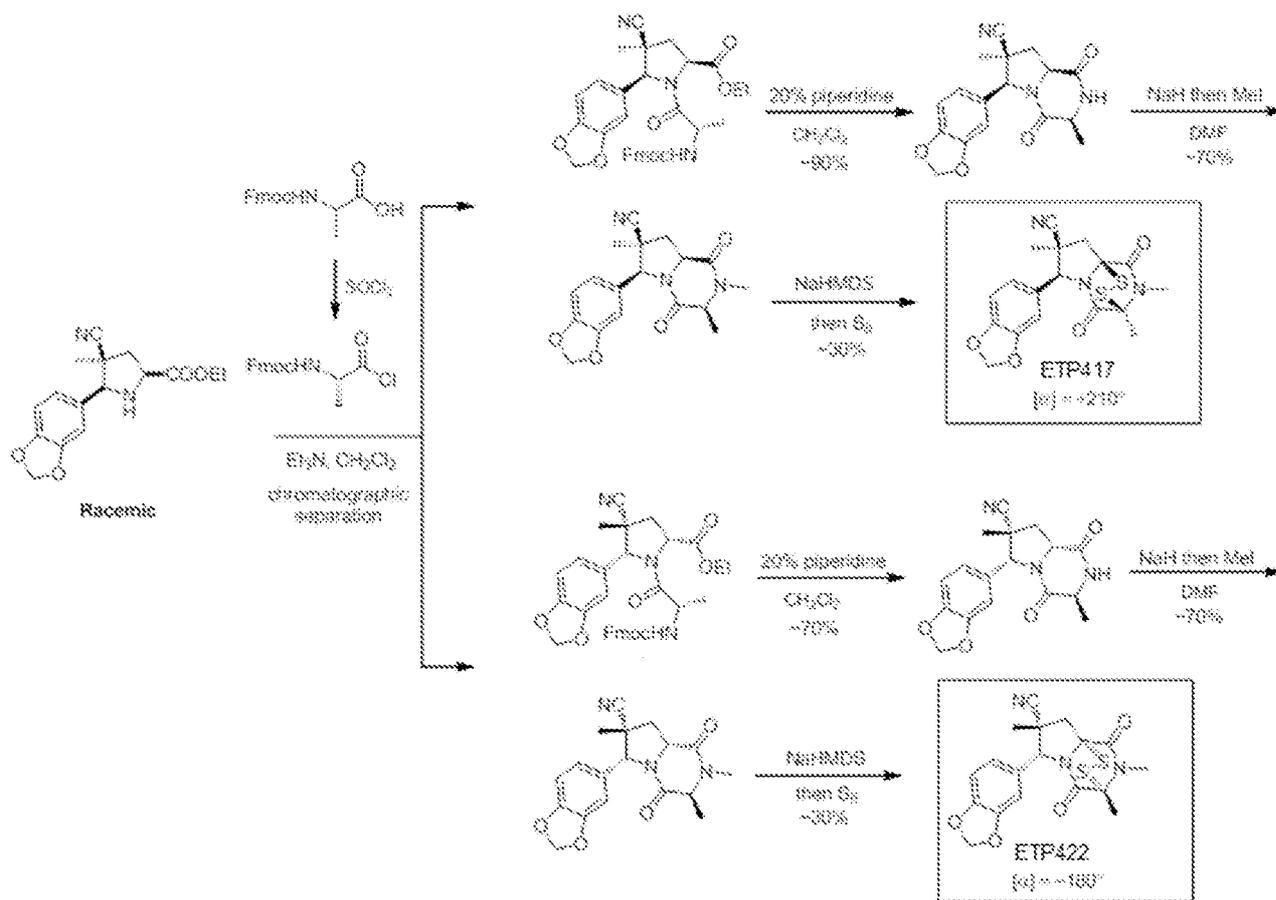




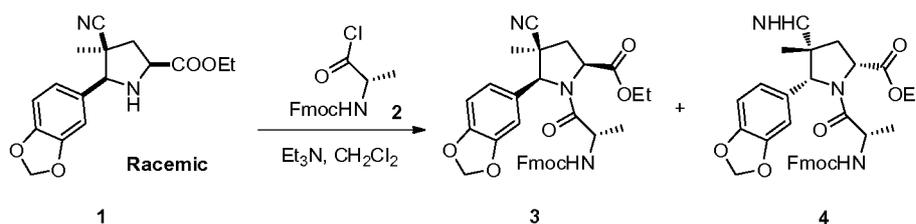
[0407] Embodiments of Formula I may be prepared as shown in Scheme 1 above. Dehydrative condensation of an aldehyde with a glycine derivative renders an intermediate imine such as **1**, which when treated with base in the presence of lithium bromide generates an azomethine ylide that subsequently undergoes a dipolar cycloaddition reaction to generate the desired pyrrolidine product such as **2**. The azomethine ylide can be generated and the cycloaddition accomplished in many ways known in the art (Grigg, R. and V. Sridharan (1993). Azomethine Ylide Cycloadditions via 1,2-Prototropy and Metallo-Dipole Formation from Imines. *Advances in Cycloaddition*. D. P. Curran. Greenwich, CT, Jai Press Inc. **3**: 161-204). For example, the cycloaddition may be carried out by simply heating the components in a solvent or by the use of other metal complexes or salts and other bases. Compounds **2** are typically generated as mixtures of diastereoisomers, the isomer exemplified by **2** can be separated from the mixture based on its reduced solubility in solvent mixtures like MeOH/DCM (1: 1). If required, the diastereoisomer products can be obtained in high purity by column chromatography; the subsequent steps can be performed with the separated stereoisomers or carried out with the mixture of stereoisomers with separation being accomplished by column chromatography, crystallization or other common techniques after the polysulfur bridge is incorporated.

[0408] The product of this cycloaddition reaction is a pyrrolidine ester, which can be converted to a dioxopiperazine in many well-known ways (Martins, M. B., Ivone, C. (2007)

- Diketopiperazines: biological activity and synthesis. *Tetrahedron* **63**, 9923-9932). For example, the pyrrolidine ester can be acylated on the free nitrogen with an α -halo acid chloride to yield the corresponding amide. These compounds can be treated with an excess of a primary amine to undergo a cyclocondensation reaction furnishing the desired diketopiperazine ring, compounds, exemplified by **3** and **4**. In general the diketopiperazine was isolated as mixture of diastereoisomers which need not be separated at this stage. Alternatively, the pyrrolidine ester can be coupled with an α -aminoester (typically protected on nitrogen) to give a dipeptide, which directly or upon removal of the nitrogen-protecting group can be cyclized to the dioxopiperazine intermediate.
- 5
- 10 **[0409]** The diketopiperazine then undergoes a sulfidation process, one example of which is illustrated in Scheme 1, to yield the desired ETP. Alternatively, the intermediate in this sequence, can be reduced and the dithiol product protected on the two sulfur atoms. The conversion of the dioxopiperazine intermediate to an ETP product can be accomplished in many ways well known in the art (Iwasa, E.; Hamashima, Y.; Sodeoka, M. (2011) Epipolythiodiketopiperazine
- 15 Alkaloids: Total Syntheses and Biological Activities *Isr. J. Chem.* *51*, 420–433. Nicolaou, K. C., et al. (2011) Synthesis and Biological Evaluation of Epidithio-, Epitetrahydro-, and bis-(Methylthio)diketopiperazines: Synthetic Methodology, Enantioselective Total Synthesis of Epicoccin G, 8,8'-epi-ent-Rostratin B, Gliotoxin, Gliotoxin G, Emethallicin E, and Haematocin and Discovery of New Antiviral and Antimalarial Agents *J. Am. Chem. Soc.*, *133*, 8150–8153.)
- 20 **[0410]** Synthetic scheme for enantioselective synthesis of ETP analogues described herein.



[0411]

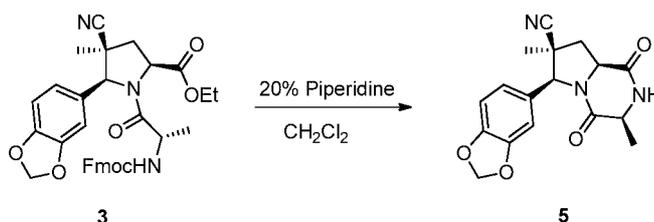


[0412] To a stirred solution of racemic **1** (2.1 g, 7 mmol) in CH_2Cl_2 (14 mL) were added Et_3N (1.4 g, 14 mmol) and acyl chloride **2** (3.25 g, 10 mmol) in CH_2Cl_2 (14 mL) at 0°C . The reaction was stirred overnight. The reaction was quenched with sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layer was dried over MgSO_4 and evaporated to dryness. The crude product was purified by silica gel column chromatography by elution with 33% $\text{EtOAc}/\text{Hexane}$ to afford 1.9 g (46%) of compound **3** and 1.7 g (40%) of compound **4**. For compound **3**: $^1\text{H NMR}$ (400MHz, CDCl_3) δ/ppm 7.75 (d, 2H, $J = 7.4$ Hz), 7.55 (d, 2H, $J = 7.4$ Hz), 7.40 (t, 2H, $J = 7.4$ Hz), 7.30 (t, 2H, $J = 7.4$ Hz), 7.30 (s, 1H), 7.19 (dd, 1H, $J = 1.4, 8.0$ Hz), 6.86 (d, 2H, $J = 7.8$

Hz), 6.00 (d, 2H, $J = 6.6$ Hz), 5.22 (s, 1H), 5.19 (d, 2H, $J = 7.8$ Hz), 4.60 (dd, 1H, $J = 7.4, 9.8$ Hz), 4.39-4.22 (m, 4H), 4.20-4.14 (m, 2H), 2.59 (dd, 1H, $J = 9.8, 13.8$ Hz), 2.35 (dd, 1H, $J = 7.0, 13.8$ Hz), 1.61 (s, 3H), 1.35 (t, 3H, $J = 7.0$ Hz), 0.98 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ /ppm 174.0, 170.2, 156.1, 148.31, 148.27, 143.70, 143.65, 141.3, 131.8, 127.75, 127.72, 127.0, 125.1, 125.0, 121.3, 120.0, 108.6, 107.8, 101.4, 70.3, 67.2, 61.9, 58.2, 47.8, 47.0, 44.5, 37.3, 24.3, 17.4, 14.1;

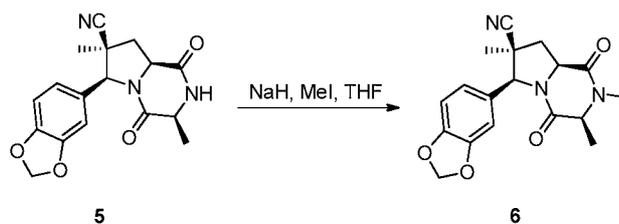
[0413] For compound **4** (main rotamer): ^1H NMR (400MHz, CDCl_3) δ /ppm 7.75 (d, 2H, $J = 7.4$ Hz), 7.55 (d, 2H, $J = 7.4$ Hz), 7.40 (t, 2H, $J = 7.4$ Hz), 7.30 (t, 2H, $J = 7.4$ Hz), 7.30 (s, 1H), 7.19 (dd, 1H, $J = 1.4, 8.0$ Hz), 7.03 (s, 1H), 6.93 (d, 1H, $J = 7.8$ Hz), 6.80 (d, 1H, $J = 8.2$ Hz), 5.95 (d, 2H, $J = 2.2$ Hz), 5.37 (dd, 1H, $J = 3.4, 8.2$ Hz), 5.27 (d, 1H, $J = 7.6$ Hz), 4.76 (s, 1H), 4.40-4.10 (m, 6H), 2.90 (dd, 1H, $J = 3.4, 13.2$ Hz), 2.41 (dd, 1H, $J = 2.3, 13.2$ Hz), 1.62 (s, 3H), 1.40 (d, 3H, $J = 7.0$ Hz), 1.39 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ /ppm 174.0, 170.9, 156.3, 147.9, 147.7, 143.64, 143.62, 141.3, 130.6, 127.8, 127.7, 127.0, 125.1, 125.0, 120.2, 120.0, 108.3, 107.0, 101.1, 70.8, 67.2, 62.6, 59.3, 48.4, 47.0, 43.4, 40.8, 23.1, 17.8, 14.1;

[0414]



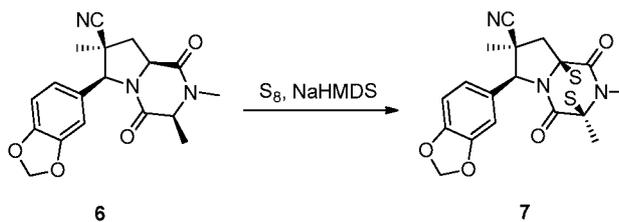
[0415] To a stirred solution of compound **3** (2.8 g, 4.7 mmol) in CH_2Cl_2 (18 mL) was added piperidine (4.0 g, 47 mmol). After 30 min, the solvent was removed. The crude product was purified by silica gel column chromatography by elution with 3% MeOH/ CH_2Cl_2 to afford 1.4 g (91%) of compound **5** as white solid. ^1H NMR (400MHz, CDCl_3) δ /ppm 6.79 (d, 2H, $J = 7.8$ Hz), 6.63 (dd, 1H, $J = 2.0, 8.2$ Hz), 6.57 (d, 2H, $J = 2.0$ Hz), 5.96 (s, 2H), 5.91 (s, 1H), 4.87 (s, 1H), 4.43 (dd, 1H, $J = 6.6, 11.0$ Hz), 4.17 (q, 1H, $J = 6.6$ Hz), 2.82 (dd, 1H, $J = 11.4, 13.4$ Hz), 2.35 (dd, 1H, $J = 6.6, 13.4$ Hz), 1.68 (s, 3H), 1.44 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ /ppm 168.9, 166.9, 148.3, 148.2, 130.8, 119.7, 108.7, 106.2, 101.4, 69.3, 57.5, 51.6, 42.8, 35.8, 25.3, 15.4;

[0416]



[0417] To a stirred solution of compound **5** (1.4 g, 4.3 mmol) in THF (43 mL) was added NaH (60%, 260 mg, 6.5 mmol) at 0 °C. After 20 min at 23 °C, MeI (1.85 g, 13 mmol) was added at 0 °C. After 2 h at 23 °C, the reaction was quenched with sat. NH₄Cl. The solvent was removed and the residue was extracted with CH₂Cl₂. The combined organic layer was dried over MgSO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography by elution with 25% EtOAc/Hexane to afford 1.25 g (86%) of compound **6**. ¹H NMR (400MHz, CDCl₃) δ/ppm 6.82 (d, 2H, *J* = 8.2 Hz), 6.73 (d, 1H, *J* = 2.0 Hz), 6.71 (s, 1H), 5.98 (s, 2H), 4.73 (dd, 1H, *J* = 6.2, 10.6 Hz), 3.88 (q, 1H, *J* = 7.0 Hz), 3.01 (s, 3H), 2.93 (dd, 1H, *J* = 6.2, 13.0 Hz), 2.26 (dd, 1H, *J* = 10.6, 13.0 Hz), 1.60 (s, 3H), 1.54 (d, 3H, *J* = 7.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ/ppm 165.9, 165.2, 148.2, 148.1, 129.3, 120.3, 119.4, 108.6, 106.1, 101.4, 70.2, 60.6, 58.4, 44.1, 41.6, 32.1, 22.7, 16.7;

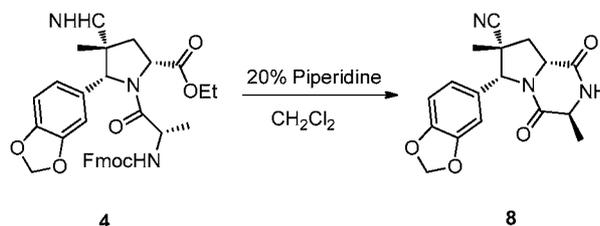
[0418]



[0419] To a suspension of elemental sulfur (300 mg, 9.4 mmol) in dry THF (10 mL) NaHMDS (0.6 M in toluene, 7.40 mL) is being added dropwise. The resulting yellow reaction mixture is stirred at ambient temperature for one minute and then combined with a slurry of the substrate **6** (340 mg, 1.0 mmol in 5 mL dry THF). A second portion of NaHMDS (0.6 M in toluene, 4.8 mL) is subsequently added resulting in an orange mixture which is stirred at ambient temperature for 30 minutes. After quenching with saturated aqueous ammonium chloride, the solvent was removed and the residue was extracted with CH₂Cl₂. The combined organic layer was dried over MgSO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography by elution with 2% EtOAc/ CH₂Cl₂ to afford 129 mg (32%) of compound **7**.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ/ppm 6.96 (s, 1H), 6.91 (s, 2H), 6.06 (s, 2H), 4.89 (s, 1H), 3.36 (d, 1H, $J = 14.5$ Hz), 3.14 (s, 3H), 3.06 (d, 1H, $J = 14.5$ Hz), 2.00 (s, 3H), 1.73 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ/ppm 165.6, 162.1, 148.6, 148.3, 127.5, 120.7, 120.3, 108.6, 107.2, 101.6, 73.4, 73.3, 72.4, 44.4, 42.8, 27.8, 24.8, 18.1. $^{[\text{D}]_{20}} = +240^\circ$, $ee\% > 99\%$

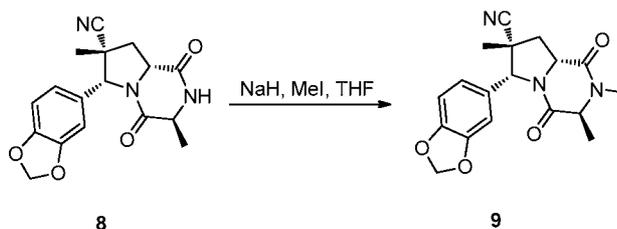
5 [0420]



[0421] See procedure as preparing compound 5. $^1\text{H NMR}$ (400MHz, $\text{DMSO-}d_6$) δ/ppm 8.45 (d, 1H, $J = 4.2$ Hz), 6.88 (d, 1H, $J = 8.2$ Hz), 6.70 (s, 1H), 6.60 (d, 1H, $J = 7.4$ Hz), 6.00 (s, 2H), 4.87 (s, 1H), 4.73 (dd, 1H, $J = 6.6, 11.0$ Hz), 3.78-3.70 (m, 1H), 2.42-2.26 (m, 2H), 1.62 (s, 3H), 1.35 (d, 3H, $J = 7.4$ Hz); $^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ/ppm 168.6, 167.6, 147.7, 147.4, 133.2, 121.4, 119.8, 108.6, 107.1, 101.7, 68.3, 55.8, 53.5, 42.6, 36.1, 24.4, 18.8;

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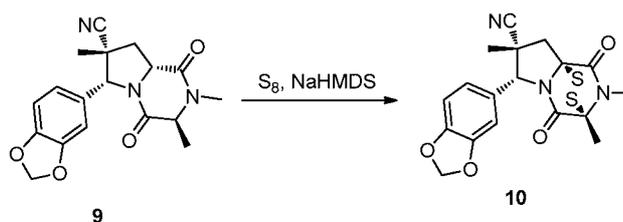
[0422]



[0423] See procedure as preparing compound 6. $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ/ppm 6.79 (d, 1H, $J = 9.0$ Hz), 6.63 (d, 1H, $J = 9.0$ Hz), 6.57 (s, 1H), 5.96 (s, 2H), 4.82 (s, 1H), 4.36 (dd, 1H, $J = 6.5, 11.0$ Hz), 3.90 (q, 1H, $J = 7.0$ Hz), 3.04 (s, 3H), 2.76 (t, 1H, $J = 7.0$ Hz), 2.45 (dd, 1H, $J = 6.5, 13.5$ Hz), 1.66 (s, 3H), 1.47 (d, 3H, $J = 7.0$ Hz); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ/ppm 166.6, 166.0, 148.2, 148.1, 130.8, 119.9, 119.8, 108.6, 106.2, 101.4, 69.6, 60.8, 56.1, 42.6, 36.7, 32.0, 25.1, 15.3;

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20 [0424]

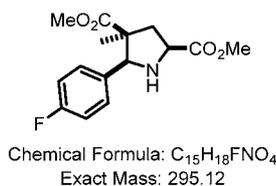


[0425] See procedure as preparing compound 7. ¹H-NMR (400 MHz, CDCl₃): δ/ppm 6.96 (s, 1H), 6.91 (s, 2H), 6.06 (s, 2H), 4.89 (s, 1H), 3.36 (d, 1H, *J* = 14.5 Hz), 3.14 (s, 3H), 3.06 (d, 1H, *J* = 14.5 Hz), 2.00 (s, 3H), 1.73 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ/ppm 165.6, 162.1, 148.6, 148.3, 127.5, 120.7, 120.3, 108.6, 107.2, 101.6, 73.4, 73.3, 72.4, 44.4, 42.8, 27.8, 24.8, 18.1. ^α[D]₂₀ = -216°, *ee*% > 95%

Example 2

[0426] **General Procedure for the Synthesis of Polyfunctionalized Pyrrolidine Esters.**

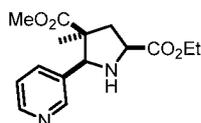
[0427] **Dimethyl *rac*-(2*S*,4*S*,5*S*)-5-(4-Fluorophenyl)-4-methylpyrrolidine-2,4-dicarboxylate:**



[0428] 4-Fluorobenzaldehyde (1.24 g, 10 mmol) was dissolved in 15 mL of MeCN containing triethylamine (1.5 mL, 11 mmol) and glycine methyl ester hydrochloride (1.35 g, 11 mmol). The reaction mixture was stirred for 5 h at room temperature. After removing the solvent *in vacuo*, the solid residue was re-dissolved in CH₂Cl₂ and washed twice from water to give the imine intermediate as colourless oil. To a solution of this material in 20 mL of THF, solid LiBr (1.1 g, 12 mmol) and triethylamine (1.7 mL, 12 mmol) were added portionwise. After 2 min, methyl methacrylate (1.5 g, 15 mmol) was added and the resulting solution was stirred at room temperature for 8 h. After evaporation of the solvent *in vacuo* and extractive work-up (3 times, CH₂Cl₂/water), the desired product was isolated as yellow oil (2.6 g, 90% yield, as a single diastereomer). In some cases the cycloadduct was isolated as a mixture of C4 epimers, which were separated by crystallization or chromatography

[0429] $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ/ppm 7.30 (2H, m), 7.03 (2H, t, $J = 8.5$ Hz), 4.09 (1H, s), 4.06 (1H, t, $J = 7.0$ Hz), 3.86 (3H, s), 3.30 (3H, s), 2.95 (1H, br. s, NH), 2.76 (1H, dd, $J = 7.0$, 13.5 Hz), 2.14 (1H, dd, $J = 13.0$, 13.5 Hz), 1.43 (s, 3H); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ/ppm 174.6 (C), 174.3 (C), 162.3 (C, $J_{\text{C-F}} = 245$ Hz), 134.7 (C, $J_{\text{C-F}} = 3$ Hz), 128.4 (2CH, d, $J_{\text{C-F}} = 8$ Hz), 115.0 (2CH, d, $J_{\text{C-F}} = 21$ Hz), 73.1 (CH), 58.8 (CH), 54.6 (C), 52.3 (CH₃), 51.5 (CH₃), 41.1 (CH₂), 22.5 (CH₃). LR-MS: 295.96; HR-MS (ESI) calculated for $\text{C}_{15}\text{H}_{18}\text{NO}_4\text{FCl}$: 296.1298 ($\text{M}+\text{H}^+$), found: 296.1302.

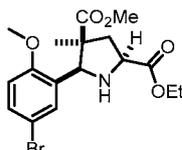
[0430] **2-Ethyl *rac*-4-Methyl (2*S*,4*S*,5*S*)-4-methyl-5-(pyridin-3-yl)pyrrolidine-2,4-dicarboxylate:**



Chemical Formula: $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4$
Exact Mass: 292.14

10 [0431] Isolated as pale yellow oil, dr (diastereomer ratio) >9:1. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ/ppm 8.26 (1H, s), 8.23 (1H, dd, $J = 1.5$, 4.5 Hz), 7.45 (1H, dd, $J = 1.5$, 8.0 Hz), 6.98 (1H, dd, $J = 4.5$, 9.0 Hz), 4.00-4.12 (2H, m), 3.85 (2H, s), 3.78 (1H, app. t, $J = 7.5$ Hz), 2.99 (3H, s), 2.48 (1H, dd, $J = 8.0$, 13.0 Hz), 1.86 (1H, dd, $J = 8.0$, 13.0 Hz), 1.17 (3H, s), 1.07 (3H, t, $J = 7.0$ Hz); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ/ppm 173.9 (C), 173.3 (C), 148.9 (CH), 148.6 (CH), 134.9 (C), 133.9 (CH), 122.8 (CH), 70.7 (CH), 60.8 (CH₂), 58.5 (CH), 54.4 (C), 51.1 (CH₃), 40.3 (CH₂), 22.4 (CH₃), 14.0 (CH₃). IR (film): ν/cm^{-1} 3380, 2981, 2950, 1732, 1430, 1210, 1110, 1029, 716. LR-MS: 293.1 ($\text{M}+\text{H}^+$); HR-MS (ESI) calculated for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$: 315.1321 ($\text{M}+\text{Na}^+$), found: 315.1315.

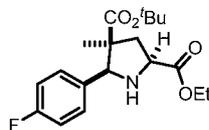
20 [0432] **2-Ethyl 4-Methyl *rac*-(2*S*,4*S*,5*S*)-5-(5-Bromo-2-methoxyphenyl)-4-methylpyrrolidine-2,4-dicarboxylate:**



Chemical Formula: $\text{C}_{17}\text{H}_{22}\text{BrNO}_5$
Exact Mass: 399.07

[0433] Isolated as brown oil (single diastereomer). ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.45 (1H, d, *J* = 2.5 Hz), 7.28 (1H, dd, *J* = 2.5, 9.0 Hz), 6.70 (1H, d, *J* = 9.0 Hz), 4.45 (1H, s), 4.25 (2H, q, *J* = 7.0 Hz), 3.96 (1H, app. t, *J* = 8.0 Hz), 3.74 (3H, s), 3.30 (3H, s), 2.72 (1H, dd, *J* = 9.0, 13.0 Hz), 2.05 (1H, dd, *J* = 9.0, 13.0 Hz), 1.36 (3H, s), 1.24 (3H, t, *J* = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 174.7 (C), 173.4 (C), 156.3 (C), 131.1 (CH), 130.4 (CH), 129.4 (C), 112.7 (C), 112.0 (CH), 66.8 (CH), 61.0 (CH₂), 59.0 (CH₃), 55.4 (CH₃), 54.5 (C), 51.3 (CH), 41.7 (CH₂), 22.8 (CH₃), 14.2 (CH₃). IR (film): ν/cm⁻¹ 3366, 2980, 2938, 2839, 2236, 1736, 1486, 1252, 1202, 1134, 1028, 809. LR-MS: 389.0 (M+Na⁺); HR-MS (ESI) calculated for C₁₆H₁₉N₂O₃BrNa: 389.0477(M+Na⁺), found: 389.0471.

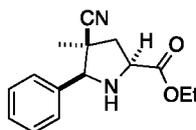
10 [0434] **4-(*tert*-Butyl) 2-Ethyl *rac*-(2*S*,4*S*,5*S*)-5-(4-Fluorophenyl)-4-methylpyrrolidine-2,4-dicarboxylate:**



Chemical Formula: C₁₉H₂₈FNO₄
Exact Mass: 351.18

[0435] Isolated as yellow oil (dr >9:1). ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.37 (2H, dd, *J* = 5.5, 8.0 Hz), 7.04 (2H, app. t, *J* = 8.0 Hz), 4.31 (2H, q, *J* = 7.0 Hz), 4.08 (1H, s), 4.03 (1H, t, *J* = 8.5 Hz), 2.69 (1H, br. s), 2.66 (1H, dd, *J* = 9.0, 13.0 Hz), 2.12 (1H, dd, *J* = 8.5, 13.0 Hz), 1.49 (3H, s), 1.36 (3H, t, *J* = 7.0 Hz), 1.13 (9H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 173.7 (C), 173.4 (C), 162.3 (C, d, *J* = 244 Hz), 135.9 (C), 128.9 (2CH, d, *J* = 8 Hz), 114.9 (2CH, d, *J* = 21 Hz), 80.8 (C), 72.3 (CH), 61.2 (CH₂), 58.9 (CH), 55.1 (C), 41.9 (CH₂), 27.6 (3CH₃), 24.3 (CH₃), 14.3 (CH₃). IR (film): ν/cm⁻¹ 3368, 2979, 2935, 1724, 1511, 1369, 1224, 1154. LR-MS: 352.2 M+H⁺; HR-MS (ESI) calculated for C₁₉H₂₆NO₄FNa: 374.1743 (M+Na⁺), found: 374.1742.

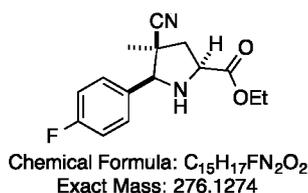
[0436] **Ethyl *rac*-(2*S*,4*S*,5*S*)-4-Cyano-4-methyl-5-phenylpyrrolidine-2-carboxylate:**



Chemical Formula: C₁₅H₁₈N₂O₂
Exact Mass: 258.1368

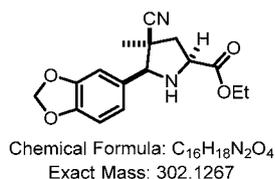
[0437] $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ/ppm 7.52 (2H, d, $J = 7.1$ Hz), 7.41-7.34 (3H, m), 4.34-4.24 (2H, m), 3.98 (1H, dd, $J = 4.2, 9.7$ Hz), 3.93 (1H, s), 2.90 (1H, s), 2.82 (1H, dd, $J = 4.2, 13.6$ Hz), 2.29 (1H, dd, $J = 9.6, 13.6$ Hz), 1.42 (3H, s), 1.34 (3H, t, $J = 7.1$ Hz); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ/ppm 173.0 (C), 136.5 (C), 128.9 (CH), 128.6 (2CH), 127.6 (2CH), 121.9 (C), 72.4 (CH), 61.7 (CH_2), 57.3 (CH), 44.1 (C), 42.5 (CH_2), 22.0 (CH_3), 14.2 (CH_3); IR (film): ν/cm^{-1} 3348, 2980, 2234, 1734, 1454; LR-MS: 281.1 $[\text{M}+\text{Na}]^+$; HR-MS (ESI) calculated for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{Na}$: 281.1266, found: 281.1263.

[0438] Ethyl *rac*-(2*S*,4*S*,5*S*)-4-Cyano-5-(4-fluorophenyl)-4-methylpyrrolidine-2-carboxylate:



[0439] $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ/ppm 7.52 (2H, dd, $J = 5.4, 8.7$ Hz), 7.09 (2H, t, $J = 8.7$ Hz), 4.34-4.24 (2H, m), 4.00 (1H, dd, $J = 4.2, 9.6$ Hz), 3.95 (1H, s), 2.83 (1H, dd, $J = 4.2, 13.7$ Hz), 2.82 (1H, s), 2.30 (1H, dd, $J = 9.6, 13.7$ Hz), 1.41 (3H, s), 1.34 (3H, t, $J = 7.1$ Hz); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ/ppm 172.9 (C), 163.2 (C, d, $J = 246$ Hz), 132.4 (C), 129.4 (2CH, d, $J = 8$ Hz), 121.8 (C), 115.7 (2CH, d, $J = 22$ Hz), 71.7 (CH), 61.9 (CH_2), 57.3 (CH), 44.0 (C), 42.2 (CH_2), 22.0 (CH_3), 14.3 (CH_3); IR (film): ν/cm^{-1} 3348, 2982, 2235, 1736, 1605, 1510; LR-MS: 299.1 $[\text{M}+\text{Na}]^+$; HR-MS (ESI) calculated for $\text{C}_{15}\text{H}_{17}\text{FN}_2\text{O}_2\text{Na}$: 299.1172, found: 299.1177.

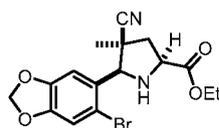
[0440] Ethyl *rac*-(2*S*,4*S*,5*S*)-5-(Benzo[d][1,3]dioxol-5-yl)-4-cyano-4-methylpyrrolidine-2-carboxylate:



[0441] Isolated as brown oil (dr = 3:2). $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ/ppm 7.12 (1H, s), 6.98 (1H, d, $J = 8.5$ Hz), 6.83 (1H, d, $J = 8.5$ Hz), 5.99 (2H, s), 4.31 (2H, q, $J = 7.0$ Hz), 3.98 (1H, dd, $J = 4.5, 9.5$ Hz), 3.89 (1H, s), 2.83 (1H, dd, $J = 4.0, 13.5$ Hz), 2.75 (1H, br. s), 2.29 (1H, dd, $J =$

9.5, 13.5 Hz), 1.44 (3H, s), 1.36 (3H, t, $J = 7.0$ Hz); ^{13}C -NMR (125 MHz, CDCl_3): δ /ppm 173.0 (C), 148.0 (C), 147.9 (C), 130.6 (C), 122.1 (C), 121.1 (CH), 108.2 (CH), 107.9 (CH), 101.3 (CH₂), 72.1 (CH), 61.6 (CH₂), 57.0 (CH), 43.8 (C), 42.1 (CH₂), 22.1 (CH₃), 14.2 (CH₃). IR (film): ν/cm^{-1} 3361, 2984, 2900, 2254, 1734, 1490, 1447, 1265, 1041, 909. LR-MS: 325.1 M+Na⁺; HR-MS (ESI) calculated for C₁₆H₁₈N₂O₄Na: 325.1164 (M+Na⁺), found: 325.1161.

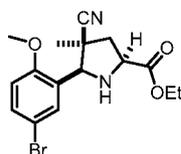
[0442] Ethyl *rac*-(2*S*,4*S*,5*R*)-5-(6-Bromobenzo[d][1,3]dioxol-5-yl)-4-cyano-4-methylpyrrolidine-2-carboxylate:



Chemical Formula: C₁₆H₁₇BrN₂O₄
Exact Mass: 380.0372

[0443] Isolated as brown oil (single diastereomer). ^1H -NMR (500 MHz, CDCl_3): δ /ppm 7.48 (1H, s), 6.96 (1H, s), 5.97 (1H, s), 5.92 (1H, s), 4.56 (1H, s), 4.20 (2H, q, $J = 7.0$ Hz), 4.00 (1H, m), 2.67 (1H, dd, $J = 6.0, 8.0$ Hz), 2.65 (1H, broad s), 2.27 (1H, dd, $J = 9.0, 13.5$ Hz), 1.53 (3H, s), 1.27 (3H, t, $J = 7.0$ Hz); ^{13}C -NMR (125 MHz, CDCl_3): δ /ppm 172.8 (C), 148.3 (C), 147.6 (C), 130.9 (C), 122.0 (C), 114.5 (C), 112.4 (CH), 109.4 (CH), 102.0 (CH₂), 68.5 (CH), 61.4 (CH₂), 57.1 (CH), 44.3 (C), 41.4 (CH₂), 23.3 (CH₃), 14.2 (CH₃). IR (film): ν/cm^{-1} 3366, 2981, 2904, 2237, 1737, 1504, 1477, 1408, 1241, 1205, 1117, 1037, 931, 846. LR-MS: 381.2 M+Na⁺.

[0444] Ethyl *rac*-(2*S*,4*S*,5*R*)-5-(5-Bromo-2-methoxyphenyl)-4-cyano-4-methylpyrrolidine-2-carboxylate :

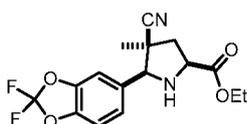


Chemical Formula: C₁₆H₁₉BrN₂O₃
Exact Mass: 366.0579

[0445] Isolated as brown oil (single diastereomer). ^1H -NMR (500 MHz, CDCl_3): δ /ppm 7.89 (1H, d, $J = 2.5$ Hz), 7.37 (1H, dd, $J = 2.5, 9.0$ Hz), 6.77 (1H, d, $J = 9.0$ Hz), 4.47 (1H, s), 4.27 (2H, q, $J = 7.5$ Hz), 3.98 (1H, t, $J = 7.5$ Hz), 3.83 (3H, s), 2.71 (1H, br s), 2.62 (1H, dd, $J = 7.0, 13.0$ Hz), 2.26 (1H, dd, $J = 8.5, 13.0$ Hz), 1.49 (3H, s), 1.34 (3H, t, $J = 7.5$ Hz); ^{13}C -NMR (125 MHz, CDCl_3): δ /ppm 172.7 (C), 156.4 (C), 131.9 (CH), 131.1 (CH), 129.1 (C), 122.3 (C), 113.1

(C), 112.2 (CH), 64.5 (CH), 61.5 (CH₂), 57.7 (CH), 55.5 (CH₃), 43.9 (C), 41.8 (CH₂), 23.6 (CH₃), 14.3 (CH₃). IR (film): ν/cm^{-1} 3366, 2980, 2938, 2904, 2839, 2236, 1736, 1486, 1463, 1252, 1202, 1134, 1028, 809. LR-MS: 389.0 M+Na⁺; HR-MS (ESI) calculated for C₁₆H₁₉N₂O₃Na: 389.0477, found: 389.0471.

5 [0446] Ethyl *rac*-(2*S*,4*S*,5*S*)-4-Cyano-5-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)-4-methylpyrrolidine-2-carboxylate:



Chemical Formula: C₁₆H₁₆F₂N₂O₄
Exact Mass: 338.1078

[0447] Isolated as yellow oil (dr = 4:1). ¹H-NMR (500 MHz, CDCl₃): δ /ppm 7.38 (1H, s), 7.22 (1H, d, *J* = 8.5 Hz), 7.06 (1H, d, *J* = 8.5 Hz), 4.24-4.34 (2H, m), 3.97 (1H, s), 3.95-4.01 (1H, m), 2.84 (1H, dd, *J* = 4.5, 9.0 Hz), 2.68 (1H, s), 2.29 (1H, dd, *J* = 4.5, 8.5 Hz), 1.44 (3H, s), 1.33 (3H, t, *J* = 9.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 172.7 (C), 144.1 (C), 133.7 (C), 133.3 (C), 131.8 (C, t, *J* = 250 Hz), 123.1 (CH), 121.6 (C), 109.3 (CH), 109.1 (CH), 71.9 (CH), 61.8 (CH₂), 57.0 (CH), 43.9 (C), 41.8 (CH₂), 22.1 (CH₃), 14.2 (CH₃). IR (film): ν/cm^{-1} 3351, 3078, 2983, 2236, 1738, 1497, 1448, 1382, 1239, 1148, 1034, 818, 703.

15 [0448] Ethyl *rac*-(2*S*,4*S*,5*S*)-5-(3,4-Bis(allyloxy)phenyl)-4-cyano-4-methylpyrrolidine-2-carboxylate:

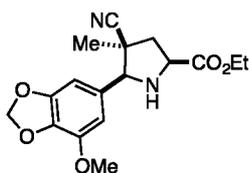


Chemical Formula: C₂₁H₂₆N₂O₄
Exact Mass: 370.1893
Molecular Weight: 370.4490

[0449] Isolated as yellow oil (dr = 4:1). ¹H-NMR (500 MHz, CDCl₃) δ /ppm 7.17 (d, *J* = 1.5 Hz, 1H), 7.01-6.99 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.13-6.04 (m, 2H), 5.47-5.40 (m, 2H), 5.31-5.26 (m, 2H), 4.66-4.60 (m, 4H), 4.33-4.26 (m, 2H), 3.96 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.85 (s, 1H), 2.82 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.75 (broad s, 1H), 2.27 (dd, *J* = 13.6, 9.7 Hz, 1H), 1.40 (s, 3H), 1.33 (t, *J* = 7.6 Hz, 3H) ppm; ¹³C-NMR (126 MHz, CDCl₃) δ /ppm 173.2 (C), 149.1 (C),

148.6 (C), 133.5 (2 x CH), 129.4 (C), 122.2 (C), 120.5 (CH), 118.0 (CH₂), 117.8 (CH₂), 113.8 (CH), 113.4 (CH), 72.4 (CH), 70.2 (CH₂), 70.0 (CH₂), 61.8 (CH₂), 57.3 (CH), 44.0 (C), 42.5 (CH₂), 22.1 (CH₃), 14.3 (CH₃) ppm; IR (film) ν/cm^{-1} 2982, 2936, 1735, 1649, 1513, 1454, 1426, 1378, 1265, 1217, 1138, 1021, 997, 929, 810 cm^{-1} ; HRMS (ESI) calcd for C₂₁H₂₆N₂O₄Na⁺ (M+Na) 393.1790, found 393.1796.

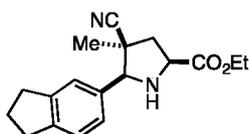
[0450] Ethyl *rac*-(2*S*,4*S*,5*S*)-4-Cyano-5-(7-methoxybenzo[d][1,3]dioxol-5-yl)-4-methylpyrrolidine-2-carboxylate:



Chemical Formula: C₁₇H₂₀N₂O₅
Exact Mass: 332,1372
Molecular Weight: 332,3560

[0451] Isolated as yellow oil (dr = 3:2). ¹H-NMR (500 MHz, CDCl₃) δ /ppm 6.78 (s, 1H), 6.67 (s, 1H), 5.96 (s, 2H), 4.29-4.22 (m, 2H), 3.93 (dd, *J* = 9.5, 4.3 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 1H), 2.78 (dd, *J* = 13.6, 4.3 Hz, 1H), 2.68 (broad s, 1H), 2.24 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.40 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C-NMR (126 MHz, CDCl₃) δ /ppm 172.9 (C), 148.8 (C), 143.6 (C), 135.6 (C), 131.4 (C), 122.0 (C), 107.1 (CH), 101.9 (CH), 101.7 (CH₂), 72.3 (CH), 61.7 (CH₂), 57.1 (CH₃), 56.7 (CH), 43.9 (C), 42.1 (CH₂), 22.2 (CH₃), 14.2 (CH₃) ppm; IR (film) ν/cm^{-1} 2979, 2235, 1735, 1635, 1510, 1452, 1381, 1323, 1291, 1202, 1138, 1094, 1043, 929, 855, 831, 733 cm^{-1} ; HRMS (ESI) calcd for C₁₇H₂₀N₂O₅Na⁺ (M+Na) 355.1270, found 355.1261.

[0452] Ethyl *rac*-(2*S*,4*S*,5*S*)-4-Cyano-5-(2,3-dihydro-1H-inden-5-yl)-4-methylpyrrolidine-2-carboxylate:

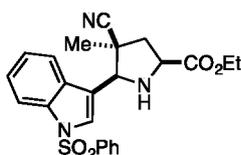


Chemical Formula: C₁₈H₂₂N₂O₂
Exact Mass: 298,1681
Molecular Weight: 298,3860

[0453] Isolated as yellow oil (dr = 1:1). ¹H-NMR (500 MHz, CDCl₃) δ 7.40 (s, 1H), 7.27-7.23 (m, 2H), 4.34-4.26 (m, 2H), 3.98 (dd, *J* = 9.6, 3.9 Hz, 1H), 3.90 (s, 1H), 2.97-2.89 (m, 4H), 2.83

(dd, $J = 13.8, 4.2$ Hz, 1H), 2.30 (dd, $J = 13.8, 9.7$ Hz, 1H), 2.09 (app. quintet, $J = 7.4$ Hz, 2H), 1.62 (broad s, 1H), 1.42 (s, 3H), 1.35 (t, $J = 7.3$ Hz, 3H) ppm; ^{13}C -NMR (126 MHz, CDCl_3) δ 173.2 (C), 145.3 (C), 144.8 (C), 134.3 (C), 125.6 (CH), 124.5 (CH), 123.4 (CH), 122.2 (C), 72.8 (CH), 61.8 (CH_2), 57.5 (CH), 44.2 (C), 42.8 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 25.6 (CH_2), 22.1 (CH₃), 14.4 (CH₃) ppm; IR (film) ν/cm^{-1} 2940, 2234, 1735, 1447, 1378, 1209, 1139, 1097, 1032, 826 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{Na}^+$ (M+Na) 321.1579, found 321.1577.

[0454] Ethyl *rac*-(2*S*,4*S*,5*S*)-4-Cyano-4-methyl-5-(1-(phenylsulfonyl)-1*H*-indol-3-yl)pyrrolidine-2-carboxylate:



Chemical Formula: $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_4\text{S}$
 Exact Mass: 437,1409
 Molecular Weight: 437,5140

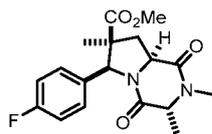
10 **[0455]** Isolated as a yellow, highly viscous oil. ^1H -NMR (500 MHz, CDCl_3) δ 7.98 (d, $J = 6.4$ Hz, 2H), 7.93 (d, $J = 8.3$ Hz, 2H), 7.59 (d, $J = 7.9$ Hz, 1H), 7.52 (t, $J = 7.4$ Hz, 1H), 7.43 (t, $J = 7.8$ Hz, 2H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.23 (t, $J = 7.6$ Hz, 1H), 4.35-4.28 (m, 2H), 4.27 (d, $J = 5.6$ Hz, 1H), 4.04-4.00 (m, 1H), 2.88 (dd, $J = 13.7, 4.3$ Hz, 1H), 2.81 (broad s, 1H), 2.33 (dd, $J = 13.7, 9.8$ Hz, 1H), 1.46 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C -NMR (126 MHz, CDCl_3) δ 172.7 (C), 137.9 (C), 135.1 (C), 134.0 (CH), 129.8 (C), 129.4 (CH), 127.2 (CH), 125.2 (CH), 125.1 (CH), 123.4 (CH), 122.2 (C), 119.8 (CH), 119.1 (C), 113.9 (CH), 64.6 (CH), 61.9 (CH_2), 57.4 (CH), 44.6 (C), 42.6 (CH_2), 22.4 (CH₃), 14.3 (CH₃) ppm; IR (film) ν/cm^{-1} 2980, 2235, 1735, 1606, 1447, 1369, 1273, 1212, 1176, 1125, 1092, 1024, 979, 858, 750, 722 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_4\text{SNa}^+$ (M+Na) 460.1307, found 460.1305.

20

Example 3

[0456] General Procedure for Forming Diketopiperazines by Sequential Reaction of Pyrrolidine Esters with 2-Chloroalkanonyl Chlorides and Amines.

[0457] Methyl *rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(4-Fluorophenyl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carboxylate:

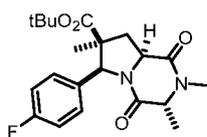


Chemical Formula: C₁₈H₂₁FN₂O₄
Exact Mass: 348.1485

[0458] The corresponding pyrrolidine (1.0 equiv) was dissolved in 10 mL of CH₂Cl₂ and cooled to 0 °C with an ice-bath. Triethylamine (1.2 equiv) was added, followed by dropwise addition of a solution of 2-chloropropionyl chloride (1.2 equiv, 50% v/v in CH₂Cl₂). This mixture was stirred for 1 h with cooling, followed by 1 h after removal of the ice-bath. The intermediate α -chloroamide is then directly extracted (3 x CH₂Cl₂) and isolated as brownish foam after removal of the volatiles *in vacuo*. The corresponding amide was re-dissolved in 10 mL of CH₂Cl₂ and combined with the equivalent volume of 40% aq MeNH₂ solution to give a biphasic mixture, which was stirred at rt for 12-16 h. Extraction of this mixture gives the crude diketopiperazine (DKP) product as yellow foam (purity 50-80%). This residue was stirred with MeOH (1 M) for 1 h, whereupon a colorless solid was obtained ~70% yield. Trituration of this material from a methanolic solution in CH₂Cl₂ (often accelerated by vigorous stirring) gave the major DKP stereoisomer as a colorless solid after filtration and drying under high vacuum. Either the pure DKP stereoisomer, or the solid 5:1 mixture of DKP isomers, could be employed in the subsequent sulfidation step.

[0459] ¹H-NMR (500 MHz, CDCl₃): δ /ppm 7.00-7.10 (2H, m), 6.91 (2H, t, J = 8.5 Hz), 4.81 (1H, s), 4.36 (1H, dd, J = 6.5, 11.5 Hz), 3.81 (1H, q, J = 9.0 Hz), 3.22 (3H, s), 2.94 (3H, s), 2.90-2.95 (1H, m), 2.16 (1H, dd, J = 6.5, 14.0 Hz), 1.53 (3H, s), 1.44 (3H, d, J = 9.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 172.1 (C), 167.3 (C), 166.9 (C), 162.3 (C, d, J = 249 Hz), 133.6 (C, d, J = 3 Hz), 128.3 (2 CH, d, J = 8 Hz), 115.2 (2 CH, d, J = 21 Hz), 69.4 (CH), 60.9 (CH), 56.9 (CH), 53.3 (C), 51.9 (CH₃), 34.4 (CH₂), 32.0 (CH₃), 24.2 (CH₃), 15.3 (CH₃). IR (film): ν /cm⁻¹ 2975, 2929, 1736, 1677, 1605, 1509, 1433, 1401, 1299, 1248, 1225, 1126, 1158, 849. LR-MS: 371.07 (M+Na⁺); HR-MS (ESI) calculated for C₁₈H₂₂N₂O₄F: 349.1564 (M+H⁺), found: 349.1570.

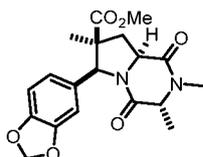
[0460] *tert*-Butyl *rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(4-Fluorophenyl)-2,3,7-trimethyl-1,4-dioxooctahydropyr-olo[1,2-*a*]pyrazine-7-carboxylate:



Chemical Formula: $C_{21}H_{27}FN_2O_4$
Exact Mass: 390.1955

[0461] 1H -NMR (500 MHz, $CDCl_3$): δ /ppm 7.06-7.13 (2H, m), 6.91-6.95 (2H, m), 4.76 (1H, s), 4.34 (1H, dd, $J = 7.0, 12.0$ Hz), 3.79 (1H, q, $J = 7.0$ Hz), 3.00 (3H, s), 2.92-3.00 (1H, m), 2.17 (1H, dd, $J = 6.5, 14.0$ Hz), 1.51 (3H, s), 1.45 (3H, d, $J = 7.0$ Hz), 1.05 (9H, s); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 170.8 (C), 167.3 (C), 166.7 (C), 162.3 (C, d, $J = 250$ Hz), 134.2 (C), 129.2 (2CH), 115.1 (2CH, d, $J = 21$ Hz), 81.4 (C), 69.3 (CH), 60.8 (CH), 56.7 (CH), 53.4 (C), 34.8 (CH₂), 31.9 (CH₃), 27.3 (3CH₃), 25.2 (CH₃), 15.2 (CH₃). IR (film): ν/cm^{-1} 2977, 2934, 1724, 1673, 1510, 1452, 1430, 1401, 1369, 1304, 1250, 1228, 1167, 1124, 848, 734. LR-MS: 413.2 (M+Na⁺); HR-MS (ESI) calculated for $C_{21}H_{27}N_2O_4FNa$: 413.1852 (M+Na⁺), found: 413.1846.

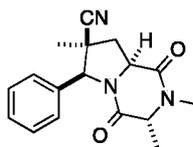
10 [0462] **Methyl *rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo-[1,2-*a*]pyrazine-7-carboxylate:**



Chemical Formula: $C_{19}H_{22}N_2O_6$
Exact Mass: 374.1478

[0463] Isolated as an 8:1 mixture of diastereomers, data for the major isomer is reported. 1H -NMR (500 MHz, $CDCl_3$): δ /ppm 6.68 (1H, d, $J = 8.0$ Hz), 6.54 (1H, d, $J = 8.0$ Hz), 6.51 (1H, s), 5.90 (2H, s), 4.78 (1H), 4.36 (1H, dd, $J = 6.5, 11.5$ Hz), 3.85 (1H, app. t, $J = 7.0$ Hz), 3.32 (3H, s), 3.03 (3H, s), 2.90-3.00 (1H, m), 2.16 (1H, dd, $J = 6.5, 8.5$ Hz), 1.53 (3H, s), 1.41 (3H, s); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 172.09 (C), 167.2 (C), 166.8 (C), 147.5 (C), 147.3 (C), 131.4 (C), 120.3 (CH), 108.0 (CH), 106.9 (CH), 101.1 (CH₂), 69.8 (CH), 60.8 (CH), 56.8 (CH₃), 53.2 (C), 51.9 (CH), 34.2 (CH₂), 32.0 (CH₃), 24.1 (CH₃), 15.2 (CH₃). LR-MS: 416.1 M+Na⁺; IR (film): ν/cm^{-1} 2953, 2949, 1735, 1672, 1490, 1432, 1294, 1245, 1122, 1037. HR-MS (ESI) calculated for $C_{19}H_{22}N_2O_6Na$: 397.1375 (M+Na⁺), found: 397.1367.

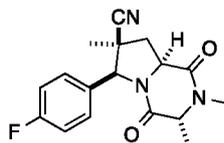
20 [0464] ***Rac*-(3*R*,6*S*,7*S*,8*aS*)-2,3,7-trimethyl-1,4-dioxo-6-phenyloctahydropyrrolo-[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: $C_{17}H_{19}N_3O_2$
Exact Mass: 297.1477

[0465] 1H -NMR (600 MHz, $CDCl_3$): δ /ppm 7.39-7.33 (3H, m), 7.12 (2H, d, $J = 7.2$ Hz), 4.91 (1H, s), 4.40 (1H, dd, $J = 6.6, 11.4$ Hz), 3.91 (1H, q, $J = 3.6, 7.2$ Hz), 3.05 (3H, s), 2.79 (1H, t, $J = 11.4$ Hz), 2.46 (1H, dd, $J = 6.6, 13.2$ Hz), 1.69 (3H, s), 1.48 (3H, d, $J = 7.2$ Hz); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 166.7 (C), 166.2 (C), 136.9 (C), 129.2 (2CH), 129.1 (2CH), 126.1 (CH), 119.9 (C), 69.8 (CH), 60.9 (CH), 56.3 (CH), 42.6 (C), 36.7 (CH_2), 32.2 (CH_3), 25.3 (CH_3), 15.4 (CH_3); IR (film): ν/cm^{-1} 2981, 2937, 2244, 1673; LR-MS: 320.1 $[M+Na]^+$; HR-MS (ESI) calculated for $C_{17}H_{19}N_3O_2Na$: 320.1375, found: 320.1380.

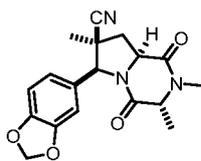
[0466] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(4-fluorophenyl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo-
10 [1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: $C_{17}H_{18}FN_3O_2$
Exact Mass: 315.1383

[0467] 1H -NMR (500 MHz, $CDCl_3$): δ /ppm 7.13-7.05 (4H, m), 4.90 (1H, s), 4.39 (1H, dd, $J = 6.5, 11.0$ Hz), 3.90 (1H, q, $J = 7.0$ Hz), 3.06 (3H, s), 2.76 (1H, t, $J = 12.0$ Hz), 2.47 (1H, dd, $J = 6.5, 13.5$ Hz), 1.69 (3H, s), 1.49 (3H, d, $J = 7.5$ Hz); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 166.8 (C), 166.1 (C), 163.0 (C, d, $J = 247$ Hz), 132.8 (C, d, $J = 3$ Hz), 127.9 (2CH, d, $J = 8$ Hz), 119.8 (C), 116.2 (2CH, d, $J = 22$ Hz), 69.2 (CH), 60.9 (CH), 56.3 (CH), 42.6 (C), 36.8 (CH_2), 32.2 (CH_3), 25.3 (CH_3), 15.4 (CH_3); IR (film): ν/cm^{-1} 2989, 2940, 2241, 1681; LR-MS: 338.1 $[M+Na]^+$; HR-MS (ESI) calculated for $C_{17}H_{18}FN_3O_2Na$: 338.1281, found: 338.1283.

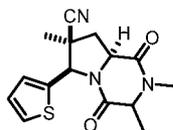
[0468] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-
20 dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₉N₃O₄
Exact Mass: 341.1376

[0469] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.79 (1H, d, *J* = 9.0 Hz), 6.63 (1H, d, *J* = 9.0 Hz), 6.57 (1H, s), 5.96 (2H, s), 4.82 (1H, s), 4.36 (1H, dd, *J* = 6.5, 11.0 Hz), 3.90 (1H, app q, *J* = 7.0 Hz), 3.04 (3H, s), 2.76 (1H, app t, *J* = 7.0 Hz), 2.45 (1H, dd, *J* = 6.5, 13.5 Hz), 1.66 (3H, s), 1.47 (3H, d, *J* = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.6 (C), 166.0 (C), 148.2 (C), 148.1 (C), 130.8 (C), 119.9 (CH), 119.8 (C), 108.6 (CH), 106.2 (CH), 101.4 (CH₂), 69.6 (CH), 60.8 (CH), 56.1 (CH), 42.6 (C), 36.7 (CH₂), 32.0 (CH₃), 25.1 (CH₃), 15.3 (CH₃). LR-MS: 364.0 M+Na⁺; IR (film) ν/cm⁻¹: 2982, 2917, 2244, 1671, 1491, 1447, 1246, 1037, 925, 721 ν/cm⁻¹. HR-MS (ESI) calculated for C₁₈H₁₉N₃O₄Na: 364.1273 (M+Na⁺), found: 364.1273.

10 [0470] ***Rac*-(6*R*,7*S*,8*aS*)-2,3,7-Trimethyl-1,4-dioxo-6-(thiophen-2-yl)octahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**

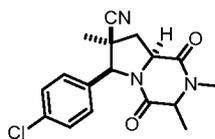


Chemical Formula: C₁₅H₁₇N₃O₂S
Exact Mass: 303.1041

[0471] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.31 (1H, m), 7.11 (1H, s), 7.06 (1H, m), 5.27 (1H, s), 4.39 (1H, dd, *J* = 6.5, 11.0 Hz), 3.95 (1H, q, *J* = 7.5 Hz), 3.08 (3H, s), 3.00 (1H, app t, *J* = 13.0 Hz), 2.56 (1H, dd, *J* = 6.5, 13.0 Hz), 1.72 (3H, s), 1.52 (3H, d, *J* = 7.5 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.9 (C), 166.0 (C), 140.4 (C), 127.5 (CH), 127.0 (CH), 125.5 (CH), 119.6 (C), 65.3 (CH), 60.8 (CH), 55.8 (CH), 42.9 (C), 36.8 (CH₂), 32.2 (CH₃), 24.5 (CH₃), 15.4 (CH₃). IR (film): ν/cm⁻¹ 2981, 2935, 2246, 1672, 1447, 1428, 1402, 1301, 1229, 1065, 915, 722. LR-MS: 326.0 M+Na⁺. HR-MS (ESI) calculated for C₁₅H₁₇N₃O₂SNa: 326.0939 (M+Na⁺), found: 326.0942.

20 326.0942.

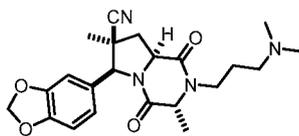
[0472] ***Rac*-(6*S*,7*S*,8*aS*)-6-(4-Chlorophenyl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₇H₁₈ClN₃O₂
Exact Mass: 331.1088

[0473] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.35 (2H, d, *J* = 8.5 Hz), 7.07 (2H, d, *J* = 8.5 Hz), 4.88 (1H, s), 4.39 (1H, dd, *J* = 6.5, 11.5 Hz), 3.90 (1H, q, *J* = 7.5 Hz), 3.06 (3H, s), 2.76 (1H, app t, *J* = 12.0 Hz), 2.48 (1H, dd, *J* = 6.5, 8.5 Hz), 1.70 (3H, s), 1.49 (3H, d, *J* = 7.5 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.7 (C), 166.0 (C), 135.4 (C), 135.1 (C), 129.4 (2CH), 127.5 (2CH), 119.7 (C), 69.2 (CH), 60.9 (CH), 56.3 (CH), 42.4 (C), 36.8 (CH₂), 32.2 (CH₃), 25.3 (CH₃), 15.4 (CH₃). IR (film): ν/cm⁻¹ 2981, 2919, 2852, 2246, 1673, 1490, 1430, 1303, 1235, 1093, 731. LR-MS: 354.0 M+Na⁺. HR-MS (ESI) calculated for C₁₇H₁₈N₃O₂ClNa: 354.0985 (M+Na⁺), found: 354.0981.

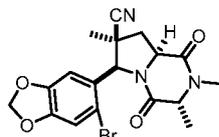
10 [0474] ***Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-2-(3-(dimethylamino)propyl)-3,7-dimethyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: C₂₂H₂₈N₄O₄
Exact Mass: 412.2111

[0475] Isolated as an 8:1 mixture of diastereomers, data for the major isomer is reported. ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.74 (1H, d, *J* = 8.0 Hz), 6.56 (1H, d, *J* = 8.0 Hz), 6.52 (1H, s), 5.91 (2H, s), 4.80 (1H, s), 4.35 (1H, dd, *J* = 6.5, 11.0 Hz), 4.02 (1H, q, *J* = 7.5 Hz), 3.83 (1H, dt, *J* = 7.5, 13.5 Hz), 3.00 (1H, dt, *J* = 7.5, 13.5 Hz), 2.74 (1H, app t, *J* = 12.0 Hz), 2.40 (1H, dd, *J* = 6.5, 13.5 Hz), 2.20-2.30 (2H, m), 2.14 (6H, s), 1.70-1.80 (2H, m), 1.62 (3H, s), 1.43 (3H, d, *J* = 6.5 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 167.1 (C), 166.3 (C), 148.3 (C), 148.2 (C), 131.0 (C), 119.9 (C), 119.7 (CH), 108.6 (CH), 106.3 (CH), 101.5 (CH₂), 69.4 (CH), 59.3 (CH), 56.3 (CH₂), 56.2 (CH), 45.4 (2CH₃), 43.3 (C), 42.7 (CH₂), 36.6 (CH₂), 25.9 (CH₂), 25.1 (CH₃), 16.0 (CH₃). IR (film): ν/cm⁻¹ 2979, 2943, 2822, 2781, 2244, 1672, 1491, 1448, 1427, 1245, 1037, 929, 811, 735. LR-MS: 435.3 M+Na⁺. HR-MS (ESI) calculated for C₂₂H₂₈N₄O₄Na: 435.2008 (M+Na⁺), found: 435.2015.

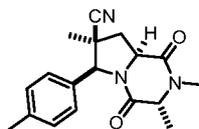
[0476] *Rac*-(3*R*,6*R*,7*S*,8*aS*)-6-(6-Bromobenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxooctahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₈BrN₃O₄
Exact Mass: 419.0481

[0477] Isolated as a 3:1 mixture of diastereomers, data for the major isomer is reported. ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.07 (1H, s), 6.34 (1H, s), 5.98 (2H, s), 5.34 (1H, s), 4.36 (1H, dd, *J* = 6.5, 12.0 Hz), 3.92 (1H, q, *J* = 7.0 Hz), 3.04 (3H, s), 2.66 (1H, app t, *J* = 13.0 Hz), 2.48 (1H, dd, *J* = 6.5, 13.0 Hz), 1.74 (3H, s), 1.47 (3H, d, *J* = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.5 (C), 166.0 (C), 148.7 (C), 148.1 (C), 129.1 (C), 119.7 (C), 115.0 (C), 113.5 (CH), 105.0 (CH), 102.3 (CH₂), 68.2 (CH), 60.8 (CH), 56.4 (CH), 42.2 (C), 37.4 (CH₂), 31.8 (CH₃), 24.9 (CH₃), 15.5 (CH₃). IR (film): ν/cm⁻¹ 2982, 2246, 1675, 1503, 1478, 1429, 1402, 1307, 1248, 1120, 1036, 928. LR-MS: 435.3 HR-MS (ESI) calculated for C₁₈H₁₈BrN₃O₄Na: 442.0378 (M+Na⁺), found: 442.0369.

[0478] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-2,3,7-Trimethyl-1,4-dioxo-6-(*p*-tolyl)octahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:

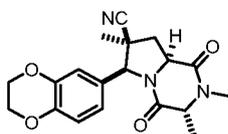


Chemical Formula: C₁₈H₂₁N₃O₂
Exact Mass: 311.1634

[0479] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.17 (2H, d, *J* = 7.5 Hz), 7.01 (2H, d, *J* = 7.5 Hz), 4.88 (1H, s), 4.38 (1H, dd, *J* = 7.0, 11.0 Hz), 3.89 (1H, q, *J* = 7.0 Hz), 3.04 (3H, s), 2.79 (1H, app t, *J* = 12.5 Hz), 2.44 (1H, dd, *J* = 6.5, 12.5 Hz), 2.32 (3H, s), 1.67 (3H, s), 1.47 (3H, d, *J* = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.7 (C), 166.2 (C), 138.9 (C), 134.0 (C), 129.8 (2CH), 125.9 (2CH), 120.0 (C), 69.6 (CH), 60.9 (CH), 56.2 (CH), 42.6 (C), 36.7 (CH₂), 32.1 (CH₃), 25.2 (CH₃), 21.3 (CH₃), 15.4 (CH₃). IR (film): ν/cm⁻¹ 3054, 2982, 2935, 2877, 2243, 1681, 1515, 1452, 1430, 1402, 1306, 1246, 1230, 1063, 804, 734. LR-MS: 334.0 M+Na⁺. HR-

MS (ESI) calculated for $C_{18}H_{21}N_3O_2Na$: 334.1531, found: 334.1536. The structure and relative configuration of this sample was confirmed by single-crystal X-ray analysis.

[0480] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2,3,7-trimethyl-1,4-dioxooctahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: $C_{19}H_{21}N_3O_4$
Exact Mass: 355.1532

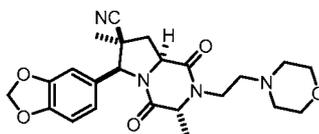
5

[0481] 1H -NMR (500 MHz, 1:1 d_4 -MeOD/ $CDCl_3$): δ /ppm 6.61 (1H, d, $J = 7.0$ Hz), 6.38 (2H, m), 4.59 (1H, s), 4.28 (1H, m), 4.00 (4H, m), 3.69 (1H, q, $J = 9.0$ Hz), 2.82 (3H, s), 2.48 (1H, app t, $J = 12.0$ Hz), 2.23 (1H, dd, $J = 8.5, 12.0$ Hz), 1.45 (3H, s), 1.26 (3H, d, $J = 9.0$ Hz); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 167.3 (C), 166.6 (C), 144.0 (C), 143.7 (C), 130.2 (C), 120.0 (C), 119.1 (CH), 117.6 (CH), 114.9 (CH), 69.3 (CH), 64.3 (2CH₂), 60.8 (CH), 56.1 (CH), 42.7 (C), 36.5 (CH₂), 31.9 (CH₃), 24.7 (CH₃), 14.9 (CH₃). IR (film): ν/cm^{-1} 3056.3, 2982.2, 2936.7, 2878.2, 2244.2, 1672.0, 1509.0, 1450.8, 1432.5, 1307.3, 1287.9, 1067.0, 886.5. LR-MS: 378.1 $M+Na^+$. HR-MS (ESI) calculated for $C_{19}H_{21}N_3O_4Na$: 378.1430, found: 378.1433.

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[0482] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-3,7-dimethyl-2-(2-morpholinoethyl)-1,4-dioxooctahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



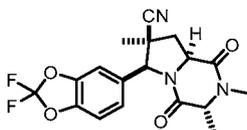
Chemical Formula: $C_{23}H_{28}N_4O_5$
Exact Mass: 440.2060

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[0483] 1H -NMR (500 MHz, 1:1 d_4 -MeOD/ $CDCl_3$): δ /ppm 6.61 (1H, d, $J = 9.5$ Hz), 6.49 (1H, d, $J = 9.5$ Hz), 6.36 (1H, s), 5.77 (2H, s), 4.67 (1H, s), 4.31 (1H, dd, $J = 6.5, 11.0$ Hz), 3.88 (1H, q, $J = 9.0$ Hz), 3.80 (1H, m), 3.44-3.50 (4H, m), 2.88-2.95 (1H, m), 2.55 (1H, app t, $J = 6.5$ Hz), 2.20-2.45 (7H, m), 1.49 (3H, s), 1.31 (3H, d, $J = 9.0$ Hz); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 167.4 (C), 166.5 (C), 148.2 (C), 148.1 (C), 131.0 (C), 120.2 (CH), 120.0 (C), 108.5 (CH), 105.8 (CH), 101.5 (CH₂), 69.4 (CH), 66.9 (2CH₂), 59.7 (CH), 56.4 (CH₂), 56.1 (CH), 53.7 (2CH₂), 42.8 (C), 41.6 (CH₂), 36.5 (CH₂), 24.8 (CH₃), 15.6 (CH₃). IR (film): ν/cm^{-1} 2955.4, 2858.2,

2812.5, 2243.7, 1672.0, 1491.0, 1448.4, 1426.9, 1295.8, 1245.8, 1115.3, 1036.5, 922.1. LR-MS: 441.3 M+H⁺. HR-MS (ESI) calculated for C₂₃H₂₈N₄O₅Na: 463.1957, found 463.1946.

[0484] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxooctahydro-pyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₇F₂N₃O₄
Molecular Weight: 377.3478

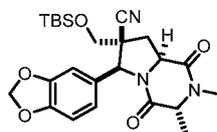
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[0485] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.07 (1H, d, *J* = 8.0 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 6.83 (1H, s), 4.88 (1H, s), 4.36-4.43 (1H, dd, *J* = 6.5, 11.5 Hz), 3.92 (1H, q, *J* = 7.0 Hz), 3.07 (3H, s), 2.76 (1H, app t, *J* = 12.0 Hz), 2.51 (1H, dd, *J* = 6.5, 13.5 Hz), 1.71 (3H, s), 1.50 (3H, d, *J* = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.8 (C), 165.9 (C), 144.2 (C), 144.1 (C), 133.3 (C), 131.7 (CF₂, t, *J* = 255 Hz), 121.9 (CH), 119.6 (C), 110.0 (CH), 107.4 (CH), 69.4 (CH), 60.5 (CH), 56.3 (CH), 42.6 (C), 36.9 (CH₂), 32.2 (CH₃), 25.3 (CH₃), 15.4 (CH₃). IR (film): ν/cm⁻¹ 2984, 2939, 2246, 1674, 1500, 1452, 1429, 1403, 1241, 1150, 912, 732. LR-MS: 400.2 (M+Na⁺); HR-MS (ESI) calculated for C₁₈H₁₇N₃O₄F₂Na: 400.1085, found: 400.1092.

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[0486] *Rac*-(3*R*,6*S*,7*R*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-7-(((tert-butyl)dimethylsilyl)oxy)methyl)-2,3-dimethyl-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-7-carbonitrile:

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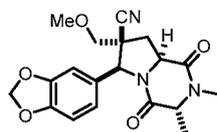
Chemical Formula: C₂₄H₃₃N₃O₅Si
Molecular Weight: 471.6290

[0487] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.73 (1H, d, *J* = 9.0 Hz), 6.2-7.0 (2H, br s), 5.95 (2H, d, *J* = 9.0 Hz), 5.35 (1H, s), 4.62 (1H, 1H, m), 3.88 (1H, q, *J* = 7.5 Hz), 3.29 (1H, d, *J* = 9.5 Hz), 3.21 (1H, d, *J* = 9.5 Hz), 3.05 (3H, s), 2.58-2.62 (1H, m), 2.26 (1H, app t, *J* = 12.0 Hz), 1.52 (3H, d, *J* = 7.5 Hz), 0.88 (9H, s), 0.01 (3H, s), -0.02 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.4 (C), 166.2 (C), 148.0 (2C), 128.2 (C), 121.7 (C), 108.5 (CH), 101.5 (CH₂), 66.6 (CH), 63.5 (CH₂), 61.1 (CH), 57.0 (CH), 49.2 (C), 33.1 (CH₂), 32.1 (CH₃), 25.7 (3CH₃), 18.2

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(C), 15.4 (CH₃), -5.6 (2CH₃), 2 aromatic CH not seen. IR (film): ν/cm^{-1} 2930, 2884, 2857, 2240, 1678, 1490, 1448, 1402, 1245, 1105, 1039, 928, 840, 780, 732. LR-MS: 494.3 (M+Na⁺); HR-MS (ESI) calculated for C₂₄H₃₃N₃O₅SiNa: 494.2087, found: 494.2068.

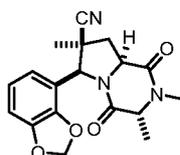
5 **[0488] *Rac*-(3*R*,6*S*,7*R*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-7-(methoxymethyl)-2,3-dimethyl-1,4-dioxo-octahydropyrrolo[1,2-a]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₉H₂₁N₃O₅
Molecular Weight: 371.3930

10 **[0489]** ¹H-NMR (500 MHz, CDCl₃): δ /ppm 6.78 (1H, d, J = 8.0 Hz), 6.65 (1H, d, J = 8.0 Hz), 6.59 (1H, s), 5.95 (2H, s), 5.03 (1H, s), 4.36 (1H, dd, J = 7.0, 11.0 Hz), 3.88 (1H, q, J = 7.0 Hz), 3.62 (2H, s), 3.48 (3H, s), 3.02 (3H, s), 2.74 (1H, app t, J = 11.5 Hz), 2.67 (1H, dd, J = 7.5, 14.0 Hz), 1.44 (3H, d, J = 7.0 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 166.7 (C), 166.2 (C), 148.3 (C), 148.2 (C), 130.8 (C), 120.0 (CH), 118.3 (C), 108.8 (CH), 106.4 (CH), 101.5 (CH₂), 74.8 (CH₂), 65.4 (CH), 60.8 (CH), 59.8 (CH₃), 56.8 (CH), 48.7 (C), 33.7 (CH₂), 32.1 (CH₃), 15.3 (CH₃).

15 **[0490] *Rac*-(3*R*,6*R*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-4-yl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-7-carbonitrile:**

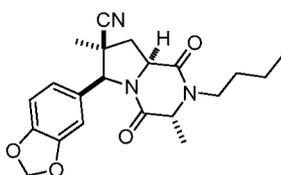


Chemical Formula: C₁₈H₁₉N₃O₄
Molecular Weight: 341.3670

20 **[0491]** ¹H-NMR (500 MHz, d₆-DMSO, 390K): δ /ppm 6.85 (2H, br s), 6.65 (1H, br s), 6.00 (1H, s), 5.92 (1H, s), 4.96 (1H, s), 4.67 (1H, dd, J = 6.5, 10.5 Hz), 3.95 (1H, q, J = 7.0 Hz), 2.97 (3H, s), 2.58-2.67 (1H, m), 2.44-2.55 (1H, m), 1.72 (3H, s), 1.46 (3H, d, J = 7.0 Hz); ¹³C-NMR (125 MHz, d₆-DMSO, 390K): δ /ppm 166.8 (C), 166.6 (C), 147.9 (C), 145.0 (C), 122.1 (CH), 121.1 (C), 120.5 (CH), 108.7 (CH), 101.4 (CH₂), 65.6 (CH), 60.6 (CH), 56.4 (CH), 42.7 (C), 38.1 (CH₂), 31.8 (CH₃), 25.0 (CH₃), 15.6 (CH₃). IR (film): ν/cm^{-1} 3056, 2981, 2895, 2244, 1672,

1460, 1432, 1402, 1251, 1066, 928, 731. LR-MS: 342.1 (M+H⁺); HR-MS (ESI) calculated for C₁₈H₁₉N₃O₄Na: 364.1273, found: 364.1267.

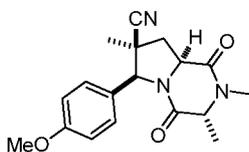
[0492] ***Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-2-butyl-3,7-dimethyl-1,4-dioxo-octahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



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[0493] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.79 (1H, d, *J* = 9.0 Hz), 6.60 (1H, d, *J* = 9.0 Hz), 6.55 (1H, s), 5.96 (2H, s), 4.82 (1H, s), 4.38 (1H, dd, *J* = 6.5, 11.0 Hz), 3.95 (1H, app q, *J* = 7.0 Hz), 2.99 (1H, m), 2.81 (1H, app t, *J* = 7.0 Hz), 2.43 (1H, dd, *J* = 6.5, 13.5 Hz), 1.60 (2H, m), 1.56 (3H, s), 1.45 (3H, d, *J* = 7.0 Hz) 1.38 (2H, m), 0.96 (3H, t, *J* = 7.2 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 167.2 (C), 166.3 (C), 148.6 (C), 148.4 (C), 131.1 (C), 120.0 (CH), 119.9 (C), 108.8 (CH), 106.4 (CH), 101.7 (CH₂), 69.7 (CH), 59.0 (CH), 56.5 (CH), 44.8 (C), 42.9 (CH₂), 36.9 (CH₂), 30.0 (CH₂), 25.4 (CH₃), 20.2 (CH₂), 16.2 (CH₃). 13.9 (CH₃), LR-MS: 406.2 M+Na⁺; IR (film): ν/cm⁻¹ 2982, 2917, 2244, 1671, 1491, 1447, 1246, 1037, 925, 721 ν/cm⁻¹. HR-MS (ESI) calculated for C₂₁H₂₅N₃O₄Na: 406.1713 (M+Na⁺), found: 406.1730.

15 [0494] ***Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(4-methoxyphenyl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**

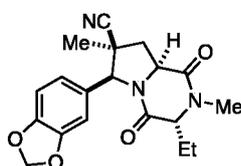


[0495] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.05 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 4.88 (1H, s), 4.39 (1H, dd, *J* = 6.5, 11.5 Hz), 3.90 (1H, q, *J* = 7.5 Hz), 3.79 (3H, s), 3.05 (3H, s), 2.80 (1H, app t, *J* = 12.0 Hz), 2.46 (1H, dd, *J* = 6.5, 8.5 Hz), 1.70 (3H, s), 1.48 (3H, d, *J* = 7.5 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.6 (C), 166.2 (C), 159.9 (C), 128.9 (C), 127.2 (2CH), 119.9 (C), 114.4 (2CH), 69.3 (CH), 60.9 (CH), 56.1 (CH), 55.2 (CH₃), 42.6 (C), 36.6 (CH₂), 32.1 (CH₃), 25.1 (CH₃), 15.3 (CH₃). IR (film): ν/cm⁻¹ 2981, 2919, 2852, 2246, 1673,

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1490, 1303, 1235, 1093, 756. HR-MS (ESI) calculated for $C_{18}H_{21}N_3O_3Na$: 350.1475 ($M+Na^+$), found: 350.1465.

[0496] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-3-ethyl-2,7-dimethyl-1,4-dioxo-octahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



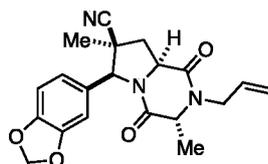
Chemical Formula: $C_{19}H_{21}N_3O_4$
Exact Mass: 355,1532
Molecular Weight: 355,3940

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[0497] Prepared from the corresponding pyrrolidine ester and 2-chlorobutanoyl chloride by conducting the reaction with methylamine at 60 °C overnight. Isolated as a 9:1 mixture of diastereomers; NMR data for the major isomer is reported. 1H -NMR (600 MHz, $CDCl_3$) δ 6.79 (d, $J = 8.0$ Hz, 1H), 6.63 (dd, $J = 8.0, 1.9$ Hz, 1H), 6.56 (t, $J = 1.9$ Hz, 1H), 5.96 (s, 2H), 4.83 (s, 10 1H), 4.41 (dd, $J = 8.0, 1.9$ Hz, 1H), 3.77 (dd, $J = 7.5, 6.3$ Hz, 1H), 3.08 (s, 3H), 2.76 (dd, $J = 13.0, 11.7$ Hz, 1H), 2.45 (dd, $J = 13.2, 6.7$ Hz, 1H), 1.95-1.92 (m, 1H), 1.91-1.85 (m, 1H), 1.66 (s, 3H), 1.07 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C -NMR (126 MHz, $CDCl_3$) δ 166.4 (C), 166.2 (C), 148.4 (C), 148.3 (C), 131.0 (C), 120.0 (CH), 119.9 (C), 108.8 (CH), 106.3 (CH), 101.6 (CH₂), 69.9 (CH), 66.8 (CH), 56.3 (CH), 42.7 (C), 37.0 (CH₂), 33.5 (CH₃), 25.4 (CH₃), 24.4 (CH₂), 10.6 (CH₃) ppm; IR (film) ν/cm^{-1} 2929, 2245, 1672, 1491, 1446, 1402, 1246, 1038, 916, 821, 730 cm^{-1} ; HRMS (ESI) calcd for $C_{19}H_{21}N_3O_4Na^+$ ($M+Na$) 378.1430, found 378.1433.

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[0498] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-2-allyl-6-(benzo[d][1,3]dioxol-5-yl)-3,7-dimethyl-1,4-dioxo-octahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



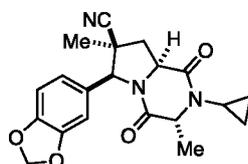
Chemical Formula: $C_{20}H_{21}N_3O_4$
Exact Mass: 367,1532
Molecular Weight: 367,4050

[0499] The cyclization to the diketopiperazine was performed in a THF/ H_2O (1:1) solvent mixture at 80 °C, overnight. 1H -NMR (600 MHz, $CDCl_3$) δ 6.80-6.78 (m, 1H), 6.63-6.61 (m,

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1H), 6.56 (d, $J = 1.6$ Hz, 1H), 5.98-5.96 (m, 2H), 5.81-5.74 (m, 1H), 5.27 (dd, $J = 10.2, 1.1$ Hz, 1H), 5.24 (dd, $J = 17.0, 1.1$ Hz, 1H), 4.84 (s, 1H), 4.50 (ddt, $J = 15.3, 5.3, 1.4$ Hz, 1H), 4.41 (dd, $J = 11.7, 6.7$ Hz, 1H), 3.97 (q, $J = 7.4$ Hz, 1H), 3.68 (dd, $J = 15.2, 6.8$ Hz, 1H), 2.82 (dd, $J = 13.3, 11.5$ Hz, 1H), 2.46 (dd, $J = 13.3, 6.8$ Hz, 1H), 1.68 (s, 3H), 1.48 (d, $J = 7.4$ Hz, 3H) ppm; ^{13}C -NMR (126 MHz, CDCl_3) δ 167.0 (C), 166.1 (C), 148.4 (C), 148.3 (C), 131.8 (CH), 131.0 (C), 119.9 (CH), 119.3 (CH₂), 108.8 (CH), 106.3 (CH), 101.6 (CH₂), 69.6 (CH), 58.2 (CH), 56.3 (CH), 54.7 (C), 47.1 (CH₂), 42.8 (C), 36.7 (CH₂), 25.4 (CH₃), 16.0 (CH₃) ppm; IR (film) ν/cm^{-1} 2924, 2853, 2244, 1674, 1505, 1448, 1427, 1294, 1246, 1184, 1101, 1038, 933, 859, 809, 735 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{Na}^+$ (M+Na) 390.1430, found 390.1438.

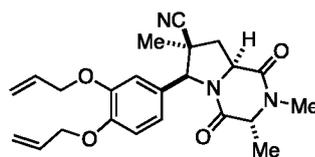
10 **[0500] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-2-cyclopropyl-3,7-dimethyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4$
Exact Mass: 367,1532
Molecular Weight: 367,4050

[0501] Cyclization to the diketopiperazine was performed using cyclopropylamine (3.5 equiv) in a THF/ H_2O (1:1) solvent mixture that was heated from 80–100°C over 2 d. ^1H -NMR (500 MHz, CDCl_3) δ 6.76 (d, $J = 8.0$ Hz, 1H), 6.56 (d, $J = 8.0$ Hz, 1H), 6.47 (s, 1H), 5.95 (s, 2H), 4.80 (s, 1H), 4.38 (dd, $J = 11.3, 6.7$ Hz, 1H), 3.98 (q, $J = 7.3$ Hz, 1H), 2.74-2.69 (m, 2H), 2.45 (dd, $J = 13.3, 6.7$ Hz, 1H), 1.65 (s, 3H), 1.49 (d, $J = 7.3$ Hz, 3H), 1.09 (dq, $J = 9.5, 6.6$ Hz, 1H), 0.88-0.83 (m, 1H), 0.79 (dq, $J = 9.5, 6.5$ Hz, 1H), 0.58 (dq, $J = 10.4, 5.2$ Hz, 1H) ppm; ^{13}C -NMR (126 MHz, CDCl_3) δ 168.2 (C), 167.2 (C), 148.3 (C), 148.2 (C), 130.9 (C), 119.9 (CH), 119.8 (CH), 108.7 (CH), 106.1 (CH), 101.5 (CH₂), 69.4 (CH), 59.8 (CH), 56.7 (CH), 42.7 (C), 36.7 (CH₂), 28.0 (CH), 25.2 (CH₃), 16.2 (CH₃), 8.7 (CH₂), 5.7 (CH₂) ppm; IR (film) ν/cm^{-1} 2984, 1675, 1490, 1424, 1376, 1245, 1189, 1036, 932, 733 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{Na}^+$ (M+Na) 390.1430, found 390.1433.

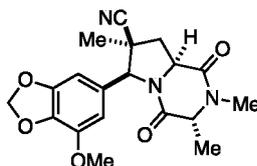
25 **[0502] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(3,4-bis(allyloxy)phenyl)-2,3,7-trimethyl-1,4-dioxooctahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: $C_{23}H_{27}N_3O_4$
 Exact Mass: 409,2002
 Molecular Weight: 409,4860

[0503] $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 6.86 (d, $J = 8.2$ Hz, 1H), 6.65-6.63 (m, 2H), 6.09-6.01 (m, 2H), 5.39 (dd, $J = 17.2$ Hz, 1.1 Hz, 1H), 5.37 (dd, $J = 17.3$ Hz, 1.2 Hz, 1H), 5.26 (app. dt, $J = 10.6, 0.2$ Hz, 2H), 4.85 (s, 1H), 4.60-4.57 (m, 4H), 4.37 (dd, $J = 11.3, 6.8$ Hz, 1H), 3.91 (q, $J = 7.2$ Hz, 1H), 3.06 (s, 3H), 2.78 (app t, $J = 12.2$ Hz, 1H), 2.44 (dd, $J = 13.3, 6.8$ Hz, 1H), 1.68 (s, 3H), 1.49 (d, $J = 7.2$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 166.8 (C), 166.3 (C), 149.2 (C), 148.7 (C), 133.4 (CH), 133.4 (CH), 129.6 (C), 119.9 (C), 118.7 (CH), 117.9 (CH₂), 117.9 (CH₂), 113.9 (CH), 112.4 (CH), 70.2 (CH₂), 69.9 (CH₂), 69.5 (CH), 61.1 (CH), 56.2 (CH), 42.7 (C), 36.7 (CH₂), 32.3 (CH₃), 25.3 (CH₃), 15.4 (CH₃) ppm; IR (film) ν/cm^{-1} 2983, 1672, 1515, 1451, 1426, 1306, 1259, 1224, 1206, 1139, 1017, 996, 924, 806, 732 cm^{-1} ; HRMS (ESI) calcd for $C_{23}H_{27}N_3O_4\text{Na}^+$ (M+Na) 432.1899, found 432.1888.

[0504] *Rac-(3R,6S,7S,8aS)-6-(7-methoxybenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-7-carbonitrile:*

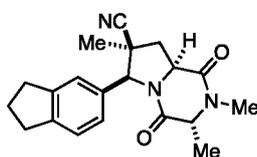


Chemical Formula: $C_{19}H_{21}N_3O_5$
 Exact Mass: 371,1481
 Molecular Weight: 371,3930

[0505] Isolated as an 8:1 mixture of diastereomers; NMR data for the major isomer is reported. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 6.34 (s, 1H), 6.24 (s, 1H), 5.97 (s, 2H), 4.81 (s, 1H), 4.36 (dd, $J = 11.3, 6.6$ Hz, 1H), 3.92 (q, $J = 7.3$ Hz, 1H), 3.89 (s, 3H), 3.05 (s, 3H), 2.78 (app. t, $J = 12.4$ Hz, 1H), 2.46 (dd, $J = 13.3, 6.6$ Hz, 1H), 1.68 (s, 3H), 1.49 (d, $J = 7.3$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 166.9 (C), 166.2 (C), 149.5 (C), 143.8 (C), 135.9 (C), 131.6 (C), 119.9 (C), 107.0 (CH), 102.0 (CH₂), 99.7 (CH), 69.8 (CH), 61.0 (CH), 56.8 (CH₃), 56.3 (CH), 42.8 (C), 36.8 (CH₂), 32.3 (CH₃), 25.4 (CH₃), 15.5 (CH₃) ppm; IR (film) ν/cm^{-1} 2981, 1143, 1673, 1512,

1452, 1433, 1402, 1324, 1240, 1199, 1135, 1093, 1043, 927, 735 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_5\text{Na}^+$ ($\text{M}+\text{Na}$) 394.1379, found 394.1371.

[0506] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(2,3-dihydro-1*H*-inden-5-yl)-2,3,7-trimethyl-1,4-dioxooctahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



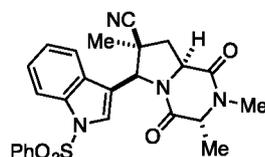
Chemical Formula: $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2$
Exact Mass: 337,1790
Molecular Weight: 337,4230

5

[0507] $^1\text{H-NMR}$ (500 MHz, CDCl_3) 7.19 (d, $J = 7.7$ Hz, 1H), 6.96 (s, 1H), 6.93 (d, $J = 7.7$ Hz, 1H), 4.89 (s, 1H), 4.38 (dd, $J = 11.6, 6.7$ Hz, 1H), 3.91 (q, $J = 7.3$ Hz, 1H), 3.07 (s, 3H), 2.90-2.80 (m, 5H), 2.45 (dd, $J = 13.3, 6.6$ Hz, 1H), 2.05 (app. quintett, $J = 7.5$ Hz, 2H), 1.69 (s, 3H), 1.49 (d, $J = 7.3$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 166.8 (C), 166.3 (C), 145.5 (C), 145.2 (C), 134.8 (C), 125.0 (CH), 123.9 (CH), 122.1 (CH), 120.1 (C), 70.1 (CH), 61.0 (CH), 56.3 (CH), 42.8 (C), 36.8 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 32.2 (CH_3), 25.4 (CH_3), 25.4 (CH_2), 15.5 (CH_2) ppm; IR (film) ν/cm^{-1} 1940, 1673, 1431, 1402, 1306, 1239, 1062, 814, 733 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2\text{Na}^+$ ($\text{M}+\text{Na}$) 360.1688, found 360.1684.

[0508] *Rac* (3*R*,6*S*,7*S*,8*aS*)-2,3,7-trimethyl-1,4-dioxo-6-(1-(phenylsulfonyl)-1*H*-indol-3-yl)octahydro-pyrrolo[1,2-*a*]pyrazine-7-carbonitrile:

15



Chemical Formula: $\text{C}_{25}\text{H}_{24}\text{N}_4\text{O}_4\text{S}$
Exact Mass: 476,1518
Molecular Weight: 476,5510

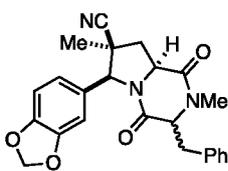
[0509] Isolated as an 7:1 mixture of diastereomers; NMR data for the major isomer is reported. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.89 (d, $J = 8.2$ Hz, 1H), 7.77 (d, $J = 7.5$ Hz, 2H), 7.51 (app. t, $J = 7.3$ Hz, 1H), 7.46-7.39 (m, 4H), 7.31 (app. t, $J = 7.3$ Hz, 1H), 7.25 (app. t, $J = 7.3$ Hz, 1H), 5.18 (s, 1H), 4.40 (dd, $J = 12.4, 6.3$ Hz, 1H), 3.92 (q, $J = 7.4$ Hz, 1H), 3.09 (s, 3H), 2.83 (app. t, $J = 11.9$ Hz, 1H), 2.57 (dd, $J = 13.3, 6.3$ Hz, 1H), 1.73 (s, 3H), 1.49 (s, 3H) ppm; $^{13}\text{C-NMR}$ (126

20

MHz, CDCl₃) δ 166.7 (C), 166.0 (C), 137.9 (C), 135.4 (C), 134.1 (CH), 129.5 (CH), 126.8 (CH), 125.6 (CH), 124.1 (CH), 123.9 (CH), 119.9 (CH), 119.6 (C), 119.5 (C), 119.4 (C), 114.1 (CH), 62.4 (CH), 60.9 (CH), 56.2 (CH), 42.2 (C), 38.1 (CH₂), 32.3 (CH₃), 25.1 (CH₃), 15.7 (CH₃) ppm; IR (film) ν/cm⁻¹ 2982, 1675, 1448, 1367, 1307, 1175, 1124, 1095, 977, 748, 725 cm⁻¹; HRMS (ESI) calcd for C₂₅H₂₄N₄O₄SNa⁺ (M+Na) 499.1416, found 499.1412.

[0510] Alternate Procedure for Forming Diketopiperazines From Substituted Prolidine Esters and Protected α-Amino Acids.

[0511] *Rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-3-benzyl-2,7-dimethyl-1,4-dioxooctahydropyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₂₄H₂₃N₃O₄
Exact Mass: 417,1689
Molecular Weight: 417,4650

10

[0512] To a solution of *N*-Boc-phenylalanine (263 mg, 1.00 mmol, 1.5 equiv) in dry CH₂Cl₂ (2 mL) at 0 °C was added *N,N*-diisopropylethylamine (0.12 mL, 0.66 mmol, 1 equiv) and BOPCl (253 mg, 1.00 mmol, 1.5 equiv) and the reaction was allowed to warm to room temperature over 1 h. After recooling to 0 °C additional *N,N*-diisopropylethylamine (0.23 mL, 1.3 mmol, 2 equiv) was added, followed by the dropwise addition of a solution of the corresponding pyrrolidine ester (200 mg, 0.66 mmol, 1 equiv) in CH₂Cl₂ (1.3 mL). The reaction was allowed to warm to room temperature overnight, after which time TLC analysis showed full conversion of the starting material. After an extractive work-up (CH₂Cl₂/water), the crude product was filtered through a silica gel plug using hexanes/ethyl acetate (1:1) as the eluent and the volatiles were removed *in vacuo*. The crude acylated pyrrolidine ester was dissolved in dry CH₂Cl₂ (2.1 mL) and cooled to 0 °C. Trifluoroacetic acid (0.8 mL) was added, the reaction allowed to warm to rt over 3 h, and the volatiles were removed under reduced pressure. The resulting residue was dissolved in a 4:1 mixture *i*-BuOH/toluene (18 mL) containing *N,N*-diisopropylethylamine (0.46 mL, 2.65 mmol, 4 equiv). The vial was sealed with a teflon cap and heated to 100 °C overnight. After an extractive work up (CH₂Cl₂/water) and concentration, two diastereomeric DKPs were separated by silica gel chromatography (eluent: hexanes/EtOAc 1:3).

25

[0513] NMR data for diastereomer A: $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 7.38-7.35 (m, 3H), 7.26-7.25 (m, 2H), 7.00 (d, $J = 3.7$ Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.63 (d, $J = 7.2$ Hz, 1H), 6.55 (s, 1H), 5.92 (s, 2H), 4.71 (s, 1H), 4.29 (app. q, $J = 4.2$ Hz, 1H), 3.31 (dd, $J = 13.9, 4.6$ Hz, 1H), 2.95 (dd, $J = 13.9, 4.4$ Hz, 1H), 2.64 (dd, $J = 11.9, 6.2$ Hz, 1H), 2.44 (app. t, $J = 12.5$ Hz, 1H),
5 2.05 (dd, $J = 13.0, 6.3$ Hz, 1H), 1.32 (s, 3H) ppm. NMR data for diastereomer B: $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ 7.37-7.34 (m, 2H), 7.32-7.29 (m, 1H), 7.22-7.19 (m, 2H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.64 (dd, $J = 8.8, 1.7$ Hz, 1H), 6.60 (d, $J = 1.8$ Hz, 1H), 6.00 (d, $J = 1.5$ Hz, 1H), 5.99 (d, $J = 1.5$ Hz, 1H), 5.69 (broad s, 1H), 4.91 (s, 1H), 4.40 (dd, $J = 11.3, 6.9$ Hz, 1H), 4.32 (dd, $J = 10.2, 4.2$ Hz, 1H), 3.51 (dd, $J = 14.7, 3.9$ Hz, 1H), 2.79 (dd, $J = 11.5, 4.1$ Hz, 1H), 2.77 (dd, $J = 10.3, 4.4$ Hz, 1H), 2.40 (dd, $J = 13.4, 6.8$ Hz, 1H), 1.68 (s, 3H) ppm.

[0514] Both DKP products were individually methylated in a separate reaction vessel by the following procedure: To the intermediate DKP (91 mg, 0.23 mmol, 1 equiv) in acetone (2.8 mL) was added K_2CO_3 (620 mg, 4.5 mmol, 20 equiv) and MeI (1.4 mL, 23 mmol, 100 equiv) and the reaction was stirred for 2 d at room temperature with the exclusion of light. After an extractive
15 work up ($\text{CH}_2\text{Cl}_2/\text{water}$), each diastereomeric DKP was obtained as amorphous solid.

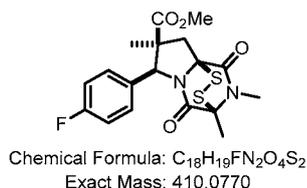
[0515] Diastereomer A: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.34-7.31 (m, 3H), 7.18-7.13 (m, 2H), 6.77 (d, $J = 7.8$ Hz, 1H), 6.59 (d, $J = 7.8$ Hz, 1H), 6.51 (s, 1H), 5.95 (s, 2H), 4.65 (s, 1H), 4.18 (t, $J = 4.1$ Hz, 1H), 3.28 (dd, $J = 14.1, 3.9$ Hz, 1H), 3.14-3.10 (m, 4H), 2.40-2.39 (m, 2H), 2.04-2.01 (m, 1H), 1.26 (s, 3H) ppm; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 166.5 (C), 165.5 (C), 148.3 (C), 148.2 (C), 135.4 (C), 131.1 (C), 129.9 (CH), 129.2 (CH), 128.1 (CH), 120.0 (C), 119.9 (CH), 108.8 (CH), 106.1 (CH), 101.5 (CH_2), 69.5 (CH), 66.4 (CH), 55.4 (CH), 42.3 (C), 36.8 (CH_2), 36.4 (CH_2), 32.4 (CH_3), 24.8 (CH_3) ppm; IR (film) ν/cm^{-1} 2934, 2247, 1673, 1505, 1491, 1446, 1403, 1304, 1247, 1102, 1053 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_4\text{Na}^+$ (M+Na) 440.1586, found 440.1580. Diastereomer B: $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.26-7.19 (m, 3H), 7.14-7.11 (m, 2H),
25 6.76 (d, $J = 8.0$ Hz, 1H), 6.55 (d, $J = 8.4$ Hz, 1H), 6.52 (s, 1H), 5.99-5.96 (m, 2H), 4.82 (s, 1H), 4.43 (t, $J = 5.2$ Hz, 1H), 4.37 (dd, $J = 11.3, 6.8$ Hz, 1H), 3.48 (dd, $J = 16.0, 5.6$ Hz, 1H), 3.42 (dd, $J = 16.0, 5.5$ Hz, 1H), 3.04 (s, 3H), 2.81 (dd, $J = 13.1, 11.5$ Hz, 1H), 2.46 (dd, $J = 13.4, 6.6$ Hz, 1H), 1.66 (s, 3H) ppm; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 168.1 (C), 165.8 (C), 148.3 (2xC), 136.5 (C), 130.8 (C), 129.0 (CH), 128.8 (CH), 127.1 (CH), 120.1 (C), 120.0 (CH), 108.8 (CH),
30 106.7 (CH), 101.2 (CH_2), 69.8 (CH), 61.3 (CH), 57.4 (CH), 42.8 (C), 37.0 (CH_2), 33.5 (CH_2),

30.9 (CH₃), 25.6 (CH₃) ppm; IR (film) ν/cm^{-1} 1675, 1504, 1491, 1448, 1390, 1306, 1244, 1039, 912, 733, 700 cm^{-1} ; HRMS (ESI) calcd for C₂₄H₂₃N₃O₄Na⁺ (M+Na) 440.1586, found 440.1577.

Example 4

[0516] General Procedure for Synthesis of Epidithiodiketopiperazines.

5 [0517] Methyl *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(4-fluorophenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carboxylate:



[0518] To a suspension of elemental sulfur (32 mg, 1.0 mmol) in dry THF (5 mL) was added a solution of NaHMDS (0.25 mL, 2 M in THF) at room temperature. After 1 min, a solution of the diketopiperazine (70 mg, 0.2 mmol, in 2 mL THF) was added, followed by a second aliquot of NaHMDS (0.25 mL, 2 M in THF) within another 2 min. The resulting orange-brown solution was stirred for 30 min at rt, cooled to 0°C and quenched by addition of aqueous NH₄Cl. After extractive work-up (CH₂Cl₂/water) and evaporation of the solvent, a yellow residue was obtained. This residue was re-dissolved in a mixture of MeOH/THF (5 mL) to which NaBH₄ (350 mg, 1 mmol) was added portionwise at 0°C. After stirring for 30 min, this mixture was quenched with aqueous NH₄Cl, extracted (CH₂Cl₂/water) and the extract was dried over Na₂SO₄. After evaporation of the solvent, a yellow residue was obtained, which was subsequently dissolved in EtOAc (10 mL). A solution of KI₃ (0.5 M, 2 mL) in water was added and the biphasic system was stirred at rt for 15 min, after which time 3 mL of saturated aqueous Na₂S₂O₃ was added to give a pale yellow EtOAc layer. Aqueous extraction and evaporation of the organic phase gives a yellow oil, which was purified by preparative TLC (Et₂O/CH₂Cl₂) to give the title compound as a yellow oil.

[0519] ¹H-NMR (500 MHz, CDCl₃): δ /ppm 7.41 (2H, m), 7.03 (2H, t, *J* = 9.0 Hz), 5.09 (1H, s), 3.36 (3H, s), 3.34 (1H, d, *J* = 14.5 Hz), 3.25 (1H, d, *J* = 14.5 Hz), 3.11 (3H, s), 1.97 (3H, s), 1.55 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 171.8 9 (C), 166.2 (C), 163.1 (C), 162.6 (C, d, *J* = 250 Hz), 131.8 (C), 129.4 (2CH, d, *J* = 8 Hz), 115.5 (2CH, d, *J* = 22 Hz), 74.6 (C), 73.4 (C),

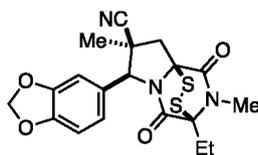
72.4 (CH), 55.1 (C), 52.3 (CH₃), 38.9 (CH₂), 27.8 (CH₃), 25.5 (CH₃), 18.4 (CH₃). IR (film): ν/cm^{-1} 2951, 1736, 1692, 1606, 1511, 1255, 1228, 1161, 1129, 848, 733. LR-MS: 432.85 (M+Na⁺); HR-MS (ESI) calculated for C₁₈H₁₉N₂O₄FS₂Na: 433.0668, found: 433.0660.

Example 5

5 [0520] Alternate Simplified General Procedure for Synthesis of Epidithiodiketopiperazines.

[0521] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-3-ethyl-2,7-dimethyl-1,4-dioxo-hexahydro-6H-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:

[0522] To a suspension of S₈ (83 mg, 0.32 mmol) in dry THF (3.4 mL) was added a solution of NaHMDS (1.7 mL, 0.93 mmol, 3.3 equiv, 2 M in THF) at room temperature over 40 sec. After 1 min, a solution of the diketopiperazine (100 mg, 0.28 mmol, in 2.6 mL THF) was added dropwise, followed by a second aliquot of NaHMDS (1.1 mL, 0.62 mmol, 2.2 equiv, 2 M in THF) within another 30-40 sec. The resulting orange-yellow solution was stirred for 50 min at rt and quenched by addition of saturated aqueous NH₄Cl. After extractive work-up (CH₂Cl₂/water) and evaporation of the solvent, a yellow-brown amorphous residue was obtained. This residue was evaporated onto 2.2 g SiO₂ and placed on top of a filter frit containing 12 g SiO₂. Washing of this SiO₂ plug with 150 mL of hexanes removes the majority of HMDS-related material. Subsequent washing with 150 mL of MeCN elutes the sulfidated products as a mixture of epidi- and epitrisulfide products (epidi:epitri usually ~9:1). These products were separated by preparative TLC (2-4% EtOAc/CH₂Cl₂). The desired epidisulfide product (R_f ~ 0.3) was isolated as an off-white solid (purity ~95%) after removal of the volatiles *in vacuo*.



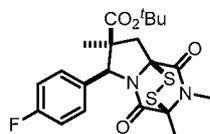
Chemical Formula: C₁₉H₁₉N₃O₄S₂
 Exact Mass: 417,0817
 Molecular Weight: 417,4980

[0523] ¹H-NMR (600 MHz, CDCl₃) δ 6.88 (s, 1H), 6.84 (app. s, 2H), 5.99 (app. m, 2H), 4.83 (s, 1H), 3.28 (d, *J* = 15.0 Hz, 1H), 3.10 (s, 3H), 3.01 (d, *J* = 15.0 Hz, 1H), 2.39 (m, 1H), 2.30 (m, 1H), 1.68 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C-NMR (126 MHz, CDCl₃) δ 166.6 (C), 161.0

(C), 148.6 (C), 148.3 (C), 127.5 (C), 120.8 (CH), 120.4 (C), 108.6 (CH), 107.3 (CH), 101.6 (CH₂), 78.0 (C), 73.5 (C), 72.6 (CH), 44.5 (C), 42.9 (CH₂), 28.8 (CH₃), 25.4 (CH₂), 24.9 (CH₃), 9.9 (CH₃) ppm; IR (film) ν/cm^{-1} 2917, 1685, 1558, 1506, 1491, 1357, 1249, 1001, 928 cm^{-1} ; HRMS (ESI) calcd for C₁₉H₁₉N₃O₄S₂Na⁺ (M+Na) 440.0715, found 440.0718.

5 [0524] At the end of the concentration process, MeOH (1-2 mL) and CH₂Cl₂ (1-2 mL) can be added and then again removed *in vacuo* to facilitate the formation of a colorless powder. In other cases, the epidi- and epitrisulfide products can be separated by column chromatography on silica gel using a mixture of CH₂Cl₂ and EtOAc as the eluent. Generally either of the two procedures described above can be used to prepare the epidithiodiketopiperazine products.

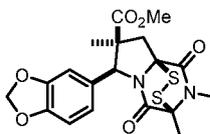
10 [0525] ***tert*-Butyl *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(4-fluorophenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carboxylate:**



Chemical Formula: C₂₁H₂₅FN₂O₄S₂
Exact Mass: 452.1240

[0526] ¹H-NMR (500 MHz, CDCl₃): δ /ppm 7.52-7.55 (2H, m), 7.09 (2H, t, J = 8.5 Hz), 5.04 (1H, s), 3.36 (1H, d, J = 14.5 Hz), 3.31 (1H, d, J = 14.5 Hz), 3.14 (3H, s), 1.99 (3H, s), 1.56 (3H, s), 1.17 (9H, s); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 170.4 (C), 166.3 (C), 163.0 (C), 161.7 (C, d, J = 247 Hz), 132.3 (C), 130.4 (2CH, d, J = 8 Hz), 115.5 (2CH, d, J = 22 Hz), 82.2 (C), 74.4 (C), 73.5 (C), 72.2 (CH), 55.0 (C), 39.4 (CH₂), 27.8 (CH₃), 27.5 (3CH₃), 26.6 (CH₃), 18.3 (CH₃). IR (film): ν/cm^{-1} 2977, 2935, 1693, 1511, 1367, 1310, 1229, 1132, 847. LR-MS: 475.1 (M+Na); HR-MS (ESI) calculated for C₂₁H₂₅N₂O₄FS₂Na: 475.1137, found: 475.1132.

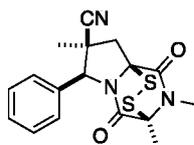
20 [0527] **Methyl *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carboxylate:**



Chemical Formula: C₁₉H₂₀N₂O₆S₂
Exact Mass: 436.0763

(1H, d, $J = 8.0$ Hz), 7.27-7.30 (1H, m), 5.10 (1H, s), 3.36 (3H, s), 3.25-3.34 (2H, m), 3.10 (3H, s), 1.96 (3H, s), 1.57 (3H, s); ^{13}C -NMR (125 MHz, CDCl_3): δ /ppm 171.4 (C), 166.2 (C), 163.1 (C), 149.8 (CH), 149.2 (CH), 135.1 (CH), 131.8 (C), 123.5 (CH), 74.6 (C), 73.4 (C), 70.5 (CH), 55.1 (C), 52.5 (CH₃), 39.1 (CH₂), 27.8 (CH₃), 25.5 (CH₃), 18.3 (CH₃). IR (film): ν/cm^{-1} 2927, 1735, 1690, 1354, 1309, 1261, 1129, 916. LR-MS: 416.1 ($\text{M}+\text{Na}^+$); HR-MS (ESI) calculated for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_4\text{S}_2\text{Na}$: 416.0715 ($\text{M}+\text{Na}^+$), found: 416.0715.

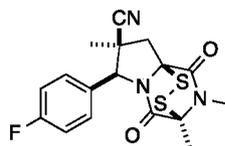
[0533] *Rac*-(3*S*,6*S*,7*S*,8*aS*,9*S*)-2,3,7-trimethyl-1,4-dioxo-6-phenylhexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{S}_2$
Exact Mass: 359.0762

10 **[0534]** ^1H -NMR (500 MHz, CDCl_3): δ /ppm 7.46-7.38 (5H, m), 4.91 (1H, s), 3.32 (1H, d, $J = 14.5$ Hz), 3.09 (3H, s), 3.00 (1H, d, $J = 14.9$ Hz), 1.94 (3H, s), 1.69 (3H, s); ^{13}C -NMR (125 MHz, CDCl_3): δ /ppm 165.7 (C), 162.2 (C), 133.8 (C), 129.6 (CH), 129.1 (2CH), 126.9 (2CH), 120.2 (C), 73.4 (C), 72.5 (CH), 44.5 (C), 43.0 (CH₂), 29.8 (C), 27.9 (CH₃), 24.9 (CH₃), 18.2 (CH₃); IR (film): ν/cm^{-1} 2917, 2849, 2361, 2341, 2241, 1705, 1680; LR-MS: 382.0 [$\text{M}+\text{Na}$]⁺;
15 HR-MS (ESI) calculated for $\text{C}_{17}\text{H}_{17}\text{N}_3\text{O}_2\text{S}_2\text{Na}$: 382.0660, found: 382.0671.

[0535] *Rac* (3*S*,6*S*,7*S*,8*aS*,9*S*)-6-(4-fluorophenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:

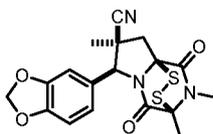


Chemical Formula: $\text{C}_{17}\text{H}_{16}\text{FN}_3\text{O}_2\text{S}_2$
Exact Mass: 377.0668

[0536] ^1H -NMR (500 MHz, CDCl_3): δ /ppm 7.37 (2H, dd, $J = 5.4, 8.4$ Hz), 7.13 (2H, t, $J = 8.7$ Hz), 4.89 (1H, s), 3.31 (1H, d, $J = 14.7$ Hz), 3.08 (3H, s), 2.99 (1H, d, $J = 15.0$ Hz), 1.94 (3H, s), 1.68 (3H, s); ^{13}C -NMR (125 MHz, CDCl_3): δ /ppm 165.6 (C), 163.4 (C, d, $J = 247$ Hz), 162.2

(C), 129.6 (C, d, $J = 3$ Hz), 128.8 (2CH, d, $J = 8$ Hz), 120.2 (C), 116.2 (2CH, d, $J = 22$ Hz), 73.52 (C), 73.46 (C), 71.9 (CH), 44.5 (C), 42.9 (CH₂), 27.9 (CH₃), 24.7 (CH₃), 18.2 (CH₃); IR (film): ν/cm^{-1} 2991, 2356, 2239, 1706, 1682, 1512; LR-MS: 400.0 [M+Na]⁺; HR-MS (ESI) calculated for C₁₇H₁₆FN₃O₂S₂: 400.0566, found: 400.0582.

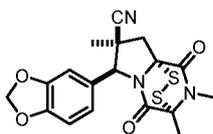
5 **[0537] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₈H₁₇N₃O₄S₂
Exact Mass: 403.0660

[0538] Major ETP stereoisomer. ¹H-NMR (500 MHz, CDCl₃): δ /ppm 6.96 (1H, s), 6.91 (2H, app. s), 6.06 (2H, s), 4.89 (1H, s), 3.36 (1H, d, $J = 14.5$ Hz), 3.14 (3H, s), 3.06 (1H, d, $J = 14.5$ Hz), 2.00 (3H, s), 1.73 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 165.6 (C), 162.1 (C), 148.6 (C), 148.3 (C), 127.5 (C), 120.7 (CH), 120.3 (C), 108.6 (CH), 107.2 (CH), 101.6 (CH₂), 73.4 (C), 73.3 (C), 72.4 (CH), 44.4 (C), 42.8 (CH₂), 27.8 (CH₃), 24.8 (CH₃), 18.1 (CH₃). IR (film): ν/cm^{-1} 2984, 2902, 2250, 1688, 1491, 1446, 1358, 1250, 1038, 731. LR-MS: 426.1 M+Na⁺; HR-MS (ESI) calculated for C₁₈H₁₇N₃O₄S₂Na: 426.0558, found: 426.0555. The constitution and relative
15 configuration of this product was confirmed by single-crystal X-ray analysis.

[0539] *Rac*-(3*R*,6*S*,7*S*,8*aR*)-6-(Benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:

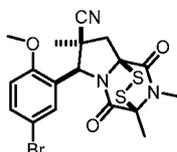


Chemical Formula: C₁₈H₁₇N₃O₄S₂
Exact Mass: 403.0660

[0540] Minor ETP stereoisomer. ¹H-NMR (500 MHz, CDCl₃): δ /ppm 6.80 (1H, d, $J = 8.0$ Hz), 6.60 (1H, d, $J = 8.0$ Hz), 6.55 (1H, s), 5.99 (2H, s), 5.03 (1H, s), 3.80 (1H, d, $J = 15.0$ Hz), 3.12 (3H, s), 2.51 (1H, d, $J = 15.0$ Hz), 1.99 (3H, s), 1.94 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 165.3 (C), 162.4 (C), 148.6 (C), 148.5 (C), 129.4 (C), 120.1 (CH), 119.6 (C), 108.9 (CH), 106.3 (CH), 101.6 (CH₂), 73.8 (C), 73.7 (C), 71.6 (CH), 43.8 (C), 42.3 (CH₂), 27.9 (CH₃), 27.2

(CH₃), 18.3 (CH₃). IR (film): ν/cm^{-1} 2988, 2940, 2900, 2249, 1694, 1504, 1448, 1355, 1248, 1111, 1038, 912, 731. LR-MS: 426.0 M+Na⁺; HR-MS (ESI) calculated for C₁₈H₁₇N₃O₄S₂Na: 426.0558, found: 426.0553.

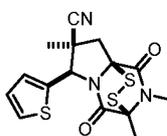
5 **[0541] *Rac*-(3*S*,6*R*,7*S*,8*aS*)-6-(5-Bromo-2-methoxyphenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₈H₁₈BrN₃O₃S₂
Exact Mass: 466.9973

10 **[0542]** ¹H-NMR (500 MHz, CDCl₃): δ /ppm 7.50 (1H, s), 7.45 (1H, dd, $J = 2.0, 8.5$ Hz), 6.83 (1H, d, $J = 8.5$ Hz), 5.49 (1H, s), 3.90 (3H, s), 3.45 (1H, d, $J = 14.5$ Hz), 3.10 (3H, s), 2.91 (1H, d, $J = 14.5$ Hz), 1.98 (3H, s), 1.65 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 165.7 (C), 162.7 (C), 155.8 (C), 133.2 (CH), 129.9 (CH), 120.0 (C), 113.4 (C), 112.5 (CH), 73.7 (C), 73.3 (C), 65.5 (CH), 55.6 (CH₃), 43.5 (C), 41.9 (CH₂), 27.9 (CH₃), 25.7 (CH₃), 18.3 (CH₃). IR (film): ν/cm^{-1} 2937, 2359, 1692, 1488, 1359, 1252, 729. LR-MS: 490.0 (M+Na); HR-MS (ESI) calculated for C₁₈H₁₈N₃O₃BrS₂Na: 489.9871, found: 489.9862.

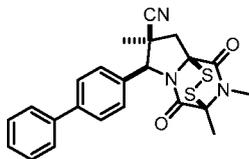
15 **[0543] *Rac*-(3*S*,6*R*,7*S*,8*aS*)-2,3,7-Trimethyl-1,4-dioxo-6-(thiophen-2-yl)hexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₅H₁₅N₃O₂S₃
Exact Mass: 365.0326

20 **[0544]** ¹H-NMR (500 MHz, CDCl₃): δ /ppm 7.36 (1H, d, $J = 4.5$ Hz), 7.30 (1H, br. s), 7.07 (1H, t, $J = 4.5$ Hz), 5.30 (1H, s), 3.43 (1H, d, $J = 14.5$ Hz), 3.00-3.15 (4H, m), 1.96 (3H, s), 1.66 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ /ppm 165.5 (C), 162.2 (C), 136.2 (C), 127.7 (CH), 127.6 (CH), 126.8 (CH), 119.6 (C), 73.4 (C), 72.9 (C), 67.3 (CH), 44.3 (C), 42.0 (CH₂), 27.9 (CH₃), 25.2 (CH₃), 18.2 (CH₃). IR (film): ν/cm^{-1} 2917, 2361, 1699, 1403, 1360, 1251, 1068, 848. LR-MS: 388.1 (M+Na⁺); HR-MS (ESI) calculated for C₁₅H₁₅N₃O₂S₃Na: 388.0224, found: 388.0221.

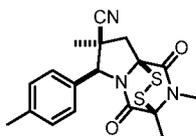
[0545] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-([1,1'-Biphenyl]-4-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: C₂₃H₂₁N₃O₂S₂
Exact Mass: 435.1075

[0546] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.72 (2H, d, *J* = 8.5 Hz), 7.66 (2H, d, *J* = 8.5 Hz),
5 7.45-7.53 (4H, m), 7.41 (1H, t, *J* = 7.5 Hz), 5.02 (1H, s), 3.41 (1H, d, *J* = 15.0 Hz), 3.16 (3H, s),
3.09 (1H, d, *J* = 15.0 Hz), 2.02 (3H, s), 1.78 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.6
(C), 162.2 (C), 142.3 (C), 140.4 (C), 132.6 (C), 128.8 (2CH), 127.7 (2CH), 127.6 (2CH), 127.2
(CH+2CH), 120.2 (C), 73.5 (C), 73.4 (C), 72.2 (CH), 44.4 (C), 42.9 (CH₂), 27.8 (CH₃), 24.8
(CH₃), 18.1 (CH₃). IR (film): ν/cm⁻¹ 2935, 2250, 1689, 1488, 1448, 1414, 1358, 1252, 910. LR-
10 MS: 458.2 (M+Na⁺); HR-MS (ESI) calculated for C₂₃H₂₁N₃O₂S₂Na: 458.0973, found: 458.0972.

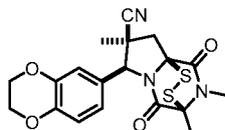
[0547] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-2,3,7-Trimethyl-1,4-dioxo-6-(*p*-tolyl)hexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₉N₃O₂S₂
Exact Mass: 373.0919

[0548] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.28-7.35 (4H, m), 4.94 (1H, s), 3.37 (1H, d, *J* =
15 15.0 Hz), 3.14 (3H, s), 3.06 (1H, d, *J* = 15.0 Hz), 2.43 (3H, s), 2.00 (3H, s), 1.74 (3H, s), ; ¹³C-
NMR (125 MHz, CDCl₃): δ/ppm 165.7 (C), 162.1 (C), 139.3 (C), 130.7 (C), 129.7 (2CH), 126.7
(2CH), 120.3 (C), 73.5 (C), 73.3 (C), 72.4 (CH), 44.5 (C), 42.9 (CH₂), 27.8 (CH₃), 24.7 (CH₃),
21.4 (CH₃), 18.1 (CH₃). IR (film): ν/cm⁻¹ 2990, 2921, 2245, 1685, 1516, 1358, 1253, 816. LR-
MS: 396.2 (M+Na⁺); HR-MS (ESI) calculated for C₁₈H₁₉N₃O₂S₂Na: 396.0816, found: 396.0800.
20 The constitution and relative configuration of this product was confirmed by single-crystal X-ray
analysis.

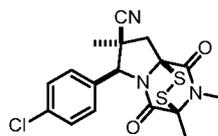
[0549] ***Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₉H₁₉N₃O₄S₂
Exact Mass: 417.0817

[0550] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.90-7.00 (3H, m), 4.88 (1H, s), 4.32 (4H, m),
5 3.36 (1H, d, *J* = 14.5 Hz), 3.14 (3H, s), 3.05 (1H, d, *J* = 14.5 Hz), 2.00 (3H, s), 1.72 (3H, s); ¹³C-
NMR (125 MHz, CDCl₃): δ/ppm 165.7 (C), 162.2 (C), 144.4 (C), 143.7 (C), 126.9 (C), 120.2
(C), 119.9 (CH), 117.9 (CH), 115.9 (CH), 73.4 (C), 73.3 (C), 72.0 (CH), 64.3 (2CH₂), 44.4 (C),
42.7 (CH₂), 27.8 (CH₃), 24.9 (CH₃), 18.1 (CH₃). IR (film): ν/cm⁻¹ 2984, 2938, 2251, 1690, 1592,
1509, 1360, 1288, 1260, 1067, 912. LR-MS: 439.9 (M+Na⁺); HR-MS (ESI) calculated for
10 C₁₉H₁₉N₃O₄S₂Na: 440.0715, found: 440.0728.

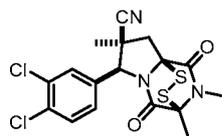
[0551] ***Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(4-Chlorophenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: C₁₇H₁₆ClN₃O₂S₂
Exact Mass: 393.0372

[0552] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.42 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 8.5 Hz),
15 4.87 (1H, s), 3.32 (1H, d, *J* = 15.0 Hz), 3.08 (3H, s), 2.99 (1H, d, *J* = 15.0 Hz), 1.94 (3H, s), 1.68
(3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.5 (C), 162.1 (C), 135.5 (C), 132.2 (C), 129.3
(2CH), 128.2 (2CH), 120.0 (C), 73.5 (C), 73.4 (C), 71.8 (CH), 44.3 (C), 42.9 (CH₂), 27.8 (CH₃),
24.7 (CH₃), 18.1 (CH₃). IR (film): ν/cm⁻¹ 2992, 2941, 2246, 1690, 1493, 1359, 1255, 1090, 825.
LR-MS: 416.2 (M+Na⁺); HR-MS (ESI) calculated for C₁₇H₁₆N₃O₂ClS₂Na: 416.0270, found:
20 416.0261.

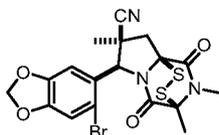
[0553] ***Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(3,4-Dichlorophenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:**



Chemical Formula: $C_{17}H_{15}Cl_2N_3O_2S_2$
Exact Mass: 426.9983

[0554] 1H -NMR (500 MHz, $CDCl_3$): δ /ppm 7.53 (1H, d, $J = 8.0$ Hz), 7.46 (1H, s), 7.25 (1H, d, $J = 8.0$ Hz), 4.85 (1H, s), 3.33 (1H, d, $J = 15.0$ Hz), 3.09 (3H, s), 3.00 (1H, d, $J = 15.0$ Hz), 1.95 (3H, s), 1.70 (3H, s); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 165.4 (C), 162.0 (C), 133.9 (2C), 133.2 (C), 131.2 (CH), 129.0 (CH), 126.2 (CH), 119.8 (C), 73.4 (2C), 71.2 (CH), 44.2 (C), 42.9 (CH₂), 27.9 (CH₃), 24.8 (CH₃), 18.1 (CH₃). IR (film): ν/cm^{-1} 2936, 2250, 1696, 1472, 1359, 1252, 1136, 1031, 912, 730. LR-MS: 449.9 (M+Na⁺); HR-MS (ESI) calculated for $C_{17}H_{15}N_3O_2Cl_2S_2Na$: 449.9880, found: 449.9853.

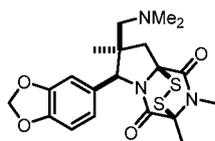
[0555] *Rac*-(3*S*,6*R*,7*S*,8*aS*)-6-(6-Bromobenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: $C_{18}H_{16}BrN_3O_4S_2$
Exact Mass: 480.9766

[0556] 1H -NMR (500 MHz, $CDCl_3$): δ /ppm 7.07 (1H, s), 7.05 (1H, s), 6.02 (2H, s), 5.22 (1H, s), 3.41 (1H, d, $J = 15.0$ Hz), 3.08 (3H, s), 2.98 (1H, d, $J = 15.0$ Hz), 1.95 (3H, s), 1.75 (3H, s); ^{13}C -NMR (125 MHz, $CDCl_3$): δ /ppm 165.5 (C), 162.2 (C), 149.1 (C), 148.3 (C), 126.8 (C), 120.0 (C), 114.4 (C), 113.2 (CH), 108.0 (CH), 102.3 (CH₂), 73.6 (C), 73.3 (C), 71.0 (CH), 44.2 (C), 42.8 (CH₂), 27.8 (CH₃), 25.5 (CH₃), 18.1 (CH₃). IR (film): ν/cm^{-1} 3043, 2986, 2913, 2243, 1694, 1504, 1480, 1355, 1242, 1118, 1037, 931, 734. LR-MS: 504.1 (M+Na⁺); HR-MS (ESI) calculated for $C_{18}H_{16}N_3O_4BrS_2Na$: 503.9663, found: 503.9647.

[0557] *Rac*-(3*S*,6*S*,7*R*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-7-((dimethylamino)methyl)-2,3,7-trimethyl-tetrahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-1,4-dione:

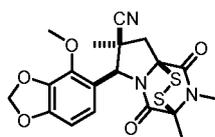


Chemical Formula: C₂₀H₂₅N₃O₄S₂
Exact Mass: 435.1286

[0558] Prepared from *rac*-(3*R*,6*S*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxo-octahydropyrrolo[1,2-*a*]-pyrazine-7-carbonitrile by conventional NiCl₂/NaBH₄ reduction of the nitrile, Eschweiler-Clarke dimethylation of the resulting primary amine and sulfidation.

5 **[0559]** ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.91 (1H, s), 6.76-6.83 (2H, m), 5.97 (2H, s), 4.77 (1H, s), 3.18 (1H, d, *J* = 14.5 Hz), 3.07 (3H, s), 2.55 (1H, d, *J* = 14.5 Hz), 2.15 (6H, s), 1.97 (2H, s), 1.94 (3H, s), 1.27 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 166.6 (C), 163.1 (C), 148.0 (C), 147.3 (C), 130.0 (C), 121.3 (CH), 108.4 (CH), 108.1 (CH), 101.3 (CH₂), 74.9 (C), 74.2 (CH), 73.5 (C), 66.1 (CH₂), 8.2 (2CH₃), 47.8 (C), 41.8 (CH₂), 27.7 (CH₃), 26.5 (CH₃), 18.4 (CH₃). IR (film): ν/cm⁻¹ 2940, 2821, 2770, 1690, 1490, 1445, 1379, 1353, 1249, 1104, 1038, 932, 734. LR-MS: 458.2 (M+Na⁺); HR-MS (ESI) calculated for C₂₀H₂₅N₃O₄S₂Na: 458.1184, found: 458.1185.

[0560] *Rac*-(3*S*,6*R*,7*S*,8*aS*)-6-(4-Methoxybenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:

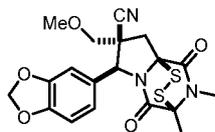


Chemical Formula: C₁₉H₁₉N₃O₅S₂
Molecular Weight: 433.4970

15 **[0561]** ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.52-6.62 (2H, m), 6.01 (2H, s), 4.84 (1H, s), 3.89 (3H, s), 3.31 (1H, d, *J* = 15.0 Hz), 3.09 (3H, s), 3.01 (1H, d, *J* = 15.0 Hz), 1.96 (3H, s), 1.68 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.5 (C), 162.0 (C), 149.2 (C), 143.8 (C), 136.0 (C), 128.1 (C), 120.2 (C), 106.1 (CH), 102.1 (CH₂), 101.2 (CH), 73.6 (C), 73.5 (C), 72.4 (CH), 56.6 (CH₃), 44.5 (C), 42.7 (CH₂), 27.9 (CH₃), 25.1 (CH₃), 18.2 (CH₃). IR (film): ν/cm⁻¹ 2940, 2902, 2241, 1696, 1636, 1513, 1453, 1358, 1250, 1201, 1130, 1093, 1044, 874, 734. LR-MS: 456.0 M+Na⁺; HR-MS (ESI) calculated for C₁₉H₁₉N₃O₅S₂Na: 456.0664, found: 456.0653.

20

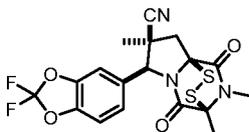
[0562] *Rac*-(3*S*,6*S*,7*R*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-7-(methoxymethyl)-2,3-dimethyl-1,4-dioxohexa-hydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: C₁₉H₁₉N₃O₅S₂
Molecular Weight: 433.4970

[0563] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.91 (1H, s), 6.80-6.88 (2H, m), 5.99 (2H, s), 5.26 (1H, s), 3.61 (1H, d, *J* = 9.5 Hz), 3.58 (1H, d, *J* = 15.0 Hz), 3.54 (1H, d, *J* = 9.5 Hz), 3.47 (3H, s), 3.08 (3H, s), 2.88 (1H, d, *J* = 15.0 Hz), 1.94 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.5 (C), 162.0 (C), 148.4 (C), 148.3 (C), 128.0 (C), 120.9 (CH), 118.4 (C), 108.7 (CH), 107.4 (CH), 101.5 (CH₂), 73.8 (C), 73.5 (C), 73.0 (CH₂), 67.2 (CH), 59.7 (CH₃), 49.6 (C), 38.5 (CH₂), 27.8 (CH₃), 18.1 (CH₃). IR (film): ν/cm⁻¹ 2993, 2928, 2898, 2250, 1693, 1497, 1491, 1447, 1358, 1250, 1118, 1038, 914, 731. LR-MS: 456.0 M+Na⁺; HR-MS (ESI) calculated for C₁₉H₁₉N₃O₅S₂Na: 456.0664, found: 456.0650.

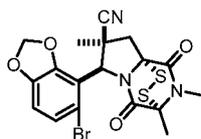
[0564] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(2,2-Difluorobenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₅F₂N₃O₄S₂
Molecular Weight: 439.4518

[0565] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.09-7.15 (3H, m), 4.89 (1H, s), 3.33 (1H, d, *J* = 14.5 Hz), 3.08 (3H, s), 3.00 (1H, d, *J* = 14.5 Hz), 1.95 (3H, s), 1.69 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.4 (C), 162.1 (C), 144.4 (C), 144.2 (C), 131.7 (C, t, *J* = 255 Hz), 130.0 (C), 122.6 (CH), 119.9 (C), 109.8 (CH), 108.3 (CH), 77.3 (C), 73.4 (C), 72.0 (CH), 44.4 (C), 42.9 (CH₂), 27.9 (CH₃), 24.8 (CH₃), 18.1 (CH₃). IR (film): ν/cm⁻¹ 2986, 2942, 2253, 1697, 1501, 1450, 1358, 1240, 1154, 1034, 903, 731. LR-MS: 462.0 M+Na⁺; HR-MS (ESI) calculated for C₁₈H₁₅N₃O₄F₂S₂Na: 462.0370, found: 462.0377.

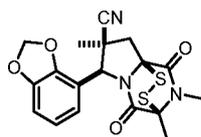
[0566] *Rac*-(3*R*,6*R*,7*S*,8*aR*)-6-(5-Bromobenzo[d][1,3]dioxol-4-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₆BrN₃O₄S₂
Molecular Weight: 482.3670

[0567] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 7.13 (1H, d, *J* = 8.5 Hz), 6.69 (1H, d, *J* = 8.5 Hz), 5.90 (1H, s), 5.80 (1H, s), 5.65 (1H, s), 3.88 (1H, d, *J* = 15.5 Hz), 3.06 (3H, s), 2.57 (1H, d, *J* = 15.5 Hz), 2.12 (3H, s), 1.95 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.5 (C), 161.6 (C), 147.6 (C), 145.1 (C), 126.4 (CH), 119.6 (C), 117.7 (C), 114.9 (C), 110.5 (CH), 102.1 (CH₂), 74.6 (C), 73.7 (C), 68.5 (CH), 44.3 (CH₂), 43.1 (C), 27.6 (CH₃), 27.5 (CH₃), 18.3 (CH₃). IR (film): ν/cm⁻¹ 2986, 2880, 2250, 1695, 1457, 1357, 1242, 1059, 1035, 932, 731. LR-MS: 503.9 M+Na⁺; HR-MS (ESI) calculated for C₁₈H₁₆N₃O₄S₂BrNa: 503.9663, found: 503.9655. The constitution and relative configuration of this product was confirmed by single-crystal X-ray analysis.

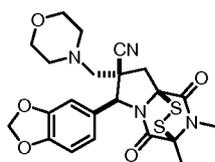
10 [0568] *Rac*-(3*S*,6*R*,7*S*,8*aS*)-6-(Benzo[d][1,3]dioxol-4-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₁₈H₁₇N₃O₄S₂
Molecular Weight: 403.4710

[0569] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.80-6.96 (3H, m), 6.02 (1H, s), 6.00 (1H, s), 5.22 (1H, s), 3.35 (1H, d, *J* = 15.0 Hz), 3.08 (3H, s), 2.98 (1H, d, *J* = 15.0 Hz), 1.95 (3H, s), 1.70 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.6 (C), 162.2 (C), 147.6 (C), 145.2 (C), 122.3 (CH), 120.1 (C), 119.5 (CH), 115.7 (C), 109.5 (CH), 101.3 (CH₂), 73.6 (C), 73.3 (C), 66.2 (CH), 44.1 (C), 42.7 (CH₂), 27.8 (CH₃), 25.1 (CH₃), 18.2 (CH₃). IR (film): ν/cm⁻¹ 2991, 2905, 2241, 1697, 1462, 1357, 1249, 1063, 1029, 931, 731. LR-MS: 426.0 M+Na⁺; HR-MS (ESI) calculated for C₁₈H₁₇N₃O₄S₂Na: 426.0558, found: 426.0552. The constitution and relative configuration of this product was confirmed by single-crystal X-ray analysis.

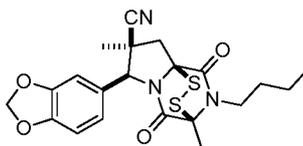
20 [0570] *Rac*-(3*S*,6*S*,7*R*,8*aS*)-6-(Benzo[d][1,3]dioxol-5-yl)-2,3-dimethyl-7-(morpholinomethyl)-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₂₂H₂₄N₄O₅S₂
Molecular Weight: 488.5770

[0571] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.96 (1H, s), 6.91 (1H, d, J = 8.0 Hz), 6.84 (1H, d, J = 7.0 Hz), 5.99 (2H, s), 5.17 (1H, s), 3.65-3.74 (4H, m), 3.56 (1H, d, J = 14.5 Hz), 3.04 (3H, s), 2.92 (1H, d, J = 14.5 Hz), 2.70-2.80 (2H, m), 2.60-2.75 (4H, m), 1.94 (3H, s); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.6 (C), 162.2 (C), 148.4 (C), 148.3 (C), 128.2 (C), 121.1 (CH), 119.7 (C), 108.7 (CH), 107.6 (CH), 101.5 (CH₂), 73.7 (C), 73.5 (C), 68.7 (CH), 67.1 (2CH₂), 63.4 (CH₂), 55.3 (2CH₂), 49.6 (C), 39.5 (CH₂), 27.9 (CH₃), 18.2 (CH₃). IR (film): ν/cm⁻¹ 2958, 2855, 2816, 2248, 1688, 1491, 1447, 1356, 1260, 1116, 1037, 914, 864, 730. LR-MS: 511.1 M+Na⁺; HR-MS (ESI) calculated for C₂₂H₂₄N₄O₅S₂Na: 511.1086, found: 511.1068.

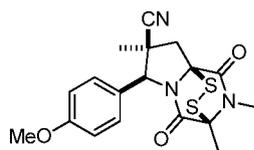
10 [0572] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-2-butyl-3,7-dimethyl-1,4-dioxohexahydro-1*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



[0573] ¹H-NMR (500 MHz, CDCl₃): δ/ppm 6.88 (1H, s), 6.82 (2H, app. s), 5.99 (2H, s), 4.81 (1H, s), 3.78, (1H, m), 3.30 (1H, d, J = 14.5 Hz), 2.99 (1H, d, J = 14.5 Hz), 1.98 (3H, s), 1.66 (3H, s), 1.62 (2H, m), 1.38 (2H, m), 0.96 (3H, t, J = 7.2 Hz); ¹³C-NMR (125 MHz, CDCl₃): δ/ppm 165.2 (C), 162.4 (C), 148.7 (C), 148.4 (C), 127.7 (C), 120.8 (CH), 120.5 (C), 108.7 (CH), 107.4 (CH), 101.7 (CH₂), 73.8 (C), 73.0 (C), 72.5 (CH), 44.6 (C), 43.3 (CH₂), 43.0 (CH₂), 29.9 (CH₂), 25.0 (CH₃), 24.8 (CH₂), 20.4 (CH₂), 17.8 (CH₃), 14.0 (CH₃). IR (film): ν/cm⁻¹ 2984, 2902, 2250, 1688, 1491, 1446, 1358, 1250, 1038, 731. HR-MS (ESI) calculated for

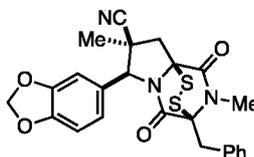
20 C₂₁H₂₃N₃O₄S₂Na: 468.1022, found: 468.1018.

[0574] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(4-methoxyphenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-1*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



[0575] $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ /ppm 7.30 (2H, d, $J = 8.5$ Hz), 6.96 (2H, d, $J = 8.5$ Hz), 4.85 (1H, s), 3.79 (3H, s), 3.28 (1H, d, $J = 15.0$ Hz), 3.08 (3H, s), 2.99 (1H, d, $J = 15.0$ Hz), 1.94 (3H, s), 1.66 (3H, s); $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): δ /ppm 165.0 (C), 162.3 (C), 159.9 (C), 128.7 (C), 127.3 (2CH), 117.8 (C), 114.7 (2CH), 73.6 (C), 73.4 (C), 72.0 (CH), 55.2 (CH₃), 44.2 (C), 42.7 (CH₂), 27.7 (CH₃), 24.8 (CH₃), 18.0 (CH₃). IR (film): ν/cm^{-1} 2988, 2940, 2246, 1690, 1493, 1359, 1255, 1093, 756. HR-MS (ESI) calculated for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{S}_2\text{Na}$: 412.0760, found: 412.0753.

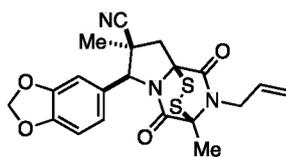
[0576] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-3-benzyl-2,7-dimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_4\text{S}_2$
Exact Mass: 479,0973
Molecular Weight: 479,5690

[0577] $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ 7.33-7.31 (m, 2H), 7.29-7.24 (m, 3H), 6.86 (s, 1H), 6.82-6.81 (m, 2H), 5.99-5.98 (m, 2H), 4.90 (s, 1H), 3.82 (d, $J = 15.3$ Hz, 1H), 3.75 (d, $J = 15.3$ Hz, 1H), 3.32 (d, $J = 14.9$ Hz, 1H), 3.07 (s, 3H), 3.02 (d, $J = 14.9$ Hz, 1H), 1.70 (s, 3H) ppm; $^{13}\text{C-NMR}$ (126 MHz, CDCl_3) δ 166.4 (C), 161.4 (C), 148.6 (C), 148.3 (C), 133.6 (C), 129.9 (CH), 128.7 (CH), 127.8 (CH), 127.4 (C), 120.8 (CH), 120.3 (C), 108.7 (CH), 107.4 (CH), 101.6 (CH₂), 77.8 (C), 73.5 (C), 72.7 (CH), 44.5 (C), 42.9 (CH₂), 36.6 (CH₂), 29.4 (CH₃), 25.0 (CH₃) ppm; IR (film) ν/cm^{-1} 2917, 1695, 1491, 1447, 1357, 1249, 1190, 1037, 931, 817 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_4\text{S}_2\text{Na}^+$ ($\text{M}+\text{Na}$) 502.0871, found 502.0867.

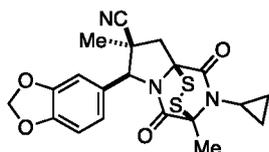
[0578] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-2-allyl-6-(benzo[d][1,3]dioxol-5-yl)-3,7-dimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₂₀H₁₉N₃O₄S₂
 Exact Mass: 429,0817
 Molecular Weight: 429,5090

[0579] ¹H-NMR (500 MHz, CDCl₃) δ 6.88 (s, 1H), 6.84 (app. s, 2H), 5.99 (s, 2H), 5.89-5.82 (m, 1H), 5.28 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 4.83 (s, 1H), 4.41-4.37 (m, 1H), 4.02 (dd, *J* = 16.2, 5.6 Hz 1H), 3.30 (d, *J* = 14.9 Hz, 1H), 3.01 (d, *J* = 14.9 Hz, 1H), 1.98 (s, 3H),
 5 1.66 (s, 3H) ppm; ¹³C-NMR (126 MHz, CDCl₃) δ 165.1 (C), 162.2 (C), 148.6 (C), 148.3 (C), 131.5 (CH), 127.6 (C), 120.7 (CH), 120.4 (C), 118.4 (CH₂), 108.6 (CH), 107.2 (CH), 101.6 (CH₂), 73.6 (C), 73.1 (C), 72.4 (CH), 45.2 (CH₂), 44.5 (C), 42.9 (CH₂), 24.8 (CH₃), 17.5 (CH₃) ppm; IR (film) v/cm⁻¹ 1688, 1491, 1446, 1359, 1249, 1191, 1103, 1038, 929 cm⁻¹; HRMS (ESI) calcd for C₂₀H₁₉N₃O₄S₂Na⁺ (M+Na) 452.0715, found 452.0719.

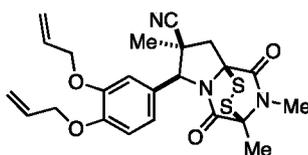
10 [0580] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(benzo[d][1,3]dioxol-5-yl)-2-cyclopropyl-3,7-dimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: C₂₀H₁₉N₃O₄S₂
 Exact Mass: 429,0817
 Molecular Weight: 429,5090

[0581] ¹H-NMR (500 MHz, CDCl₃) δ 6.87 (s, 1H), 6.84-6.81 (app. s, 2H), 5.99 (s, 2H), 4.80 (s, 1H), 3.27 (d, *J* = 14.9 Hz, 1H), 2.93 (d, *J* = 14.9 Hz, 1H), 2.57-2.53 (m, 1H), 2.12 (s, 3H),
 15 1.66 (s, 3H), 1.29-1.24 (m, 1H), 1.06-0.97 (m, 2H), 0.96-0.90 (m, 1H) ppm; ¹³C-NMR (126 MHz, CDCl₃) δ 165.7 (C), 162.3 (C), 148.6 (C), 148.3 (C), 127.6 (C), 120.7 (CH), 120.4 (C), 108.6 (CH), 107.2 (CH), 101.6 (CH₂), 74.4 (C), 74.1 (C), 72.4 (CH), 44.5 (C), 42.9 (CH₂), 25.8 (CH), 24.8 (CH₃), 17.8 (CH₃), 8.2 (CH₂), 7.7 (CH₂) ppm; IR (film) v/cm⁻¹ 1696, 1491, 1446, 1348, 1248, 1189, 1037, 930, 735 cm⁻¹; HRMS (ESI) calcd for C₂₀H₁₉N₃O₄S₂Na⁺ (M+Na)
 20 452.0715, found 452.0702.

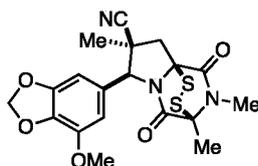
[0582] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(3,4-bis(allyloxy)phenyl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitrile:



Chemical Formula: $C_{23}H_{25}N_3O_4S_2$
 Exact Mass: 471,1286
 Molecular Weight: 471,5900

[0583] 1H -NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.92-6.88 (m, 2H), 6.11-6.03 (m, 2H), 5.45-5.38 (m, 2H), 5.29-5.24 (m, 2H), 4.87 (s, 1H), 4.63-4.60 (m, 4H), 3.31 (d, $J = 14.8$ Hz, 1H), 3.08 (s, 3H), 2.98 (d, $J = 14.8$ Hz, 1H), 1.95 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C -NMR (126 MHz, $CDCl_3$) δ 165.6 (C), 162.2 (C), 149.3 (C), 148.8 (C), 133.4 (CH), 133.3 (CH), 126.5 (C), 120.3 (CH), 119.8, 117.9 (CH₂), 117.8 (CH₂), 113.7 (CH), 112.2 (CH), 73.8 (C), 73.6 (C), 72.4 (C), 70.0 (CH₂), 69.9 (CH₂), 44.5 (C), 42.8 (CH₂), 27.9 (CH₃), 25.1 (CH₃), 18.3 (CH₃) ppm; IR (film) ν/cm^{-1} 1695, 1607, 1593, 1516, 1424, 1380, 1360, 1262, 1218, 1141, 996, 919, 731 cm^{-1} ; HRMS (ESI) calcd for $C_{23}H_{25}N_3O_4S_2Na^+$ (M+Na) 494.1184, found 494.1188.

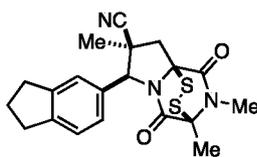
[0584] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(7-methoxybenzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexa-hydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: $C_{19}H_{19}N_3O_5S_2$
 Exact Mass: 433,0766
 Molecular Weight: 433,4970

[0585] 1H -NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.58 (s, 1H), 6.00 (m, 2H), 4.84 (s, 1H), 3.89 (s, 3H), 3.31 (d, $J = 14.8$ Hz, 1H), 3.08 (s, 3H), 2.99 (d, $J = 14.8$ Hz, 1H), 1.95 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C -NMR (126 MHz, $CDCl_3$) δ 165.5 (C), 162.1 (C), 149.3 (C), 143.9 (C), 136.1 (C), 128.2 (C), 120.2 (C), 106.5 (CH), 102.0 (CH₂), 101.3 (CH), 73.7 (C), 73.6 (C), 72.5 (CH₂), 56.7 (CH₃), 44.5 (C), 42.8 (CH₂), 27.9 (CH₃), 25.2 (CH₃), 18.2 (CH₃) ppm; IR (film) ν/cm^{-1} 2984, 2250, 1696, 1637, 1512, 1453, 1358, 1246, 1201, 1129, 1093, 1044, 913, 731 cm^{-1} ; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_5S_2Na^+$ (M+Na) 456.0664, found 456.0648.

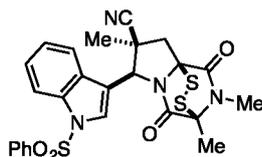
[0586] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-6-(2,3-dihydro-1H-inden-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



Chemical Formula: $C_{20}H_{21}N_3O_2S_2$
 Exact Mass: 399,1075
 Molecular Weight: 399,5270

[0587] 1H -NMR (500 MHz, $CDCl_3$) δ 7.26 (d, $J = 7.2$ Hz, 1H), 7.20 (s, 1H), 7.15 (d, $J = 7.2$ Hz, 1H), 4.87 (s, 1H), 3.30 (d, $J = 14.9$ Hz, 1H), 3.07 (s, 3H), 3.00 (d, $J = 14.9$ Hz, 1H), 2.94-2.89 (m, 4H), 2.08 (app. quintet, $J = 7.5$ Hz, 2H), 1.93 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C -NMR (126 MHz, $CDCl_3$) δ 165.8 (C), 162.2 (C), 145.8 (C), 145.0 (C), 131.5 (C), 124.9 (CH), 124.8 (CH), 122.9 (CH), 120.5 (C), 73.6 (C), 73.4 (C), 72.8 (CH), 44.6 (C), 43.0 (CH_2), 33.0 (CH_2), 32.8 (CH_2), 27.9 (CH_3), 25.4 (CH_2), 24.8 (CH_3), 18.2 (CH_3) ppm; IR (film) ν/cm^{-1} 2941, 2251, 1696, 1440, 1359, 1254, 1202, 1145, 1112, 1067, 1030, 911, 731 cm^{-1} ; HRMS (ESI) calcd for $C_{20}H_{21}N_3O_2S_2Na^+$ (M+Na) 422.0973, found 422.0965.

10 [0588] *Rac*-(3*S*,6*S*,7*S*,8*aS*)-2,3,7-trimethyl-1,4-dioxo-6-(1-(phenylsulfonyl)-1H-indol-3-yl)hexahydro-6H-3,8a-epidithiopyrrolo[1,2-a]pyrazine-7-carbonitrile:



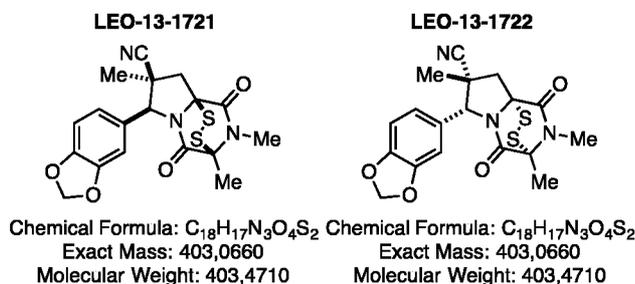
Chemical Formula: $C_{25}H_{22}N_4O_4S_3$
 Exact Mass: 538,0803
 Molecular Weight: 538,6550

[0589] 1H -NMR (500 MHz, $CDCl_3$) δ 7.96 (d, $J = 8.4$ Hz, 1H), 7.86-7.84 (m, 3H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 7.42 (t, $J = 7.8$ Hz, 2H), 7.34 (t, $J = 7.7$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 1H), 5.29 (s, 1H), 3.43 (d, $J = 14.7$ Hz, 1H), 3.10 (s, 3H), 3.05 (d, $J = 14.7$ Hz, 1H), 1.96 (s, 3H), 1.70 (s, 3H) ppm; ^{13}C -NMR (126 MHz, $CDCl_3$) δ 165.5 (C), 162.0 (C), 137.8 (C), 135.3 (C), 134.2 (CH), 129.4 (CH), 128.9 (C), 127.1 (CH), 125.8 (CH), 125.5 (CH), 123.8 (CH), 120.1 (C), 119.5 (CH), 116.6 (C), 114.1 (CH), 73.6 (C), 73.3 (C), 64.2 (CH), 43.8 (C), 42.8 (CH_2), 28.0 (CH_3), 25.2 (CH_3), 18.3 (CH_3) ppm; IR (film) ν/cm^{-1} 2360, 1696, 1447, 1361, 1214, 1176, 1120, 1095, 974, 747, 725, 684 cm^{-1} ; HRMS (ESI) calcd for $C_{25}H_{22}N_4O_4S_3Na^+$ (M+Na) 561.0701, found 561.0703.

Example 6

[0590] Separation of Enantiomers of ETP Products.

[0591] Isolation of (3*S*,6*S*,7*S*,8*aS*)- and (3*R*,6*R*,7*R*,8*aR*)-6-(benzo[d][1,3]dioxol-5-yl)-2,3,7-trimethyl-1,4-dioxohexahydro-6*H*-3,8*a*-epidithiopyrrolo[1,2-*a*]pyrazine-7-carbonitriles



5

[0592] The two enantiomers were separated by preparative chiral HPLC (stationary phase: CHIRALPAK IA (250 x 50 mm i.d., 5 micron), mobile phase: reagent alcohol 100%), flow rate 2.5 mL/min). The enantiomeric excess was determined by means of analytical chiral HPLC (stationary phase CHIRALPAK IA-3 (50 x 4.6 mm i.d., 3 micron), mobile phase: reagent alcohol 100%, flow rate 1 mL/min, 254 nm): (3*S*,6*S*,7*S*,8*aS*)-enantiomer: $t_{\text{ret}} = 1.40$ min; (3*R*,6*R*,7*R*,8*aR*)-enantiomer: $t_{\text{ret}} = 2.11$ min.

[0593] Absolute configuration was assigned on the basis of CD data (Figure 36) and existing precedent [Carmack, M.; Neubert, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 7134–7136. Hauser, D.; Weber, H. P.; Sigg, H. P. *Helv. Chim. Acta* **1970**, *53*, 1061–1073. Minato, H.; Matsumoto, M.; Katayama, T. *J. Chem. Soc. D.* **1971**, 44–45. Nagarajan, R.; Woody, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 7212–7222. Woody, R. W. *Tetrahedron* **1973**, *29*, 1273–1283].

Example 7

[0594] **Cell culture:** HT1080, 293T cells and the pancreatic cancer cell lines Panc1, BxPC3, SU.86.86 were obtained from ATCC (Manassas, VA). Panc1, HT1080 and 293T cells were maintained in DMEM medium (Mediatech, Manassas, VA) supplemented with 10% heat inactivated FBS (Gemini Bio-products, West Sacramento, CA). BxPC3 and SU.86.86 cells were maintained in RPMI-1640 medium (Mediatech) supplemented with 10% heat inactivated FBS.

20

[0595] **MTS assay:** Panc1, BxPC3, or SU.86.86 cells were seeded in a 96-well plate at a density of 7500 cells/well prior to treatment with increasing amounts of ETP69 or DMSO vehicle control. Forty-eight hours post treatment cells were incubated with the MTS substrate (CellTiter 96 AQueous One Solution Cell Proliferation Assay, Promega, Madison, WI) according to the manufacturer's instructions. The absorbance was measured at 490 nm using a 96-well plate reader (Synergy 4, Biotek), and the data were normalized to the absorbance of DMSO-treated cells. IC₅₀ values were determined using GraphPad Prism's non-linear regression function. See Figures 11, 21-25.

[0596] **Lentiviral vector production:** 293T cells were plated at a density of 4×10^6 cells per 10-cm culture dish. Cells were co-transfected by calcium phosphate co-precipitation with either 20 μ l of pPACK packaging plasmid mix (SBI, Mountain View, CA) and 15 μ g of pLKO.1-SUV39H1 shRNA (TRCN0000275322, Sigma St. Louis, MO) or pLKO.1-non-silencing shRNA (Sigma). The culture medium was replaced with fresh medium after 6 h. Supernatant was collected 24 h and 48 h after transfection. To determine the viral titers, 10^5 HT1080 cells were seeded in a six-well plate and transduced with various dilutions of the vector in the presence of 4 μ g of Polybrene/ml (Sigma, St. Louis, MO). The culture medium was replaced 48 h later with fresh medium containing puromycin (Sigma) at a concentration of 1.5 μ g/ml. Puromycin-resistant colonies were counted 10 days after transduction. The pancreatic cancer cells (Panc1, BxPC3 and SU.86.86) were transduced with the viral vectors at a MOI of 0.5. Transduced cells were selected with puromycin (1.5 μ g/ml for BxPC3 and SU.86.86; 2 μ g/ml for Panc1). See Figs 24-26.

[0597] **QPCR:** Total RNA was isolated from cells using the RNeasy kit (Qiagen). The Tetro cDNA kit (Bioline) and SensiFast Probe kit (Bioline) were used to reverse-transcribe and amplify total RNA according to the manufacturer's protocol. The ProbeFinder software (Roche Applied Science) was used to design the primer sets for *SUV39H1*, *p53* and *GAPDH* and to select the respective probes from the Universal ProbeLibrary (Roche Applied Science). Probe # 13 and the following primers were used for the SUV39H1 assay: 5' gtcattggagtacgtgggagag and 5' cctgacggctgtagatctgg. Probe # 21 and the following primers were used for the p53 assay: 5' tagtgtggtggtgcctatg and 5' cacatgtagttgtagtggatggtg Probe #60 and the following primers were used for the GAPDH assay: 5' agccacatcgctcagacac and 5' gcccaatagaccaaattcc. All samples

were run in triplicates. Amplifications were performed on a Bio-Rad CFX96 Touch Multiple-Color Real-time PCR Detection System. The data were normalized to the *GAPDH* expression and the relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

[0598] Senescence assay: Panc1 cells were seeded at a density of 3×10^4 cells per well in a 24-well plate. The cells were then treated with 100 nM ETP69 or 0.3% DMSO (vehicle control). Panc-1 and SU.86.86 cells expressing SUV39H1 shRNA or a non-targeting (NT) control shRNA were also seeded in 24-well plates at a density of 3×10^4 cells/well and 5×10^4 cells/well, respectively. After 5 days, cells were washed with PBS, fixed with 3% formaldehyde/PBS, and stained over night at 37 °C with a freshly prepared staining solution (1 mg/ml 5-bromo-4-chloro-3-indolyl b-D-galactoside in 40 mM citric acid / sodium phosphate, pH 6.0, 5 mM potassium ferrocyanide, 5 mM potassium ferricyanide, 150 mM NaCl, 2 mM MgCl₂). The blue stain indicates senescence-associated β -galactosidase activity. Photographs were taken with a 10x or a 20x objective under brightfield illumination using an INFINITY2 digital CCD camera (Lumenera, Canada) mounted on a Nikon Eclipse TS100 inverted microscope. See Figures 29-31.

[0599] Migration (“wound healing”) assay: Panc1, BxPC3 and SU.86.86 pancreatic cancer cells expressing SUV39H1 shRNA or a non-targeting (NT) control shRNA were grown in 6-well plates. Upon reaching confluence the cell monolayers were scratched with a pipette tip to create uniform “wounds”. Cells were then allowed to migrate into the denuded area. Photographs were taken with a 10x objective under brightfield illumination at 0 h and 24 h using an INFINITY2 digital CCD camera (Lumenera, Canada) mounted on a Nikon Eclipse TS100 inverted microscope. See Figure 32.

Example 8

[0600] FLT3 inhibition studies: The kinase assays *in vitro* were performed with recombinant FLT3 protein using the HotSpot protocol (Reaction Biology Corp, Malvern, PA). Briefly, proteins, freshly prepared substrates and ³³P-ATP (specific activity 0.01 μ Ci/ μ l final) were mixed in reaction buffer (20 mM HEPES pH 7.5, 10 mM MgCl₂, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na₃VO₄, 2 mM DTT) in the presence of DMSO as control or S enantiomer of ETP69. The mixtures were reacted for 120 min at room temperature. Samples

were transferred onto P81 ion exchange paper and filters were extensively washed with 0.75% phosphoric acid. The radioactivities were monitored.

[0601] Western blot analyses were performed with specific antibodies. Briefly, human A2058 melanoma, DU145 prostate, A549 non-small lung and SKOV3 ovarian cancer cells were treated with ETP69. Whole-cell lysates (40 μ g) or histone extracts (10 μ g) were resolved by SDS-PAGE. Primary specific antibodies to histone H3 and histone H3 (trimethyl K9) were incubated in PBS (pH 7.5) with 0.1% (v/v) Tween-20 and 5% (w/v) BSA with gentle agitation overnight at 4°C. Other specific antibodies were diluted in PBS (pH 7.5) with 5% (w/v) nonfat milk and 0.1% (v/v) Tween-20 over night at 4°C. Horseradish peroxidase-conjugated secondary antibodies were incubated in PBS (pH 7.5) with 5% (w/v) nonfat milk and 0.1% (v/v) Tween-20 for 1 h at room temperature. Positive immuno-reactive proteins were detected using the ECL system (Pierce, Rockford, IL).

[0602] For histone methyltransferase (HMT), DNA methyltransferase (DNMT) and Histone acetyltransferase (HAT) assays *in vitro*, human recombinant HMT, DNMT and HAT proteins were mixed with substrates in the reaction buffer (50 mM Tris-HCl (pH 8.5), 5 mM MgCl₂, 50 mM NaCl, 1 mM DTT, 1 mM PMSF, 1% DMSO), including histone H3, histone H4, nucleosomes, or core histone. Racemic ETP69, S enantiomer or DMSO as a vehicle control was preincubated in the mixture. Next, for HMTs and DNMT assays, 1 mM of ³H-SAM was added to the mixture for the reaction initiation and conversion of ³H-SAM + histone L-lysine to SAH + histone N⁶-[methyl-³H]-L-lysine was monitored with miniaturized radioligand-filter binding platform. For p300 HAT assays, the conversion of acetyl-³H-acetyl coenzyme A to coenzyme A was monitored. The reactions were carried out at 30°C. IC₅₀ values were determined using Excel and GraphPad Prism software.

[0603] **In vivo xenograft procedures for lung cancer, melanoma, and ovarian cancer (see Figures 15-18):** Human A2058 melanoma cells (3 x 10⁶) were resuspended in serum-free RPMI1640 medium and subcutaneously injected into the flank of 5-6 weeks old Athymic female nude mouse (NCI). When palpable tumor sizes reached at approximately 100 mm³, mice were divided into two groups (vehicle = 5, treatment = 5). Then, ETP69 was administered with intraperitoneal (IP) injection at 20 mg/kg with vehicle (10% DMSO + 0.5% Teen 20 + 89.5% saline), once daily for 13 days. Tumor volumes were calculated by the formula $1/2a \times b^2$, where a

is the long diameter, and b is the short diameter. Tumor volumes correlate with tumor weights. The statistical significance of group differences was analyzed using a Student's t-test with the two-tailed distribution. *P* values less than 0.05 were considered statistically significant.

[0604] Human A549 non-small lung cancer cells (5×10^6) were resuspended in serum-free DMEM medium and Matrigel (ration of 1:1) and subcutaneously injected into the flank of 5-6 weeks old female NOD/SCID/ IL-2rg(ko)(NSG). When palpable tumor sizes reached at approximately 50 mm^3 , mice were divided into two groups (vehicle = 10, treatment = 10). Then, ETP69 was orally administered at 10 mg/kg with vehicle (10% DMSO + 30% Solutol + 60% saline), once daily for 31 days. Tumor volumes were calculated by the formula $1/2a \times b^2$, where a is the long diameter, and b is the short diameter. Tumor volumes correlate with tumor weights. The statistical significance of group differences was analyzed using a Student's t-test with the two-tailed distribution. *P* values less than 0.05 were considered statistically significant.

[0605] Human MV4-11 acute myeloid leukemia (AML) cancer cells (5×10^6) that have FLT-ITD mutations were resuspended in serum-free RPMI1640 medium and Matrigel (ration of 1:1) and subcutaneously injected into the flank of 5-6 weeks old female NOD/SCID/ IL-2rg(ko)(NSG). When palpable tumor sizes reached at approximately 50 mm^3 , mice were divided into three groups (vehicle = 9, 5 mg/kg dose group = 8, 10 dose mg/kg group = 8). Then, S enantiomer was orally administered at 5 mg/kg or 10 mg/kg with vehicle (10% DMSO + 30% Solutol + 60% saline), once daily for 20 days. Tumor volumes were calculated by the formula $1/2a \times b^2$, where a is the long diameter, and b is the short diameter. Tumor volumes correlate with tumor weights. The statistical significance of group differences was analyzed using a Student's t-test with the two-tailed distribution. *P* values less than 0.05 were considered statistically significant.

[0606] Human SKOV3 cancer cells (4×10^6) were resuspended in serum-free McCoy's medium and Matrigel (ration of 1:1) and subcutaneously injected into the flank of 5-6 weeks old female NOD/SCID/ IL-2rg(ko)(NSG). When palpable tumor sizes reached at approximately 50 mm^3 , mice were divided into two groups (vehicle = 9, treatment = 9). Then, ETP69 was administered with IP injection at 2.5 mg/kg with vehicle (5% DMSO + 15% Solutol + 80% H₂O), once daily for 18 days. Tumor volumes were calculated by the formula $1/2a \times b^2$, where a is the long diameter, and b is the short diameter. Tumor volumes correlate with tumor weights.

The statistical significance of group differences was analyzed using a Student's t-test with the two-tailed distribution. *P* values less than 0.05 were considered statistically significant.

[0607] Cell testing assays with ETP derivatives in combination with DNMT inhibitors and multi-kinase inhibitors (See Figures 12-14): MTS assays were performed for cell

5 viability for combination study with ETP69 plus DNMT inhibitors or mutikinase inhibitor. Human SKOV3 ovarian and A549 non-small cancer cells were seeded in 96-well plates (5000/well), incubated overnight at 37°C in 5% CO₂, and exposed to ETP69 plus azacitidine, decitabine or sorafenib for 48. Dimethyl sulfoxide (DMSO) was used as the vehicle control. Viable cell numbers were determined by tetrazolium conversion to its formazan dye and
10 absorbance was measured at 490 nm using an automated ELISA plate reader. Each experiment was performed in quadruplicate.

[0608] Induction of p16, p53, p21waf1 and p27 (Figures 8 and 9): Western blot analyses

were performed with specific antibodies. Briefly, human A2058 melanoma, DU145 prostate, A549 non-small lung and SKOV3 ovarian cancer cells were treated with ETP69. Whole-cell
15 lysates (40 g) were resolved by SDS-PAGE. Primary specific antibodies to p53, p21^{WAF1}, p27(Kip1), p16 and Actin were diluted in PBS (pH 7.5) with 5% (w/v) nonfat milk and 0.1% (v/v) Tween-20 over night at 4°C. Horseradish peroxidase-conjugated secondary antibodies were incubated in PBS (pH 7.5) with 5% (w/v) nonfat milk and 0.1% (v/v) Tween-20 for 1 h at room
20 temperature. Positive immuno-reactive proteins were detected using the ECL system (Pierce, Rockford, IL).

[0609] Apoptosis determinations (Figure 11): Apoptosis assays of human SKOV3 ovarian cancer cells based on loss of membrane integrity were carried out using Annexin V-FITC.

Briefly, cells were seeded in 6-well plates, incubated overnight at 37°C in 5% (v/v) CO₂ and exposed to ETP69 in a dose-dependent manner for 48 h. DMSO was used as the vehicle control.
25 Cells were analyzed using a FACScan flow cytometer to quantify fluorescence. Apoptotic cells were defined as Annexin V-FITC positive. Each experiment was performed in quadruplicate.

[0610] IC50 determinations for ovarian, liver, pancreatic, CML, AML cancer cell lines

(See e.g. Figures 4, 6, 21-25, 34): MTS assays were performed for cell viability. SKOV3 ovarian cancer, Huh-7 hepatocellular carcinoma, MIA-PaCa2 pancreatic cancer, KCL-22 CML,
30 T315I mutant KCL-22 CML, MOLM-13 AML and MV4-11 AML cells were seeded in 96-well

plates (5000 cells/well for solid tumors, 10000 cells/well for blood tumors), incubated overnight at 37°C in 5% CO₂, and exposed to racemic ETP69 or S enantiomer in a dose-dependent manner for 48 h. Dimethyl sulfoxide (DMSO) was used as the vehicle control. Viable cell numbers were determined by tetrazolium conversion to its formazan dye and absorbance was measured at 490 nm using an automated ELISA plate reader. Each experiment was performed in quadruplicate.

Example 9

ETP analogue activity

[0611] It was found that the prepared ETPs show different IC₅₀ values ranging from 0.1 to > 5 μM. In general, the aromatic rings incorporated at an early stage seem to have little effect on the observed activities; however, the presence of a nitrile group rather than different esters enhances the potency of such compounds significantly. As such ETP69 was identified as a promising lead structure with an IC₅₀ falling in between the monomeric and dimeric ETP natural products (~0.6 and 0.07 μM).

[0612] ETP69 was screened against a number of transferases and demonstrate about ten times more potency against several transferases than chaetocin itself. In addition, the data obtained suggests that ETP69 is selective against histone methyltransferases (SUV39H1; G9a) over histone acetylases (p300) and DNA methyl transferases (DNMT1).

[0613] ETP69 shows no significant toxicity up to concentrations of 20 mg/kg with intraperitoneal injection (IP) or oral administration.

VI. References

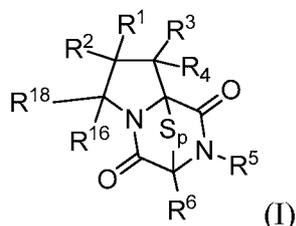
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VII. Embodiments:

[0635] **Embodiment 1:** A compound having the formula:



- 5 wherein, p is 2, 3 or 4; R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -
 Cl₃, -CN, -CHO, -OR^{33A}, -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -
 SO_{n1}OR^{34A}, -SO_{n1}NR^{34A}R^{35A}, -NHN^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHN^{34A}R^{35A},
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 10 unsubstituted aryl, or substituted or unsubstituted heteroaryl; R² is hydrogen, halogen, -N₃, -CF₃,
 -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33B}, -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -
 SO_{n2}R^{34b}, -SO_{n2}OR^{34B}, -SO_{n2}NR^{34B}R^{35B}, -NHN^{34B}R^{35B}, -ONR^{34B}R^{35B}, -NHC(O)NHN^{34B}R^{35B},
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 15 unsubstituted aryl, or substituted or unsubstituted heteroaryl; R³ is hydrogen, halogen, -N₃, -CF₃,
 -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33C}, -NR^{34C}R^{35C}, -COOR^{33C}, -CONR^{34C}R^{35C}, -NO₂, -SR^{36C}, -
 SO_{n3}R^{34C}, -SO_{n3}OR^{34C}, -SO_{n3}NR^{34C}R^{35C}, -NHN^{34C}R^{35C}, -ONR^{34C}R^{35C}, -NHC(O)NHN^{34C}R^{35C},
 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; R⁴ is hydrogen, halogen, -N₃, -CF₃,
 -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33D}, -NR^{34D}R^{35D}, -COOR^{33D}, -CONR^{34D}R^{35D}, -NO₂, -SR^{36D}, -
 SO_{n4}R^{34D}, -SO_{n4}OR^{34D}, -SO_{n4}NR^{34D}R^{35D}, -NHN^{34D}R^{35D}, -ONR^{34D}R^{35D}, -
 NHC(O)NHN^{34D}R^{35D}, substituted or unsubstituted alkyl, substituted or unsubstituted
 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 25 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R⁵
 is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33E}, -NR^{34E}R^{35E}, -COOR^{33E},

$-\text{CONR}^{34\text{E}}\text{R}^{35\text{E}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{E}}$, $-\text{SO}_{n5}\text{R}^{34\text{E}}$, $-\text{SO}_{n5}\text{OR}^{34\text{E}}$, $-\text{SO}_{n5}\text{NR}^{34\text{E}}\text{R}^{35\text{E}}$, $-\text{NHNr}^{34\text{E}}\text{R}^{35\text{E}}$, $-\text{ONR}^{34\text{E}}\text{R}^{35\text{E}}$, $-\text{NHC(O)NHNr}^{34\text{E}}\text{R}^{35\text{E}}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^6 is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33\text{F}}$, $-\text{NR}^{34\text{F}}\text{R}^{35\text{F}}$, $-\text{COOR}^{33\text{F}}$, $-\text{CONR}^{34\text{F}}\text{R}^{35\text{F}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{F}}$, $-\text{SO}_{n6}\text{R}^{34\text{F}}$, $-\text{SO}_{n6}\text{OR}^{34\text{F}}$, $-\text{SO}_{n6}\text{NR}^{34\text{F}}\text{R}^{35\text{F}}$, $-\text{NHNr}^{34\text{F}}\text{R}^{35\text{F}}$, $-\text{ONR}^{34\text{F}}\text{R}^{35\text{F}}$, $-\text{NHC(O)NHNr}^{34\text{F}}\text{R}^{35\text{F}}$, substituted 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^{16} is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33\text{G}}$, $-\text{NR}^{34\text{G}}\text{R}^{35\text{G}}$, $-\text{COOR}^{33\text{G}}$, $-\text{CONR}^{34\text{G}}\text{R}^{35\text{G}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{G}}$, $-\text{SO}_{n7}\text{R}^{34\text{G}}$, $-\text{SO}_{n7}\text{OR}^{34\text{G}}$, $-\text{SO}_{n7}\text{NR}^{34\text{G}}\text{R}^{35\text{G}}$, $-\text{NHNr}^{34\text{G}}\text{R}^{35\text{G}}$, $-\text{ONR}^{34\text{G}}\text{R}^{35\text{G}}$, $-\text{NHC(O)NHNr}^{34\text{G}}\text{R}^{35\text{G}}$, substituted 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^{18} is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33\text{H}}$, $-\text{NR}^{34\text{H}}\text{R}^{35\text{H}}$, $-\text{COOR}^{33\text{H}}$, $-\text{CONR}^{34\text{H}}\text{R}^{35\text{H}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{H}}$, $-\text{SO}_{n8}\text{R}^{34\text{H}}$, $-\text{SO}_{n8}\text{OR}^{34\text{H}}$, $-\text{SO}_{n8}\text{NR}^{34\text{H}}\text{R}^{35\text{H}}$, $-\text{NHNr}^{34\text{H}}\text{R}^{35\text{H}}$, $-\text{ONR}^{34\text{H}}\text{R}^{35\text{H}}$, $-\text{NHC(O)NHNr}^{34\text{H}}\text{R}^{35\text{H}}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $\text{R}^{33\text{A}}$, $\text{R}^{34\text{A}}$, $\text{R}^{35\text{A}}$, $\text{R}^{36\text{A}}$, $\text{R}^{33\text{B}}$, $\text{R}^{34\text{B}}$, $\text{R}^{35\text{B}}$, $\text{R}^{36\text{B}}$, $\text{R}^{33\text{C}}$, $\text{R}^{34\text{C}}$, $\text{R}^{35\text{C}}$, $\text{R}^{36\text{C}}$, $\text{R}^{33\text{D}}$, $\text{R}^{34\text{D}}$, $\text{R}^{35\text{D}}$, $\text{R}^{36\text{D}}$, $\text{R}^{33\text{E}}$, $\text{R}^{34\text{E}}$, $\text{R}^{35\text{E}}$, $\text{R}^{36\text{E}}$, $\text{R}^{33\text{F}}$, $\text{R}^{34\text{F}}$, $\text{R}^{35\text{F}}$, $\text{R}^{36\text{F}}$, $\text{R}^{33\text{G}}$, $\text{R}^{34\text{G}}$, $\text{R}^{35\text{G}}$, $\text{R}^{36\text{G}}$, $\text{R}^{33\text{H}}$, $\text{R}^{34\text{H}}$, $\text{R}^{35\text{H}}$, and $\text{R}^{36\text{H}}$ are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_1 , n_2 , n_3 , n_4 , n_5 , n_6 , n_7 , and n_8 are independently 1 or 2.

[0636] Embodiment 2: The compound of embodiment 1, wherein R^{18} is substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0637] Embodiment 3: The compound of embodiments 1 or 2, wherein R^{18} is $\text{R}^{18\text{a}}$ -substituted or unsubstituted 5 membered heterocycloalkyl, $\text{R}^{18\text{a}}$ -substituted or unsubstituted 6 membered aryl, $\text{R}^{18\text{a}}$ -substituted or unsubstituted 6 membered heteroaryl, $\text{R}^{18\text{a}}$ -substituted or unsubstituted

6,6 fused ring aryl-heterocycloalkyl, R^{18a}-substituted or unsubstituted 6,5 fused ring aryl-heterocycloalkyl, R^{18a}-substituted or unsubstituted 5,6 fused ring aryl-heterocycloalkyl; R^{18a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, R^{18b}-substituted or unsubstituted C₁-C₈ alkyl, R^{18b}-substituted or unsubstituted 2 to 8 membered heteroalkyl, R^{18b}-substituted or unsubstituted 3 to 8 membered cycloalkyl, R^{18b}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{18b}-substituted or unsubstituted 5 to 6 membered aryl, or R^{18b}-substituted or unsubstituted 5 to 6 membered heteroaryl; and R^{18b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0638] Embodiment 4: The compound of embodiments 1-3, wherein R^{18a} is halogen, -SO₂Ph, R^{18b}-substituted or unsubstituted C₁-C₅ alkyl, or R^{18b}-substituted or unsubstituted 2 to 5 membered heteroalkyl, unsubstituted 5 to 6 membered heterocycloalkyl, or unsubstituted phenyl; and R^{18b} is halogen, unsubstituted C₁-C₈ alkyl, or unsubstituted 2 to 8 membered heteroalkyl.

[0639] Embodiment 5: The compound of embodiments 1-4, wherein said R^{18a}-substituted 5 membered heterocycloalkyl is an R^{18a}-substituted thiophenyl, R^{18a}-substituted thiazolyl, R^{18a}-substituted oxazolyl, or R^{18a}-substituted imidazolyl; and R^{18a} is halogen, unsubstituted C₁-C₅ alkyl, or unsubstituted 2 to 5 membered heteroalkyl.

[0640] Embodiment 6: The compound of embodiment 1-3, wherein R¹⁸ is unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

[0641] Embodiment 7: The compound of any one of embodiments 1 to 6, wherein R¹⁶ is hydrogen.

[0642] Embodiment 8: The compound of any one of embodiments 1 to 6, wherein R³ and R⁴ are hydrogen.

[0643] Embodiment 9: The compound of any one of embodiments 1 to 6, wherein R¹ is -CN or unsubstituted 2 to 5 membered heteroalkyl.

[0644] **Embodiment 10:** The compound of embodiments 1-9, wherein R¹ is -CN.

[0645] **Embodiment 11:** The compound of embodiments 1-9, wherein R¹ is -COOR^{33A}, wherein R^{33A} is C₁-C₃ unsubstituted alkyl.

[0646] **Embodiment 12:** The compound of any one of embodiments 1 to 6 or 10-11, wherein
5 R² is -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2a}-substituted or unsubstituted C₁-
C₃ alkyl, or 2 to 3 membered R^{2a}-substituted or unsubstituted heteroalkyl; R^{2a} is -N₃, -CF₃, -
CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -
SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2b}-substituted or unsubstituted C₁-C₅ alkyl, R^{2b}-
10 substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{2b}-substituted or unsubstituted 3 to 6
membered heterocycloalkyl, R^{2b}-substituted or unsubstituted 5 or 6 membered aryl, or R^{2b}-
substituted or unsubstituted 5 or 6 membered heteroaryl; and R^{2b} is halogen, -N₃, -CF₃, -CCl₃, -
CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -
SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8
15 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 6
membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6
membered heteroaryl.

[0647] **Embodiment 13:** The compound of any one of embodiments 1 to 6 or 10-11, wherein
R² is methyl or methoxy.

20 [0648] **Embodiment 14:** The compound of any one of embodiments 1 to 6 or 10-11, wherein
R² is R^{2a}-substituted or unsubstituted C₁-C₅ alkyl, or R^{2a}-substituted or unsubstituted 2 to 5
membered heteroalkyl, and R^{2a} is unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted
5 or 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.

[0649] **Embodiment 15:** The compound of any one of embodiments 1 to 6 or 10-11, wherein
25 R^{2a} is unsubstituted pyridinyl.

[0650] **Embodiment 16:** The compound of any one of embodiments 1 to 6 or 10 to 11,
wherein R² is C₁-C₅ substituted or unsubstituted heteroalkyl.

[0651] **Embodiment 17:** The compound of any one of embodiments 1 to 6 or 10-11, wherein R^2 is a polar substituent.

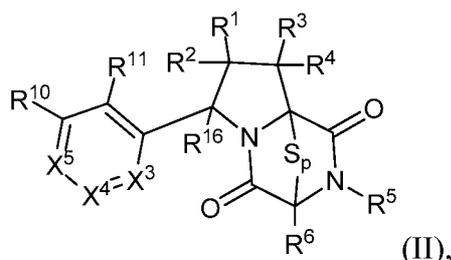
[0652] **Embodiment 18:** The compound of embodiments 1-17, wherein R^5 and R^6 are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, unsubstituted alkyl, or unsubstituted cycloalkyl.

[0653] **Embodiment 19:** The compound of embodiments 1-18, wherein R^5 and R^6 are independently hydrogen, unsubstituted C_1 - C_3 alkyl or membered 3 to 5 cycloalkyl.

[0654] **Embodiment 20:** The compound of embodiments 1-18, wherein R^5 and R^6 are independently hydrogen, methyl, ethyl, allyl, or cyclopropyl.

[0655] **Embodiment 21:** The compound of any one of embodiments 1 to 6, or 10 to 11, or 18, wherein p is 2.

[0656] **Embodiment 22:** The compound of embodiments 1-21 having the formula:



15 wherein, X^3 is N or CR^7 ; X^4 is N or CR^8 ; X^5 is N or CR^9 ; R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNR^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNR^{34I}R^{35I}$, 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; R^8 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33J}$, $-NR^{34J}R^{35J}$, $-COOR^{33J}$, $-CONR^{34J}R^{35J}$, $-NO_2$, $-SR^{36J}$, $-SO_{n10}R^{34J}$, $-SO_{n10}OR^{34J}$, $-SO_{n10}NR^{34J}R^{35J}$, $-NHNR^{34J}R^{35J}$, $-ONR^{34J}R^{35J}$, $-NHC(O)NHNR^{34J}R^{35J}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

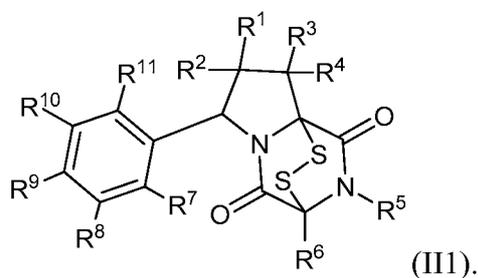
unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^9 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33K}$, $-NR^{34K}R^{35K}$, $-COOR^{33K}$, $-CONR^{34K}R^{35K}$, $-NO_2$, $-SR^{36K}$, $-SO_{n11}R^{34K}$, $-SO_{n11}OR^{34K}$, $-SO_{n11}NR^{34K}R^{35K}$, $-NHNr^{34K}R^{35K}$, $-ONR^{34K}R^{35K}$, $-NHC(O)NHNr^{34K}R^{35K}$, substituted or unsubstituted alkyl, substituted or unsubstituted

5 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNr^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNr^{34L}R^{35L}$, substituted or

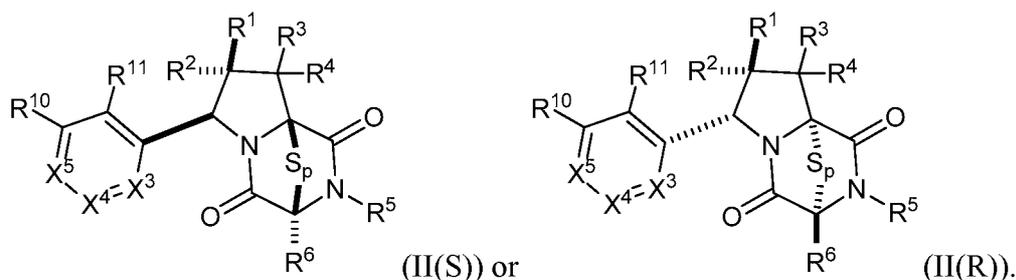
10 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} ,

15 R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} , and R^{36L} , are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_9 , n_{10} , n_{11} , and n_{12} are independently 1 or 2.

20 **[0657] Embodiment 23:** The compound of embodiments 1-22 having the formula:



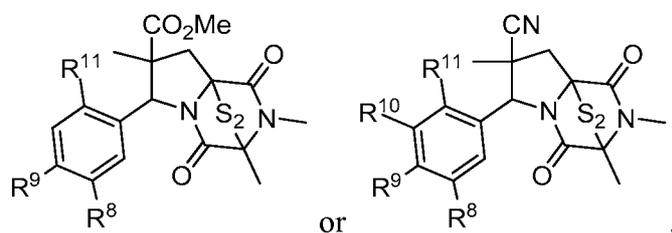
[0658] Embodiment 24: The compound of embodiments 1-22 having the formula:



[0659] **Embodiment 25:** The compound of embodiments 1-22, wherein R¹ is -CN or unsubstituted 2 to 5 membered heteroalkyl.

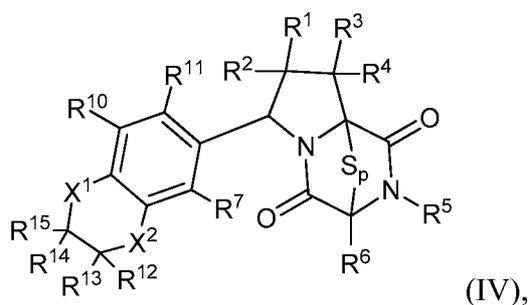
[0660] **Embodiment 26:** The compound of any one of embodiments 1-25, wherein R³ and R⁴ are hydrogen.

[0661] **Embodiment 27:** The compound of embodiments 1-22 having formula:



wherein, R⁸ is hydrogen or -OR³³; R⁹, R¹⁰, and R¹¹ are independently hydrogen or halogen; and R³³ is hydrogen, or unsubstituted alkyl.

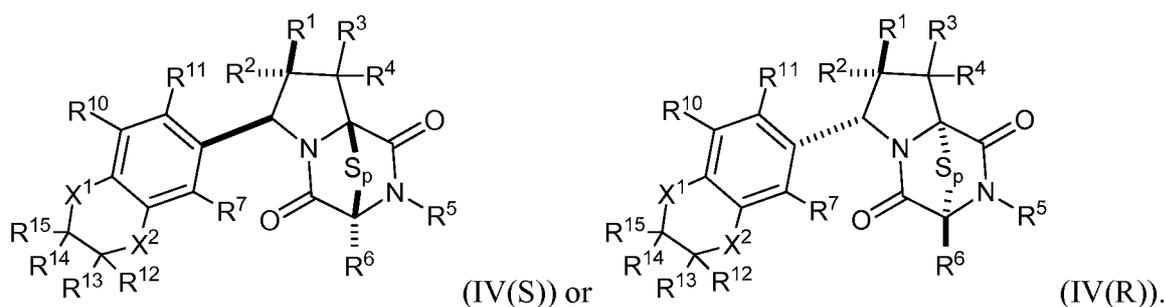
10 [0662] **Embodiment 28:** The compound of embodiments 1 or 22 having formula:



wherein, X¹ is CR²¹R^{21A}, O, NR^{21A}, or S; X² is CR²²R^{22A}, O, NR^{22A}, or S; R¹², R¹³, R¹⁴, R¹⁵, R²¹, R^{21A}, R²², and R^{22A} are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -SO_{n13}NR^{34M}R^{35M}, -NHNHNR^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHNHNR^{34M}R^{35M},

substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_{13} is 1 or 2.

[0663] Embodiment 29: The compound of embodiment 28 having formula:



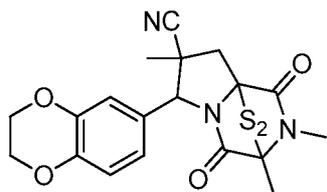
[0664] Embodiment 30: The compound of embodiments 28-29, wherein R^1 is $-CN$ or unsubstituted 2 to 5 membered heterocycloalkyl.

nEmbodiment 31: The compound of any one of embodiments 28-30, wherein R^3 and R^4 are hydrogen.

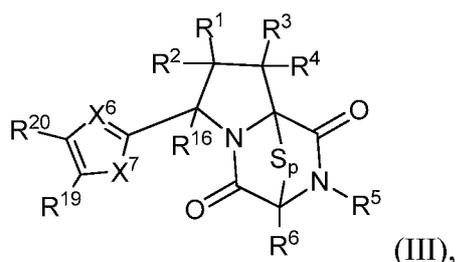
[0665] Embodiment 32: The compound of any one of embodiments 28-30, wherein R^{10} and R^{11} are hydrogen.

[0666] Embodiment 33: The compound of any one of embodiments 28-30, wherein R^{12} , R^{13} , R^{14} , and R^{15} are hydrogen.

[0667] Embodiment 34: The compound of embodiments 28-33 having formula:

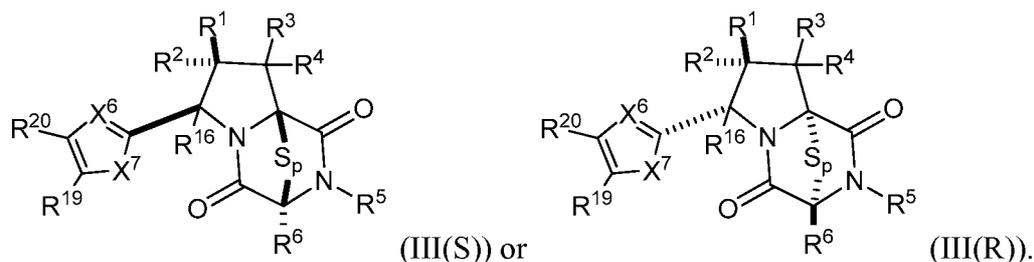


[0668] Embodiment 35: The compound of embodiment 1 having formula:



wherein, X⁶ is CR²¹ or N; X⁷ is CR²²R²³, S, O, or NR²³; R¹⁹, R²⁰, R²¹, R²² and R²³ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -SO_{n13}NR^{34M}R^{35M}, -NHN^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHN^{34M}R^{35M}, substituted 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^{33M}, R^{34M}, R^{35M}, and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n13 is 1 or 2.

[0669] Embodiment 36: The compound of any one of embodiments 1 or 35 having formula:

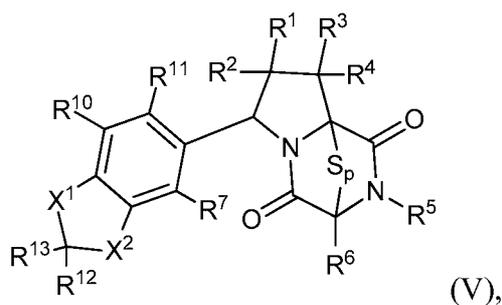


[0670] Embodiment 37: The compound of embodiments 35-36, wherein R¹ is -CN or unsubstituted 2 to 5 membered heteroalkyl.

[0671] Embodiment 38: The compound of any one of embodiments 35 to 37, wherein R³ and R⁴ are hydrogen.

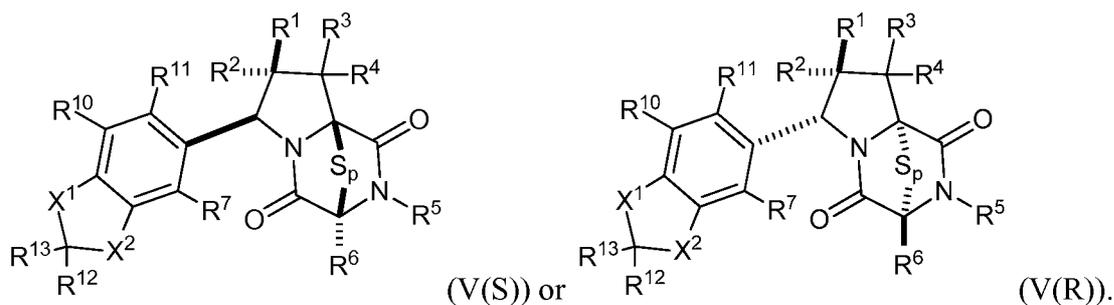
[0672] Embodiment 39: The compound of any one of embodiments 35 to 37, wherein R¹⁹ and R²⁰ are hydrogen.

[0673] Embodiment 40: The compound of embodiment 1 having formula:

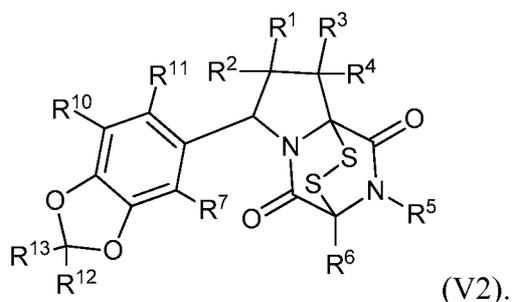


wherein, X¹ is CR²¹R^{21A}, O, NR^{21A}, or S; X² is CR²²R^{22A}, O, NR^{22A}, or S; R⁷ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33I}, -NR^{34I}R^{35I}, -COOR^{33I}, -CONR^{34I}R^{35I}, -NO₂, -SR^{36I}, -SO_{n9}R^{34I}, -SO_{n9}OR^{34I}, -SO_{n9}NR^{34I}R^{35I}, -NHN^{34I}R^{35I}, -ONR^{34I}R^{35I}, -NHC(O)NHN^{34I}R^{35I}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹⁰ and R¹¹ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33L}, -NR^{34L}R^{35L}, -COOR^{33L}, -CONR^{34L}R^{35L}, -NO₂, -SR^{36L}, -SO_{n12}R^{34L}, -SO_{n12}OR^{34L}, -SO_{n12}NR^{34L}R^{35L}, -NHN^{34L}R^{35L}, -ONR^{34L}R^{35L}, -NHC(O)NHN^{34L}R^{35L}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R¹², R¹³, R²¹, R^{21A}, R²² and R^{22A} are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -SO_{n13}NR^{34M}R^{35M}, -NHN^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHN^{34M}R^{35M}, substituted 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^{33M}, R^{34M}, R^{35M}, and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n₉, n₁₁, and n₁₃ are independently 1 or 2.

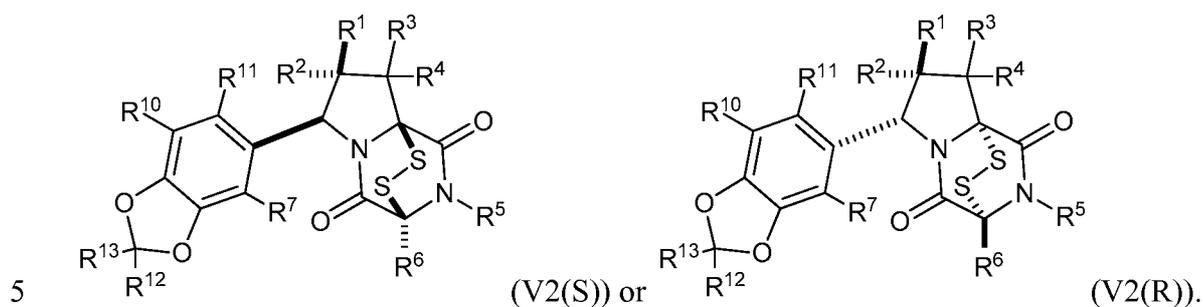
[0674] Embodiment 41: The compound of embodiment 40 having formula:



[0675] **Embodiment 42:** The compound of embodiments 40-41 having formula:



[0676] **Embodiment 43:** The compound of embodiments 40-42 having formula:



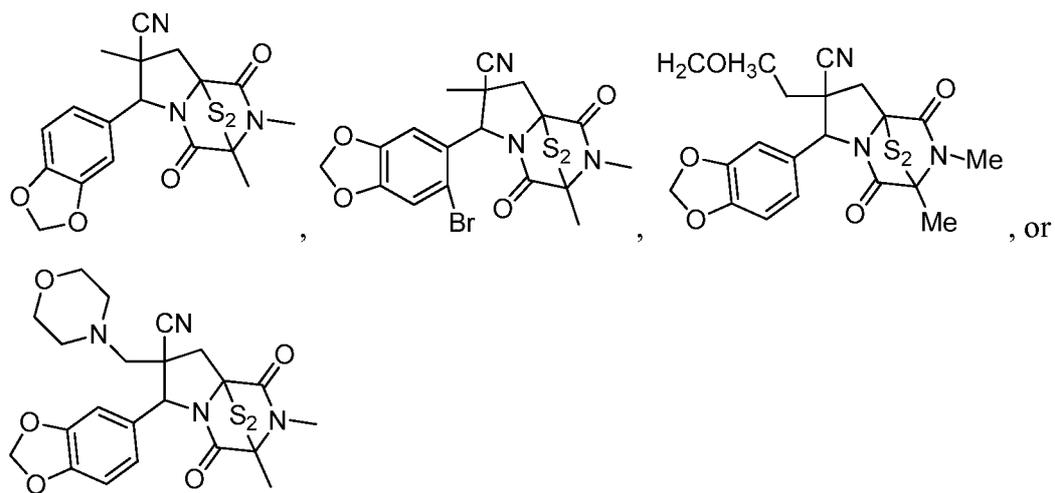
[0677] **Embodiment 44:** The compound of embodiments 40-43, wherein R¹ is -CN or unsubstituted 2 to 5 membered heteroalkyl.

[0678] **Embodiment 45:** The compound of any one of embodiments 40 to 44, wherein R³ and R⁴ are hydrogen.

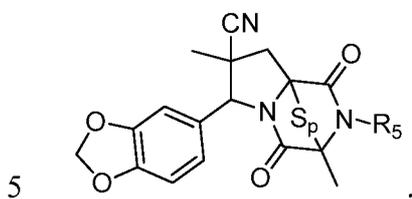
10 [0679] **Embodiment 46:** The compound of any one of embodiments 40 to 45, wherein R¹² and R¹³ are hydrogen.

[0680] **Embodiment 47:** The compound of any one of embodiments 40 to 46, wherein R¹⁰ and R¹¹ are hydrogen.

[0681] **Embodiment 48:** The compound of any one of embodiments 1, 40-47 having formula:

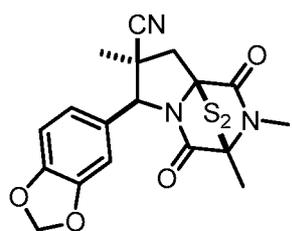


[0682] **Embodiment 49:** The compound of any one of embodiments 1, 40-47 having formula:

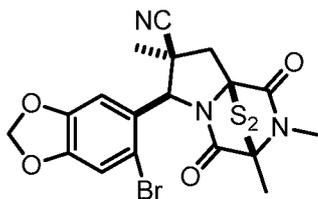


wherein; R^5 is unsubstituted 3 to 5 membered cycloalkyl, or R^{5a} -substituted or unsubstituted C_1 - C_5 alkyl; R^{5a} is unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered heterocycloalkyl, and p is 2 or 3.

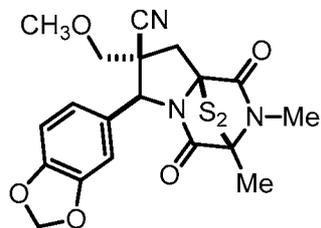
[0683] **Embodiment 50:** The compound of any one of embodiments 1, 40- 49 having formula:



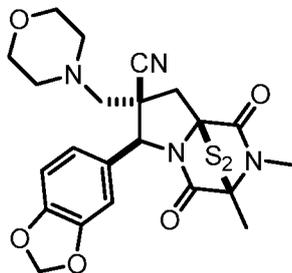
(ETP69),



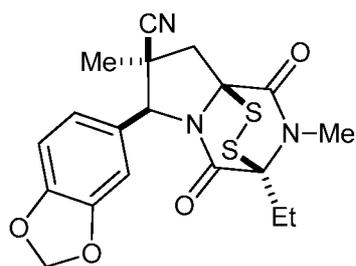
(ETP128),



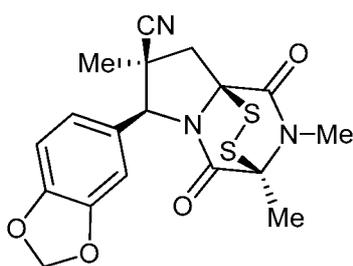
(ETP344),



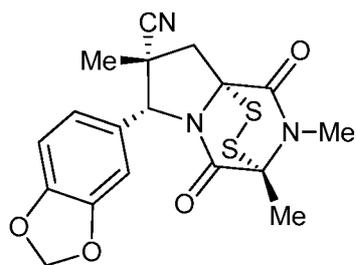
(ETP382),



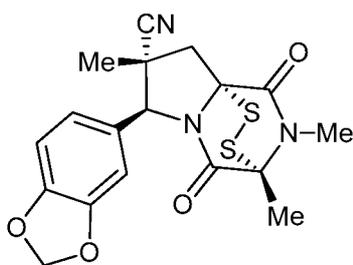
(ETP406),



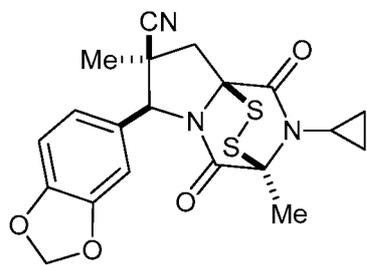
(ETP417),



(ETP422),



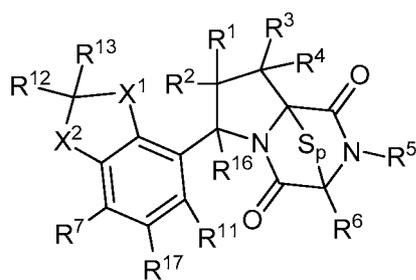
(ETP425), or



(ETP452).

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[0684] **Embodiment 51:** The compound of embodiment 1 having formula:

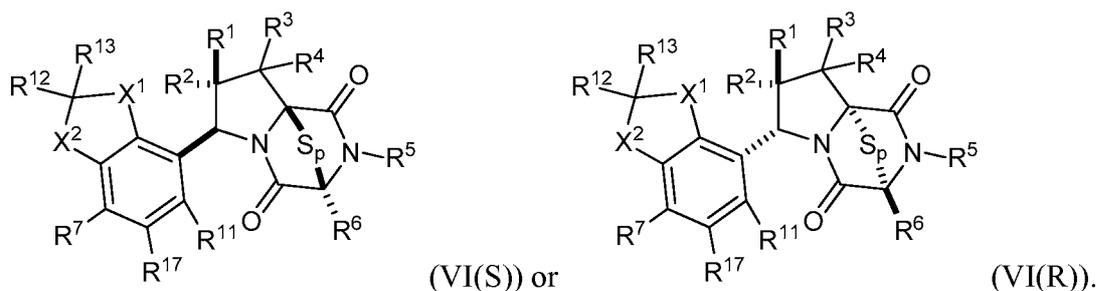


(VI),

wherein, X¹ is CR²¹R^{21A}, O, NR^{21A}, or S; X² is CR²²R^{22A}, O, NR^{22A}, or S; R⁷ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33I}, -NR^{34I}R^{35I}, -COOR^{33I}, -CONR^{34I}R^{35I}, -NO₂, -SR^{36I}, -SO_{n9}R^{34I}, -SO_{n9}OR^{34I}, -SO_{n9}NR^{34I}R^{35I}, -NHN^{34I}R^{35I}, -ONR^{34I}R^{35I}, -NHC(O)NHN^{34I}R^{35I}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33L}, -NR^{34L}R^{35L}, -COOR^{33L}, -CONR^{34L}R^{35L}, -NO₂, -SR^{36L}, -SO_{n12}R^{34L}, -SO_{n12}OR^{34L}, -SO_{n12}NR^{34L}R^{35L}, -NHN^{34L}R^{35L}, -ONR^{34L}R^{35L}, -NHC(O)NHN^{34L}R^{35L}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R¹², R¹³, R²¹, R^{21A}, R²², and R^{22A} are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -SO_{n13}NR^{34M}R^{35M}, -NHN^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHN^{34M}R^{35M}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹⁷ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33P}, -NR^{34P}R^{35P}, -COOR^{33P}, -CONR^{34P}R^{35P}, -NO₂, -SR^{36P}, -SO_{n15}R^{34P}, -SO_{n15}OR^{34P}, -SO_{n15}NR^{34P}R^{35P}, -NHN^{34P}R^{35P}, -ONR^{34P}R^{35P}, -NHC(O)NHN^{34P}R^{35P}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a substituted or

unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33L} , R^{34L} , R^{35L} , R^{36L} , R^{33M} , R^{34M} , R^{35M} , R^{36M} , R^{33P} , R^{34P} , R^{35P} , and R^{36P} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_9 , n_{12} , n_{13} and n_{15} are independently 1 or 2.

[0685] Embodiment 52: The compound of embodiment 51 having formula:



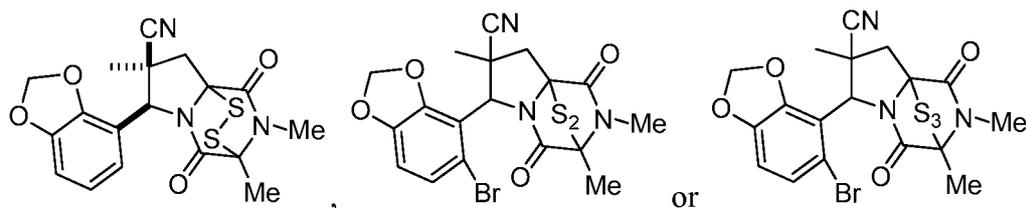
[0686] Embodiment 53: The compound of embodiments 51-52, wherein R^1 is $-CN$ or unsubstituted 2 to 5 membered heteroalkyl.

[0687] Embodiment 54: The compound of any one of embodiments 51 to 53, wherein R^3 and R^4 are hydrogen.

[0688] Embodiment 55: The compound of any one of embodiments 51 to 53, wherein R^{12} and R^{13} are hydrogen.

[0689] Embodiment 56: The compound of any one of embodiments 51 to 53, wherein R^7 , R^{10} , and R^{17} are hydrogen.

[0690] Embodiment 57: The compound of embodiments 51-56 having formula:



[0691] Embodiment 58: The compound of any one of embodiments 1-57, wherein R^2 is a polar substituent.

[0692] **Embodiment 59:** The compound of any one of embodiments 1-58, wherein R² is -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2a}-substituted or unsubstituted C₁-C₃ alkyl, or 1 to 3 membered R^{2a}-substituted or unsubstituted heteroalkyl; R^{2a} is -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2b}-substituted or unsubstituted C₁-C₅ alkyl, R^{2b}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{2b}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2b}-substituted or unsubstituted 5 or 6 membered aryl, or R^{2b}-substituted or unsubstituted 5 or 6 membered heteroaryl; R^{2b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

[0693] **Embodiment 60:** The compound of any one of embodiments 1-59, wherein R² is R^{2a}-substituted or unsubstituted C₁-C₃ alkyl, or 2 to 3 membered R^{2a}-substituted or unsubstituted heteroalkyl, wherein R^{2a} is unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 or 6 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.

[0694] **Embodiment 61:** The compound of any one of embodiments 1-60, wherein R² is unsubstituted methyl or unsubstituted methoxy.

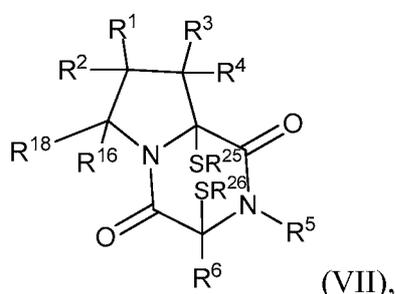
[0695] **Embodiment 62:** The compound of any one of embodiments 1-61, wherein R^{2a} is unsubstituted pyridine.

[0696] **Embodiment 63:** The compound of any one of embodiments 1-62, wherein R⁵ and R⁶ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, unsubstituted alkyl, or unsubstituted cycloalkyl.

[0697] **Embodiment 64:** The compound of any one of embodiments 1-63, wherein R⁵ and R⁶ are independently hydrogen, C₁-C₃ unsubstituted alkyl or 3 to 5 membered cycloalkyl.

[0698] **Embodiment 65:** The compound of any one of embodiments 1-64, wherein R⁵ and R⁶ are independently hydrogen, unsubstituted methyl, unsubstituted ethyl, unsubstituted allyl, or unsubstituted cyclopropyl.

[0699] **Embodiment 66:** A compound having formula:



wherein R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A}, -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A}, -SO_{n1}NR^{34A}R^{35A}, -NHN^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHN^{34A}R^{35A}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33B}, -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -SO_{n2}R^{34B}, -SO_{n2}OR^{34B}, -SO_{n2}NR^{34B}R^{35B}, -NHN^{34B}R^{35B}, -ONR^{34B}R^{35B}, -NHC(O)NHN^{34B}R^{35B}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R³ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33C}, -NR^{34C}R^{35C}, -COOR^{33C}, -CONR^{34C}R^{35C}, -NO₂, -SR^{36C}, -SO_{n3}R^{34C}, -SO_{n3}OR^{34C}, -SO_{n3}NR^{34C}R^{35C}, -NHN^{34C}R^{35C}, -ONR^{34C}R^{35C}, -NHC(O)NHN^{34C}R^{35C}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R⁴ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33D}, -NR³⁴R^{35D}, -COOR^{33D}, -CONR^{34D}R^{35D}, -NO₂, -SR^{36D}, -SO_{n4}R^{34D}, -SO_{n4}OR^{34D}, -SO_{n4}NR^{34D}R^{35D}, -NHN^{34D}R^{35D}, -ONR^{34D}R^{35D}, -NHC(O)NHN^{34D}R^{35D}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

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unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33E}$, $-NR^{34E}R^{35E}$, $-COOR^{33E}$, $-CONR^{34E}R^{35E}$, $-NO_2$, $-SR^{36E}$, $-SO_{n5}R^{34E}$, $-SO_{n5}OR^{34E}$, $-SO_{n5}NR^{34E}R^{35E}$, $-NHN R^{34E}R^{35E}$, $-ONR^{34E}R^{35E}$, $-NHC(O)NHN R^{34E}R^{35E}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

5 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^6 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33F}$, $-NR^{34F}R^{35F}$, $-COOR^{33F}$, $-CONR^{34F}R^{35F}$, $-NO_2$, $-SR^{36F}$, $-SO_{n6}R^{34F}$, $-SO_{n6}OR^{34F}$, $-SO_{n6}NR^{34F}R^{35F}$, $-NHN R^{34F}R^{35F}$, $-ONR^{34F}R^{35F}$, $-NHC(O)NHN R^{34F}R^{35F}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

10 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{16} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33G}$, $-NR^{34G}R^{35G}$, $-COOR^{33G}$, $-CONR^{34G}R^{35G}$, $-NO_2$, $-SR^{36G}$, $-SO_{n7}R^{34G}$, $-SO_{n7}OR^{34G}$, $-SO_{n7}NR^{34G}R^{35G}$, $-NHN R^{34G}R^{35G}$, $-ONR^{34G}R^{35G}$, $-NHC(O)NHN R^{34G}R^{35G}$, substituted or unsubstituted alkyl, substituted or

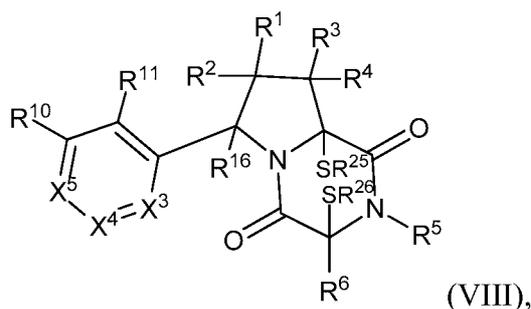
15 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{18} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33H}$, $-NR^{34H}R^{35H}$, $-COOR^{33H}$, $-CONR^{34H}R^{35H}$, $-NO_2$, $-SR^{36H}$, $-SO_{n8}R^{34H}$, $-SO_{n8}OR^{34H}$, $-SO_{n8}NR^{34H}R^{35H}$, $-NHN R^{34H}R^{35H}$, $-ONR^{34H}R^{35H}$, $-NHC(O)NHN R^{34H}R^{35H}$, substituted or unsubstituted alkyl,

20 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} , R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} , and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or

25 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; n_1 , n_2 , n_3 , n_4 , n_5 , n_6 , n_7 , and n_8 are independently 1 or 2; and R^{25} and R^{26} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

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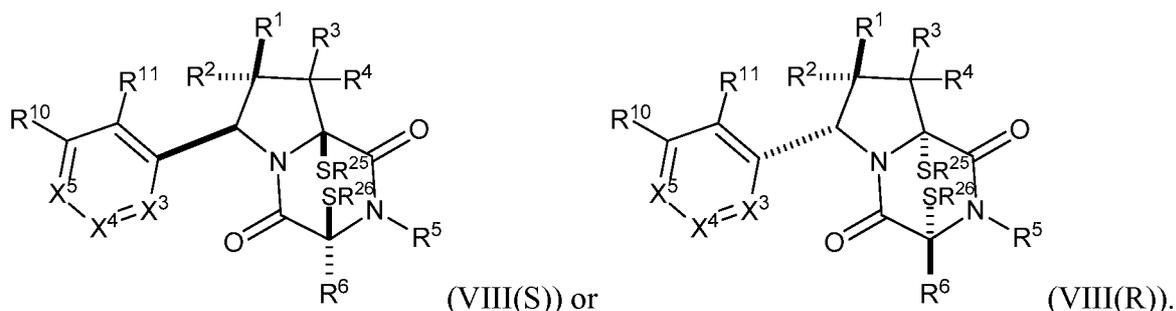
[0700] **Embodiment 67:** The compound of embodiment 66 having the formula:



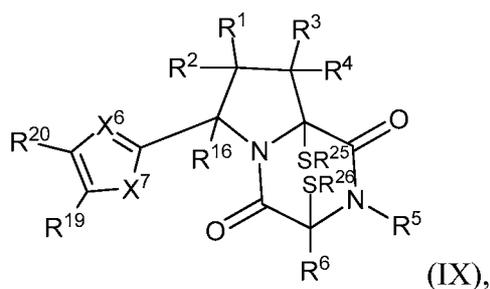
wherein, X^3 is N or CR^7 ; X^4 is N or CR^8 ; X^5 is N or CR^9 ; R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHN R^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHN R^{34I}R^{35I}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33J}$, $-NR^{34J}R^{35J}$, $-COOR^{33J}$, $-CONR^{34J}R^{35J}$, $-NO_2$, $-SR^{36J}$, $-SO_{n10}R^{34J}$, $-SO_{n10}OR^{34J}$, $-SO_{n10}NR^{34J}R^{35J}$, $-NHN R^{34J}R^{35J}$, $-ONR^{34J}R^{35J}$, $-NHC(O)NHN R^{34J}R^{35J}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33K}$, $-NR^{34K}R^{35K}$, $-COOR^{33K}$, $-CONR^{34K}R^{35K}$, $-NO_2$, $-SR^{36K}$, $-SO_{n11}R^{34K}$, $-SO_{n11}OR^{34K}$, $-SO_{n11}NR^{34K}R^{35K}$, $-NHN R^{34K}R^{35K}$, $-ONR^{34K}R^{35K}$, $-NHC(O)NHN R^{34K}R^{35K}$, substituted 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} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHN R^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHN R^{34L}R^{35L}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or

unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} , R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} , and R^{36L} , are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_9 , n_{10} , n_{11} , and n_{12} are independently 1 or 2.

[0701] Embodiment 68: The compound of embodiments 66 or 67 having the formula

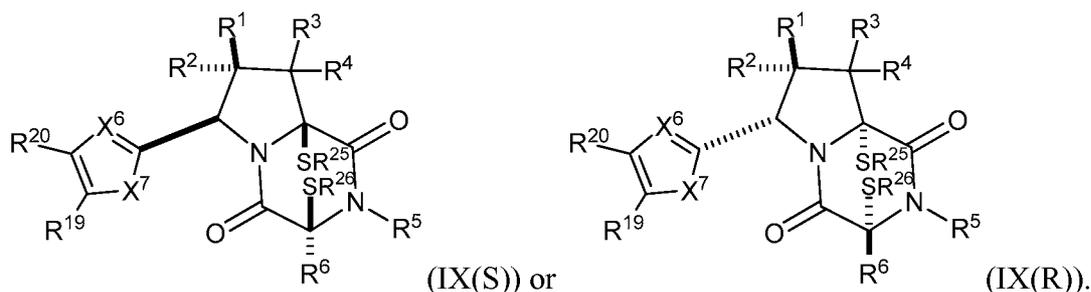


[0702] Embodiment 69: The compound of embodiments 66-68 having the formula

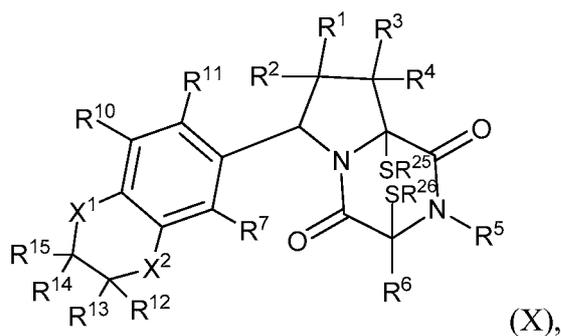


X^6 is CR^{21} or N; X^7 is $CR^{22}R^{23}$, S, O, or NR^{23} ; R^{19} , R^{20} , R^{21} , R^{22} and R^{23} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n_{13}}R^{34M}$, $-SO_{n_{13}}OR^{34M}$, $-SO_{n_{13}}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHN R^{34M}R^{35M}$, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_{13} is 1 or 2.

[0703] **Embodiment 70:** The compound of embodiments 66 - 69 having the formula:

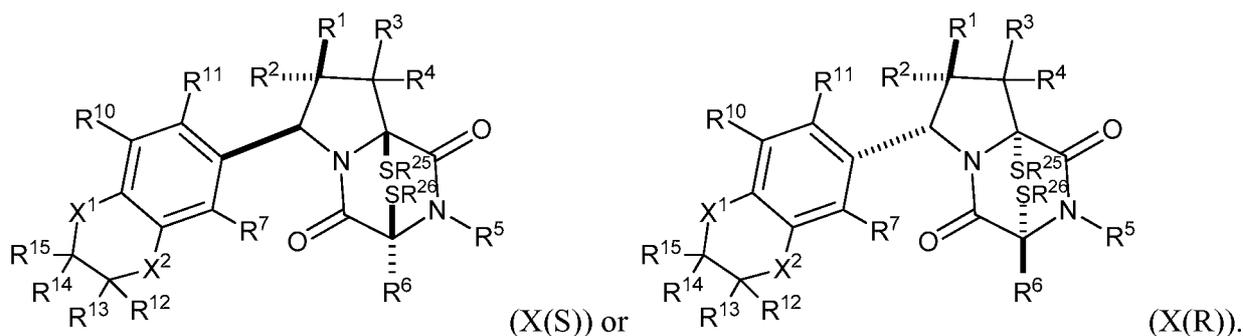


[0704] **Embodiment 71:** The compound of embodiments 66-70 having the formula:

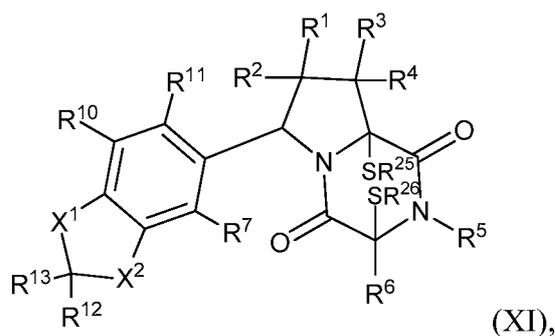


- 5 wherein X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S; X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHN R^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
- 10 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
- 15 n_{13} is 1 or 2.

[0705] **Embodiment 72:** The compound of embodiments 66 - 71 having the formula:



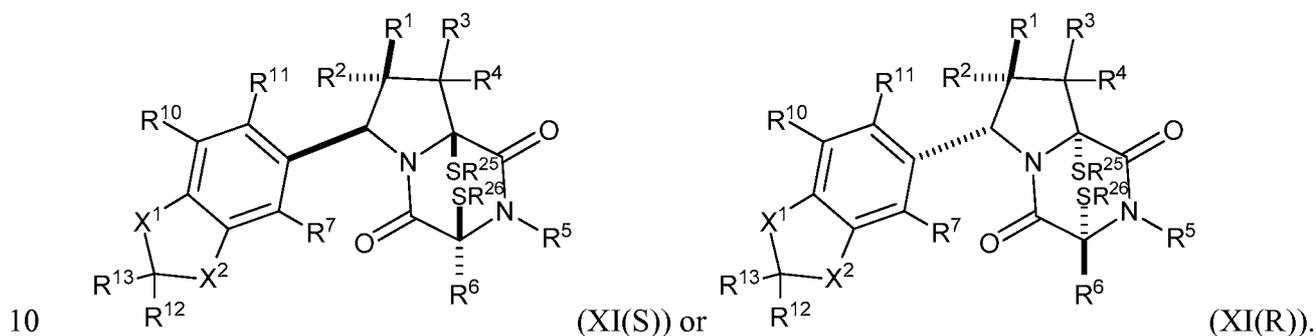
[0706] Embodiment 73: The compound of embodiments 66 -72 having the formula:



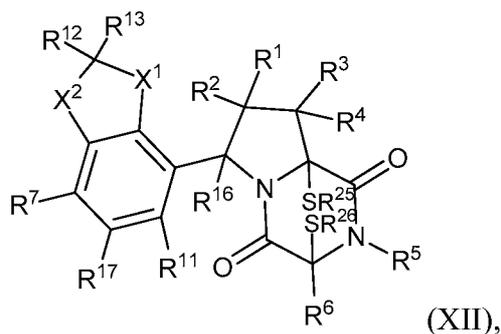
wherein, X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S; X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHN R^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHN R^{34I}R^{35I}$, substituted 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} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHN R^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHN R^{34L}R^{35L}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, -

SO_{n13}NR^{34M}R^{35M}, -NHN^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHN^{34M}R^{35M}, substituted 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^{33M}, R^{34M}, R^{35M}, and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n9, n11, and n13 are independently 1 or 2.

[0707] Embodiment 74: The compound of embodiments 66 - 73 having the formula:



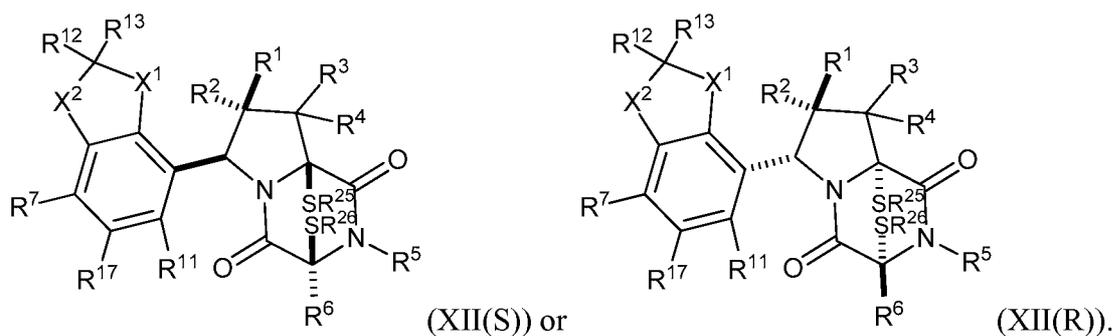
[0708] Embodiment 75: The compound of embodiments 66 - 74 having the formula:



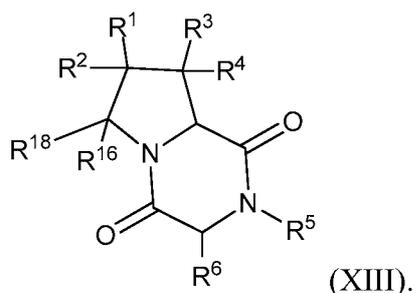
wherein, X¹ is CR²¹R^{21A}, O, NR^{21A}, or S; X² is CR²²R^{22A}, O, NR^{22A}, or S; and R⁷ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33I}, -NR^{34I}R^{35I}, -COOR^{33I}, -CONR^{34I}R^{35I}, -NO₂, -SR^{36I}, -SO_{n9}R^{34I}, -SO_{n9}OR^{34I}, -SO_{n9}NR^{34I}R^{35I}, -NHN^{34I}R^{35I}, -ONR^{34I}R^{35I}, -NHC(O)NHN^{34I}R^{35I}, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33L}, -NR^{34L}R^{35L}, -COOR^{33L},

$-\text{CONR}^{34\text{L}}\text{R}^{35\text{L}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{L}}$, $-\text{SO}_{\text{n}12}\text{R}^{34\text{L}}$, $-\text{SO}_{\text{n}12}\text{OR}^{34\text{L}}$, $-\text{SO}_{\text{n}12}\text{NR}^{34\text{L}}\text{R}^{35\text{L}}$, $-\text{NHNR}^{34\text{L}}\text{R}^{35\text{L}}$, $-\text{ONR}^{34\text{L}}\text{R}^{35\text{L}}$, $-\text{NHC}(\text{O})\text{NHNR}^{34\text{L}}\text{R}^{35\text{L}}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R^{12} , R^{13} , R^{21} , $\text{R}^{21\text{A}}$, R^{22} , and $\text{R}^{22\text{A}}$ are independently hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33\text{M}}$, $-\text{NR}^{34\text{M}}\text{R}^{35\text{M}}$, $-\text{COOR}^{33\text{M}}$, $-\text{CONR}^{34\text{M}}\text{R}^{35\text{M}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{M}}$, $-\text{SO}_{\text{n}13}\text{R}^{34\text{M}}$, $-\text{SO}_{\text{n}13}\text{OR}^{34\text{M}}$, $-\text{SO}_{\text{n}13}\text{NR}^{34\text{M}}\text{R}^{35\text{M}}$, $-\text{NHNR}^{34\text{M}}\text{R}^{35\text{M}}$, $-\text{ONR}^{34\text{M}}\text{R}^{35\text{M}}$, $-\text{NHC}(\text{O})\text{NHNR}^{34\text{M}}\text{R}^{35\text{M}}$, substituted 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^{17} is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33\text{P}}$, $-\text{NR}^{34\text{P}}\text{R}^{35\text{P}}$, $-\text{COOR}^{33\text{P}}$, $-\text{CONR}^{34\text{P}}\text{R}^{35\text{P}}$, $-\text{NO}_2$, $-\text{SR}^{36\text{P}}$, $-\text{SO}_{\text{n}15}\text{R}^{34\text{P}}$, $-\text{SO}_{\text{n}15}\text{OR}^{34\text{P}}$, $-\text{SO}_{\text{n}15}\text{NR}^{34\text{P}}\text{R}^{35\text{P}}$, $-\text{NHNR}^{34\text{P}}\text{R}^{35\text{P}}$, $-\text{ONR}^{34\text{P}}\text{R}^{35\text{P}}$, $-\text{NHC}(\text{O})\text{NHNR}^{34\text{P}}\text{R}^{35\text{P}}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; $\text{R}^{33\text{I}}$, $\text{R}^{34\text{I}}$, $\text{R}^{35\text{I}}$, $\text{R}^{36\text{I}}$, $\text{R}^{33\text{L}}$, $\text{R}^{34\text{L}}$, $\text{R}^{35\text{L}}$, $\text{R}^{36\text{L}}$, $\text{R}^{33\text{M}}$, $\text{R}^{34\text{M}}$, $\text{R}^{35\text{M}}$, $\text{R}^{36\text{M}}$, $\text{R}^{33\text{P}}$, $\text{R}^{34\text{P}}$, $\text{R}^{35\text{P}}$, and $\text{R}^{36\text{P}}$ are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n9, n12, n13 and n15 are independently 1 or 2.

[0709] Embodiment 76: The compound of embodiments 66 - 75 having the formula:



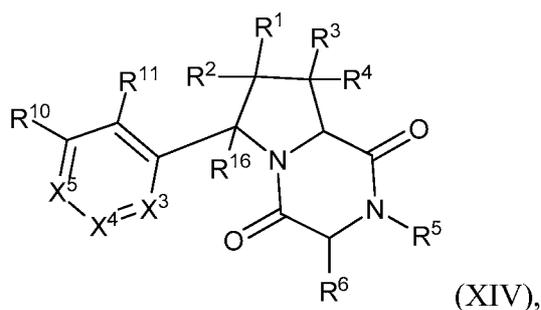
[0710] **Embodiment 77:** A compound having the formula:



wherein, R^1 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33A}$,
 5 $-NR^{34A}R^{35A}$, $-COOR^{33A}$, $-CONR^{34A}R^{35A}$, $-NO_2$, $-SR^{36A}$, $-SO_{n1}R^{34A}$, $-SO_{n1}OR^{34A}$,
 $-SO_{n1}NR^{34A}R^{35A}$, $-NHR^{34A}R^{35A}$, $-ONR^{34A}R^{35A}$, $-NHC(O)NHR^{34A}R^{35A}$, substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 10 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33B}$, $-NR^{34B}R^{35B}$, $-COOR^{33B}$, $-CONR^{34B}R^{35B}$, $-NO_2$, $-SR^{36B}$, $-SO_{n2}R^{34B}$,
 $-SO_{n2}OR^{34B}$, $-SO_{n2}NR^{34B}R^{35B}$, $-NHR^{34B}R^{35B}$, $-ONR^{34B}R^{35B}$, $-NHC(O)NHR^{34B}R^{35B}$, substituted
 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 15 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33C}$, $-NR^{34C}R^{35C}$, $-COOR^{33C}$, $-CONR^{34C}R^{35C}$, $-NO_2$, $-SR^{36C}$, $-SO_{n3}R^{34C}$,
 $-SO_{n3}OR^{34C}$, $-SO_{n3}NR^{34C}R^{35C}$, $-NHR^{34C}R^{35C}$, $-ONR^{34C}R^{35C}$, $-NHC(O)NHR^{34C}R^{35C}$, substituted
 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 20 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33D}$, $-NR^{34D}R^{35D}$, $-COOR^{33D}$, $-CONR^{34D}R^{35D}$, $-NO_2$, $-SR^{36D}$, $-SO_{n4}R^{34D}$, -

$\text{SO}_{n4}\text{OR}^{34D}$, $-\text{SO}_{n4}\text{NR}^{34D}\text{R}^{35D}$, $-\text{NHNr}^{34D}\text{R}^{35D}$, $-\text{ONR}^{34D}\text{R}^{35D}$, $-\text{NHC(O)NHNr}^{34D}\text{R}^{35D}$,
substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$,
5 $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33E}$, $-\text{NR}^{34E}\text{R}^{35E}$, $-\text{COOR}^{33E}$, $-\text{CONR}^{34E}\text{R}^{35E}$, $-\text{NO}_2$, $-\text{SR}^{36E}$,
 $-\text{SO}_{n5}\text{R}^{34E}$, $-\text{SO}_{n5}\text{OR}^{34E}$, $-\text{SO}_{n5}\text{NR}^{34E}\text{R}^{35E}$, $-\text{NHNr}^{34E}\text{R}^{35E}$, $-\text{ONR}^{34E}\text{R}^{35E}$, $-\text{NHC(O)NHNr}^{34E}\text{R}^{35E}$,
substituted 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, $-\text{N}_3$, $-\text{CF}_3$,
10 $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33F}$, $-\text{NR}^{34F}\text{R}^{35F}$, $-\text{COOR}^{33F}$, $-\text{CONR}^{34F}\text{R}^{35F}$, $-\text{NO}_2$, $-\text{SR}^{36F}$,
 $-\text{SO}_{n6}\text{R}^{34F}$, $-\text{SO}_{n6}\text{OR}^{34F}$, $-\text{SO}_{n6}\text{NR}^{34F}\text{R}^{35F}$, $-\text{NHNr}^{34F}\text{R}^{35F}$, $-\text{ONR}^{34F}\text{R}^{35F}$, $-\text{NHC(O)NHNr}^{34F}\text{R}^{35F}$,
substituted 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^{16} is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$,
15 $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33G}$, $-\text{NR}^{34G}\text{R}^{35G}$, $-\text{COOR}^{33G}$,
 $-\text{CONR}^{34G}\text{R}^{35G}$, $-\text{NO}_2$, $-\text{SR}^{36G}$, $-\text{SO}_{n7}\text{R}^{34G}$, $-\text{SO}_{n7}\text{OR}^{34G}$, $-\text{SO}_{n7}\text{NR}^{34G}\text{R}^{35G}$, $-\text{NHNr}^{34G}\text{R}^{35G}$,
 $-\text{ONR}^{34G}\text{R}^{35G}$, $-\text{NHC(O)NHNr}^{34G}\text{R}^{35G}$, substituted 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^{18} is hydrogen, halogen, $-\text{N}_3$, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{CN}$, $-\text{CHO}$, $-\text{OR}^{33H}$, $-\text{NR}^{34H}\text{R}^{35H}$,
 $-\text{COOR}^{33H}$, $-\text{CONR}^{34H}\text{R}^{35H}$, $-\text{NO}_2$, $-\text{SR}^{36H}$, $-\text{SO}_{n8}\text{R}^{34H}$, $-\text{SO}_{n8}\text{OR}^{34H}$, $-\text{SO}_{n8}\text{NR}^{34H}\text{R}^{35H}$,
 $-\text{NHNr}^{34H}\text{R}^{35H}$, $-\text{ONR}^{34H}\text{R}^{35H}$, $-\text{NHC(O)NHNr}^{34H}\text{R}^{35H}$, substituted or unsubstituted alkyl,
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
25 heteroaryl; R^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} ,
 R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} ,
and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
30 $n1$, $n2$, $n3$, $n4$, $n5$, $n6$, $n7$, and $n8$ are independently 1 or 2.

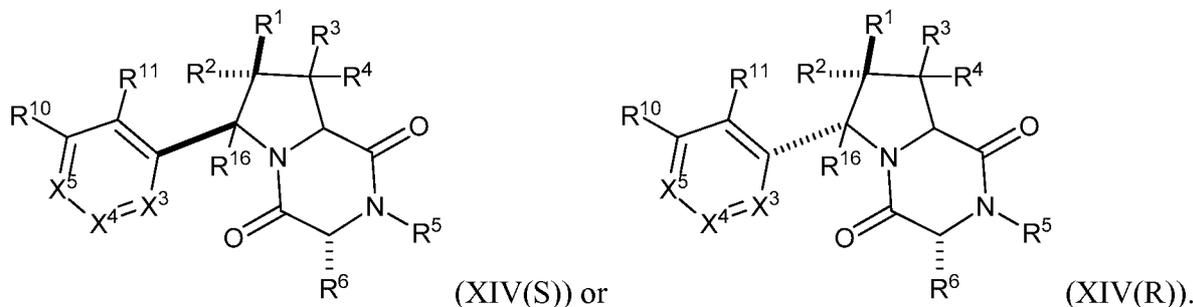
[0711] Embodiment 78: The compound of embodiment 77 having formula



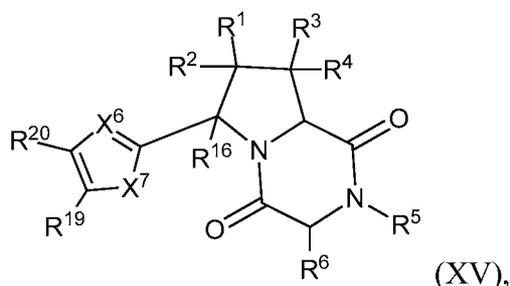
- wherein, X^3 is N or CR^7 ; X^4 is N or CR^8 ; X^5 is N or CR^9 ; R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNr^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNr^{34I}R^{35I}$,
- 5 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^8 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33J}$, $-NR^{34J}R^{35J}$, $-COOR^{33J}$, $-CONR^{34J}R^{35J}$, $-NO_2$, $-SR^{36J}$, $-SO_{n10}R^{34J}$, $-SO_{n10}OR^{34J}$, $-SO_{n10}NR^{34J}R^{35J}$, $-NHNr^{34J}R^{35J}$, $-ONR^{34J}R^{35J}$, $-NHC(O)NHNr^{34J}R^{35J}$,
- 10 substituted 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, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33K}$, $-NR^{34K}R^{35K}$, $-COOR^{33K}$, $-CONR^{34K}R^{35K}$, $-NO_2$, $-SR^{36K}$, $-SO_{n11}R^{34K}$, $-SO_{n11}OR^{34K}$, $-SO_{n11}NR^{34K}R^{35K}$, $-NHNr^{34K}R^{35K}$, $-ONR^{34K}R^{35K}$, $-NHC(O)NHNr^{34K}R^{35K}$,
- 15 $-NHC(O)NHNr^{34K}R^{35K}$, substituted 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} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNr^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNr^{34L}R^{35L}$,
- 20 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} , R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} , and R^{36L} , are independently hydrogen,
- 25

substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n9, n10, n11, and n12 are independently 1 or 2.

5 [0712] **Embodiment 79:** The compound of embodiments 77 - 78 having formula:

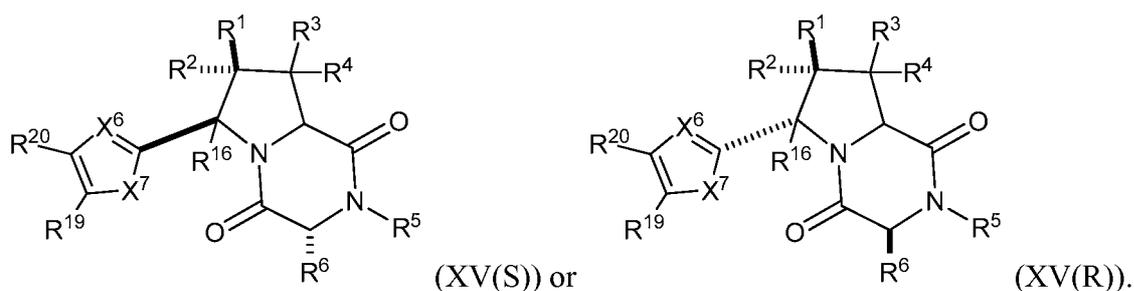


[0713] **Embodiment 80:** The compound of embodiment 77 having formula:

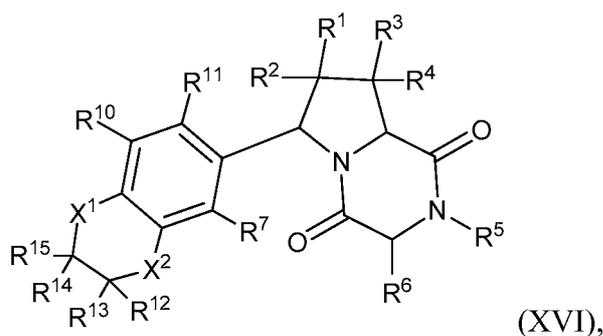


10 wherein, X⁶ is CR²¹ or N; X⁷ is CR²²R²³, S, O, or NR²³; R¹⁹, R²⁰, R²¹, R²² and R²³ are
 15 independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -
 NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -
 SO_{n13}NR^{34M}R^{35M}, -NHNr^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHNr^{34M}R^{35M}, 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; R^{33M}, R^{34M}, R^{35M}, and R^{36M} are independently hydrogen,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n13 is 1 or 2.

[0714] **Embodiment 81:** The compound of embodiments 77 or 80 having formula:

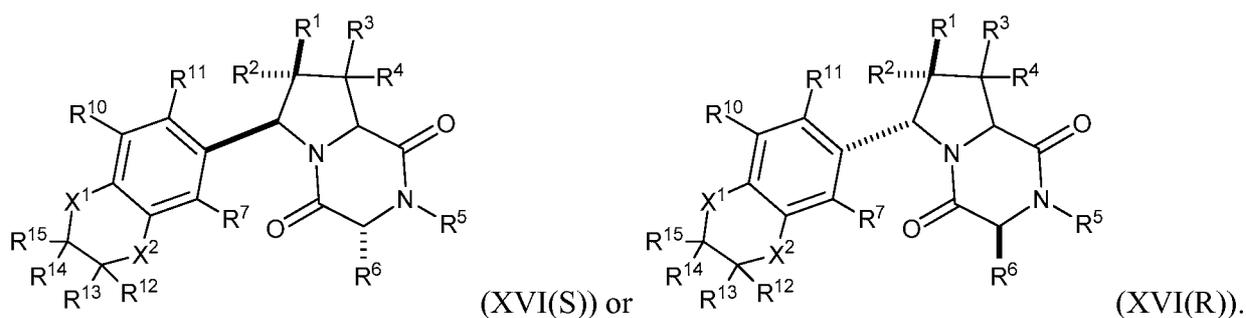


[0715] **Embodiment 82:** The compound of embodiment 77 having formula:

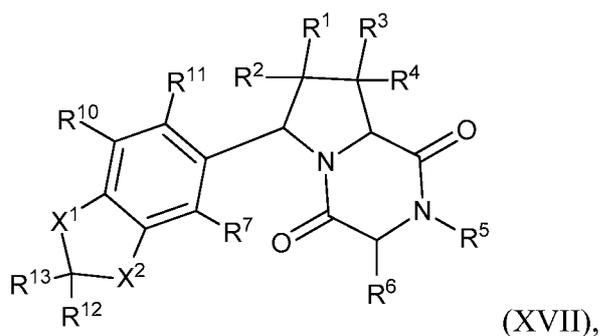


wherein, X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S; X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_{13} is 1 or 2.

[0716] **Embodiment 83:** The compound of embodiments 77 or 82 having formula:



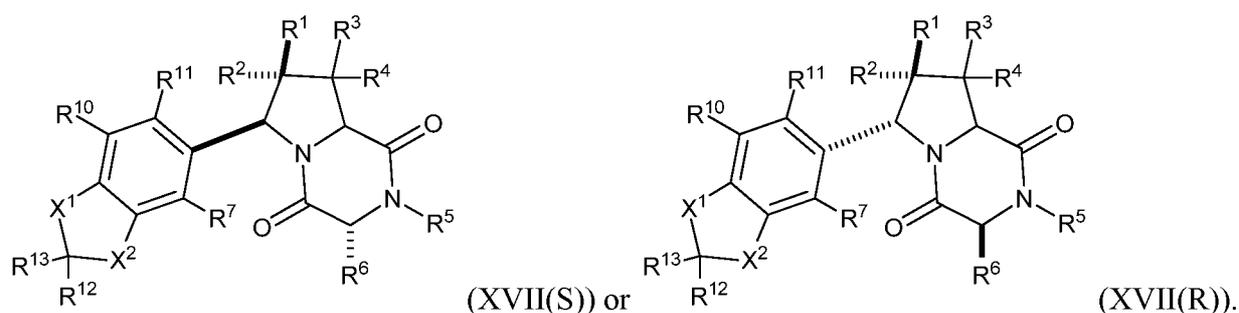
[0717] **Embodiment 84:** The compound of embodiment 77 having formula



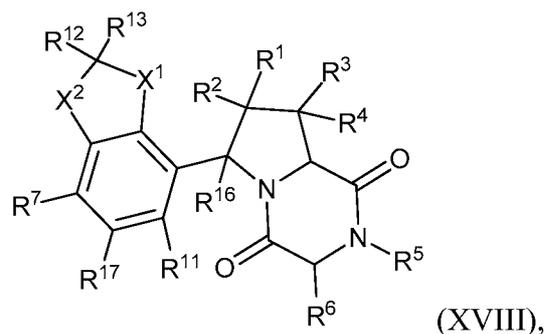
wherein, X¹ is CR²¹R^{21A}, O, NR^{21A}, or S; X² is CR²²R^{22A}, O, NR^{22A}, or S; R⁷ is hydrogen,
 5 halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33I}, -NR^{34I}R^{35I}, -COOR^{33I}, -
 CONR^{34I}R^{35I}, -NO₂, -SR^{36I}, -SO_{n9}R^{34I}, -SO_{n9}OR^{34I}, -SO_{n9}NR^{34I}R^{35I}, -NHN^{34I}R^{35I}, -ONR^{34I}R^{35I},
 -NHC(O)NHN^{34I}R^{35I}, substituted or unsubstituted alkyl, substituted or unsubstituted
 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R¹⁰
 10 and R¹¹ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33L},
 -NR^{34L}R^{35L}, -COOR^{33L}, -CONR^{34L}R^{35L}, -NO₂, -SR^{36L}, -SO_{n12}R^{34L}, -SO_{n12}OR^{34L}, -
 SO_{n12}NR^{34L}R^{35L}, -NHN^{34L}R^{35L}, -ONR^{34L}R^{35L}, -NHC(O)NHN^{34L}R^{35L}, 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, or are optionally joined together to form a substituted or
 unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or
 unsubstituted aryl, or a substituted or unsubstituted heteroaryl; R¹², R¹³, R²¹, R^{21A}, R²² and R^{22A}
 are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -
 NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -
 20 SO_{n13}NR^{34M}R^{35M}, -NHN^{34M}R^{35M}, -ONR^{34M}R^{35M}, -NHC(O)NHN^{34M}R^{35M}, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and n_9 , n_{11} , and n_{13} are independently 1 or 2.

[0718] Embodiment 85: The compound of embodiments 77 or 84 having formula



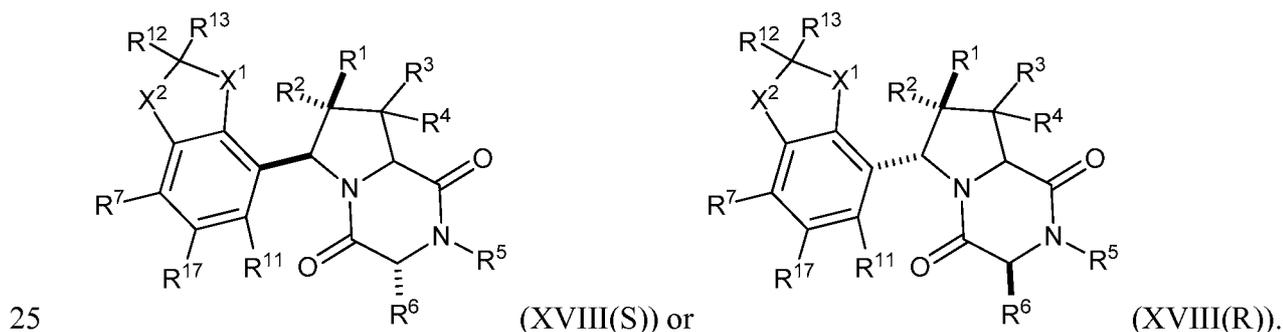
[0719] Embodiment 86: The compound of embodiment 77 having formula



wherein, X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S; X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNR^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNR^{34I}R^{35I}$, substituted 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^{11} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNR^{34L}R^{35L}$, -

ONR^{34L}R^{35L}, -NHC(O)NHR^{34L}R^{35L}, substituted or unsubstituted alkyl, substituted or
 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or
 are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or
 5 unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or
 unsubstituted heteroaryl; R¹², R¹³, R²¹, R^{21A}, R²², and R^{22A} are independently hydrogen, halogen,
 -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33M}, -NR^{34M}R^{35M}, -COOR^{33M}, -CONR^{34M}R^{35M}, -
 NO₂, -SR^{36M}, -SO_{n13}R^{34M}, -SO_{n13}OR^{34M}, -SO_{n13}NR^{34M}R^{35M}, -NHR^{34M}R^{35M}, -ONR^{34M}R^{35M},
 -NHC(O)NHR^{34M}R^{35M}, 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; R¹⁷
 is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33P}, -NR^{34P}R^{35P}, -COOR^{33P},
 -CONR^{34P}R^{35P}, -NO₂, -SR^{36P}, -SO_{n15}R^{34P}, -SO_{n15}OR^{34P}, -SO_{n15}NR^{34P}R^{35P}, -NHR^{34P}R^{35P}, -
 ONR^{34P}R^{35P}, -NHC(O)NHR^{34P}R^{35P}, substituted or unsubstituted alkyl, substituted or
 15 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or
 are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a substituted or
 unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or
 unsubstituted heteroaryl; R^{33I}, R^{34I}, R^{35I}, R^{36I}, R^{33L}, R^{34L}, R^{35L}, R^{36L}, R^{33M}, R^{34M}, R^{35M}, R^{36M},
 20 R^{33P}, R^{34P}, R^{35P}, and R^{36P} are independently hydrogen, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 heteroaryl; and n9, n12, n13 and n15 are independently 1 or 2.

[0720] Embodiment 87: The compound of embodiments 77 or 86 having formula



- [0721] **Embodiment 88:** The compound of embodiment 1, wherein said compound is an epigenetic inhibitor.
- [0722] **Embodiment 89:** The compound of embodiment 88, wherein said compound inhibits the activity of HMT SUV39H1.
- 5 [0723] **Embodiment 90:** The compound of embodiments 88 - 89, wherein said compound specifically inhibits the activity of HMT SUV39H1.
- [0724] **Embodiment 91:** The compound of embodiments 88-90, wherein said compound inhibits the activity of HMT G9a.
- [0725] **Embodiment 92:** The compound of embodiments 88-91, wherein said compound
10 specifically inhibits the activity of HMT G9a
- [0726] **Embodiment 93:** The compound of any one of embodiments 88 - 92, wherein said compound inhibits the activity of HMT SUV39H1 and the activity of HMT G9a.
- [0727] **Embodiment 94:** The compound of any one of embodiments 88 - 93, wherein said compound specifically inhibits the activity of HMT SUV39H1 and the activity of HMT G9a.
- 15 [0728] **Embodiment 95:** The compound of embodiment 1, wherein said compound inhibits H3K9 trimethylation or dimethylation.
- [0729] **Embodiment 96:** A method of treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of one of embodiment 1.
- 20 [0730] **Embodiment 97:** The method of embodiments 95-96, wherein said cancer is a solid or blood tumor.
- [0731] **Embodiment 98:** The method of embodiments 96 or 97, wherein said cancer is ovarian cancer, breast cancer, lung cancer, leukemia, AML, CML, lymphoma, pancreatic cancer, kidney cancer, melanoma, liver cancer, colon cancer, sarcoma, multiple myeloma, brain cancer, or
25 prostate cancer.
- [0732] **Embodiment 99:** The method of embodiments 96 - 98, further comprising administering at least one additional anticancer agent.

- [0733] **Embodiment 100:** The method of embodiments 96 to 99, wherein said at least one additional anticancer agent comprises an epigenetic inhibitor or a multi-kinase inhibitor.
- [0734] **Embodiment 101:** The method of embodiments 96 to 100, wherein said method comprises administering a first amount of said compound and a second amount of at least one
5 additional anticancer agent, wherein the first amount and second amount are together an effective amount to provide a synergistic therapeutic effect.
- [0735] **Embodiment 102:** The method of embodiments 96 to 101, wherein said additional anticancer agent is an epigenetic inhibitor.
- [0736] **Embodiment 103:** The method of embodiments 96 or 102, wherein said epigenetic
10 inhibitor is azacitidine or decitadine.
- [0737] **Embodiment 104:** The method of embodiments 96 to 103, wherein said compound and said epigenetic inhibitor are co-administered as a pharmaceutical composition.
- [0738] **Embodiment 105:** The method embodiments 96 - 101, wherein said additional anticancer agent is a multi-kinase inhibitor.
- 15 [0739] **Embodiment 106:** The method of embodiments 96 - 105, wherein said multi-kinase inhibitor is sorafenib.
- [0740] **Embodiment 107:** The method of embodiment 96-105, wherein said compound and said multi-kinase inhibitor are co-administered as a pharmaceutical composition.
- [0741] **Embodiment 108:** The method of embodiments 96 to 107, wherein said cancer is
20 ovarian cancer.
- [0742] **Embodiment 109:** A pharmaceutical composition comprising a compound of embodiment 1 and a pharmaceutically acceptable excipient.
- [0743] **Embodiment 110:** A pharmaceutical composition comprising a compound of embodiment 1 and at least one additional anticancer agent.
- 25 [0744] **Embodiment 111:** The pharmaceutical composition of embodiment 110, wherein said at least one additional anticancer agent comprises a multi-kinase inhibitor or an epigenetic inhibitor.

[0745] **Embodiment 112:** The pharmaceutical composition of embodiments 110 or 111, wherein said combination includes a first amount of said compound and a second amount of a multi-kinase inhibitor, wherein the first amount and second amount are together an effective amount to provide a synergistic therapeutic effect.

5 [0746] **Embodiment 113:** The pharmaceutical composition of embodiments 110 to 112, wherein said combination includes a first amount of said compound and a second amount of an epigenetic inhibitor, wherein the first amount and second amount are together an effective amount to provide a synergistic therapeutic effect.

[0747] **Embodiment 114:** The pharmaceutical composition of embodiments 110 to 113,
10 wherein said combination includes a first amount of said compound, a second amount of a multi-kinase inhibitor, an a third amount of an epigenetic inhibitor, wherein the first amount, second, and third amounts are together an effective amount to provide a synergistic therapeutic effect.

[0748] **Embodiment 115:** The pharmaceutical composition of any one of embodiments 109 to 113, wherein said multi-kinase inhibitor is sorafenib and said epigenetic inhibitor is azacitidine
15 or decitadine.

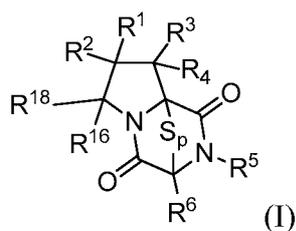
[0749] **Embodiment 116:** The pharmaceutical composition of any one of embodiments 109 to 115, for use in cancer.

[0750] **Embodiment 117:** The pharmaceutical composition of any one of embodiments 109 to 116, for use in solid and blood tumors, including ovarian cancer, breast cancer, lung cancer,
20 leukemia, AML, CML, lymphoma, pancreatic cancer, kidney cancer, melanoma, liver cancer, colon cancer, sarcoma, multiple myeloma, brain cancer, or prostate cancer.

[0751] **Embodiment 118:** The pharmaceutical composition of any one of embodiments 109 to 117, for use in non-small cell lung cancer.

[0752] **Embodiment 119:** The pharmaceutical composition of any one of embodiments 109 to
25 118, wherein said compound and said multi-kinase inhibitor or said epigenetic inhibitor are co-administered as a single dosage form.

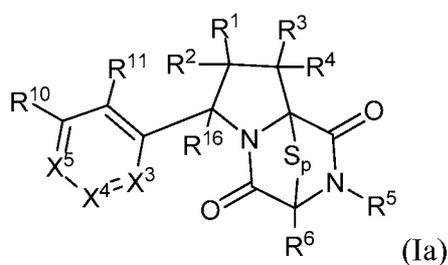
[0753] **Embodiment 120:** A compound having the formula:



wherein, p is 2, 3 or 4; and R¹, R², R³, R⁴, R⁵, R⁶, R¹⁶, and R¹⁸ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0754] Embodiment 121: The compound of embodiment 120, wherein R¹⁸ is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

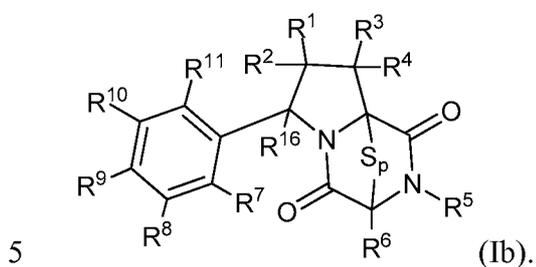
[0755] Embodiment 122: The compound of embodiment 120-121 having the formula:



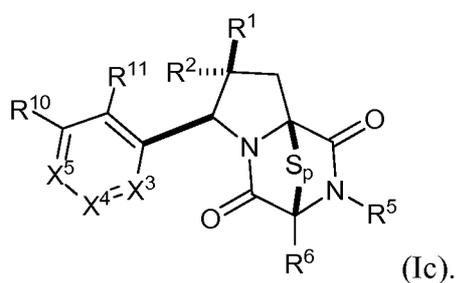
wherein, X³ is N or CR⁷; X⁴ is N or CR⁸; X⁵ is N or CR⁹; R⁷, R¹⁰ and R¹¹ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R⁸ and R⁹ are independently hydrogen, halogen, -N₃, -NO₂, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -OCH₃, -NHCNHNH₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, wherein R⁸ and R⁹ are optionally

joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl; and p is 2, 3, or 4.

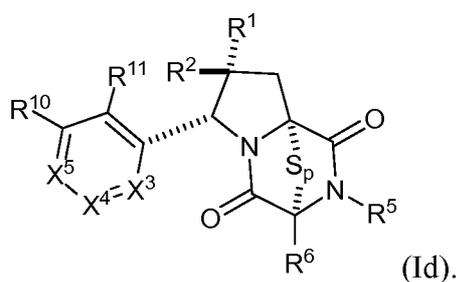
[0756] Embodiment 123: The compound of embodiment 120-122 having the formula:



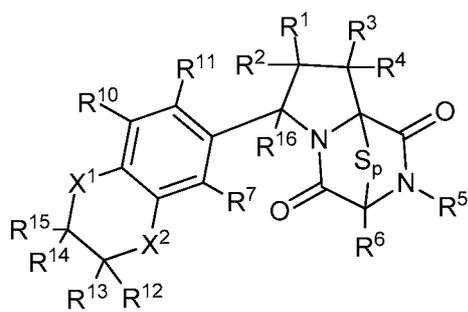
[0757] Embodiment 124: The compound of embodiment 120-122 having the formula:



[0758] Embodiment 125: The compound of embodiment 120-122 having the formula:

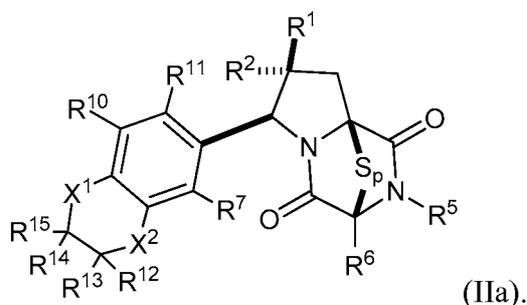


10 **[0759] Embodiment 126:** The compound of any one of embodiments 122-125 having formula:

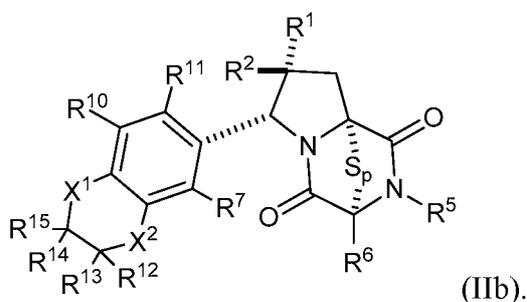


wherein, X^1 and X^2 are independently CH_2 , O, NH, N, S, or Se; and R^{12} , R^{13} , R^{14} , and R^{15} are independently hydrogen, halogen, $-N_3$, $-NO_2$, $-CF_3$, CCl_3 , CBr_3 , Cl_3 , $-CN$, $-OH$, $-NH_2$, $-COOH$, $CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, 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, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

10 **[0760] Embodiment 127:** The compound of embodiment 126 having formula:

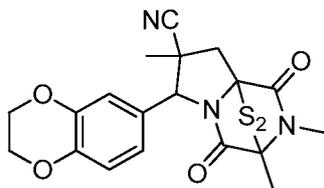


[0761] Embodiment 128: The compound of embodiment 127 having formula:

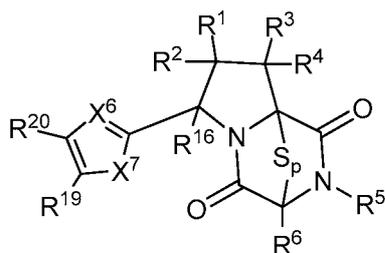


[0762] Embodiment 129: The compound of one of embodiments 120 to 129, wherein p is 2.

[0763] **Embodiment 130:** The compound of any one of embodiments 126-129 having formula:



[0764] **Embodiment 131:** The compound of embodiment 120 having formula:



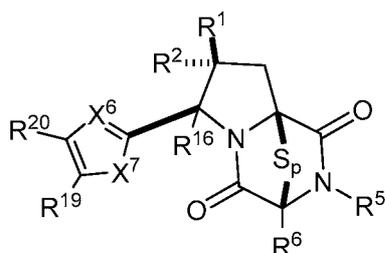
5

wherein, X^6 is CH, CR^{21} , S, O, or N; X^7 is CH_2 , CR^{22} , S, O, N, or NH; R^{19} , R^{20} , R^{21} , and R^{22} are independently hydrogen, halogen, $-N_3$, $-NO_2$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$; 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, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

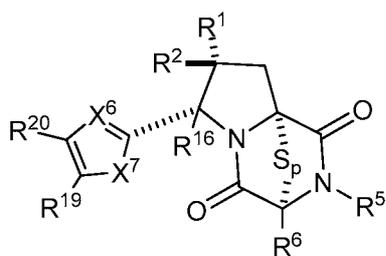
10

[0765] **Embodiment 132:** The compound of any one of embodiments 120 or 131 having formula:

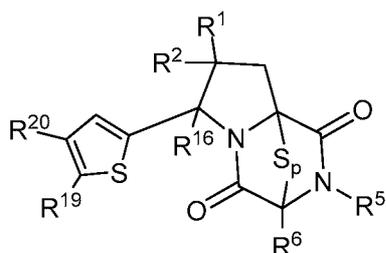
15



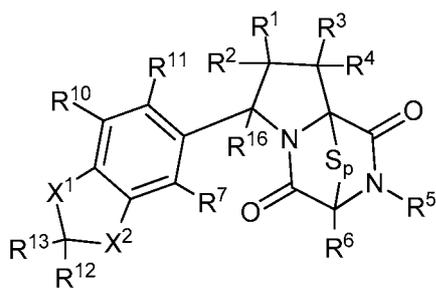
[0766] **Embodiment 133:** The compound of any one of embodiments 120 or 131 having formula:



[0767] **Embodiment 134:** The compound of any one of embodiments 120 or 131-133 having formula

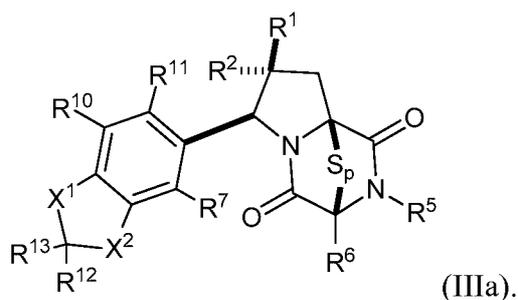


5 [0768] **Embodiment 135:** The compound of any one of embodiments 120-125 having formula:

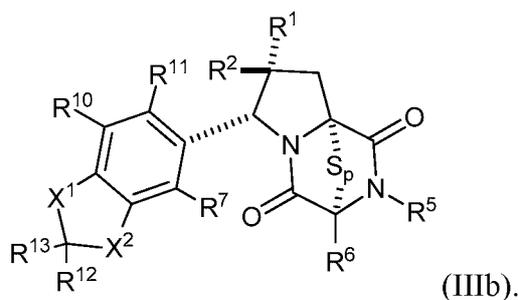


wherein, R^{12} and R^{13} are independently hydrogen, halogen, $-N_3$, $-CF_3$, CCl_3 , CBr_3 , Cl_3 , $-CN$, $-OH$, $-NH_2$, $-COOH$, $CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

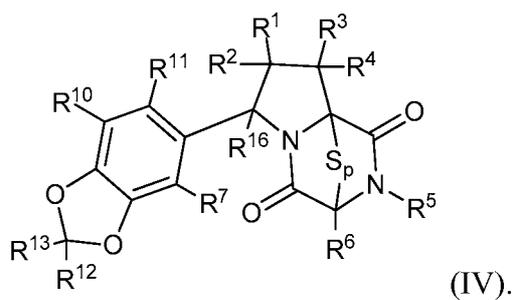
[0769] **Embodiment 136:** The compound of embodiment 135 having formula:



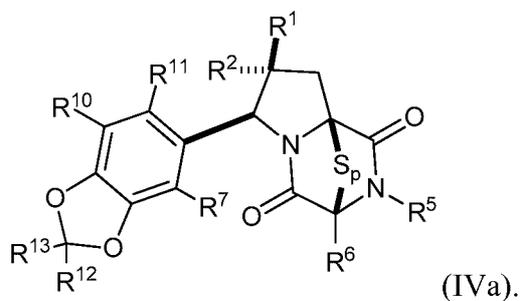
[0770] **Embodiment 137:** The compound of embodiment 135 having formula:



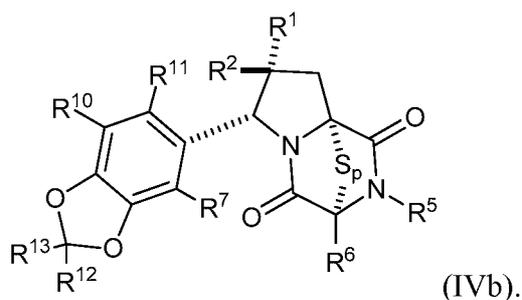
[0771] **Embodiment 138:** The compound of any one of embodiments 120-125 or 135-137
5 having formula:



[0772] **Embodiment 139:** The compound of embodiment 138 having formula:



[0773] **Embodiment 140:** The compound of embodiment 138 having formula:



[0774] **Embodiment 141:** The compound of any one of embodiments 135 to 140, wherein p is 2.

[0775] **Embodiment 142:** The compound of any one of embodiment 120-128 or 135-141, wherein R¹ is halogen, -N₃, -NO₂, -CF₃, CCl₃, CBr₃, Cl₃, -CN, -CHO, -CONH₂, or substituted or unsubstituted heteroalkyl.

[0776] **Embodiment 143:** The compound of any one of embodiments 120-128 or 135-142, wherein R² is halogen, -N₃, -NO₂, -CF₃, CCl₃, CBr₃, Cl₃, -CN, -CHO, -CONH₂, or substituted or unsubstituted heteroalkyl.

[0777] **Embodiment 144:** The compound of any one of embodiments 120-128 or 135-142, wherein R¹ is CN.

[0778] **Embodiment 145:** The compound of any one of embodiments 120-128 or 135-144, wherein R¹ is C₁-C₅ substituted or unsubstituted heteroalkyl.

[0779] **Embodiment 146:** The compound of any one of embodiments 1120-128 or 135-145, wherein R² is CN.

[0780] **Embodiment 147:** The compound of any one of embodiments 120-128 or 135-146, wherein R² is C₁-C₅ substituted or unsubstituted heteroalkyl.

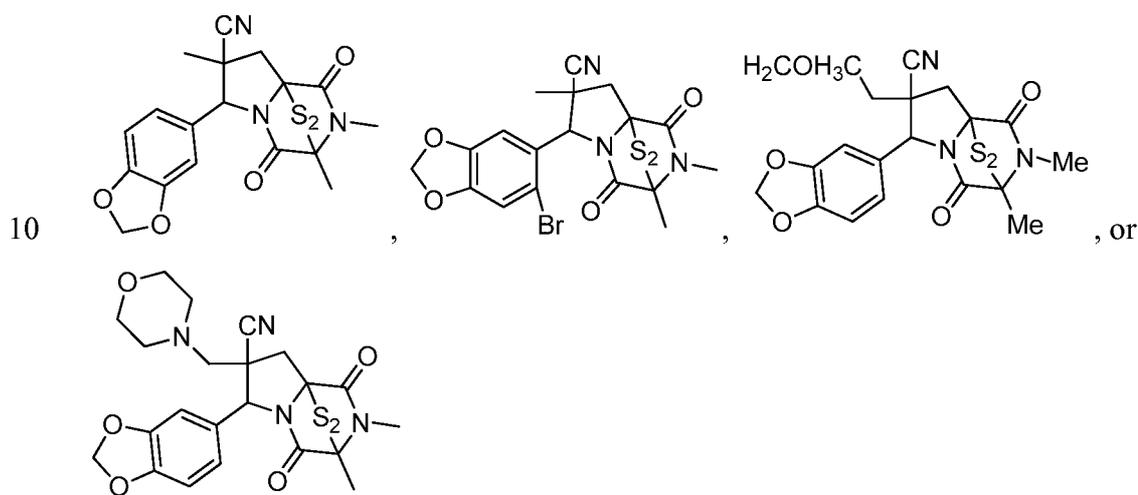
[0781] **Embodiment 148:** The compound of embodiment 142, wherein said substituted or substituted heteroalkyl provides polarity.

[0782] **Embodiment 149:** The compound of any one of embodiments 120-128, 135-148, wherein R⁶ is hydrogen, 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.

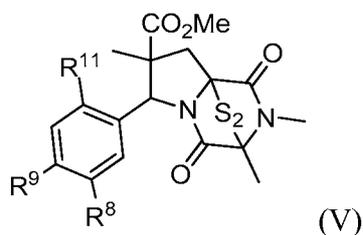
[0783] Embodiment 150: The compound of any one of embodiments, 120-122, 126, 135, or 138, wherein R¹⁶ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, C₁-C₃ substituted or unsubstituted alkyl, or C₁-C₃ substituted or unsubstituted heteroalkyl.

[0784] Embodiment 151: The compound of any one of embodiments 120-128 or 135-140, wherein p is 3.

[0785] Embodiment 152: The compound of any one of embodiments 135, 136, 138, or 140 having formula:

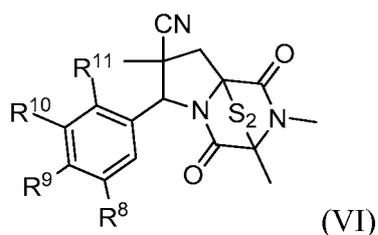


[0786] Embodiment 153: The compound of any one of embodiments 120-125 having formula:



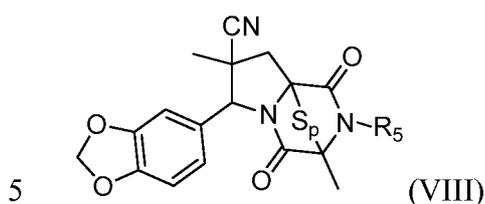
15 wherein, R⁸ is hydrogen or OCH₃; and R⁹ and R¹¹ are independently hydrogen or halogen.

[0787] Embodiment 154: The compound of any one of embodiments 120-125 having formula:



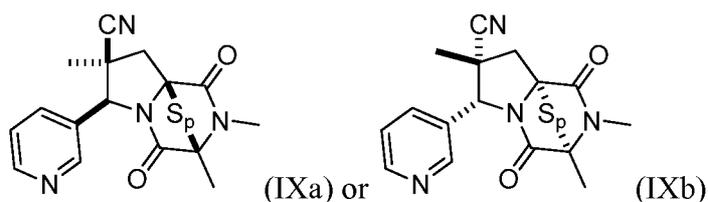
wherein, R^8 is hydrogen or $-OCH_3$; and R^9 , R^{10} , and R^{11} are independently hydrogen or halogen.

[0788] Embodiment 155: The compound of any one of embodiments 135-140 having formula:



wherein; R^5 is unsubstituted alkyl, unsubstituted heteroalkyl, or unsubstituted heterocycloalkyl; and p is 2 or 3.

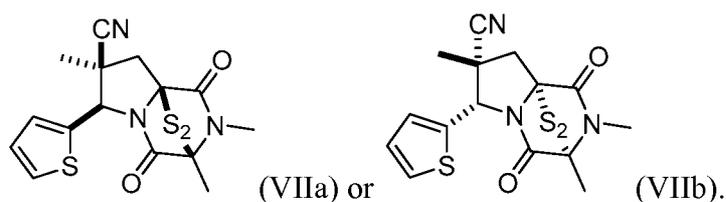
[0789] Embodiment 156: The compound of embodiment 120 having the formula:



10 wherein, p is 2 or 4.

[0790] Embodiment 157: The compound of embodiment 155 or 156 wherein p is 2. .

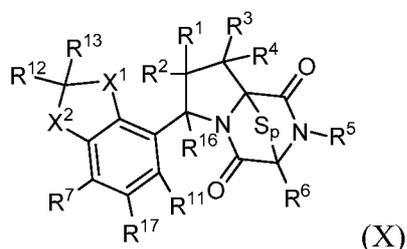
[0791] Embodiment 158: The compound of embodiment 120 having the formula:



15 **[0792] Embodiment 159:** The compound of any one of embodiments 120-128 or 135-140, wherein R^1 is CN and R^2 is substituted or unsubstituted C_2 - C_{20} alkyl, substituted or unsubstituted

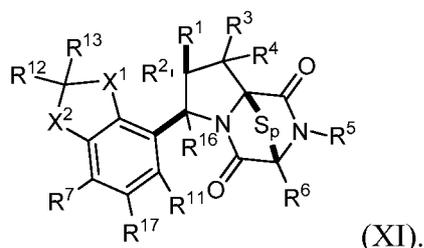
C₂-C₂₀ heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0793] **Embodiment 160:** A compound having formula:

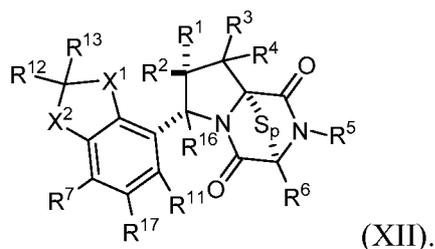


- 5 wherein, R¹⁷ is hydrogen, halogen, -N₃, -NO₂, -, -CF₃, CCl₃, CBr₃, Cl₃, -CN, -OH, -NH₂, -COOH, CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂; substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally bonded together
10 to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl.

[0794] **Embodiment 161:** The compound of embodiment 160 having formula:

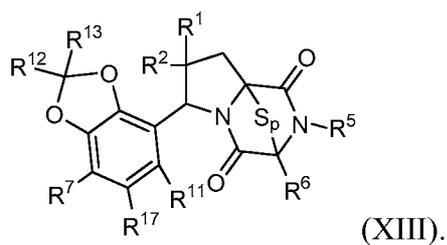


[0795] **Embodiment 162:** The compound of embodiment 160 having formula:

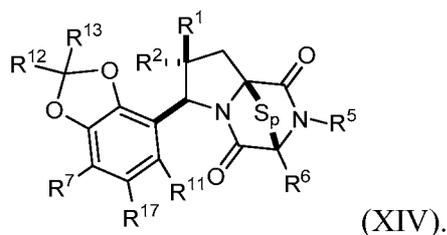


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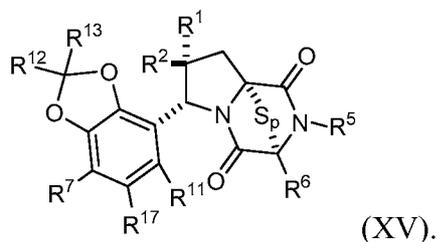
[0796] **Embodiment 163:** The compound of embodiment 160 having formula:



[0797] **Embodiment 164:** The compound of any one of embodiments 160 or 163 having formula:

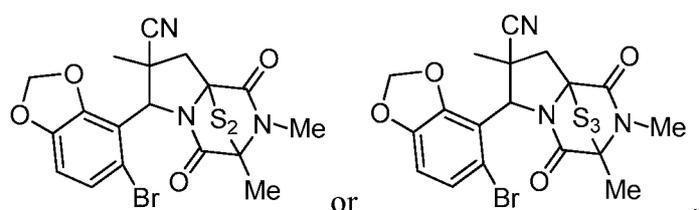


5 [0798] **Embodiment 165:** The compound of any one of embodiments 152 or 160 having formula:

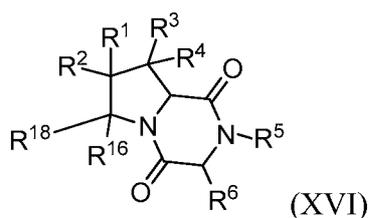


[0799] **Embodiment 166:** The compound of any one of embodiments 160-165 wherein p is 2.

10 [0800] **Embodiment 167:** The compound of any one of embodiments 160-165 having formula:

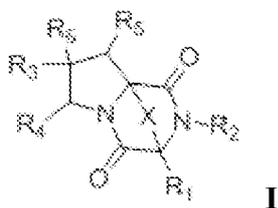


[0801] **Embodiment 168:** A compound having the formula:



- wherein, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^{16} , and R^{18} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, 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.

[0802] Embodiment 169: A compound of Formula I:



- wherein: X is selected from S_2 , S_3 , or S_4 ; R_1 is selected from H, alkyl, $-C(=O)O$ -alkyl, alkoxy, R_7NHR_7 , R_7NHR_8 , R_7 cycloalkyl, R_7 aryl, R_7 morpholinyl, heteroarylalkyl, R_7 piperazinyl, or R_7 piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R_2 is selected from H, alkyl, R_7NHR_7 , R_7NHR_8 , R_7 cycloalkyl, R_7 aryl, R_7 morpholinyl, heteroarylalkyl, R_7 piperazinyl, or R_7 piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R_3 is selected from H, alkyl, aryl, heteroaryl, nitrile, F, Cl, OAc, $-O$ -alkyl, or $-O$ -aryl; R_4 is selected from alkyl, haloalkyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, benzodioxanyl, dioxanyl, benzoxazinyl, piperadiny-1-methyl, heterocycle, indolyl, pyridinyl, piperazinyl, furyl, thienyl, heteroarylalkyl, or phenyl, or optionally substituted variants thereof; R_5 is selected from H, aryl, alkyl, haloalkyl, heteroaryl, phenyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, heterocycle, indolyl, or pyridinyl, or optionally substituted variants thereof; R_6 is selected from CN, NO_2 , $-S(O)_2$ alkyl, $-S(O)_2$ aryl, $-S(O)_2R_7$, $-S(O)_2CH_2CN$, $-(C=O)NH_2$, $-(N=H)OMe$, $-(C=O)(CH_2)_{1-4}CN$, $-(C=O)(CH_2)_{1-4}SO_2R_7$, -

(C=O)(CH₂)₁₋₄CO₂R₇, -(C=O)(CH₂)₁₋₄CO₂H, -(C=O)(CH₂)₁₋₄CH₂NH₂, -(C=O)(CH₂)₁₋₄CH₂NHCOR₅, -(C=O)(CH₂)₁₋₄CH₂NR₁R₂, (CH₂)₁₋₄OH, -(C=O)OH, -(C=O)O-alkyl, CH₂NHR₉, or CHR₁₀NHR₁₁; R₇ is alkyl; R₈ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₉ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; R₁₀ is selected from alkyl, aryl or heteroaryl; and R₁₁ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy.

[0803] Embodiment 170: The compound of embodiment 169, wherein X is S₂.

[0804] Embodiment 171: The compound of embodiments 169-170, wherein R₁ is methyl.

[0805] Embodiment 172: The compound of any one of the embodiments 169-171, wherein R₂ is methyl.

[0806] Embodiment 173: The compound of any one of embodiments 169-172, wherein R₃ is methyl.

[0807] Embodiment 174: The compound of any one of embodiments 169-173, wherein R₄ is selected from benzodioxinyl, phenyl optionally substituted with one or more substituents selected from the group consisting of halo and alkoxy, or piperonyl.

[0808] Embodiment 175: The compound of embodiment 174, wherein R₄ is piperonyl.

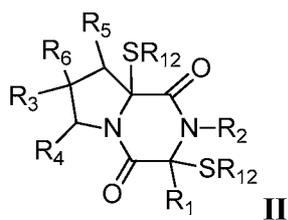
[0809] Embodiment 176: The compound of any one of embodiments 169-175, wherein R₅ is H.

[0810] Embodiment 177: The compound of any one of embodiments 169-175, wherein R₅ is an aryl optionally substituted with one or more groups selected from -OH, -CN, NO₂, -C(=O), halo, haloalkyl, haloaryl, and heteroarylalkyl.

[0811] Embodiment 178: The compound of any one of embodiments 169-177, wherein R₆ is selected from the group consisting of CN, -(C=O)O-tBu and -(C=O)OMe.

[0812] Embodiment 179: The compound of any one of embodiments 169-178, wherein R₇ is alkyl.

[0813] Embodiment 180: A compound of Formula II:

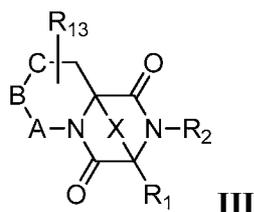


wherein: R₁ is selected from H, alkyl, -C(=O)O-alkyl, -C(=O)OR₇aryl, alkoxy, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₃ is selected from H, alkyl, aryl, heteroaryl, nitrile, F, Cl, OAc, O-alkyl, and O-aryl; R₄ is selected from alkyl, haloalkyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, benzodioxanyl, dioxanyl, benzoxazinyl, piperadinyll-1-methyl, heterocycle, indolyl, pyridinyl, piperazinyl, furyl, thienyl, heteroarylalkyl, or phenyl, or optionally substituted variants thereof; R₅ is selected from H, aryl, alkyl, haloalkyl, heteroaryl, phenyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, heterocycle, indolyl, or pyridinyl, or optionally substituted variants thereof; R₆ is selected from CN, NO₂, -S(O)₂alkyl, -S(O)₂aryl, -S(O)₂R₇, -S(O)₂CH₂CN, -(C=O)NH₂, -(N=H)OMe, -(C=O)(CH₂)₁₋₄CN; -(C=O)(CH₂)₁₋₄SO₂R₇; -(C=O)(CH₂)₁₋₄CO₂R₇; -(C=O)(CH₂)₁₋₄CO₂H; -(C=O)(CH₂)₁₋₄CH₂NH₂; -(C=O)(CH₂)₁₋₄CH₂NHCOR₅; -(C=O)(CH₂)₁₋₄CH₂NR₁R₂; (CH₂)₁₋₄OH, -(C=O)OH, -(C=O)O-alkyl; CH₂NHR₉, or CHR₁₀NHR₁₁; R₇ is alkyl; R₈ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₉ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; R₁₀ is selected from alkyl, aryl or heteroaryl; R₁₁ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; and R₁₂ is selected from methyl or a thiol-protecting group.

[0814] Embodiment 181: The compound of embodiment 180, wherein R₄ is selected from benzodioxinyl, phenyl optionally substituted with one or more substituents selected from the group consisting of halo and alkoxy, or piperonyl.

[0815] Embodiment 182: The compound of embodiment 180, wherein R₅ is an aryl optionally substituted with one or more groups selected from -OH, -CN, NO₂, -C(=O), halo, haloalkyl, haloaryl, and heteroarylalkyl.

[0816] **Embodiment 183:** A compound of Formula III:



wherein: X is selected from S₂, S₃, or S₄; R₁ is selected from H, alkyl, -C(=O)O, alkyl, alkoxy, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₇ is alkyl; R₈ is selected from selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₁₃ is selected from H, alkyl, aryl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, sulfonamide or optionally substituted variants thereof; A is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; B is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; C is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; and R₁₄ is selected from the group consisting of alkyl, aryl, acyl, and -O-carboxy.

[0817] **Embodiment 184:** The compound of embodiment 183, wherein R₁ is methyl.

[0818] **Embodiment 185:** The compound of any one of embodiments 183-184, wherein R₂ is methyl.

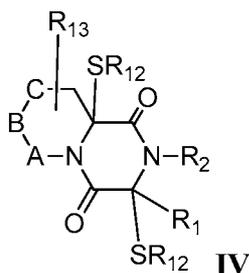
[0819] **Embodiment 186:** The compound of any one of embodiments 183-185, wherein A is selected from C=O, NH, NR₁₄, O, S, and SO₂, and both B and C are CH₂.

[0820] **Embodiment 187:** The compound of any one of embodiments 183-185, wherein B is selected from C=O, NH, NR₁₄, O, S, and SO₂, and both A and C are CH₂.

[0821] **Embodiment 188:** The compound of any one of embodiments 183-185, wherein C is selected from C=O, NH, NR₁₄, O, S, and SO₂, and both A and B are CH₂.

[0822] **Embodiment 189:** The compound of any one of embodiments 183-185, wherein each of A, B and C is CH₂.

[0823] **Embodiment 190:** A compound from the genus of Formula IV:



wherein: X is selected from S₂, S₃, or S₄; R₁ is selected from H, alkyl, -C(=O)O, alkyl, alkoxy, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₇ is alkyl; R₈ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₁₂ is selected from methyl or a thiol-protecting group; R₁₃ is selected from H, alkyl, aryl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide or optionally substituted variants thereof; A is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; B is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; C is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; and R₁₄ is selected from the group consisting of alkyl, aryl, acyl, and -O-carboxy.

[0824] **Embodiment 191:** The compound of embodiment 190, wherein R₁ is selected from methyl or hydrogen.

[0825] **Embodiment 192:** The compound of embodiments 190-191, wherein R₂ is selected from methyl or hydrogen.

[0826] **Embodiment 193:** The compound of any one of embodiments 190-192, wherein R₁₃ is piperonyl.

[0827] **Embodiment 194:** The compound of any one of embodiments 190-192, wherein R₁₃ is a phenyl substituted with one or more substituents selected from halo and alkoxy.

[0828] **Embodiment 195:** The compound of any one of embodiments 190-192, wherein R₁₃ is hydrogen.

[0829] **Embodiment 196:** The compound of any one of embodiments 190-192, wherein R₁₃ is CN.

5 [0830] **Embodiment 197:** The compound of any one of embodiments 190-192, wherein R₁₃ is -C(=O)O-alkyl.

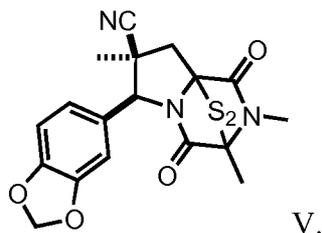
[0831] **Embodiment 198:** The compound of any one of embodiments 190-197, wherein A is selected from C=O, NH, NR₁₄, O, S, and SO₂, and both B and C are CH₂.

10 [0832] **Embodiment 199** The compound of any one of embodiments 190-197, wherein B is selected from C=O, NH, NR₁₄, O, S, and SO₂, and both A and C are CH₂.

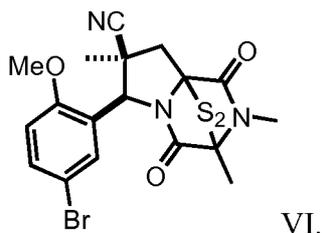
[0833] **Embodiment 200:** The compound of any one of embodiments 190-197, wherein C is selected from C=O, NH, NR₁₄, O, S, and SO₂, and both A and B are CH₂.

[0834] **Embodiment 201:** The compound of any one of embodiments 189-196, wherein each of A, B and C is CH₂.

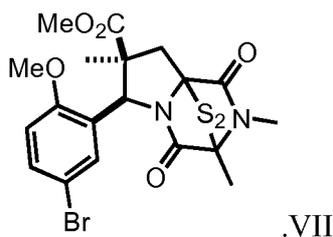
15 [0835] **Embodiment 202:** A compound of Formula V for treating a diseased state:



[0836] **Embodiment 203:** A compound of Formula VI for treating a diseased state:



[0837] **Embodiment 204:** A compound of Formula VII for treating a diseased state:



[0838] **Embodiment 205:** A pharmaceutically acceptable salt, prodrug, hydrate, solvate, or acid salt hydrate of the compound of any one of embodiments 170-204.

[0839] **Embodiment 206:** A pharmaceutical composition comprising an effective amount of a compound of any one of embodiments 170-204 or a pharmaceutically acceptable salt, prodrug, hydrate, solvate, or acid salt hydrate of the compound of embodiment 205.

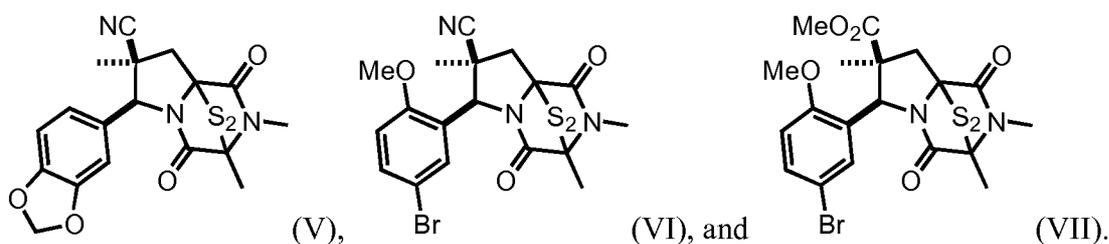
[0840] **Embodiment 207:** The pharmaceutical composition of embodiment 206, wherein the composition contains a stereoisomer, prodrug, pharmaceutically acceptable salt, hydrate, solvate, acid salt hydrate, N -oxide, prodrug ester, or isomeric crystalline form of the compound.

[0841] **Embodiment 208:** The pharmaceutical composition of any one of embodiments 206-207, wherein the compound is mixed with a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0842] **Embodiment 209:** A method of dysregulating a histone methyltransferase comprising administering an effective amount of a compound of any one of embodiments 170-204, a pharmaceutically-acceptable salt, prodrug, hydrate, solvate, or acid salt hydrate of embodiment 205, or a pharmaceutical composition of any one of embodiments 206-208 to a subject in need thereof.

[0843] **Embodiment 210:** The method of embodiment 209, wherein the subject is a human.

[0844] **Embodiment 211:** The method of any one of embodiments 209-210, wherein the compound is selected from group consisting of:

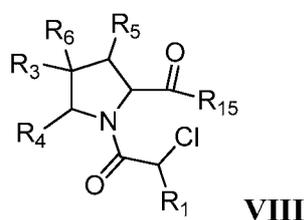


[0845] Embodiment 212: A method for treating or preventing a disease condition comprising administering an effective amount of the compound of any one of embodiments 170-204, a pharmaceutically-acceptable salt, prodrug, hydrate, solvate, or acid salt hydrate of embodiment 205, or a pharmaceutical composition of any one of embodiments 206-208 to a subject in need of.

[0846] Embodiment 213: The method of embodiment 212, wherein the disease condition is selected from cancer, diabetes, an infectious disease, an autoimmune disease, or pain.

[0847] Embodiment 214: The method of embodiment 213, wherein the cancer is selected from prostate cancer, ovarian cancer, pancreatic cancer, chronic myelogenous (or myeloid) leukemia, or melanoma.

[0848] Embodiment 215: A compound of Formula VIII:



wherein: X is selected from S₂, S₃, or S₄; R₁ is selected from H, or alkyl, -C(=O)O-alkyl, alkoxy, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₃ is selected from H, alkyl, aryl or heteroaryl; R₄ is selected from alkyl, haloalkyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, benzodioxanyl, dioxanyl, benzoxazinyl, piperadinyl-1-methyl, heterocycle, indolyl, pyridinyl, piperazinyl, furyl, thienyl, heteroarylalkyl, or phenyl, or optionally substituted variants thereof; R₅ is selected from H, aryl, alkyl, haloalkyl, heteroaryl, phenyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, heterocycle, indolyl, or pyridinyl, or optionally substituted variants thereof; R₆ is selected from CN, NO₂, -S(O)₂alkyl, -S(O)₂aryl, -S(O)₂R₇, -S(O)₂CH₂CN, -(C=O)NH₂, -(N=H)OMe, -(C=O)(CH₂)₁₋₄CN; -(C=O)(CH₂)₁₋₄SO₂R₇; -(C=O)(CH₂)₁₋₄CO₂R₇; -(C=O)(CH₂)₁₋₄CO₂H; -(C=O)(CH₂)₁₋₄CH₂NH₂; -(C=O)(CH₂)₁₋₄CH₂NHCOR₅; -(C=O)(CH₂)₁₋₄CH₂NR₁R₂; (CH₂)₁₋₄OH, -(C=O)OH, -(C=O)O-alkyl; CH₂NHR₉ or CHR₁₀NHR₁₁; R₇ is selected from H or alkyl; R₈ is

selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₉ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; R₁₀ is selected from alkyl, aryl or heteroaryl; and R₁₁ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; and R₁₅ is selected from -OH, -Oaryl, -Oalkyl, Cl, F, -O-carboxy, or N₃.

5 **[0849] Embodiment 216:** The compound of embodiment 215, wherein R₁ is methyl.

[0850] Embodiment 217: The compound of embodiments 215-216, wherein R₃ is methyl.

[0851] Embodiment 218: The compound of any one of embodiments 215-216, wherein R₄ is selected from benzodioxinyl, phenyl optionally substituted with one or more substituents selected from the group consisting of halo and alkoxy, or piperonyl.

10 **[0852] Embodiment 219:** The compound of embodiment 218, wherein R₄ is piperonyl.

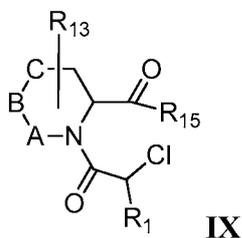
[0853] Embodiment 220: The compound of any one of embodiments 215-219, wherein R₅ is H.

[0854] Embodiment 221: The compound of any one of embodiments 215-219, wherein R₅ is an aryl optionally substituted with one or more groups selected from -OH, -CN, NO₂, -C(=O),

15 halo, haloalkyl, haloaryl, and heteroarylalkyl.

[0855] Embodiment 222: The compound of any one of embodiments 215-219, wherein R₆ is selected from the group consisting of CN, -(C=O)O-tBu and -(C=O)OMe.

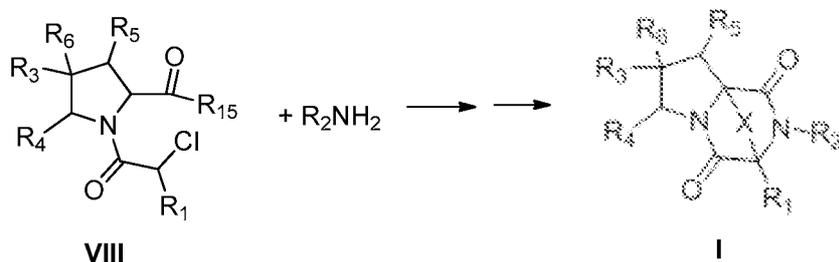
[0856] Embodiment 223: A compound of Formula IX:



20 wherein: X is selected from S₂, S₃, or S₄; R₁ is selected from H, alkyl, -C(=O)O, alkyl, alkoxy, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the

piperazine ring; R_7 is selected from H or alkyl; R_8 is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO_2 , CN, $-\text{C}(=\text{O})\text{O}$ -alkyl, sulfonyl, or sulfonamide; R_{13} is selected from H, alkyl, aryl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO_2 , CN, $-\text{C}(=\text{O})\text{O}$ -alkyl, sulfonyl, or sulfonamide; or optionally substituted variants thereof; A is selected from the group consisting of CH_2 , $\text{C}=\text{O}$, NH, NR_{14} , O, S, and SO_2 ; B is selected from the group consisting of CH_2 , $\text{C}=\text{O}$, NH, NR_{14} , O, S, and SO_2 ; C is selected from the group consisting of CH_2 , $\text{C}=\text{O}$, NH, NR_{14} , O, S, and SO_2 ; and R_{15} is selected from the group consisting of alkyl, aryl, acyl, and $-\text{O}$ -carboxy.

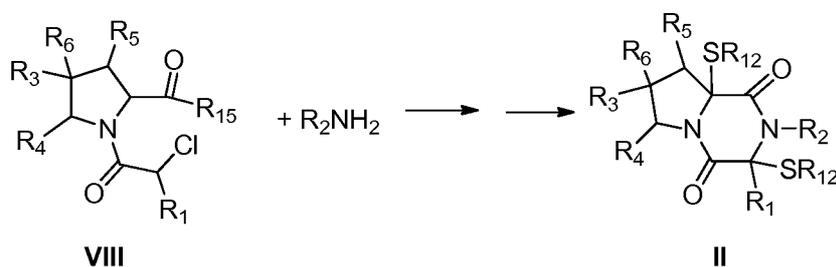
[0857] Embodiment 224: A method for synthesizing a compound of embodiment 170, comprising reacting a compound of Formula VIII with R_2NH_2 to form a diketopiperazine ring; introducing the sulfur ring to form a compound of Formula I:



wherein X is selected from S_2 , S_3 , or S_4 ; R_1 is selected from H, alkyl, $-\text{C}(=\text{O})\text{O}$ -alkyl, alkoxy, R_7NHR_7 , R_7NHR_8 , $\text{R}_7\text{cycloalkyl}$, R_7aryl , $\text{R}_7\text{morpholinyl}$, heteroarylalkyl, $\text{R}_7\text{piperazinyl}$, or $\text{R}_7\text{piperazinyl}$ with an alkyl group substituted off the 4-N position of the piperazine ring; R_2 is selected from H, alkyl, R_7NHR_7 , R_7NHR_8 , $\text{R}_7\text{cycloalkyl}$, R_7aryl , $\text{R}_7\text{morpholinyl}$, heteroarylalkyl, $\text{R}_7\text{piperazinyl}$, or $\text{R}_7\text{piperazinyl}$ with an alkyl group substituted off the 4-N position of the piperazine ring; R_3 is selected from H, alkyl, aryl or heteroaryl; R_4 is selected from alkyl, haloalkyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, benzodioxanyl, dioxanyl, benzoxazinyl, piperadinyl-1-methyl, heterocycle, indolyl, pyridinyl, piperazinyl, furyl, thienyl, heteroarylalkyl, or phenyl, or optionally substituted variants thereof; R_5 is selected from H, aryl, alkyl, haloalkyl, heteroaryl, phenyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, heterocycle, indolyl, or pyridinyl, or optionally substituted variants thereof; R_6 is selected from CN, NO_2 , $-\text{S}(\text{O})_2\text{alkyl}$, $-\text{S}(\text{O})_2\text{aryl}$, $-\text{S}(\text{O})_2\text{R}_7$, $-\text{S}(\text{O})_2\text{CH}_2\text{CN}$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{N}(\text{H})\text{OMe}$, $-\text{C}(=\text{O})(\text{CH}_2)_{1-4}\text{CN}$; $-\text{C}(=\text{O})(\text{CH}_2)_{1-4}\text{SO}_2\text{R}_7$; $-\text{C}(=\text{O})(\text{CH}_2)_{1-4}\text{CO}_2\text{R}_7$; -

(C=O)(CH₂)₁₋₄CO₂H; -(C=O)(CH₂)₁₋₄CH₂NH₂; -(C=O)(CH₂)₁₋₄CH₂NHCOR₅; -(C=O)(CH₂)₁₋₄CH₂NR₁R₂; (CH₂)₁₋₄OH, -(C=O)OH, -(C=O)O-alkyl; CH₂NHR₉ or CHR₁₀NHR₁₁; R₇ is selected from H or alkyl; R₈ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₉ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; R₁₀ is selected from alkyl, aryl or heteroaryl; R₁₁ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; and R₁₅ is selected from -OH, -Oaryl, -Oalkyl, Cl, F, -O-carboxy, or N₃.

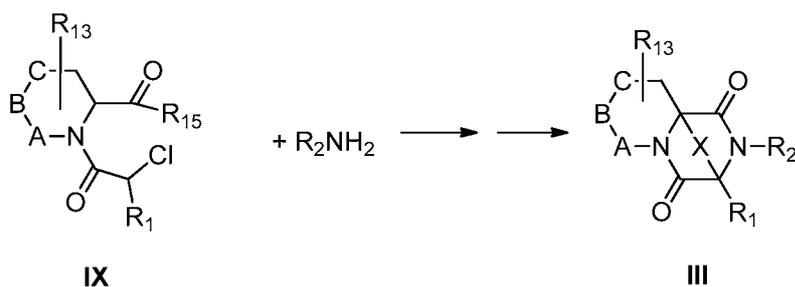
[0858] Embodiment 225: A method of synthesizing a compound of embodiment 180 comprising: reacting a compound of Formula VIII with R₂NH₂ to form a diketopiperazine ring; introducing two thioether substituents to form a compound of Formula II:



wherein: R₁ is selected from H, alkyl, -C(=O)O-alkyl, -C(=O)OR₇aryl, alkoxy, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, or R₇piperazinyl, R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₃ is selected from H, alkyl, aryl, heteroaryl, nitrile, F, Cl, OAc, O-alkyl, or O-aryl; R₄ is selected from alkyl, haloalkyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, benzodioxanyl, dioxanyl, benzoxazinyl, piperadinyll-1-methyl, heterocycle, indolyl, pyridinyl, piperazinyl, furyl, thienyl, heteroarylalkyl, or phenyl, or optionally substituted variants thereof; R₅ is selected from H, aryl, alkyl, haloalkyl, heteroaryl, phenyl, biphenyl, thiophenyl, piperidyl, morpholinyl, imidazolyl, piperonyl, benzyl, cycloalkyl, benzodioxinyl, dioxinyl, heterocycle, indolyl, or pyridinyl, or optionally substituted variants thereof; R₆ is selected from CN, NO₂, -S(O)₂alkyl, -S(O)₂aryl, -S(O)₂R₇, -S(O)₂CH₂CN, -(C=O)NH₂, -(N=H)OMe, -(C=O)(CH₂)₁₋₄CN; -(C=O)(CH₂)₁₋₄SO₂R₇; -(C=O)(CH₂)₁₋₄CO₂R₇; -(C=O)(CH₂)₁₋₄CO₂H; -(C=O)(CH₂)₁₋₄CH₂NH₂; -(C=O)(CH₂)₁₋₄CH₂NHCOR₅; -(C=O)(CH₂)₁₋

4CH₂NR₁R₂; (CH₂)₁₋₄OH, -(C=O)OH, -(C=O)O-alkyl; CH₂NHR₉, CHR₁₀NHR₁₁; R₇ is alkyl; R₈ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₉ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; R₁₀ is selected from alkyl, aryl or heteroaryl; R₁₁ is selected from H, alkyl, aryl, heteroaryl, acyl, or -O-carboxy; R₁₂ is selected from methyl or a thiol-protecting group; and R₁₅ is selected from -OH, -Oaryl, -Oalkyl, Cl, F, -O-carboxy, or N₃.

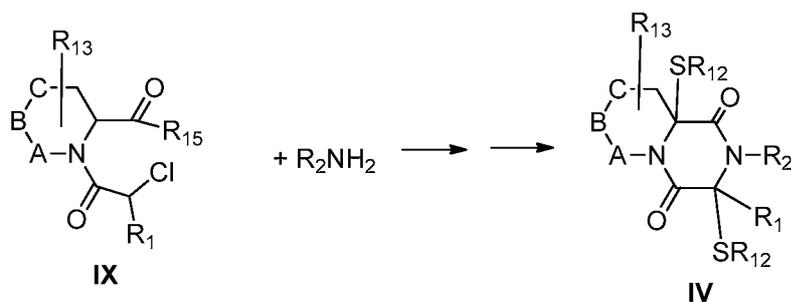
[0859] Embodiment 226: A method for synthesizing a compound of embodiment 183 comprising: reacting a compound of Formula VIII with R₂NH₂ to form a diketopiperazine ring; introducing the sulfur ring to form a compound of Formula III:



10
15
20
25

wherein: X is selected from S₂, S₃, or S₄; R₁ is selected from H, alkyl, -C(=O)O, alkyl, alkoxy, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₇ is alkyl; R₈ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₁₃ is selected from H, alkyl, aryl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; or optionally substituted variants thereof; A is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; B is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; C is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; and R₁₅ is -OH, -Oaryl, -Oalkyl, Cl, F, -O-carboxy, or N₃.

[0860] Embodiment 227: A method for synthesizing a compound of embodiment 190 comprising: reacting a compound of Formula VIII with R₂NH₂ to form a diketopiperazine ring; introducing two thioether substituents to form a compound of Formula IV:



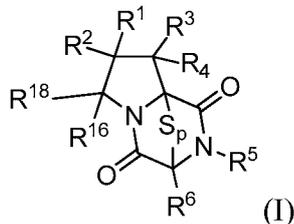
wherein: X is selected from S₂, S₃, or S₄; R₁ is selected from H, alkyl, -C(=O)O, alkyl, alkoxy, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₂ is

5 selected from H, alkyl, R₇NHR₇, R₇NHR₈, R₇cycloalkyl, R₇aryl, R₇morpholinyl, heteroarylalkyl, R₇piperazinyl, or R₇piperazinyl with an alkyl group substituted off the 4-N position of the piperazine ring; R₃ is alkyl; R₄ is selected from alkyl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; R₅ is selected from methyl or a thiol-protecting group; R₆ is selected from H, alkyl, aryl, heteroaryl, halo, alkoxy, thioalkyl, haloalkyl, NO₂, CN, -C(=O)O-alkyl, sulfonyl, or sulfonamide; or optionally substituted variants thereof; A is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; B is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; C is selected from the group consisting of CH₂, C=O, NH, NR₁₄, O, S, and SO₂; R₁₄ is selected from the group consisting of alkyl, aryl, acyl, and -O-carboxy; and R₁₅ is selected from -OH, -Oaryl, -Oalkyl,

10 Cl, F, -O-carboxy, or N₃.

WHAT IS CLAIMED IS:

1 1. A compound having the formula:



2
3 wherein,

4 p is 2, 3 or 4;

5 R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A},
6 -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A},
7 -SO_{n1}NR^{34A}R^{35A}, -NHNr^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHNr^{34A}R^{35A}, substituted or
8 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
9 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
10 substituted or unsubstituted heteroaryl;

11 R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33B},
12 -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -SO_{n2}R^{34b}, -SO_{n2}OR^{34B}, -SO_{n2}NR^{34B}R^{35B},
13 -NHNr^{34B}R^{35B}, -ONR^{34B}R^{35B}, -NHC(O)NHNr^{34B}R^{35B}, substituted or unsubstituted alkyl,
14 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
15 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
16 heteroaryl;

17 R³ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33C},
18 -NR^{34C}R^{35C}, -COOR^{33C}, -CONR^{34C}R^{35C}, -NO₂, -SR^{36C}, -SO_{n3}R^{34C}, -SO_{n3}OR^{34C}, -SO_{n3}NR^{34C}R^{35C},
19 -NHNr^{34C}R^{35C}, -ONR^{34C}R^{35C}, -NHC(O)NHNr^{34C}R^{35C}, substituted or unsubstituted alkyl,
20 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
21 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
22 heteroaryl;

23 R⁴ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33D},
24 -NR³⁴R^{35D}, -COOR^{33D}, -CONR^{34D}R^{35D}, -NO₂, -SR^{36D}, -SO_{n4}R^{34D}, -SO_{n4}OR^{34D},
25 -SO_{n4}NR^{34D}R^{35D}, -NHNr^{34D}R^{35D}, -ONR^{34D}R^{35D}, -NHC(O)NHNr^{34D}R^{35D}, substituted or
26 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

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

29 R^5 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33E}$,
 30 $-NR^{34E}R^{35E}$, $-COOR^{33E}$, $-CONR^{34E}R^{35E}$, $-NO_2$, $-SR^{36E}$, $-SO_{n5}R^{34E}$, $-SO_{n5}OR^{34E}$, $-SO_{n5}NR^{34E}R^{35E}$,
 31 $-NHN R^{34E}R^{35E}$, $-ONR^{34E}R^{35E}$, $-NHC(O)NHN R^{34E}R^{35E}$, substituted or unsubstituted alkyl,
 32 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 33 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 34 heteroaryl;

35 R^6 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33F}$,
 36 $-NR^{34F}R^{35F}$, $-COOR^{33F}$, $-CONR^{34F}R^{35F}$, $-NO_2$, $-SR^{36F}$, $-SO_{n6}R^{34F}$, $-SO_{n6}OR^{34F}$, $-SO_{n6}NR^{34F}R^{35F}$,
 37 $-NHN R^{34F}R^{35F}$, $-ONR^{34F}R^{35F}$, $-NHC(O)NHN R^{34F}R^{35F}$, substituted or unsubstituted alkyl,
 38 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 39 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 40 heteroaryl;

41 R^{16} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33G}$,
 42 $-NR^{34G}R^{35G}$, $-COOR^{33G}$, $-CONR^{34G}R^{35G}$, $-NO_2$, $-SR^{36G}$, $-SO_{n7}R^{34G}$, $-SO_{n7}OR^{34G}$,
 43 $-SO_{n7}NR^{34G}R^{35G}$, $-NHN R^{34G}R^{35G}$, $-ONR^{34G}R^{35G}$, $-NHC(O)NHN R^{34G}R^{35G}$, substituted or
 44 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 45 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 46 substituted or unsubstituted heteroaryl;

47 R^{18} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33H}$,
 48 $-NR^{34H}R^{35H}$, $-COOR^{33H}$, $-CONR^{34H}R^{35H}$, $-NO_2$, $-SR^{36H}$, $-SO_{n8}R^{34H}$, $-SO_{n8}OR^{34H}$,
 49 $-SO_{n8}NR^{34H}R^{35H}$, $-NHN R^{34H}R^{35H}$, $-ONR^{34H}R^{35H}$, $-NHC(O)NHN R^{34H}R^{35H}$, substituted or
 50 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 51 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 52 substituted or unsubstituted heteroaryl;

53 R^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} ,
 54 R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} ,
 55 and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 56 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 57 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

58 n1, n2, n3, n4, n5, n6, n7, and n8 are independently 1 or 2.

1 2. The compound of claim 1, wherein R¹⁸ is substituted or unsubstituted
2 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

1 3. The compound of claims 2, wherein R¹⁸ is R^{18a}-substituted or
2 unsubstituted 5 membered heterocycloalkyl, R^{18a}-substituted or unsubstituted 6 membered aryl,
3 R^{18a}-substituted or unsubstituted 6 membered heteroaryl, R^{18a}-substituted or unsubstituted 6,6
4 fused ring aryl-heterocycloalkyl, R^{18a}-substituted or unsubstituted 6,5 fused ring aryl-
5 heterocycloalkyl, R^{18a}-substituted or unsubstituted 5,6 fused ring aryl-heterocycloalkyl;
6 R^{18a} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH,
7 -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂,
8 -NHC(O)NHNH₂, R^{18b}-substituted or unsubstituted C₁-C₈ alkyl, R^{18b}-substituted or
9 unsubstituted 2 to 8 membered heteroalkyl, R^{18b}-substituted or unsubstituted 3 to 8 membered
10 cycloalkyl, R^{18b}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{18b}-substituted
11 or unsubstituted 5 to 6 membered aryl, or R^{18b}-substituted or unsubstituted 5 to 6 membered
12 heteroaryl; and

13 R^{18b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH,
14 -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
15 unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8
16 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6
17 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

1 4. The compound of claim 3, wherein R^{18a} is halogen, -SO₂Ph, R^{18b}-
2 substituted or unsubstituted C₁-C₅ alkyl, or R^{18b}-substituted or unsubstituted 2 to 5 membered
3 heteroalkyl, unsubstituted 5 to 6 membered heterocycloalkyl, or unsubstituted phenyl; and

4 R^{18b} is halogen, unsubstituted C₁-C₈ alkyl, or unsubstituted 2 to 8 membered
5 heteroalkyl.

1 5. The compound of claim 4, wherein said R^{18a}-substituted 5 membered
2 heterocycloalkyl is an R^{18a}-substituted thiophenyl, R^{18a}-substituted thiazolyl, R^{18a}-substituted
3 oxazolyl, or R^{18a}-substituted imidazolyl; and

4 R^{18a} is halogen, unsubstituted C₁-C₅ alkyl, or unsubstituted 2 to 5 membered
5 heteroalkyl.

1 6. The compound of claim 3, wherein R¹⁸ is unsubstituted heterocycloalkyl,
2 unsubstituted aryl, or unsubstituted heteroaryl.

1 7. The compound of any one of claims 1 to 6, wherein R¹⁶ is hydrogen.

1 8. The compound of any one of claims 1 to 6, wherein R³ and R⁴ are
2 hydrogen.

1 9. The compound of any one of claims 1 to 6, wherein R¹ is -CN or
2 unsubstituted 2 to 5 membered heteroalkyl.

1 10. The compound of claim 1, wherein R¹ is -CN.

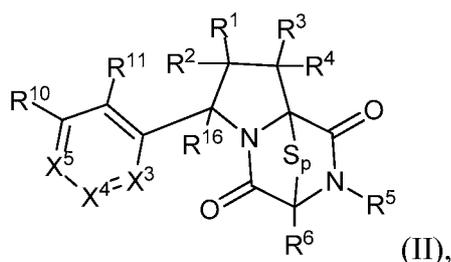
1 11. The compound of claim 1, wherein R¹ is -COOR^{33A}, wherein R^{33A} is C₁-
2 C₃ unsubstituted alkyl.

1 12. The compound of any one of claims 1 to 6 or 10-11, wherein R² is -N₃,
2 -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -
3 SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2a}-substituted or unsubstituted C₁-C₃
4 alkyl, or 2 to 3 membered R^{2a}-substituted or unsubstituted heteroalkyl;

5 R^{2a} is -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH,
6 -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2b}-
7 substituted or unsubstituted C₁-C₅ alkyl, R^{2b}-substituted or unsubstituted 2 to 5 membered
8 heteroalkyl, R^{2b}-substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2b}-substituted
9 or unsubstituted 5 or 6 membered aryl, or R^{2b}-substituted or unsubstituted 5 or 6 membered
10 heteroaryl; and

11 R^{2b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH,
12 -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
13 unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8
14 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6
15 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

- 1 13. The compound of any one of claims 1 to 6 or 10-11, wherein R² is methyl
2 or methoxy.
- 1 14. The compound of any one of claims 1 to 6 or 10-11, wherein R² is R^{2a}-
2 substituted or unsubstituted C₁-C₅ alkyl, or R^{2a}-substituted or unsubstituted 2 to 5 membered
3 heteroalkyl, and
4 R^{2a} is unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 or 6
5 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.
- 1 15. The compound of any one of claims 1 to 6 or 10-11, wherein R^{2a} is
2 unsubstituted pyridinyl.
- 1 16. The compound of any one of claims 1 to 6 or 10 to 11, wherein R² is
2 substituted or unsubstituted C₁-C₅ heteroalkyl.
- 1 17. The compound of any one of claims 1 to 6 or 10-11, wherein R² is a polar
2 substituent.
- 1 18. The compound of claim 1, wherein R⁵ and R⁶ are independently hydrogen,
2 halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH,
3 -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, unsubstituted alkyl, or unsubstituted
4 cycloalkyl.
- 1 19. The compound of claims 1 or 18, wherein R⁵ and R⁶ are independently
2 hydrogen, unsubstituted C₁-C₃ alkyl or unsubstituted 3 to 5 membered cycloalkyl.
- 1 20. The compound of claims 1 or 18, wherein R⁵ and R⁶ are independently
2 hydrogen, methyl, ethyl, allyl or cyclopropyl.
- 1 21. The compound of any one of claims 1 to 6, or 10 to 11, or 18, wherein p is
2 2.
- 1 22. The compound of claim 1 having the formula:

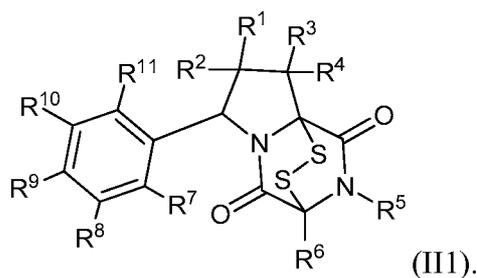


- 2
- 3 wherein,
- 4 X^3 is N or CR⁷;
- 5 X^4 is N or CR⁸;
- 6 X^5 is N or CR⁹;
- 7 R^7 is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33I},
- 8 -NR^{34I}R^{35I}, -COOR^{33I}, -CONR^{34I}R^{35I}, -NO₂, -SR^{36I}, -SO_{n9}R^{34I}, -SO_{n9}OR^{34I}, -SO_{n9}NR^{34I}R^{35I}, -
- 9 NHNR^{34I}R^{35I}, -ONR^{34I}R^{35I}, -NHC(O)NHNR^{34I}R^{35I}, substituted or unsubstituted alkyl, substituted
- 10 or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
- 11 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
- 12 R^8 is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33J},
- 13 -NR^{34J}R^{35J}, -COOR^{33J}, -CONR^{34J}R^{35J}, -NO₂, -SR^{36J}, -SO_{n10}R^{34J}, -SO_{n10}OR^{34J}, -SO_{n10}NR^{34J}R^{35J}, -
- 14 NHNR^{34J}R^{35J}, -ONR^{34J}R^{35J}, -NHC(O)NHNR^{34J}R^{35J}, substituted or unsubstituted alkyl,
- 15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
- 16 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
- 17 heteroaryl;
- 18 R^9 is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33K},
- 19 -NR^{34K}R^{35K}, -COOR^{33K}, -CONR^{34K}R^{35K}, -NO₂, -SR^{36K}, -SO_{n11}R^{34K}, -SO_{n11}OR^{34K},
- 20 -SO_{n11}NR^{34K}R^{35K}, -NHNR^{34K}R^{35K}, -ONR^{34K}R^{35K}, -NHC(O)NHNR^{34K}R^{35K}, substituted or
- 21 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
- 22 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
- 23 substituted or unsubstituted heteroaryl;
- 24 R^{10} and R^{11} are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃,
- 25 -Cl₃, -CN, -CHO, -OR^{33L}, -NR^{34L}R^{35L}, -COOR^{33L}, -CONR^{34L}R^{35L}, -NO₂, -SR^{36L}, -SO_{n12}R^{34L},
- 26 -SO_{n12}OR^{34L}, -SO_{n12}NR^{34L}R^{35L}, -NHNR^{34L}R^{35L}, -ONR^{34L}R^{35L}, -NHC(O)NHNR^{34L}R^{35L},
- 27 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
- 28 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

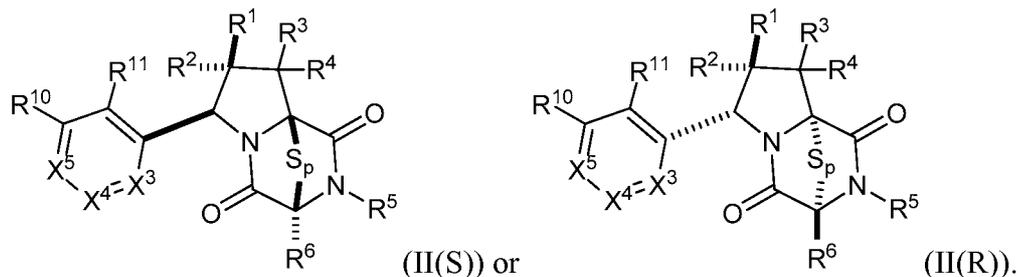
29 unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to
 30 form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a
 31 substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

32 R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} , R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} ,
 33 and R^{36L} , are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 34 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 35 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
 36 n_9 , n_{10} , n_{11} , and n_{12} are independently 1 or 2.

1 23. The compound of claim 22 having the formula:



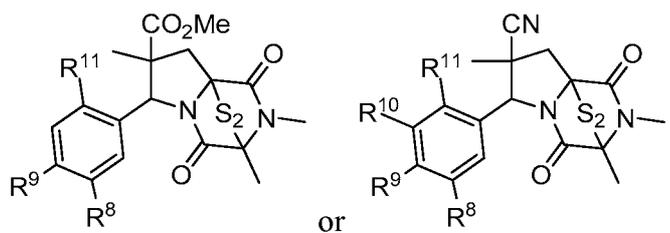
1 24. The compound of claim 22 having the formula:



1 25. The compound of claim 22, wherein R^1 is $-CN$ or unsubstituted 2 to 5
 2 membered heteroalkyl.

1 26. The compound of any one of claims 22 to 25, wherein R^3 and R^4 are
 2 hydrogen.

1 27. The compound of claim 22 having formula:



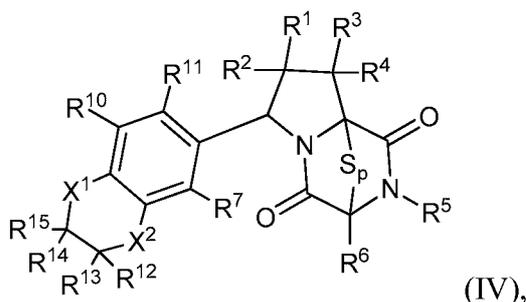
2
3 wherein,

4 R^8 is hydrogen or $-OR^{33J}$;

5 R^9 , R^{10} , and R^{11} are independently hydrogen or halogen; and

6 R^{33J} is hydrogen, or unsubstituted alkyl.

1 28. The compound of claim 22 having formula:



2
3 wherein,

4 X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

5 X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and

6 R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen,
7 $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$,

8 $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$,

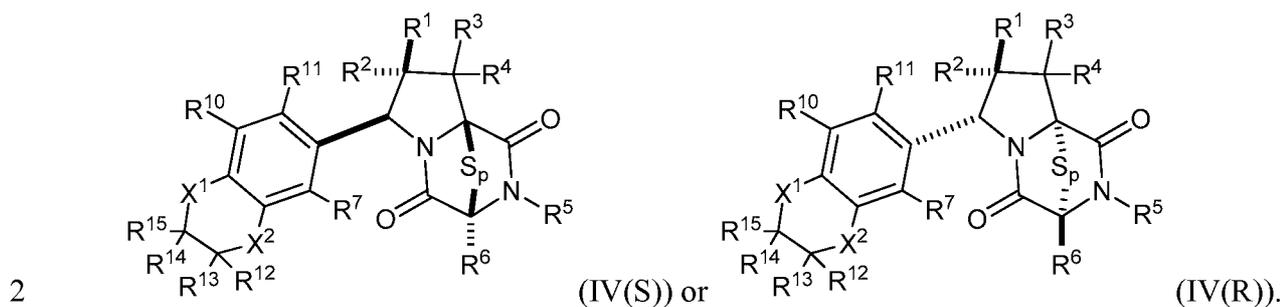
9 $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or

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

12 R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or
13 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
14 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
15 substituted or unsubstituted heteroaryl; and

16 n_{13} is 1 or 2.

1 29. The compound of claim 28 having formula:



1 30. The compound of claim 28, wherein R¹ is -CN or unsubstituted 2 to 5
2 membered heterocycloalkyl.

1 31. The compound of any one of claims 28 to 30, wherein R³ and R⁴ are
2 hydrogen.

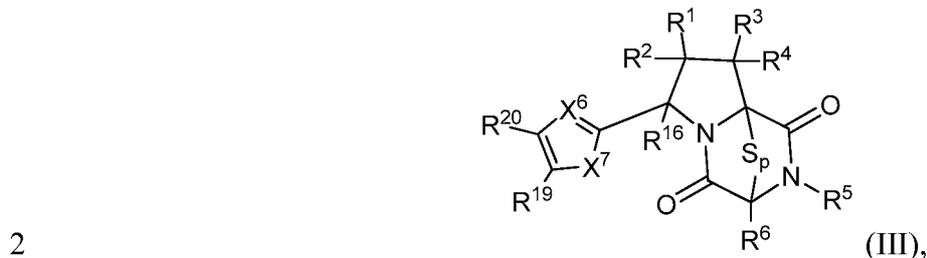
1 32. The compound of any one of claims 28 to 30, wherein R¹⁰ and R¹¹ are
2 hydrogen.

1 33. The compound of any one of claims 28 to 30, wherein R¹², R¹³, R¹⁴, and
2 R¹⁵ are hydrogen.

1 34. The compound of claim 28 having formula:



1 35. The compound of claim 1 having formula:



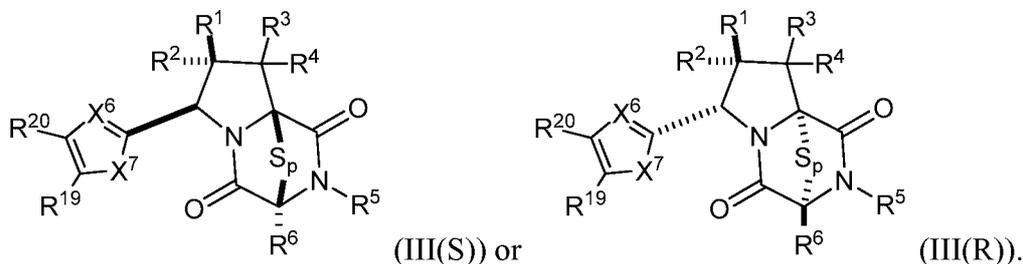
3 wherein,

4 X⁶ is CR²¹ or N;

5 X⁷ is CR²²R²³, S, O, or NR²³;

6 R^{19} , R^{20} , R^{21} , R^{22} and R^{23} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$,
 7 $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$,
 8 $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$,
 9 $-NHC(O)NHN R^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or unsubstituted
 10 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 11 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 12 R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or
 13 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 14 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 15 substituted or unsubstituted heteroaryl; and
 16 n_{13} is 1 or 2.

1 36. The compound of any one of claims 1 or 35 having formula:

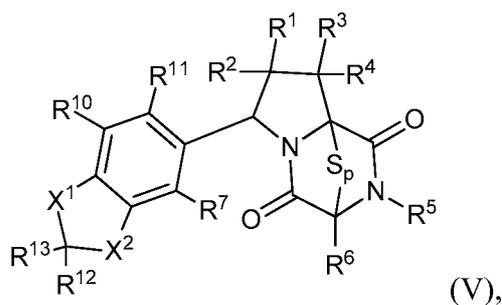


1 37. The compound of claim 35, wherein R^1 is $-CN$ or unsubstituted 2 to 5
 2 membered heteroalkyl.

1 38. The compound of any one of claims 35 to 37, wherein R^3 and R^4 are
 2 hydrogen.

1 39. The compound of any one of claims 35 to 37, wherein R^{19} and R^{20} are
 2 hydrogen.

1 40. The compound of claim 1 having formula:



wherein,

X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S;

R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNr^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNr^{34I}R^{35I}$, substituted 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} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNr^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNr^{34L}R^{35L}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

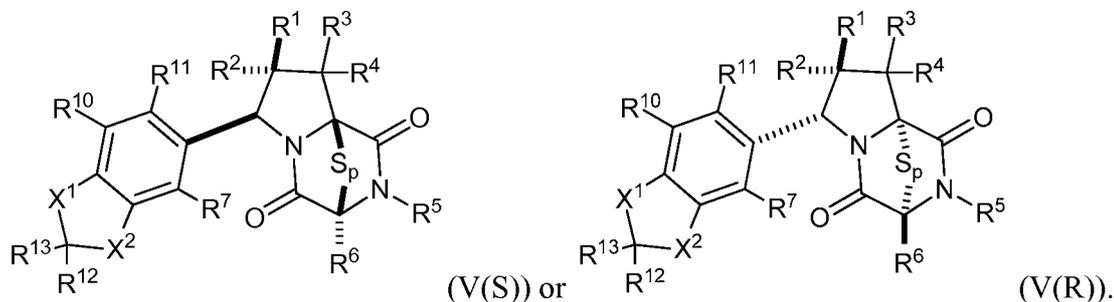
R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

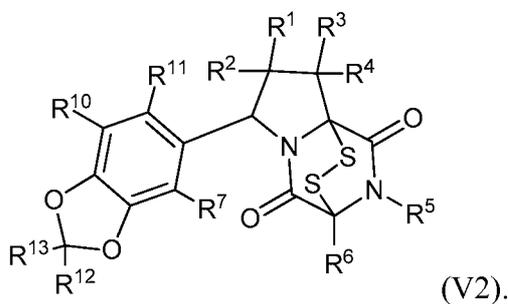
28 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 29 substituted or unsubstituted heteroaryl; and

30 n₉, n₁₁, and n₁₃ are independently 1 or 2.

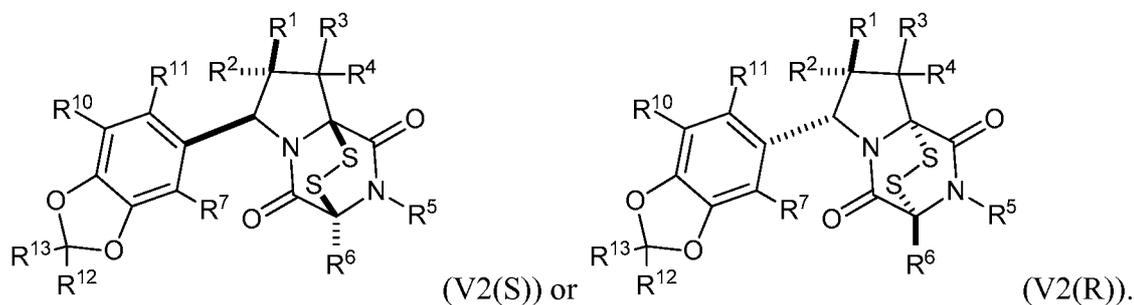
1 41. The compound of claim 40 having formula:



1 42. The compound of claim 40 having formula:



1 43. The compound of claim 42 having formula:



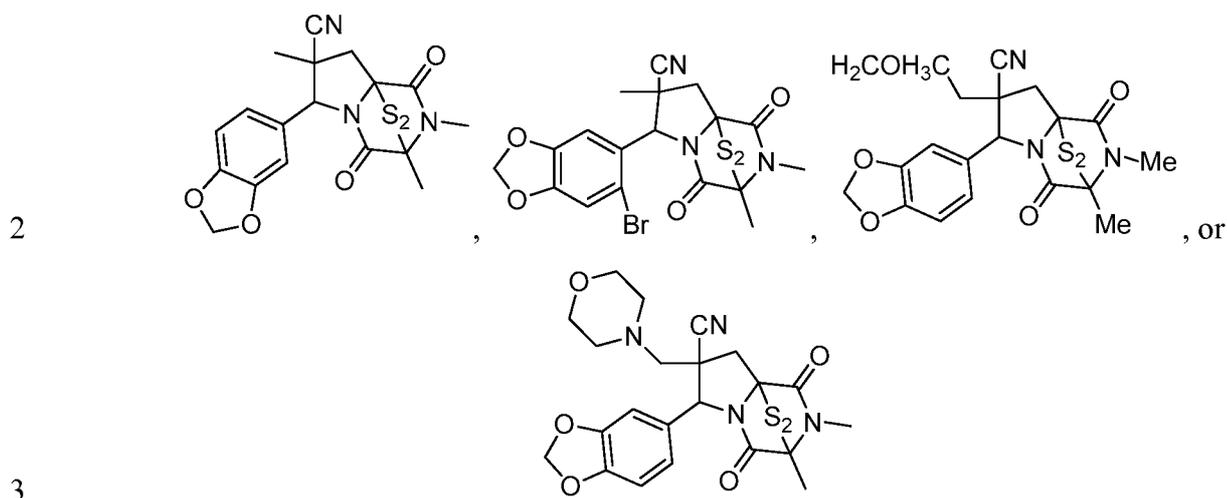
1 44. The compound of claim 40, wherein R¹ is -CN or unsubstituted 2 to 5
 2 membered heteroalkyl.

1 45. The compound of any one of claims 40 to 44, wherein R³ and R⁴ are
 2 hydrogen.

1 46. The compound of any one of claims 40 to 44, wherein R¹² and R¹³ are
2 hydrogen.

1 47. The compound of any one of claims 40 to 44, wherein R¹⁰ and R¹¹ are
2 hydrogen.

1 48. The compound of any one of claims 1, 40, or 41-44 having formula:



1 49. The compound of any one of claims 1, 40, or 41 having formula:



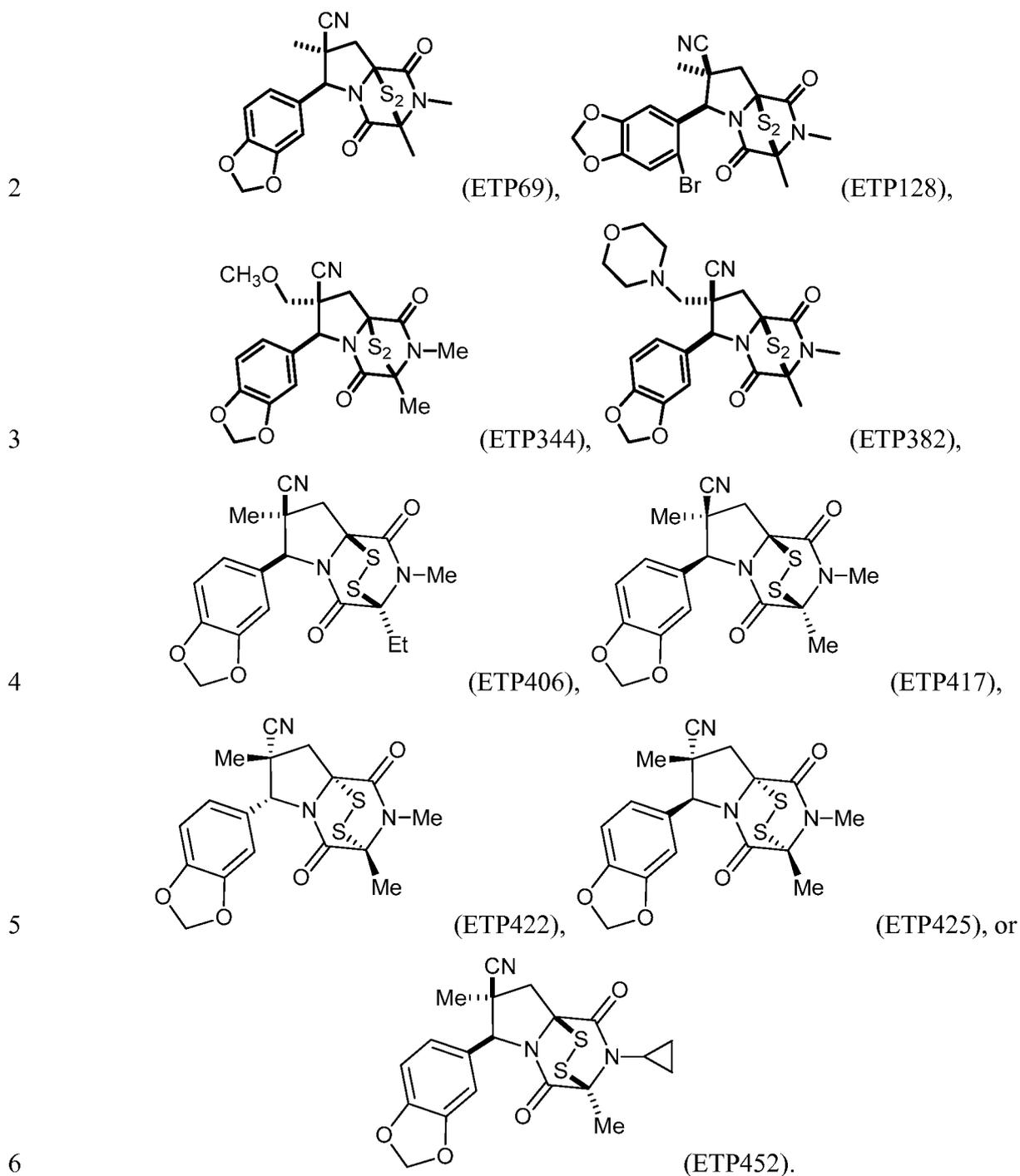
wherein;

4 R⁵ is unsubstituted 3 to 5 membered cycloalkyl, or R^{5a}-substituted or
5 unsubstituted C₁-C₅ alkyl;

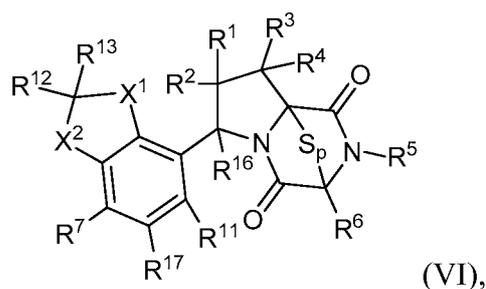
6 R^{5a} is unsubstituted 2 to 5 membered heteroalkyl or 5 to 6 membered
7 heterocycloalkyl, and

8 p is 2 or 3.

1 50. The compound of any one of claims 1, 40, 41-44 or 49 having formula:



1 51. The compound of claim 1 having formula:



wherein,

X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and

R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNr^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNr^{34I}R^{35I}$, substituted 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^{11} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNr^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNr^{34L}R^{35L}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

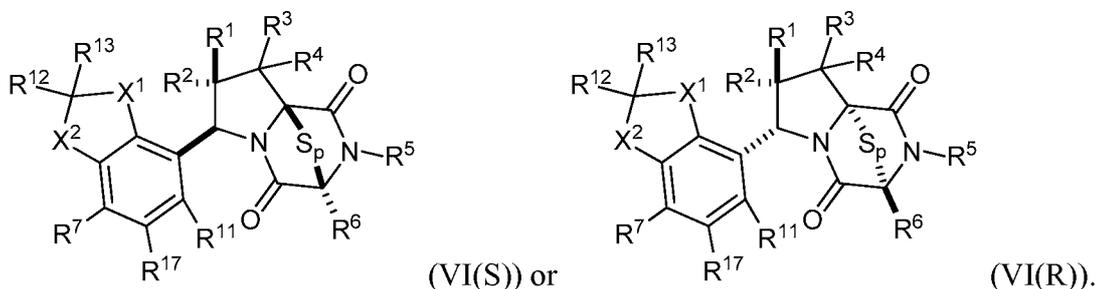
R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted 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^{17} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33P}$, $-NR^{34P}R^{35P}$, $-COOR^{33P}$, $-CONR^{34P}R^{35P}$, $-NO_2$, $-SR^{36P}$, $-SO_{n15}R^{34P}$, $-SO_{n15}OR^{34P}$, $-SO_{n15}NR^{34P}R^{35P}$, $-NHNr^{34P}R^{35P}$, $-ONR^{34P}R^{35P}$, $-NHC(O)NHNr^{34P}R^{35P}$, substituted or unsubstituted alkyl,

29 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 30 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 31 heteroaryl, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a
 32 substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted
 33 or unsubstituted heteroaryl;

34 R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33L} , R^{34L} , R^{35L} , R^{36L} , R^{33M} , R^{34M} , R^{35M} , R^{36M} , R^{33P} , R^{34P} ,
 35 R^{35P} , and R^{36P} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 36 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 37 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
 38 n_9 , n_{12} , n_{13} and n_{15} are independently 1 or 2.

1 52. The compound of claim 51 having formula:



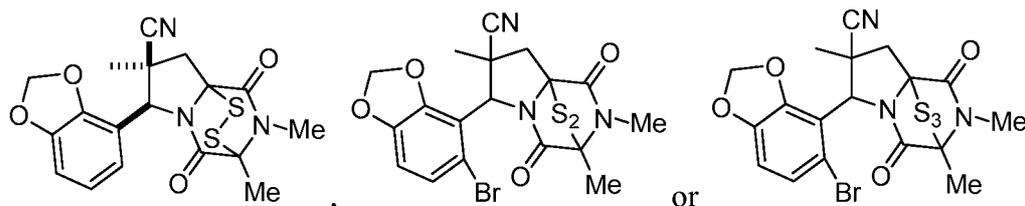
1 53. The compound of claim 51, wherein R^1 is $-\text{CN}$ or unsubstituted 2 to 5
 2 membered heteroalkyl.

1 54. The compound of any one of claims 51 to 53, wherein R^3 and R^4 are
 2 hydrogen.

1 55. The compound of any one of claims 51 to 53, wherein R^{12} and R^{13} are
 2 hydrogen.

1 56. The compound of any one of claims 51 to 53, wherein R^7 , R^{10} , and R^{17} are
 2 hydrogen.

1 57. The compound of claim 51 having formula:



2

1 58. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R² is a polar substituent.

1 59. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R² is -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
3 -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2a}-substituted or
4 unsubstituted C₁-C₃ alkyl, or R^{2a}-substituted or unsubstituted 2 to 3 membered heteroalkyl;

5 R^{2a} is -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂,
6 -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂Ph, -SO₂NH₂, -NHNH₂, -ONH₂, R^{2b}-substituted or
7 unsubstituted C₁-C₅ alkyl, R^{2b}-substituted or unsubstituted 2 to 5 membered heteroalkyl, R^{2b}-
8 substituted or unsubstituted 3 to 6 membered heterocycloalkyl, R^{2b}-substituted or unsubstituted 5
9 or 6 membered aryl, or R^{2b}-substituted or unsubstituted 5 or 6 membered heteroaryl;

10 R^{2b} is halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -
11 CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂,
12 unsubstituted C₁-C₈ alkyl, unsubstituted 2 to 8 membered heteroalkyl, unsubstituted 3 to 8
13 membered cycloalkyl, unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 to 6
14 membered aryl, or unsubstituted 5 to 6 membered heteroaryl.

1 60. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R² is R^{2a}-substituted or unsubstituted C₁-C₃ alkyl, or R^{2a}-substituted or unsubstituted 2
3 to 3 membered heteroalkyl, wherein

4 R^{2a} is unsubstituted 3 to 6 membered heterocycloalkyl, unsubstituted 5 or 6
5 membered aryl, or unsubstituted 5 or 6 membered heteroaryl.

1 61. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R² is methyl or methoxy.

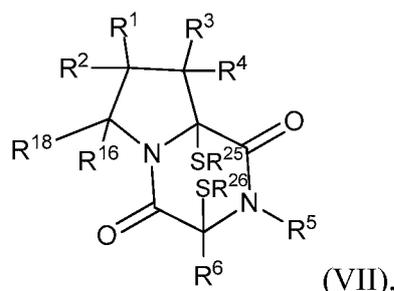
1 62. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R^{2a} is pyridinyl.

1 63. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R⁵ and R⁶ are independently hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN,
3 -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂,
4 -ONH₂, unsubstituted alkyl, or unsubstituted cycloalkyl.

1 64. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R⁵ and R⁶ are independently hydrogen, C₁-C₃ unsubstituted alkyl or 3 to 5 membered
3 cycloalkyl.

1 65. The compound of any one of claims 22-25, 28-30, 35-37, 40-44 or 51-53,
2 wherein R⁵ and R⁶ are independently hydrogen, methyl, ethyl, allyl, or cyclopropyl.

1 66. A compound having formula:



2 wherein;

3 R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A},
4 -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A},
5 -SO_{n1}NR^{34A}R^{35A}, -NHNr^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHNr^{34A}R^{35A}, substituted or
6 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
7 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
8 substituted or unsubstituted heteroaryl;

9 R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33B},
10 -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -SO_{n2}R^{34b}, -SO_{n2}OR^{34B}, -SO_{n2}NR^{34B}R^{35B},
11 -NHNr^{34B}R^{35B}, -ONR^{34B}R^{35B}, -NHC(O)NHNr^{34B}R^{35B}, substituted or unsubstituted alkyl,
12 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
13 substituted or unsubstituted heteroaryl;

14 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
15 heteroaryl;

16 R^3 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33C}$,
17 $-NR^{34C}R^{35C}$, $-COOR^{33C}$, $-CONR^{34C}R^{35C}$, $-NO_2$, $-SR^{36C}$, $-SO_{n3}R^{34C}$, $-SO_{n3}OR^{34C}$, $-SO_{n3}NR^{34C}R^{35C}$,
18 $-NHNR^{34C}R^{35C}$, $-ONR^{34C}R^{35C}$, $-NHC(O)NHNR^{34C}R^{35C}$, substituted or unsubstituted alkyl,
19 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
20 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
21 heteroaryl;

22 R^4 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33D}$,
23 $-NR^{34R}R^{35D}$, $-COOR^{33D}$, $-CONR^{34D}R^{35D}$, $-NO_2$, $-SR^{36D}$, $-SO_{n4}R^{34D}$, $-SO_{n4}OR^{34D}$,
24 $-SO_{n4}NR^{34D}R^{35D}$, $-NHNR^{34D}R^{35D}$, $-ONR^{34D}R^{35D}$, $-NHC(O)NHNR^{34D}R^{35D}$, substituted or
25 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
26 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
27 substituted or unsubstituted heteroaryl;

28 R^5 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33E}$,
29 $-NR^{34E}R^{35E}$, $-COOR^{33E}$, $-CONR^{34E}R^{35E}$, $-NO_2$, $-SR^{36E}$, $-SO_{n5}R^{34E}$, $-SO_{n5}OR^{34E}$, $-SO_{n5}NR^{34E}R^{35E}$,
30 $-NHNR^{34E}R^{35E}$, $-ONR^{34E}R^{35E}$, $-NHC(O)NHNR^{34E}R^{35E}$, substituted or unsubstituted alkyl,
31 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
32 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
33 heteroaryl;

34 R^6 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33F}$,
35 $-NR^{34F}R^{35F}$, $-COOR^{33F}$, $-CONR^{34F}R^{35F}$, $-NO_2$, $-SR^{36F}$, $-SO_{n6}R^{34F}$, $-SO_{n6}OR^{34F}$, $-SO_{n6}NR^{34F}R^{35F}$,
36 $-NHNR^{34F}R^{35F}$, $-ONR^{34F}R^{35F}$, $-NHC(O)NHNR^{34F}R^{35F}$, substituted or unsubstituted alkyl,
37 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
38 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
39 heteroaryl;

40 R^{16} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33G}$,
41 $-NR^{34G}R^{35G}$, $-COOR^{33G}$, $-CONR^{34G}R^{35G}$, $-NO_2$, $-SR^{36G}$, $-SO_{n7}R^{34G}$, $-SO_{n7}OR^{34G}$,
42 $-SO_{n7}NR^{34G}R^{35G}$, $-NHNR^{34G}R^{35G}$, $-ONR^{34G}R^{35G}$, $-NHC(O)NHNR^{34G}R^{35G}$, substituted or
43 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

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

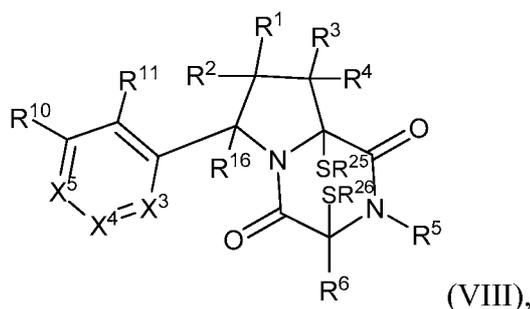
46 R^{18} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33H}$,
 47 $-NR^{34H}R^{35H}$, $-COOR^{33H}$, $-CONR^{34H}R^{35H}$, $-NO_2$, $-SR^{36H}$, $-SO_{n8}R^{34H}$, $-SO_{n8}OR^{34H}$,
 48 $-SO_{n8}NR^{34H}R^{35H}$, $-NHNr^{34H}R^{35H}$, $-ONR^{34H}R^{35H}$, $-NHC(O)NHNr^{34H}R^{35H}$, substituted or
 49 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 50 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 51 substituted or unsubstituted heteroaryl;

52 R^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} ,
 53 R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} ,
 54 and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 55 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 56 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

57 n_1 , n_2 , n_3 , n_4 , n_5 , n_6 , n_7 , and n_8 are independently 1 or 2; and

58 R^{25} and R^{26} are independently hydrogen, substituted or unsubstituted alkyl,
 59 substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, or substituted or
 60 unsubstituted heteroaryl.

1 67. The compound of claim 66 having the formula:



2
 3 wherein,
 4 X^3 is N or CR^7 ;
 5 X^4 is N or CR^8 ;
 6 X^5 is N or CR^9 ;
 7 R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$,
 8 $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$,
 9 $-NHNr^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNr^{34I}R^{35I}$, substituted or unsubstituted alkyl, substituted

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

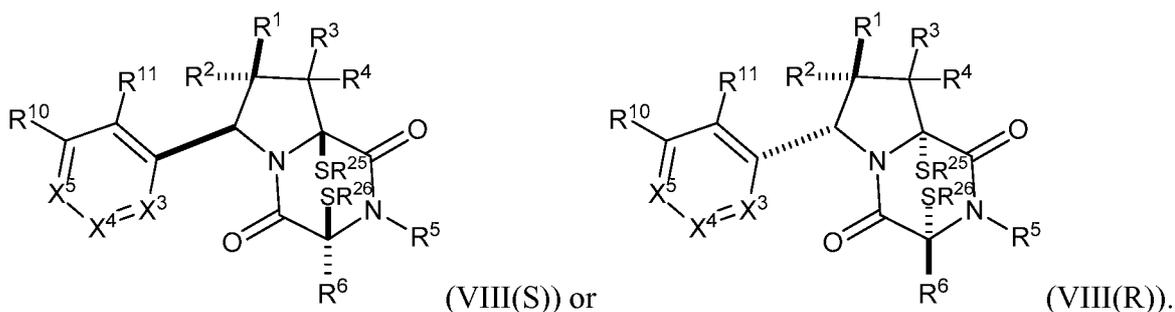
12 R^8 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33J}$,
 13 $-NR^{34J}R^{35J}$, $-COOR^{33J}$, $-CONR^{34J}R^{35J}$, $-NO_2$, $-SR^{36J}$, $-SO_{n10}R^{34J}$, $-SO_{n10}OR^{34J}$, $-SO_{n10}NR^{34J}R^{35J}$,
 14 $-NHR^{34J}R^{35J}$, $-ONR^{34J}R^{35J}$, $-NHC(O)NHR^{34J}R^{35J}$, substituted or unsubstituted alkyl,
 15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 16 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 17 heteroaryl;

18 R^9 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33K}$,
 19 $-NR^{34K}R^{35K}$, $-COOR^{33K}$, $-CONR^{34K}R^{35K}$, $-NO_2$, $-SR^{36K}$, $-SO_{n11}R^{34K}$, $-SO_{n11}OR^{34K}$,
 20 $-SO_{n11}NR^{34K}R^{35K}$, $-NHR^{34K}R^{35K}$, $-ONR^{34K}R^{35K}$, $-NHC(O)NHR^{34K}R^{35K}$, substituted or
 21 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 22 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 23 substituted or unsubstituted heteroaryl;

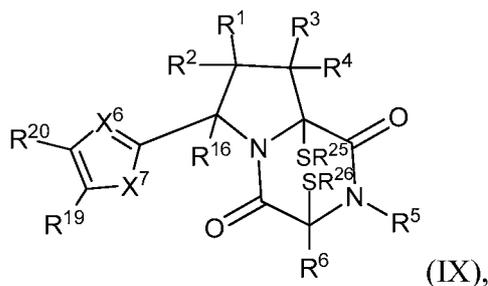
24 R^{10} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 25 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$,
 26 $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHR^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHR^{34L}R^{35L}$,
 27 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 28 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 29 unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to
 30 form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a
 31 substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

32 R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} , R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} ,
 33 and R^{36L} , are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 34 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 35 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
 36 n_9 , n_{10} , n_{11} , and n_{12} are independently 1 or 2.

1 68. The compound of claims 66 or 67 having the formula



1 69. The compound of claim 66 having the formula



3 wherein,

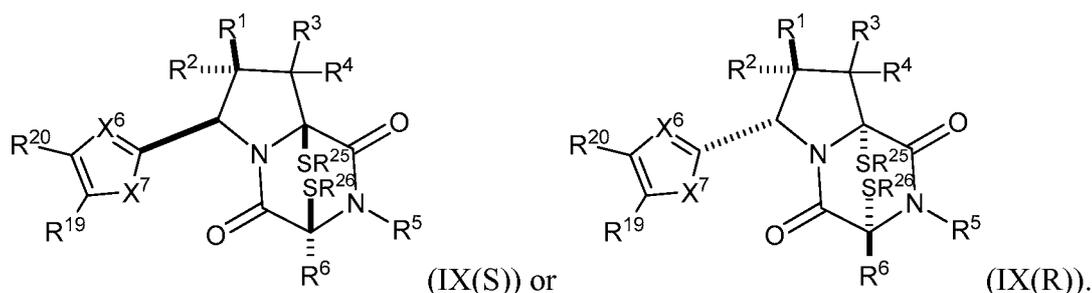
4 X^6 is CR^{21} or N;

5 X^7 is $CR^{22}R^{23}$, S, O, or NR^{23} ;

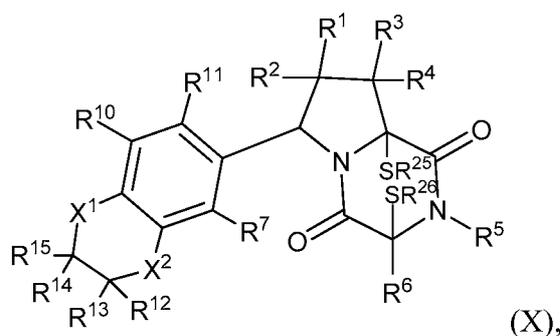
6 R^{19} , R^{20} , R^{21} , R^{22} and R^{23} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$,
 7 $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$,
 8 $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNHNR^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$,
 9 $-NHC(O)NHNHNR^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or unsubstituted
 10 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 11 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 12 R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or
 13 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 14 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 15 substituted or unsubstituted heteroaryl; and

16 n_{13} is 1 or 2.

1 70. The compound of claims 66 or 69 having the formula:



1 71. The compound of claim 66 having the formula:



3 wherein,

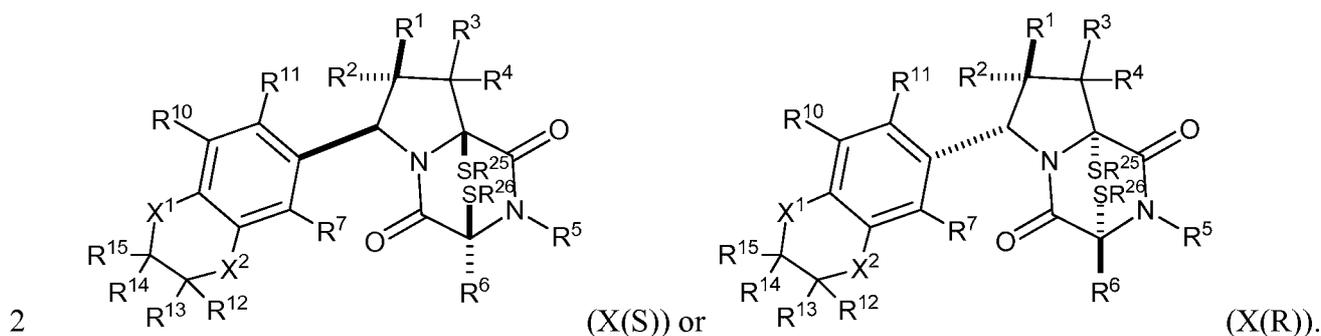
4 X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

5 X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and

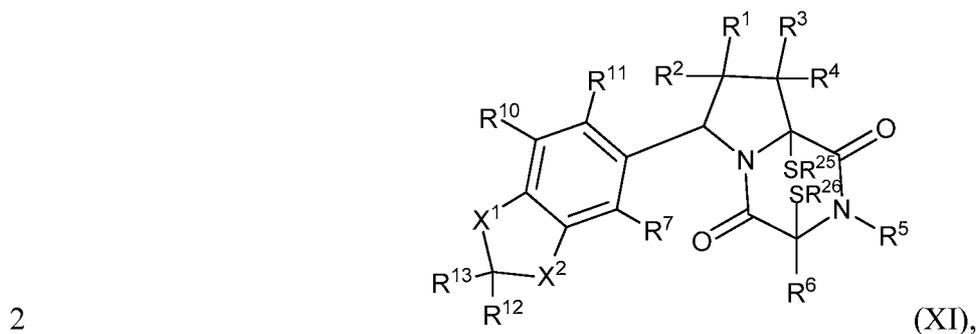
6 R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen,
 7 $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$,
 8 $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$,
 9 $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or
 10 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 11 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 12 R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or
 13 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 14 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 15 substituted or unsubstituted heteroaryl; and

16 n_{13} is 1 or 2.

1 72. The compound of claims 66 or 71 having the formula:



1 73. The compound of claim 66 having the formula:



3 wherein,

4 X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

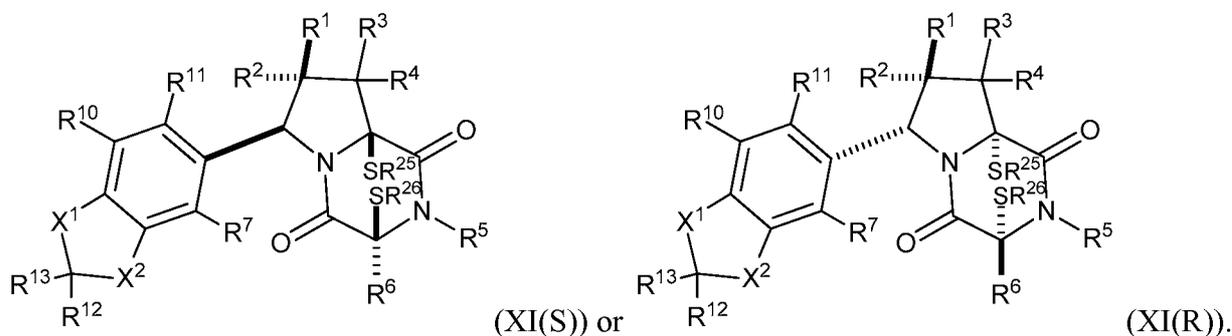
5 X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S;

6 R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$,
 7 $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$,
 8 $-NHNr^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNr^{34I}R^{35I}$, substituted or unsubstituted alkyl,
 9 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 10 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 11 heteroaryl;

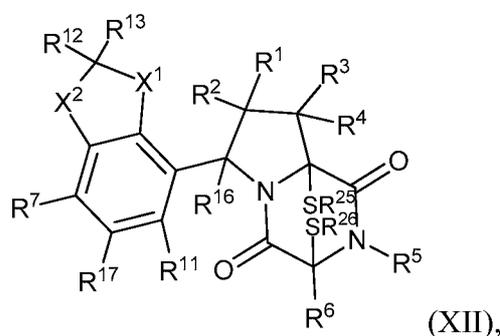
12 R^{10} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 13 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$,
 14 $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNr^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNr^{34L}R^{35L}$,
 15 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 16 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 17 unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to
 18 form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a
 19 substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

20 R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$,
 21 $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$,
 22 $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$,
 23 $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or
 24 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 25 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;
 26 R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or
 27 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 28 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 29 substituted or unsubstituted heteroaryl; and
 30 n_9 , n_{11} , and n_{13} are independently 1 or 2.

1 74. The compound of claims 66 or 73 having the formula:



1 75. The compound of claim 66 having the formula:



3 wherein,

4 X^1 is $CR^{21}R^{21A}$, O , NR^{21A} , or S ;

5 X^2 is $CR^{22}R^{22A}$, O , NR^{22A} , or S ; and

6 R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$,
 7 $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$,
 8 $-NHN R^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHN R^{34I}R^{35I}$, substituted or unsubstituted alkyl,
 9 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 10 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 11 heteroaryl;

12 R^{11} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$,
 13 $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$,
 14 $-SO_{n12}NR^{34L}R^{35L}$, $-NHN R^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHN R^{34L}R^{35L}$, substituted or
 15 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 16 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 17 substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or
 18 unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or
 19 unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

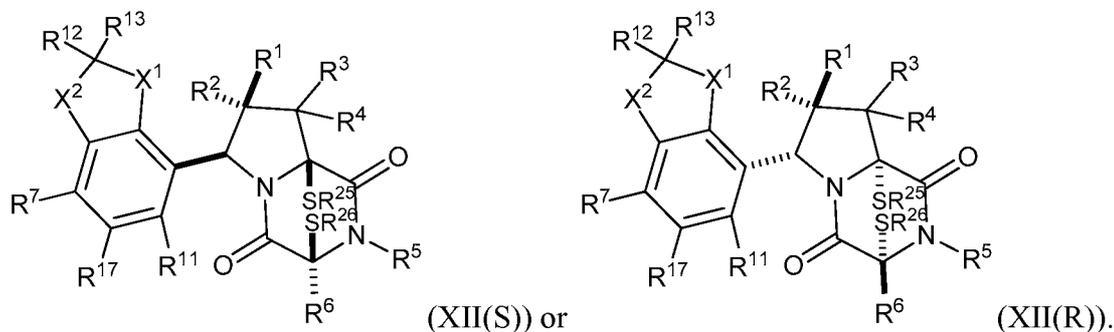
20 R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$,
 21 $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$,
 22 $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$,
 23 $-NHC(O)NHN R^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or unsubstituted
 24 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 25 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

26 R^{17} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33P}$, $-$
 27 $NR^{34P}R^{35P}$, $-COOR^{33P}$, $-CONR^{34P}R^{35P}$, $-NO_2$, $-SR^{36P}$, $-SO_{n15}R^{34P}$, $-SO_{n15}OR^{34P}$, $-SO_{n15}NR^{34P}R^{35P}$,
 28 $-NHN R^{34P}R^{35P}$, $-ONR^{34P}R^{35P}$, $-NHC(O)NHN R^{34P}R^{35P}$, substituted or unsubstituted alkyl,
 29 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 30 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 31 heteroaryl, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a
 32 substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted
 33 or unsubstituted heteroaryl;

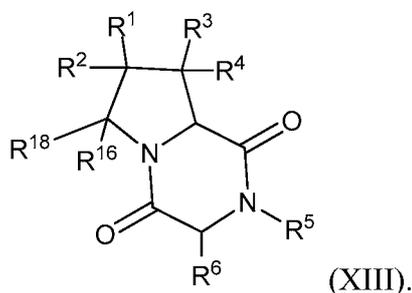
34 R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33L} , R^{34L} , R^{35L} , R^{36L} , R^{33M} , R^{34M} , R^{35M} , R^{36M} , R^{33P} , R^{34P} ,
 35 R^{35P} , and R^{36P} are independently hydrogen, substituted or unsubstituted alkyl, substituted or

36 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 37 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
 38 n9, n12, n13 and n15 are independently 1 or 2.

1 76. The compound of claims 66 or 75 having the formula:



1 77. A compound having the formula:



3 wherein,

4 R¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33A},
 5 -NR^{34A}R^{35A}, -COOR^{33A}, -CONR^{34A}R^{35A}, -NO₂, -SR^{36A}, -SO_{n1}R^{34A}, -SO_{n1}OR^{34A},
 6 -SO_{n1}NR^{34A}R^{35A}, -NHNr^{34A}R^{35A}, -ONR^{34A}R^{35A}, -NHC(O)NHNr^{34A}R^{35A}, substituted or
 7 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 8 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 9 substituted or unsubstituted heteroaryl;

10 R² is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33B},
 11 -NR^{34B}R^{35B}, -COOR^{33B}, -CONR^{34B}R^{35B}, -NO₂, -SR^{36B}, -SO_{n2}R^{34b}, -SO_{n2}OR^{34B}, -SO_{n2}NR^{34B}R^{35B},
 12 -NHNr^{34B}R^{35B}, -ONR^{34B}R^{35B}, -NHC(O)NHNr^{34B}R^{35B}, substituted or unsubstituted alkyl,
 13 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 14 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 15 heteroaryl;

16 R^3 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33C}$,
 17 $-NR^{34C}R^{35C}$, $-COOR^{33C}$, $-CONR^{34C}R^{35C}$, $-NO_2$, $-SR^{36C}$, $-SO_{n3}R^{34C}$, $-SO_{n3}OR^{34C}$, $-SO_{n3}NR^{34C}R^{35C}$,
 18 $-NHN R^{34C}R^{35C}$, $-ONR^{34C}R^{35C}$, $-NHC(O)NHN R^{34C}R^{35C}$, substituted or unsubstituted alkyl,
 19 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 20 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 21 heteroaryl;

22 R^4 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33D}$,
 23 $-NR^{34D}R^{35D}$, $-COOR^{33D}$, $-CONR^{34D}R^{35D}$, $-NO_2$, $-SR^{36D}$, $-SO_{n4}R^{34D}$, $-SO_{n4}OR^{34D}$,
 24 $-SO_{n4}NR^{34D}R^{35D}$, $-NHN R^{34D}R^{35D}$, $-ONR^{34D}R^{35D}$, $-NHC(O)NHN R^{34D}R^{35D}$, substituted or
 25 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 26 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 27 substituted or unsubstituted heteroaryl;

28 R^5 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33E}$,
 29 $-NR^{34E}R^{35E}$, $-COOR^{33E}$, $-CONR^{34E}R^{35E}$, $-NO_2$, $-SR^{36E}$, $-SO_{n5}R^{34E}$, $-SO_{n5}OR^{34E}$, $-SO_{n5}NR^{34E}R^{35E}$,
 30 $-NHN R^{34E}R^{35E}$, $-ONR^{34E}R^{35E}$, $-NHC(O)NHN R^{34E}R^{35E}$, substituted or unsubstituted alkyl,
 31 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 32 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 33 heteroaryl;

34 R^6 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33F}$,
 35 $-NR^{34F}R^{35F}$, $-COOR^{33F}$, $-CONR^{34F}R^{35F}$, $-NO_2$, $-SR^{36F}$, $-SO_{n6}R^{34F}$, $-SO_{n6}OR^{34F}$, $-SO_{n6}NR^{34F}R^{35F}$,
 36 $-NHN R^{34F}R^{35F}$, $-ONR^{34F}R^{35F}$, $-NHC(O)NHN R^{34F}R^{35F}$, substituted or unsubstituted alkyl,
 37 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 38 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 39 heteroaryl;

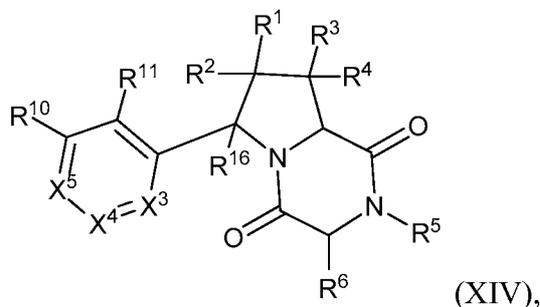
40 R^{16} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33G}$,
 41 $-NR^{34G}R^{35G}$, $-COOR^{33G}$, $-CONR^{34G}R^{35G}$, $-NO_2$, $-SR^{36G}$, $-SO_{n7}R^{34G}$, $-SO_{n7}OR^{34G}$,
 42 $-SO_{n7}NR^{34G}R^{35G}$, $-NHN R^{34G}R^{35G}$, $-ONR^{34G}R^{35G}$, $-NHC(O)NHN R^{34G}R^{35G}$, substituted or
 43 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 44 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 45 substituted or unsubstituted heteroaryl;

46 R^{18} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33H}$,
 47 $-NR^{34H}R^{35H}$, $-COOR^{33H}$, $-CONR^{34H}R^{35H}$, $-NO_2$, $-SR^{36H}$, $-SO_{n8}R^{34H}$, $-SO_{n8}OR^{34H}$,
 48 $-SO_{n8}NR^{34H}R^{35H}$, $-NHN R^{34H}R^{35H}$, $-ONR^{34H}R^{35H}$, $-NHC(O)NHN R^{34H}R^{35H}$, substituted or
 49 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 50 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 51 substituted or unsubstituted heteroaryl;

52 R^{33A} , R^{34A} , R^{35A} , R^{36A} , R^{33B} , R^{34B} , R^{35B} , R^{36B} , R^{33C} , R^{34C} , R^{35C} , R^{36C} , R^{33D} , R^{34D} ,
 53 R^{35D} , R^{36D} , R^{33E} , R^{34E} , R^{35E} , R^{36E} , R^{33F} , R^{34F} , R^{35F} , R^{36F} , R^{33G} , R^{34G} , R^{35G} , R^{36G} , R^{33H} , R^{34H} , R^{35H} ,
 54 and R^{36H} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 55 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 56 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

57 $n1, n2, n3, n4, n5, n6, n7,$ and $n8$ are independently 1 or 2.

1 78. The compound of claim 77 having formula



2
 3 wherein,

4 X^3 is N or CR^7 ;

5 X^4 is N or CR^8 ;

6 X^5 is N or CR^9 ;

7 R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$,
 8 $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$,
 9 $-NHN R^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHN R^{34I}R^{35I}$, substituted or unsubstituted alkyl, substituted
 10 or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 11 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

12 R^8 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33J}$,
 13 $-NR^{34J}R^{35J}$, $-COOR^{33J}$, $-CONR^{34J}R^{35J}$, $-NO_2$, $-SR^{36J}$, $-SO_{n10}R^{34J}$, $-SO_{n10}OR^{34J}$, $-SO_{n10}NR^{34J}R^{35J}$,
 14 $-NHN R^{34J}R^{35J}$, $-ONR^{34J}R^{35J}$, $-NHC(O)NHN R^{34J}R^{35J}$, substituted or unsubstituted alkyl,

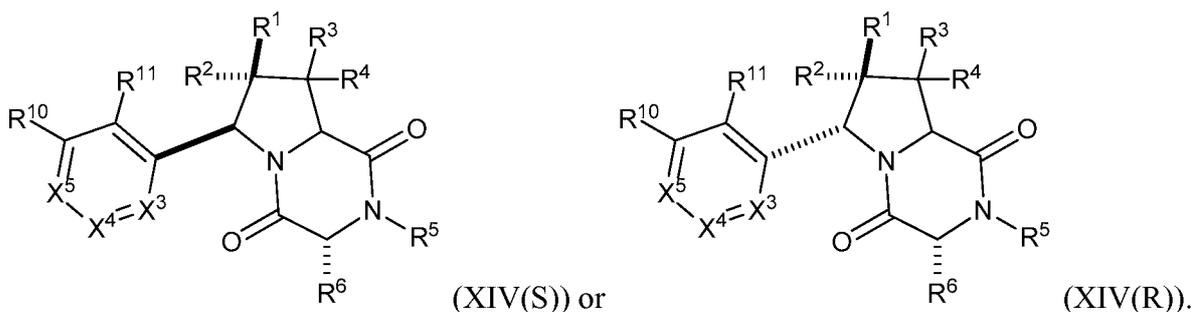
15 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 16 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 17 heteroaryl;

18 R^9 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33K}$,
 19 $-NR^{34K}R^{35K}$, $-COOR^{33K}$, $-CONR^{34K}R^{35K}$, $-NO_2$, $-SR^{36K}$, $-SO_{n11}R^{34K}$, $-SO_{n11}OR^{34K}$,
 20 $-SO_{n11}NR^{34K}R^{35K}$, $-NHN R^{34K}R^{35K}$, $-ONR^{34K}R^{35K}$, $-NHC(O)NHN R^{34K}R^{35K}$, substituted or
 21 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 22 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 23 substituted or unsubstituted heteroaryl;

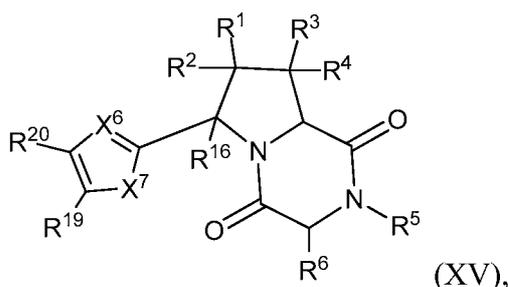
24 R^{10} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$,
 25 $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$,
 26 $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHN R^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHN R^{34L}R^{35L}$,
 27 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 28 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 29 unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to
 30 form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a
 31 substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

32 R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33J} , R^{34J} , R^{35J} , R^{36J} , R^{33K} , R^{34K} , R^{35K} , R^{36K} , R^{33L} , R^{34L} , R^{35L} ,
 33 and R^{36L} , are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 34 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 35 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
 36 n_9 , n_{10} , n_{11} , and n_{12} are independently 1 or 2.

1 79. The compound of claims 77 or 78 having formula:



1 80. The compound of claim 77 having formula:



wherein,

X^6 is CR^{21} or N;

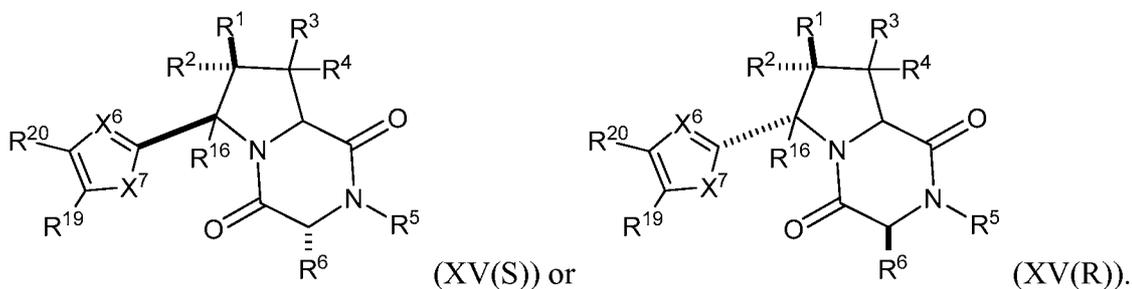
X^7 is $CR^{22}R^{23}$, S, O, or NR^{23} ;

R^{19} , R^{20} , R^{21} , R^{22} and R^{23} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHN R^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

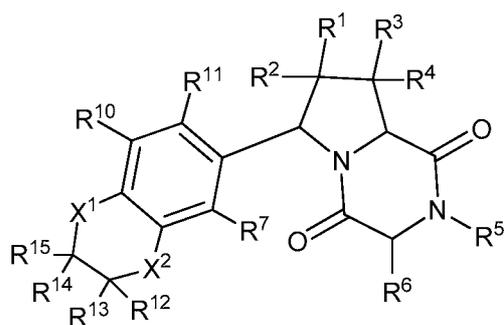
R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n_{13} is 1 or 2.

81. The compound of claims 77 or 80 having formula:



82. The compound of claim 77 having formula:



(XVI),

wherein,

X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S; and

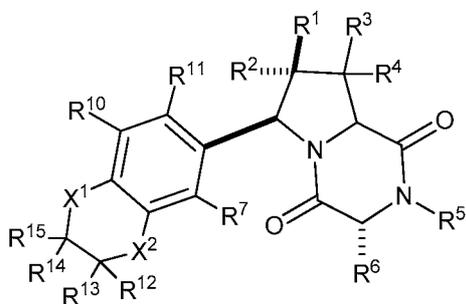
R^{12} , R^{13} , R^{14} , R^{15} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or

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

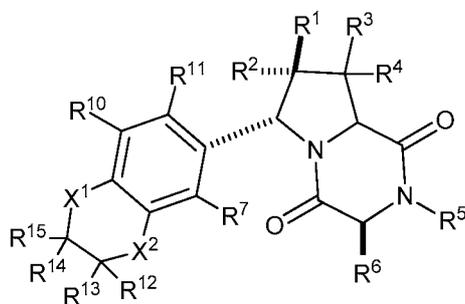
R^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

n_{13} is 1 or 2.

83. The compound of claims 77 or 82 having formula:

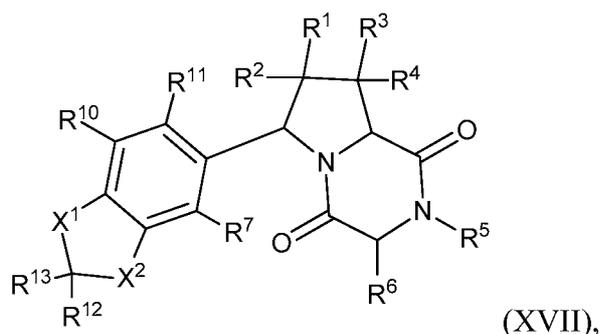


(XVI(S)) or



(XVI(R)).

84. The compound of claim 77 having formula



X^1 is $CR^{21}R^{21A}$, O, NR^{21A} , or S;

X^2 is $CR^{22}R^{22A}$, O, NR^{22A} , or S;

R^7 is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33I}$, $-NR^{34I}R^{35I}$, $-COOR^{33I}$, $-CONR^{34I}R^{35I}$, $-NO_2$, $-SR^{36I}$, $-SO_{n9}R^{34I}$, $-SO_{n9}OR^{34I}$, $-SO_{n9}NR^{34I}R^{35I}$, $-NHNr^{34I}R^{35I}$, $-ONR^{34I}R^{35I}$, $-NHC(O)NHNr^{34I}R^{35I}$, substituted 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} and R^{11} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33L}$, $-NR^{34L}R^{35L}$, $-COOR^{33L}$, $-CONR^{34L}R^{35L}$, $-NO_2$, $-SR^{36L}$, $-SO_{n12}R^{34L}$, $-SO_{n12}OR^{34L}$, $-SO_{n12}NR^{34L}R^{35L}$, $-NHNr^{34L}R^{35L}$, $-ONR^{34L}R^{35L}$, $-NHC(O)NHNr^{34L}R^{35L}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

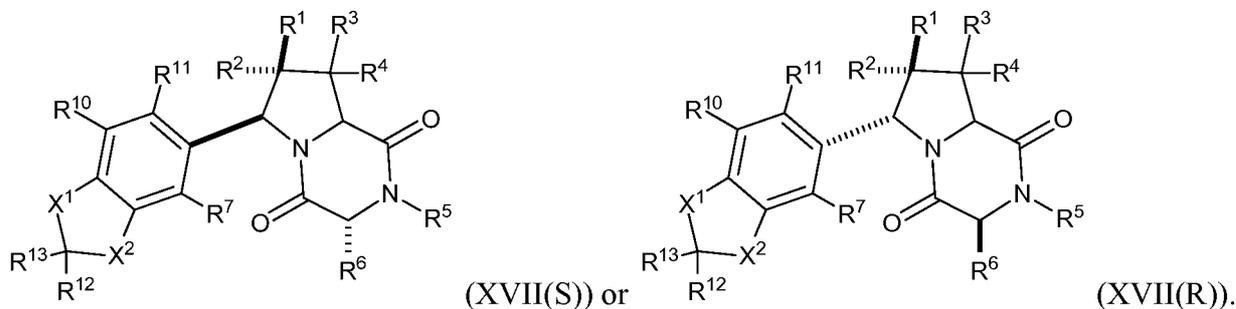
R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$, $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHNr^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$, $-NHC(O)NHNr^{34M}R^{35M}$, substituted 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^{33M} , R^{34M} , R^{35M} , and R^{36M} are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

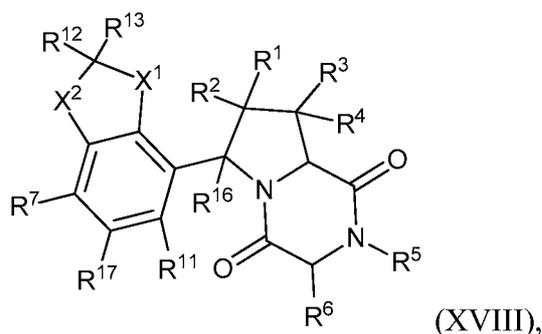
27 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 28 substituted or unsubstituted heteroaryl; and

29 n₉, n₁₁, and n₁₃ are independently 1 or 2.

1 85. The compound of claims 77 or 84 having formula



1 86. The compound of claim 77 having formula



3 X¹ is CR²¹R^{21A}, O, NR^{21A}, or S;

4 X² is CR²²R^{22A}, O, NR^{22A}, or S; and

5 R⁷ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33I},
 6 -NR^{34I}R^{35I}, -COOR^{33I}, -CONR^{34I}R^{35I}, -NO₂, -SR^{36I}, -SO_{n9}R^{34I}, -SO_{n9}OR^{34I}, -SO_{n9}NR^{34I}R^{35I},
 7 -NHNr^{34I}R^{35I}, -ONR^{34I}R^{35I}, -NHC(O)NHNr^{34I}R^{35I}, substituted or unsubstituted alkyl,

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

11 R¹¹ is hydrogen, halogen, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OR^{33L},
 12 -NR^{34L}R^{35L}, -COOR^{33L}, -CONR^{34L}R^{35L}, -NO₂, -SR^{36L}, -SO_{n12}R^{34L}, -SO_{n12}OR^{34L},

13 -SO_{n12}NR^{34L}R^{35L}, -NHNr^{34L}R^{35L}, -ONR^{34L}R^{35L}, -NHC(O)NHNr^{34L}R^{35L}, substituted or

14 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

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

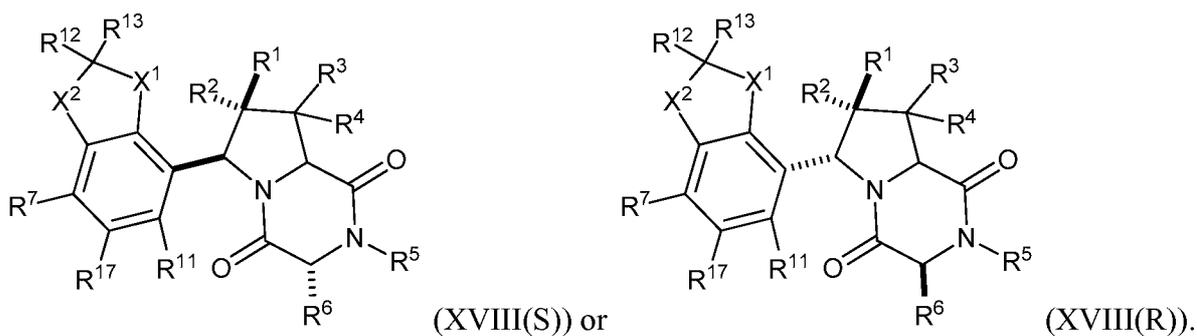
16 substituted or unsubstituted heteroaryl, or are optionally joined together to form a substituted or
 17 unsubstituted cycloalkyl, a substituted or unsubstituted heterocycloalkyl, a substituted or
 18 unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

19 R^{12} , R^{13} , R^{21} , R^{21A} , R^{22} , and R^{22A} are independently hydrogen, halogen, $-N_3$, $-CF_3$,
 20 $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33M}$, $-NR^{34M}R^{35M}$, $-COOR^{33M}$, $-CONR^{34M}R^{35M}$, $-NO_2$,
 21 $-SR^{36M}$, $-SO_{n13}R^{34M}$, $-SO_{n13}OR^{34M}$, $-SO_{n13}NR^{34M}R^{35M}$, $-NHN R^{34M}R^{35M}$, $-ONR^{34M}R^{35M}$,
 22 $-NHC(O)NHN R^{34M}R^{35M}$, substituted or unsubstituted alkyl, substituted or unsubstituted
 23 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 24 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

25 R^{17} is hydrogen, halogen, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OR^{33P}$, $-$
 26 $NR^{34P}R^{35P}$, $-COOR^{33P}$, $-CONR^{34P}R^{35P}$, $-NO_2$, $-SR^{36P}$, $-SO_{n15}R^{34P}$, $-SO_{n15}OR^{34P}$, $-SO_{n15}NR^{34P}R^{35P}$, $-$
 27 $NHN R^{34P}R^{35P}$, $-ONR^{34P}R^{35P}$, $-NHC(O)NHN R^{34P}R^{35P}$, substituted or unsubstituted alkyl,
 28 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 29 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 30 heteroaryl, or are optionally bonded together to form a substituted or unsubstituted cycloalkyl, a
 31 substituted or unsubstituted heterocycloalkyl, a substituted or unsubstituted aryl, or a substituted
 32 or unsubstituted heteroaryl;

33 R^{33I} , R^{34I} , R^{35I} , R^{36I} , R^{33L} , R^{34L} , R^{35L} , R^{36L} , R^{33M} , R^{34M} , R^{35M} , R^{36M} , R^{33P} , R^{34P} ,
 34 R^{35P} , and R^{36P} are independently hydrogen, substituted or unsubstituted alkyl, substituted or
 35 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 36 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and
 37 n_9 , n_{12} , n_{13} and n_{15} are independently 1 or 2.

1 87. The compound of claims 77 or 86 having formula



- 1 88. The compound of claim 1, wherein said compound is an epigenetic
2 inhibitor.
- 1 89. The compound of claim 88, wherein said compound inhibits the activity of
2 HMT SUV39H1.
- 1 90. The compound of claims 88 or 89, wherein said compound specifically
2 inhibits the activity of HMT SUV39H1.
- 1 91. The compound of claim 88, wherein said compound inhibits the activity of
2 HMT G9a.
- 1 92. The compound of claims 88 or 91, wherein said compound specifically
2 inhibits the activity of HMT G9a
- 1 93. The compound of any one of claims 88 to 92, wherein said compound
2 inhibits the activity of HMT SUV39H1 and the activity of HMT G9a.
- 1 94. The compound of of any one of claims 88 to 93, wherein said compound
2 specifically inhibits the activity of HMT SUV39H1 and the activity of HMT G9a.
- 1 95. The compound of claim 1, wherein said compound inhibits H3K9
2 trimethylation or dimethylation.
- 1 96. A method of treating cancer, said method comprising administering to a
2 subject in need thereof a therapeutically effective amount of a compound of one of claim 1.
- 1 97. The method of claim 96, wherein said cancer is a solid or blood tumor.
- 1 98. The method of claims 96 or 97, wherein said cancer is ovarian cancer,
2 breast cancer, lung cancer, leukemia, AML, CML, lymphoma, pancreatic cancer, kidney cancer,
3 melanoma, liver cancer, colon cancer, sarcoma, multiple myeloma, brain cancer, or prostate
4 cancer.

1 99. The method of claim 96 to 98, further comprising administering at least
2 one additional anticancer agent.

1 100. The method of claim 96 to 99, wherein said at least one additional
2 anticancer agent comprises an epigenetic inhibitor or a multi-kinase inhibitor.

1 101. The method of claim 99 to 100, wherein said method comprises
2 administering a first amount of said compound and a second amount of at least one additional
3 anticancer agent, wherein the first amount and second amount are together an effective amount
4 to provide a synergistic therapeutic effect.

1 102. The method of claim 99 to 101, wherein said additional anticancer agent is
2 an epigenetic inhibitor.

1 103. The method of claims 101 or 102, wherein said epigenetic inhibitor is
2 azacitidine or decitadine.

1 104. The method of claims 102 to 103, wherein said compound and said
2 epigenetic inhibitor are co-administered as a pharmaceutical composition.

3 105. The method claims 100 or 101, wherein said additional anticancer agent
4 is a multi-kinase inhibitor.

1 106. The method of claims 101 or 105, wherein said multi-kinase inhibitor is
2 sorafenib.

1 107. The method of claim 105, wherein said compound and said multi-kinase
2 inhibitor are co-administered as a pharmaceutical composition.

1 108. The method of claim 99 to 107, wherein said cancer is ovarian cancer.

1 109. A pharmaceutical composition comprising a compound of claim 1 and a
2 pharmaceutically acceptable excipient.

1 110. A pharmaceutical composition comprising a compound of claim 1 and at
2 least one additional anticancer agent.

1 111. The pharmaceutical composition of claim 110, wherein said at least one
2 additional anticancer agent comprises a multi-kinase inhibitor or an epigenetic inhibitor.

1 112. The pharmaceutical composition of claims 110 or 111, wherein said
2 combination includes a first amount of said compound and a second amount of a multi-kinase
3 inhibitor, wherein the first amount and second amount are together an effective amount to
4 provide a synergistic therapeutic effect.

1 113. The pharmaceutical composition of claim 110 to 112, wherein said
2 combination includes a first amount of said compound and a second amount of an epigenetic
3 inhibitor, wherein the first amount and second amount are together an effective amount to
4 provide a synergistic therapeutic effect.

1 114. The pharmaceutical composition of claim 110 to 113, wherein said
2 combination includes a first amount of said compound, a second amount of a multi-kinase
3 inhibitor, an a third amount of an epigenetic inhibitor, wherein the first amount, second, and
4 third amounts are together an effective amount to provide a synergistic therapeutic effect.

1 115. The pharmaceutical composition of any one of claims 109 to 113, wherein
2 said multi-kinase inhibitor is sorafenib and said epigenetic inhibitor is azacitidine or decitadine.

1 116. The pharmaceutical composition of any one of claims 109 to 115, for use
2 in cancer.

1 117. The pharmaceutical composition of any one of claims 109 to 116, for use
2 in solid and blood tumors, including ovarian cancer, breast cancer, lung cancer, leukemia, AML,
3 CML, lymphoma, pancreatic cancer, kidney cancer, melanoma, liver cancer, colon cancer,
4 sarcoma, multiple myeloma, brain cancer, or prostate cancer.

1 118. The pharmaceutical composition of any one of claims 109 to 117, for use
2 in non-small cell lung cancer.

1 119. The pharmaceutical composition of any one of claims 109 to 118, wherein
2 said compound and said multi-kinase inhibitor or said epigenetic inhibitor are co-administered as
3 a single dosage form.

Figure 1

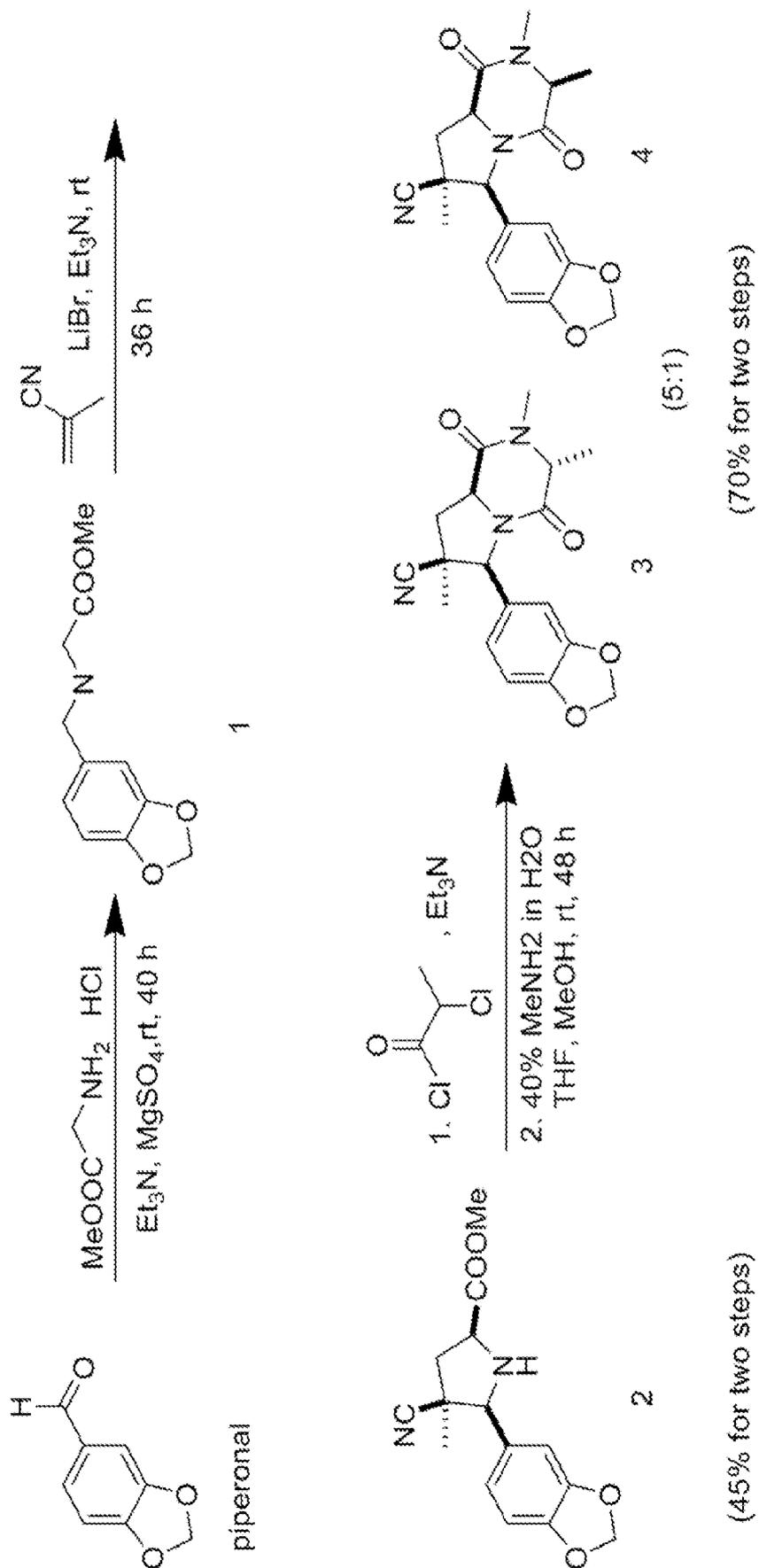


Figure 1

Figure 2

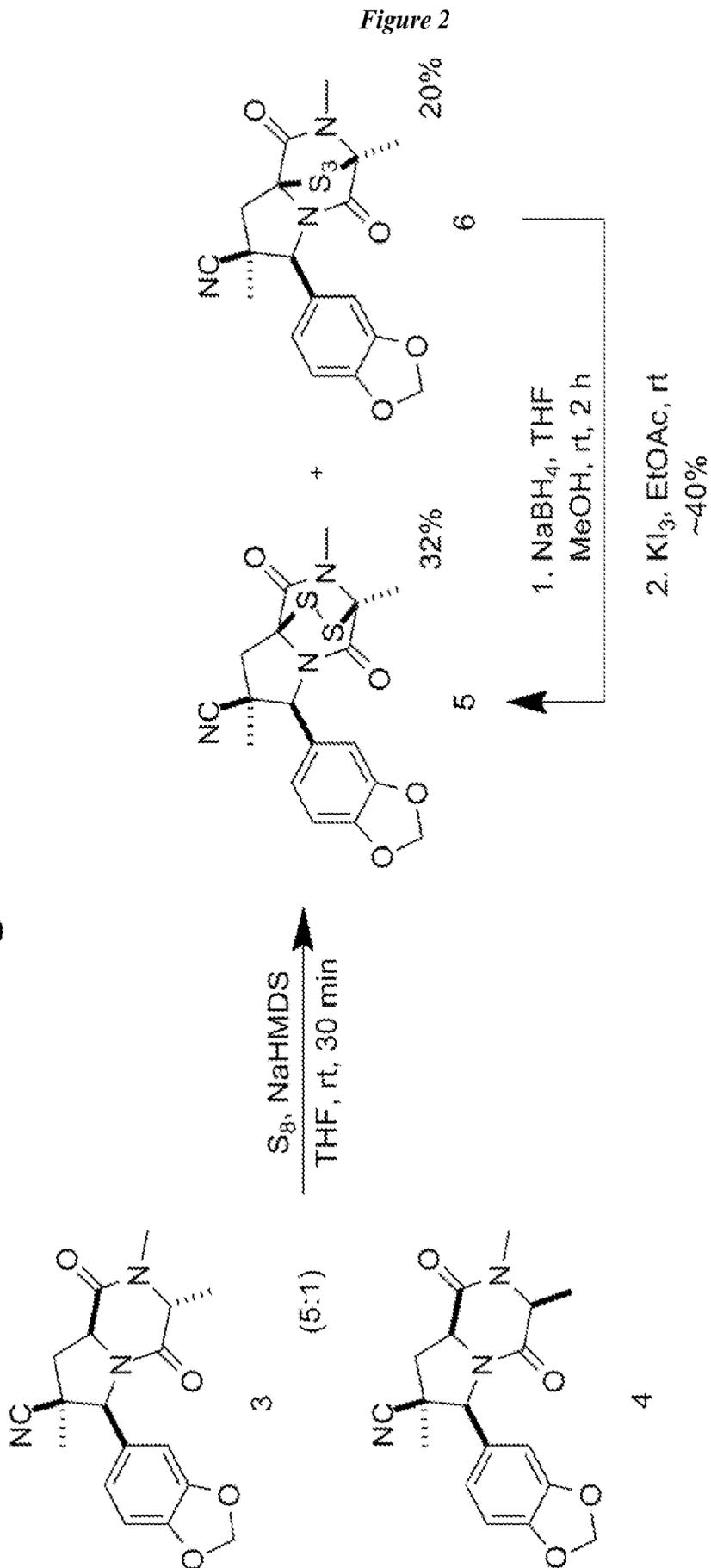


Figure 3

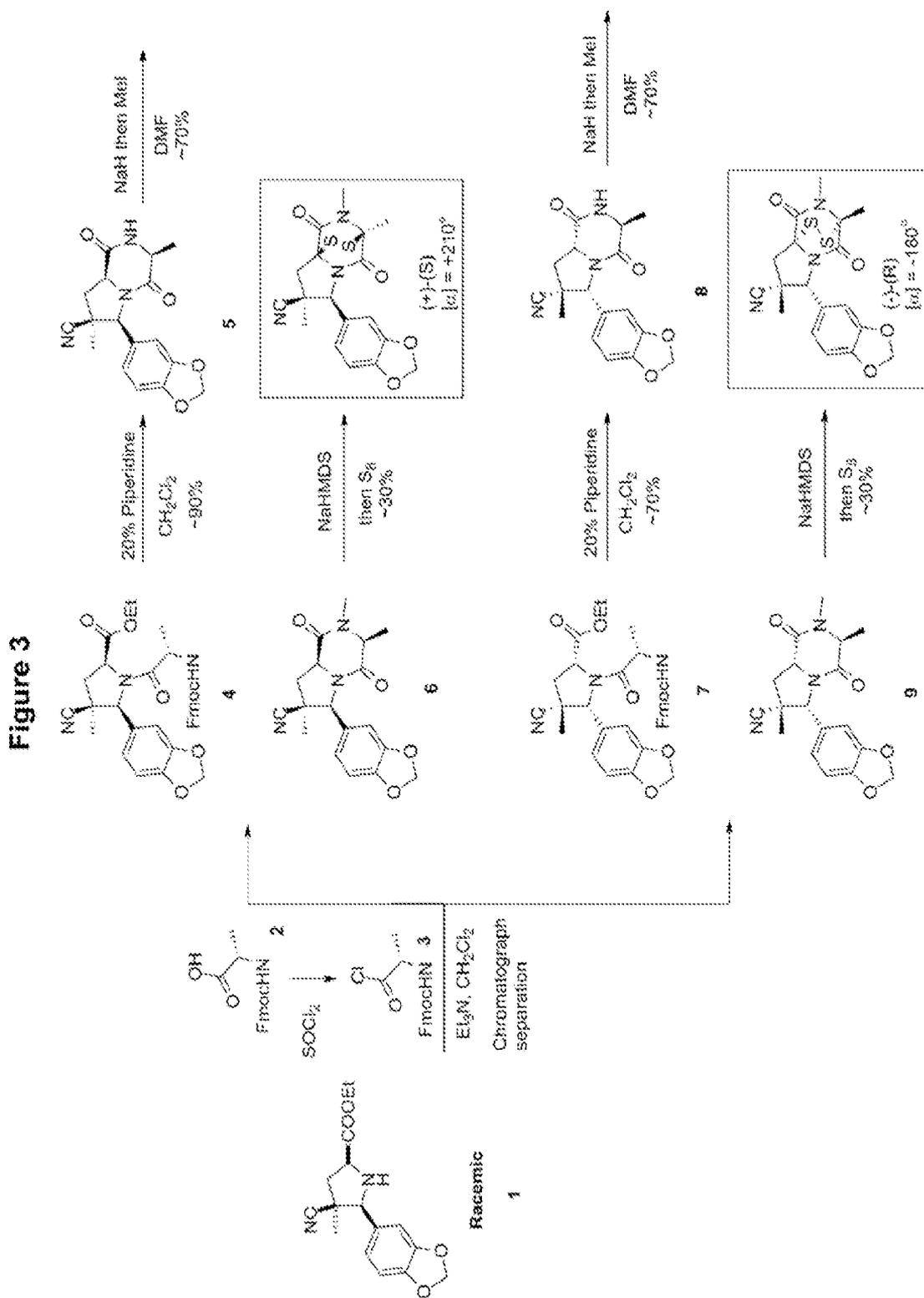


Figure 4

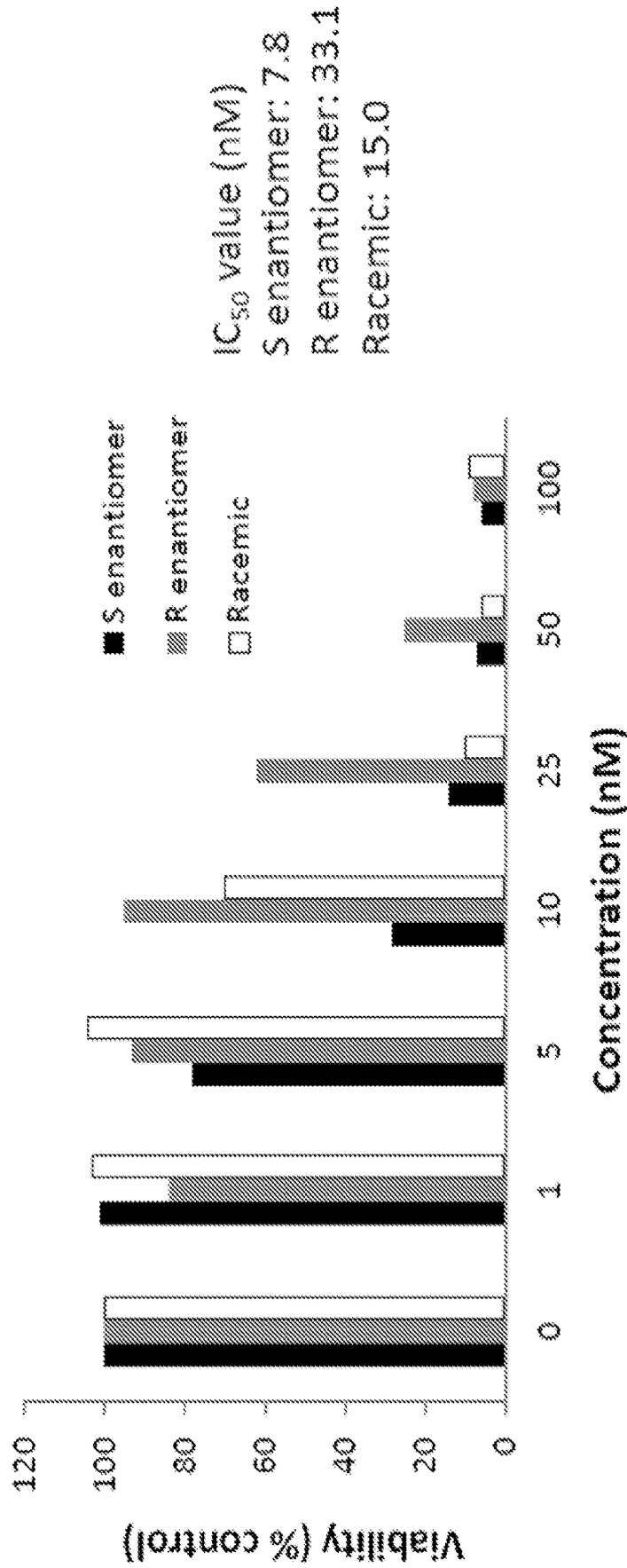


Figure 5

Figure 5

IC50 Summary:

Methyltransferase:	Substrate:	Compound stock	Compound IC50* (M):			Chaetocin IC50* (M):
			Rac	S	R	
1 G9a	Histone H3	10 mM				1.97E-06
2 G9a	Histone H3	1 mM	>1.00E-05			2.39E-06
3 SUV39H1	Histone H3	10 mM	1.16E-06	1.51E-06	2.09E-06	2.01E-07
4 SUV39H1	Histone H3	1 mM	1.16E-06	1.44E-06	1.76E-06	2.57E-07

* Empty cells indicate no inhibition or compound activity that could not be fit to an IC50 curve

ND

Indicates compound not tested against enzyme

Figure 6

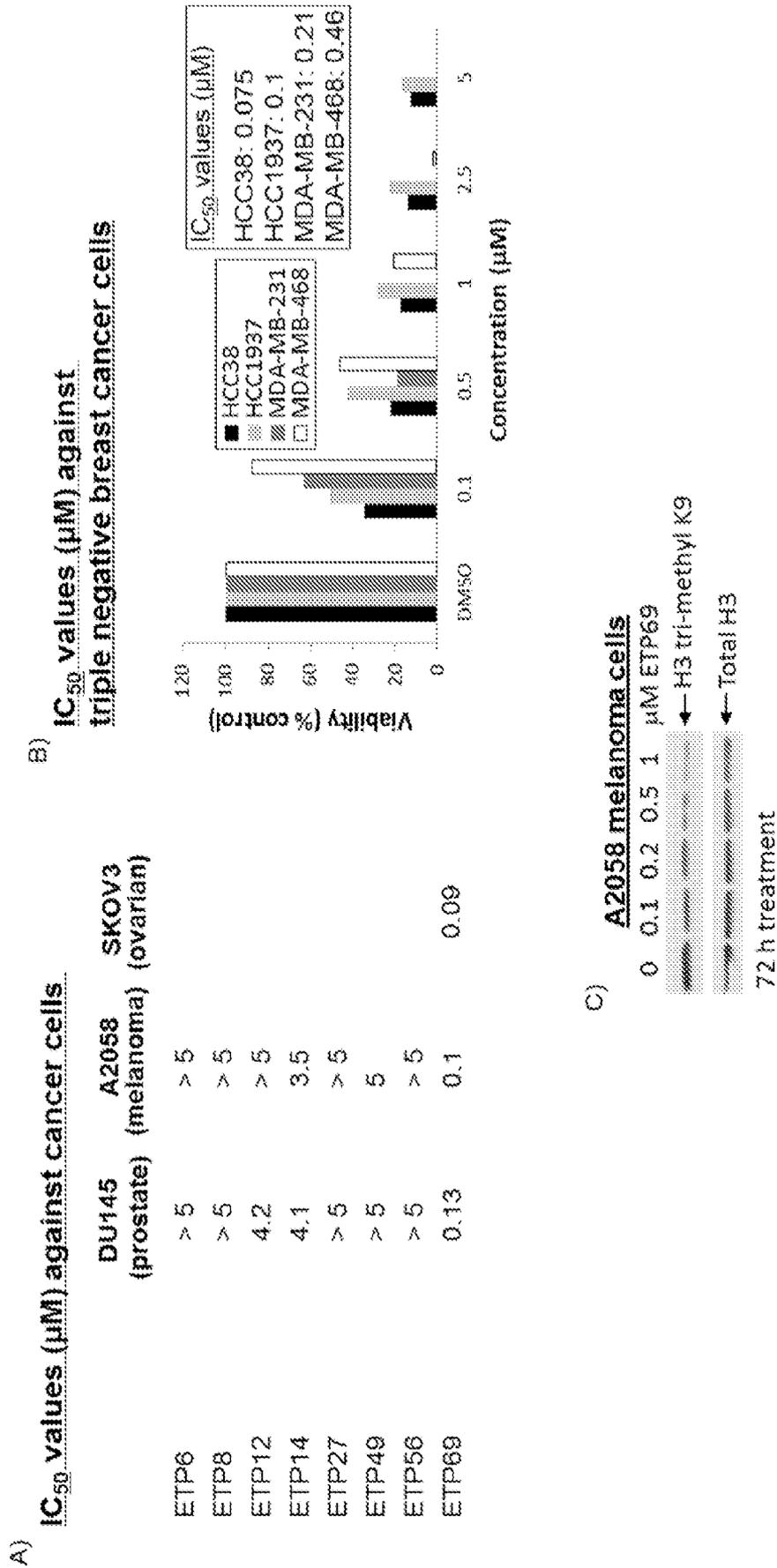


Figure 6

Figure 7

Inhibition of Histone-modifying enzymes *in vitro*

His. Methyltransferase	IC ₅₀ value (μM)	
	ETP69	**Chaetocin
DOT1	> 10	N/A
EZH1	> 10	N/A
EZH2	> 10	N/A
GLP	6.31	0.69
MLL1	4.24	0.22
MLL2	8.4	0.4
MLL3	> 10	0.28
MLL4	> 10	0.31
NSD2	2.79	0.24
SET1b	1.64	0.21
SET7/9	> 10	N/A
SET8	> 10	N/A
SETMAR	> 10	N/A
SMYD2	> 10	N/A
SUV39H1	0.084	0.33
SUV39H2	3.31	0.48
G9a	0.251	0.16
His. Acetyltransferase		
p300	> 10	N/A
DNA Methyltransferase		
DNMT1	> 10	N/A

Figure 8

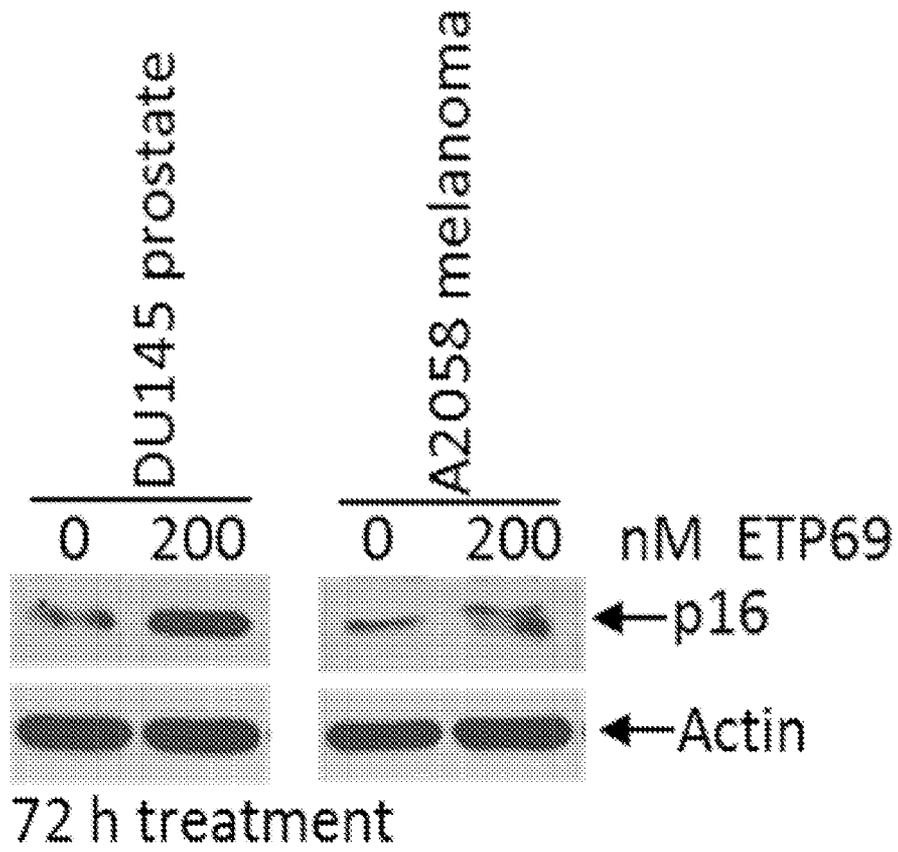


Figure 9

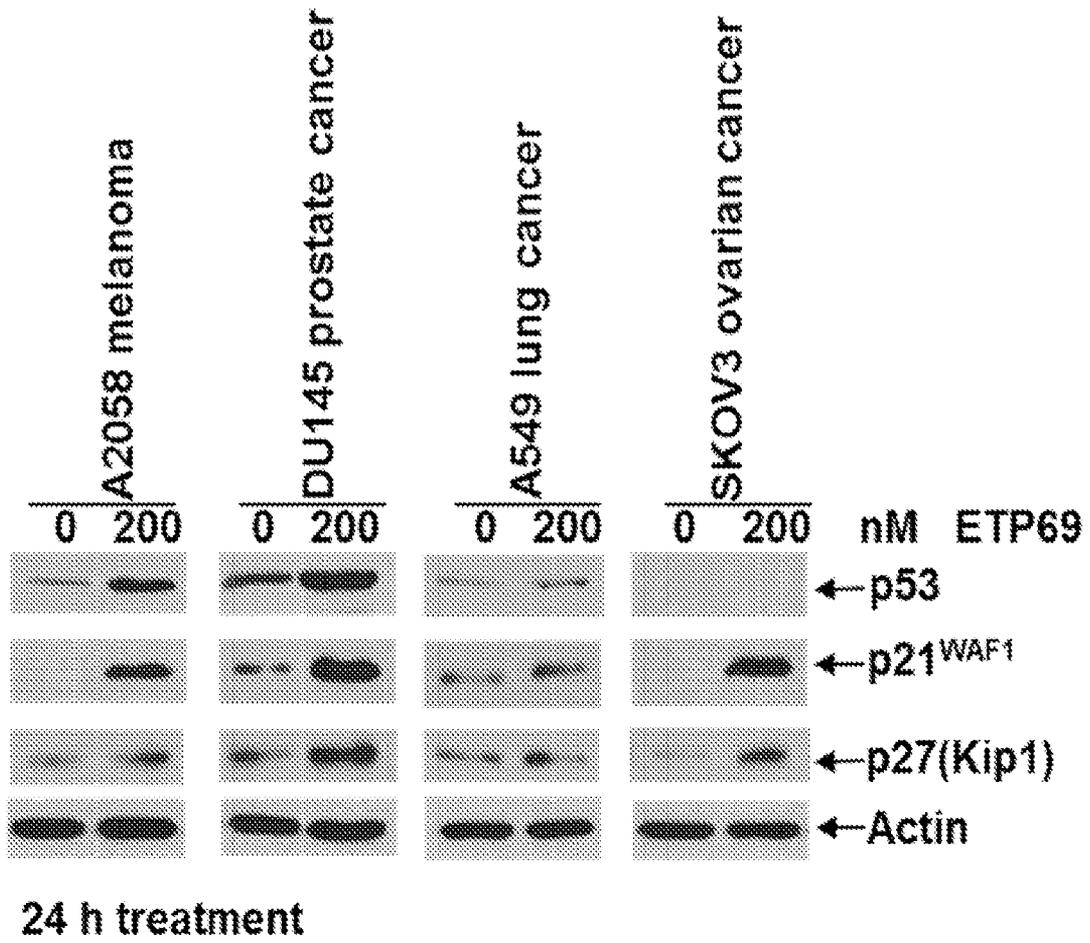


Figure 10

Activity (%)

Conc.(M)	S enantiomer
1.00E-04	108.14
3.33E-05	105.67
1.11E-05	106.39
3.70E-06	108.95
1.23E-06	105.37
4.12E-07	104.94
1.37E-07	107.59
4.57E-08	99.18
1.52E-08	98.50
5.08E-09	94.98
DMSO	94.69

Figure 11

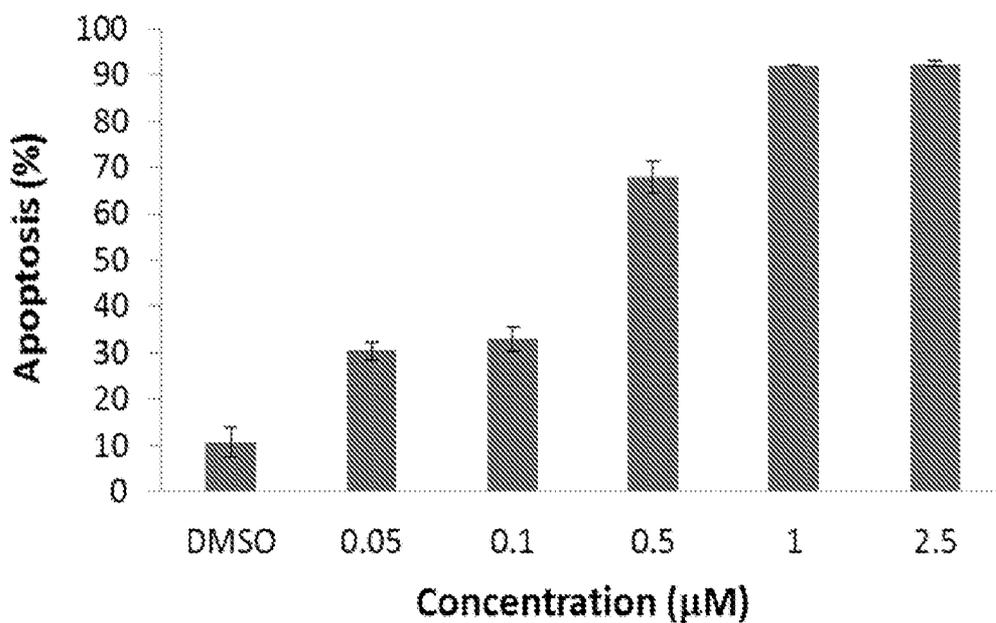


Figure 12

Figure 12

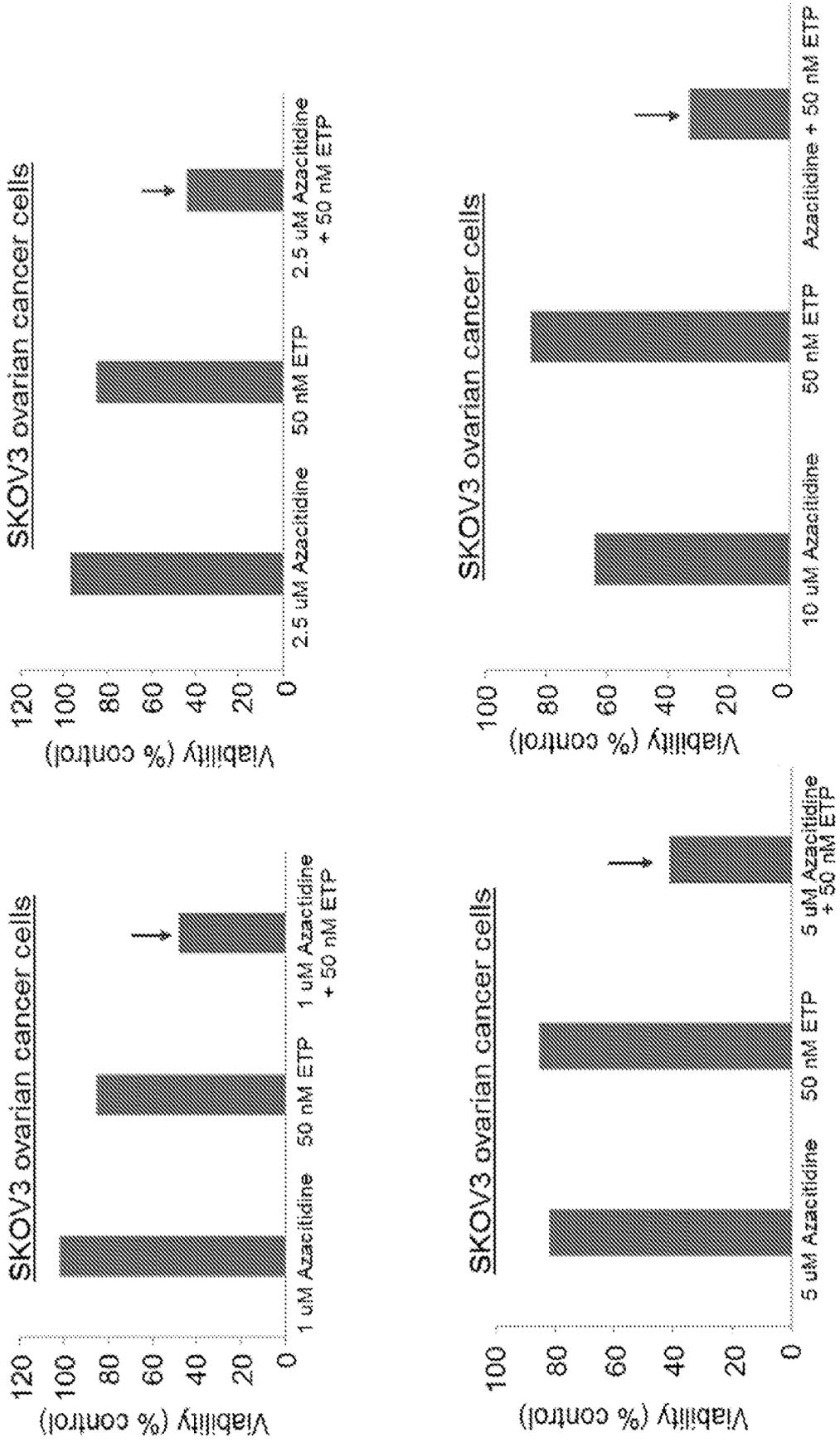


Figure 13

Figure 13

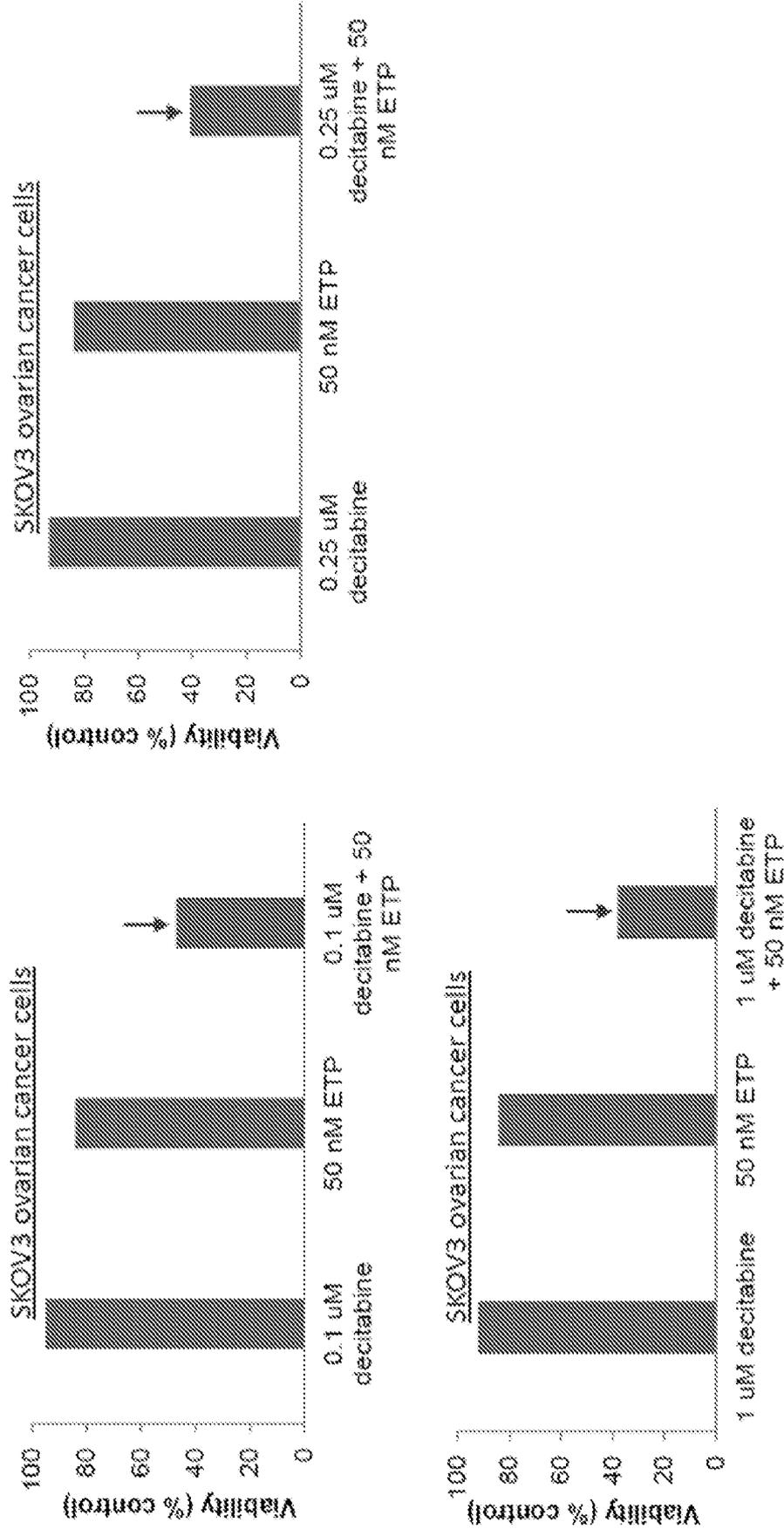


Figure 14

Figure 14

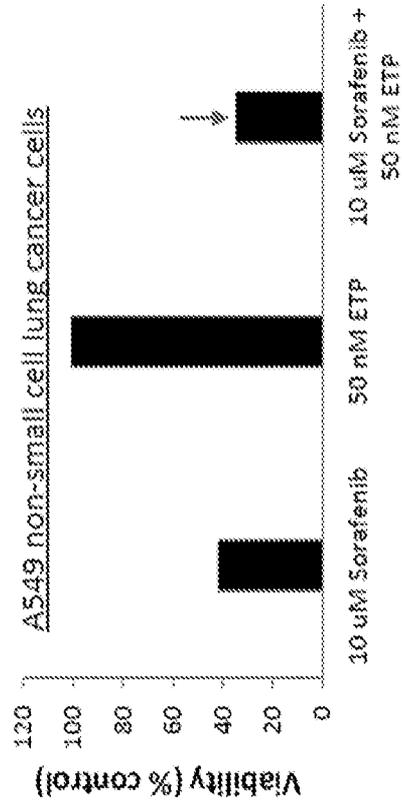
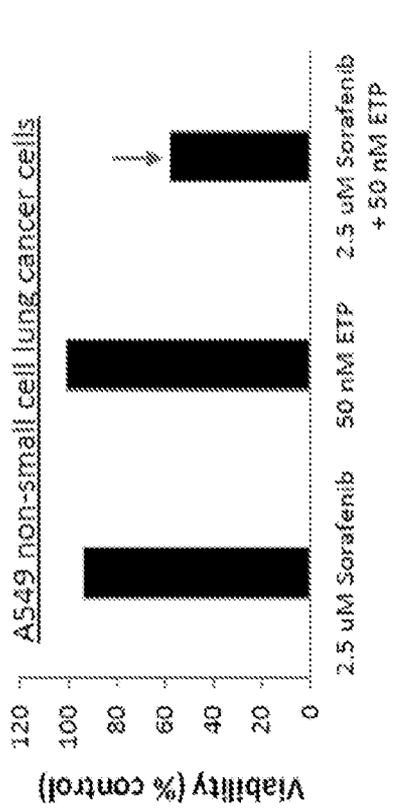
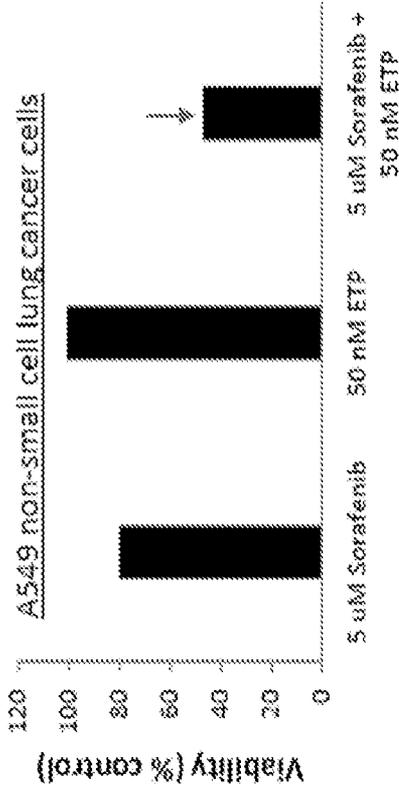


Figure 15

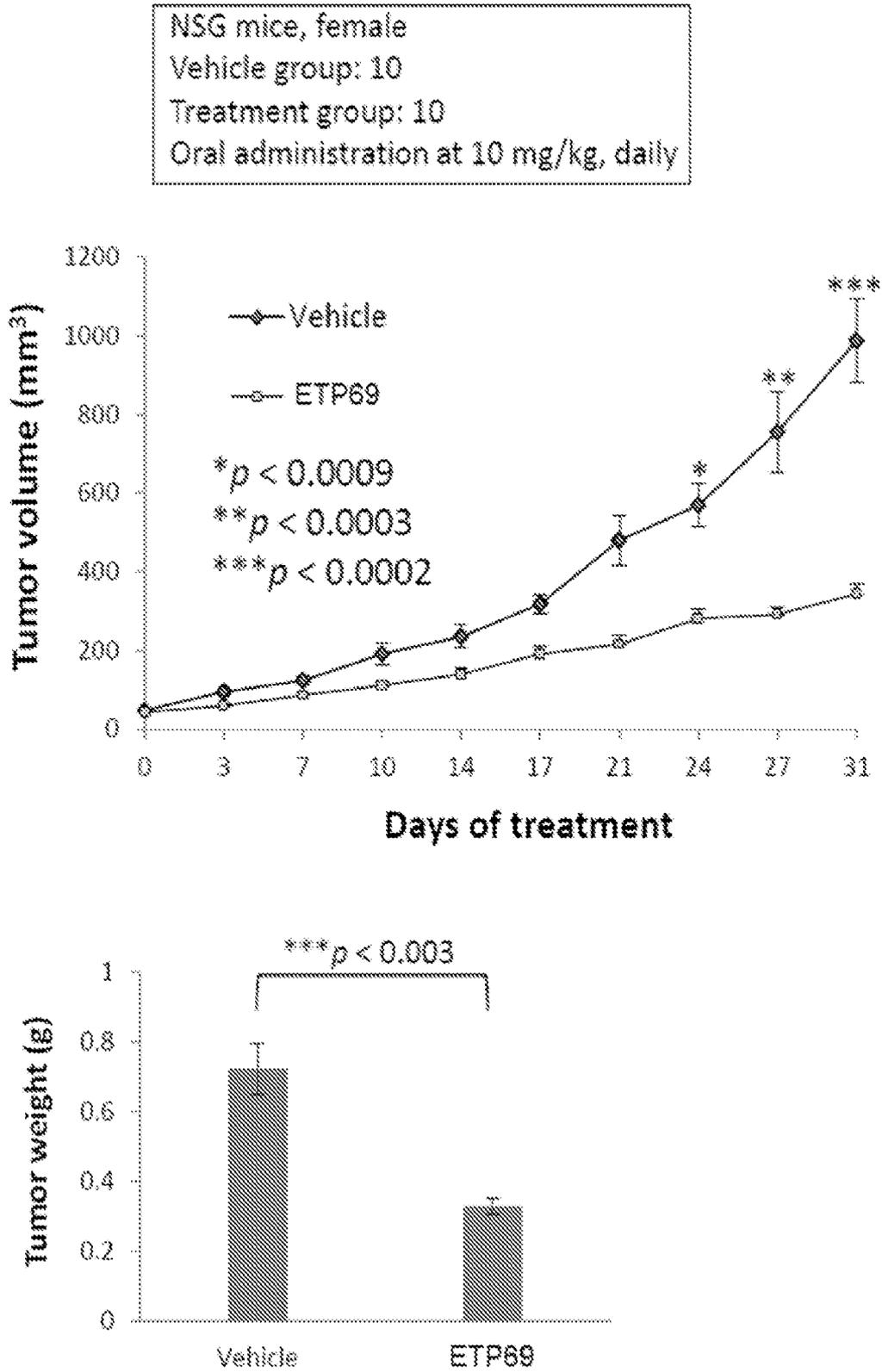


Figure 16

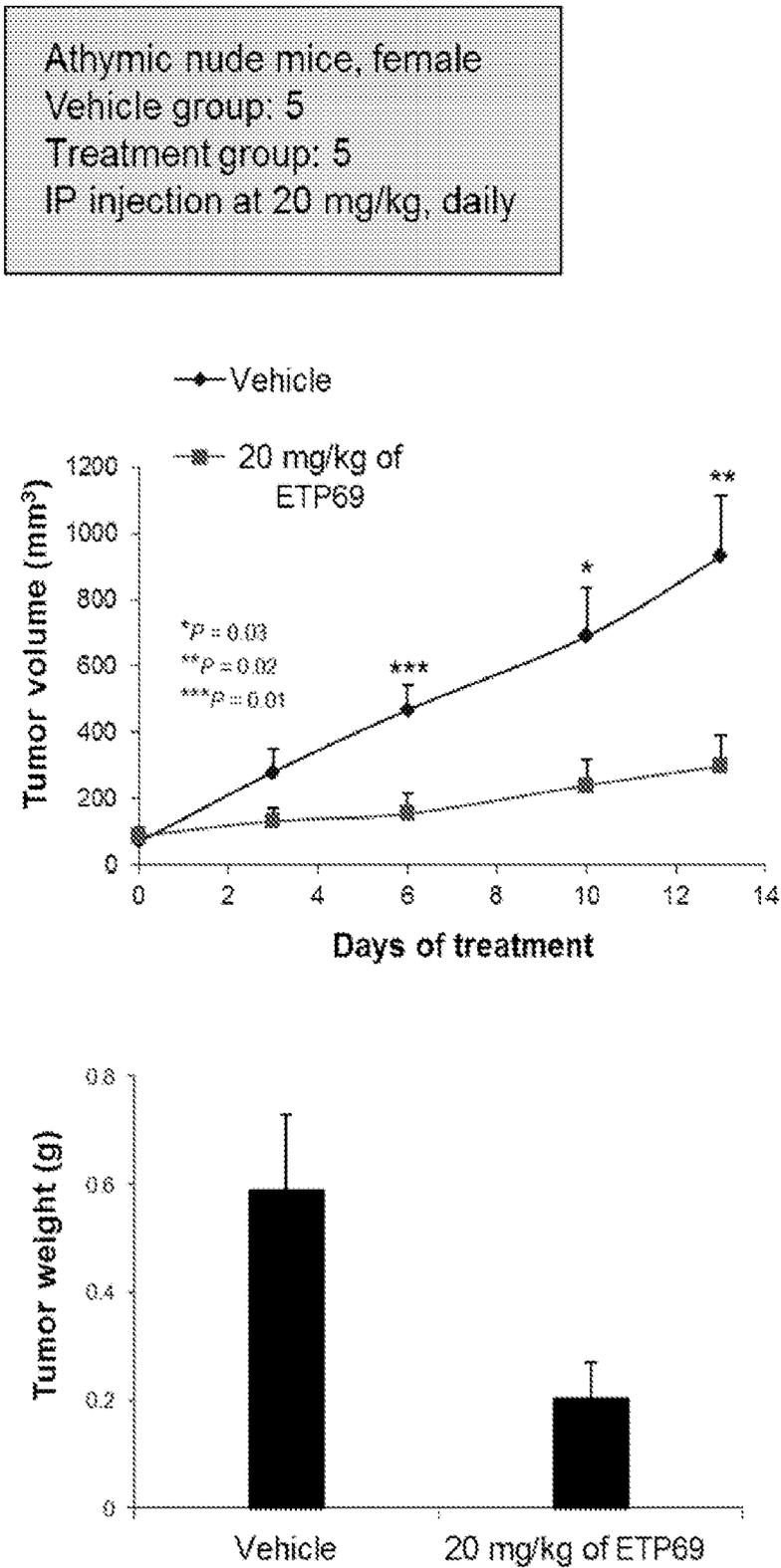


Figure 17

NSG mice, female
Vehicle group: 9
Treatment group: 9
IP injection at 2.5 mg/kg, daily
Vehicle: 5% DMSO + 15% Solutol + 80% water
Significant efficacy, $p < 0.05$

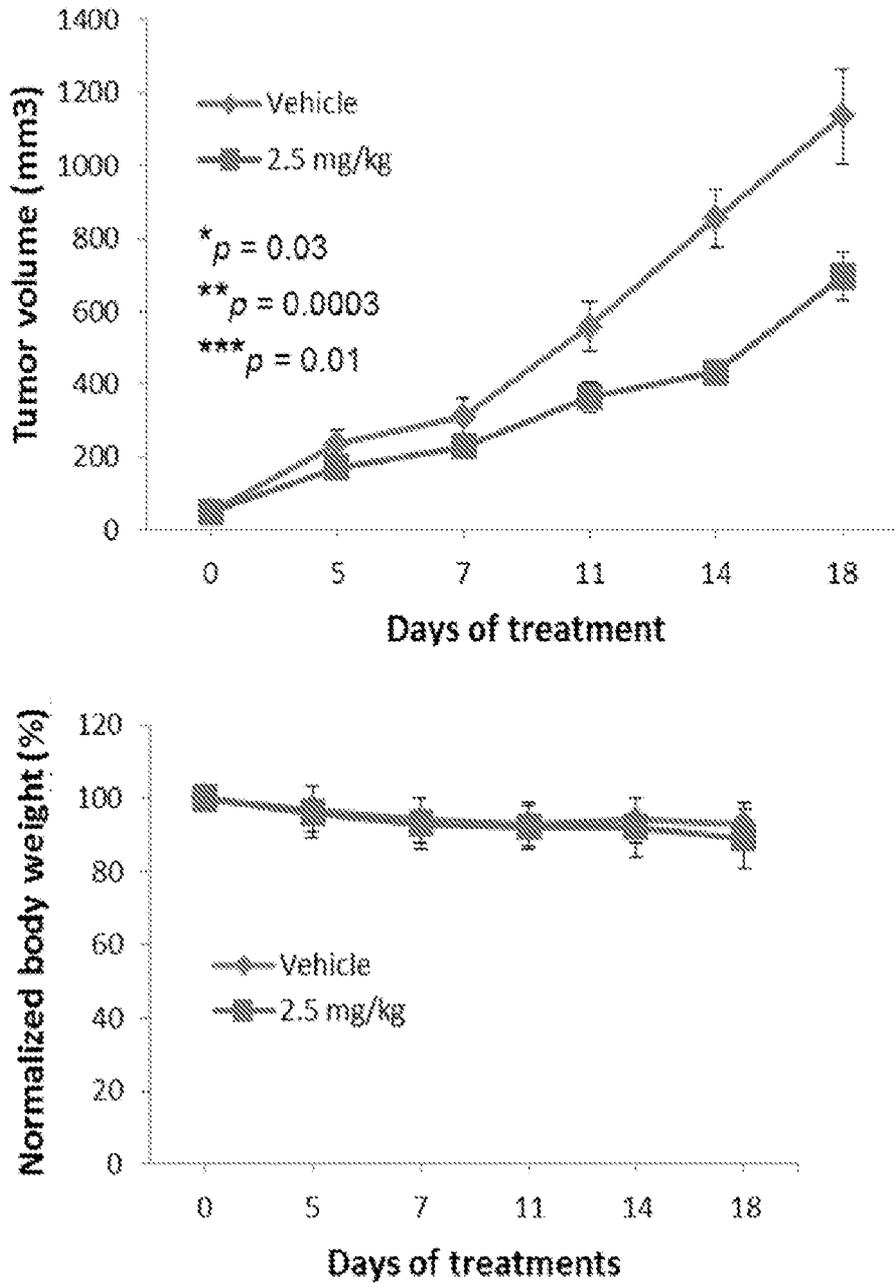


Figure 18

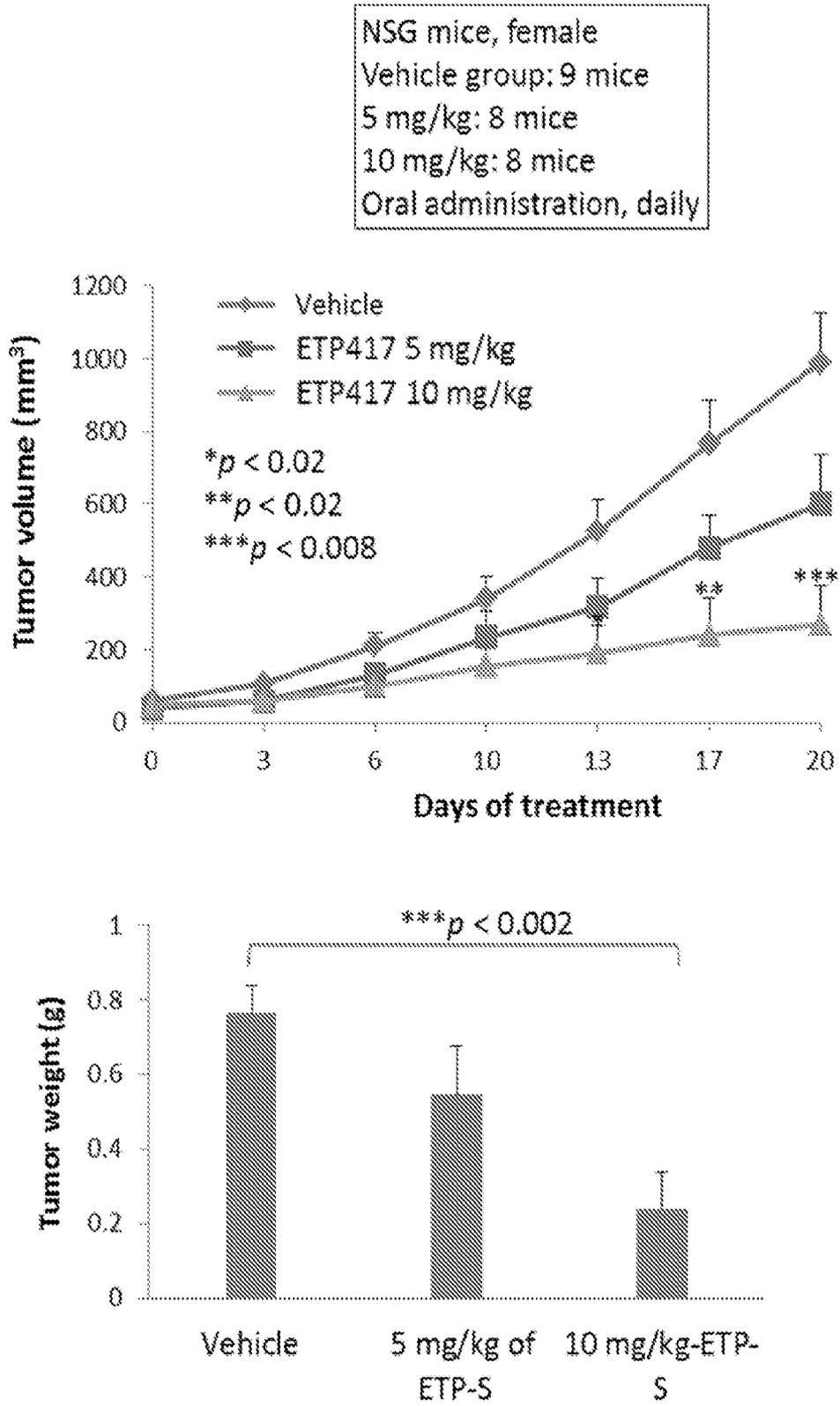


Figure 19

Intraperitoneal (20 mg/kg)				
Time point (hr)	Mouse #	Conc. (ng/mL)	Average (ng/mL)	SD
0 (predose)	141	BLOQ	ND	ND
	142	BLOQ		
	143	BLOQ		
0.25	105	13700	9053	4025
	106	6630		
	107	6830		
0.50	108	4200	4740	480
	109	5120		
	110	4900		
1.0	111	17200	8057	7919
	112	3550		
	113	3420		
2.0	114	3500	2870	764
	115	2020		
	116	3090		
4.0	117	2120	4000	3256
	118	2120		
	119	7760		
8.0	120	824	696	193
	121	791		
	122	474		
Pharmacokinetic Parameters				
$C_{max}(\pm SE, \text{ng/mL})$			9053 \pm 2324	
t_{max} (hr)			0.25	
$t_{1/2}$ (hr)			2.41	
$AUC_{last} (\pm SE, \text{hr}\cdot\text{ng/mL})$			27781 \pm 6664	
AUC_{∞} (hr·ng/mL)			30206	

Figure 20

Oral (20 mg/kg)				
Time point (hr)	Mouse #	Conc. (ng/mL)	Average (ng/mL)	SD
0 (predose)	141	BLOQ	ND	ND
	142	BLOQ		
	143	BLOQ		
0.25	123	5000	4677	293
	124	4430		
	125	4600		
0.50	126	4970	4820	167
	127	4640		
	128	4850		
1.0	129	3780	3327	605
	130	3560		
	131	2640		
2.0	132	5010	3440	1356
	133	2790		
	134	2520		
4.0	135	1410	1820	376
	136	1900		
	137	2150		
8.0	138	645	612	322
	139	275		
	140	917		
Pharmacokinetic Parameters				
C _{max} (±SE, ng/mL)			4820 ± 96.4	
t _{max} (hr)			0.50	
t _{1/2} (hr)			2.43	
AUC _{last} (±SE, hr·ng/mL)			17316 ± 1427	
AUC _∞ (hr·ng/mL)			19461	

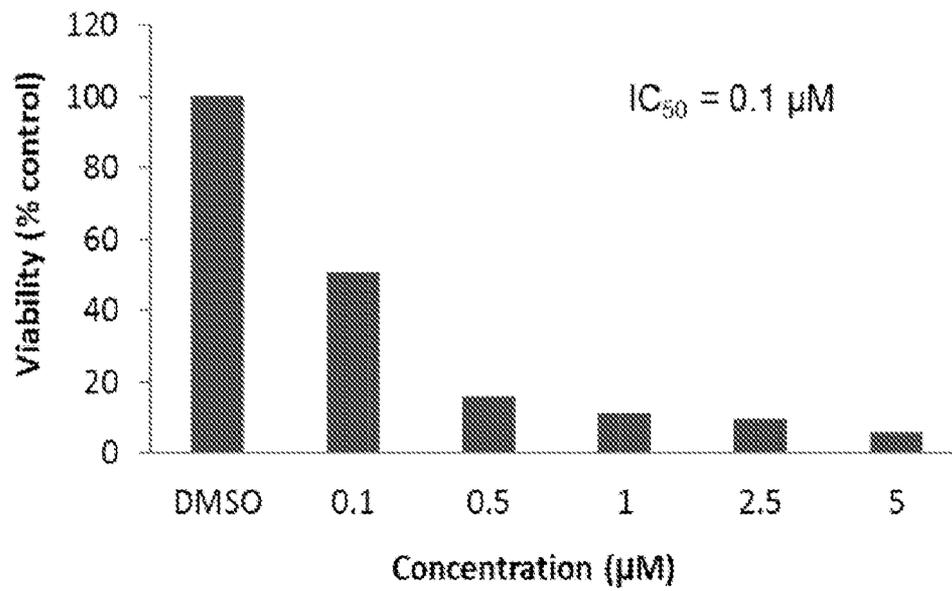
Figure 21

Figure 22

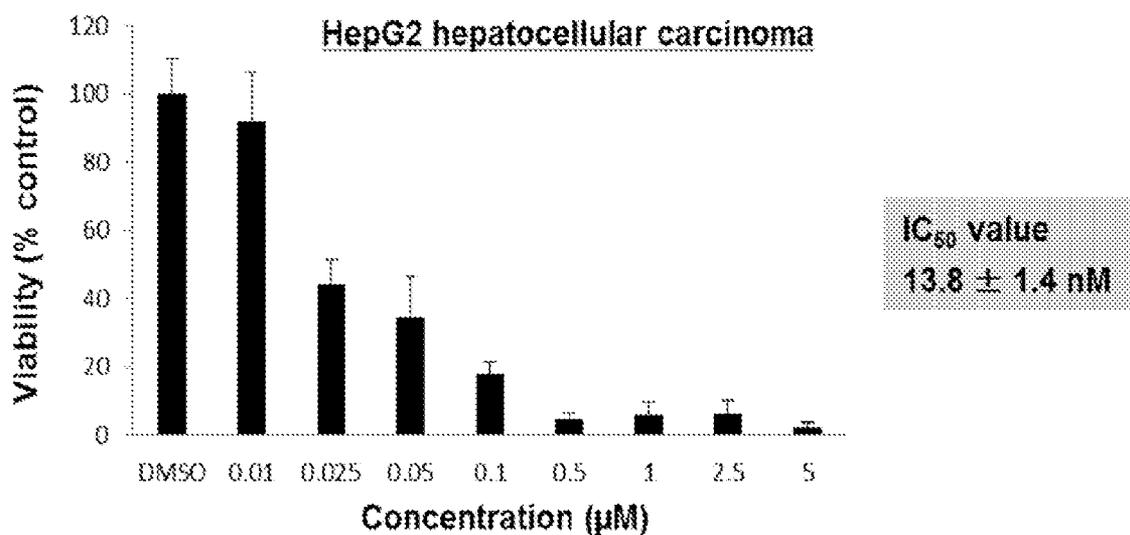
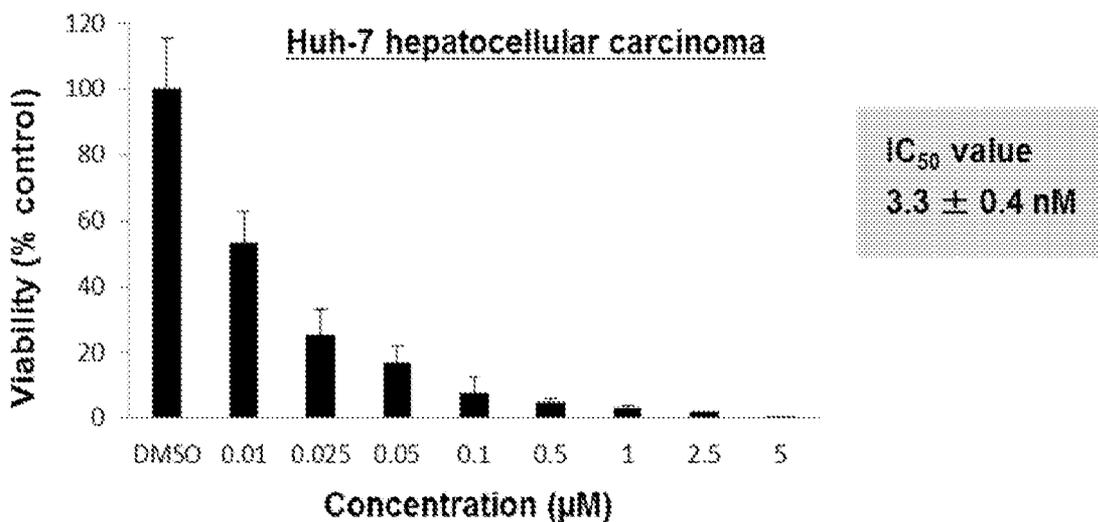


Figure 23

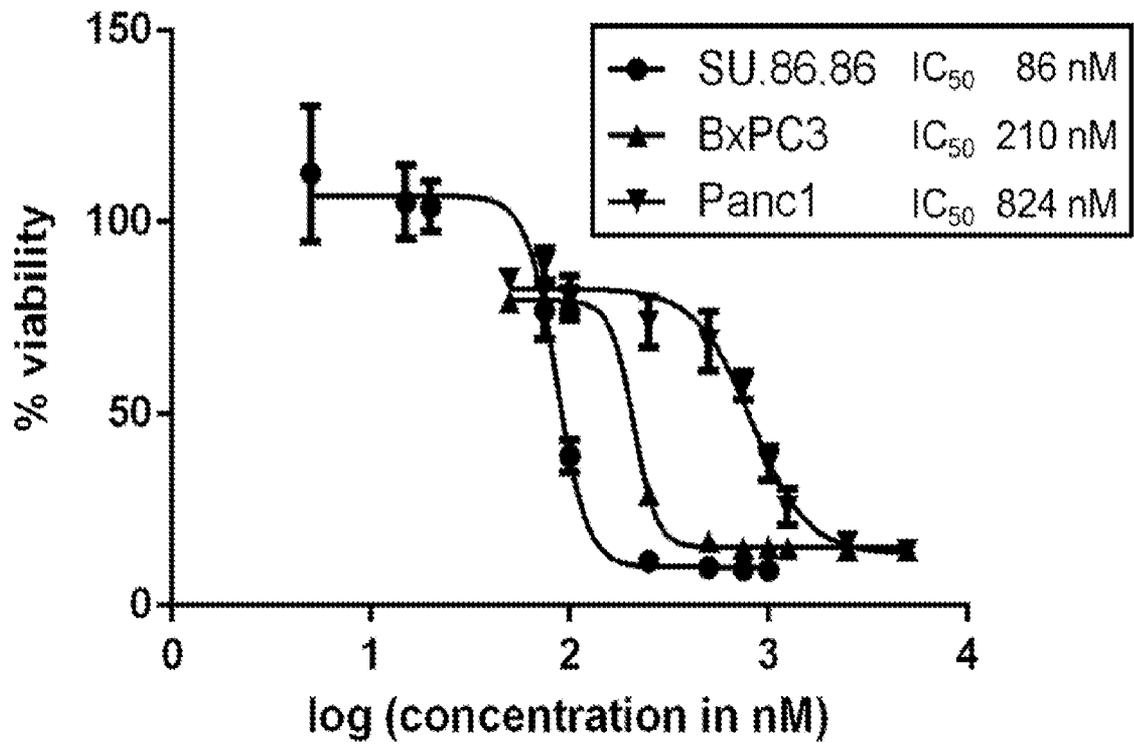


Figure 24

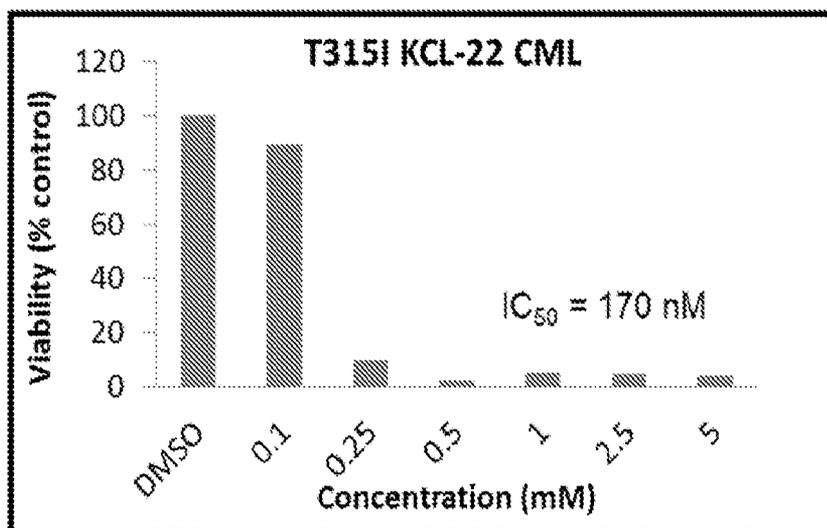
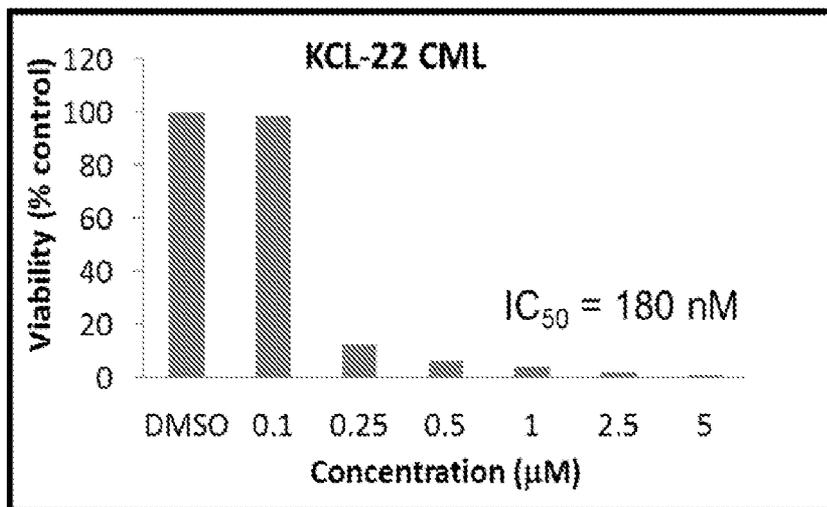
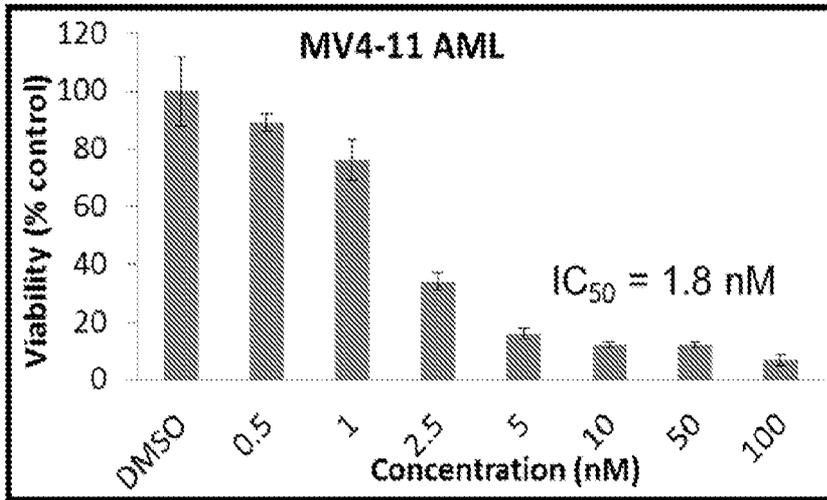
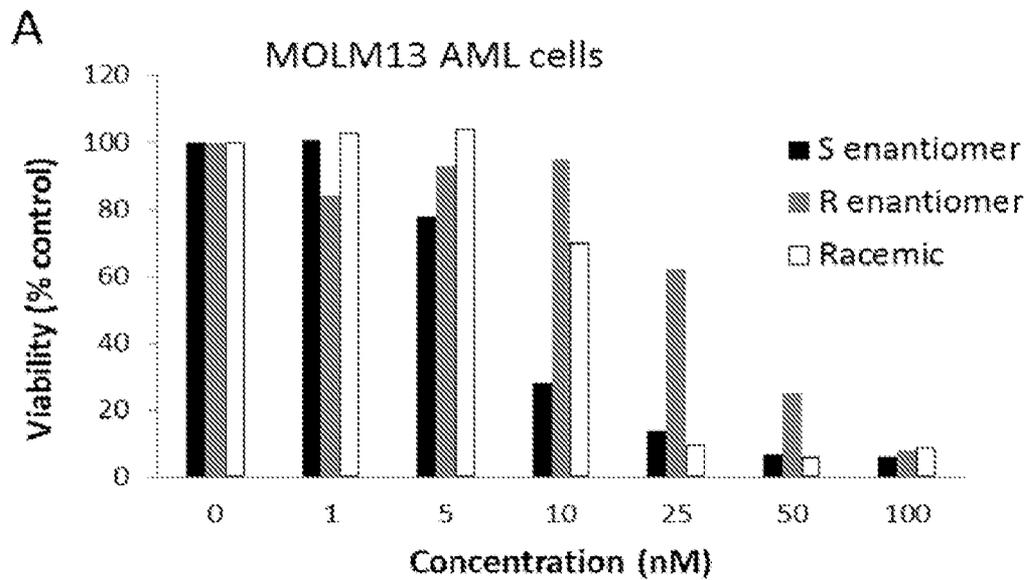
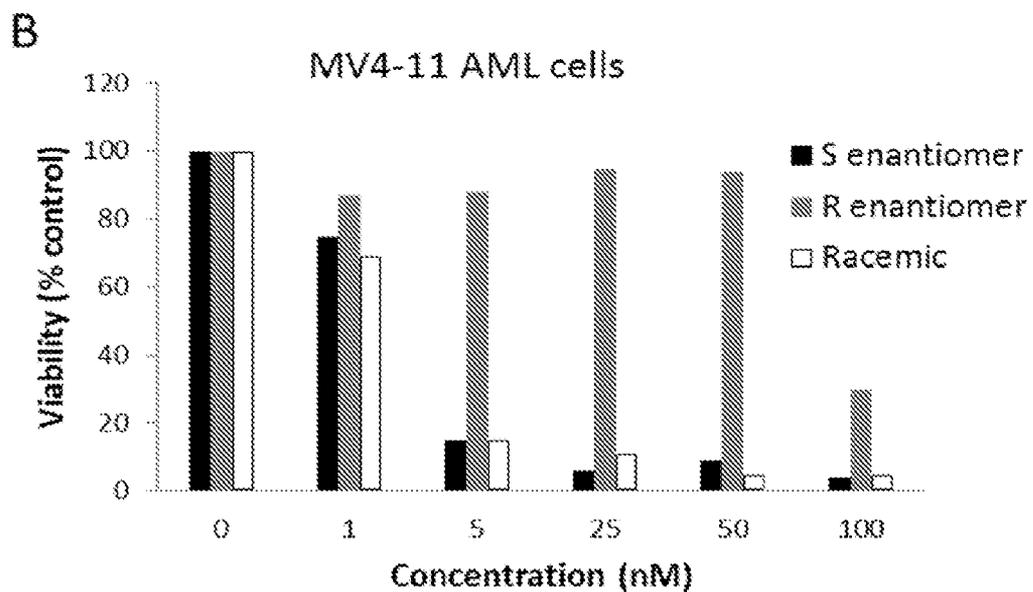


Figure 25



IC₅₀ value (nM)
 S enantiomer: 7.8
 R enantiomer: 33.1
 Racemic: 15.0



IC₅₀ value (nM)
 S enantiomer: 2.7
 R enantiomer: 85.5
 Racemic: 2.4

Figure 26

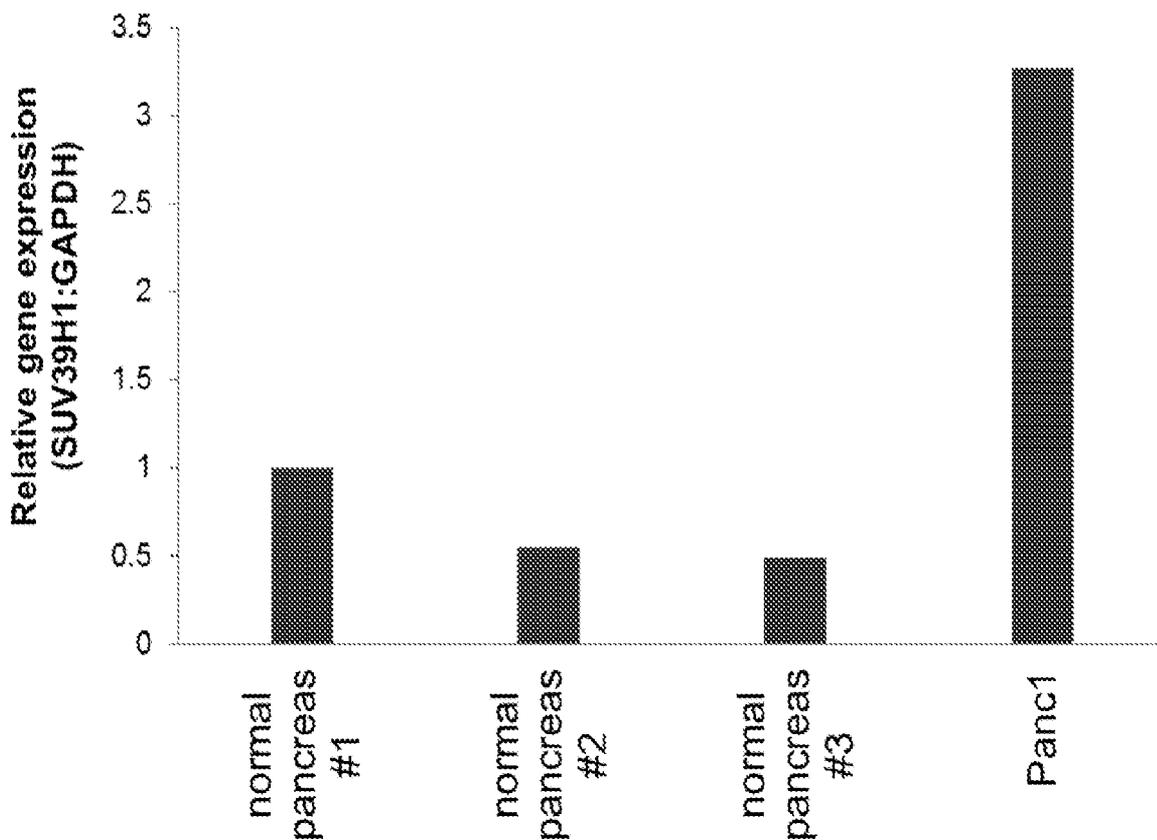


Figure 27

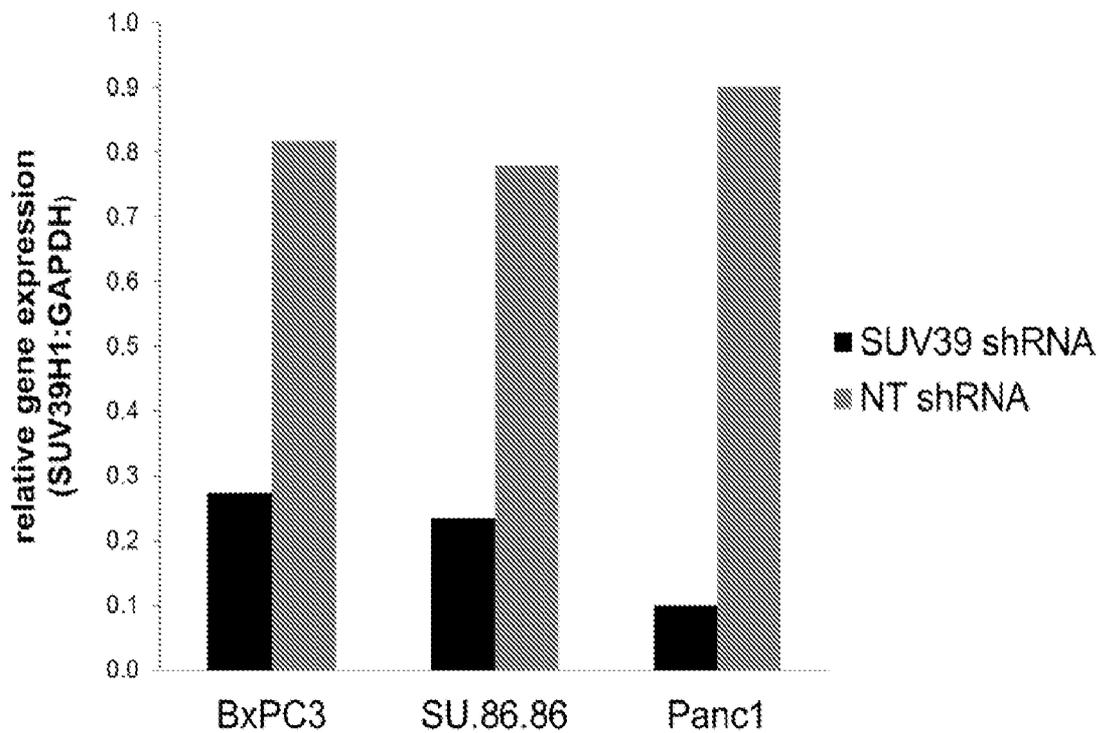


Figure 28

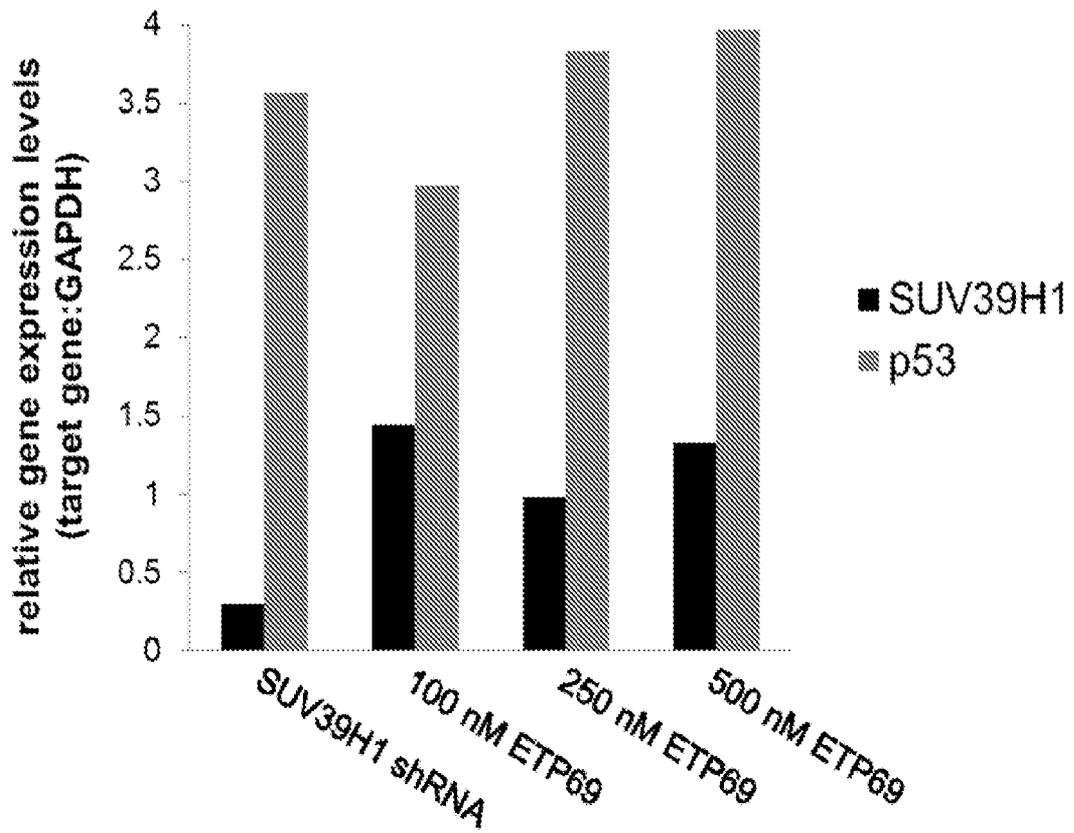


Figure 29

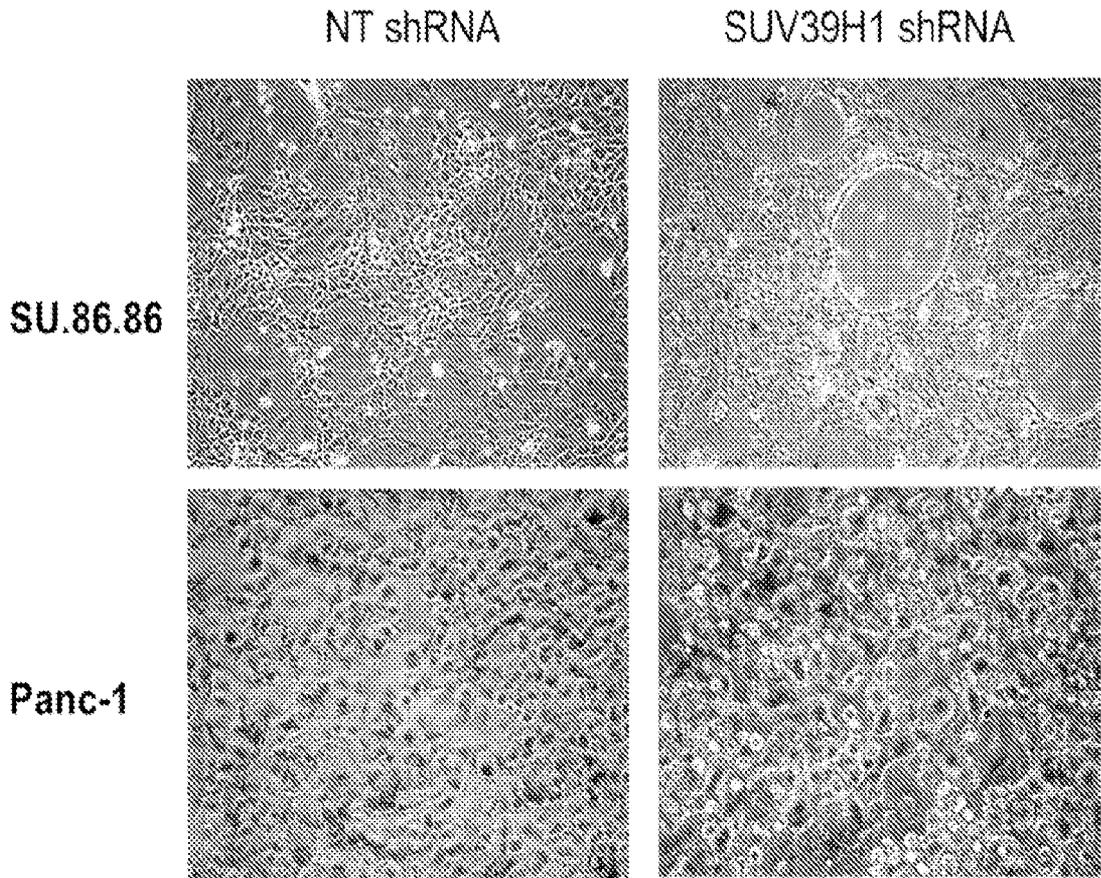


Figure 30

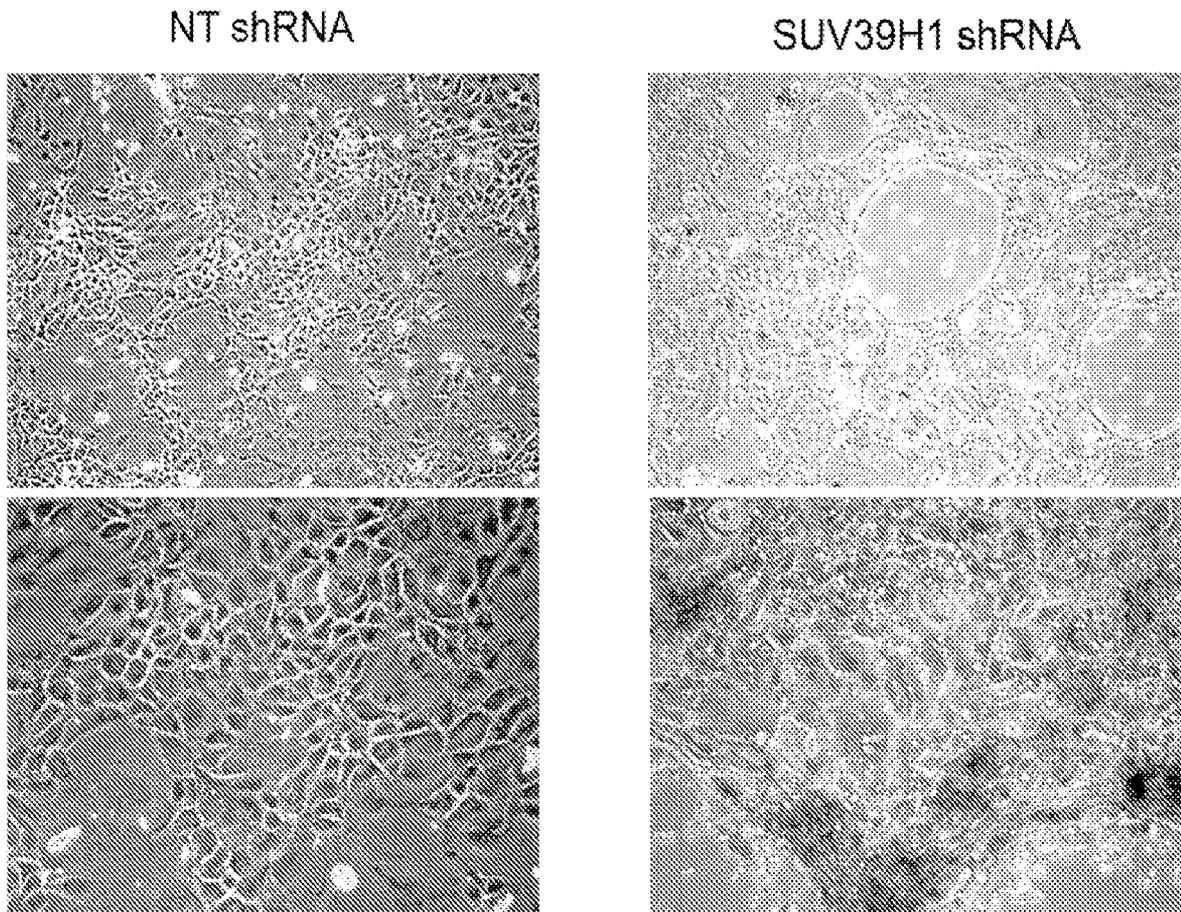
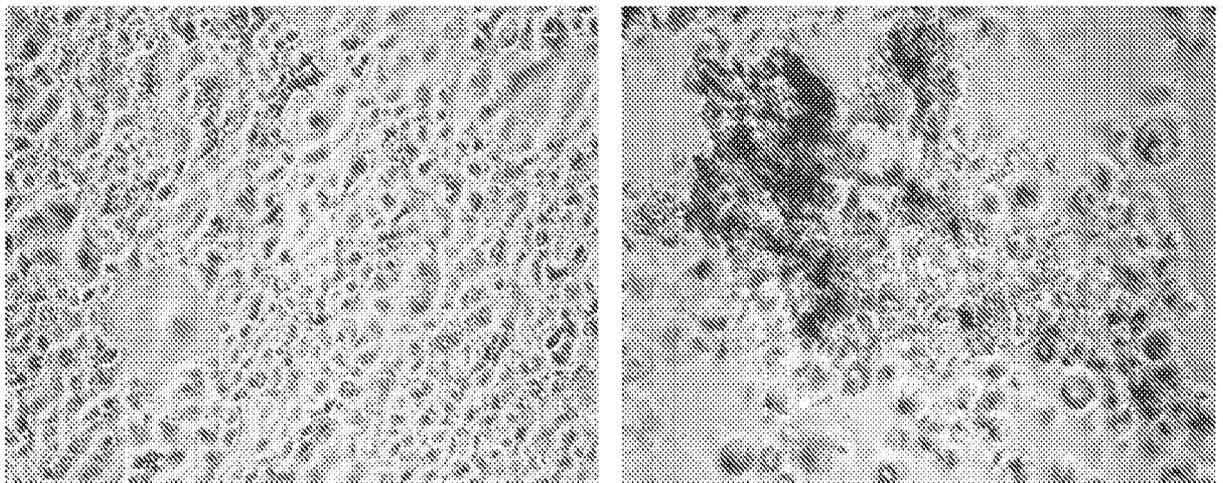


Figure 31

Senescence-associated β -galactosidase activity



DMSO

100 nM ETP69

Figure 32

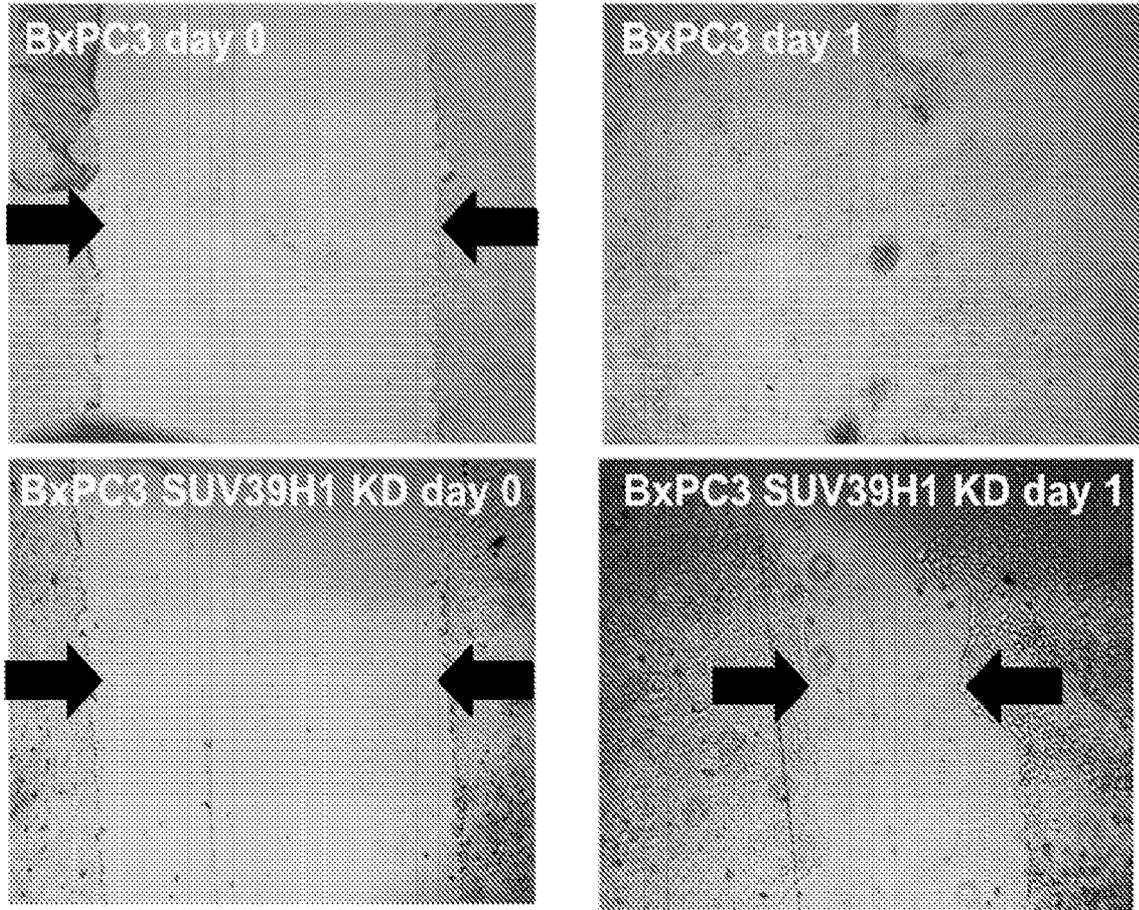


Figure 33

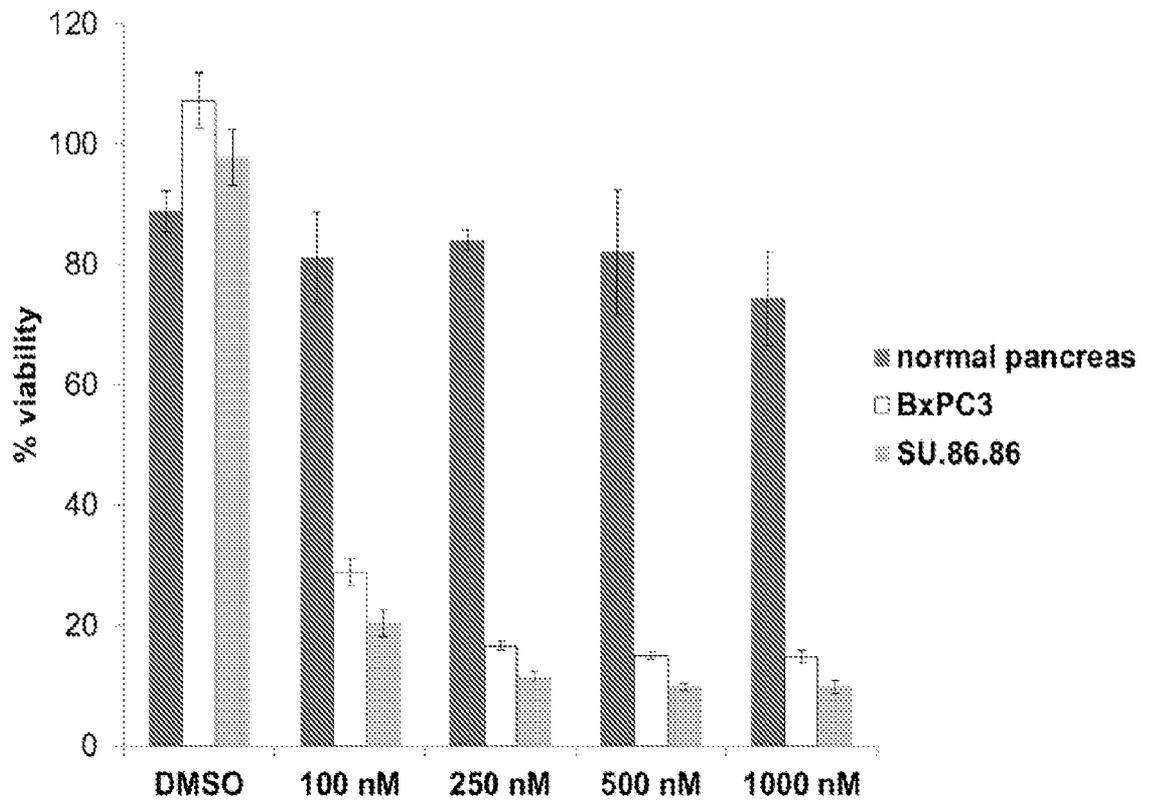
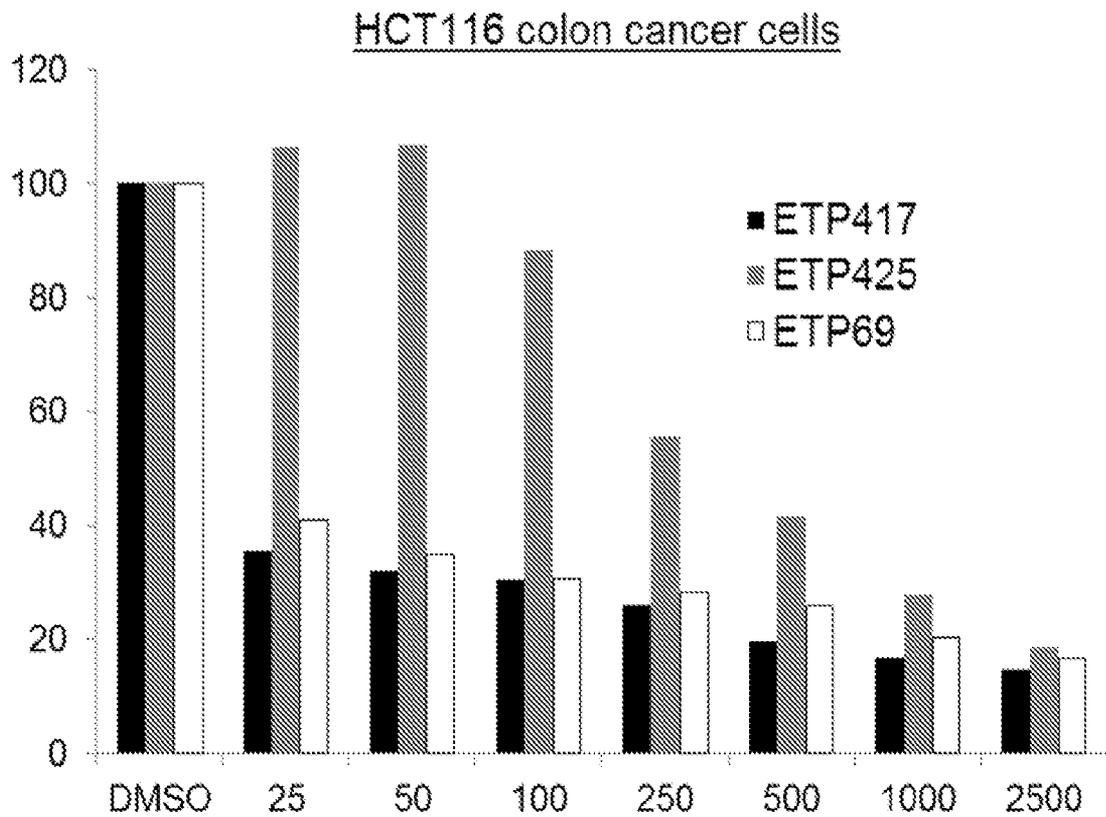
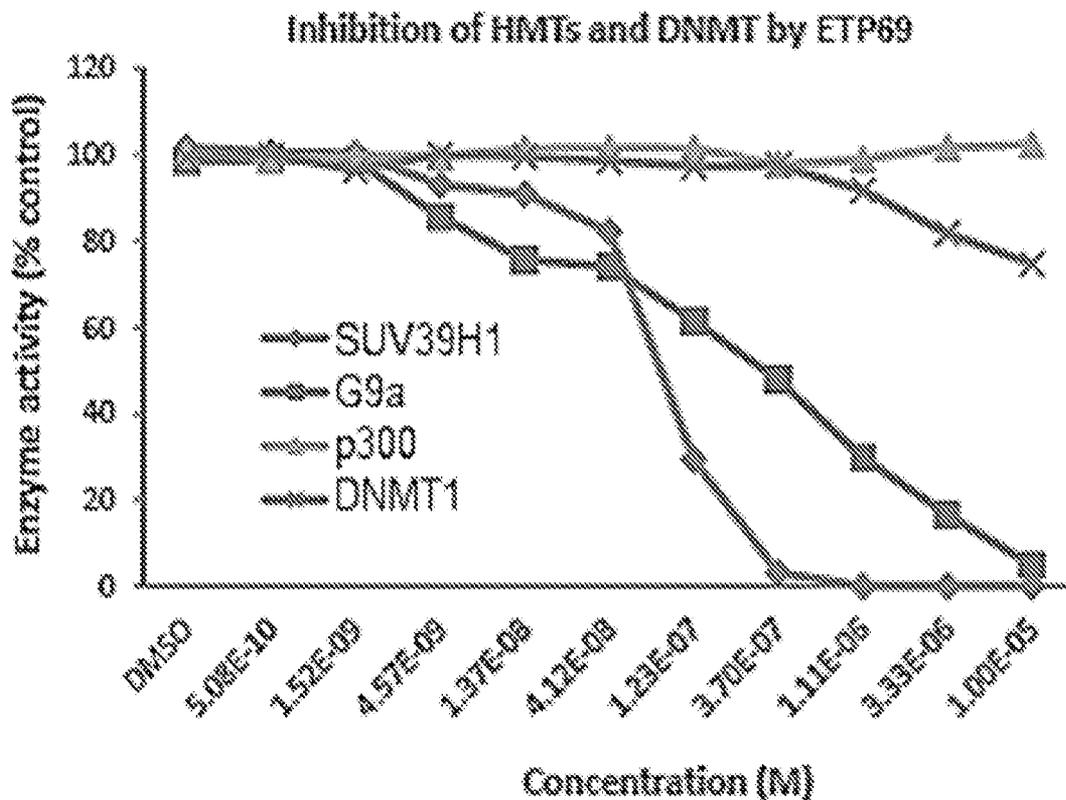


Figure 34



Compound	IC ₅₀ value (nM)
ETP417	19
ETP422	339
ETP69	21

Figure 35



IC₅₀ value (uM)

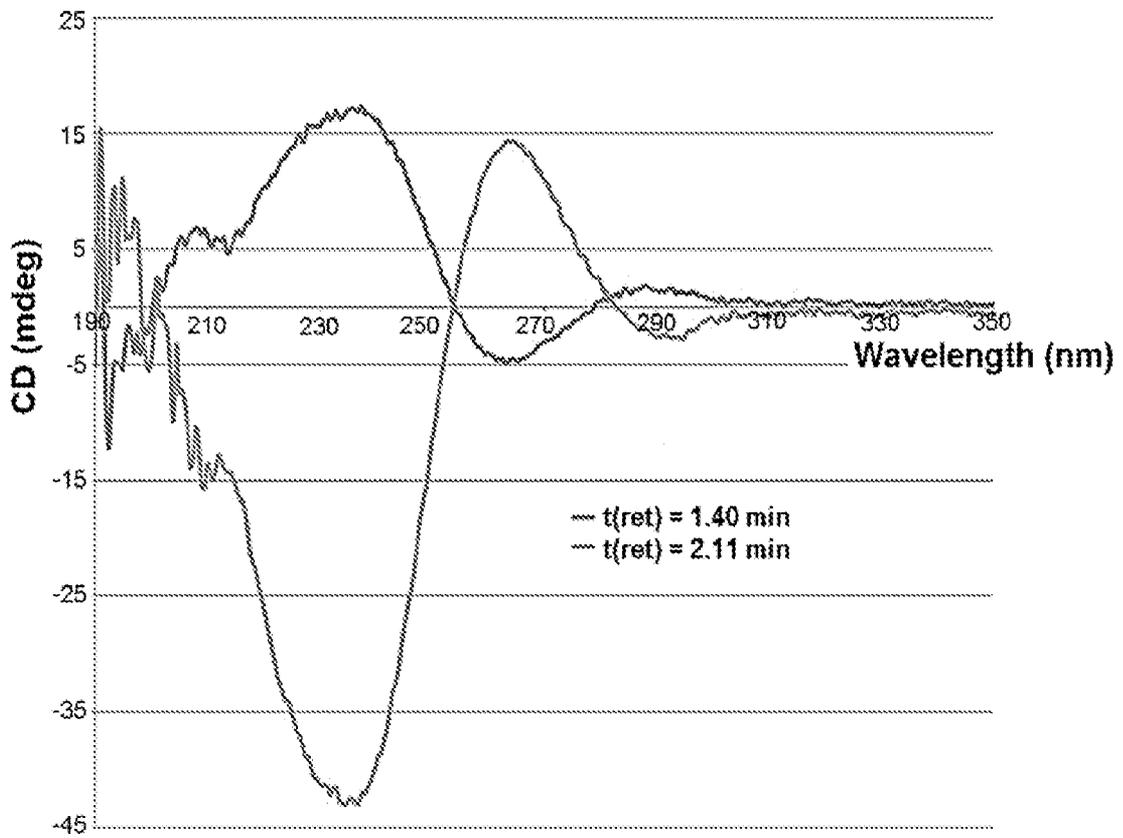
SUV39H1: 0.084

G9a: 0.25

p300: > 10

DNMT1: > 10

Figure 36



A. CLASSIFICATION OF SUBJECT MATTER**C07D 513/08(2006.01)i, C07D 513/18(2006.01)i, A61K 31/547(2006.01)i, A61P 35/00(2006.01)i**

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)

C07D 513/08; A61K 31/404; C07D 307/22; A01N 43/60; A61K 31/12; A01N 43/58; C07D 513/18; A61K 31/547; A61P 35/00

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal), NCBI (Pubchem Compound Database), Google & Keywords:epidithiopyrrolo[1,2-a]pyrazine, dioxooctahydropyrrolo[1,2'a]pyrazine, cancer.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LARRY E. OVERMAN et al., `Construction of Epidithiodioxopiperazines by Directed Oxidation of Hydroxyproline-Derived Dioxopiperazines`, Organic Letters, 2007, Vol. 9, No. 25, pp. 5267-5270	1,7,18-21,66,88-92,95
A	See compound 23.	2-6,8-17,22-37,40-49,51-57,67-87,109-112
X	ELISABETH OEHLER et al., `Ueber Amino saeuren und Peptide, XV. Hydroxyl-substituierte Cyclodipeptide durch Ringschluss von Pyruvoylamino-saeureamiden, II. Zweifacher Ringschluss`, Chemische Berichte, 1975, Vol. 108, No. 9, pp. 2907-2916 See compounds 17 and 20.	1,7-8,18-21,88-92,95
X	HANS POISEL et al., Ueber Aminosaeuren und Peptide, XVI. Ueber Dehydro-aminosaeuren, III. Additionen an alpha-iminocarbonsaeuren`, Chemische Berichte, 1975, Vol. 108, No. 9, pp. 2917-2922 See compound 19.	1,7-8,18-21,88-92,95

 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

10 February 2014 (10.02.2014)

Date of mailing of the international search report

11 February 2014 (11.02.2014)

Name and mailing address of the ISA/KR


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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/066252

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PubChemCompound, datasheet [online compound summary] Retrieved from the Internet: <URL: http://pubchem.ncbi.nlm.nih.gov/search/search.cgi > See CID 98951 (2005.03.26), CID 99895 (create date: 2005-03-26), CID 194922 (create date: 2005-08-09), CID 23747861 (create date: 2008-02-20), CID 23747863 (create date: 2008-02-20) etc.	77-79
X	US 8044103 B2 (ALAN P. KOZIKOWSKI et al.) 25 October 2011 See compounds (3a)-(16a); claim 5.	77
X	US 2010-0305182 A1 (HELEN E. BLACKWELL et al.) 02 December 2010 See compounds 41-43; claim 25.	77
X	US 7186721 B2 (BERND PESCHKE et al.) 06 March 2007 See formula V; compound of step C in example 1.	77

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

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

1. Claims Nos.: 96-108
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 96-108 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. Claims Nos.: 107
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 107 is unsearchable because it is worded in reference to multiple dependent claims.
3. Claims Nos.: 38-39, 50, 58-65, 93-94, 99-106, 108, 113-119
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2013/066252

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