



(51) International Patent Classification:

A61K 31/44 (2006.01) A61K 31/451 (2006.01)
A61K 31/445 (2006.01) A61K 31/4462 (2006.01)

(21) International Application Number:

PCT/US2016/031344

(22) International Filing Date:

6 May 2016 (06.05.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/157,915 6 May 2015 (06.05.2015) US
62/158,356 7 May 2015 (07.05.2015) US

(71) Applicants: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, Twelfth Floor, Oakland, CA 94607 (US). **LEIDOS BIOMEDICAL RESEARCH, INC.** [US/US]; P.O. Box B, 1050 Boyles Street, Frederick, Maryland 21702 (US).

(72) Inventors: **MCCORMICK, Frank**; 5 Bernice St, San Francisco, CA 94103 (US). **RENSLO, Adam, R.**; 5359 Shafter Ave., Oakland, CA 94618 (US). **TURNER, David**; 1560 3rd St, Apt. 406A, San Francisco, CA 94158 (US). **GYSIN, Stephan**; Reiterstrasse 55, 4054 Basel (CH). **MACIAG, Anna, E.**; 9214 Charterhouse Rd., Frederick, MD 21704 (US). **CHERTOV, Oleg**; 9005 Mountainberry Court, Frederick, MD 21702 (US).

(74) Agents: **NOMURA, Anson, M.** et al.; Mintz Levin Cohn Ferris Glovsky and Popeo, P.C., 3580 Carmel Mountain Road, Suite 300, San Diego, CA 92130-6768 (US).

(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, 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.

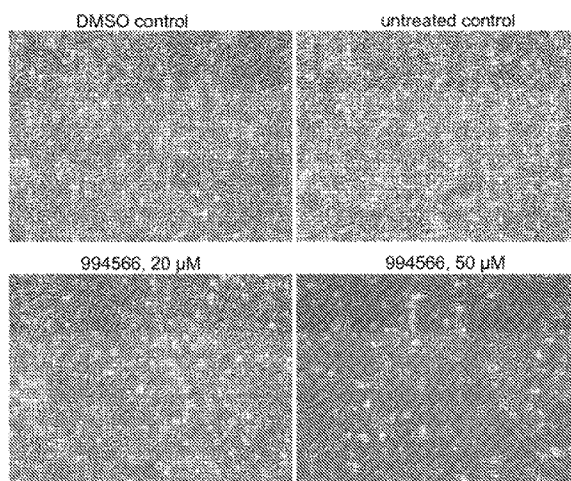
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: K-RAS MODULATORS

FIG. 37



(57) Abstract: Provided herein, *inter alia*, are methods and compounds for inhibiting K-Ras and for treating cancer.

K-Ras Modulators

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/157,915, filed May 6, 2015, and U.S. Provisional Application No. 62/158,356, filed May 7, 2015 which are incorporated herein by reference in their entirety and for all purposes.

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

[0002] The Sequence Listing written in file 48536-569001WO_ST25.txt, created May 3, 2016, 10,641 bytes, machine format IBM-PC, MS Windows operating system, is hereby incorporated by reference.

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

[0003] This invention was made with government support under Contract No. HHSN261200800001E awarded by the National Cancer Institute. The government has certain rights in the invention.

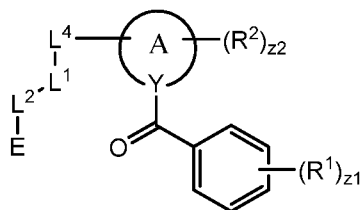
BACKGROUND OF THE INVENTION

[0004] K-Ras is the most frequently mutated oncogene in human cancer. Past attempts to directly modulate the activity of this enzyme have been unsuccessful. Ras proteins are small guanine nucleotide-binding proteins that act as molecular switches by cycling between active GTP-bound and inactive GDP-bound conformations. The Ras proteins play a critical role in the regulation of cell proliferation, differentiation, and survival. Dysregulation of the Ras signaling pathway is almost invariably associated with disease. Hyper-activating somatic mutations in Ras are among the most common lesions found in human cancer. Although mutation of any one of the three Ras isoforms (K-Ras, N-Ras, or H-Ras) has been shown to lead to oncogenic transformation, K-Ras mutations are by far the most common in human cancer. For example, K-Ras mutations are known to be often associated with pancreatic, colorectal and non-small-cell lung carcinomas. Similarly, H-Ras mutations are common in cancers such as papillary thyroid cancer, lung cancers and skin cancers. Finally, N-Ras mutations occur frequently in hepatocellular carcinoma. There is a need in the art for effective Ras inhibitors and anticancer compounds. Disclosed herein are solutions to these and other problems in the art.

BRIEF SUMMARY OF THE INVENTION

[0005] Described herein, inter alia, is the use of covalent (e.g. reversible or irreversible) modulators to target a Ras (e.g., K-Ras) protein, including but not limited to oncogenic mutants.

[0006] In an aspect is provided a compound having the formula:



(I) wherein, Y is N or CH; Ring A is a C₃-C₇ cycloalkyl or 3 to 7

membered heterocycloalkyl; R¹ is independently halogen, CX¹₃, -CHX¹₂, -

CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHN⁷R⁸, -ONR⁷R⁸, -NHC(=O)NHN⁷R⁸,
-NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -

NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl,

substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or substituted or unsubstituted heteroaryl; L¹ is a bond, substituted or

unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
arylene, substituted or unsubstituted heteroarylene; L² is a

bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -

NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-,

-NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-,

substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or

unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
unsubstituted arylene, substituted or unsubstituted heteroarylene; L⁴ is a
bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -

NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-, substituted or unsubstituted C₁-C₃ alkylene, substituted or

unsubstituted 2 to 3 membered heteroalkylene; E is an electrophilic moiety; R² is independently

oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHN¹¹R¹²,
-ONR¹¹R¹², -NHC(=O)NHN¹¹R¹²,
-NHC(O)NR¹¹R¹², -N(O)_{m2}, -NR¹¹R¹², -C(O)R¹⁴, -C(O)-OR¹⁴, -C(O)NR¹¹R¹², -OR¹⁵, -

$\text{NR}^{11}\text{SO}_2\text{R}^{15}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{OR}^{14}$, $-\text{OCX}_3^2$, $-\text{OCHX}_2^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents
 5 bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl; R^4 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^7 , R^8 , R^9 , R^{10} , $\text{R}^{7\text{B}}$, $\text{R}^{8\text{B}}$, $\text{R}^{9\text{B}}$, $\text{R}^{10\text{B}}$,
 10 R^{11} , R^{12} , R^{14} , and R^{15} are independently hydrogen, halogen, $-\text{CX}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}(\text{O})\text{NHNH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 15 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 and R^8 substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X,
 20 X^1 , and X^2 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$; n_1 , n_2 , v_1 , and v_2 are independently an integer from 0 to 4; m_1 and m_2 are independently an integer from 1 to 2; z_1 is independently an integer from 0 to 5; and z_2 is independently an integer from 0 to 10.

[0007] In another aspect is provided a pharmaceutical composition including a compound described herein and a pharmaceutically acceptable excipient.

25 **[0008]** In another aspect, a method of treating a disease in a patient in need of such treatment is provided. In embodiments, the disease is cancer.

[0009] In another aspect is provided a method of reducing the level of activity of a K-Ras protein (e.g., human K-Ras 4B), the method including contacting the K-Ras protein with a compound described herein (including in embodiments, examples, figures, and tables).

30 **[0010]** In another aspect, a method of modulating a K-Ras protein is provided. The method including contacting the K-Ras protein with an effective amount of a compound described herein (including in embodiments, examples, figures, and tables).

[0011] In another aspect is provided, a K-Ras protein covalently (e.g., reversibly or irreversibly) bonded to a compound, for example a compound as described herein (including modulators, inhibitors, or in embodiments, examples, and tables).

BRIEF DESCRIPTION OF THE DRAWINGS

- 5 [0012] FIGS. 1A-1C. LC-MS data from screen with His-K-Ras 4B (G12V) and (G12V/C185S). K refers to His-K-Ras 4B (G12V) (24823 Da) not bound to compound. B refers to His-K-Ras 4B (G12V) (24899 Da) bound to β Me. C: His-K-Ras 4B (G12V) (25114.5 Da for 3G4 vs. 25178Da for 6B9) bound to tethering compound. Kmut refers to His-K-Ras 4B (G12V/C185S) (24808 Da) not bound to compound.
- 10 [0013] FIGS. 2A-2D. Exemplary compounds from screen and derivatives thereof, 3G4 (phenyl thiazole containing compound) and derivatives wherein disulfide of 3G4 replaced with alternative electrophilic moieties. FIG. 2A depicts the structure of SMDC 917069, also referred to herein as 3G4. FIG. 2B depicts the structure of SMDC 963109. FIG. 2C depicts the structure of SMDC 963108. FIG. 2D depicts the structure of SMDC 963107.
- 15 [0014] FIGS. 3A-3C. Exemplary compounds from screen and derivatives thereof, including 6B9 (nipecotic acid derivative), 3G4 (phenyl thiazole containing compound); disulfide moiety of 6B9 was replaced with other electrophilic moieties, including tetrafluoro-phenoxy (FB9, also referred to herein as SMDC 959899) or difluoro-phenoxy (53, also referred to herein as SMDC 963153); disulfide of 3G4 replaced with alternative electrophilic moieties.
- 20 [0015] FIGS. 4A-4D Exemplary compounds from screen and derivatives thereof, including 6B9 (nipecotic acid derivative and derivatives wherein the disulfide moiety of 6B9 was replaced with other electrophilic moieties, including tetrafluoro-phenoxy (FB9) or difluoro-phenoxy (53). Derivatives of 6B9 with other electrophilic moieties.
- [0016] FIGS. 5A-5B. Exemplary compounds capable of binding to K-Ras.
- 25 [0017] FIGS. 6A-6B. Compound FB9; electrophile is the tetra fluorophenoxy-group which is also the leaving group after the thioether linkage between the cysteine thiol and the rest of FB9, depicted in FIG. 6B.
- [0018] FIG. 7A-7B. In Vitro Prenylation Assays with Purified K-Ras and FTase or GGTase. A fluorescent substrate for farnesyl transferase, 3,7-dimethyl-8-(7-nitro-benzo[1,2,5]oxadiazol-4-
- 30 ylamino) -octa-2,6-diene-1- pyrophosphate (NBD-GPP), has similar kinetics as the natural

substrate for farnesyl pyrophosphate. FIG. 7A is with concentrations of 3G4. FIG. 7B is with concentrations of 6B9.

[0019] FIGS. 8A-8B. In vitro prenylation with 6B9 tethering compound.

[0020] FIG. 9. In vitro prenylation comparing N-Ras with different compounds; 1. KRAS4B wt CT; 2. KRAS4B mut CT; 3. 50 μ M 6B9; 4. 20 μ M 6B9; 5. 8 μ M 6B9; 6. 3.2 μ M 6B9; 7. 1.3 μ M 6B9; and 8. 0.5 μ M 6B9. A fluorescent substrate for farnesyl transferase, 3,7-dimethyl-8-(7-nitro-benzo[1,2,5]oxadiazol-4-ylamino) -octa-2,6-diene-1- pyrophosphate (NBD-GPP), has similar kinetics as the natural substrate for farnesyl pyrophosphate.

[0021] FIG. 10. BIAcore Experiment with 3G4 on K-Ras 4B; Surface Plasmon Resonance (SPR) and ForteBio/Octet Experiment showing whether 3G4 and 6B9 Fragment (LB9) had a secondary non-covalent interaction site in K-Ras 4B; experiment should show whether compounds interact with K-Ras 4B at 2 sites (e.g., the covalent site which is the CAAX-box cysteine and a non-covalent site); SPR experiments with K-Ras 4B G12V/C185S so that only possible non-covalent interaction; binding curve of 3G4 with K-Ras 4B G12V/C185S; Binding Curve of Compound 3G4 with K-Ras C186S, demonstrating potential non-covalent interaction.

[0022] FIGS. 11A-11B. ForteBio / Octet Assays; Measures compound binding to protein: association versus dissociation, steady state; Tested Avi-tagged Kras G12D with Fragments of FB9 and FB9D (parts of FB9/FB9D that make non-covalent interactions); LB9: = fragment of FB9; DB9: = fragment of FB9D; Avi-tagged K-Ras G12D was loaded with GTPyS/Mg; Curve with LB9 better than with DB9; Kd for LB9 around 17 μ M.

[0023] FIGS. 12A-12B. Measuring Conformational Changes Induced by Adding 3G4; Second Harmonic Generation (SHG) Experiments; SHG experiments were designed in order to see whether compound 3G4 induces any conformational change in K-Ras 4B; FPLC purified K-Ras was labelled either with EDA-GTP-ATTO 390, a fluorescent GTP analog, or PyMPO-Maleimide, a fluorescent dye that labels cysteines, or PyMPO-SE, another fluorescent dye that labels amines; Labeled K-Ras 4B was immobilized via His-tag on the surface of a chip and the experiments were performed in the presence of DMSO or 3G4 compound; 2 experiments with K-Ras 4B G12V/C185S labelled either with EDA-GTP-ATTO 390 or PyMPO-Maleimide. Fluorescent dyes, EDA-GTP-ATT0 390 and PyMPO-Maleimide, that have second harmonic generation activity were used.

[0024] FIGS. 13A-13E. Binding Assay of FB9 to either GTPyS or GDP bound K-Ras G12D; Binding of FB9 to His-tagged K-Ras wt, G12D, G12V and His-tagged K-Ras G12V/C185S was

compared; Proteins were loaded with GTPyS/Mg; Binding reaction with FB9 was done at RT for 4 hours; Rec full length G12D became loaded with either GDP or GTPyS and Mg²⁺; ~10μM protein was bound to 100μM electrophile compound at RT and time points were taken after 5 and 23 hours; Compound 6B9 had a tetrafluoro-phenoxy electrophile modification (FB9);

- 5 Compound bound better when K-Ras was in complex with GTPyS/Mg²⁺; In the case of K-Ras / GDP/Mg²⁺ the protein got significantly labelled at a second site after 5h. FIG. 13B and FIG. 13D were performed after 5 hours. FIG. 13C and FIG. 13E were performed at 23 hours.

[0025] FIG. 14A-14D. Binding of Electrophilic 6B9 Derivative (FB9) to Different Oncogenic His-K-Ras 4B.

- 10 **[0026]** FIGS. 15A-15D. Experiments with Stereoisomers of Difluorophenoxy-6B9; Kras G12D/GTPyS/Mg²⁺, DMSO control, 2h incubation at RT; The binding of FB9 to Kras G12D was compared with the stereoisomers of Difluorophenoxy-6B9 (53, 54); FB9 bound 100% after 2h incubation; Difluorophenoxy-6B9 (compound '53') bound to about 62% compared to FB9 under the same condition; The stereoisomer ('54') of compound '53' bound to roughly 35% compared to FB9 which is roughly 50% of compound '53'; Partial stereospecific interaction.
- 15

[0027] FIGS. 16A-16B. Binding Comparison of FB9 and FB9D to K-Ras (G12D), GTPyS/Mg; Original compound (FB9): 50μM for 2.5h at RT; The binding of FB9 with its enantiomer FB9D was also compared; FB9 bound about 25-30% better than FB9D, shows partial stereoselectivity.

- 20 **[0028]** FIGS. 17A-17B. Modifications of 3G4 (phenyl thiazole) and relative binding as determined by mass spectrometry. FIG. 17B depicts the extent of the KRas labeling relative to compound TC-1.

[0029] FIGS. 18A-18B. Additional Modifications of 3G4 and mass spectrometry binding assays.

- 25 **[0030]** FIGS. 19A-19C. Different Electrophiles of Compound 3G4 (Tetrafluoro-phenoxy-3G4, Difluoro-phenoxy-3G4, Fimethyl-phenoxy-3G4); certain electrophilic modifications resulted in reduced binding in the present assay; 3G4 may find different pocket than 6B9 (e.g., makes different contacts or interactions).

- [0031]** FIGS. 20A-20C. Reactivity of Tetrafluorophenoxy-6B9 (FB9) with BME; experiment was done with 1mM FB9 and minus or plus 5mM BME at 37°C. Time points were taken at 0,
- 30

18, and 55 minutes; graphs show the area under curve vs time; analysis of the reduction of the free compound peak shows about 25% product coming up after 55 minutes.

[0032] FIGS. 21A-21C. Interaction of FB9 with Kras in the absence or presence of BME; at RT for the indicated times; titrating in BME results in reactivity of the compound being reduced; BME itself did not react with the protein.

[0033] FIG. 22. Cell Based Assays with G12D expressing RAS-less MEFS; Ras-less cells exogenously expressing K-Ras G12D were stimulated with EGF for 30 and 60 minutes. Concomitantly FB9 was added at various concentrations. Similar experiments were done with pancreatic cell lines expressing various oncogenic mutations. Changes at K-Ras protein levels are visible. Growth curves were also performed.

[0034] FIG. 23. Time course EGF stimulation in combination with FB9 treatment (L3.6pl G12D).

[0035] FIG. 24. Stimulation with EGF in combination with FB9, Erlotinib, Carfilzomib treatment (L3.6pl G12D).

[0036] FIGS. 25A-25B. Time course EGF stimulation in combination with FB9 treatment (L3.6pl G12D).

[0037] FIG. 26. Time course EGF stimulation in combination with FB9 treatment (L3.6pl G12D).

[0038] FIG. 27. Comparing Gel Mobility and Antibody Reactivity of Different Purified K-Ras 4B Forms. E. Coli: unprocessed K-ras 4B purified from E. coli. Fme: processed K-ras 4B purified from SF9 cells. FB9: unprocessed K-ras 4B labeled with FB9 to about 70%.

[0039] FIG. 28. Time Course: Short and Long.

[0040] FIG. 29. Different Extraction Techniques and Antibody Comparison. Experiment #1 and #2 were performed at the same time, and in the same media solutions and cells (L3.6pl (G12D)); pellet fraction did not completely go into solution. The pellet fraction recognized by the Santa Cruz antibody shows two bands. The upper band is K-Ras.

[0041] FIG. 30. Growth Curves with human pancreatic cancer cell lines over 24 hours:EGF plus FB9, or EGF plus FB9 plus Erlotinib.

[0042] FIG. 31. Growth Curves with human pancreatic cancer cell lines over 24 hours:EGF plus FB9, or EGF plus FB9 plus Erlotinib.

[0043] FIGS. 32A-32B. FIG. 32A: K-ras 4B wild type C-terminus: Compound 3G4. FIG. 32B: K-ras 4B mutant C-terminus (C185S): compound 3G4.

[0044] FIG. 33. Identification of Kras G12D bound to tetrafluorophenoxy-6B9.

[0045] FIG. 34. Time Course: Short and Long.

5 [0046] FIG. 35. Cell uptake experiment showing stability of 994566 in MiaPaCa-2 cells within 24-h. Cells plated 1×10^6 on Petri dishes were treated, with 994566 in complete medium). Cells were collected into 200 μ l acetonitrile, lysate was centrifuged $15,000g \times 15$ min, filtered into HPLC vials and analyzed by LC/MS for the presence of the parent compound.

[0047] FIG. 36. Modification of fmeKRAS4b by FB9. Recombinant fmeKRAS4b was loaded
10 with GDP or GppNHp (a nonhydrolyzable analogue of GTP), then reacted with FB9 at 37 °C for 100 min. The MALDI-TOF analysis revealed that covalent modification of the protein by FB9 (350 Da mass addition) was more pronounced when GTP analogue was present.

[0048] FIG. 37. Vinyl sulfonamide analogue of FB9, compound 994566, inhibited
15 proliferation of mouse embryonic fibroblasts (MEF) expressing Kras4B G12D. Cells were serum-starved overnight, followed by treatment with 994566 and EGF (30 ng/ml). Medium was changed to complete (10% FBS) after 8 h, then compound was added again. Images were taken after 72 h in culture.

[0049] FIGS. 38A-38B. FIG. 38A: Vinyl sulfonamide analogue of FB9, compound 994566,
20 decreased Kras protein expression in mouse embryonic fibroblasts (MEF) expressing Kras4B G12D. Cells were serum-starved overnight, followed by treatment with 994566 and EGF (30 ng/ml). Medium was changed to complete (10% FBS) after 8 h, then compound was added again. Cell lysates were collected after 96 h in culture. FIG. 38B: Structures of vinyl acrylamide (left) and vinyl sulfonamide (right) analogues of FB9.

[0050] FIG. 39. Vinyl sulfonamide analogue of FB9, compound 994566, decreased Kras
25 protein expression in mouse embryonic fibroblasts (MEF) expressing Kras4B G12D after 24-h treatment. Cells were serum-starved overnight, followed by treatment with 994566 or 994565, followed immediately by EGF (30 ng/ml). Cells harvested after 24 h were processed for Western blot analysis.

[0051] FIG. 40. Conformations of the protein showing H95 is on the surface and exposed as
30 drug-accessible.

[0052] FIG. 41. Control sample. Mouse lung epithelial cell line stably transduced with HA-tagged Kras4B G12V was used in this experiment. HA-Kras4BG12V expression was induced with doxycycline for 48h, then cells were treated with a close analogue of FB9, compound 993784. Kras protein was purified from cell lysate using immunoaffinity chromatography followed by SDS-PAGE, then subjected to MALDI-TOF analysis of modification to Kras protein. Characteristic fragment of peptide modified with the compound was detected (bottom panel). This fragment was not present in the control sample (second panel from the top).

[0053] FIG. 42. Sequence of KRAS4b used in MALDI-TOF experiments

GMTEYKLVVVGAGGVGKSALTIQLIQNHVFVDEYDPTIEDSYRKQVVIDGETCLLDILDT
 AGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDSIEDVPMVLVGN
 KCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEKMSKDGK
 KKKKKSKTKCVIM (SEQ ID NO:1).

[0054] FIG. 43. MALDI-TOF spectra of KRAS4B (SEQ ID NO:1) modified by FB9.

[0055] FIG. 44. MALDI-TOF MS (linear mode) of the Glu-C digest (overnight, RT) of FB9-modified full-size (1-188) KRAS4b. The sequences listed within FIG. 44 are DIHHYRE (SEQ ID NO:2), GKKKKKKSKTKCVIM (SEQ ID NO:3), and KMSKDGKKKKKKSKTKCVIM (SEQ ID NO:4).

[0056] FIGS. 45A-45B. Identification of residues modified by FB9 on KRAS 4b. FIG. 45A: Peptides obtained after digestion by Glu-C were further digested by trypsin. FIG. 45B: Common fragments and a comparison of fragmentation spectra of peptides 969.485 and 1320.614.

[0057] FIGS. 46A-46B. FIG. 46A: The sequence of the protein used for experiment, specifically GGTEYKLVVVGAGGVGKSALTIQLIQNHVFVDEYDPTIEDSYRKQVVIDGETC
 LLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDSIEDV
 PMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEK
 MSKDGKKKKKKSKTKC (SEQ ID NO:5). FIG. 46B: MALDI-TOF spectrum of the FME-Kras4b protein modified by FB9.

[0058] FIG. 47. MALDI-TOF analysis of peptides modified by FB9 in Kras4b. The sequences listed within FIG. 47 are SFEDIHHYR (SEQ ID NO:6), SFEDIHHYREQIKR (SEQ ID NO:7), SFEDIHHYREQIK (SEQ ID NO:8), and DSEDVPMVLVGNKCDLPSR (SEQ ID NO:9).

I. Definitions

[0059] 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.

- 5 [0060] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0061] 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
10 multivalent radicals, having the number of carbon atoms designated (i.e., $\text{C}_1\text{-C}_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, homologs and isomers of, for example, n-pentyl, n-
15 hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker ($-\text{O}-$).

20 [0062] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer
25 carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0063] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., 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
30 nitrogen heteroatom may optionally be quaternized). The heteroatom(s) (e.g., O, N, P, S, B, As, or Si) may be placed at any interior position of the heteroalkyl group or at the position at which

the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N(CH}_3\text{)-CH}_3$, $-\text{CH}_2\text{-S-CH}_2\text{-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)}_2\text{-CH}_3$, $-\text{CH=CH-O-CH}_3$, $-\text{Si(CH}_3\text{)}_3$, $-\text{CH}_2\text{-CH=N-OCH}_3$, $-\text{CH=CH-N(CH}_3\text{)-CH}_3$, $-\text{O-CH}_3$, $-\text{O-CH}_2\text{-CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{-NH-OCH}_3$ and $-\text{CH}_2\text{-O-Si(CH}_3\text{)}_3$.

[0064] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2\text{-CH}_2\text{-S-CH}_2\text{-CH}_2\text{-}$ and $-\text{CH}_2\text{-S-CH}_2\text{-CH}_2\text{-NH-CH}_2\text{-}$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylendioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C(O)}_2\text{R}'$ represents both $-\text{C(O)}_2\text{R}'$ and $-\text{R}'\text{C(O)}_2\text{-}$. 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 $-\text{C(O)R}'$, $-\text{C(O)NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, 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.

[0065] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl,” respectively. Cycloalkyl and heteroalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively.

[0066] 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.

[0067] 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.

[0068] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 5 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. Likewise, a 6,6-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 6 members, and wherein at least one ring is a heteroaryl ring. And a 6,5-fused ring heteroarylene refers to two rings fused together, wherein one ring has 6 members and the other ring has 5 members, and wherein at least one ring is a heteroaryl ring. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, naphthyl, pyrrolyl, pyrazolyl, pyridazinyl, triazinyl, pyrimidinyl, imidazolyl, pyrazinyl, purinyl, oxazolyl, isoxazolyl, thiazolyl, furyl, thienyl, pyridyl, pyrimidyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, benzofuran, isobenzofuranyl, indolyl, isoindolyl, benzothiophenyl, isoquinolyl, quinoxalyl, quinolyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. An “arylene”

and a “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from an aryl and heteroaryl, respectively. A heteroaryl group substituent may be -O- bonded to a ring heteroatom nitrogen.

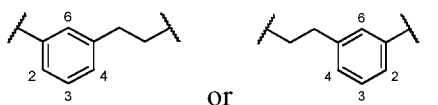
[0069] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different.

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.

[0070] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0071] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0072] The term “alkylarylene” as an arylylene moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



[0073] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylylene linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, -N₃, -CF₃, -CCl₃, -CBr₃, -CI₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂CH₃, -SO₃H, , -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted C₁-C₅

alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0074] 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.

[0075] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'C(O)NR''R''', -NR'C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''R''', -CN, -NO₂, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the 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)CH₂CH₃, and the like).

[0076] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'C(O)NR''R''', -NR'C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''R''', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to the total number of open valences on the

aromatic ring system; and where R', R'', R''', and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described
5 herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0077] 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,
10 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),
15 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
20 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
25 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.

[0078] 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
30 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.

- 5 **[0079]** 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.

- 20 **[0080]** As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0081] A “substituent group,” as used herein, means a group selected from the following moieties:

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

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

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

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

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

- 5 (a) oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and
- 10 (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl,
- 15 unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl.

[0082] A “size-limited substituent” or “size-limited substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl.

[0083] A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀

aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0084] In some embodiments, each substituted group described in the compounds herein is substituted with at least one substituent group. More specifically, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene described in the compounds herein are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. In other embodiments, at least one or all of these groups are substituted with at least one lower substituent group.

[0085] In other embodiments of the compounds herein, each substituted or unsubstituted alkyl may be a substituted or unsubstituted C₁-C₂₀ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₈ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 8 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 10 membered heteroaryl. In some embodiments of the compounds herein, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₂₀ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₈ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 8 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 10 membered heteroarylene.

[0086] In some embodiments, each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and/or each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl. In some

embodiments, each substituted or unsubstituted alkylene is a substituted or unsubstituted C₁-C₈ alkylene, each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene, each substituted or unsubstituted cycloalkylene is a substituted or unsubstituted C₃-C₇ cycloalkylene, each substituted or unsubstituted heterocycloalkylene is a substituted or unsubstituted 3 to 7 membered heterocycloalkylene, each substituted or unsubstituted arylene is a substituted or unsubstituted C₆-C₁₀ arylene, and/or each substituted or unsubstituted heteroarylene is a substituted or unsubstituted 5 to 9 membered heteroarylene. In some embodiments, the compound is a chemical species set forth in the Examples section, figures, or tables below.

10 **[0087]** Certain compounds of the present invention possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention
15 do not include those that are known in art to be too unstable to synthesize and/or isolate. The present invention is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise,
20 it is intended that the compounds include both E and Z geometric isomers.

[0088] 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.

25 **[0089]** 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.

[0090] 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.

30 **[0091]** Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

[0092] 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.

[0093] 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.

[0094] It should be noted that throughout the application that alternatives are written in Markush groups, for example, each amino acid position that contains more than one possible amino acid. It is specifically contemplated that each member of the Markush group should be considered separately, thereby comprising another embodiment, and the Markush group is not to be read as a single unit.

[0095] "Analog," or "analogue" is used in accordance with its plain ordinary meaning within Chemistry and Biology and refers to a chemical compound that is structurally similar to another compound (i.e., a so-called "reference" compound) but differs in composition, e.g., in the replacement of one atom by an atom of a different element, or in the presence of a particular functional group, or the replacement of one functional group by another functional group, or the absolute stereochemistry of one or more chiral centers of the reference compound. Accordingly, an analog is a compound that is similar or comparable in function and appearance but not in structure or origin to a reference compound.

[0096] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted $\text{C}_1\text{-C}_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted $\text{C}_1\text{-C}_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0097] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group

is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol or additional number 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

5 defined within the scope of the definition of R¹³ and optionally differently.

[0098] A “detectable moiety” as used herein refers to a moiety that can be covalently or noncovalently attached to a compound or biomolecule that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The

10 detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dies, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include

15 gadolinium, iron oxide and iron platinum, and manganese.

[0099] Description of compounds of the present invention are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently

20 unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0100] 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,

25 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

30

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

[0101] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0102] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound may differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0103] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0104] 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.

[0105] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer.

[0106] A polypeptide, or a cell is “recombinant” when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0107] “Co-administer” it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.* to reduce metabolic degradation). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0108] A “cell” as used herein, refers to a cell carrying out metabolic or other function sufficient to preserve or replicate its genomic DNA. A cell can be identified by well-known

methods in the art including, for example, presence of an intact membrane, staining by a particular dye, ability to produce progeny or, in the case of a gamete, ability to combine with a second gamete to produce a viable offspring. Cells may include prokaryotic and eukaryotic cells. Prokaryotic cells include but are not limited to bacteria. Eukaryotic cells include but are not limited to yeast cells and cells derived from plants and animals, for example mammalian, insect (*e.g.*, spodoptera) and human cells. Cells may be useful when they are naturally nonadherent or have been treated not to adhere to surfaces, for example by trypsinization.

[0109] The terms “treating” or “treatment” refers to any indicia of success in the treatment or amelioration of an injury, disease, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient’s physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation. For example, the certain methods presented herein successfully treat cancer by decreasing the incidence of cancer and or causing remission of cancer. In some embodiments of the compositions or methods described herein, treating cancer includes slowing the rate of growth or spread of cancer cells, reducing metastasis, or reducing the growth of metastatic tumors. The term “treating” and conjugations thereof, include prevention of an injury, pathology, condition, or disease.

[0110] An “effective amount” is an amount sufficient for a compound to accomplish a stated purpose relative to the absence of the compound (*e.g.* achieve the effect for which it is administered, treat a disease, reduce enzyme activity, increase enzyme activity, reduce signaling pathway, reduce one or more symptoms of a disease or condition (*e.g.* reduce signaling pathway stimulated by GTP bound Ras (*e.g.* K-Ras), reduce the signaling pathway activity of Ras, , reduce the signaling pathway activity of K-Ras, reduce the signaling pathway activity of K-Ras4A, reduce the signaling pathway activity of K-Ras4B, reduce the signaling pathway activity of H-Ras, reduce the signaling pathway activity of N-Ras, reduce the signaling pathway activity of a mutant K-Ras, inhibit the binding of K-Ras to SOS, inhibit the binding of K-Ras to a GEF, reduce the localization of K-Ras to a membrane, reduce the prenylation of K-Ras, inhibit the localization of K-Ras to a membrane, inhibit the prenylation of K-Ras). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a

“therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g.,

5 preventing or delaying the onset (or reoccurrence) of an injury, disease, pathology or condition, or reducing the likelihood of the onset (or reoccurrence) of an injury, disease, pathology, or condition, or their symptoms. The full prophylactic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a prophylactically effective amount may be administered in one or more administrations. An

10 “activity decreasing amount,” as used herein, refers to an amount of antagonist required to decrease the activity of an enzyme relative to the absence of the antagonist. A “function disrupting amount,” as used herein, refers to the amount of antagonist required to disrupt the function of an enzyme or protein relative to the absence of the antagonist (e.g. disrupt the protein-protein interaction between K-Ras and a signaling pathway binding protein such as

15 PI3K, disrupt the interaction of K-Ras and GEF, disrupt the interaction of K-Ras and SOS, disrupt the interaction of K-Ras with Raf, disrupt the localization of K-Ras to a membrane, disrupt the prenylation of K-Ras). 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*
20 *Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and *Remington: The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0111] “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
25 treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity (e.g. signaling pathway) of a protein (e.g. Ras, K-Ras, mutant K-Ras, K-Ras G12C, K-Ras G12D, K-Ras G13C, K-Ras G13D, K-Ras G12V, K-Ras G12S) in the absence of a compound as described
30 herein (including embodiments, examples, figures, or Tables).

[0112] “Contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules, or cells) to become sufficiently proximal to react, interact or physically touch. It

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

[0113] 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 (e.g. Ras, K-Ras, H-Ras, N-Ras, K-Ras4A, K-Ras4B, mutant Ras, mutant K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S). In some embodiments, the protein may be K-Ras. In some embodiments, the protein may be a mutant K-Ras (e.g. K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S). In some embodiments, the protein may be K-Ras4A. In some embodiments, the protein may be K-Ras4B. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[0114] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein (e.g. decreasing the signaling pathway stimulated by GTP bound Ras (e.g. K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S), nucleotide exchange, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, SOS binding, GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, membrane localization, prenylation 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 signal transduction pathway or signaling pathway (e.g. reduction of a pathway involving GTP bound Ras (e.g. K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S), reduction of a pathway involving mutant K-Ras (e.g. K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S)). Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating the signaling pathway or enzymatic activity or the amount of a protein (e.g. K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S). In some embodiments, inhibition refers to inhibition of interactions of Ras (K-Ras, K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G13D, K-Ras G12V, K-Ras G12S) with signaling pathway binding partners (e.g. PI3K, SOS, Raf). In some embodiments, inhibition refers to inhibition of interactions of Ras with a GEF (e.g. SOS). In some embodiments,

inhibition refers to inhibition of Ras prenylation. In some embodiments, inhibition refers to inhibition of Ras localization. In some embodiments, inhibition refers to inhibition of Ras membrane localization.

[0115] The term “modulator” refers to a composition that increases or decreases the level of a

5 target molecule or the function (e.g., effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, SOS binding, prenylation, localization) of a target molecule or the physical state (e.g. Ras subcellular localization, Ras post-translational processing, Ras post-translational modifications (prenylation)) of the target of the molecule (e.g. a target may be K-Ras and the function may be to hydrolyze GTP or activate a signaling pathway that is activated
10 by GTP bound K-Ras, interaction of K-Ras with protein binding partners (e.g. PI3K, SOS, Raf)) relative to the absence of the composition. In some embodiments, a K-Ras disease modulator is a compound that reduces the severity of one or more symptoms of a disease associated with K-Ras (e.g. cancer, metastatic cancer) relative to the absence of the compound. A K-Ras modulator is a compound that increases or decreases the activity or function or level of activity or level of
15 function of K-Ras or level of K-Ras or level of K-Ras in a particular physical state relative to the absence of the compound. A mutant K-Ras modulator is a compound that that increases or decreases the activity or function or level of activity or level of function of mutant K-Ras or level of mutant K-Ras or level of mutant K-Ras in a particular physical state relative to the absence of the compound. A K-Ras G12C modulator, K-Ras G12D modulator, K-Ras G13C modulator, K-Ras G12V modulator, K-Ras G12S modulator, or K-Ras G13D modulator is a compound that
20 increases or decreases the activity or function or level of activity or level of function of that particular mutant K-Ras or level of that particular mutant K-Ras or level of that particular mutant K-Ras in a particular physical state relative to the absence of the compound. A K-Ras inhibitor is a compound that decreases the activity or function or level of activity or level of function of K-Ras or level of K-Ras or level of K-Ras in a particular physical state relative to the absence of
25 the compound. A mutant K-Ras inhibitor is a compound that that decreases the activity or function or level of activity or level of function of mutant K-Ras or level of mutant K-Ras or level of mutant K-Ras in a particular physical state relative to the absence of the compound. A K-Ras G12C inhibitor, K-Ras G12D inhibitor, K-Ras G13C inhibitor, K-Ras G12V inhibitor, K-Ras G12S inhibitor, or K-Ras G13D inhibitor is a compound that decreases the activity or
30 function or level of activity or level of function of that particular mutant K-Ras or level of that particular mutant K-Ras or level of that particular mutant K-Ras in a particular physical state relative to the absence of the compound.

[0116] The term “modulate” is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. “Modulation” refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule.

[0117] “Patient” or “subject in need thereof” refers to a living organism suffering from or prone to a disease or condition that can be treated by administration of a pharmaceutical composition as provided herein. Non-limiting examples include humans, other mammals, bovines, rats, mice, dogs, monkeys, goat, sheep, cows, deer, and other non-mammalian animals.

In some embodiments, a patient is human.

[0118] “Disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. In some embodiments, the disease is a disease related to (e.g. caused by) a Ras. In some embodiments, the disease is a disease related to (e.g. caused by) a K-Ras (e.g. K-Ras G12C, G13C, G12D, G12V, G12S, or G13D) or aberrant K-Ras signaling pathway activity (e.g. lung cancer, breast cancer, colon cancer, colorectal cancer, pancreatic cancer, leukemia). Examples of diseases, disorders, or conditions include, but are not limited to cancer. Examples of diseases, disorders, or conditions include, but are not limited to MYH-associated polyposis. In some instances, “disease” or “condition” refers to cancer. In some instances, “disease” or “condition” refers to MYH-associated polyposis. In some further instances, “cancer” refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, etc., including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin’s lymphomas (e.g., Burkitt’s, Small Cell, and Large Cell lymphomas), Hodgkin’s lymphoma, leukemia (including AML, ALL, and CML), or multiple myeloma.

[0119] As used herein, the term “cancer” refers to all types of cancer, neoplasm or malignant tumors found in mammals (e.g. humans), including leukemia, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus, Medulloblastoma, colorectal cancer, pancreatic cancer. Additional examples include, Hodgkin’s Disease, Non-Hodgkin’s Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma

multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary
 macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insulanoma, malignant
 carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas,
 thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant
 5 hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or
 exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal
 cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0120] 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
 10 leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically
 classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the
 type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3)
 the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic
 (subleukemic). Exemplary leukemias that may be treated with a compound or method provided
 15 herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia,
 acute granulocytic leukemia, chronic granulocytic leukemia, acute promyelocytic leukemia, adult
 T-cell leukemia, aleukemic leukemia, a leukocythemetic leukemia, basophylic leukemia, blast cell
 leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia,
 eosinophilic leukemia, Gross' leukemia, hairy-cell leukemia, hemoblastic leukemia,
 20 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,
 25 Naegeli leukemia, plasma cell leukemia, multiple myeloma, plasmacytic leukemia,
 promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia,
 subleukemic leukemia, or undifferentiated cell leukemia.

[0121] 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
 30 a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound or method
 provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma,
 myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft
 part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma,

embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectatic sarcoma.

[0122] The term "melanoma" is taken to mean a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular melanoma, subungual melanoma, or superficial spreading melanoma.

[0123] The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound or method provided herein include, for example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, 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, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma

mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, 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, tuberos carcinoma, verrucous carcinoma, or carcinoma villosum.

[0124] “Ras associated cancer” (also referred to herein as “Ras related cancer”) refers to a cancer caused by aberrant Ras activity or signaling. A “cancer associated with aberrant K-Ras activity” (also referred to herein as “K-Ras related cancer”) is a cancer caused by aberrant K-Ras activity or signaling (e.g. a mutant K-Ras). K-Ras related cancers may include lung cancer, non-small cell lung cancer, breast cancer, leukemia, pancreatic cancer, colon cancer, colorectal cancer. Other cancers that are associated with aberrant activity of one or more of Ras, K-Ras, H-Ras, N-Ras, mutant K-Ras (including K-Ras G12C, K-Ras G13C, K-Ras G12D, K-Ras G12V, K-Ras G12S, K-Ras G13D mutants), mutant N-Ras, and mutant H-Ras are well known in the art and determining such cancers are within the skill of a person of skill in the art.

[0125] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer’s solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0126] The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it.

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

[0127] As used herein, the term "administering" means oral administration, administration as a suppository, topical contact, intravenous, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal).

Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies, for example cancer therapies such as chemotherapy, hormonal therapy, radiotherapy, or immunotherapy. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (*e.g.* to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0128] The term "administer (or administering) a Ras inhibitor" means administering a compound that inhibits the activity or level (*e.g.* amount) or level of a signaling pathway of one or more Ras proteins (*e.g.* a Ras inhibitor, K-Ras inhibitor, N-Ras inhibitor, H-Ras inhibitor, mutant K-Ras inhibitor, K-Ras G12C inhibitor, K-Ras G12V inhibitor, K-Ras G12S inhibitor, K-Ras G13C inhibitor, K-Ras G12D inhibitor, K-Ras G13D inhibitor) to a subject. Administration may include, without being limited by mechanism, allowing sufficient time for the Ras inhibitor to reduce the activity of one or more Ras proteins or for the Ras inhibitor to reduce one or more symptoms of a disease (*e.g.* cancer, wherein the Ras inhibitor may arrest the cell cycle, slow the cell cycle, reduce DNA replication, reduce cell replication, reduce cell growth, reduce metastasis, or cause cell death). The term "administer (or administering) a K-Ras inhibitor"

means administering a compound that inhibits the activity or level (e.g. amount) or level of a signaling pathway of one or more K-Ras proteins (K-Ras, mutant K-Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G12D, K-Ras G13C, K-Ras G13D).

[0129] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating a disease associated with cells expressing a particular Ras, K-Ras, mutant K-Ras (e.g. cancer), or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0130] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another.

[0131] As a non-limiting example, the compounds described herein can be co-administered with conventional chemotherapeutic agents including alkylating agents (*e.g.*, cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepea, nitrosoureas, *etc.*), anti-metabolites (*e.g.*, 5-fluorouracil, azathioprine, methotrexate, leucovorin, capecitabine, cytarabine, floxuridine, fludarabine, gemcitabine, pemetrexed, raltitrexed, *etc.*), plant alkaloids (*e.g.*, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (*e.g.*, irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (*e.g.*, doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (*e.g.* cisplatin, oxaloplatin, carboplatin, *etc.*), and the like.

[0132] The compounds described herein can also be co-administered with conventional hormonal therapeutic agents including, but not limited to, steroids (*e.g.*, dexamethasone), finasteride, aromatase inhibitors, tamoxifen, and gonadotropin-releasing hormone agonists (GnRH) such as goserelin.

[0133] Additionally, the compounds described herein can be co-administered with conventional immunotherapeutic agents including, but not limited to, immunostimulants (*e.g.*,

Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (*e.g.*, anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (*e.g.*, anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), and radioimmunotherapy (*e.g.*, anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , *etc.*).

[0134] In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc , ^{64}Cu , ^{67}Cu , ^{89}Sr , ^{86}Y , ^{87}Y , ^{90}Y , ^{105}Rh , ^{111}Ag , ^{111}In , $^{117\text{m}}\text{Sn}$, ^{149}Pm , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi , optionally conjugated to antibodies directed against tumor antigens.

[0135] In therapeutic use for the treatment of cancer, compound utilized in the pharmaceutical compositions of the present invention may be administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.01 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 200 mg/kg, or about 1 mg/kg to about 100 mg/kg, or about 10 mg/kg to about 50 mg/kg, can be used. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound or drug being employed. For example, dosages can be empirically determined considering the type and stage of cancer diagnosed in a particular patient. The dose administered to a patient, in the context of the present invention, should be sufficient to affect a beneficial therapeutic response in the patient over time. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a compound in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

[0136] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent.

[0137] The term “associated” or “associated with” in the context of a substance or substance activity or function associated with a disease (*e.g.* a protein associated disease, a cancer associated with aberrant Ras activity, K-Ras associated cancer, mutant K-Ras associated cancer, activated K-Ras associated cancer, K-Ras G12C associated cancer, K-Ras G12V associated

cancer, K-Ras G12S associated cancer, K-Ras G13C associated cancer, K-Ras G12D associated cancer, K-Ras G13D associated cancer) means that the disease (e.g. cancer) is caused by (in whole or in part), or a symptom of the disease is caused by (in whole or in part) the substance or substance activity or function. For example, a cancer associated with aberrant Ras activity or function may be a cancer that results (entirely or partially) from aberrant Ras activity or function (e.g. enzyme activity, protein-protein interaction, signaling pathway) or a cancer wherein a particular symptom of the disease is caused (entirely or partially) by aberrant Ras activity or function. As used herein, what is described as being associated with a disease, if a causative agent, could be a target for treatment of the disease. For example, a cancer associated with aberrant Ras activity or function or a Ras associated cancer, may be treated with a Ras modulator or Ras inhibitor, in the instance where increased Ras activity or function (e.g. signaling pathway activity) causes the cancer. For example, a cancer associated with K-Ras G12V may be a cancer that a subject with K-Ras G12V is at higher risk of developing as compared to a subject without K-Ras G12V.

[0138] The term “aberrant” as used herein refers to different from normal. When used to describe enzymatic activity, aberrant refers to activity that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning the aberrant activity to a normal or non-disease-associated amount (e.g. by administering a compound or using a method as described herein), results in reduction of the disease or one or more disease symptoms.

[0139] “Anti-cancer agent” is used in accordance with its plain ordinary meaning and refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells. In some embodiments, an anti-cancer agent is a chemotherapeutic. In some embodiments, an anti-cancer agent is an agent identified herein having utility in methods of treating cancer. In some embodiments, an anti-cancer agent is an agent approved by the FDA or similar regulatory agency of a country other than the USA, for treating cancer. Examples of anti-cancer agents include, but are not limited to, MEK (e.g. MEK1, MEK2, or MEK1 and MEK2) inhibitors (e.g. XL518, CI-1040, PD035901, selumetinib/ AZD6244, GSK1120212/ trametinib, GDC-0973, ARRY-162, ARRY-300, AZD8330, PD0325901, U0126, PD98059, TAK-733, PD318088, AS703026, BAY 869766), alkylating agents (e.g., cyclophosphamide, ifosfamide, chlorambucil, busulfan, melphalan, mechlorethamine, uramustine, thiotepea, nitrosoureas, nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, melphalan), ethylenimine and methylmelamines (e.g.,

hexamethylmelamine, thiotepa), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomustine, semustine, streptozocin), triazenes (decarbazine)), anti-metabolites (e.g., 5-azathioprine, leucovorin, capecitabine, fludarabine, gemcitabine, pemetrexed, raltitrexed, folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine, Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin), *etc.*), plant alkaloids (e.g., vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, paclitaxel, docetaxel, *etc.*), topoisomerase inhibitors (e.g., irinotecan, topotecan, amsacrine, etoposide (VP16), etoposide phosphate, teniposide, *etc.*), antitumor antibiotics (e.g., doxorubicin, adriamycin, daunorubicin, epirubicin, actinomycin, bleomycin, mitomycin, mitoxantrone, plicamycin, *etc.*), platinum-based compounds (e.g. cisplatin, oxaloplatin, carboplatin), anthracenedione (e.g., mitoxantrone), substituted urea (e.g., hydroxyurea), methyl hydrazine derivative (e.g., procarbazine), adrenocortical suppressant (e.g., mitotane, aminoglutethimide), epipodophyllotoxins (e.g., etoposide), antibiotics (e.g., daunorubicin, doxorubicin, bleomycin), enzymes (e.g., L-asparaginase), inhibitors of mitogen-activated protein kinase signaling (e.g. U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002, Syk inhibitors, mTOR inhibitors, antibodies (e.g., rituxan), gossypol, genasense, polyphenol E, Chlorofusin, all trans-retinoic acid (ATRA), bryostatin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), 5-aza-2'-deoxycytidine, all trans retinoic acid, doxorubicin, vincristine, etoposide, gemcitabine, imatinib (Gleevec.RTM.), geldanamycin, 17-N-Allylamino-17-Demethoxygeldanamycin (17-AAG), flavopiridol, LY294002, bortezomib, trastuzumab, BAY 11-7082, PKC412, PD184352, 20-epi-1, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; broprimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole;

- CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol;
- 5 cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantraquinones; cycloplattam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol;
- 10 duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate;
- 15 galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole;
- 20 isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin;
- 25 loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocil; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone;
- 30 mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin;

nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide
 modulators; nitroxide antioxidant; nitrullin; O6-benzylguanine; octreotide; okicenone;
 oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer;
 ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic
 5 acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan
 polysulfate sodium; pentostatin; pentozole; perflubron; perfosfamide; perillyl alcohol;
 phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride;
 pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum
 complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin;
 10 prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based
 immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein
 tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins;
 pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists;
 raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP
 15 inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII
 retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safinol;
 saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence
 derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction
 modulators; single chain antigen-binding protein; sizofuran; sobuzoxane; sodium borocaptate;
 20 sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid;
 spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-
 cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive
 intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans;
 tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur;
 25 tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide;
 tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin
 mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone;
 tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem
 cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin;
 30 tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex;
 urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide;
 variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin;
 vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin
 stimalamer, Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin;

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

sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, (e.g. Taxol.TM (i.e. paclitaxel), Taxotere.TM, compounds comprising the taxane skeleton, Erbulozole (i.e. R-55104), Dolastatin 10 (i.e. DLS-10 and NSC-376128), Mivobulin isethionate (i.e. as CI-980), Vincristine, NSC-639829, Discodermolide (i.e. as NVP-XX-A-296), ABT-751 (Abbott, i.e. E-7010), Altorhyrtins (e.g. Altorhyrtin A and Altorhyrtin C), Spongistatins (e.g. Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (i.e. LU-103793 and NSC-D-669356), Epothilones (e.g. Epothilone A, Epothilone B, Epothilone C (i.e. desoxyepothilone A or dEpoA), Epothilone D (i.e. KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (i.e. BMS-310705), 21-hydroxyepothilone D (i.e. Desoxyepothilone F and dEpoF), 26-fluoroepothilone, steroids (e.g., dexamethasone), finasteride, aromatase inhibitors, gonadotropin-releasing hormone agonists (GnRH) such as goserelin or leuprolide, adrenocorticosteroids (e.g., prednisone), progestins (e.g., hydroxyprogesterone caproate, megestrol acetate, medroxyprogesterone acetate), estrogens (e.g., diethylstilbestrol, ethinyl estradiol), antiestrogen (e.g., tamoxifen), androgens (e.g., testosterone propionate, fluoxymesterone), antiandrogen (e.g., flutamide), immunostimulants (e.g., Bacillus Calmette-Guérin (BCG), levamisole, interleukin-2, alpha-interferon, *etc.*), monoclonal antibodies (e.g., anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22 monoclonal antibody-pseudomonas exotoxin conjugate, *etc.*), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ¹¹¹In, ⁹⁰Y, or ¹³¹I, *etc.*), triptolide, homoharringtonine, dactinomycin, doxorubicin, epirubicin, topotecan, itraconazole, vindesine, cerivastatin, vincristine, deoxyadenosine, sertraline, pitavastatin, irinotecan, clofazimine, 5-nonyloxytryptamine, vemurafenib, dabrafenib, erlotinib, gefitinib, EGFR inhibitors, epidermal growth factor receptor (EGFR)-targeted therapy or therapeutic (e.g. gefitinib (Iressa™), erlotinib (Tarceva™), cetuximab (Erbix™), lapatinib (Tykerb™), panitumumab (Vectibix™), vandetanib (Caprelsa™), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, BMS-599626), sorafenib, imatinib, sunitinib, dasatinib, Ras inhibitors, or the like.

[0140] “Chemotherapeutic” or “chemotherapeutic agent” is used in accordance with its plain ordinary meaning and refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

[0141] The term “Electrophilic” as used herein refers to a chemical group that is capable of accepting electron density. An “electrophilic substituent”, “electrophilic chemical moiety”, or “electrophilic moiety” refers to an electron-poor chemical group, substituent, or moiety (monovalent chemical group), which may react with an electron-donating group, such as a nucleophile, by accepting an electron pair or electron density to form a bond. In some embodiments, the electrophilic substituent of the compound is capable of reacting with a cysteine residue. In some embodiments, the electrophilic substituent is capable of forming a covalent bond with a cysteine residue (e.g., K-ras cysteine residue, residue corresponding to C185 of human K-Ras 4B) and may be referred to as a “covalent cysteine modifier moiety” or “covalent cysteine modifier substituent”. The covalent bond formed between the electrophilic substituent and the sulfhydryl group of the cysteine may be a reversible or irreversible bond. In some embodiments, the electrophilic substituent is capable of forming a covalent bond with a histidine residue (e.g., K-ras histidine residue, residue corresponding to H95 of human K-Ras 4B) and may be referred to as a “covalent histidine modifier moiety” or “covalent histidine modifier substituent”. The covalent bond formed between the electrophilic substituent and the histidine may be a reversible or irreversible bond.

[0142] “Nucleophilic” as used herein refers to a chemical group that is capable of donating electron density.

[0143] The term “Ras” refers to one or more of the family of human Ras GTPase proteins (e.g. K-Ras, H-Ras, N-Ras). The term “K-Ras” refers to the nucleotide sequences or proteins of human K-Ras (e.g. human K-Ras4A (NP_203524.1), human K-Ras4B (NP_004976.2), or both K-Ras4A and K-Ras4B). The term “K-Ras” includes both the wild-type form of the nucleotide sequences or proteins as well as any mutants thereof. In some embodiments, “K-Ras” is wild-type K-Ras. In some embodiments, “K-Ras” is one or more mutant forms. The term “K-Ras” XYZ refers to a nucleotide sequence or protein of a mutant K-Ras wherein the Y numbered amino acid of K-Ras that has an X amino acid in the wildtype instead has a Z amino acid in the mutant (e.g. K-Ras G12C has a G in wildtype protein but a C in the K-Ras G12C mutant protein). In some embodiments K-Ras refers to K-Ras4A and K-Ras4B. In some embodiments, K-Ras refers to K-Ras4A. In some embodiments, K-Ras refers to K-Ras4B. In embodiments K-Ras refers to a protein having an amino acid sequence described herein.

[0144] The term “Ras inhibitor test compound” as used herein refers to a compound that is being characterized in an assay for the ability to inhibit an activity, function, or level (e.g. amount) of a Ras protein. The term “K-Ras inhibitor test compound” as used herein refers to a compound that is being characterized in an assay for the ability to inhibit an activity, function, or level (e.g. amount) of K-Ras protein.

[0145] The term “signaling pathway” as used herein refers to a series of interactions between cellular and optionally extra-cellular components (e.g. proteins, nucleic acids, small molecules, ions, lipids) that conveys a change in one component to one or more other components, which in turn may convey a change to additional components, which is optionally propagated to other signaling pathway components. For example, binding of a K-Ras with a compound as described herein may result in a change in one or more protein-protein interactions of the K-Ras or interactions between the K-Ras and a membrane, resulting in changes in cell growth, proliferation, or survival.

[0146] An amino acid residue in a protein “corresponds” to a given residue when it occupies the same essential structural position within the protein as the given residue. For example, a selected residue in a selected protein corresponds to Gly 12 of Human K-Ras4A or Human K-Ras 4B or both when the selected residue occupies the same essential spatial or other structural relationship as Gly 12 in Human K-Ras4A or Human K-Ras 4B or both. In some embodiments, where a selected protein is aligned for maximum homology with the Human K-Ras4A or Human K-Ras 4B protein, the position in the aligned selected protein aligning with Gly 12 is said to correspond to Gly 12. Instead of a primary sequence alignment, a three dimensional structural alignment can also be used, e.g., where the structure of the selected protein is aligned for maximum correspondence with the Human K-Ras4A or Human K-Ras 4B protein and the overall structures compared. In this case, an amino acid that occupies the same essential position as Gly 12 in the structural model is said to correspond to the Gly 12 residue. Another example is wherein a selected residue in a selected protein corresponds to C185 of Human K-Ras 4B when the selected residue (e.g., cysteine residue) occupies essential the same sequence, spatial, or other structural position within the protein as C185 in Human K-Ras 4B.

[0147] The terms “unsubstituted vinyl sulfone moiety”, “unsubstituted vinyl sulfonamide moiety”, “unsubstituted fluoro(C₁-C₄)alkylketone moiety”, “unsubstituted chloro(C₁-C₄)alkylketone moiety”, “unsubstituted acrylamide moiety”, “unsubstituted disulfide moiety”, “unsubstituted thiol moiety”, “unsubstituted phosphonate moiety”, “unsubstituted aldehyde moiety”, “unsubstituted enone moiety”, “unsubstituted diazomethylketone moiety”,

“unsubstituted diazomethylamide moiety”, “unsubstituted cyanocyclopropyl carboxamide moiety”, “unsubstituted epoxide moiety”, “unsubstituted epoxyketone moiety”, “unsubstituted epoxyamide moiety”, “unsubstituted aryl aldehyde moiety”, “unsubstituted aryl dialdehyde moiety”, “unsubstituted dialdehyde moiety”, “unsubstituted nitrogen mustard moiety”,

- 5 “unsubstituted propargyl moiety”, or “unsubstituted propargylamide moiety” are used according to their plain ordinary chemical meaning and refer to those monovalent chemical groups named having the lowest molecular weight for each such group while obeying the rules of chemical valency. A substituted form of one of the named groups may be substituted with one or more of any of the substituent groups described herein while obeying the rules of chemical valency.

- 10 **[0148]** H-Ras WT Human

[0149] MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY RKQVVIDGET
CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC VFAINNTKSF EDIHQYREQI
KRVKDSDDVP MVLVGKNC DL AARTVESRQA QDLARSYGIP YIETSAKTRQ
GVEDAFYTLV REIRQHKLRLK LNPPDESGPG CMSCKCVLS (SEQ ID NO:10)

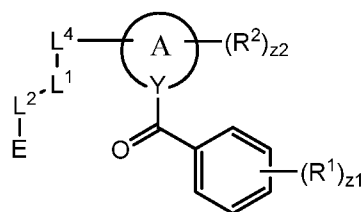
- 15 **[0150]** K-Ras 4A WT Human

[0151] mteyklvvvg aggvgksalt iqliqnhfvd eydptiedsy rkqvvidget clldildtag qeysamrdq
ymrtgegflc vfainntksf edihhyreqi krkdsedvp mvlvgnkcdl psrtvdtkqa qdlarsygip fietsaktrq
rvedafytlv reirqyrkk iskeektpgc vkikkciim (SEQ ID NO:11)

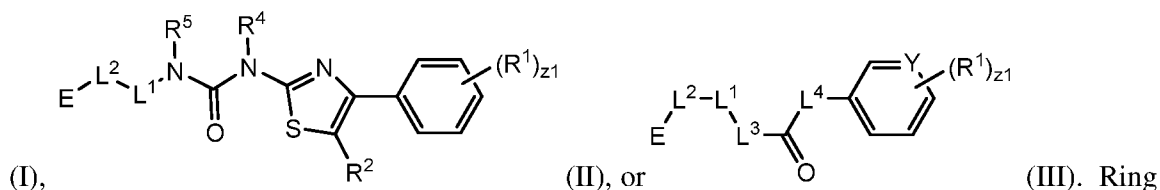
[0152] K-Ras 4B WT Human

- 20 **[0153]** mteyklvvvg aggvgksalt iqliqnhfvd eydptiedsy rkqvvidget clldildtag qeysamrdq
ymrtgegflc vfainntksf edihhyreqi krkdsedvp mvlvgnkcdl psrtvdtkqa qdlarsygip fietsaktrq
gvddafytlv reirkhkekm skdgkkkkkk sktkcvim (SEQ ID NO:12)

II. Compounds



[0154] In an aspect is provided a compound having the formula:

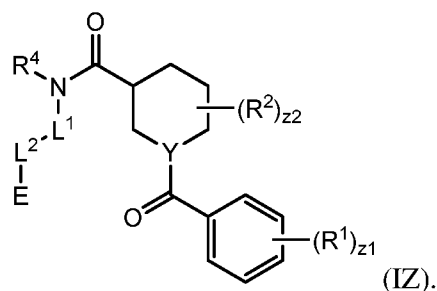


A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl. Y is N or CH or C. R¹ is

- 5 independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸,
 -NHN⁷R⁸, -ONR⁷R⁸, -NHC(=O)NHN⁷R⁸,
 -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -
 NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl,
 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 10 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
 heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, or substituted or unsubstituted heteroaryl. L¹ is a
 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7A}-, -NR^{7A}C(O)-, -C(O)NR^{7A}-, -SO₂NR^{7A}-, -
 15 NR^{7A}SO₂-, -OC(O)NR^{7A}-, -NR^{7A}C(O)O-, -CR^{9A}=NO-, -ON=CR^{9A}-, -NR^{8A}C(O)NR^{7A}-,
 -NR^{8A}C(=NR^{10A})NR^{7A}-, -NR^{8A}C(=NR^{10A})-, -C(=NR^{10A})NR^{7A}-, -OC(=NR^{10A})-,
 -C(=NR^{10A})O-, substituted or unsubstituted alkylene, substituted or unsubstituted
 heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted
 heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted
 20 heteroarylene. L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -
 NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -
 NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-,
 -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or
 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted
 25 cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted
 arylene, substituted or unsubstituted heteroarylene. L³ is a
 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁵-, -NR⁵C(O)-, -C(O)NR⁵-, -SO₂NR⁵-, -

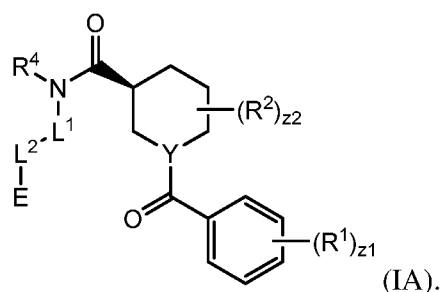
NR^5SO_2- , $-\text{OC}(\text{O})\text{NR}^5-$, $-\text{NR}^5\text{C}(\text{O})\text{O}-$, substituted or unsubstituted C_1 - C_6 alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene. L^4 is a bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{S}(\text{O})_2-$, $-\text{NR}^4-$, $-\text{NR}^4\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^4-$, $-\text{SO}_2\text{NR}^4-$, $-\text{NR}^4\text{SO}_2-$, $-\text{NR}^4\text{SO}_2-$, $-\text{OC}(\text{O})\text{NR}^4-$, $-\text{NR}^4\text{C}(\text{O})\text{O}-$, substituted or unsubstituted C_1 - C_3 alkylene, substituted or unsubstituted 2 to 3 membered heteroalkylene. E is an electrophilic moiety. R^2 is independently hydrogen, oxo, halogen, CX^2_3 , $-\text{CHX}^2_2$, $-\text{CH}_2\text{X}^2$, $-\text{CN}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_{n2}\text{R}^{14}$, $-\text{SO}_{v2}\text{NR}^{11}\text{R}^{12}$, $-\text{NHNR}^{11}\text{R}^{12}$, $-\text{ONR}^{11}\text{R}^{12}$, $-\text{NHC}(\text{O})\text{NHNR}^{11}\text{R}^{12}$, $-\text{NHC}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{N}(\text{O})_{m2}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{C}(\text{O})-\text{OR}^{14}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{OR}^{15}$, $-\text{NR}^{11}\text{SO}_2\text{R}^{15}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{OR}^{14}$, $-\text{OCX}^2_3$, $-\text{OCHX}^2_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^4 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^5 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^7 , R^8 , R^9 , R^{10} , R^{7A} , R^{8A} , R^{9A} , R^{10A} , R^{7B} , R^{8B} , R^{9B} , R^{10B} , R^{11} , R^{12} , R^{14} , and R^{15} are independently hydrogen, halogen, $-\text{CX}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}(\text{O})\text{NHNH}_2$, $-\text{NHC}(\text{O})\text{NH}_2$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 and R^8 substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each X, X^1 , and X^2 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$. The symbols $n1$, $n2$, $v1$, and $v2$ are independently an integer from 0 to 4. The symbols $m1$ and $m2$ are independently an integer

from 1 to 2. The symbol z_1 is independently an integer from 0 to 5. The symbol z_2 is independently an integer from 0 to 10.



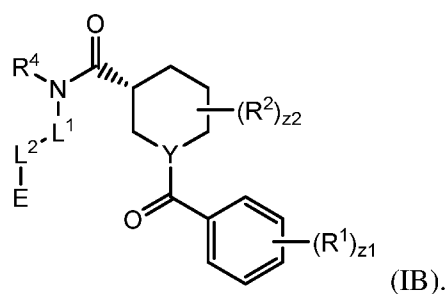
[0155] In embodiments, the compound has the formula:

R^1 , R^2 , R^4 , L^1 , L^2 , E, Y z_1 and z_2 are as described herein.



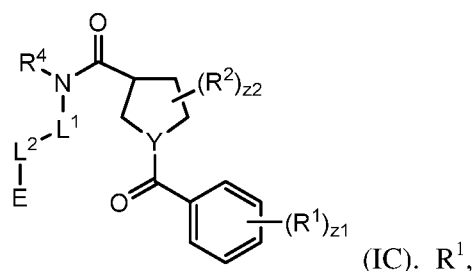
5 **[0156]** In embodiments, the compound has the formula:

R^1 , R^2 , R^4 , L^1 , L^2 , E, Y z_1 and z_2 are as described herein.



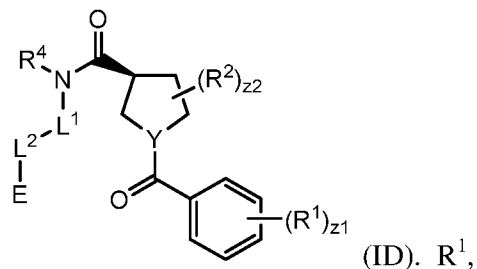
[0157] In embodiments, the compound has the formula:

R^1 , R^2 , R^4 , L^1 , L^2 , E, Y z_1 and z_2 are as described herein.



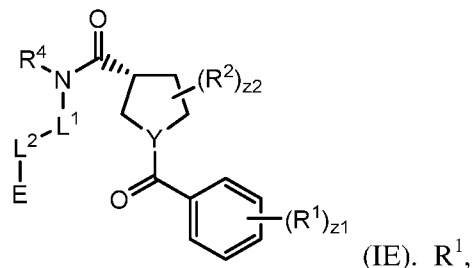
[0158] In embodiments, the compound has the formula:

10 R^2 , R^4 , L^1 , L^2 , E, Y z_1 and z_2 are as described herein.



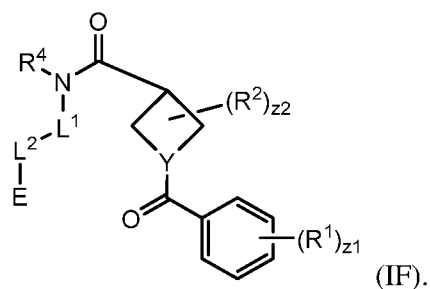
[0159] In embodiments, the compound has the formula:

R^2 , R^4 , L^1 , L^2 , E, Y $z1$ and $z2$ are as described herein.



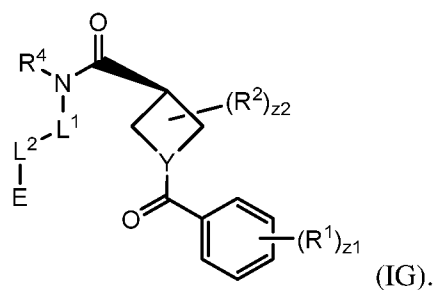
[0160] In embodiments, the compound has the formula:

R^2 , R^4 , L^1 , L^2 , E, Y $z1$ and $z2$ are as described herein.



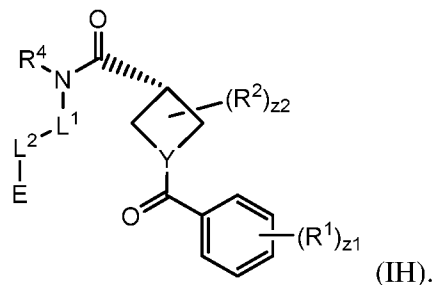
5 **[0161]** In embodiments, the compound has the formula:

R^1 , R^2 , R^4 , L^1 , L^2 , E, Y $z1$ and $z2$ are as described herein.



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

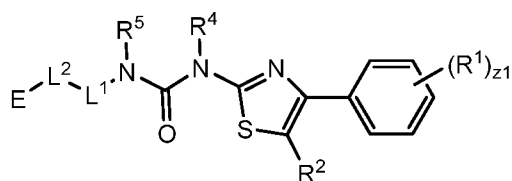
R^1 , R^2 , R^4 , L^1 , L^2 , E, Y $z1$ and $z2$ are as described herein.



[0163] In embodiments, the compound has the formula:

R^1 , R^2 , R^4 , L^1 , L^2 , E, Y z_1 and z_2 are as described herein.

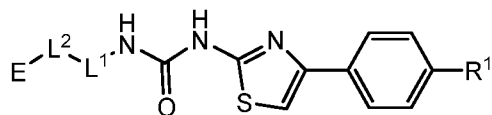
[0164] In embodiments, the compound has the formula:



(II). R^1 , R^2 , R^4 , R^5 , L^1 , L^2 , E, and z_1 are as described

5 herein.

[0165] In embodiments of the compound of formula II, R^2 , R^4 , and R^5 are hydrogen. In

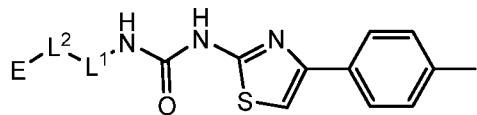


embodiments, the compound has the formula:

L^1 , L^2 , and E, are as described herein.

(IIA). R^1 ,

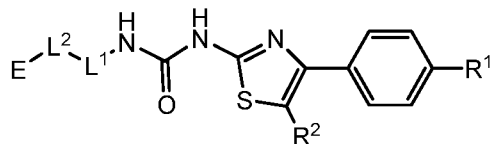
[0166] In embodiments, the compound has the formula:



(IIB). L^1 , L^2 , and E are as described herein (e.g., for

formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims).

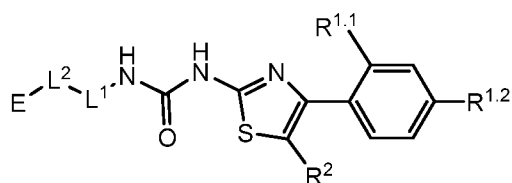
[0167] In embodiments, the compound has the formula:



(IIC). R^1 , R^2 , L^1 , L^2 , and E are as described herein (e.g.,

for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims).

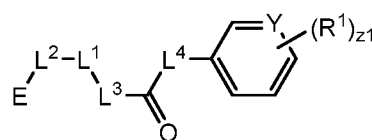
[0168] In embodiments, the compound has the formula:



(IID). R^1 , R^2 , L^1 , L^2 , and E are as described herein

(e.g., for formulae I, II, III, VI, VI, and embodiments thereof or in examples, figures, tables, or claims). $R^{1.1}$ and $R^{1.2}$ have the values of R^1 . $R^{1.1}$ and $R^{1.2}$ may be optionally different halogens

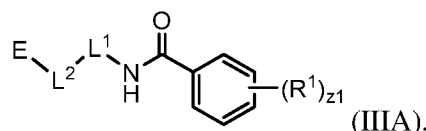
5 (e.g., F and/or Cl). R^1 may be halogen (e.g., F or Cl). R^2 may be unsubstituted methyl.



[0169] In embodiments, the compound has the formula:

(III).

R^1 , L^1 , L^2 , L^3 , L^4 , E, Y, and $z1$ are as described herein.



[0170] In embodiments, the compound has the formula:

(IIIA).

R^1 , L^1 , L^2 , E, and $z1$ are as described herein.

- 10 [0171] In embodiments, L^3 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHCH(CH₃)C(O)NH-, or unsubstituted C₁-C₃ alkylene. In embodiments, L^4 is a bond, -CH₂O-, -C(O)-, -NH-, or -O-. In embodiments, L^3 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(CH₃)C(O)NH-, or unsubstituted C₁-C₃ alkylene and L^4 is a bond, -CH₂O-, -C(O)-, -NH-, or -O-. In embodiments, L^3 is a bond. In
- 15 embodiments, L^3 is a bond. In embodiments, L^3 is -O-. In embodiments, L^3 is -C(O)-. In embodiments, L^3 is -S-. In embodiments, L^3 is -SO-. In embodiments, L^3 is -S(O)₂-. In embodiments, L^3 is -NR⁵-. In embodiments, L^3 is -NH-. In embodiments, L^3 is -NR⁵C(O)-. In embodiments, L^3 is -NHC(O)-. In embodiments, L^3 is -C(O)NR⁵-. In embodiments, L^3 is -C(O)NH-. In embodiments, L^3 is -SO₂NR⁵-. In embodiments, L^3 is -SO₂NH-. In
- 20 embodiments, L^3 is -NR⁵SO₂-. In embodiments, L^3 is -NHSO₂-. In embodiments, L^3 is -OC(O)NR⁵-. In embodiments, L^3 is -OC(O)NH-. In embodiments, L^3 is -NR⁵C(O)O-. In embodiments, L^3 is -NHC(O)O-. In embodiments, L^3 is substituted or unsubstituted C₁-C₆ alkylene. In embodiments, L^3 is substituted or unsubstituted 2 to 6 membered heteroalkylene. In embodiments, L^3 is unsubstituted methylene. In embodiments, L^3 is a bond.

[0172] In embodiments, L^4 is a bond. In embodiments, L^4 is -O-. In embodiments, L^4 is -C(O)-. In embodiments, L^4 is -S-. In embodiments, L^4 is -SO-. In embodiments, L^4 is -S(O)₂-. In embodiments, L^4 is -NR⁴-. In embodiments, L^4 is -NR⁴C(O)-. In embodiments, L^4 is -C(O)NR⁴-. In embodiments, L^4 is -SO₂NR⁴-. In embodiments, L^4 is -NR⁴SO₂-. In
 5 embodiments, L^4 is -OC(O)NR⁴-. In embodiments, L^4 is -NR⁴C(O)O-. In embodiments, L^4 is substituted or unsubstituted C₁-C₃ alkylene. In embodiments, L^4 is substituted or unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^4 is -NH-. In embodiments, L^4 is -NHC(O)-. In embodiments, L^4 is -C(O)NH-. In embodiments, L^4 is -SO₂NH-. In embodiments, L^4 is -NHSO₂-. In embodiments, L^4 is -NHSO₂-. In embodiments, L^4 is -OC(O)NH-. In
 10 embodiments, L^4 is -NHC(O)O-. In embodiments, L^4 is unsubstituted C₁-C₃ alkylene. In embodiments, L^4 is unsubstituted 2 to 3 membered heteroalkylene. In embodiments, L^4 is -CH₂NH-. In embodiments, L^4 is an unsubstituted methylene.

[0173] In embodiments, Ring A is a C₃-C₇ cycloalkyl. In embodiments, Ring A is a 3 to 7 membered heterocycloalkyl. In embodiments, Ring A is a C₅-C₇ cycloalkyl. In embodiments,
 15 Ring A is a 5 to 7 membered heterocycloalkyl. In embodiments, Ring A is a C₃ cycloalkyl. In embodiments, Ring A is a C₄ cycloalkyl. In embodiments, Ring A is a C₅ cycloalkyl. In embodiments, Ring A is a C₆ cycloalkyl. In embodiments, Ring A is a C₇ cycloalkyl. In embodiments, Ring A is a saturated C₃ cycloalkyl. In embodiments, Ring A is a saturated C₄ cycloalkyl. In embodiments, Ring A is a saturated C₅ cycloalkyl. In embodiments, Ring A is a saturated C₆ cycloalkyl. In embodiments, Ring A is a saturated C₇ cycloalkyl. In embodiments,
 20 Ring A is an unsaturated C₃ cycloalkyl. In embodiments, Ring A is an unsaturated C₄ cycloalkyl. In embodiments, Ring A is an unsaturated C₅ cycloalkyl. In embodiments, Ring A is an unsaturated C₆ cycloalkyl. In embodiments, Ring A is an unsaturated C₇ cycloalkyl. In embodiments, Ring A is a 3 membered heterocycloalkyl. In embodiments, Ring A is a 4
 25 membered heterocycloalkyl. In embodiments, Ring A is a 5 membered heterocycloalkyl. In embodiments, Ring A is a 6 membered heterocycloalkyl. In embodiments, Ring A is a 7 membered heterocycloalkyl. In embodiments, Ring A is a saturated 3 membered heterocycloalkyl. In embodiments, Ring A is a saturated 4 membered heterocycloalkyl. In embodiments, Ring A is a saturated 5 membered heterocycloalkyl. In embodiments, Ring A is a saturated 6 membered heterocycloalkyl. In embodiments, Ring A is a saturated 7 membered
 30 heterocycloalkyl. In embodiments, Ring A is an unsaturated 3 membered heterocycloalkyl. In embodiments, Ring A is an unsaturated 4 membered heterocycloalkyl. In embodiments, Ring A is an unsaturated 5 membered heterocycloalkyl. In embodiments, Ring A is an unsaturated 6 membered heterocycloalkyl. In embodiments, Ring A is an unsaturated 7 membered

heterocycloalkyl. In embodiments, Ring A is an aziridinyl. In embodiments, Ring A is an aziriny. In embodiments, Ring A is a diaziridinyl. In embodiments, Ring A is a diaziriny. In embodiments, Ring A is an azetidiny. In embodiments, Ring A is an azety. In embodiments, Ring A is a diazetidinyl. In embodiments, Ring A is adiazety. In embodiments, Ring A is a piperidinyl. In embodiments, Ring A is pyrrolidinyl. In embodiments, Ring A is azepanyl. In 5
embodiments, Ring A is a N-piperidinyl. In embodiments, Ring A is N-pyrrolidinyl. In embodiments, Ring A is N-azepanyl. In embodiments, Ring A is a 1-piperidinyl. In embodiments, Ring A is 1-pyrrolidinyl. In embodiments, Ring A is 1-azepanyl. In embodiments, Ring A is piperazinyl. In embodiments, Ring A is imidazolidinyl. In 10
embodiments, Ring A is pyrazolidinyl. In embodiments, Ring A is oxazolidinyl. In embodiments, Ring A is isoxazolidinyl. In embodiments, Ring A is thiazolidinyl. In embodiments, Ring A is isothiazolidinyl. In embodiments, Ring A is pyridinyl. In embodiments, Ring A is pyranly. In embodiments, Ring A is thiopyranly. In embodiments, Ring A is oxany. In embodiments, Ring A is thianly. In embodiments, Ring A is morpholinyl. 15
In embodiments, Ring A is thiomorpholinyl. In embodiments, Ring A is dioxany. In embodiments, Ring A is dithianly. In embodiments, Ring A is diazinyl. In embodiments, Ring A is oxazinyl. In embodiments, Ring A is thiazinyl. In embodiments, Ring A is dioxinyl. In embodiments, Ring A is dithiinyl.

[0174] In embodiments, Y is CH. In embodiments, Y is N. In embodiments, Y is C.

20 **[0175]** In embodiments, R¹ is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -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, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, 25
substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹ is independently
halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -COOH, -OCX¹₃, -OCHX¹₂, -CH₃, -CH₂CH₃, -OC
H₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R¹ is independently halogen or -OCH₃.
30 In embodiments, R¹ is substituted or unsubstituted C₁-C₆ alkyl. In embodiments, R¹ is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R¹ is substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R¹ is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R¹ is substituted or unsubstituted C₆ aryl. In

embodiments, R^1 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is independently halogen. In embodiments, R^1 is independently $-CX^1_3$. In embodiments, R^1 is independently $-CHX^1_2$. In embodiments, R^1 is independently $-CH_2X^1$. In embodiments, R^1 is independently $-OH$. In embodiments, R^1 is independently $-SH$. In embodiments, R^1 is independently $-COOH$. In embodiments, R^1 is independently $-OCX^1_3$. In embodiments, R^1 is independently $-OCHX^1_2$. In embodiments, R^1 is independently $-CH_3$. In embodiments, R^1 is independently $-CH_2CH_3$. In embodiments, R^1 is independently $-OCH_3$. In embodiments, R^1 is independently $-OCH_2CH_3$. In embodiments, R^1 is independently $-SCH_3$. In embodiments, R^1 is independently $-SCH_2CH_3$. In embodiments, R^1 is independently $-Cl$ or $-OCH_3$. In

embodiments, R^1 is independently halogen, $-CX^1_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-OCX^1_3$, $-OCHX^1_2$, $-CHX^1_2$, $-CH_2X^1$, substituted or unsubstituted C_1 - C_8 alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is independently halogen, $-CX^1_3$, $-CN$, unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^1 is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R^1 is independently unsubstituted methyl. In embodiments, R^1 is independently unsubstituted ethyl. In embodiments, R^1 is independently unsubstituted propyl. In embodiments, R^1 is independently unsubstituted n-propyl. In embodiments, R^1 is independently unsubstituted isopropyl. In embodiments, R^1 is independently unsubstituted butyl. In embodiments, R^1 is independently unsubstituted n-butyl. In embodiments, R^1 is independently unsubstituted isobutyl. In embodiments, R^1 is independently unsubstituted tert-butyl. In embodiments, R^1 is independently unsubstituted pentyl. In embodiments, R^1 is independently unsubstituted hexyl. In embodiments, R^1 is independently unsubstituted heptyl. In embodiments, R^1 is independently unsubstituted octyl. In embodiments, R^1 is independently $-F$. In embodiments, R^1 is independently $-Cl$. In embodiments, R^1 is independently $-Br$. In embodiments, R^1 is independently $-I$. In embodiments, R^1 is independently unsubstituted methoxy. In embodiments, R^1 is independently unsubstituted ethoxy. In embodiments, R^1 is independently $-CF_3$. In embodiments, R^1 is independently $-CCl_3$. In embodiments, R^1 is an unsubstituted isopropyl. In embodiments, R^1 is an unsubstituted phenyl. In embodiments, R^1 is an unsubstituted pyridyl. In embodiments, R^1 is independently halogen. In embodiments, R^1 is independently $-CX^1_3$. In embodiments, R^1 is independently $-CHX^1_2$. In embodiments, R^1 is independently $-CH_2X^1$. In embodiments, R^1 is

independently -CN. In embodiments, R^1 is independently -OH. In embodiments, R^1 is independently -NH₂. In embodiments, R^1 is independently -COOH. In embodiments, R^1 is independently -CONH₂. In embodiments, R^1 is independently -NO₂. In embodiments, R^1 is independently -SH. In embodiments, R^1 is independently -SO₂Cl. In embodiments, R^1 is independently -SO₃H. In embodiments, R^1 is independently -SO₄H. In embodiments, R^1 is independently -SO₂NH₂. In embodiments, R^1 is independently -NHNH₂. In embodiments, R^1 is independently -ONH₂. In embodiments, R^1 is independently -NHC(O)NHNH₂. In embodiments, R^1 is independently -NHC(O)NH₂. In embodiments, R^1 is independently -NHSO₂H. In embodiments, R^1 is independently -NHC(O)H. In embodiments, R^1 is independently -NHC(O)OH. In embodiments, R^1 is independently -NHOH. In embodiments, R^1 is independently -OCX₃¹. In embodiments, R^1 is independently -OCHX₂¹. In embodiments, R^1 is independently substituted or unsubstituted alkyl. In embodiments, R^1 is independently substituted or unsubstituted heteroalkyl. In embodiments, R^1 is independently substituted or unsubstituted cycloalkyl. In embodiments, R^1 is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R^1 is independently substituted or unsubstituted aryl. In embodiments, R^1 is independently substituted or unsubstituted heteroaryl. In embodiments, R^1 is independently substituted alkyl. In embodiments, R^1 is independently substituted heteroalkyl. In embodiments, R^1 is independently substituted cycloalkyl. In embodiments, R^1 is independently substituted heterocycloalkyl. In embodiments, R^1 is independently substituted aryl. In embodiments, R^1 is independently substituted heteroaryl. In embodiments, R^1 is independently substituted alkyl. In embodiments, R^1 is independently unsubstituted heteroalkyl. In embodiments, R^1 is independently unsubstituted cycloalkyl. In embodiments, R^1 is independently unsubstituted heterocycloalkyl. In embodiments, R^1 is independently unsubstituted aryl. In embodiments, R^1 is independently unsubstituted heteroaryl. In embodiments, R^1 is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R^1 is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^1 is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^1 is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^1 is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R^1 is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^1 is independently substituted C₁-C₈ alkyl. In embodiments, R^1 is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R^1 is independently substituted C₃-C₈ cycloalkyl. In embodiments, R^1 is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^1 is independently substituted C₆-C₁₀ aryl. In embodiments, R^1 is independently

- substituted 5 to 10 membered heteroaryl. In embodiments, R^1 is independently unsubstituted C_1 - C_8 alkyl. In embodiments, R^1 is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^1 is independently unsubstituted C_3 - C_8 cycloalkyl. In embodiments, R^1 is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^1 is
- 5 independently unsubstituted C_6 - C_{10} aryl. In embodiments, R^1 is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^1 is independently substituted or unsubstituted C_1 - C_4 alkyl. In embodiments, R^1 is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^1 is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In embodiments, R^1 is independently substituted or unsubstituted 3 to 6 membered
- 10 heterocycloalkyl. In embodiments, R^1 is independently substituted or unsubstituted phenyl. In embodiments, R^1 is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^1 is independently substituted C_1 - C_4 alkyl. In embodiments, R^1 is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R^1 is independently substituted C_3 - C_6 cycloalkyl. In embodiments, R^1 is independently substituted 3 to 6 membered heterocycloalkyl.
- 15 In embodiments, R^1 is independently substituted phenyl. In embodiments, R^1 is independently substituted 5 to 6 membered heteroaryl. In embodiments, R^1 is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^1 is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^1 is independently unsubstituted C_3 - C_6 cycloalkyl. In embodiments, R^1 is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^1 is
- 20 independently unsubstituted phenyl. In embodiments, R^1 is independently unsubstituted 5 to 6 membered heteroaryl.

- [0176]** In embodiments, $R^{1.1}$ is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^1_3$, $-OCHX^1_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_6 aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^{1.1}$ is independently
- 25 halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OH$, $-SH$, $-COOH$, $-OCX^1_3$, $-OCHX^1_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-SCH_3$, or $-SCH_2CH_3$. In embodiments, $R^{1.1}$ is independently halogen or $-OCH_3$. In embodiments, $R^{1.1}$ is substituted or unsubstituted C_1 - C_6 alkyl. In embodiments, $R^{1.1}$ is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, $R^{1.1}$ is substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1.1}$ is substituted or unsubstituted 3 to 8

membered heterocycloalkyl. In embodiments, $R^{1.1}$ is substituted or unsubstituted C_6 aryl. In
 embodiments, $R^{1.1}$ is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments,
 $R^{1.1}$ is independently halogen. In embodiments, $R^{1.1}$ is independently $-CX^1_3$. In embodiments,
 $R^{1.1}$ is independently $-CHX^1_2$. In embodiments, $R^{1.1}$ is independently $-CH_2X^1$. In embodiments,
 5 $R^{1.1}$ is independently $-OH$. In embodiments, $R^{1.1}$ is independently $-SH$. In embodiments, $R^{1.1}$ is
 independently $-COOH$. In embodiments, $R^{1.1}$ is independently $-OCX^1_3$. In embodiments, $R^{1.1}$ is
 independently $-OCHX^1_2$. In embodiments, $R^{1.1}$ is independently $-CH_3$. In embodiments, $R^{1.1}$ is
 independently $-CH_2CH_3$. In embodiments, $R^{1.1}$ is independently $-OCH_3$. In embodiments, $R^{1.1}$ is
 independently $-OCH_2CH_3$. In embodiments, $R^{1.1}$ is independently $-SCH_3$. In embodiments, $R^{1.1}$
 10 is independently $-SCH_2CH_3$. In embodiments, $R^{1.1}$ is independently $-Cl$ or $-OCH_3$. In
 embodiments, $R^{1.1}$ is independently
 halogen, $-CX^1_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-OCX^1_3$, $-OCHX^1_2$, $-CHX^1_2$, $-C$
 H_2X^1 , substituted or unsubstituted C_1 - C_8 alkyl, or substituted or unsubstituted 2 to 8 membered
 heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8
 15 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5
 to 6 membered heteroaryl. In embodiments, $R^{1.1}$ is independently halogen, $-CX^1_3$, $-CN$,
 unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, $R^{1.1}$ is
 independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or
 unsubstituted tert-butyl. In embodiments, $R^{1.1}$ is independently unsubstituted methyl. In
 20 embodiments, $R^{1.1}$ is independently unsubstituted ethyl. In embodiments, $R^{1.1}$ is independently
 unsubstituted propyl. In embodiments, $R^{1.1}$ is independently unsubstituted n-propyl. In
 embodiments, $R^{1.1}$ is independently unsubstituted isopropyl. In embodiments, $R^{1.1}$ is
 independently unsubstituted butyl. In embodiments, $R^{1.1}$ is independently unsubstituted n-butyl.
 In embodiments, $R^{1.1}$ is independently unsubstituted isobutyl. In embodiments, $R^{1.1}$ is
 25 independently unsubstituted tert-butyl. In embodiments, $R^{1.1}$ is independently unsubstituted
 pentyl. In embodiments, $R^{1.1}$ is independently unsubstituted hexyl. In embodiments, $R^{1.1}$ is
 independently unsubstituted heptyl. In embodiments, $R^{1.1}$ is independently unsubstituted octyl.
 In embodiments, $R^{1.1}$ is independently $-F$. In embodiments, $R^{1.1}$ is independently $-Cl$. In
 embodiments, $R^{1.1}$ is independently $-Br$. In embodiments, $R^{1.1}$ is independently $-I$. In
 30 embodiments, $R^{1.1}$ is independently unsubstituted methoxy. In embodiments, $R^{1.1}$ is
 independently unsubstituted ethoxy. In embodiments, $R^{1.1}$ is independently $-CF_3$. In
 embodiments, $R^{1.1}$ is independently $-CCl_3$. In embodiments, $R^{1.1}$ is an unsubstituted isopropyl.
 In embodiments, $R^{1.1}$ is an unsubstituted phenyl. In embodiments, $R^{1.1}$ is an unsubstituted
 pyridyl. In embodiments, $R^{1.1}$ is independently halogen. In embodiments, $R^{1.1}$ is

independently $-CX^1_3$. In embodiments, $R^{1.1}$ is independently $-CHX^1_2$. In embodiments, $R^{1.1}$ is independently $-CH_2X^1$. In embodiments, $R^{1.1}$ is independently $-CN$. In embodiments, $R^{1.1}$ is independently $-OH$. In embodiments, $R^{1.1}$ is independently $-NH_2$. In embodiments, $R^{1.1}$ is independently $-COOH$. In embodiments, $R^{1.1}$ is independently $-CONH_2$. In embodiments, $R^{1.1}$ is independently $-NO_2$. In embodiments, $R^{1.1}$ is independently $-SH$. In embodiments, $R^{1.1}$ is independently $-SO_2Cl$. In embodiments, $R^{1.1}$ is independently $-SO_3H$. In embodiments, $R^{1.1}$ is independently $-SO_4H$. In embodiments, $R^{1.1}$ is independently $-SO_2NH_2$. In embodiments, $R^{1.1}$ is independently $-NHNH_2$. In embodiments, $R^{1.1}$ is independently $-ONH_2$. In embodiments, $R^{1.1}$ is independently $-NHC(O)NHNH_2$. In embodiments, $R^{1.1}$ is independently $-NHC(O)NH_2$. In embodiments, $R^{1.1}$ is independently $-NHSO_2H$. In embodiments, $R^{1.1}$ is independently $-NHC(O)H$. In embodiments, $R^{1.1}$ is independently $-NHC(O)OH$. In embodiments, $R^{1.1}$ is independently $-NHOH$. In embodiments, $R^{1.1}$ is independently $-OCX^1_3$. In embodiments, $R^{1.1}$ is independently $-OCHX^1_2$. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted alkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted aryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted heteroaryl. In embodiments, $R^{1.1}$ is independently substituted alkyl. In embodiments, $R^{1.1}$ is independently substituted heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted aryl. In embodiments, $R^{1.1}$ is independently substituted heteroaryl. In embodiments, $R^{1.1}$ is independently unsubstituted alkyl. In embodiments, $R^{1.1}$ is independently unsubstituted heteroalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted cycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted heterocycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted aryl. In embodiments, $R^{1.1}$ is independently unsubstituted heteroaryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C_1 - C_8 alkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C_6 - C_{10} aryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, $R^{1.1}$ is independently substituted C_1 - C_8 alkyl. In embodiments, $R^{1.1}$ is independently substituted 2 to 8 membered heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1.1}$ is independently

- substituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted C_6 - C_{10} aryl. In embodiments, $R^{1.1}$ is independently substituted 5 to 10 membered heteroaryl. In embodiments, $R^{1.1}$ is independently unsubstituted C_1 - C_8 alkyl. In embodiments, $R^{1.1}$ is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, $R^{1.1}$ is
- 5 independently unsubstituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted C_6 - C_{10} aryl. In embodiments, $R^{1.1}$ is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C_1 - C_4 alkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 2 to 4 membered
- 10 heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted C_3 - C_6 cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted phenyl. In embodiments, $R^{1.1}$ is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^{1.1}$ is independently substituted C_1 - C_4 alkyl. In embodiments, $R^{1.1}$ is
- 15 independently substituted 2 to 4 membered heteroalkyl. In embodiments, $R^{1.1}$ is independently substituted C_3 - C_6 cycloalkyl. In embodiments, $R^{1.1}$ is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently substituted phenyl. In embodiments, $R^{1.1}$ is independently substituted 5 to 6 membered heteroaryl. In embodiments, $R^{1.1}$ is independently unsubstituted C_1 - C_4 alkyl. In embodiments, $R^{1.1}$ is independently unsubstituted 2
- 20 to 4 membered heteroalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted C_3 - C_6 cycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, $R^{1.1}$ is independently unsubstituted phenyl. In embodiments, $R^{1.1}$ is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^{1.1}$ is independently hydrogen.
- 25 **[0177]** In embodiments, $R^{1.2}$ is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^1_3$, $-OCHX^1_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl,
- 30 substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_6 aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^{1.2}$ is independently
- halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OH$, $-SH$, $-COOH$, $-OCX^1_3$, $-OCHX^1_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-SCH_3$, or $-SCH_2CH_3$. In embodiments, $R^{1.2}$ is independently halogen or $-OCH_3$.

In embodiments, $R^{1,2}$ is substituted or unsubstituted C_1 - C_6 alkyl. In embodiments, $R^{1,2}$ is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, $R^{1,2}$ is substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1,2}$ is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1,2}$ is substituted or unsubstituted C_6 aryl. In

5 In embodiments, $R^{1,2}$ is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^{1,2}$ is independently halogen. In embodiments, $R^{1,2}$ is independently $-CX^1_3$. In embodiments, $R^{1,2}$ is independently $-CHX^1_2$. In embodiments, $R^{1,2}$ is independently $-CH_2X^1$. In embodiments, $R^{1,2}$ is independently $-OH$. In embodiments, $R^{1,2}$ is independently $-SH$. In embodiments, $R^{1,2}$ is independently $-COOH$. In embodiments, $R^{1,2}$ is independently $-OCX^1_3$. In embodiments, $R^{1,2}$ is

10 independently $-OCHX^1_2$. In embodiments, $R^{1,2}$ is independently $-CH_3$. In embodiments, $R^{1,2}$ is independently $-CH_2CH_3$. In embodiments, $R^{1,2}$ is independently $-OCH_3$. In embodiments, $R^{1,2}$ is independently $-OCH_2CH_3$. In embodiments, $R^{1,2}$ is independently $-SCH_3$. In embodiments, $R^{1,2}$ is independently $-SCH_2CH_3$. In embodiments, $R^{1,2}$ is independently $-Cl$ or $-OCH_3$. In

embodiments, $R^{1,2}$ is independently

15 halogen, $-CX^1_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-OCX^1_3$, $-OCHX^1_2$, $-CHX^1_2$, $-C$
 H_2X^1 , substituted or unsubstituted C_1 - C_8 alkyl, or substituted or unsubstituted 2 to 8 membered
heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8
membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5
to 6 membered heteroaryl. In embodiments, $R^{1,2}$ is independently halogen, $-CX^1_3$, $-CN$,

20 unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, $R^{1,2}$ is
independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or
unsubstituted tert-butyl. In embodiments, $R^{1,2}$ is independently unsubstituted methyl. In
embodiments, $R^{1,2}$ is independently unsubstituted ethyl. In embodiments, $R^{1,2}$ is independently
unsubstituted propyl. In embodiments, $R^{1,2}$ is independently unsubstituted n-propyl. In

25 embodiments, $R^{1,2}$ is independently unsubstituted isopropyl. In embodiments, $R^{1,2}$ is
independently unsubstituted butyl. In embodiments, $R^{1,2}$ is independently unsubstituted n-butyl.
In embodiments, $R^{1,2}$ is independently unsubstituted isobutyl. In embodiments, $R^{1,2}$ is
independently unsubstituted tert-butyl. In embodiments, $R^{1,2}$ is independently unsubstituted
pentyl. In embodiments, $R^{1,2}$ is independently unsubstituted hexyl. In embodiments, $R^{1,2}$ is

30 independently unsubstituted heptyl. In embodiments, $R^{1,2}$ is independently unsubstituted octyl.
In embodiments, $R^{1,2}$ is independently $-F$. In embodiments, $R^{1,2}$ is independently $-Cl$. In
embodiments, $R^{1,2}$ is independently $-Br$. In embodiments, $R^{1,2}$ is independently $-I$. In
embodiments, $R^{1,2}$ is independently unsubstituted methoxy. In embodiments, $R^{1,2}$ is
independently unsubstituted ethoxy. In embodiments, $R^{1,2}$ is independently $-CF_3$. In

embodiments, $R^{1,2}$ is independently $-CCl_3$. In embodiments, $R^{1,2}$ is an unsubstituted isopropyl. In embodiments, $R^{1,2}$ is an unsubstituted phenyl. In embodiments, $R^{1,2}$ is an unsubstituted pyridyl. In embodiments, $R^{1,2}$ is independently halogen. In embodiments, $R^{1,2}$ is independently $-CX^1_3$. In embodiments, $R^{1,2}$ is independently $-CHX^1_2$. In embodiments, $R^{1,2}$ is independently $-CH_2X^1$. In embodiments, $R^{1,2}$ is independently $-CN$. In embodiments, $R^{1,2}$ is independently $-OH$. In embodiments, $R^{1,2}$ is independently $-NH_2$. In embodiments, $R^{1,2}$ is independently $-COOH$. In embodiments, $R^{1,2}$ is independently $-CONH_2$. In embodiments, $R^{1,2}$ is independently $-NO_2$. In embodiments, $R^{1,2}$ is independently $-SH$. In embodiments, $R^{1,2}$ is independently $-SO_2Cl$. In embodiments, $R^{1,2}$ is independently $-SO_3H$. In embodiments, $R^{1,2}$ is independently $-SO_4H$. In embodiments, $R^{1,2}$ is independently $-SO_2NH_2$. In embodiments, $R^{1,2}$ is independently $-NHNH_2$. In embodiments, $R^{1,2}$ is independently $-ONH_2$. In embodiments, $R^{1,2}$ is independently $-NHC(O)NHNH_2$. In embodiments, $R^{1,2}$ is independently $-NHC(O)NH_2$. In embodiments, $R^{1,2}$ is independently $-NHSO_2H$. In embodiments, $R^{1,2}$ is independently $-NHC(O)H$. In embodiments, $R^{1,2}$ is independently $-NHC(O)OH$. In embodiments, $R^{1,2}$ is independently $-NHOH$. In embodiments, $R^{1,2}$ is independently $-OCX^1_3$. In embodiments, $R^{1,2}$ is independently $-OCHX^1_2$. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted alkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted heteroalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted cycloalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted heterocycloalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted aryl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted heteroaryl. In embodiments, $R^{1,2}$ is independently substituted alkyl. In embodiments, $R^{1,2}$ is independently substituted heteroalkyl. In embodiments, $R^{1,2}$ is independently substituted cycloalkyl. In embodiments, $R^{1,2}$ is independently substituted heterocycloalkyl. In embodiments, $R^{1,2}$ is independently substituted aryl. In embodiments, $R^{1,2}$ is independently substituted heteroaryl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted C_1 - C_8 alkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted C_6 - C_{10} aryl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted 5 to 10

membered heteroaryl. In embodiments, $R^{1,2}$ is independently substituted C_1 - C_8 alkyl. In
embodiments, $R^{1,2}$ is independently substituted 2 to 8 membered heteroalkyl. In embodiments,
 $R^{1,2}$ is independently substituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1,2}$ is independently
substituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1,2}$ is independently substituted
5 C_6 - C_{10} aryl. In embodiments, $R^{1,2}$ is independently substituted 5 to 10 membered heteroaryl. In
embodiments, $R^{1,2}$ is independently unsubstituted C_1 - C_8 alkyl. In embodiments, $R^{1,2}$ is
independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, $R^{1,2}$ is
independently unsubstituted C_3 - C_8 cycloalkyl. In embodiments, $R^{1,2}$ is independently
unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, $R^{1,2}$ is independently
10 unsubstituted C_6 - C_{10} aryl. In embodiments, $R^{1,2}$ is independently unsubstituted 5 to 10
membered heteroaryl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted C_1 - C_4
alkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted 2 to 4 membered
heteroalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted C_3 - C_6
cycloalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted 3 to 6 membered
15 heterocycloalkyl. In embodiments, $R^{1,2}$ is independently substituted or unsubstituted phenyl. In
embodiments, $R^{1,2}$ is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In
embodiments, $R^{1,2}$ is independently substituted C_1 - C_4 alkyl. In embodiments, $R^{1,2}$ is
independently substituted 2 to 4 membered heteroalkyl. In embodiments, $R^{1,2}$ is independently
substituted C_3 - C_6 cycloalkyl. In embodiments, $R^{1,2}$ is independently substituted 3 to 6 membered
20 heterocycloalkyl. In embodiments, $R^{1,2}$ is independently substituted phenyl. In embodiments,
 $R^{1,2}$ is independently substituted 5 to 6 membered heteroaryl. In embodiments, $R^{1,2}$ is
independently unsubstituted C_1 - C_4 alkyl. In embodiments, $R^{1,2}$ is independently unsubstituted 2
to 4 membered heteroalkyl. In embodiments, $R^{1,2}$ is independently unsubstituted C_3 - C_6
cycloalkyl. In embodiments, $R^{1,2}$ is independently unsubstituted 3 to 6 membered
25 heterocycloalkyl. In embodiments, $R^{1,2}$ is independently unsubstituted phenyl. In embodiments,
 $R^{1,2}$ is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, $R^{1,2}$ is
independently hydrogen.

[0178] In embodiments, z_1 is 2. In embodiments, z_1 is 3. In embodiments, z_1 is 0. In
embodiments, z_1 is 1. In embodiments, z_1 is 4. In embodiments, z_1 is 5.

30 **[0179]** In embodiments, R^2 is independently hydrogen, oxo, halogen, CX^2_3 , $-CHX^2_2$, $-$
 CH_2X^2 , $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$,
 $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-$
 $NHC(O)OH$, $-NHOH$, $-OCX^2_3$, $-OCHX^2_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or

- unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently oxo, halogen, CX²₃, -CHX²₂, -
- 5 CH₂X², -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, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆
- 10 aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently hydrogen, halogen, CX²₃, -CHX²₂, -CH₂X², -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, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or
- 15 unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently oxo, halogen, -CX²₃, -CHX²₂, -CH₂X², -OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OC
- 20 H₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R² is independently hydrogen, halogen, -CX²₃, -CHX²₂, -CH₂X², -OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OC H₂CH₃, -SCH₃, or -SCH₂CH₃. In embodiments, R² is independently hydrogen. In embodiments, R² is independently halogen. In embodiments, R² is independently unsubstituted methyl. In
- 25 embodiments, two adjacent R² substituents or two R² substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl. In embodiments, two adjacent R² substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R² is independently halogen, -CX²₃, -CHX²₂, -
- 30 CH₂X², -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, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆

aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^2 is independently

halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OH$, $-SH$, $-COOH$, $-OCX^2_3$, $-OCHX^2_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-SCH_3$, or $-SCH_2CH_3$. In embodiments, R^2 is independently halogen or $-OCH_3$.

- 5 In embodiments, R^2 is substituted or unsubstituted C_1 - C_6 alkyl. In embodiments, R^2 is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^2 is substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, R^2 is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^2 is substituted or unsubstituted C_6 aryl. In embodiments, R^2 is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments,
- 10 R^2 is independently halogen. In embodiments, R^2 is independently $-CX^2_3$. In embodiments, R^2 is independently $-CHX^2_2$. In embodiments, R^2 is independently $-CH_2X^2$. In embodiments, R^2 is independently $-OH$. In embodiments, R^2 is independently $-SH$. In embodiments, R^2 is independently $-COOH$. In embodiments, R^2 is independently $-OCX^2_3$. In embodiments, R^2 is independently $-OCHX^2_2$. In embodiments, R^2 is independently $-CH_3$. In embodiments, R^2 is
- 15 independently $-CH_2CH_3$. In embodiments, R^2 is independently $-OCH_3$. In embodiments, R^2 is independently $-OCH_2CH_3$. In embodiments, R^2 is independently $-SCH_3$. In embodiments, R^2 is independently $-SCH_2CH_3$. In embodiments, R^2 is independently $-Cl$ or $-OCH_3$. In embodiments, R^2 is independently
- 20 halogen, $-CX^2_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-OCX^2_3$, $-OCHX^2_2$, $-CHX^2_2$, $-CH_2X^2$, substituted or unsubstituted C_1 - C_8 alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^2 is independently halogen, $-CX^2_3$, $-CN$, unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^2 is
- 25 independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R^2 is independently unsubstituted methyl. In embodiments, R^2 is independently unsubstituted ethyl. In embodiments, R^2 is independently unsubstituted propyl. In embodiments, R^2 is independently unsubstituted n-propyl. In embodiments, R^2 is independently unsubstituted isopropyl. In embodiments, R^2 is independently
- 30 unsubstituted butyl. In embodiments, R^2 is independently unsubstituted n-butyl. In embodiments, R^2 is independently unsubstituted isobutyl. In embodiments, R^2 is independently unsubstituted tert-butyl. In embodiments, R^2 is independently unsubstituted pentyl. In embodiments, R^2 is independently unsubstituted hexyl. In embodiments, R^2 is independently unsubstituted heptyl. In embodiments, R^2 is independently unsubstituted octyl. In embodiments,

R^2 is independently -F. In embodiments, R^2 is independently -Cl. In embodiments, R^2 is independently -Br. In embodiments, R^2 is independently -I. In embodiments, R^2 is independently unsubstituted methoxy. In embodiments, R^2 is independently unsubstituted ethoxy. In embodiments, R^2 is independently -CF₃. In embodiments, R^2 is independently -CCl₃.
 5 In embodiments, R^2 is an unsubstituted isopropyl. In embodiments, R^2 is an unsubstituted phenyl. In embodiments, R^2 is an unsubstituted pyridyl. In embodiments, R^2 is independently halogen. In embodiments, R^2 is independently -CX₃². In embodiments, R^2 is independently -CHX₂². In embodiments, R^2 is independently -CH₂X². In embodiments, R^2 is independently -CN. In embodiments, R^2 is independently -OH. In embodiments, R^2 is
 10 independently -NH₂. In embodiments, R^2 is independently -COOH. In embodiments, R^2 is independently -CONH₂. In embodiments, R^2 is independently -NO₂. In embodiments, R^2 is independently -SH. In embodiments, R^2 is independently -SO₂Cl. In embodiments, R^2 is independently -SO₃H. In embodiments, R^2 is independently -SO₄H. In embodiments, R^2 is independently -SO₂NH₂. In embodiments, R^2 is independently -NHNH₂. In embodiments, R^2 is
 15 independently -ONH₂. In embodiments, R^2 is independently -NHC(O)NHNH₂. In embodiments, R^2 is independently -NHC(O)NH₂. In embodiments, R^2 is independently -NHSO₂H. In embodiments, R^2 is independently -NHC(O)H. In embodiments, R^2 is independently -NHC(O)OH. In embodiments, R^2 is independently -NHOH. In embodiments, R^2 is independently -OCX₃². In embodiments, R^2 is independently -OCHX₂². In embodiments, R^2
 20 is independently substituted or unsubstituted alkyl. In embodiments, R^2 is independently substituted or unsubstituted heteroalkyl. In embodiments, R^2 is independently substituted or unsubstituted cycloalkyl. In embodiments, R^2 is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R^2 is independently substituted or unsubstituted aryl. In embodiments, R^2 is independently substituted or unsubstituted heteroaryl. In embodiments, R^2 is
 25 independently substituted alkyl. In embodiments, R^2 is independently substituted heteroalkyl. In embodiments, R^2 is independently substituted cycloalkyl. In embodiments, R^2 is independently substituted heterocycloalkyl. In embodiments, R^2 is independently substituted aryl. In embodiments, R^2 is independently substituted heteroaryl. In embodiments, R^2 is independently unsubstituted alkyl. In embodiments, R^2 is independently unsubstituted heteroalkyl. In
 30 embodiments, R^2 is independently unsubstituted cycloalkyl. In embodiments, R^2 is independently unsubstituted heterocycloalkyl. In embodiments, R^2 is independently unsubstituted aryl. In embodiments, R^2 is independently unsubstituted heteroaryl. In embodiments, R^2 is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R^2 is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^2

- is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R² is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R² is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R² is independently substituted C₁-C₈ alkyl. In embodiments, R² is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R² is independently substituted C₃-C₈ cycloalkyl. In embodiments, R² is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is independently substituted C₆-C₁₀ aryl. In embodiments, R² is independently substituted 5 to 10 membered heteroaryl. In embodiments, R² is independently unsubstituted C₁-C₈ alkyl. In embodiments, R² is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R² is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R² is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R² is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R² is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R² is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R² is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R² is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R² is independently substituted or unsubstituted phenyl. In embodiments, R² is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R² is independently substituted C₁-C₄ alkyl. In embodiments, R² is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently substituted C₃-C₆ cycloalkyl. In embodiments, R² is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R² is independently substituted phenyl. In embodiments, R² is independently substituted 5 to 6 membered heteroaryl. In embodiments, R² is independently unsubstituted C₁-C₄ alkyl. In embodiments, R² is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently unsubstituted C₃-C₆ cycloalkyl. In embodiments, R² is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R² is independently unsubstituted phenyl. In embodiments, R² is independently unsubstituted 5 to 6 membered heteroaryl.
- [0180] In embodiments, z₂ is 0. In embodiments, z₂ is 1. In embodiments, z₂ is 2. In embodiments, z₂ is 3. In embodiments, z₂ is 4. In embodiments, z₂ is 5. In embodiments, z₂ is 6. In embodiments, z₂ is 7. In embodiments, z₂ is 8. In embodiments, z₂ is 9. In embodiments, z₂ is 10.

[0181] In embodiments, R⁴ is hydrogen. In embodiments, R⁵ is hydrogen. In embodiments, R⁴ is unsubstituted methyl. In embodiments, R⁴ is unsubstituted ethyl. In embodiments, R⁴ is unsubstituted propyl. In embodiments, R⁴ is unsubstituted butyl. In embodiments, R⁵ is unsubstituted methyl. In embodiments, R⁵ is unsubstituted ethyl. In embodiments, R⁵ is unsubstituted propyl. In embodiments, R⁵ is unsubstituted butyl. In embodiments, R⁴ is substituted or unsubstituted alkyl. In embodiments, R⁴ is substituted or unsubstituted heteroalkyl. In embodiments, R⁴ is substituted or unsubstituted cycloalkyl. In embodiments, R⁴ is substituted or unsubstituted heterocycloalkyl. In embodiments, R⁴ is substituted or unsubstituted aryl. In embodiments, R⁴ is substituted or unsubstituted heteroaryl. In embodiments, R⁵ is substituted or unsubstituted alkyl. In embodiments, R⁵ is substituted or unsubstituted heteroalkyl. In embodiments, R⁵ is substituted or unsubstituted cycloalkyl. In embodiments, R⁵ is substituted or unsubstituted heterocycloalkyl. In embodiments, R⁵ is substituted or unsubstituted aryl. In embodiments, R⁵ is substituted or unsubstituted heteroaryl.

[0182] In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7A}-, -NR^{7A}C(O)-, -C(O)NR^{7A}-, -SO₂NR^{7A}-, -NR^{7A}SO₂-, -OC(O)NR^{7A}-, -NR^{7A}C(O)O-, -CR^{9A}=NO-, -ON=CR^{9A}-, -NR^{8A}C(O)NR^{7A}-, -NR^{8A}C(=NR^{10A})NR^{7A}-, -NR^{8A}C(=NR^{10A})-, -C(=NR^{10A})NR^{7A}-, -OC(=NR^{10A})-, -C(=NR^{10A})O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0183] In embodiments, L¹ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0184] In embodiments, L^1 is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^1 is a bond, unsubstituted C_1 - C_4 alkylene, or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^1 is a bond. In embodiments, L^1 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L^1 is a bond. In embodiments, L^1 is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C_1 - C_4 alkylene, or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^1 is -NH-. In embodiments, L^1 is -CH(CH₂Cl)CH₂-. In embodiments, L^1 is -C(O)CH(CH₂Cl)CH₂-. In embodiments, L^1 is -NHC(O)CH(CH₂Cl)CH₂-. In embodiments, L^1 is halo-substituted C_1 - C_4 alkylene. In embodiments, L^1 is halo-substituted C_2 - C_4 alkylene. In embodiments, L^1 is halo-substituted C_3 - C_4 alkylene. In embodiments, L^1 is halo-substituted C_3 alkylene. In embodiments, L^1 is a bond. In embodiments, L^1 is -O-. In embodiments, L^1 is -C(O)-. In embodiments, L^1 is -S-. In embodiments, L^1 is -SO-. In embodiments, L^1 is -S(O)₂-. In embodiments, L^1 is -NH-. In embodiments, L^1 is -NHC(O)-. In embodiments, L^1 is -C(O)NH-. In embodiments, L^1 is -SO₂NH-. In embodiments, L^1 is -NHSO₂-. In embodiments, L^1 is -OC(O)NH-. In embodiments, L^1 is -NHC(O)O-. In embodiments, L^1 is -CH=NO-. In embodiments, L^1 is -ON=CH-. In embodiments, L^1 is -NHC(O)NH-. In embodiments, L^1 is -NHC(=NH)NH-. In embodiments, L^1 is -NHC(=NH)-. In embodiments, L^1 is -C(=NH)NH-. In embodiments, L^1 is -OC(=NH)-. In embodiments, L^1 is -C(=NH)O-.

[0185] In embodiments, L^1 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7A}-, -NR^{7A}C(O)-, -C(O)NR^{7A}-, -SO₂NR^{7A}-, -NR^{7A}SO₂-, -OC(O)NR^{7A}-, -NR^{7A}C(O)O-, -CR^{9A}=NO-, -ON=CR^{9A}-, -NR^{8A}C(O)NR^{7A}-, -NR^{8A}C(=NR^{10A})NR^{7A}-, -NR^{8A}C(=NR^{10A})-, -C(=NR^{10A})NR^{7A}-, -OC(=NR^{10A})-, -C(=NR^{10A})O-, R^{7A}-substituted or unsubstituted alkylene (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{7A}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7A}-substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{7A}-substituted or unsubstituted

heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7A} -substituted or unsubstituted arylene (e.g., C_6-C_{10} , C_{10} , or phenylene), or R^{7A} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0186] In embodiments, L^1 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -

- 5 NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, R^{7A} -substituted or unsubstituted alkylene (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{7A} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7A} -substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{7A} -substituted or
 10 unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7A} -substituted or unsubstituted arylene (e.g., C_6-C_{10} , C_{10} , or phenylene), or R^{7A} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0187] In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -

- 15 NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted
 20 cycloalkylene (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C_6-C_{10} , C_{10} , or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0188] In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -

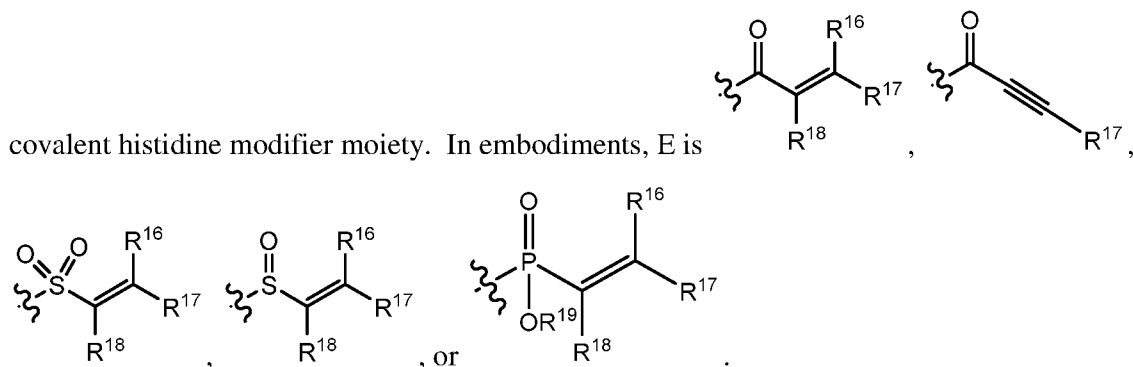
- 25 NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), substituted or unsubstituted
 30 heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C_6-C_{10} , C_{10} , or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

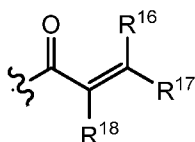
- [0189] In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NH₂SO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L^2 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene. In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NH₂SO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene. In embodiments, L^2 is a bond. In embodiments, L^2 is -NH-. In embodiments, L^2 is -CH(CH₂Cl)CH₂-. In embodiments, L^2 is -C(O)CH(CH₂Cl)CH₂-. In embodiments, L^2 is -NHC(O)CH(CH₂Cl)CH₂-. In embodiments, L^2 is -NHC(O)-. In embodiments, L^2 is -NH-. In embodiments, L^2 is halo-substituted C₁-C₄ alkylene. In embodiments, L^2 is halo-substituted C₂-C₄ alkylene. In embodiments, L^2 is halo-substituted C₃-C₄ alkylene. In embodiments, L^2 is halo-substituted C₃ alkylene.
- [0190] In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, R^{7B}-substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{7B}-substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7B}-substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{7B}-substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7B}-substituted or unsubstituted arylene (e.g., C₆-C₁₀, C₁₀, or phenylene), or R^{7B}-substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NH₂SO₂-, -OC(O)NH-, -NHC(O)O-, -CH=NO-, -ON=CH-, -NHC(O)NH-, -NHC(=NH)NH-, -NHC(=NH)-, -C(=NH)NH-, -OC(=NH)-, -C(=NH)O-, R^{7B}-substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{7B}-substituted or

unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{7B} -substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{7B} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{7B} -substituted or unsubstituted arylene (e.g., C_6 - C_{10} , C_{10} , or phenylene), or R^{7B} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0191] In embodiments, L^2 is . Ring C is a substituted or unsubstituted heterocycloalkylene or substituted or unsubstituted heteroarylene. In embodiments, Ring C is a substituted or unsubstituted 5 to 6 membered heterocycloalkylene or substituted or unsubstituted 5 to 6 membered heteroarylene. In embodiments, Ring C is an R^{7B} -substituted or unsubstituted heterocycloalkylene or R^{7B} -substituted or unsubstituted heteroarylene. In embodiments, Ring C is a R^{7B} -substituted or unsubstituted 5 to 6 membered heterocycloalkylene or R^{7B} -substituted or unsubstituted 5 to 6 membered heteroarylene.

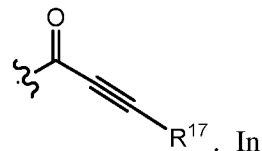
[0192] In embodiments, E is a covalent cysteine modifier moiety. In embodiments, E is a



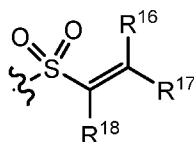


In embodiments, E is

. In embodiments, E is

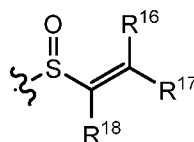


. In

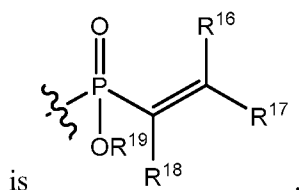


embodiments, E is

. In embodiments, E is



. In embodiments, E



is

.

[0193] R^{16} is independently hydrogen, halogen, CX^{16}_3 , $-CHX^{16}_2$, -

- 5 CH_2X^{16} , $-CN$, $-SO_2Cl$, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHN R^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$, $-NHC(=O)NHN R^{16A}R^{16B}$, $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
- 10 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{17} is independently hydrogen, halogen, CX^{17}_3 , $-CHX^{17}_2$, $-CH_2X^{17}$, $-CN$, $-SO_2Cl$, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHN R^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC(=O)NHN R^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$,
- 15 $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{18} is independently hydrogen, halogen, CX^{18}_3 , $-CHX^{18}_2$, $-CH_2X^{18}$, $-CN$, $-SO_2Cl$, $-SO_{n18}R^{18D}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHN R^{18A}R^{18B}$,
- 20 $-ONR^{18A}R^{18B}$, $-NHC(=O)NHN R^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18C}$, $-C(O)-OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, $-OR^{18D}$, $-NR^{18A}SO_2R^{18D}$, $-NR^{18A}C(O)R^{18C}$, $-NR^{18A}C(O)OR^{18C}$, $-NR^{18A}OR^{18C}$, $-OCX^{18}_3$, $-OCHX^{18}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
- 25 unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{19} is independently hydrogen,

- halogen, CX^{19}_3 , $-CHX^{19}_2$, $-CH_2X^{19}$, $-CN$, $-SO_2Cl$, $-SO_{n19}R^{19D}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHN R^{19A}R^{19B}$, $-ONR^{19A}R^{19B}$, $-NHC(=O)NHN R^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-C(O)R^{19C}$, $-C(O)-OR^{19C}$, $-C(O)NR^{19A}R^{19B}$, $-OR^{19D}$, $-NR^{19A}SO_2R^{19D}$, $-NR^{19A}C(O)R^{19C}$, $-NR^{19A}C(O)OR^{19C}$, $-NR^{19A}OR^{19C}$, $-OCX^{19}_3$, $-OCHX^{19}_2$,
- 5 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. R^{16A} , R^{16B} , R^{16C} , R^{16D} , R^{17A} , R^{17B} , R^{17C} , R^{17D} , R^{18A} , R^{18B} , R^{18C} , R^{18D} , R^{19A} , R^{19B} , R^{19C} , R^{19D} , are independently hydrogen, halogen, $-CX_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, -
- 10 SO_2NH_2 , $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be
- 15 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
- 20 heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. Each X , X^{16} , X^{17} , X^{18} and X^{19} is independently $-F$, $-Cl$, $-Br$, or $-I$. The symbols $n16$, $n17$, $n18$, $n19$, $v16$, $v17$, $v18$, and $v19$ are independently an integer from 0 to 4. The symbols $m16$, $m17$, $m18$, and $m19$ are independently an integer from 1 to 2. In embodiments, R^{18} is -
- 25 CN . In embodiments, R^{16} is unsubstituted methyl. In embodiments, R^{17} is unsubstituted methyl. In embodiments, R^{19} is unsubstituted methyl. In embodiments, R^{18} is hydrogen. In embodiments, R^{16} is hydrogen. In embodiments, R^{17} is hydrogen. In embodiments, R^{19} is hydrogen.

- [0194] X may independently be $-F$. X may independently be $-Cl$. X may independently be -
- 30 Br . X may independently be $-I$. X^{16} may independently be $-F$. X^{16} may independently be $-Cl$. X^{16} may independently be $-Br$. X^{16} may independently be $-I$. X^{17} may independently be $-F$. X^{17} may independently be $-Cl$. X^{17} may independently be $-Br$. X^{17} may independently be $-I$. X^{18} may independently be $-F$. X^{18} may independently be $-Cl$. X^{18} may independently be $-Br$.

X^{18} may independently be $-I$. X^{19} may independently be $-F$. X^{19} may independently be $-Cl$.
 X^{19} may independently be $-Br$. X^{19} may independently be $-I$.

[0195] n_{16} may independently be 0. n_{16} may independently be 1. n_{16} may independently be 2. n_{16} may independently be 3. n_{16} may independently be 4. n_{17} may independently be 0.

5 n_{17} may independently be 1. n_{17} may independently be 2. n_{17} may independently be 3. n_{17} may independently be 4. n_{18} may independently be 0. n_{18} may independently be 1. n_{18} may independently be 2. n_{18} may independently be 3. n_{18} may independently be 4. n_{19} may independently be 0. n_{19} may independently be 1. n_{19} may independently be 2. n_{19} may independently be 3. n_{19} may independently be 4.

10 **[0196]** v_{16} may independently be 0. v_{16} may independently be 1. v_{16} may independently be 2. v_{16} may independently be 3. v_{16} may independently be 4. v_{17} may independently be 0. v_{17} may independently be 1. v_{17} may independently be 2. v_{17} may independently be 3. v_{17} may independently be 4. v_{18} may independently be 0. v_{18} may independently be 1. v_{18} may independently be 2. v_{18} may independently be 3. v_{18} may independently be 4. v_{19} may independently be 0. v_{19} may independently be 1. v_{19} may independently be 2. v_{19} may independently be 3. v_{19} may independently be 4.

[0197] m_{16} may independently be 1. m_{16} may independently be 2. m_{17} may independently be 1. m_{17} may independently be 2. m_{18} may independently be 1. m_{18} may independently be 2. m_{19} may independently be 1. m_{19} may independently be 2.

20 **[0198]** In embodiments, R^{16} is hydrogen. In embodiments, R^{16} is halogen. In embodiments, R^{16} is CX^{16}_3 . In embodiments, R^{16} is $-CHX^{16}_2$. In embodiments, R^{16} is $-CH_2X^{16}$. In embodiments, R^{16} is $-CN$. In embodiments, R^{16} is $-SO_{n_{16}}R^{16D}$. In embodiments, R^{16} is $-SO_{v_{16}}NR^{16A}R^{16B}$. In embodiments, R^{16} is $-NHNr^{16A}R^{16B}$. In embodiments, R^{16} is $-ONR^{16A}R^{16B}$. In embodiments, R^{16} is $-NHC(=O)NHNr^{16A}R^{16B}$. In embodiments, R^{16} is $-NHC(O)NR^{16A}R^{16B}$. In embodiments, R^{16} is $-N(O)_{m_{16}}$. In embodiments, R^{16} is $-NR^{16A}R^{16B}$. In embodiments, R^{16} is $-C(O)R^{16C}$. In embodiments, R^{16} is $-C(O)-OR^{16C}$. In embodiments, R^{16} is $-C(O)NR^{16A}R^{16B}$. In embodiments, R^{16} is $-OR^{16D}$. In embodiments, R^{16} is $-NR^{16A}SO_2R^{16D}$. In embodiments, R^{16} is $-NR^{16A}C(O)R^{16C}$. In embodiments, R^{16} is $-NR^{16A}C(O)OR^{16C}$. In embodiments, R^{16} is $-NR^{16A}OR^{16C}$. In embodiments, R^{16} is $-OCX^{16}_3$. In embodiments, R^{16} is $-OCHX^{16}_2$. In embodiments, R^{16} is substituted or unsubstituted alkyl. In embodiments, R^{16} is substituted or unsubstituted heteroalkyl. In embodiments, R^{16} is substituted or unsubstituted cycloalkyl. In embodiments, R^{16} is substituted or unsubstituted heterocycloalkyl. In

embodiments, R^{16} is substituted or unsubstituted aryl. In embodiments, R^{16} is substituted or unsubstituted heteroaryl. In embodiments, R^{16} is substituted alkyl. In embodiments, R^{16} is substituted heteroalkyl. In embodiments, R^{16} is substituted cycloalkyl. In embodiments, R^{16} is substituted heterocycloalkyl. In embodiments, R^{16} is substituted aryl. In embodiments, R^{16} is substituted heteroaryl. In embodiments, R^{16} is unsubstituted alkyl. In embodiments, R^{16} is unsubstituted heteroalkyl. In embodiments, R^{16} is unsubstituted cycloalkyl. In embodiments, R^{16} is unsubstituted heterocycloalkyl. In embodiments, R^{16} is unsubstituted aryl. In embodiments, R^{16} is unsubstituted heteroaryl. In embodiments, R^{16} is unsubstituted methyl. In embodiments, R^{16} is unsubstituted ethyl. In embodiments, R^{16} is unsubstituted propyl. In embodiments, R^{16} is unsubstituted isopropyl. In embodiments, R^{16} is unsubstituted butyl. In embodiments, R^{16} is unsubstituted tert-butyl. In embodiments, R^{16} is $-\text{CH}_2\text{Ph}$. In embodiments, R^{16} is independently halogen, $-\text{CX}^{16}_3$, $-\text{CHX}^{16}_2$, $-\text{CH}_2\text{X}^{16}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCX}^{16}_3$, $-\text{OCHX}^{16}_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_6 aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{16} is independently halogen, $-\text{CX}^{16}_3$, $-\text{CHX}^{16}_2$, $-\text{CH}_2\text{X}^{16}$, $-\text{OH}$, $-\text{SH}$, $-\text{COOH}$, $-\text{OCX}^{16}_3$, $-\text{OCHX}^{16}_2$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{SCH}_3$, or $-\text{SCH}_2\text{CH}_3$. In embodiments, R^{16} is independently halogen or $-\text{OCH}_3$. In embodiments, R^{16} is substituted or unsubstituted C_1 - C_6 alkyl. In embodiments, R^{16} is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{16} is substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, R^{16} is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{16} is substituted or unsubstituted C_6 aryl. In embodiments, R^{16} is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{16} is independently halogen. In embodiments, R^{16} is independently $-\text{CX}^{16}_3$. In embodiments, R^{16} is independently $-\text{CHX}^{16}_2$. In embodiments, R^{16} is independently $-\text{CH}_2\text{X}^{16}$. In embodiments, R^{16} is independently $-\text{OH}$. In embodiments, R^{16} is independently $-\text{SH}$. In embodiments, R^{16} is independently $-\text{COOH}$. In embodiments, R^{16} is independently $-\text{OCX}^{16}_3$. In embodiments, R^{16} is independently $-\text{OCHX}^{16}_2$. In embodiments, R^{16} is independently $-\text{CH}_3$. In embodiments, R^{16} is independently $-\text{CH}_2\text{CH}_3$. In embodiments, R^{16} is independently $-\text{OCH}_3$. In embodiments, R^{16} is independently $-\text{OCH}_2\text{CH}_3$. In embodiments, R^{16} is independently $-\text{SCH}_3$. In embodiments, R^{16} is independently $-\text{SCH}_2\text{CH}_3$. In embodiments, R^{16} is independently $-\text{Cl}$ or $-\text{OCH}_3$. In

embodiments, R^{16} is independently halogen, $-CX^{16}_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-OCX^{16}_3$, $-OCHX^{16}_2$, $-CHX^{16}_2$, $-CH_2X^{16}$, substituted or unsubstituted C_1 - C_8 alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{16} is independently halogen, $-CX^{16}_3$, $-CN$, unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{16} is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R^{16} is independently unsubstituted methyl. In embodiments, R^{16} is independently unsubstituted ethyl. In embodiments, R^{16} is independently unsubstituted propyl. In embodiments, R^{16} is independently unsubstituted n-propyl. In embodiments, R^{16} is independently unsubstituted isopropyl. In embodiments, R^{16} is independently unsubstituted butyl. In embodiments, R^{16} is independently unsubstituted n-butyl. In embodiments, R^{16} is independently unsubstituted isobutyl. In embodiments, R^{16} is independently unsubstituted tert-butyl. In embodiments, R^{16} is independently unsubstituted pentyl. In embodiments, R^{16} is independently unsubstituted hexyl. In embodiments, R^{16} is independently unsubstituted heptyl. In embodiments, R^{16} is independently unsubstituted octyl. In embodiments, R^{16} is independently $-F$. In embodiments, R^{16} is independently $-Cl$. In embodiments, R^{16} is independently $-Br$. In embodiments, R^{16} is independently $-I$. In embodiments, R^{16} is independently unsubstituted methoxy. In embodiments, R^{16} is independently unsubstituted ethoxy. In embodiments, R^{16} is independently $-CF_3$. In embodiments, R^{16} is independently $-CCl_3$. In embodiments, R^{16} is an unsubstituted isopropyl. In embodiments, R^{16} is an unsubstituted phenyl. In embodiments, R^{16} is an unsubstituted pyridyl. In embodiments, R^{16} is independently halogen. In embodiments, R^{16} is independently $-CX^{16}_3$. In embodiments, R^{16} is independently $-CHX^{16}_2$. In embodiments, R^{16} is independently $-CH_2X^{16}$. In embodiments, R^{16} is independently $-CN$. In embodiments, R^{16} is independently $-OH$. In embodiments, R^{16} is independently $-NH_2$. In embodiments, R^{16} is independently $-COOH$. In embodiments, R^{16} is independently $-CONH_2$. In embodiments, R^{16} is independently $-NO_2$. In embodiments, R^{16} is independently $-SH$. In embodiments, R^{16} is independently $-SO_2Cl$. In embodiments, R^{16} is independently $-SO_3H$. In embodiments, R^{16} is independently $-SO_4H$. In embodiments, R^{16} is independently $-SO_2NH_2$. In embodiments, R^{16} is independently $-NHNH_2$. In embodiments, R^{16} is independently $-ONH_2$. In embodiments, R^{16} is independently $-NHC(O)NHNH_2$. In embodiments, R^{16} is independently $-NHC(O)NH_2$. In embodiments, R^{16} is independently $-NHSO_2H$. In embodiments, R^{16} is independently $-NHC(O)H$. In

embodiments, R^{16} is independently -NHC(O)OH. In embodiments, R^{16} is independently -NHOH. In embodiments, R^{16} is independently -OCX¹⁶₃. In embodiments, R^{16} is independently -OCHX¹⁶₂. In embodiments, R^{16} is independently substituted or unsubstituted alkyl. In embodiments, R^{16} is independently substituted or unsubstituted heteroalkyl. In 5 embodiments, R^{16} is independently substituted or unsubstituted cycloalkyl. In embodiments, R^{16} is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R^{16} is independently substituted or unsubstituted aryl. In embodiments, R^{16} is independently substituted or unsubstituted heteroaryl. In embodiments, R^{16} is independently substituted alkyl. In embodiments, R^{16} is independently substituted heteroalkyl. In embodiments, R^{16} is 10 independently substituted cycloalkyl. In embodiments, R^{16} is independently substituted heterocycloalkyl. In embodiments, R^{16} is independently substituted aryl. In embodiments, R^{16} is independently substituted heteroaryl. In embodiments, R^{16} is independently unsubstituted alkyl. In embodiments, R^{16} is independently unsubstituted heteroalkyl. In embodiments, R^{16} is 15 independently unsubstituted cycloalkyl. In embodiments, R^{16} is independently unsubstituted heterocycloalkyl. In embodiments, R^{16} is independently unsubstituted aryl. In embodiments, R^{16} is independently unsubstituted heteroaryl. In embodiments, R^{16} is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R^{16} is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{16} is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{16} is independently substituted or unsubstituted 3 to 8 20 membered heterocycloalkyl. In embodiments, R^{16} is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R^{16} is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{16} is independently substituted C₁-C₈ alkyl. In embodiments, R^{16} is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R^{16} is independently substituted C₃-C₈ cycloalkyl. In embodiments, R^{16} is independently 25 substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{16} is independently substituted C₆-C₁₀ aryl. In embodiments, R^{16} is independently substituted 5 to 10 membered heteroaryl. In embodiments, R^{16} is independently unsubstituted C₁-C₈ alkyl. In embodiments, R^{16} is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{16} is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{16} is independently unsubstituted 3 to 8 30 membered heterocycloalkyl. In embodiments, R^{16} is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R^{16} is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{16} is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R^{16} is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{16} is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R^{16} is

independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{16} is independently substituted or unsubstituted phenyl. In embodiments, R^{16} is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{16} is independently substituted C_1 - C_4 alkyl. In embodiments, R^{16} is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R^{16} is independently substituted C_3 - C_6 cycloalkyl. In embodiments, R^{16} is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{16} is independently substituted phenyl. In embodiments, R^{16} is independently substituted 5 to 6 membered heteroaryl. In embodiments, R^{16} is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^{16} is independently unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{16} is independently unsubstituted C_3 - C_6 cycloalkyl. In embodiments, R^{16} is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{16} is independently unsubstituted phenyl. In embodiments, R^{16} is independently unsubstituted 5 to 6 membered heteroaryl.

[0199] In embodiments, R^{16A} is hydrogen. In embodiments, R^{16A} is $-CX_3$. In embodiments, R^{16A} is $-CN$. In embodiments, R^{16A} is $-COOH$. In embodiments, R^{16A} is $-CONH_2$. In embodiments, R^{16A} is $-CHX_2$. In embodiments, R^{16A} is $-CH_2X$. In embodiments, R^{16A} is unsubstituted methyl. In embodiments, R^{16A} is unsubstituted ethyl. In embodiments, R^{16A} is unsubstituted propyl. In embodiments, R^{16A} is unsubstituted isopropyl. In embodiments, R^{16A} is unsubstituted butyl. In embodiments, R^{16A} is unsubstituted tert-butyl.

[0200] In embodiments, R^{16B} is hydrogen. In embodiments, R^{16B} is $-CX_3$. In embodiments, R^{16B} is $-CN$. In embodiments, R^{16B} is $-COOH$. In embodiments, R^{16B} is $-CONH_2$. In embodiments, R^{16B} is $-CHX_2$. In embodiments, R^{16B} is $-CH_2X$. In embodiments, R^{16B} is unsubstituted methyl. In embodiments, R^{16B} is unsubstituted ethyl. In embodiments, R^{16B} is unsubstituted propyl. In embodiments, R^{16B} is unsubstituted isopropyl. In embodiments, R^{16B} is unsubstituted butyl. In embodiments, R^{16B} is unsubstituted tert-butyl.

[0201] In embodiments, R^{16C} is hydrogen. In embodiments, R^{16C} is $-CX_3$. In embodiments, R^{16C} is $-CN$. In embodiments, R^{16C} is $-COOH$. In embodiments, R^{16C} is $-CONH_2$. In embodiments, R^{16C} is $-CHX_2$. In embodiments, R^{16C} is $-CH_2X$. In embodiments, R^{16C} is unsubstituted methyl. In embodiments, R^{16C} is unsubstituted ethyl. In embodiments, R^{16C} is unsubstituted propyl. In embodiments, R^{16C} is unsubstituted isopropyl. In embodiments, R^{16C} is unsubstituted butyl. In embodiments, R^{16C} is unsubstituted tert-butyl.

[0202] In embodiments, R^{16D} is hydrogen. In embodiments, R^{16D} is $-CX_3$. In embodiments, R^{16D} is $-CN$. In embodiments, R^{16D} is $-COOH$. In embodiments, R^{16D} is $-CONH_2$. In embodiments, R^{16D} is $-CHX_2$. In embodiments, R^{16D} is $-CH_2X$. In embodiments, R^{16D} is unsubstituted methyl. In embodiments, R^{16D} is unsubstituted ethyl. In embodiments, R^{16D} is unsubstituted propyl. In embodiments, R^{16D} is unsubstituted isopropyl. In embodiments, R^{16D} is unsubstituted butyl. In embodiments, R^{16D} is unsubstituted tert-butyl.

[0203] In embodiments, R^{17} is hydrogen. In embodiments, R^{17} is halogen. In embodiments, R^{17} is CX^{17}_3 . In embodiments, R^{17} is $-CHX^{17}_2$. In embodiments, R^{17} is $-CH_2X^{17}$. In embodiments, R^{17} is $-CN$. In embodiments, R^{17} is $-SO_{n17}R^{17D}$. In embodiments, R^{17} is $-SO_{v17}NR^{17A}R^{17B}$. In embodiments, R^{17} is $-NHN R^{17A}R^{17B}$. In embodiments, R^{17} is $-ONR^{17A}R^{17B}$. In embodiments, R^{17} is $-NHC=(O)NHN R^{17A}R^{17B}$. In embodiments, R^{17} is $-NHC(O)NR^{17A}R^{17B}$. In embodiments, R^{17} is $-N(O)_{m17}$. In embodiments, R^{17} is $-NR^{17A}R^{17B}$. In embodiments, R^{17} is $-C(O)R^{17C}$. In embodiments, R^{17} is $-C(O)-OR^{17C}$. In embodiments, R^{17} is $-C(O)NR^{17A}R^{17B}$. In embodiments, R^{17} is $-OR^{17D}$. In embodiments, R^{17} is $-NR^{17A}SO_2R^{17D}$. In embodiments, R^{17} is $-NR^{17A}C(O)R^{17C}$. In embodiments, R^{17} is $-NR^{17A}C(O)OR^{17C}$. In embodiments, R^{17} is $-NR^{17A}OR^{17C}$. In embodiments, R^{17} is $-OCX^{17}_3$. In embodiments, R^{17} is $-OCHX^{17}_2$. In embodiments, R^{17} is substituted or unsubstituted alkyl. In embodiments, R^{17} is substituted or unsubstituted heteroalkyl. In embodiments, R^{17} is substituted or unsubstituted cycloalkyl. In embodiments, R^{17} is substituted or unsubstituted heterocycloalkyl. In embodiments, R^{17} is substituted or unsubstituted aryl. In embodiments, R^{17} is substituted or unsubstituted heteroaryl. In embodiments, R^{17} is substituted alkyl. In embodiments, R^{17} is substituted heteroalkyl. In embodiments, R^{17} is substituted cycloalkyl. In embodiments, R^{17} is substituted heterocycloalkyl. In embodiments, R^{17} is substituted aryl. In embodiments, R^{17} is substituted heteroaryl. In embodiments, R^{17} is unsubstituted alkyl. In embodiments, R^{17} is unsubstituted heteroalkyl. In embodiments, R^{17} is unsubstituted cycloalkyl. In embodiments, R^{17} is unsubstituted heterocycloalkyl. In embodiments, R^{17} is unsubstituted aryl. In embodiments, R^{17} is unsubstituted heteroaryl. In embodiments, R^{17} is unsubstituted methyl. In embodiments, R^{17} is unsubstituted ethyl. In embodiments, R^{17} is unsubstituted propyl. In embodiments, R^{17} is unsubstituted isopropyl. In embodiments, R^{17} is unsubstituted butyl. In embodiments, R^{17} is unsubstituted tert-butyl. In embodiments, R^{17} is $-CH_2Ph$.

[0204] In embodiments, R^{17A} is hydrogen. In embodiments, R^{17A} is $-CX_3$. In embodiments, R^{17A} is $-CN$. In embodiments, R^{17A} is $-COOH$. In embodiments, R^{17A} is $-CONH_2$. In embodiments, R^{17A} is $-CHX_2$. In embodiments, R^{17A} is $-CH_2X$. In embodiments, R^{17A} is

unsubstituted methyl. In embodiments, R^{17A} is unsubstituted ethyl. In embodiments, R^{17A} is unsubstituted propyl. In embodiments, R^{17A} is unsubstituted isopropyl. In embodiments, R^{17A} is unsubstituted butyl. In embodiments, R^{17A} is unsubstituted tert-butyl.

5 [0205] In embodiments, R^{17B} is hydrogen. In embodiments, R^{17B} is $-CX_3$. In embodiments, R^{17B} is $-CN$. In embodiments, R^{17B} is $-COOH$. In embodiments, R^{17B} is $-CONH_2$. In embodiments, R^{17B} is $-CHX_2$. In embodiments, R^{17B} is $-CH_2X$. In embodiments, R^{17B} is unsubstituted methyl. In embodiments, R^{17B} is unsubstituted ethyl. In embodiments, R^{17B} is unsubstituted propyl. In embodiments, R^{17B} is unsubstituted isopropyl. In embodiments, R^{17B} is unsubstituted butyl. In embodiments, R^{17B} is unsubstituted tert-butyl.

10 [0206] In embodiments, R^{17C} is hydrogen. In embodiments, R^{17C} is $-CX_3$. In embodiments, R^{17C} is $-CN$. In embodiments, R^{17C} is $-COOH$. In embodiments, R^{17C} is $-CONH_2$. In embodiments, R^{17C} is $-CHX_2$. In embodiments, R^{17C} is $-CH_2X$. In embodiments, R^{17C} is unsubstituted methyl. In embodiments, R^{17C} is unsubstituted ethyl. In embodiments, R^{17C} is unsubstituted propyl. In embodiments, R^{17C} is unsubstituted isopropyl. In embodiments, R^{17C} is unsubstituted butyl. In embodiments, R^{17C} is unsubstituted tert-butyl.

[0207] In embodiments, R^{17D} is hydrogen. In embodiments, R^{17D} is $-CX_3$. In embodiments, R^{17D} is $-CN$. In embodiments, R^{17D} is $-COOH$. In embodiments, R^{17D} is $-CONH_2$. In embodiments, R^{17D} is $-CHX_2$. In embodiments, R^{17D} is $-CH_2X$. In embodiments, R^{17D} is unsubstituted methyl. In embodiments, R^{17D} is unsubstituted ethyl. In embodiments, R^{17D} is unsubstituted propyl. In embodiments, R^{17D} is unsubstituted isopropyl. In embodiments, R^{17D} is unsubstituted butyl. In embodiments, R^{17D} is unsubstituted tert-butyl.

[0208] In embodiments, R^{18} is hydrogen. In embodiments, R^{18} is halogen. In embodiments, R^{18} is CX^{18}_3 . In embodiments, R^{18} is $-CHX^{18}_2$. In embodiments, R^{18} is $-CH_2X^{18}$. In embodiments, R^{18} is $-CN$. In embodiments, R^{18} is $-SO_{n18}R^{18D}$. In embodiments, R^{18} is $-SO_{v18}NR^{18A}R^{18B}$. In embodiments, R^{18} is $-NHN R^{18A}R^{18B}$. In embodiments, R^{18} is $-ONR^{18A}R^{18B}$. In embodiments, R^{18} is $-NHC(=O)NHN R^{18A}R^{18B}$. In embodiments, R^{18} is $-NHC(O)NR^{18A}R^{18B}$. In embodiments, R^{18} is $-N(O)_{m18}$. In embodiments, R^{18} is $-NR^{18A}R^{18B}$. In embodiments, R^{18} is $-C(O)R^{18C}$. In embodiments, R^{18} is $-C(O)-OR^{18C}$. In embodiments, R^{18} is $-C(O)NR^{18A}R^{18B}$. In embodiments, R^{18} is $-OR^{18D}$. In embodiments, R^{18} is $-NR^{18A}SO_2R^{18D}$. In embodiments, R^{18} is $-NR^{18A}C(O)R^{18C}$. In embodiments, R^{18} is $-NR^{18A}C(O)OR^{18C}$. In embodiments, R^{18} is $-NR^{18A}OR^{18C}$. In embodiments, R^{18} is $-OCX^{18}_3$. In embodiments, R^{18} is $-OCHX^{18}_2$. In embodiments, R^{18} is substituted or unsubstituted alkyl. In embodiments, R^{18} is

substituted or unsubstituted heteroalkyl. In embodiments, R^{18} is substituted or unsubstituted cycloalkyl. In embodiments, R^{18} is substituted or unsubstituted heterocycloalkyl. In embodiments, R^{18} is substituted or unsubstituted aryl. In embodiments, R^{18} is substituted or unsubstituted heteroaryl. In embodiments, R^{18} is substituted alkyl. In embodiments, R^{18} is substituted heteroalkyl. In embodiments, R^{18} is substituted cycloalkyl. In embodiments, R^{18} is substituted heterocycloalkyl. In embodiments, R^{18} is substituted aryl. In embodiments, R^{18} is substituted heteroaryl. In embodiments, R^{18} is unsubstituted alkyl. In embodiments, R^{18} is unsubstituted heteroalkyl. In embodiments, R^{18} is unsubstituted cycloalkyl. In embodiments, R^{18} is unsubstituted heterocycloalkyl. In embodiments, R^{18} is unsubstituted aryl. In embodiments, R^{18} is unsubstituted heteroaryl. In embodiments, R^{18} is unsubstituted methyl. In embodiments, R^{18} is unsubstituted ethyl. In embodiments, R^{18} is unsubstituted propyl. In embodiments, R^{18} is unsubstituted isopropyl. In embodiments, R^{18} is unsubstituted butyl. In embodiments, R^{18} is unsubstituted tert-butyl. In embodiments, R^{18} is $-\text{CH}_2\text{Ph}$.

[0209] In embodiments, R^{18A} is hydrogen. In embodiments, R^{18A} is $-\text{CX}_3$. In embodiments, R^{18A} is $-\text{CN}$. In embodiments, R^{18A} is $-\text{COOH}$. In embodiments, R^{18A} is $-\text{CONH}_2$. In embodiments, R^{18A} is $-\text{CHX}_2$. In embodiments, R^{18A} is $-\text{CH}_2\text{X}$. In embodiments, R^{18A} is unsubstituted methyl. In embodiments, R^{18A} is unsubstituted ethyl. In embodiments, R^{18A} is unsubstituted propyl. In embodiments, R^{18A} is unsubstituted isopropyl. In embodiments, R^{18A} is unsubstituted butyl. In embodiments, R^{18A} is unsubstituted tert-butyl.

[0210] In embodiments, R^{18B} is hydrogen. In embodiments, R^{18B} is $-\text{CX}_3$. In embodiments, R^{18B} is $-\text{CN}$. In embodiments, R^{18B} is $-\text{COOH}$. In embodiments, R^{18B} is $-\text{CONH}_2$. In embodiments, R^{18B} is $-\text{CHX}_2$. In embodiments, R^{18B} is $-\text{CH}_2\text{X}$. In embodiments, R^{18B} is unsubstituted methyl. In embodiments, R^{18B} is unsubstituted ethyl. In embodiments, R^{18B} is unsubstituted propyl. In embodiments, R^{18B} is unsubstituted isopropyl. In embodiments, R^{18B} is unsubstituted butyl. In embodiments, R^{18B} is unsubstituted tert-butyl.

[0211] In embodiments, R^{18C} is hydrogen. In embodiments, R^{18C} is $-\text{CX}_3$. In embodiments, R^{18C} is $-\text{CN}$. In embodiments, R^{18C} is $-\text{COOH}$. In embodiments, R^{18C} is $-\text{CONH}_2$. In embodiments, R^{18C} is $-\text{CHX}_2$. In embodiments, R^{18C} is $-\text{CH}_2\text{X}$. In embodiments, R^{18C} is unsubstituted methyl. In embodiments, R^{18C} is unsubstituted ethyl. In embodiments, R^{18C} is unsubstituted propyl. In embodiments, R^{18C} is unsubstituted isopropyl. In embodiments, R^{18C} is unsubstituted butyl. In embodiments, R^{18C} is unsubstituted tert-butyl.

[0212] In embodiments, R^{18D} is hydrogen. In embodiments, R^{18D} is $-CX_3$. In embodiments, R^{18D} is $-CN$. In embodiments, R^{18D} is $-COOH$. In embodiments, R^{18D} is $-CONH_2$. In embodiments, R^{18D} is $-CHX_2$. In embodiments, R^{18D} is $-CH_2X$. In embodiments, R^{18D} is unsubstituted methyl. In embodiments, R^{18D} is unsubstituted ethyl. In embodiments, R^{18D} is unsubstituted propyl. In embodiments, R^{18D} is unsubstituted isopropyl. In embodiments, R^{18D} is unsubstituted butyl. In embodiments, R^{18D} is unsubstituted tert-butyl.

[0213] In embodiments, R^{19} is hydrogen. In embodiments, R^{19} is halogen. In embodiments, R^{19} is CX^{19}_3 . In embodiments, R^{19} is $-CHX^{19}_2$. In embodiments, R^{19} is $-CH_2X^{19}$. In embodiments, R^{19} is $-CN$. In embodiments, R^{19} is $-SO_{n19}R^{19D}$. In embodiments, R^{19} is $-SO_{v19}NR^{19A}R^{19B}$. In embodiments, R^{19} is $-NHNr^{19A}R^{19B}$. In embodiments, R^{19} is $-ONR^{19A}R^{19B}$. In embodiments, R^{19} is $-NHC=(O)NHNr^{19A}R^{19B}$. In embodiments, R^{19} is $-NHC(O)NR^{19A}R^{19B}$. In embodiments, R^{19} is $-N(O)_{m19}$. In embodiments, R^{19} is $-NR^{19A}R^{19B}$. In embodiments, R^{19} is $-C(O)R^{19C}$. In embodiments, R^{19} is $-C(O)-OR^{19C}$. In embodiments, R^{19} is $-C(O)NR^{19A}R^{19B}$. In embodiments, R^{19} is $-OR^{19D}$. In embodiments, R^{19} is $-NR^{19A}SO_2R^{19D}$. In embodiments, R^{19} is $-NR^{19A}C(O)R^{19C}$. In embodiments, R^{19} is $-NR^{19A}C(O)OR^{19C}$. In embodiments, R^{19} is $-NR^{19A}OR^{19C}$. In embodiments, R^{19} is $-OCX^{19}_3$. In embodiments, R^{19} is $-OCHX^{19}_2$. In embodiments, R^{19} is substituted or unsubstituted alkyl. In embodiments, R^{19} is substituted or unsubstituted heteroalkyl. In embodiments, R^{19} is substituted or unsubstituted cycloalkyl. In embodiments, R^{19} is substituted or unsubstituted heterocycloalkyl. In embodiments, R^{19} is substituted or unsubstituted aryl. In embodiments, R^{19} is substituted or unsubstituted heteroaryl. In embodiments, R^{19} is substituted alkyl. In embodiments, R^{19} is substituted heteroalkyl. In embodiments, R^{19} is substituted cycloalkyl. In embodiments, R^{19} is substituted heterocycloalkyl. In embodiments, R^{19} is substituted aryl. In embodiments, R^{19} is substituted heteroaryl. In embodiments, R^{19} is unsubstituted alkyl. In embodiments, R^{19} is unsubstituted heteroalkyl. In embodiments, R^{19} is unsubstituted cycloalkyl. In embodiments, R^{19} is unsubstituted heterocycloalkyl. In embodiments, R^{19} is unsubstituted aryl. In embodiments, R^{19} is unsubstituted heteroaryl. In embodiments, R^{19} is unsubstituted methyl. In embodiments, R^{19} is unsubstituted ethyl. In embodiments, R^{19} is unsubstituted propyl. In embodiments, R^{19} is unsubstituted isopropyl. In embodiments, R^{19} is unsubstituted butyl. In embodiments, R^{19} is unsubstituted tert-butyl. In embodiments, R^{19} is $-CH_2Ph$.

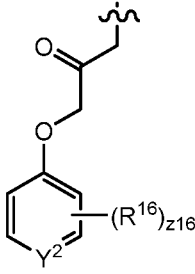
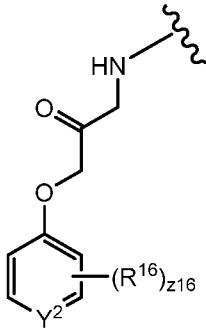
[0214] In embodiments, R^{19A} is hydrogen. In embodiments, R^{19A} is $-CX_3$. In embodiments, R^{19A} is $-CN$. In embodiments, R^{19A} is $-COOH$. In embodiments, R^{19A} is $-CONH_2$. In embodiments, R^{19A} is $-CHX_2$. In embodiments, R^{19A} is $-CH_2X$. In embodiments, R^{19A} is

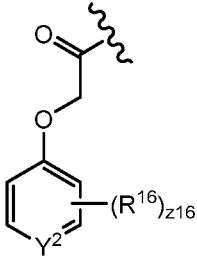
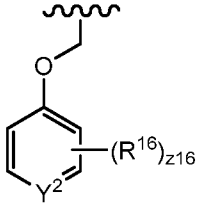
unsubstituted methyl. In embodiments, R^{19A} is unsubstituted ethyl. In embodiments, R^{19A} is unsubstituted propyl. In embodiments, R^{19A} is unsubstituted isopropyl. In embodiments, R^{19A} is unsubstituted butyl. In embodiments, R^{19A} is unsubstituted tert-butyl.

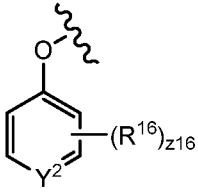
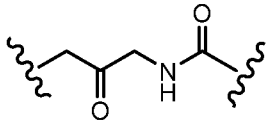
5 [0215] In embodiments, R^{19B} is hydrogen. In embodiments, R^{19B} is $-CX_3$. In embodiments, R^{19B} is $-CN$. In embodiments, R^{19B} is $-COOH$. In embodiments, R^{19B} is $-CONH_2$. In embodiments, R^{19B} is $-CHX_2$. In embodiments, R^{19B} is $-CH_2X$. In embodiments, R^{19B} is unsubstituted methyl. In embodiments, R^{19B} is unsubstituted ethyl. In embodiments, R^{19B} is unsubstituted propyl. In embodiments, R^{19B} is unsubstituted isopropyl. In embodiments, R^{19B} is unsubstituted butyl. In embodiments, R^{19B} is unsubstituted tert-butyl.

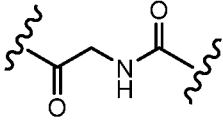
10 [0216] In embodiments, R^{19C} is hydrogen. In embodiments, R^{19C} is $-CX_3$. In embodiments, R^{19C} is $-CN$. In embodiments, R^{19C} is $-COOH$. In embodiments, R^{19C} is $-CONH_2$. In embodiments, R^{19C} is $-CHX_2$. In embodiments, R^{19C} is $-CH_2X$. In embodiments, R^{19C} is unsubstituted methyl. In embodiments, R^{19C} is unsubstituted ethyl. In embodiments, R^{19C} is unsubstituted propyl. In embodiments, R^{19C} is unsubstituted isopropyl. In embodiments, R^{19C} is
15 unsubstituted butyl. In embodiments, R^{19C} is unsubstituted tert-butyl.

[0217] In embodiments, R^{19D} is hydrogen. In embodiments, R^{19D} is $-CX_3$. In embodiments, R^{19D} is $-CN$. In embodiments, R^{19D} is $-COOH$. In embodiments, R^{19D} is $-CONH_2$. In
embodiments, R^{19D} is $-CHX_2$. In embodiments, R^{19D} is $-CH_2X$. In embodiments, R^{19D} is
unsubstituted methyl. In embodiments, R^{19D} is unsubstituted ethyl. In embodiments, R^{19D} is
20 unsubstituted propyl. In embodiments, R^{19D} is unsubstituted isopropyl. In embodiments, R^{19D} is
unsubstituted butyl. In embodiments, R^{19D} is unsubstituted tert-butyl.

[0218] In embodiments, E is . In embodiments, E is . In

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

is . In embodiments, $-L^2-L^1-L^4-$ is . In

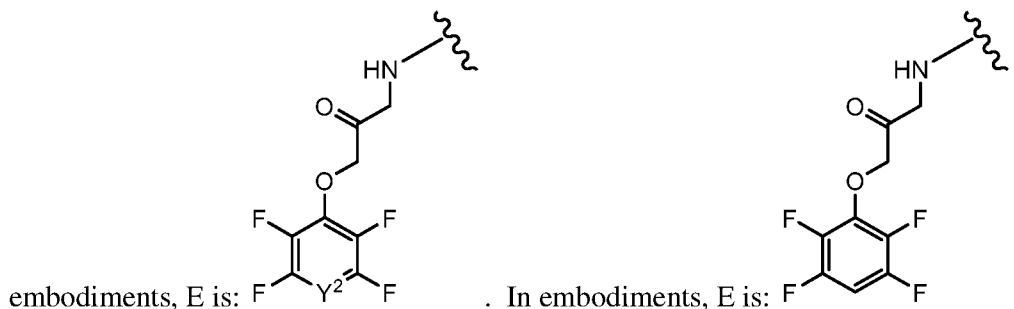
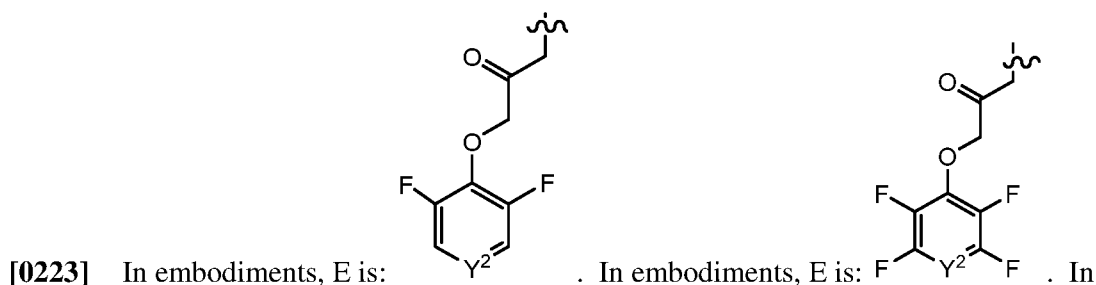
embodiments, $-L^2-L^1-L^4-$ is . In embodiments, $-L^2-L^1-L^4-$ is $-\text{CH}_2\text{NHC(O)}-$.

- 5 [0219] In embodiments, R^{16} is independently halogen, CX^{16}_3 , $-\text{CHX}^{16}_2$, $-\text{CH}_2\text{X}^{16}$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCX}^{16}_3$, $-\text{OCHX}^{16}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In
- 10 embodiments, R^{16} is independently halogen. In embodiments, R^{16} is independently $-\text{F}$.

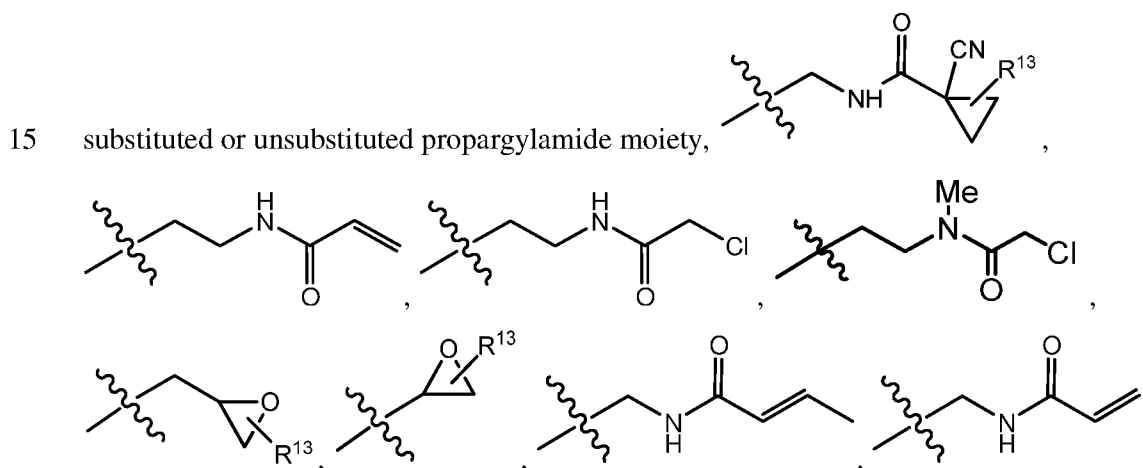
[0220] Y^2 is N or CH. In embodiments, Y^2 is CH. In embodiments, Y^2 is N.

[0221] The symbol z_{16} is an integer from 0 to 4. Each X^{16} is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$.

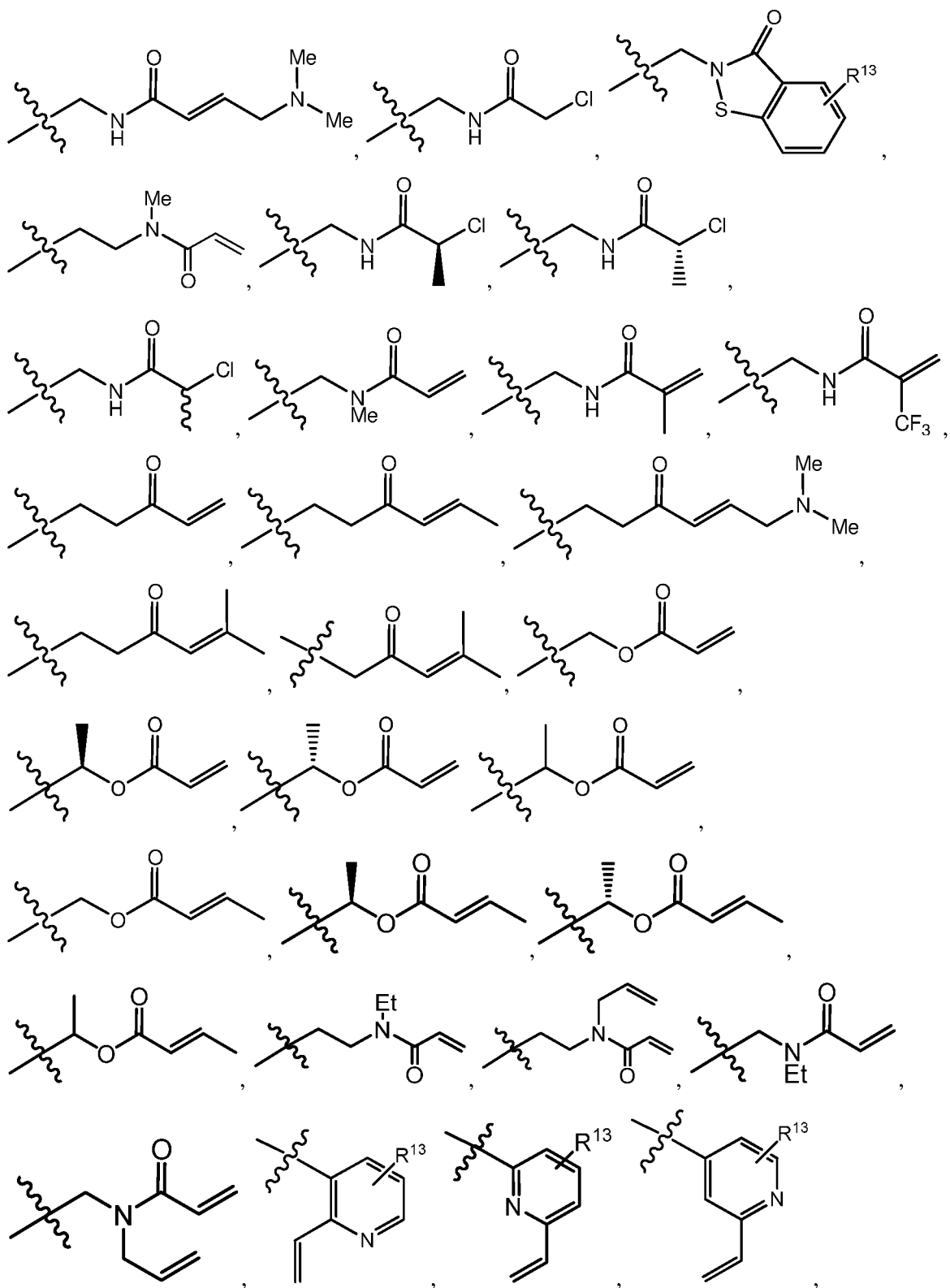
- [0222] In embodiments, z_{16} is 4. In embodiments, z_{16} is 2. In embodiments, z_{16} is 1. In
- 15 embodiments, z_{16} is 0. In embodiments, z_{16} is 3.

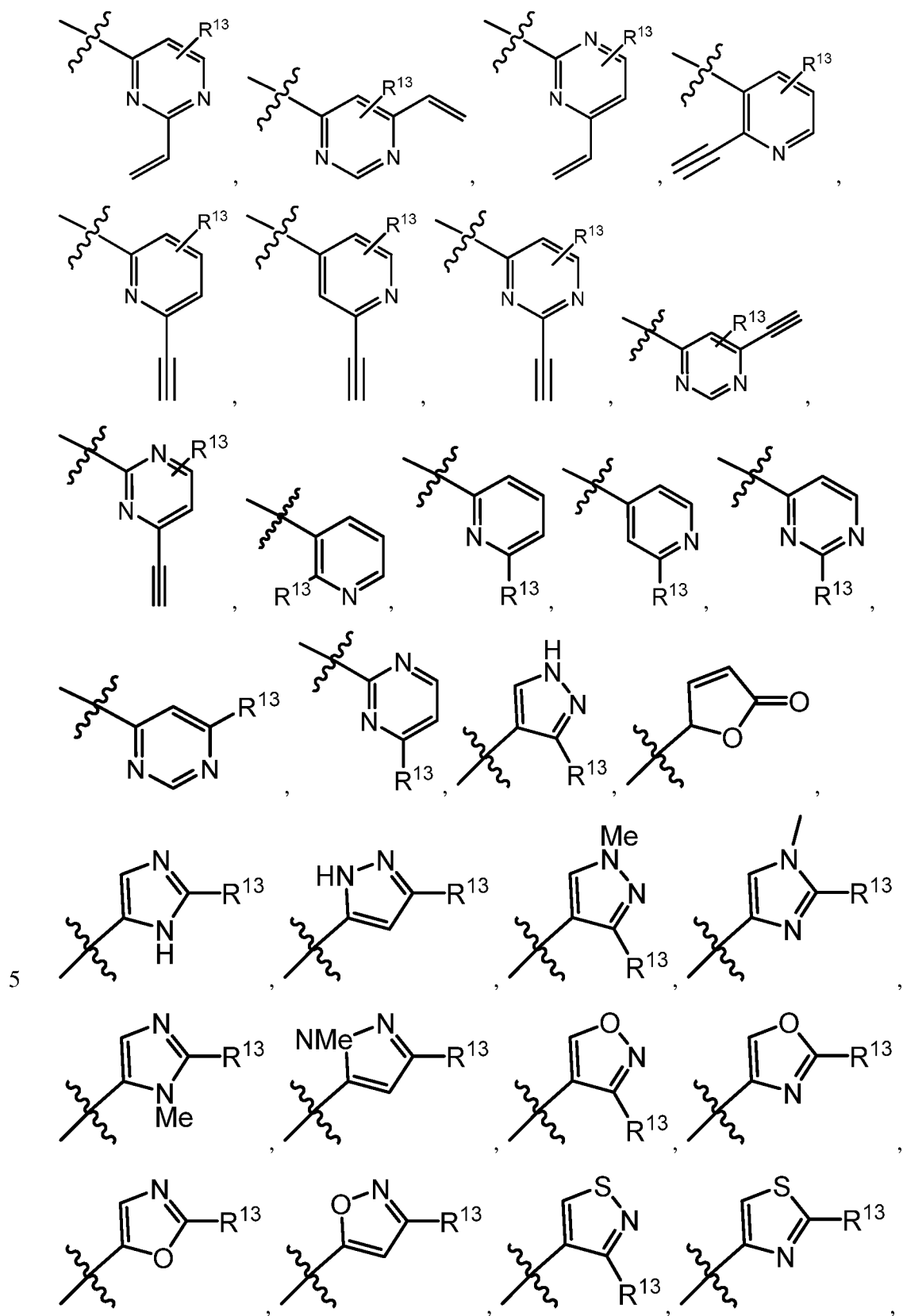


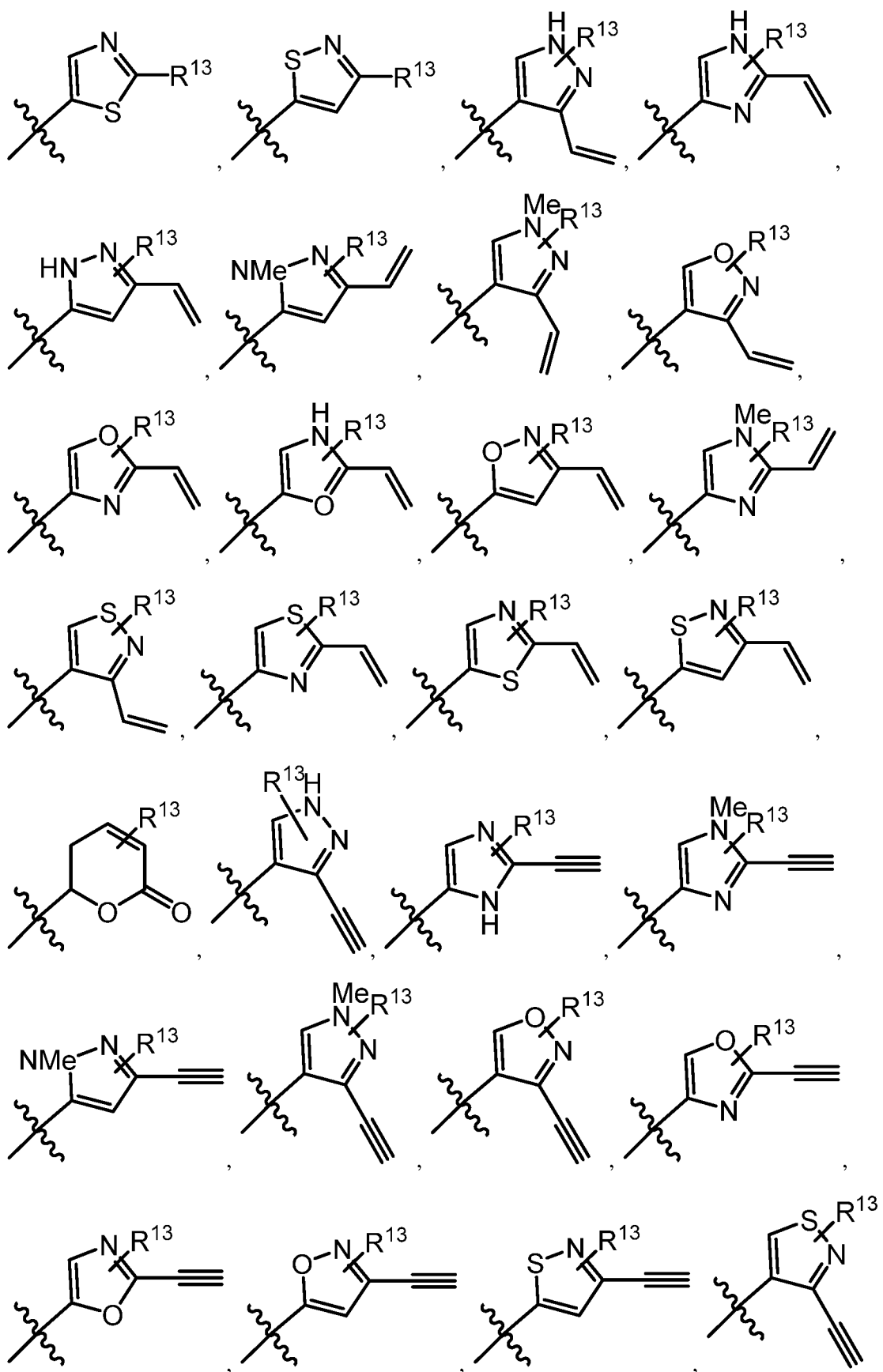
[0224] In embodiments, E comprises a substituted or unsubstituted vinyl sulfone moiety, substituted or unsubstituted vinyl sulfonamide moiety, substituted or unsubstituted fluoro(C₁-C₄)alkylketone moiety, substituted or unsubstituted chloro(C₁-C₄)alkylketone moiety, substituted or unsubstituted acrylamide moiety, substituted or unsubstituted disulfide moiety, substituted or unsubstituted thiol moiety, substituted or unsubstituted phosphonate moiety, substituted or unsubstituted aldehyde moiety, substituted or unsubstituted enone moiety, substituted or unsubstituted diazomethylketone moiety, substituted or unsubstituted diazomethylamide moiety, substituted or unsubstituted cyanocyclopropyl carboxamide moiety, substituted or unsubstituted epoxide moiety, substituted or unsubstituted epoxyketone moiety, substituted or unsubstituted epoxyamide moiety, substituted or unsubstituted aryl aldehyde moiety, substituted or unsubstituted aryl dialdehyde moiety, substituted or unsubstituted dialdehyde moiety, substituted or unsubstituted nitrogen mustard moiety, substituted or unsubstituted propargyl moiety,

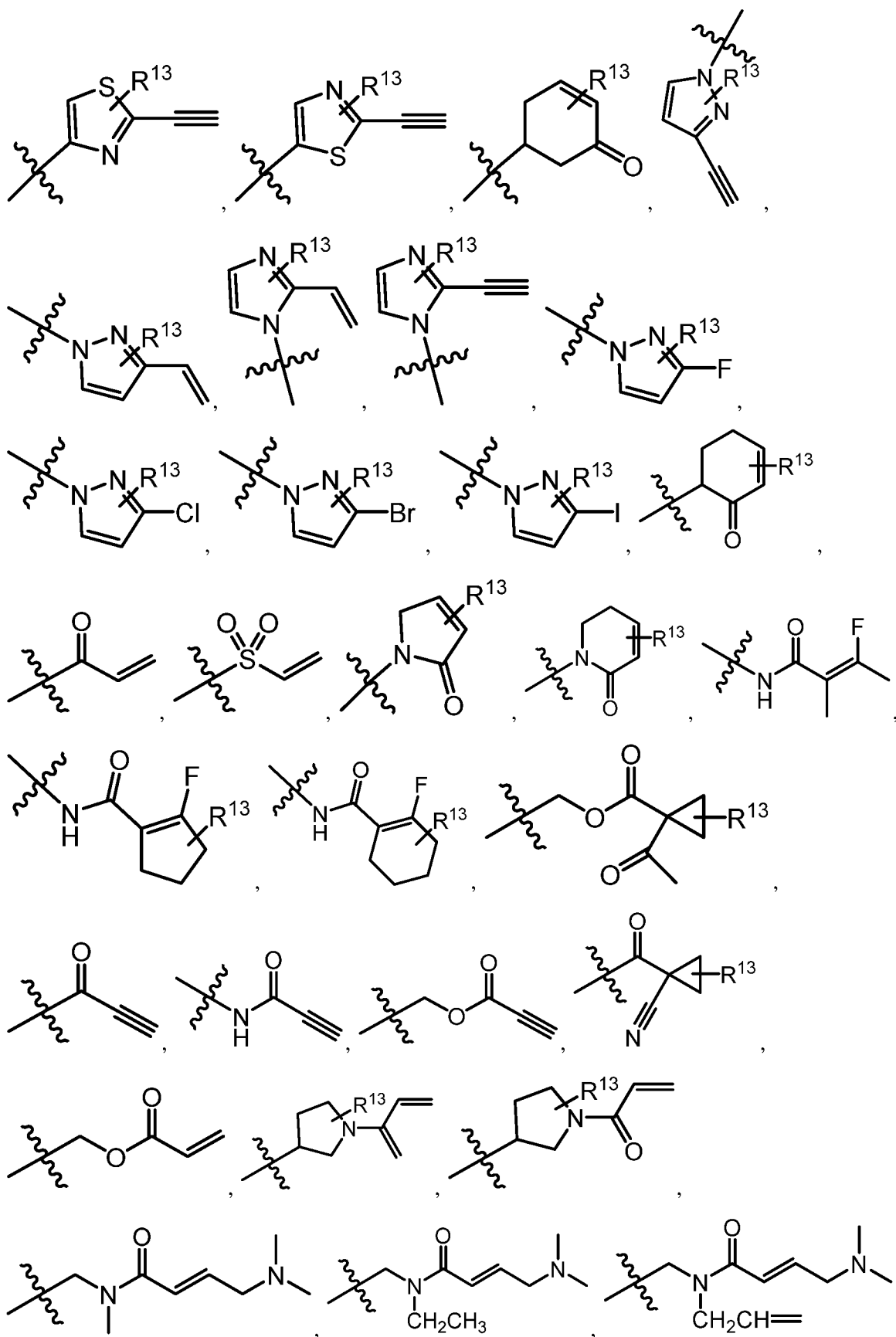


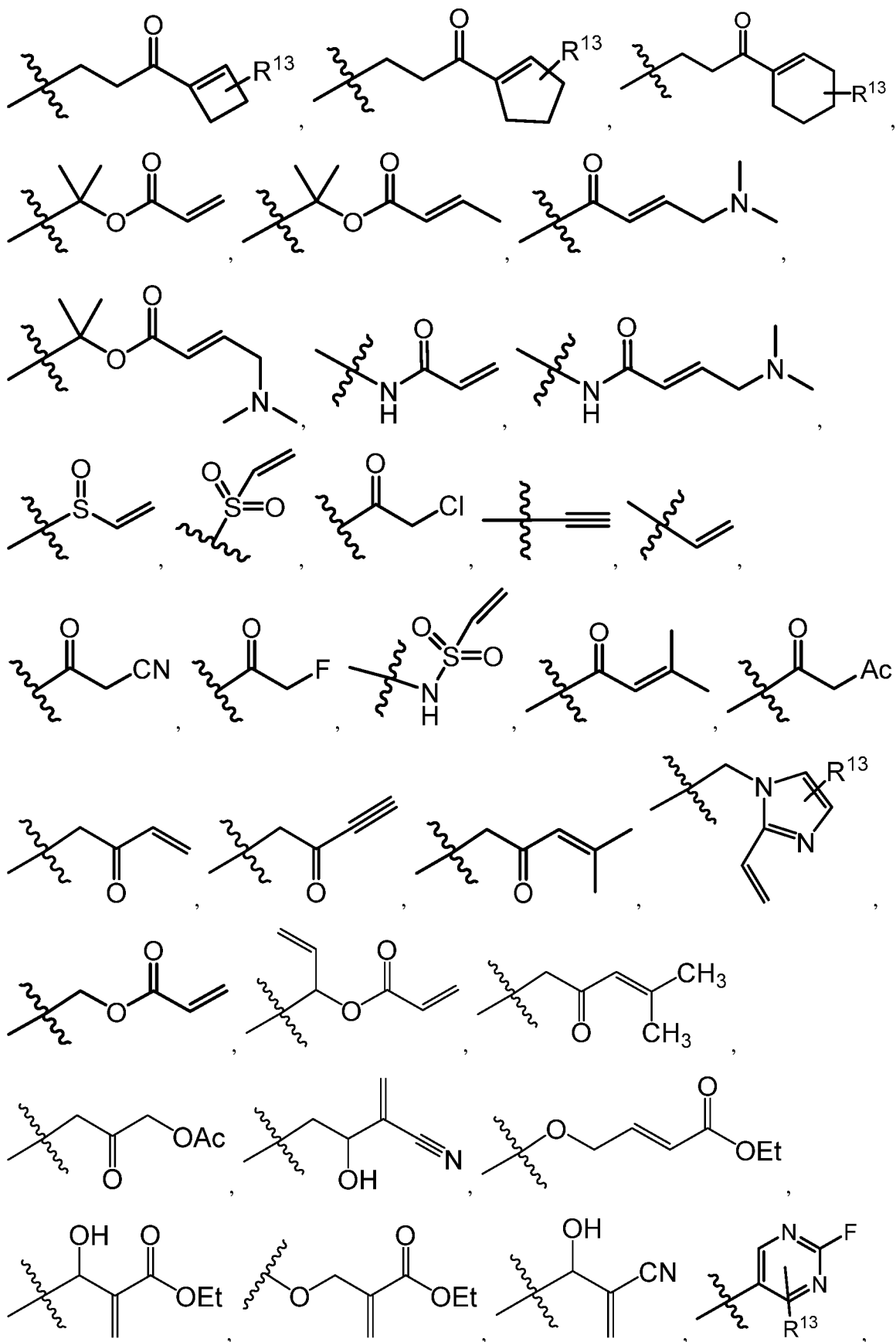
5

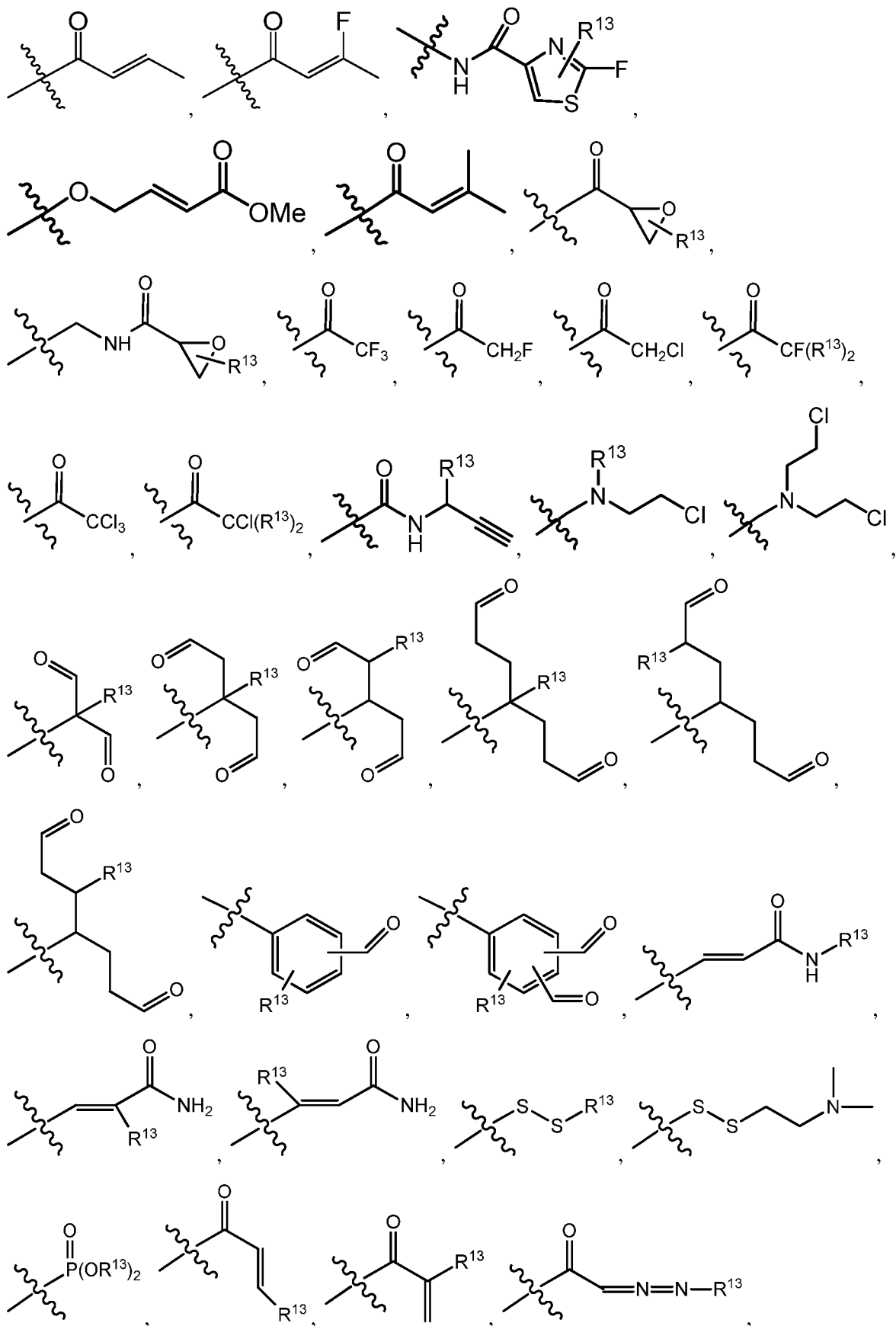


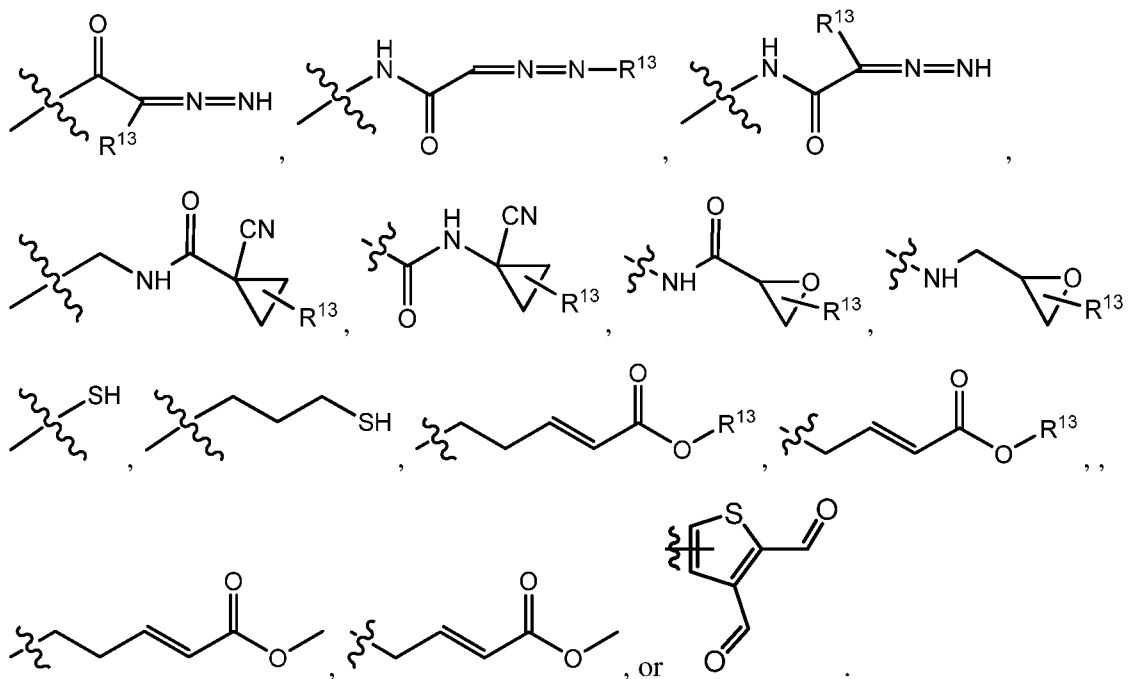




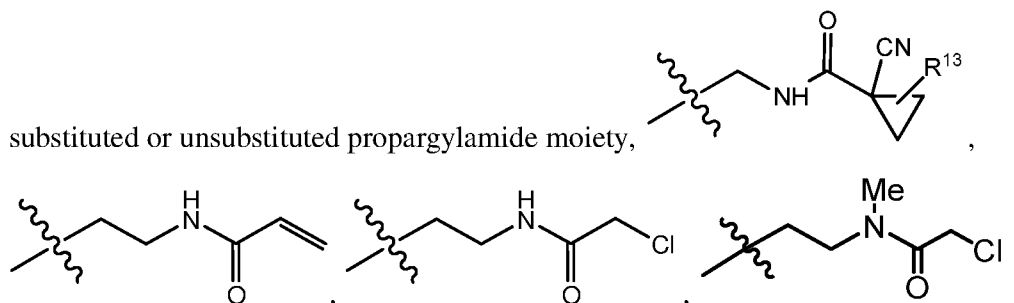


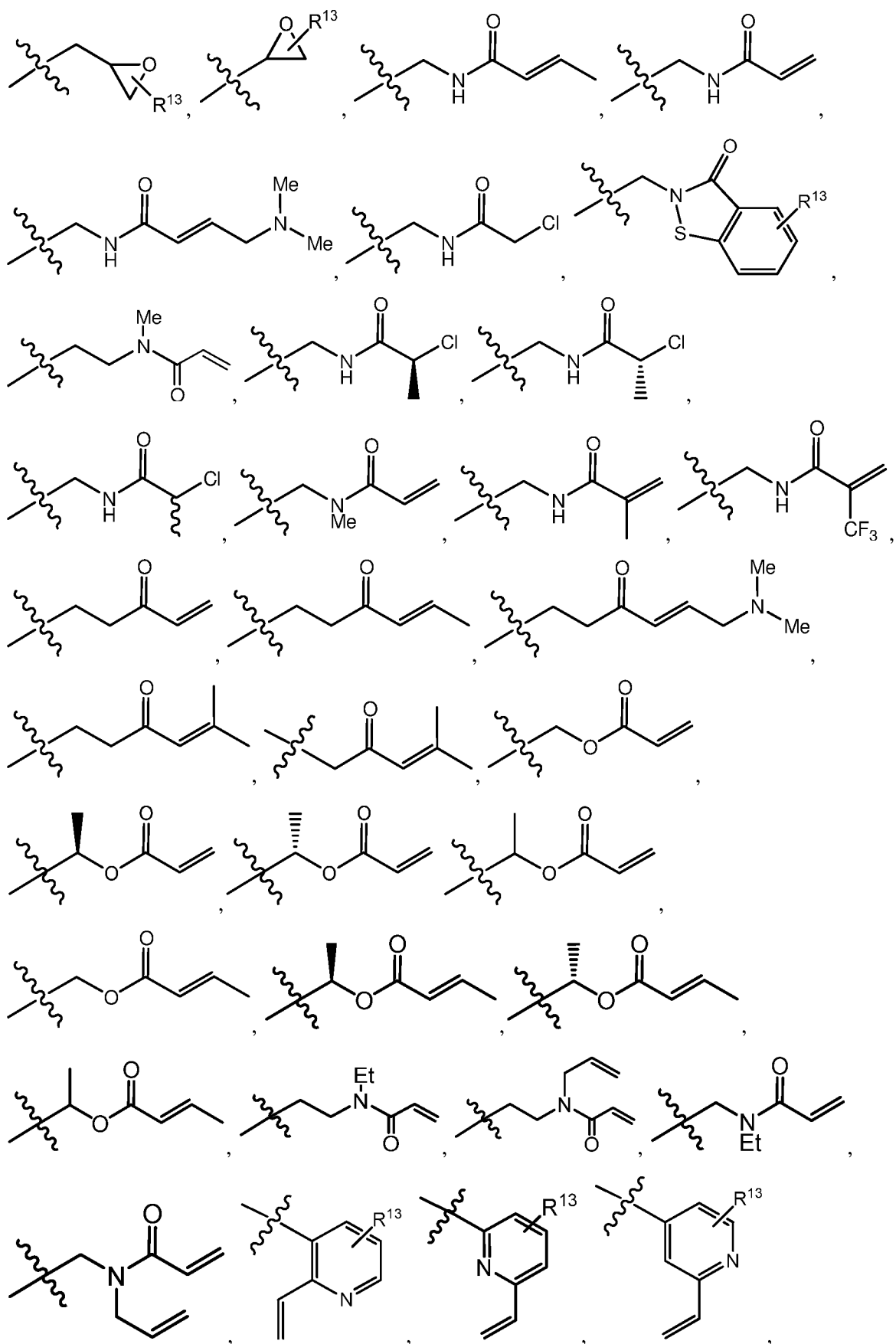


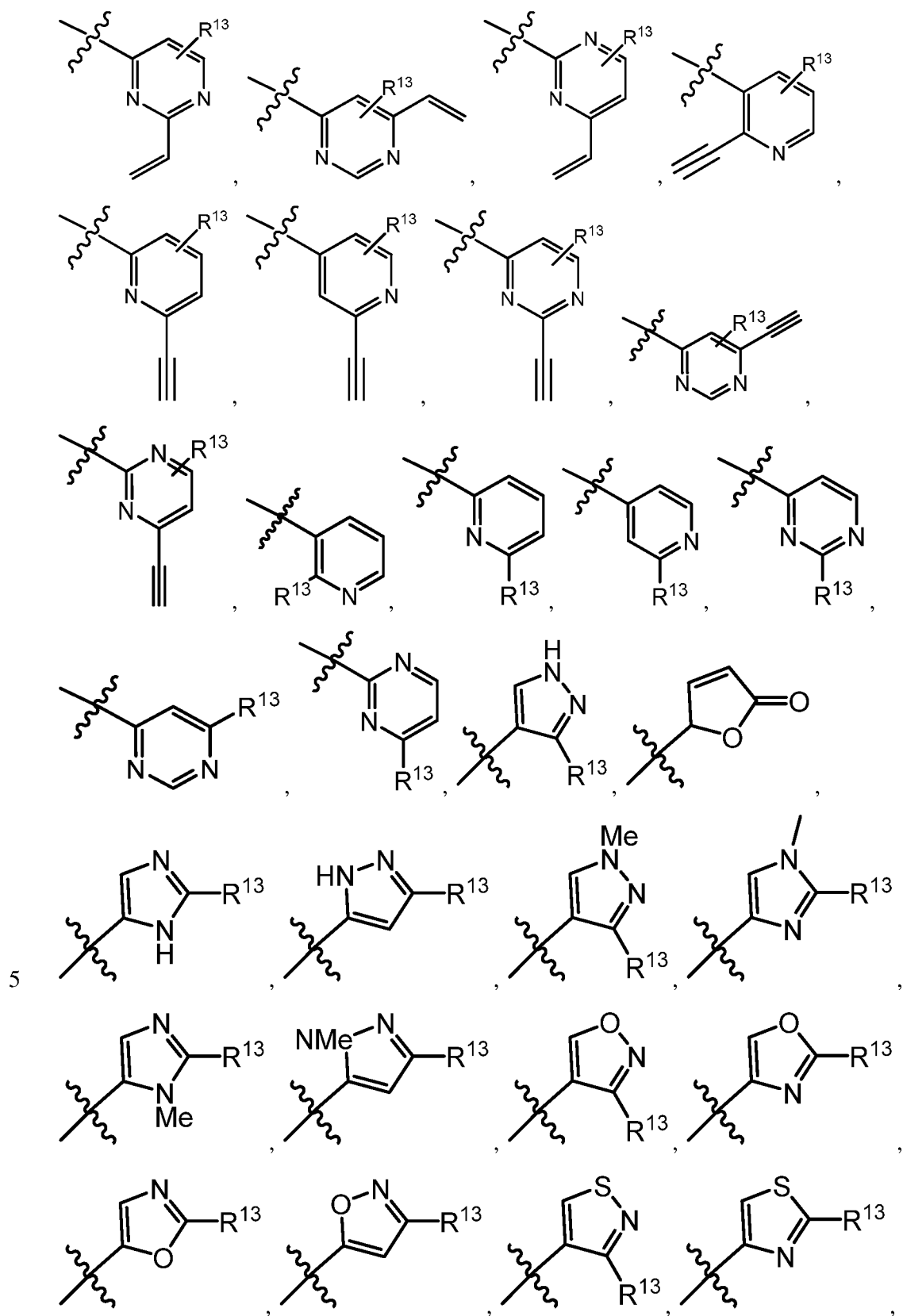


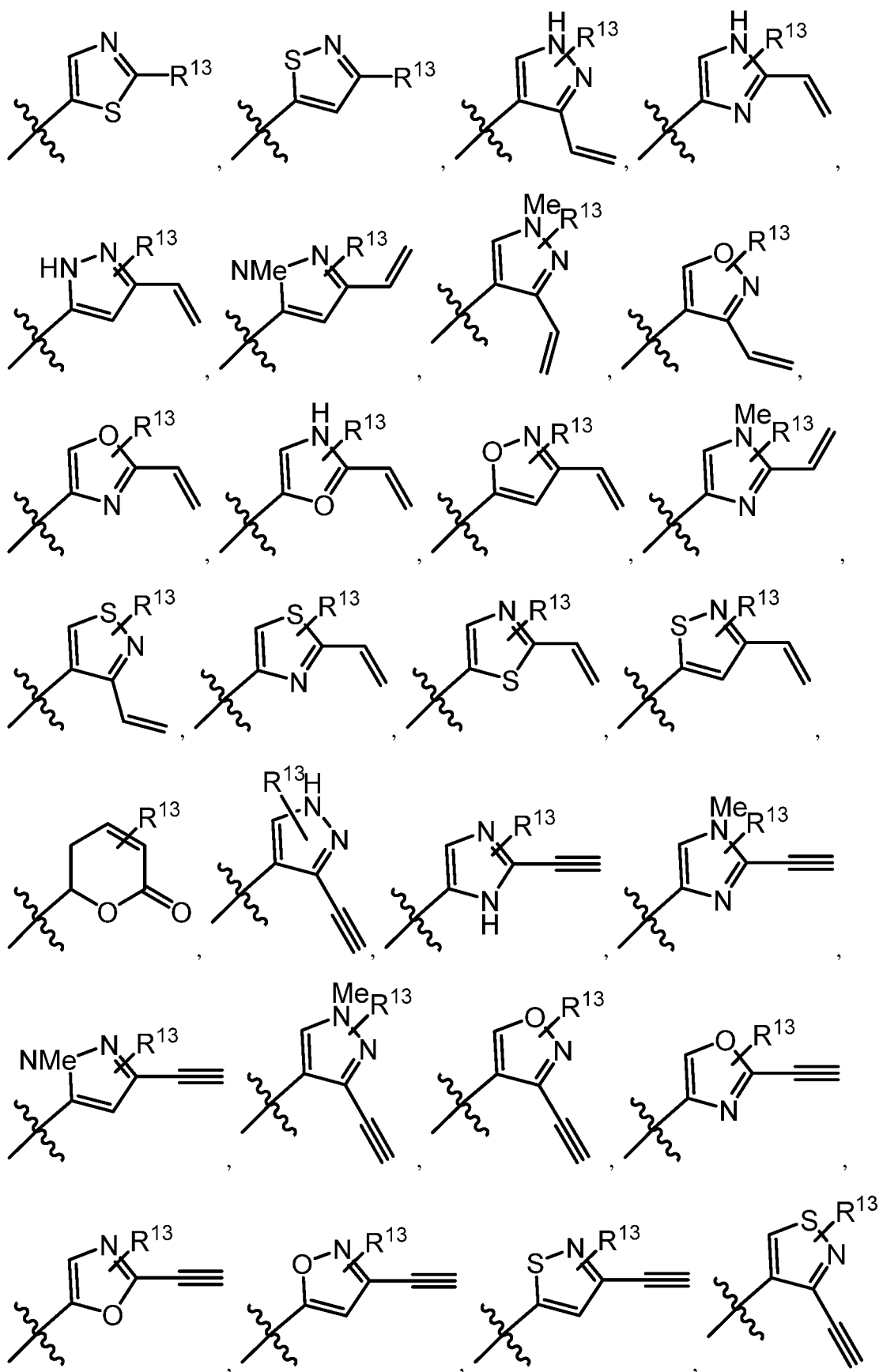


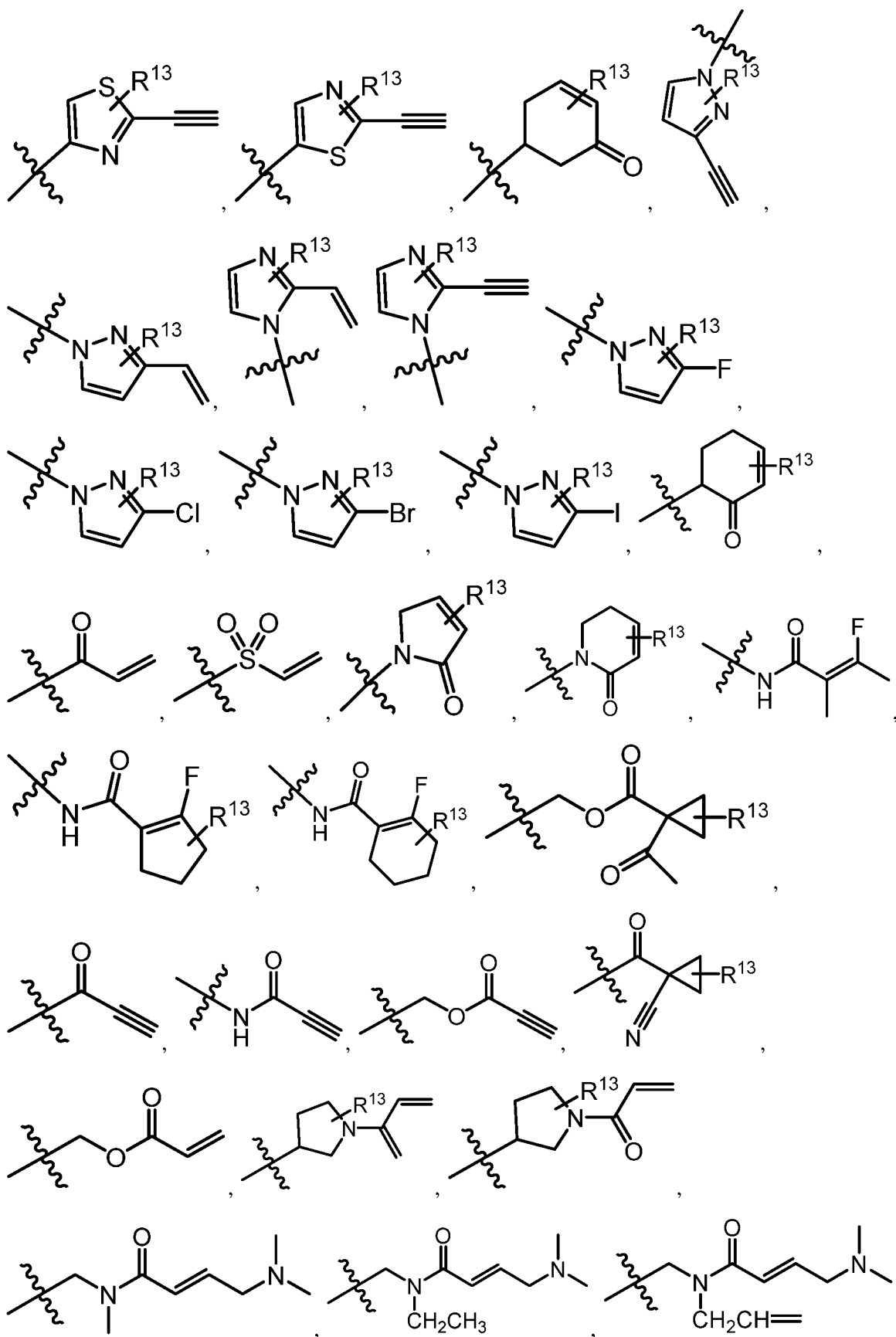
- 5 [0225] In embodiments, E is a substituted or unsubstituted vinyl sulfone moiety, substituted or unsubstituted vinyl sulfonamide moiety, substituted or unsubstituted fluoro(C₁-C₄)alkylketone moiety, substituted or unsubstituted chloro(C₁-C₄)alkylketone moiety, substituted or unsubstituted acrylamide moiety, substituted or unsubstituted disulfide moiety, substituted or unsubstituted thiol moiety, substituted or unsubstituted phosphonate moiety, substituted or
- 10 unsubstituted aldehyde moiety, substituted or unsubstituted enone moiety, substituted or unsubstituted diazomethylketone moiety, substituted or unsubstituted diazomethylamide moiety, substituted or unsubstituted cyanocyclopropyl carboxamide moiety, substituted or unsubstituted epoxide moiety, substituted or unsubstituted epoxyketone moiety, substituted or unsubstituted epoxyamide moiety, substituted or unsubstituted aryl aldehyde moiety, substituted or
- 15 unsubstituted aryl dialdehyde moiety, substituted or unsubstituted dialdehyde moiety, substituted or unsubstituted nitrogen mustard moiety, substituted or unsubstituted propargyl moiety,

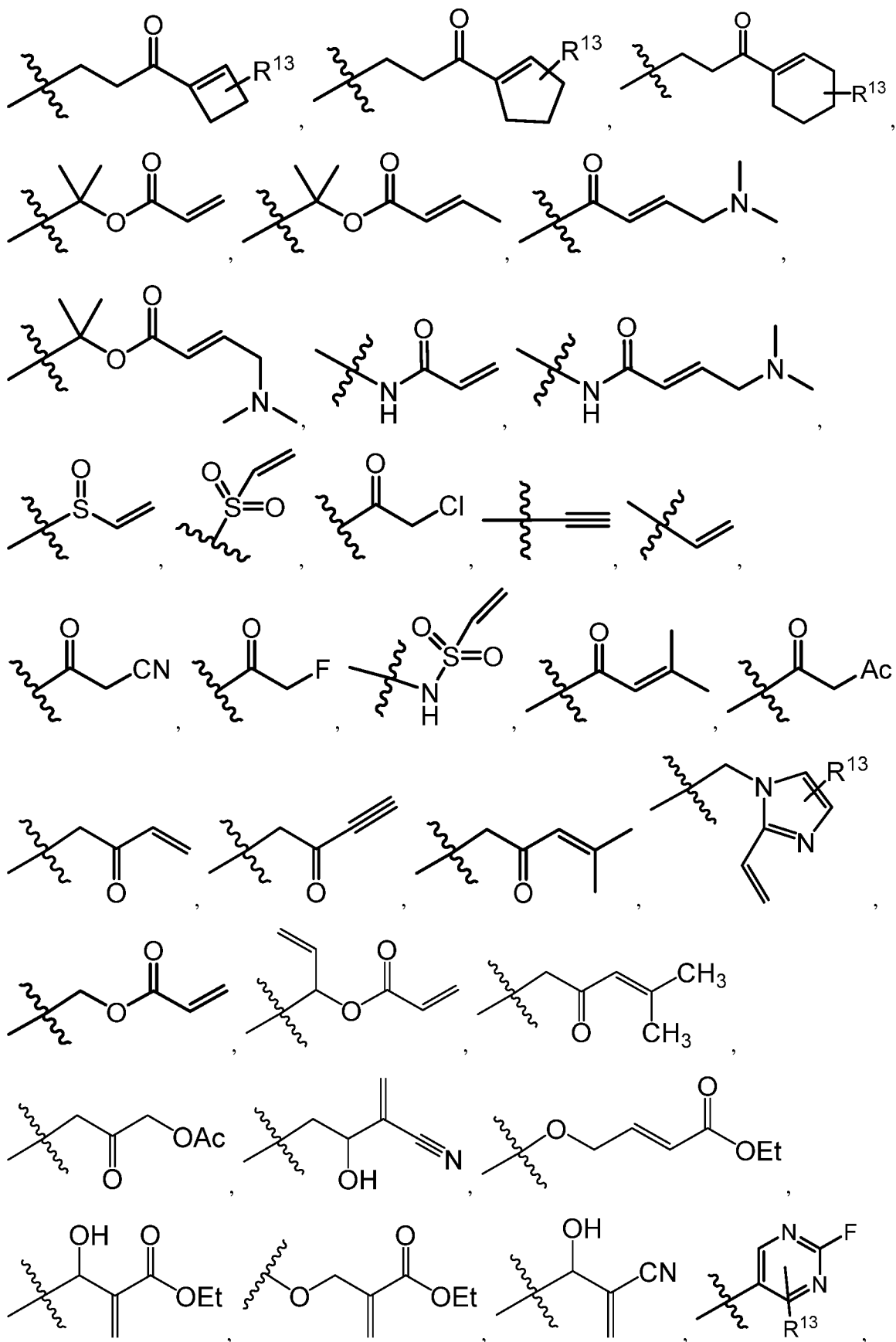


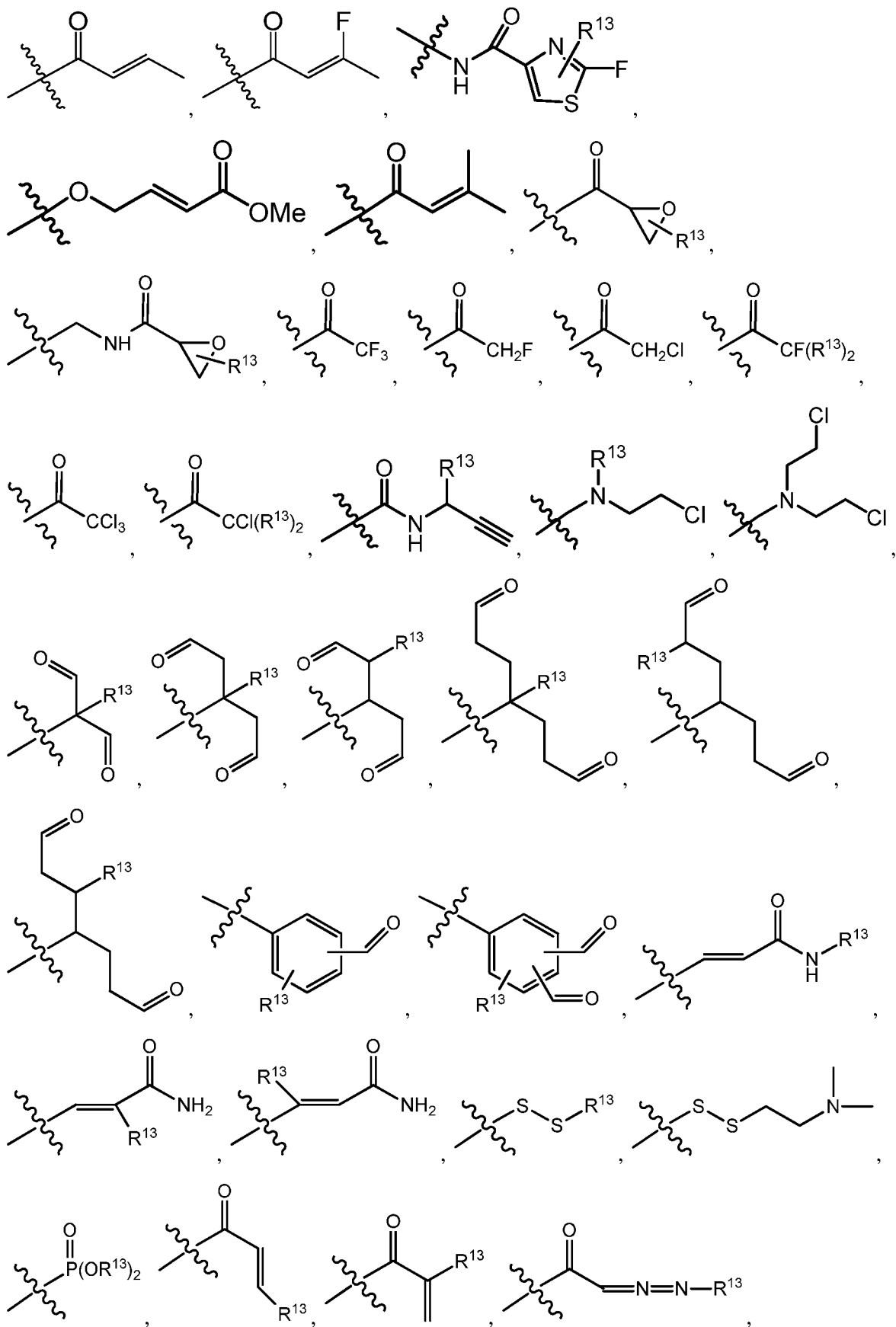


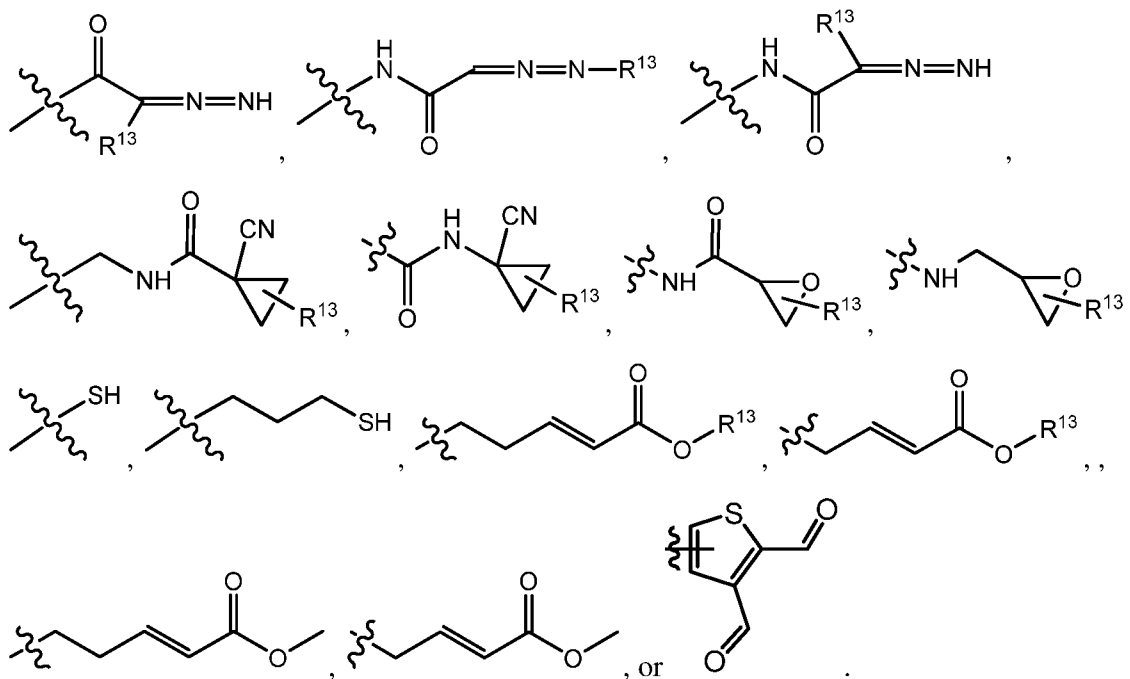












- 5 **[0226]** In embodiments, E is an unsubstituted vinyl sulfone moiety, unsubstituted vinyl sulfonamide moiety, unsubstituted fluoro(C₁-C₄)alkylketone moiety, unsubstituted chloro(C₁-C₄)alkylketone moiety, unsubstituted acrylamide moiety, unsubstituted disulfide moiety, unsubstituted thiol moiety, unsubstituted phosphonate moiety, unsubstituted aldehyde moiety, unsubstituted enone moiety, unsubstituted diazomethylketone moiety, unsubstituted
- 10 diazomethylamide moiety, unsubstituted cyanocyclopropyl carboxamide moiety, unsubstituted epoxide moiety, unsubstituted epoxyketone moiety, unsubstituted epoxyamide moiety, unsubstituted aryl aldehyde moiety, unsubstituted aryl dialdehyde moiety, unsubstituted dialdehyde moiety, unsubstituted nitrogen mustard moiety, unsubstituted propargyl moiety, or unsubstituted propargylamide moiety.
- 15 **[0227]** R¹³ is independently hydrogen, oxo, halogen, CX¹³₃, -CHX¹³₂, -CH₂X¹³, -CN, -SO_{n13}R²², -SO_{v13}NR²⁰R²¹, -NHN²⁰R²¹, -ONR²⁰R²¹, -NHC(=O)NHN²⁰R²¹, -NHC(O)NR²⁰R²¹, -N(O)_{m13}, -NR²⁰R²¹, -C(O)R²², -C(O)-OR²², -C(O)NR²⁰R²¹, -OR²³, -NR²⁰SO₂R²³, -NR²⁰C(O)R²², -NR²⁰C(O)OR²², -NR²⁰OR²², -OCX¹³₃, -OCHX¹³₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
- 20 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; an R²⁰ and R²¹ substituent bonded to the same atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. In embodiments, R¹³ is independently hydrogen. In embodiments, R¹³ is independently substituted or unsubstituted alkyl. In embodiments, R¹³ is independently oxo,

halogen, CX^{13}_3 , $-CHX^{13}_2$, $-CH_2X^{13}$, $-CN$, $-SO_{n13}R^{22}$, $-SO_{v13}NR^{20}R^{21}$, $-NHN R^{20}R^{21}$, $-ONR^{20}R^{21}$, $-NHC(=O)NHN R^{20}R^{21}$, $-NHC(O)NR^{20}R^{21}$, $-N(O)_{m13}$, $-NR^{20}R^{21}$, $-C(O)R^{22}$, $-C(O)-OR^{22}$, $-C(O)NR^{20}R^{21}$, $-OR^{23}$, $-NR^{20}SO_2R^{23}$, $-NR^{20}C(O)R^{22}$, $-NR^{20}C(O)OR^{22}$, $-NR^{20}OR^{22}$, $-OCX^{13}_3$, $-OCHX^{13}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R^{13} is independently substituted or unsubstituted heteroalkyl. In embodiments, R^{13} is independently substituted or unsubstituted cycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted heterocycloalkyl.

10 In embodiments, R^{13} is independently substituted or unsubstituted aryl. In embodiments, R^{13} is independently substituted or unsubstituted heteroaryl. In embodiments, R^{13} is independently halogen, $-CX^{13}_3$, $-CHX^{13}_2$, $-CH_2X^{13}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH SO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{13}_3$, $-OCHX^{13}_2$, substituted or unsubstituted C_1 - C_6 alkyl,

15 substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_6 aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently halogen, $-CX^{13}_3$, $-CHX^{13}_2$, $-CH_2X^{13}$, $-OH$, $-SH$, $-COOH$, $-OCX^{13}_3$, $-OCHX^{13}_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-SCH_3$, or $-SCH_2CH_3$. In embodiments, R^{13} is independently halogen or $-OCH_3$. In embodiments, R^{13} is substituted or unsubstituted C_1 - C_6 alkyl. In embodiments, R^{13} is substituted or unsubstituted 2 to 6 membered heteroalkyl. In embodiments, R^{13} is substituted or unsubstituted C_3 - C_8 cycloalkyl. In embodiments, R^{13} is substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{13} is substituted or unsubstituted C_6 aryl. In

25 embodiments, R^{13} is substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently halogen. In embodiments, R^{13} is independently $-CX^{13}_3$. In embodiments, R^{13} is independently $-CHX^{13}_2$. In embodiments, R^{13} is independently $-CH_2X^{13}$. In embodiments, R^{13} is independently $-OH$. In embodiments, R^{13} is independently $-SH$. In embodiments, R^{13} is independently $-COOH$. In embodiments, R^{13} is independently $-OCX^{13}_3$. In embodiments, R^{13} is independently $-OCHX^{13}_2$. In embodiments, R^{13} is independently $-CH_3$. In embodiments, R^{13} is independently $-CH_2CH_3$. In embodiments, R^{13} is independently $-OCH_3$. In embodiments, R^{13} is independently $-OCH_2CH_3$. In embodiments, R^{13} is independently $-SCH_3$. In embodiments, R^{13} is independently $-SCH_2CH_3$. In embodiments, R^{13} is independently $-Cl$ or $-OCH_3$. In

30 embodiments, R^{13} is independently

halogen, $-CX^{13}_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-OCX^{13}_3$, $-OCHX^{13}_2$, $-CHX^{13}_2$, $-CH_2X^{13}$, substituted or unsubstituted C_1 - C_8 alkyl, or substituted or unsubstituted 2 to 8 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted phenyl, or substituted or

5 unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently halogen, $-CX^{13}_3$, $-CN$, unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{13} is independently unsubstituted methyl, unsubstituted ethyl, unsubstituted isopropyl, or unsubstituted tert-butyl. In embodiments, R^{13} is independently unsubstituted methyl. In embodiments, R^{13} is independently unsubstituted ethyl. In embodiments, R^{13} is

10 independently unsubstituted propyl. In embodiments, R^{13} is independently unsubstituted n-propyl. In embodiments, R^{13} is independently unsubstituted isopropyl. In embodiments, R^{13} is independently unsubstituted butyl. In embodiments, R^{13} is independently unsubstituted n-butyl. In embodiments, R^{13} is independently unsubstituted isobutyl. In embodiments, R^{13} is independently unsubstituted tert-butyl. In embodiments, R^{13} is independently unsubstituted

15 pentyl. In embodiments, R^{13} is independently unsubstituted hexyl. In embodiments, R^{13} is independently unsubstituted heptyl. In embodiments, R^{13} is independently unsubstituted octyl. In embodiments, R^{13} is independently $-F$. In embodiments, R^{13} is independently $-Cl$. In embodiments, R^{13} is independently $-Br$. In embodiments, R^{13} is independently $-I$. In embodiments, R^{13} is independently unsubstituted methoxy. In embodiments, R^{13} is

20 independently unsubstituted ethoxy. In embodiments, R^{13} is independently $-CF_3$. In embodiments, R^{13} is independently $-CCl_3$. In embodiments, R^{13} is an unsubstituted isopropyl. In embodiments, R^{13} is an unsubstituted phenyl. In embodiments, R^{13} is an unsubstituted pyridyl. In embodiments, R^{13} is independently halogen. In embodiments, R^{13} is independently $-CX^{13}_3$. In embodiments, R^{13} is independently $-CHX^{13}_2$. In embodiments, R^{13} is independently $-CH_2X^{13}$.

25 In embodiments, R^{13} is independently $-CN$. In embodiments, R^{13} is independently $-OH$. In embodiments, R^{13} is independently $-NH_2$. In embodiments, R^{13} is independently $-COOH$. In embodiments, R^{13} is independently $-CONH_2$. In embodiments, R^{13} is independently $-NO_2$. In embodiments, R^{13} is independently $-SH$. In embodiments, R^{13} is independently $-SO_2Cl$. In embodiments, R^{13} is independently $-SO_3H$. In embodiments, R^{13} is independently $-SO_4H$. In

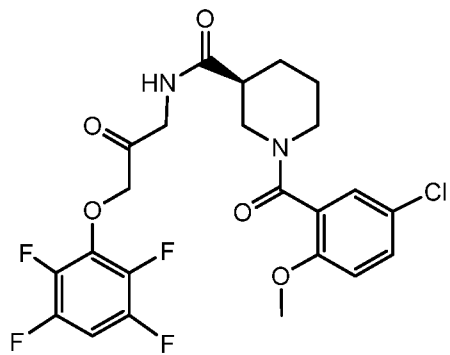
30 embodiments, R^{13} is independently $-SO_2NH_2$. In embodiments, R^{13} is independently $-NHNH_2$. In embodiments, R^{13} is independently $-ONH_2$. In embodiments, R^{13} is independently $-NHC(O)NHNH_2$. In embodiments, R^{13} is independently $-NHC(O)NH_2$. In embodiments, R^{13} is independently $-NHSO_2H$. In embodiments, R^{13} is independently $-NHC(O)H$. In embodiments, R^{13} is independently $-NHC(O)OH$. In embodiments, R^{13} is

independently -NHOH. In embodiments, R^{13} is independently -OCX¹³₃. In embodiments, R^{13} is independently -OCHX¹³₂. In embodiments, R^{13} is independently substituted or unsubstituted alkyl. In embodiments, R^{13} is independently substituted or unsubstituted heteroalkyl. In embodiments, R^{13} is independently substituted or unsubstituted cycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted heterocycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted aryl. In embodiments, R^{13} is independently substituted or unsubstituted heteroaryl. In embodiments, R^{13} is independently substituted alkyl. In embodiments, R^{13} is independently substituted heteroalkyl. In embodiments, R^{13} is independently substituted cycloalkyl. In embodiments, R^{13} is independently substituted heterocycloalkyl. In embodiments, R^{13} is independently substituted aryl. In embodiments, R^{13} is independently substituted heteroaryl. In embodiments, R^{13} is independently unsubstituted alkyl. In embodiments, R^{13} is independently unsubstituted heteroalkyl. In embodiments, R^{13} is independently unsubstituted cycloalkyl. In embodiments, R^{13} is independently unsubstituted heterocycloalkyl. In embodiments, R^{13} is independently unsubstituted aryl. In embodiments, R^{13} is independently unsubstituted heteroaryl. In embodiments, R^{13} is independently substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R^{13} is independently substituted or unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{13} is independently substituted or unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R^{13} is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{13} is independently substituted C₁-C₈ alkyl. In embodiments, R^{13} is independently substituted 2 to 8 membered heteroalkyl. In embodiments, R^{13} is independently substituted C₃-C₈ cycloalkyl. In embodiments, R^{13} is independently substituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{13} is independently substituted C₆-C₁₀ aryl. In embodiments, R^{13} is independently substituted 5 to 10 membered heteroaryl. In embodiments, R^{13} is independently unsubstituted C₁-C₈ alkyl. In embodiments, R^{13} is independently unsubstituted 2 to 8 membered heteroalkyl. In embodiments, R^{13} is independently unsubstituted C₃-C₈ cycloalkyl. In embodiments, R^{13} is independently unsubstituted 3 to 8 membered heterocycloalkyl. In embodiments, R^{13} is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R^{13} is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{13} is independently substituted or unsubstituted C₁-C₄ alkyl. In embodiments, R^{13} is independently substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^{13} is independently substituted or unsubstituted C₃-C₆ cycloalkyl. In embodiments, R^{13} is independently substituted or unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments,

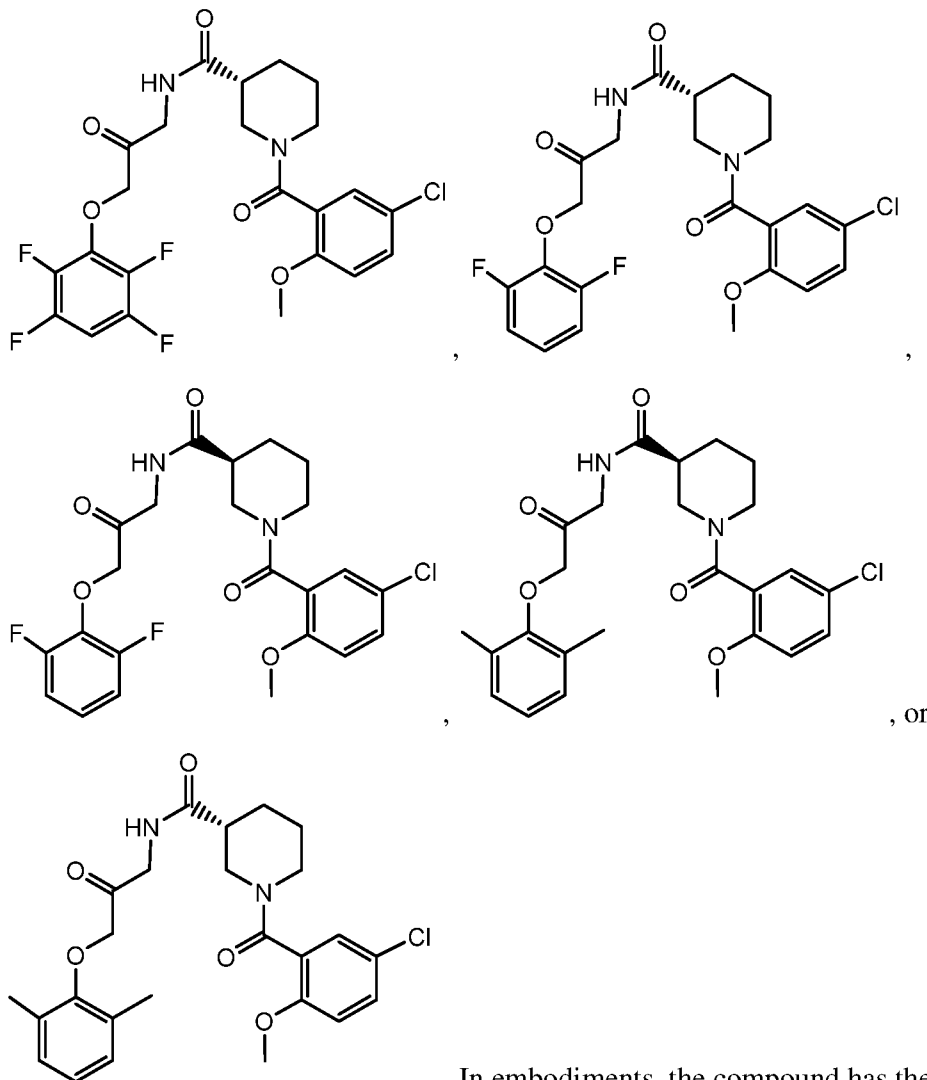
R^{13} is independently substituted or unsubstituted phenyl. In embodiments, R^{13} is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently substituted C_1 - C_4 alkyl. In embodiments, R^{13} is independently substituted 2 to 4 membered heteroalkyl. In embodiments, R^{13} is independently substituted C_3 - C_6 cycloalkyl. In
 5 embodiments, R^{13} is independently substituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{13} is independently substituted phenyl. In embodiments, R^{13} is independently substituted 5 to 6 membered heteroaryl. In embodiments, R^{13} is independently unsubstituted C_1 - C_4 alkyl. In embodiments, R^{13} is independently unsubstituted 2 to 4 membered heteroalkyl. In
 10 embodiments, R^{13} is independently unsubstituted C_3 - C_6 cycloalkyl. In embodiments, R^{13} is independently unsubstituted 3 to 6 membered heterocycloalkyl. In embodiments, R^{13} is independently unsubstituted phenyl. In embodiments, R^{13} is independently unsubstituted 5 to 6 membered heteroaryl.

[0228] R^{20} , R^{21} , R^{22} , and R^{23} are independently hydrogen, halogen, $-CX^A_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$,
 15 $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^A_3$, $-OCHX^A_2$, $-CHX^A_2$, $-CH_2X^A$, substituted 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^{20} and R^{21} substituents bonded to the same nitrogen atom may optionally be joined
 20 to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

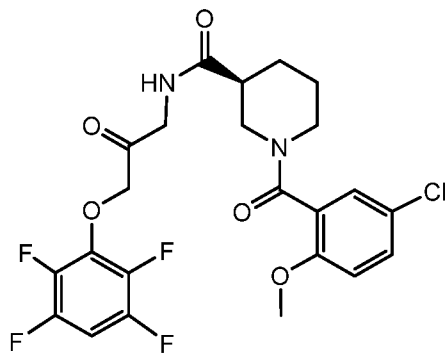
[0229] Each X^A and X^{13} is independently $-F$, $-Cl$, $-Br$, or $-I$. The symbols n_{13} and v_{13} are independently an integer from 0 to 4. The symbol m_{13} is independently an integer from 1 to 2.



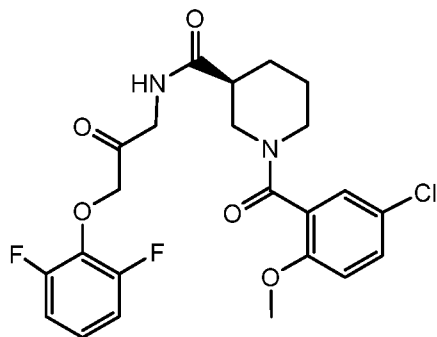
[0230] In embodiments, the compound has the formula:



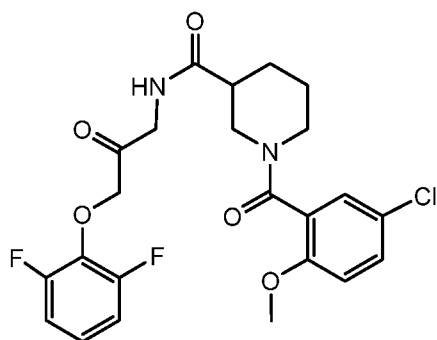
. In embodiments, the compound has the formula:



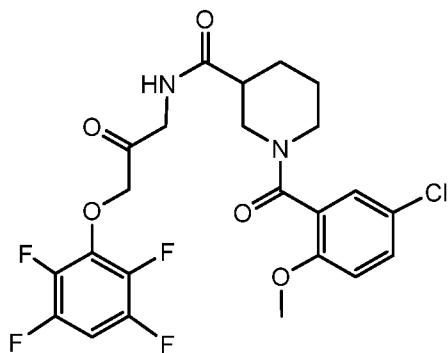
. In embodiments, the compound has the formula:



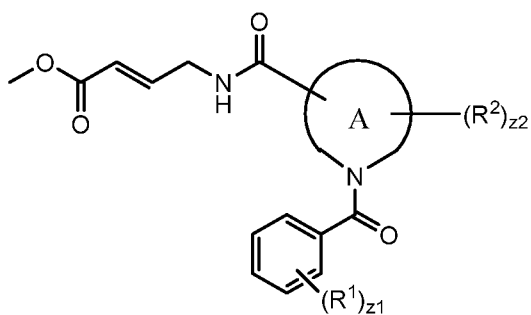
. In embodiments, the compound has the formula:



. In embodiments, the compound has the formula:

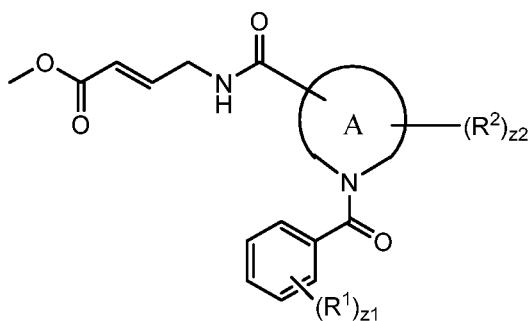


[0231] In embodiments, the compound has the formula:

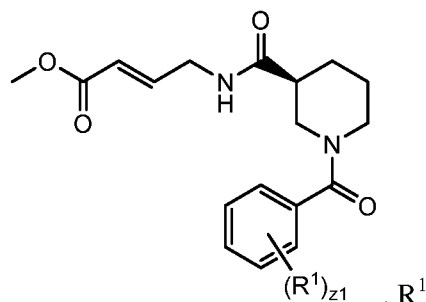


. Ring A, R^1 , $z1$, R^2 , and $z2$ are as described herein.

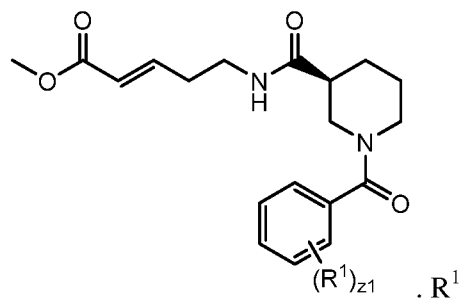
[0232] In embodiments, the compound has the formula:



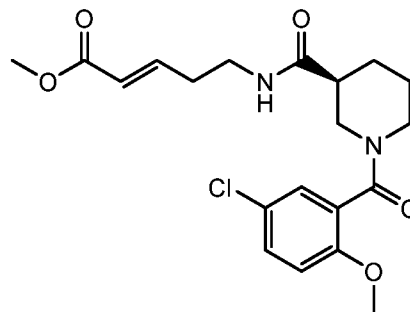
. Ring A, R^1 , $z1$, R^2 , and $z2$ are as described herein.



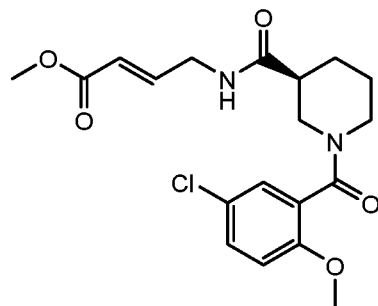
5 [0233] In embodiments, the compound has the formula:
and $z1$ are as described herein.



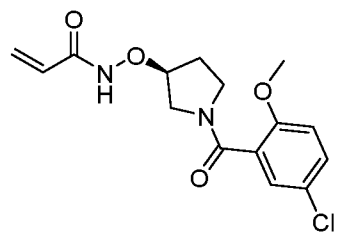
[0234] In embodiments, the compound has the formula:
and $z1$ are as described herein.



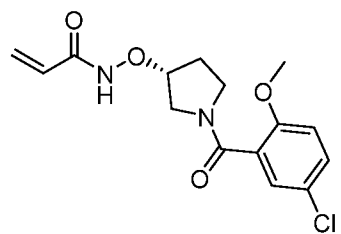
[0235] In embodiments, the compound has the formula:



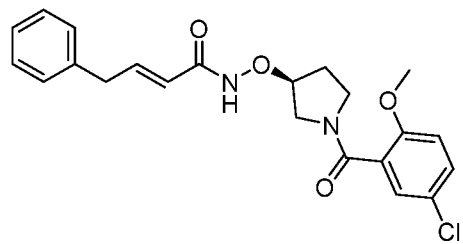
[0236] In embodiments, the compound has the formula:



[0237] In embodiments, the compound has the formula:

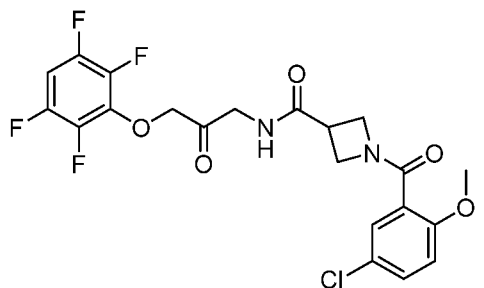


[0238] In embodiments, the compound has the formula:

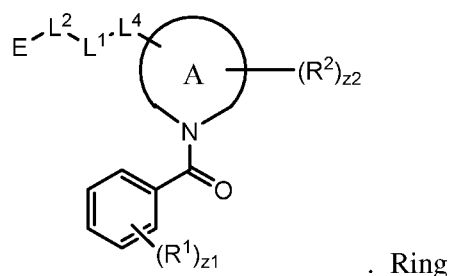
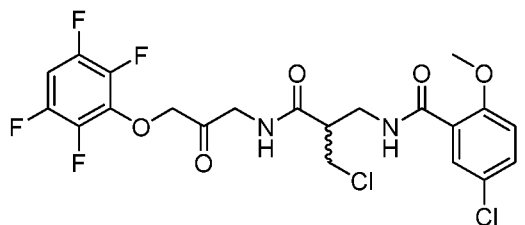


5 [0239] In embodiments, the compound has the formula:

[0240] In embodiments, the compound has the formula:

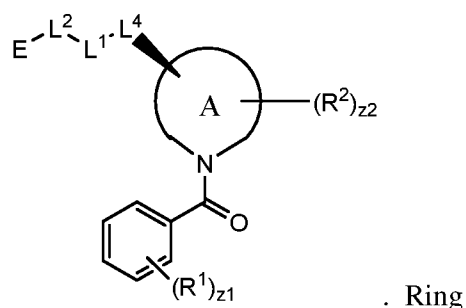


[0241] In embodiments, the compound has the formula:



5 [0242] In embodiments, the compound has the formula:

A, R¹, z₁, R², z₂, L¹, L², L⁴, and E are as described herein.



[0243] In embodiments, the compound has the formula:

A, R¹, z₁, R², z₂, L¹, L², L⁴, and E are as described herein.

[0244] In embodiments, Ring A is a 5 to 7 membered heterocycloalkyl. In embodiments, Ring

10 A is a 3 to 5 membered heterocycloalkyl. In embodiments, Ring A is pyrrolidinyl. In

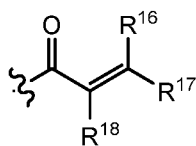
embodiments, Ring A is piperidinyl. In embodiments, Ring A is azetidiny. In embodiments, Y is N.

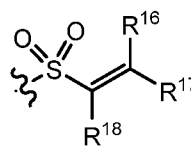
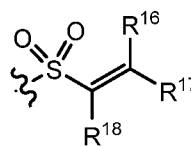
[0245] In embodiments, R^1 is independently halogen, CX^1_3 , $-CHX^1_2$, $-CH_2X^1$, $-CN$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_2$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^1_3$, $-OCHX^1_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R^1 is independently halogen, $-CF_3$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, substituted or unsubstituted C_1 - C_4 alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R^1 is independently halogen, $-CF_3$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, unsubstituted C_1 - C_4 alkyl, or unsubstituted 2 to 4 membered heteroalkyl.

[0246] In embodiments, L^1 is a bond. In embodiments, L^1 is $-NH-$.

[0247] In embodiments, L^2 is a bond. In embodiments, L^2 is $-NH-$.

[0248] In embodiments, L^4 is a bond. In embodiments, L^4 is substituted or unsubstituted C_1 - C_3 alkylene. In embodiments, L^4 is unsubstituted methylene.



[0249] In embodiments, E is . In embodiments, E is .

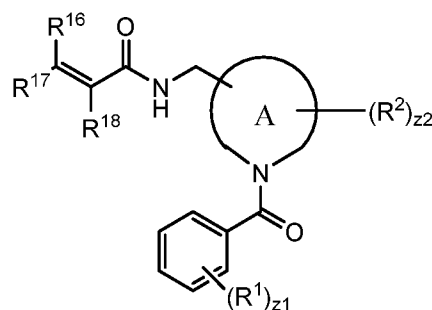
[0250] In embodiments, R^{16} is unsubstituted methyl. In embodiments, R^{17} is unsubstituted methyl. In embodiments, R^{18} is unsubstituted methyl. In embodiments, R^{18} is hydrogen. In embodiments, R^{16} is hydrogen. In embodiments, R^{17} is hydrogen. In embodiments, R^{16} is $-CH_2N(CH_3)_2$. In embodiments, R^{17} is $-CH_2N(CH_3)_2$. In embodiments, R^{18} is $-CH_2N(CH_3)_2$. In embodiments, R^{16} is $-CH_2CH_2N(CH_3)_2$. In embodiments, R^{17} is $-CH_2CH_2N(CH_3)_2$. In embodiments, R^{17} is $-CH_2Ph$. In embodiments, R^{18} is $-CH_2CH_2N(CH_3)_2$.

[0251] In embodiments, R^2 is independently halogen, CX^2_3 , $-CHX^2_2$, $-CH_2X^2$, $-CN$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_2$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^2_3$, $-OCHX^2_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl. In embodiments, R^2 is independently halogen, $-CF_3$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$,

substituted or unsubstituted C₁-C₄ alkyl, or substituted or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently halogen, -CF₃, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, unsubstituted C₁-C₄ alkyl, or unsubstituted 2 to 4 membered heteroalkyl. In embodiments, R² is independently -Cl. In

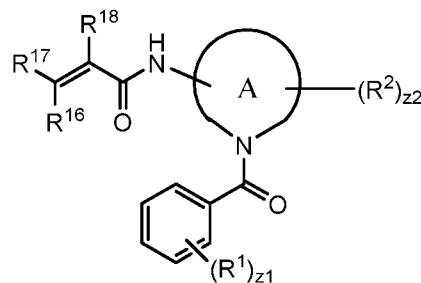
5 embodiments, R² is independently -F. In embodiments, R² is independently -Br. In embodiments, R² is independently -I. In embodiments, R² is independently -OCH₃. In embodiments, R² is independently -OCH₂CH₃.

[0252] In embodiments, z1 is 2. In embodiments, z2 is 0.



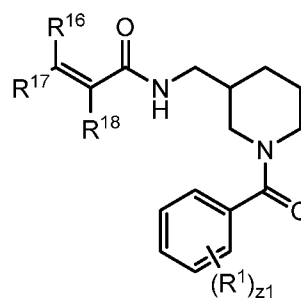
[0253] In embodiments, the compound has the formula:

- 10 Ring A, R¹, z1, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.

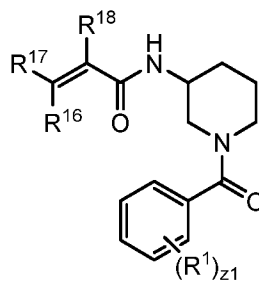


[0254] In embodiments, the compound has the formula:

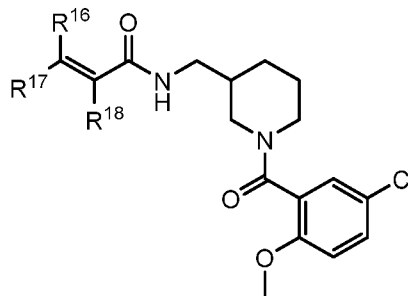
Ring A, R¹, z1, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



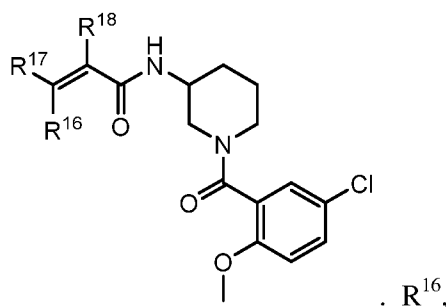
- 15 [0255] In embodiments, the compound has the formula: R¹, z1, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



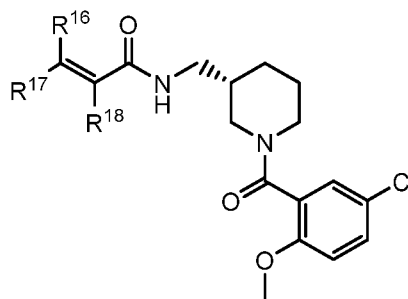
[0256] In embodiments, the compound has the formula:
 $(R^1)_{z1}$. R^1 , $z1$, R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



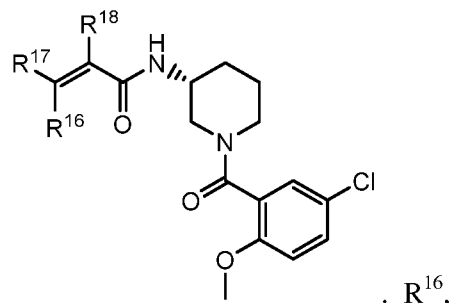
[0257] In embodiments, the compound has the formula:
 R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



5 [0258] In embodiments, the compound has the formula:
 R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.

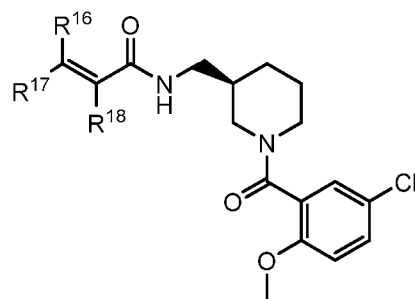


[0259] In embodiments, the compound has the formula:
 R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



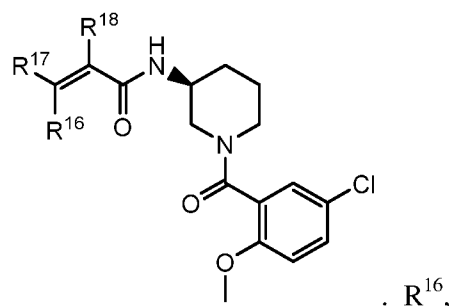
[0260] In embodiments, the compound has the formula:

R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



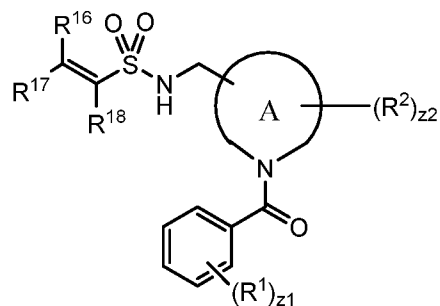
[0261] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



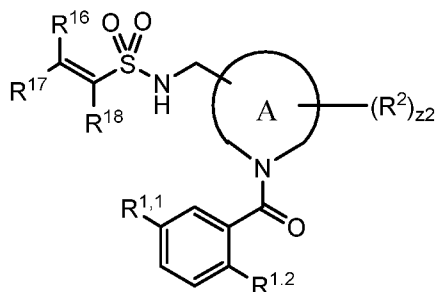
5 [0262] In embodiments, the compound has the formula:

R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.

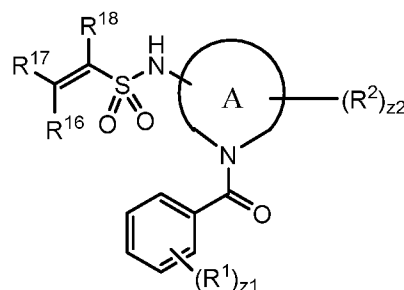


[0263] In embodiments, the compound has the formula:

Ring A, R¹, z1, R², z2, R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen. In embodiments, the compound has the formula:

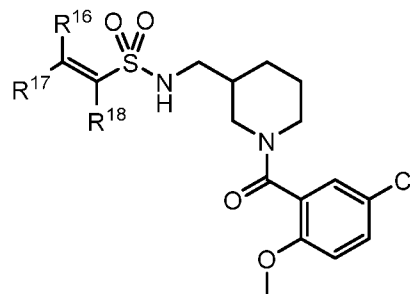


. Ring A, R^2 , $z2$, R^{16} , R^{17} , and R^{18} are as described herein. In
embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. $R^{1.1}$ and $R^{1.2}$ have the values of R^1 . $R^{1.1}$ may be
halogen. $R^{1.1}$ may be hydrogen. $R^{1.1}$ may be $-Cl$. $R^{1.2}$ may be hydrogen. $R^{1.2}$ may be
unsubstituted 2 to 4 membered heteroalkyl. $R^{1.2}$ may be unsubstituted 2 to 3 membered
5 heteroalkyl. $R^{1.2}$ may be unsubstituted methoxy. $R^{1.2}$ may be unsubstituted ethoxy. $R^{1.2}$ may be
unsubstituted propoxy.



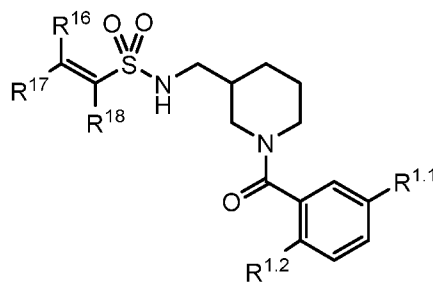
[0264] In embodiments, the compound has the formula:

Ring A, R^1 , $z1$, R^2 , $z2$, R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and
 R^{18} are hydrogen.



10 [0265] In embodiments, the compound has the formula:

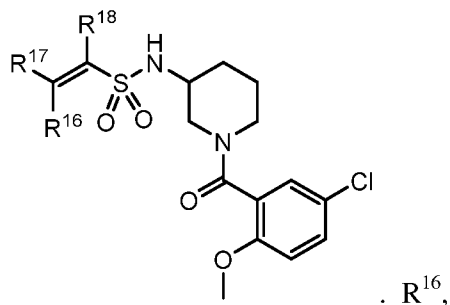
R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. In



embodiments, the compound has the formula:

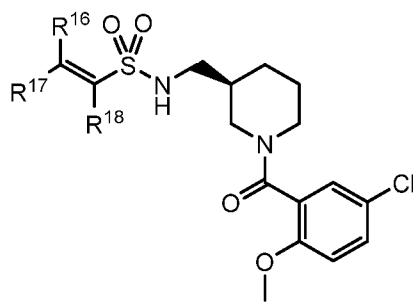
. R^{16} , R^{17} , and
 R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. $R^{1.1}$ and $R^{1.2}$ have

the values of R^1 . $R^{1.1}$ may be halogen. $R^{1.1}$ may be hydrogen. $R^{1.1}$ may be $-Cl$. $R^{1.2}$ may be hydrogen. $R^{1.2}$ may be unsubstituted 2 to 4 membered heteroalkyl. $R^{1.2}$ may be unsubstituted 2 to 3 membered heteroalkyl. $R^{1.2}$ may be unsubstituted methoxy. $R^{1.2}$ may be unsubstituted ethoxy. $R^{1.2}$ may be unsubstituted propoxy.



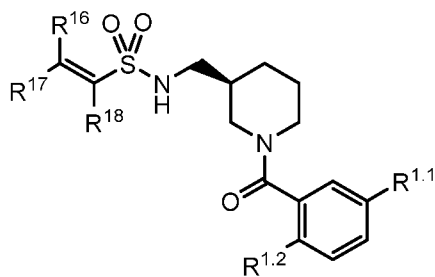
5 [0266] In embodiments, the compound has the formula:

R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



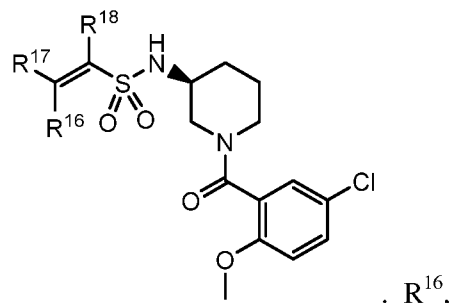
[0267] In embodiments, the compound has the formula:

R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. In



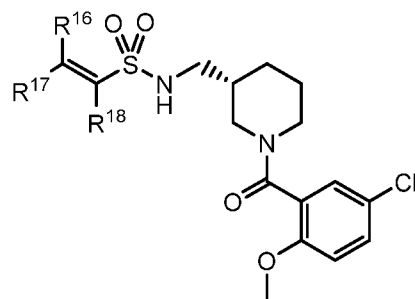
embodiments, the compound has the formula:

10 R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. $R^{1.1}$ and $R^{1.2}$ have the values of R^1 . $R^{1.1}$ may be halogen. $R^{1.1}$ may be hydrogen. $R^{1.1}$ may be $-Cl$. $R^{1.2}$ may be hydrogen. $R^{1.2}$ may be unsubstituted 2 to 4 membered heteroalkyl. $R^{1.2}$ may be unsubstituted 2 to 3 membered heteroalkyl. $R^{1.2}$ may be unsubstituted methoxy. $R^{1.2}$ may be unsubstituted ethoxy. $R^{1.2}$ may be unsubstituted propoxy.



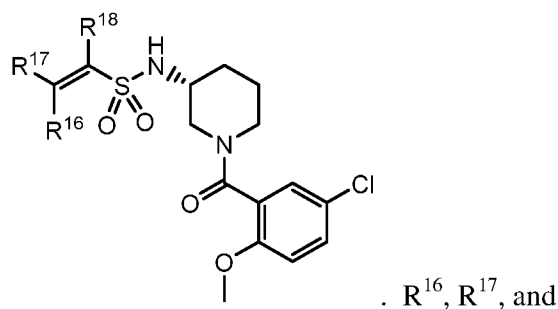
[0268] In embodiments, the compound has the formula:

R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



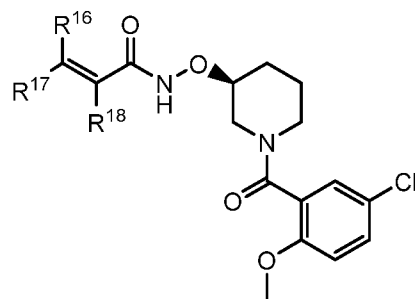
[0269] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



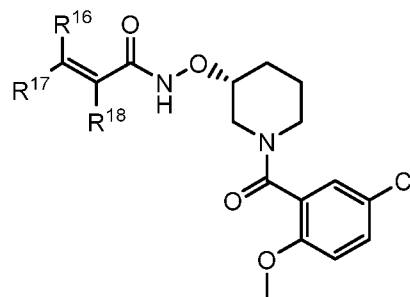
5 In embodiments, the compound has the formula:

R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



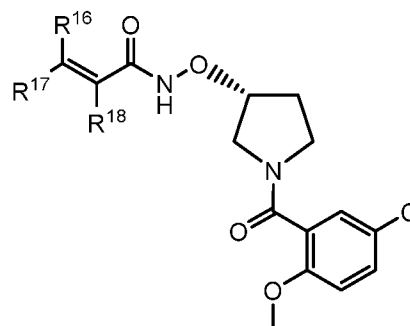
[0270] In embodiments, the compound has the formula:

R¹⁶, R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.



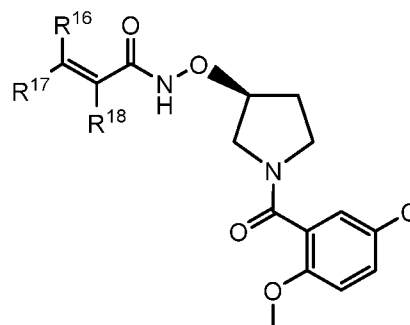
[0271] In embodiments, the compound has the formula:

R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



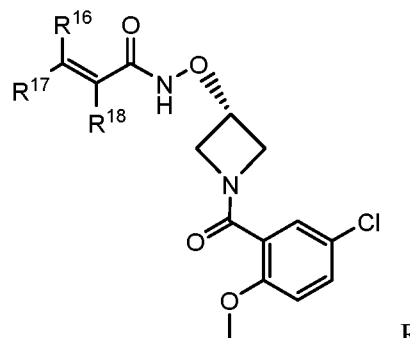
[0272] In embodiments, the compound has the formula:

R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.



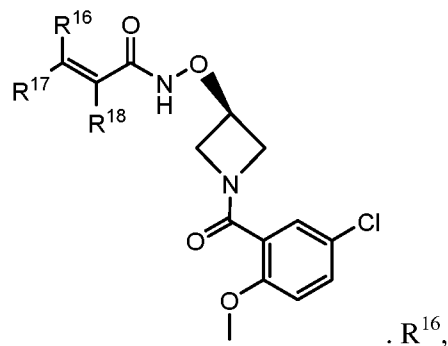
5 [0273] In embodiments, the compound has the formula:

R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. In embodiments, R^{16} and R^{18} are hydrogen and R^{17} is $-\text{CH}_2\text{Ph}$.



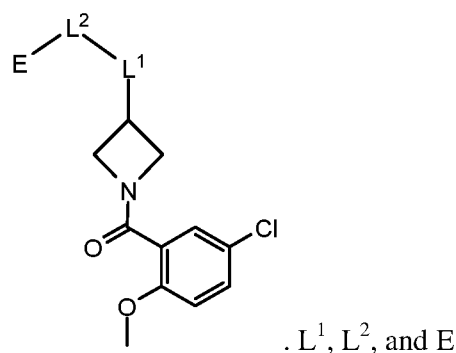
[0274] In embodiments, the compound has the formula:

R^{16} , R^{17} , and R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen.

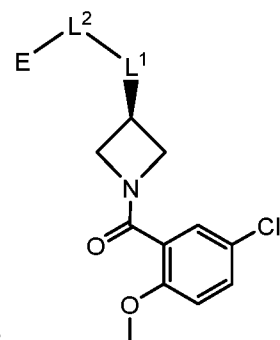


[0275] In embodiments, the compound has the formula:

R¹⁷, and R¹⁸ are as described herein. In embodiments, R¹⁶, R¹⁷, and R¹⁸ are hydrogen.

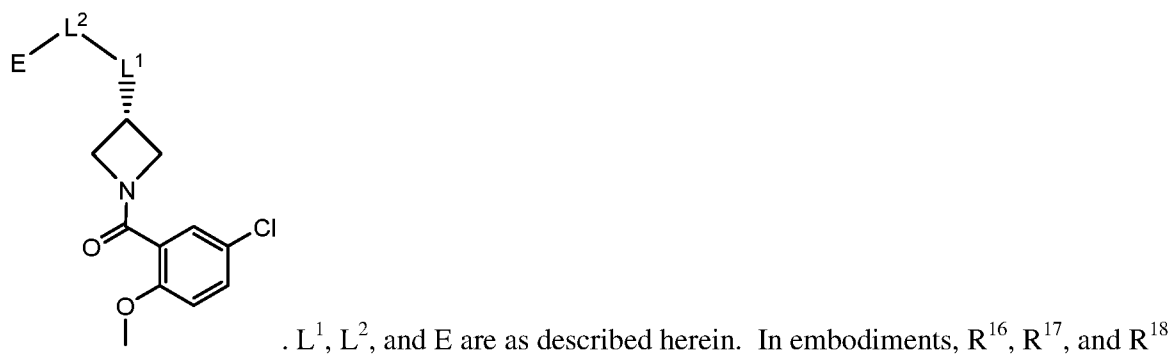


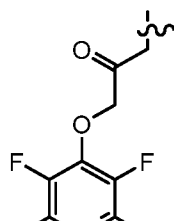
[0276] In embodiments, the compound has the formula:



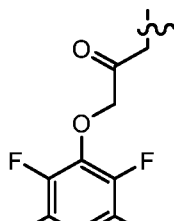
are as described herein. In embodiments, the compound has the formula:

5 L¹, L², and E are as described herein. In embodiments, the compound has the formula:

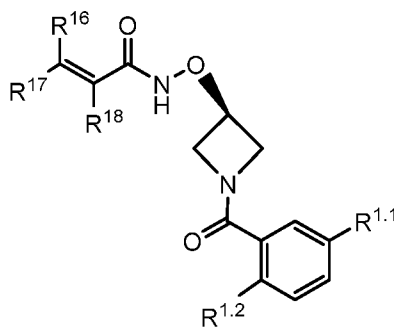




are hydrogen. In embodiments, E is: $\text{F}-\text{C}_6\text{H}_2(\text{F})-\text{Y}^2-\text{F}$ and Y^2 is as described herein. In



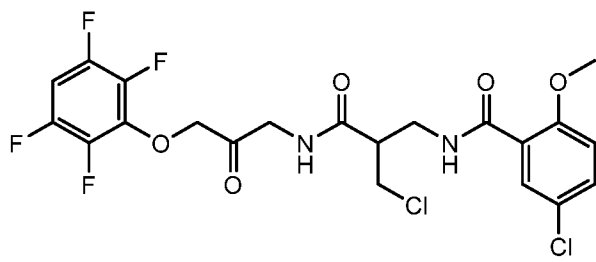
embodiments, E is: $\text{F}-\text{C}_6\text{H}_2(\text{F})-\text{F}$. In embodiments, E is: $\text{F}-\text{C}_6\text{H}_3(\text{F})-\text{N}-\text{F}$. In embodiments, L^1 is $-\text{C}(\text{O})-$. In embodiments, L^2 is $-\text{NH}-$.



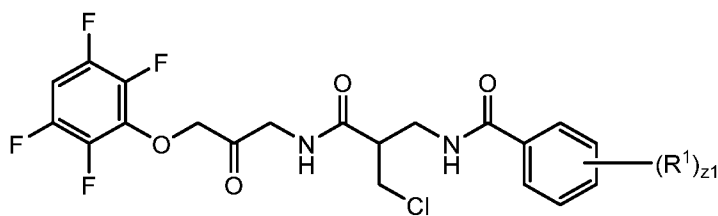
In embodiments, the compound has the formula:

- 5 R^{18} are as described herein. In embodiments, R^{16} , R^{17} , and R^{18} are hydrogen. $\text{R}^{1.1}$ and $\text{R}^{1.2}$ have the values of R^1 . $\text{R}^{1.1}$ may be halogen. $\text{R}^{1.1}$ may be hydrogen. $\text{R}^{1.1}$ may be $-\text{Cl}$. $\text{R}^{1.2}$ may be hydrogen. $\text{R}^{1.2}$ may be unsubstituted 2 to 4 membered heteroalkyl. $\text{R}^{1.2}$ may be unsubstituted 2 to 3 membered heteroalkyl. $\text{R}^{1.2}$ may be unsubstituted methoxy. $\text{R}^{1.2}$ may be unsubstituted ethoxy. $\text{R}^{1.2}$ may be unsubstituted propoxy.

- 10 [0277] In embodiments, the compound has the formula:



(IIIB). In embodiments, the compound has the

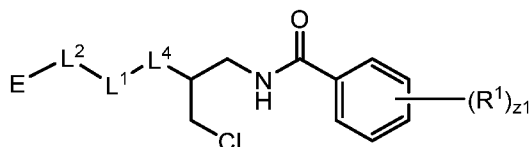


formula:

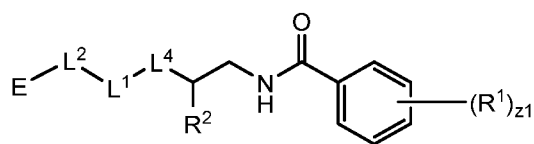
(IIIB). R^1 and $z1$ are as

described herein.

[0278] In embodiments, the compound has the formula:



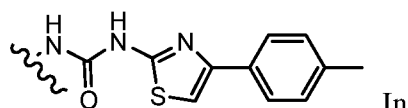
. R^1 , L^1 , L^2 , L^4 , E , and $z1$ are as described herein.



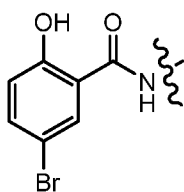
5 In embodiments, the compound has the formula:

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

[0279] In embodiments, the compound includes

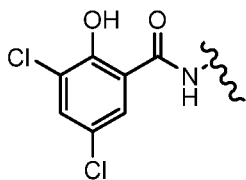


. In

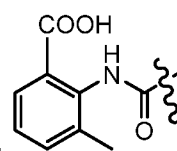


embodiments, the compound includes

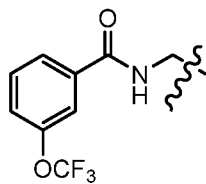
. In embodiments, the compound includes



. In embodiments, the compound includes

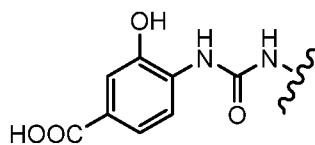


. In embodiments,

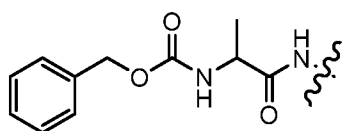


10 the compound includes

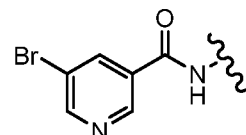
. In embodiments, the compound includes



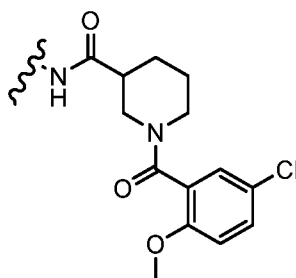
. In embodiments, the compound includes



. In embodiments, the compound includes

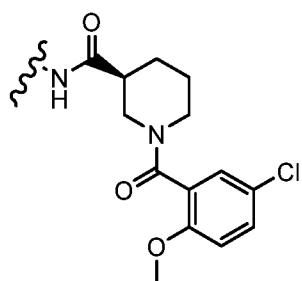


. In



embodiments, the compound includes

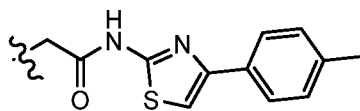
. In embodiments, the compound



includes

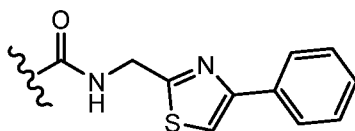
. In embodiments, the compound is a compound described herein, including in an example, figures, or table.

5 In embodiments, the compound includes

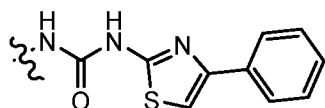


. In embodiments, the

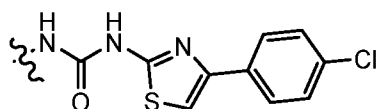
compound includes



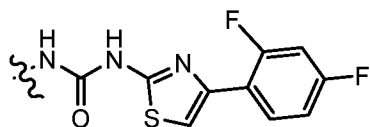
. In embodiments, the compound includes



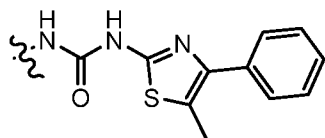
. In embodiments, the compound includes



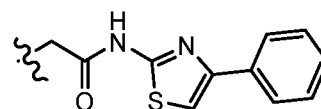
. In embodiments, the compound includes



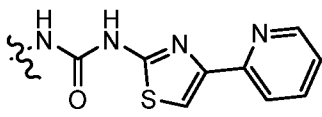
. In embodiments, the compound includes

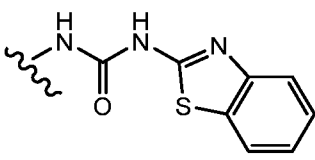


. In embodiments, the compound includes

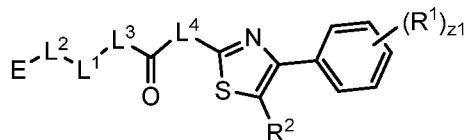


10

. In embodiments, the compound includes . In embodiments, the

compound includes .

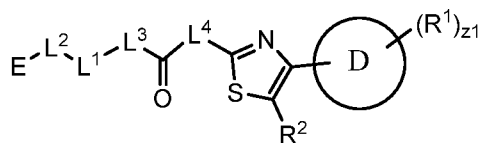
[0280] In an aspect is provided a compound having the formula:



(IV). R^1 , R^2 , R^4 , R^5 , L^1 , L^2 , L^3 , L^4 , E , and $z1$ are as

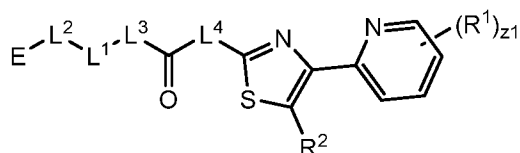
- 5 described herein (e.g., for formulae I, II, III, and embodiments thereof or in examples, figures, tables, or claims). L^4 may be $-N(R^4)-$. L^4 may be $-CH_2N(R^4)-$. L^3 may be $-N(R^5)-$. L^3 may be a bond. L^4 may be a bond. R^4 and R^5 may be hydrogen. L^3 may be unsubstituted methylene. L^3 may be unsubstituted ethylene. L^3 may be unsubstituted n-propylene. L^3 may be unsubstituted n-butylene. R^2 may be unsubstituted methyl. R^2 may be hydrogen.

10 **[0281]** In an aspect is provided a compound having the formula:

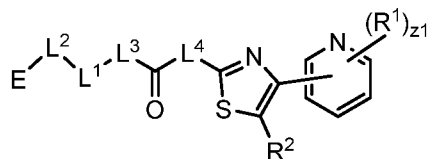


(V). R^1 , R^2 , R^4 , R^5 , L^1 , L^2 , L^3 , L^4 , E , and $z1$ are as

- described herein (e.g., for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims). L^4 may be $-N(R^4)-$. L^4 may be $-N(H)-$. L^4 may be $-CH_2N(R^4)-$. L^3 may be $-N(R^5)-$. L^3 may be $-N(H)-$. L^3 may be a bond. L^4 may be a bond. R^4 and R^5 may be hydrogen. L^3 may be unsubstituted methylene. L^3 may be unsubstituted ethylene. L^3 may be unsubstituted n-propylene. L^3 may be unsubstituted n-butylene. R^2 may be unsubstituted methyl. R^2 may be hydrogen. Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In embodiments, Ring D is C_3 - C_8 cycloalkyl, 3 to 8 membered heterocycloalkyl, C_6 - C_{10} aryl, or 5 to 10 membered heteroaryl. In embodiments, Ring D is C_3 - C_8 cycloalkyl. In embodiments, Ring D is 3 to 8 membered heterocycloalkyl. In embodiments, Ring D is C_6 - C_{10} aryl. In embodiments, Ring D is 5 to 10 membered heteroaryl. In embodiments, Ring D is phenyl. In embodiments, Ring D is 5 to 9 membered heteroaryl. In embodiments, Ring D is 5 to 6 membered heteroaryl. In embodiments, Ring D is 5 membered heteroaryl. In embodiments, Ring D is 6 membered heteroaryl. In embodiments, Ring D is pyridyl. In embodiments, the compound is
- 15
- 20

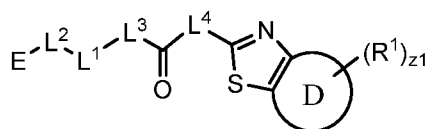


. $R^1, R^2, R^4, R^5, L^1, L^2, L^3, L^4, E$, and $z1$ are as described herein (e.g., for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims). In embodiments, $z1$ is 0. In embodiments, the compound is



. $R^1, R^2, R^4, R^5, L^1, L^2, L^3, L^4, E$, and $z1$ are as described herein (e.g., for formulae I, II, III, VI, and embodiments thereof or in examples, figures, tables, or claims).

[0282] In an aspect is provided a compound having the formula:



(VI). $R^1, R^2, R^4, R^5, L^1, L^2, L^3, L^4, E$, and $z1$ are as described herein (e.g., for formulae I, II, III, IV, V, and embodiments thereof or in examples, figures, tables, or claims). L^4 may be $-N(R^4)-$. L^4 may be $-N(H)-$. L^4 may be $-CH_2N(R^4)-$. L^3 may be $-N(R^5)-$. L^3 may be $-N(H)-$. L^3 may be a bond. L^4 may be a bond. R^4 and R^5 may be hydrogen. L^3 may be unsubstituted methylene. L^3 may be unsubstituted ethylene. L^3 may be unsubstituted n-propylene. L^3 may be unsubstituted n-butylene. R^2 may be unsubstituted methyl. R^2 may be hydrogen. Ring D is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In embodiments, Ring D is C_3 - C_8 cycloalkyl, 3 to 8 membered heterocycloalkyl, C_6 - C_{10} aryl, or 5 to 10 membered heteroaryl. In embodiments, Ring D is C_3 - C_8 cycloalkyl. In embodiments, Ring D is 3 to 8 membered heterocycloalkyl. In embodiments, Ring D is C_6 - C_{10} aryl. In embodiments, Ring D is 5 to 10 membered heteroaryl. In embodiments, Ring D is phenyl. In embodiments, Ring D is 5 to 9 membered heteroaryl. In embodiments, Ring D is 5 to 6 membered heteroaryl. In embodiments, Ring D is 5 membered heteroaryl. In embodiments, Ring D is 6 membered heteroaryl. In embodiments, Ring D is pyridyl.

[0283] In embodiments, R^1 is independently hydrogen, oxo, halogen, $-CX^1_3$, $-CHX^1_2$, $-OCH_2X^1$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^1_3$, $-OCHX^1_2$, R^{30} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{30} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8

- membered, 2 to 6 membered, or 2 to 4 membered), R^{30} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{30} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{30} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^1 is independently oxo, halogen, $-CX^1_3$, $-CHX^1_2$, $-OCH_2X^1$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^1_3$, $-OCHX^1_2$, R^{30} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{30} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{30} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{30} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{30} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{30} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^1 is halogen. In embodiments, X^1 is F.
- 15 **[0284]** R^{30} is independently oxo, halogen, $-CX^{30}_3$, $-CHX^{30}_2$, $-OCH_2X^{30}$, $-OCHX^{30}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{30}_3$, $-OCHX^{30}_2$, R^{31} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{31} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{31} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{31} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{31} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{31} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{30} is halogen. In embodiments, X^{30} is F.
- 25 **[0285]** R^{31} is independently oxo, halogen, $-CX^{31}_3$, $-CHX^{31}_2$, $-OCH_2X^{31}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{31}_3$, $-OCHX^{31}_2$, R^{32} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{32} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{32} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{32} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{32} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{32} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
- 30

C₁₀, C₁₀, or phenyl), or R³²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³¹ is halogen. In embodiments, X³¹ is F.

[0286] In embodiments, R² is independently hydrogen, oxo,

halogen, -CX²₃, -CHX²₂, -OCH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

- 5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²₃, -OCHX²₂, R³³-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R³³-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R³³-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R³³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). In embodiments, R² is independently oxo,
halogen, -CX²₃, -CHX²₂, -OCH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
15 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²₃, -OCHX²₂, R³³-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R³³-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R³³-substituted or unsubstituted aryl (e.g., C₆-
20 C₁₀, C₁₀, or phenyl), or R³³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X² is halogen. In embodiments, X² is F.

[0287] R³³ is independently oxo,

halogen, -CX³³₃, -CHX³³₂, -OCH₂X³³, -OCHX³³₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -

- 25 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³³₃, -OCHX³³₂, R³⁴-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁴-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁴-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁴-substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁴-substituted or unsubstituted aryl
30 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X³³ is halogen. In embodiments, X³³ is F.

[0288] R³⁴ is independently oxo,

halogen, -CX³⁴₃, -CHX³⁴₂, -OCH₂X³⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁴₃, -OCHX³⁴₂, R³⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁴ is halogen. In embodiments, X³⁴ is F.

[0289] In embodiments, R³ is independently hydrogen, oxo,
 10 halogen, -CX³₃, -CHX³₂, -OCH₂X³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³₃, -OCHX³₂, R³⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁶-substituted or unsubstituted cycloalkyl
 15 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³ is halogen. In embodiments, X³ is F.

[0290] R³⁶ is independently oxo,
 20 halogen, -CX³⁶₃, -CHX³⁶₂, -OCH₂X³⁶, -OCHX³⁶₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁶₃, -OCHX³⁶₂, R³⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R³⁷-substituted or unsubstituted
 25 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R³⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R³⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R³⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X³⁶ is halogen. In embodiments, X³⁶ is F.

[0291] R³⁷ is independently oxo,
 30 halogen, -CX³⁷₃, -CHX³⁷₂, -OCH₂X³⁷, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX³⁷₃, -OCHX³⁷₂, R³⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R³⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R^{38} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{38} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{38} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{38} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{37} is halogen. In embodiments, X^{37} is F.

[0292] In embodiments, R^4 is independently hydrogen, oxo, halogen, $-CX^4_3$, $-CHX^4_2$, $-OCH_2X^4$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^4_3$, $-OCHX^4_2$, R^{39} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{39} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{39} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{39} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{39} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{39} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^4 is halogen. In embodiments, X^4 is F.

[0293] R^{39} is independently oxo, halogen, $-CX^{39}_3$, $-CHX^{39}_2$, $-OCH_2X^{39}$, $-OCHX^{39}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{39}_3$, $-OCHX^{39}_2$, R^{40} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{40} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{40} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{40} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{40} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{40} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{39} is halogen. In embodiments, X^{39} is F.

[0294] R^{40} is independently oxo, halogen, $-CX^{40}_3$, $-CHX^{40}_2$, $-OCH_2X^{40}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{40}_3$, $-OCHX^{40}_2$, R^{41} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{41} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{41} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{41} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{41} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{41} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{40} is halogen. In embodiments, X^{40} is F.

C₁₀, C₁₀, or phenyl), or R⁴¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁰ is halogen. In embodiments, X⁴⁰ is F.

[0295] In embodiments, R⁵ is independently hydrogen, oxo,

halogen, -CX⁵₃, -CHX⁵₂, -OCH₂X⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵₃, -OCHX⁵₂, R⁴²-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁴²-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R⁴²-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁴²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁵ is halogen. In embodiments, X⁵ is F.

[0296] R⁴² is independently oxo,

halogen, -CX⁴²₃, -CHX⁴²₂, -OCH₂X⁴², -OCHX⁴²₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

15 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴²₃, -OCHX⁴²₂, R⁴³-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴³-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴³-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴³-substituted or unsubstituted heterocycloalkyl (e.g.,
20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴³-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴³-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁴² is halogen. In embodiments, X⁴² is F.

[0297] R⁴³ is independently oxo,

halogen, -CX⁴³₃, -CHX⁴³₂, -OCH₂X⁴³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

25 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴³₃, -OCHX⁴³₂, R⁴⁴-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁴-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
30 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁴-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁴⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁴³ is halogen. In embodiments, X⁴³ is F.

[0298] In embodiments, R^6 is independently hydrogen, oxo, halogen, $-CX^6_3$, $-CHX^6_2$, $-OCH_2X^6$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^6_3$, $-OCHX^6_2$, R^{45} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{45} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{45} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{45} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{45} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{45} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^6 is halogen. In embodiments, X^6 is F.

[0299] R^{45} is independently oxo, halogen, $-CX^{45}_3$, $-CHX^{45}_2$, $-OCH_2X^{45}$, $-OCHX^{45}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{45}_3$, $-OCHX^{45}_2$, R^{46} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{46} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{46} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{46} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{46} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{46} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{45} is halogen. In embodiments, X^{45} is F.

[0300] R^{46} is independently oxo, halogen, $-CX^{46}_3$, $-CHX^{46}_2$, $-OCH_2X^{46}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{46}_3$, $-OCHX^{46}_2$, R^{47} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{47} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{47} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{47} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{47} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{47} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{46} is halogen. In embodiments, X^{46} is F.

[0301] In embodiments, R^7 is independently hydrogen, oxo, halogen, $-CX^7_3$, $-CHX^7_2$, $-OCH_2X^7$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^7_3$, $-OCHX^7_2$, R^8 -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^8 -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^8 -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^8 -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^8 -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^8 -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^7 is halogen. In embodiments, X^7 is F.

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷₃, -OCHX⁷₂, R⁴⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷ is halogen. In embodiments, X⁷ is F.

[0302] R⁴⁸ is independently oxo,

halogen, -CX⁴⁸₃, -CHX⁴⁸₂, -OCH₂X⁴⁸, -OCHX⁴⁸₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
 10 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁸₃, -OCHX⁴⁸₂, R⁴⁹-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁴⁹-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁴⁹-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁴⁹-substituted or unsubstituted heterocycloalkyl (e.g.,
 15 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁴⁹-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁴⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). X⁴⁸ is halogen. In embodiments, X⁴⁸ is F.

[0303] R⁴⁹ is independently oxo,

halogen, -CX⁴⁹₃, -CHX⁴⁹₂, -OCH₂X⁴⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 20 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁴⁹₃, -OCHX⁴⁹₂, R⁵⁰-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁰-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 25 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁰-substituted or unsubstituted aryl (e.g., C₆-
 C₁₀, C₁₀, or phenyl), or R⁵⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
 membered, or 5 to 6 membered). X⁴⁹ is halogen. In embodiments, X⁴⁹ is F.

[0304] In embodiments, R⁸ is independently hydrogen, oxo,

halogen, -CX⁸₃, -CHX⁸₂, -OCH₂X⁸, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 30 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸₃, -OCHX⁸₂, R⁵¹-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁵¹-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸ is halogen. In embodiments, X⁸ is F.

- 5 [0305] R⁵¹ is independently oxo, halogen, -CX⁵¹₃, -CHX⁵¹₂, -OCH₂X⁵¹, -OCHX⁵¹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵¹₃, -OCHX⁵¹₂, R⁵²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵²-substituted or unsubstituted heteroalkyl
- 10 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵²-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵¹ is halogen. In embodiments, X⁵¹ is F.

- 15 [0306] R⁵² is independently oxo, halogen, -CX⁵²₃, -CHX⁵²₂, -OCH₂X⁵², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵²₃, -OCHX⁵²₂, R⁵³-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
- 20 membered, 2 to 6 membered, or 2 to 4 membered), R⁵³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵³-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵² is halogen. In embodiments, X⁵² is F.

- 25 [0307] In embodiments, R⁹ is independently hydrogen, oxo, halogen, -CX⁹₃, -CHX⁹₂, -OCH₂X⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹₃, -OCHX⁹₂, R⁵⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
- 30 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁴-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁴-substituted or unsubstituted aryl (e.g., C₆-

C₁₀, C₁₀, or phenyl), or R⁵⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹ is halogen. In embodiments, X⁹ is F.

[0308] R⁵⁴ is independently oxo,

halogen, -CX⁵⁴₃, -CHX⁵⁴₂, -OCH₂X⁵⁴, -OCHX⁵⁴₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

5 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵⁴₃, -OCHX⁵⁴₂, R⁵⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁵-substituted or unsubstituted heterocycloalkyl (e.g., 10 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵⁴ is halogen. In embodiments, X⁵⁴ is F.

[0309] R⁵⁵ is independently oxo,

halogen, -CX⁵⁵₃, -CHX⁵⁵₂, -OCH₂X⁵⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

15 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁵⁵₃, -OCHX⁵⁵₂, R⁵⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁶-substituted or unsubstituted heterocycloalkyl (e.g., 20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁵⁵ is halogen. In embodiments, X⁵⁵ is F.

[0310] In embodiments, R¹⁰ is independently hydrogen, oxo,

halogen, -CX¹⁰₃, -CHX¹⁰₂, -OCH₂X¹⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

25 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁰₃, -OCHX¹⁰₂, R⁵⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁵⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁵⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁵⁷-substituted or unsubstituted heterocycloalkyl (e.g., 30 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁵⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁵⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁰ is halogen. In embodiments, X¹⁰ is F.

[0311] R^{57} is independently oxo,

halogen, $-CX^{57}_3$, $-CHX^{57}_2$, $-OCH_2X^{57}$, $-OCHX^{57}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-S$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{57}_3$, $-OCHX^{57}_2$, R^{58} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{58} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{58} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{58} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{58} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{58} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{57} is halogen. In embodiments, X^{57} is F.

[0312] R^{58} is independently oxo,

halogen, $-CX^{58}_3$, $-CHX^{58}_2$, $-OCH_2X^{58}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{58}_3$, $-OCHX^{58}_2$, R^{59} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{59} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{59} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{59} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{59} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{59} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{58} is halogen. In embodiments, X^{58} is F.

[0313] In embodiments, R^{7A} is independently hydrogen, oxo,

halogen, $-CX^{7A}_3$, $-CHX^{7A}_2$, $-OCH_2X^{7A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{7A}_3$, $-OCHX^{7A}_2$, R^{48A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{48A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{48A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{48A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7A} is independently oxo, halogen, $-CX^{7A}_3$, $-CHX^{7A}_2$, $-OCH_2X^{7A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{7A}_3$, $-OCHX^{7A}_2$, R^{48A} -substituted or unsubstituted

alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{48A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{7A} is halogen. In embodiments, X^{7A} is F.

[0314] R^{48A} is independently oxo, halogen, -CX^{48A}₃, -CHX^{48A}₂, -OCH₂X^{48A}, -OCHX^{48A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{48A}₃, -OCHX^{48A}₂, R^{49A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{49A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{49A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{49A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{49A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48A} is halogen. In embodiments, X^{48A} is F.

[0315] R^{49A} is independently oxo, halogen, -CX^{49A}₃, -CHX^{49A}₂, -OCH₂X^{49A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{49A}₃, -OCHX^{49A}₂, R^{50A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{50A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{50A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{50A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{50A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{50A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{49A} is halogen. In embodiments, X^{49A} is F.

[0316] In embodiments, R^{8A} is independently hydrogen, oxo, halogen, -CX^{8A}₃, -CHX^{8A}₂, -OCH₂X^{8A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{8A}₃, -OCHX^{8A}₂, R^{51A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{51A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{51A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{51A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{51A} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{51A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8A} is halogen. In embodiments, X^{8A} is F.

[0317] R^{51A} is independently oxo,

- 5 halogen, $-CX^{51A}_3$, $-CHX^{51A}_2$, $-OCH_2X^{51A}$, $-OCHX^{51A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{51A}_3$, $-OCHX^{51A}_2$, R^{52A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{52A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{52A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{52A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{52A} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{52A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{51A} is halogen. In embodiments, X^{51A} is F.

[0318] R^{52A} is independently oxo,

- 15 halogen, $-CX^{52A}_3$, $-CHX^{52A}_2$, $-OCH_2X^{52A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{52A}_3$, $-OCHX^{52A}_2$, R^{53A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{53A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{53A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{53A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{53A} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{53A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{52A} is halogen. In embodiments, X^{52A} is F.

[0319] In embodiments, R^{9A} is independently hydrogen, oxo,

- 25 halogen, $-CX^{9A}_3$, $-CHX^{9A}_2$, $-OCH_2X^{9A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9A}_3$, $-OCHX^{9A}_2$, R^{54A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{54A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{54A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{54A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{54A} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{54A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{9A} is halogen. In embodiments, X^{9A} is F.

[0320] R^{54A} is independently oxo,

halogen, $-CX^{54A}_3$, $-CHX^{54A}_2$, $-OCH_2X^{54A}$, $-OCHX^{54A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{54A}_3$, $-OCHX^{54A}_2$, R^{55A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{55A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{55A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{55A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54A} is halogen. In embodiments, X^{54A} is F.

[0321] R^{55A} is independently oxo,

halogen, $-CX^{55A}_3$, $-CHX^{55A}_2$, $-OCH_2X^{55A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{55A}_3$, $-OCHX^{55A}_2$, R^{56A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{56A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{56A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{56A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{56A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{56A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{55A} is halogen. In embodiments, X^{55A} is F.

[0322] In embodiments, R^{10A} is independently hydrogen, oxo,

halogen, $-CX^{10A}_3$, $-CHX^{10A}_2$, $-OCH_2X^{10A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{10A}_3$, $-OCHX^{10A}_2$, R^{57A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{57A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{57A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{57A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{57A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{57A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{10A} is halogen. In embodiments, X^{10A} is F.

[0323] R^{57A} is independently oxo,

halogen, $-CX^{57A}_3$, $-CHX^{57A}_2$, $-OCH_2X^{57A}$, $-OCHX^{57A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-$

NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{57A}₃, -OCHX^{57A}₂, R^{58A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{58A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{58A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{58A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{58A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{58A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{57A} is halogen. In embodiments, X^{57A} is F.

[0324] R^{58A} is independently oxo,

halogen, -CX^{58A}₃, -CHX^{58A}₂, -OCH₂X^{58A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{58A}₃, -OCHX^{58A}₂, R^{59A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{59A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{59A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{59A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{59A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{59A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{58A} is halogen. In embodiments, X^{58A} is F.

[0325] In embodiments, R^{7B} is independently hydrogen, oxo,

halogen, -CX^{7B}₃, -CHX^{7B}₂, -OCH₂X^{7B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{7B}₃, -OCHX^{7B}₂, R^{48B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{48B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{48B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{7B} is independently oxo, halogen, -CX^{7B}₃, -CHX^{7B}₂, -OCH₂X^{7B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{7B}₃, -OCHX^{7B}₂, R^{48B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{48B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{48B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{48B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{48B} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{48B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{7B} is halogen. In embodiments, X^{7B} is F.

[0326] R^{48B} is independently oxo,

- 5 halogen, $-CX^{48B}_3$, $-CHX^{48B}_2$, $-OCH_2X^{48B}$, $-OCHX^{48B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{48B}_3$, $-OCHX^{48B}_2$, R^{49B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{49B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{49B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{49B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{49B} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{49B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{48B} is halogen. In embodiments, X^{48B} is F.

[0327] R^{49B} is independently oxo,

- 15 halogen, $-CX^{49B}_3$, $-CHX^{49B}_2$, $-OCH_2X^{49B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{49B}_3$, $-OCHX^{49B}_2$, R^{50B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{50B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{50B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{50B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{50B} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{50B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{49B} is halogen. In embodiments, X^{49B} is F.

[0328] In embodiments, R^{8B} is independently hydrogen, oxo,

- 25 halogen, $-CX^{8B}_3$, $-CHX^{8B}_2$, $-OCH_2X^{8B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{8B}_3$, $-OCHX^{8B}_2$, R^{51B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), R^{51B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{51B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), R^{51B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{51B} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or R^{51B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{8B} is halogen. In embodiments, X^{8B} is F.

[0329] R^{51B} is independently oxo,

halogen, $-CX^{51B}_3$, $-CHX^{51B}_2$, $-OCH_2X^{51B}$, $-OCHX^{51B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{51B}_3$, $-OCHX^{51B}_2$, R^{52B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{52B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{52B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{52B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{52B} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{52B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{51B} is halogen. In embodiments, X^{51B} is F.

[0330] R^{52B} is independently oxo,

halogen, $-CX^{52B}_3$, $-CHX^{52B}_2$, $-OCH_2X^{52B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{52B}_3$, $-OCHX^{52B}_2$, R^{53B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{53B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{53B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{53B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{53B} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{53B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{52B} is halogen. In embodiments, X^{52B} is F.

[0331] In embodiments, R^{9B} is independently hydrogen, oxo,

halogen, $-CX^{9B}_3$, $-CHX^{9B}_2$, $-OCH_2X^{9B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{9B}_3$, $-OCHX^{9B}_2$, R^{54B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{54B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{54B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{54B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{54B} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{54B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{9B} is halogen. In embodiments, X^{9B} is F.

[0332] R^{54B} is independently oxo,

halogen, $-CX^{54B}_3$, $-CHX^{54B}_2$, $-OCH_2X^{54B}$, $-OCHX^{54B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-$

NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{54B}₃, -OCHX^{54B}₂, R^{55B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{55B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{55B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{55B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{55B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{55B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{54B} is halogen. In embodiments, X^{54B} is F.

[0333] R^{55B} is independently oxo,

halogen, -CX^{55B}₃, -CHX^{55B}₂, -OCH₂X^{55B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{55B}₃, -OCHX^{55B}₂, R^{56B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{56B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{56B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{56B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{56B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{56B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{55B} is halogen. In embodiments, X^{55B} is F.

[0334] In embodiments, R^{10B} is independently hydrogen, oxo,

halogen, -CX^{10B}₃, -CHX^{10B}₂, -OCH₂X^{10B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{10B}₃, -OCHX^{10B}₂, R^{57B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{57B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{57B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{57B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{57B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{57B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{10B} is halogen. In embodiments, X^{10B} is F.

[0335] R^{57B} is independently oxo,

halogen, -CX^{57B}₃, -CHX^{57B}₂, -OCH₂X^{57B}, -OCHX^{57B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{57B}₃, -OCHX^{57B}₂, R^{58B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{58B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{58B}-substituted or unsubstituted

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{58B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{58B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{58B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{57B} is halogen. In embodiments, X^{57B} is F.

- 5 [0336] R^{58B} is independently oxo,
halogen, -CX^{58B}₃, -CHX^{58B}₂, -OCH₂X^{58B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{58B}₃, -OCHX^{58B}₂, R^{59B}-substituted or unsubstituted
alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{59B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
10 membered, 2 to 6 membered, or 2 to 4 membered), R^{59B}-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{59B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R^{59B}-substituted or unsubstituted aryl (e.g.,
C₆-C₁₀, C₁₀, or phenyl), or R^{59B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
to 9 membered, or 5 to 6 membered). X^{58B} is halogen. In embodiments, X^{58B} is F.
- 15 [0337] In embodiments, R¹¹ is independently hydrogen, oxo,
halogen, -CX¹¹₃, -CHX¹¹₂, -OCH₂X¹¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹¹₃, -OCHX¹¹₂, R⁶⁰-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
20 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁰-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁰-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁶⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X¹¹ is halogen. In embodiments, X¹¹ is F.
- 25 [0338] R⁶⁰ is independently oxo,
halogen, -CX⁶⁰₃, -CHX⁶⁰₂, -OCH₂X⁶⁰, -OCHX⁶⁰₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁰₃, -OCHX⁶⁰₂, R⁶¹-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶¹-substituted or unsubstituted heteroalkyl
30 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶¹-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶¹-substituted or unsubstituted heterocycloalkyl (e.g.,
3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶¹-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁰ is halogen. In embodiments, X⁶⁰ is F.

[0339] R⁶¹ is independently oxo,

halogen, -CX⁶¹₃, -CHX⁶¹₂, -OCH₂X⁶¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶¹₃, -OCHX⁶¹₂, R⁶²-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁶²-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 10 membered, 3 to 6 membered, or 5 to 6 membered), R⁶²-substituted or unsubstituted aryl (e.g., C₆-
 C₁₀, C₁₀, or phenyl), or R⁶²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
 membered, or 5 to 6 membered). X⁶¹ is halogen. In embodiments, X⁶¹ is F.

[0340] In embodiments, R¹² is independently hydrogen, oxo,

halogen, -CX¹²₃, -CHX¹²₂, -OCH₂X¹², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 15 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹²₃, -OCHX¹²₂, R⁶³-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁶³-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 20 membered, 3 to 6 membered, or 5 to 6 membered), R⁶³-substituted or unsubstituted aryl (e.g., C₆-
 C₁₀, C₁₀, or phenyl), or R⁶³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
 membered, or 5 to 6 membered). X¹² is halogen. In embodiments, X¹² is F.

[0341] R⁶³ is independently oxo,

halogen, -CX⁶³₃, -CHX⁶³₂, -OCH₂X⁶³, -OCHX⁶³₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
 25 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶³₃, -OCHX⁶³₂, R⁶⁴-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁴-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁴-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁴-substituted or unsubstituted heterocycloalkyl (e.g.,
 30 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁴-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). X⁶³ is halogen. In embodiments, X⁶³ is F.

[0342] R^{64} is independently oxo,

halogen, $-CX^{64}_3$, $-CHX^{64}_2$, $-OCH_2X^{64}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=O$, $-NHNH_2$, $-NHC=O$, $-NH_2$, $-NHSO_2H$, $-NHC=O$, $-H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{64}_3$, $-OCHX^{64}_2$, R^{65} -substituted or unsubstituted alkyl

5 (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{65} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{65} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{65} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{65} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{65} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{64} is halogen. In embodiments, X^{64} is F.

[0343] In embodiments, R^{13} is independently hydrogen, oxo,

halogen, $-CX^{13}_3$, $-CHX^{13}_2$, $-OCH_2X^{13}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=O$, $-NHNH_2$, $-NHC=O$, $-NH_2$, $-NHSO_2H$, $-NHC=O$, $-H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{13}_3$, $-OCHX^{13}_2$, R^{66} -substituted or unsubstituted alkyl

15 (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{66} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{66} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{66} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{66} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{66} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{13} is halogen. In embodiments, X^{13} is F.

[0344] R^{66} is independently oxo,

halogen, $-CX^{66}_3$, $-CHX^{66}_2$, $-OCH_2X^{66}$, $-OCHX^{66}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=O$, $-NHNH_2$, $-NHC=O$, $-NH_2$, $-NHSO_2H$, $-NHC=O$, $-H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{66}_3$, $-OCHX^{66}_2$, R^{67} -substituted or

25 unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{67} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{67} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{67} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{67} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{67} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{66} is halogen. In embodiments, X^{66} is F.

[0345] R^{67} is independently oxo,

halogen, $-CX^{67}_3$, $-CHX^{67}_2$, $-OCH_2X^{67}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=O$, $-NHNH_2$, $-NHC=O$, $-NH_2$, $-NHSO_2H$, $-NHC=O$, $-H$

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁷₃, -OCHX⁶⁷₂, R⁶⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁷ is halogen. In embodiments, X⁶⁷ is F.

[0346] In embodiments, R¹⁴ is independently hydrogen, oxo, halogen, -CX¹⁴₃, -CHX¹⁴₂, -OCH₂X¹⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁴₃, -OCHX¹⁴₂, R⁶⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁶⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁶⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁶⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁶⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁶⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁴ is halogen. In embodiments, X¹⁴ is F.

[0347] R⁶⁹ is independently oxo, halogen, -CX⁶⁹₃, -CHX⁶⁹₂, -OCH₂X⁶⁹, -OCHX⁶⁹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁶⁹₃, -OCHX⁶⁹₂, R⁷⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁶⁹ is halogen. In embodiments, X⁶⁹ is F.

[0348] R⁷⁰ is independently oxo, halogen, -CX⁷⁰₃, -CHX⁷⁰₂, -OCH₂X⁷⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁰₃, -OCHX⁷⁰₂, R⁷¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷¹-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁰ is halogen. In embodiments, X⁷⁰ is F.

- 5 **[0349]** In embodiments, R¹⁵ is independently hydrogen, oxo, halogen, -CX¹⁵₃, -CHX¹⁵₂, -OCH₂X¹⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX¹⁵₃, -OCHX¹⁵₂, R⁷²-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷²-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁵ is halogen. In embodiments, X¹⁵ is F.

- 15 **[0350]** R⁷² is independently oxo, halogen, -CX⁷²₃, -CHX⁷²₂, -OCH₂X⁷², -OCHX⁷²₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX⁷²₃, -OCHX⁷²₂, R⁷³-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷³-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷³-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷² is halogen. In embodiments, X⁷² is F.

- 25 **[0351]** R⁷³ is independently oxo, halogen, -CX⁷³₃, -CHX⁷³₂, -OCH₂X⁷³, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX⁷³₃, -OCHX⁷³₂, R⁷⁴-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁴-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁴-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

C₁₀, C₁₀, or phenyl), or R⁷⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁷³ is halogen. In embodiments, X⁷³ is F.

[0352] In embodiments, R¹⁶ is independently hydrogen, oxo,

halogen, -CX¹⁶₃, -CHX¹⁶₂, -OCH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, R⁷⁵-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁵-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁵-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁷⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X¹⁶ is halogen. In embodiments, X¹⁶ is F.

[0353] R⁷⁵ is independently oxo,

halogen, -CX⁷⁵₃, -CHX⁷⁵₂, -OCH₂X⁷⁵, -OCHX⁷⁵₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

15 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁵₃, -OCHX⁷⁵₂, R⁷⁶-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁶-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁶-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁶-substituted or unsubstituted heterocycloalkyl (e.g.,
20 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁶-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁷⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁷⁵ is halogen. In embodiments, X⁷⁵ is F.

[0354] R⁷⁶ is independently oxo,

halogen, -CX⁷⁶₃, -CHX⁷⁶₂, -OCH₂X⁷⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

25 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁷⁶₃, -OCHX⁷⁶₂, R⁷⁷-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁷⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁷⁷-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁷⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
30 membered, 3 to 6 membered, or 5 to 6 membered), R⁷⁷-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁷⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁷⁶ is halogen. In embodiments, X⁷⁶ is F.

[0355] In embodiments, R^{17} is independently hydrogen, oxo, halogen, $-CX^{17}_3$, $-CHX^{17}_2$, $-OCH_2X^{17}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{17}_3$, $-OCHX^{17}_2$, R^{78} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{78} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{78} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{78} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{78} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17} is halogen. In embodiments, X^{17} is F.

[0356] R^{78} is independently oxo, halogen, $-CX^{78}_3$, $-CHX^{78}_2$, $-OCH_2X^{78}$, $-OCHX^{78}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{78}_3$, $-OCHX^{78}_2$, R^{79} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{79} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{79} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{79} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78} is halogen. In embodiments, X^{78} is F.

[0357] R^{79} is independently oxo, halogen, $-CX^{79}_3$, $-CHX^{79}_2$, $-OCH_2X^{79}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{79}_3$, $-OCHX^{79}_2$, R^{80} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{80} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{80} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{80} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79} is halogen. In embodiments, X^{79} is F.

[0358] In embodiments, R^{18} is independently hydrogen, oxo, halogen, $-CX^{18}_3$, $-CHX^{18}_2$, $-OCH_2X^{18}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{18}_3$, $-OCHX^{18}_2$, R^{80} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{80} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{80} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{80} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79} is halogen. In embodiments, X^{79} is F.

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁸₃, -OCHX¹⁸₂, R⁸¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁸ is halogen. In embodiments, X¹⁸ is F.

[0359] R⁸¹ is independently oxo,

halogen, -CX⁸¹₃, -CHX⁸¹₂, -OCH₂X⁸¹, -OCHX⁸¹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S
 10 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸¹₃, -OCHX⁸¹₂, R⁸²-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸²-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸²-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸²-substituted or unsubstituted heterocycloalkyl (e.g.,
 15 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸²-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸²-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). X⁸¹ is halogen. In embodiments, X⁸¹ is F.

[0360] R⁸² is independently oxo,

halogen, -CX⁸²₃, -CHX⁸²₂, -OCH₂X⁸², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 20 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸²₃, -OCHX⁸²₂, R⁸³-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁸³-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 25 membered, 3 to 6 membered, or 5 to 6 membered), R⁸³-substituted or unsubstituted aryl (e.g., C₆-
 C₁₀, C₁₀, or phenyl), or R⁸³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
 membered, or 5 to 6 membered). X⁸² is halogen. In embodiments, X⁸² is F.

[0361] In embodiments, R¹⁹ is independently hydrogen, oxo,

halogen, -CX¹⁹₃, -CHX¹⁹₂, -OCH₂X¹⁹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -
 30 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁹₃, -OCHX¹⁹₂, R⁸⁴-substituted or unsubstituted alkyl
 (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁴-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁴-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁴-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁴-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁹ is halogen. In embodiments, X¹⁹ is F.

- 5 **[0362]** R⁸⁴ is independently oxo, halogen, -CX⁸⁴₃, -CHX⁸⁴₂, -OCH₂X⁸⁴, -OCHX⁸⁴₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁴₃, -OCHX⁸⁴₂, R⁸⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁵-substituted or unsubstituted heteroalkyl
- 10 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸⁴ is halogen. In embodiments, X⁸⁴ is F.
- 15 **[0363]** R⁸⁵ is independently oxo, halogen, -CX⁸⁵₃, -CHX⁸⁵₂, -OCH₂X⁸⁵, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁵₃, -OCHX⁸⁵₂, R⁸⁶-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁶-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
- 20 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁶-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁶-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁶-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁶-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸⁵ is halogen. In embodiments, X⁸⁵ is F.
- 25 **[0364]** In embodiments, R^{16A} is independently hydrogen, oxo, halogen, -CX^{16A}₃, -CHX^{16A}₂, -OCH₂X^{16A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16A}₃, -OCHX^{16A}₂, R^{75A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
- 30 membered, 2 to 6 membered, or 2 to 4 membered), R^{75A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75A}-substituted or unsubstituted aryl (e.g.,

C₆-C₁₀, C₁₀, or phenyl), or R^{75A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16A} is halogen. In embodiments, X^{16A} is F.

[0365] R^{75A} is independently oxo,

halogen, -CX^{75A}₃, -CHX^{75A}₂, -OCH₂X^{75A}, -OCHX^{75A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
 5 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75A}₃, -OCHX^{75A}₂, R^{76A}-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76A}-substituted or unsubstituted heteroalkyl
 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76A}-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76A}-substituted or unsubstituted heterocycloalkyl (e.g.,
 10 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76A}-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). X^{75A} is halogen. In embodiments, X^{75A} is F.

[0366] R^{76A} is independently oxo,

halogen, -CX^{76A}₃, -CHX^{76A}₂, -OCH₂X^{76A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 15 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76A}₃, -OCHX^{76A}₂, R^{77A}-substituted or unsubstituted
 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{77A}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 20 membered, 3 to 6 membered, or 5 to 6 membered), R^{77A}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{77A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 to 9 membered, or 5 to 6 membered). X^{76A} is halogen. In embodiments, X^{76A} is F.

[0367] In embodiments, R^{17A} is independently hydrogen, oxo,

halogen, -CX^{17A}₃, -CHX^{17A}₂, -OCH₂X^{17A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 25 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17A}₃, -OCHX^{17A}₂, R^{78A}-substituted or unsubstituted
 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 membered, 2 to 6 membered, or 2 to 4 membered), R^{78A}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 30 membered, 3 to 6 membered, or 5 to 6 membered), R^{78A}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{78A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 to 9 membered, or 5 to 6 membered). X^{17A} is halogen. In embodiments, X^{17A} is F.

[0368] R^{78A} is independently oxo,

halogen, $-CX^{78A}_3$, $-CHX^{78A}_2$, $-OCH_2X^{78A}$, $-OCHX^{78A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{78A}_3$, $-OCHX^{78A}_2$, R^{79A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{79A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{79A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{79A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78A} is halogen. In embodiments, X^{78A} is F.

[0369] R^{79A} is independently oxo,

halogen, $-CX^{79A}_3$, $-CHX^{79A}_2$, $-OCH_2X^{79A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{79A}_3$, $-OCHX^{79A}_2$, R^{80A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{80A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{80A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{80A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79A} is halogen. In embodiments, X^{79A} is F.

[0370] In embodiments, R^{18A} is independently hydrogen, oxo,

halogen, $-CX^{18A}_3$, $-CHX^{18A}_2$, $-OCH_2X^{18A}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{18A}_3$, $-OCHX^{18A}_2$, R^{81A} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{81A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81A} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{81A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81A} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{81A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18A} is halogen. In embodiments, X^{18A} is F.

[0371] R^{81A} is independently oxo,

halogen, $-CX^{81A}_3$, $-CHX^{81A}_2$, $-OCH_2X^{81A}$, $-OCHX^{81A}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-$

NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{81A}₃, -OCHX^{81A}₂, R^{82A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{82A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{82A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{82A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81A} is halogen. In embodiments, X^{81A} is F.

[0372] R^{82A} is independently oxo,

halogen, -CX^{82A}₃, -CHX^{82A}₂, -OCH₂X^{82A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{82A}₃, -OCHX^{82A}₂, R^{83A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{83A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{83A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{83A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82A} is halogen. In embodiments, X^{82A} is F.

[0373] In embodiments, R^{19A} is independently hydrogen, oxo,

halogen, -CX^{19A}₃, -CHX^{19A}₂, -OCH₂X^{19A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{19A}₃, -OCHX^{19A}₂, R^{84A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{84A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{84A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{84A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19A} is halogen. In embodiments, X^{19A} is F.

[0374] R^{84A} is independently oxo,

halogen, -CX^{84A}₃, -CHX^{84A}₂, -OCH₂X^{84A}, -OCHX^{84A}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{84A}₃, -OCHX^{84A}₂, R^{85A}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85A}-substituted or unsubstituted

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84A} is halogen. In embodiments, X^{84A} is F.

5 [0375] R^{85A} is independently oxo,
 halogen, -CX^{85A}₃, -CHX^{85A}₂, -OCH₂X^{85A}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85A}₃, -OCHX^{85A}₂, R^{86A}-substituted or unsubstituted
 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 10 membered, 2 to 6 membered, or 2 to 4 membered), R^{86A}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{86A}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{86A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 to 9 membered, or 5 to 6 membered). X^{85A} is halogen. In embodiments, X^{85A} is F.

15 [0376] In embodiments, R^{16B} is independently hydrogen, oxo,
 halogen, -CX^{16B}₃, -CHX^{16B}₂, -OCH₂X^{16B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16B}₃, -OCHX^{16B}₂, R^{75B}-substituted or unsubstituted
 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 20 membered, 2 to 6 membered, or 2 to 4 membered), R^{75B}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{75B}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{75B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 to 9 membered, or 5 to 6 membered). X^{16B} is halogen. In embodiments, X^{16B} is F.

25 [0377] R^{75B} is independently oxo,
 halogen, -CX^{75B}₃, -CHX^{75B}₂, -OCH₂X^{75B}, -OCHX^{75B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂
 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75B}₃, -OCHX^{75B}₂, R^{76B}-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76B}-substituted or unsubstituted heteroalkyl
 30 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76B}-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76B}-substituted or unsubstituted heterocycloalkyl (e.g.,
 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76B}-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{75B} is halogen. In embodiments, X^{75B} is F.

[0378] R^{76B} is independently oxo,

halogen, -CX^{76B}₃, -CHX^{76B}₂, -OCH₂X^{76B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

- 5 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76B}₃, -OCHX^{76B}₂, R^{77B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{77B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{77B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{76B} is halogen. In embodiments, X^{76B} is F.

[0379] In embodiments, R^{17B} is independently hydrogen, oxo,

halogen, -CX^{17B}₃, -CHX^{17B}₂, -OCH₂X^{17B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

- 15 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17B}₃, -OCHX^{17B}₂, R^{78B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{78B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{78B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17B} is halogen. In embodiments, X^{17B} is F.

[0380] R^{78B} is independently oxo,

halogen, -CX^{78B}₃, -CHX^{78B}₂, -OCH₂X^{78B}, -OCHX^{78B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

- 25 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78B}₃, -OCHX^{78B}₂, R^{79B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{79B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{79B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{79B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78B} is halogen. In embodiments, X^{78B} is F.

[0381] R^{79B} is independently oxo,

halogen, $-CX^{79B}_3$, $-CHX^{79B}_2$, $-OCH_2X^{79B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{79B}_3$, $-OCHX^{79B}_2$, R^{80B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{80B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{80B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80B} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{80B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79B} is halogen. In embodiments, X^{79B} is F.

[0382] In embodiments, R^{18B} is independently hydrogen, oxo,

halogen, $-CX^{18B}_3$, $-CHX^{18B}_2$, $-OCH_2X^{18B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{18B}_3$, $-OCHX^{18B}_2$, R^{81B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{81B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{81B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81B} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{81B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18B} is halogen. In embodiments, X^{18B} is F.

[0383] R^{81B} is independently oxo,

halogen, $-CX^{81B}_3$, $-CHX^{81B}_2$, $-OCH_2X^{81B}$, $-OCHX^{81B}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{81B}_3$, $-OCHX^{81B}_2$, R^{82B} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{82B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82B} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{82B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82B} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{82B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81B} is halogen. In embodiments, X^{81B} is F.

[0384] R^{82B} is independently oxo,

halogen, $-CX^{82B}_3$, $-CHX^{82B}_2$, $-OCH_2X^{82B}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHHSO_2H$, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{82B}₃, -OCHX^{82B}₂, R^{83B}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{83B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{83B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{83B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82B} is halogen. In embodiments, X^{82B} is F.

[0385] In embodiments, R^{19B} is independently hydrogen, oxo,

halogen, -CX^{19B}₃, -CHX^{19B}₂, -OCH₂X^{19B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{19B}₃, -OCHX^{19B}₂, R^{84B}-substituted or unsubstituted

alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R^{84B}-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered, 3 to 6 membered, or 5 to 6 membered), R^{84B}-substituted or unsubstituted aryl (e.g.,

C₆-C₁₀, C₁₀, or phenyl), or R^{84B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5

to 9 membered, or 5 to 6 membered). X^{19B} is halogen. In embodiments, X^{19B} is F.

[0386] R^{84B} is independently oxo,

halogen, -CX^{84B}₃, -CHX^{84B}₂, -OCH₂X^{84B}, -OCHX^{84B}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -

NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{84B}₃, -OCHX^{84B}₂, R^{85B}-substituted or

unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85B}-substituted or unsubstituted heteroalkyl

(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85B}-substituted or unsubstituted

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85B}-substituted or unsubstituted heterocycloalkyl (e.g.,

3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85B}-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10

membered, 5 to 9 membered, or 5 to 6 membered). X^{84B} is halogen. In embodiments, X^{84B} is F.

[0387] R^{85B} is independently oxo,

halogen, -CX^{85B}₃, -CHX^{85B}₂, -OCH₂X^{85B}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85B}₃, -OCHX^{85B}₂, R^{86B}-substituted or unsubstituted

alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8

membered, 2 to 6 membered, or 2 to 4 membered), R^{86B}-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{86B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85B} is halogen. In embodiments, X^{85B} is F.

- 5 [0388] In embodiments, R^{16C} is independently hydrogen, oxo, halogen, -CX^{16C}₃, -CHX^{16C}₂, -OCH₂X^{16C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16C}₃, -OCHX^{16C}₂, R^{75C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{75C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16C} is halogen. In embodiments, X^{16C} is F.
- 10
- 15 [0389] R^{75C} is independently oxo, halogen, -CX^{75C}₃, -CHX^{75C}₂, -OCH₂X^{75C}, -OCHX^{75C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75C}₃, -OCHX^{75C}₂, R^{76C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{75C} is halogen. In embodiments, X^{75C} is F.
- 20
- 25 [0390] R^{76C} is independently oxo, halogen, -CX^{76C}₃, -CHX^{76C}₂, -OCH₂X^{76C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76C}₃, -OCHX^{76C}₂, R^{77C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{77C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{77C}-substituted or unsubstituted aryl (e.g.,
- 30

C₆-C₁₀, C₁₀, or phenyl), or R^{77C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{76C} is halogen. In embodiments, X^{76C} is F.

[0391] In embodiments, R^{17C} is independently hydrogen, oxo,

halogen, -CX^{17C}₃, -CHX^{17C}₂, -OCH₂X^{17C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

- 5 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17C}₃, -OCHX^{17C}₂, R^{78C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{78C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{78C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{78C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17C} is halogen. In embodiments, X^{17C} is F.

[0392] R^{78C} is independently oxo,

halogen, -CX^{78C}₃, -CHX^{78C}₂, -OCH₂X^{78C}, -OCHX^{78C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂

- 15 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78C}₃, -OCHX^{78C}₂, R^{79C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{79C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{79C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{79C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78C} is halogen. In embodiments, X^{78C} is F.

[0393] R^{79C} is independently oxo,

halogen, -CX^{79C}₃, -CHX^{79C}₂, -OCH₂X^{79C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -

- 25 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{79C}₃, -OCHX^{79C}₂, R^{80C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{80C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{80C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{80C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79C} is halogen. In embodiments, X^{79C} is F.

[0394] In embodiments, R^{18C} is independently hydrogen, oxo, halogen, $-CX^{18C}_3$, $-CHX^{18C}_2$, $-OCH_2X^{18C}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{18C}_3$, $-OCHX^{18C}_2$, R^{81C} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{81C} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81C} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{81C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81C} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{81C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18C} is halogen. In embodiments, X^{18C} is F.

[0395] R^{81C} is independently oxo, halogen, $-CX^{81C}_3$, $-CHX^{81C}_2$, $-OCH_2X^{81C}$, $-OCHX^{81C}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{81C}_3$, $-OCHX^{81C}_2$, R^{82C} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{82C} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82C} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{82C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82C} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{82C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81C} is halogen. In embodiments, X^{81C} is F.

[0396] R^{82C} is independently oxo, halogen, $-CX^{82C}_3$, $-CHX^{82C}_2$, $-OCH_2X^{82C}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, $-NHC=(O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{82C}_3$, $-OCHX^{82C}_2$, R^{83C} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{83C} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83C} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{83C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83C} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{83C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82C} is halogen. In embodiments, X^{82C} is F.

[0397] In embodiments, R^{19C} is independently hydrogen, oxo, halogen, $-CX^{19C}_3$, $-CHX^{19C}_2$, $-OCH_2X^{19C}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC=(O)NHNH_2$, $-NHC=(O)NH_2$, $-NHSO_2H$, -

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{19C}₃, -OCHX^{19C}₂, R^{84C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{84C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{84C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{84C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{84C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{84C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19C} is halogen. In embodiments, X^{19C} is F.

[0398] R^{84C} is independently oxo,

halogen, -CX^{84C}₃, -CHX^{84C}₂, -OCH₂X^{84C}, -OCHX^{84C}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{84C}₃, -OCHX^{84C}₂, R^{85C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84C} is halogen. In embodiments, X^{84C} is F.

[0399] R^{85C} is independently oxo,

halogen, -CX^{85C}₃, -CHX^{85C}₂, -OCH₂X^{85C}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{85C}₃, -OCHX^{85C}₂, R^{86C}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{86C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{86C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85C} is halogen. In embodiments, X^{85C} is F.

[0400] In embodiments, R^{16D} is independently hydrogen, oxo,

halogen, -CX^{16D}₃, -CHX^{16D}₂, -OCH₂X^{16D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{16D}₃, -OCHX^{16D}₂, R^{75D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{75D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{75D}-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{75D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{75D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{75D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{16D} is halogen. In embodiments, X^{16D} is F.

- 5 [0401] R^{75D} is independently oxo,
 halogen, -CX^{75D}₃, -CHX^{75D}₂, -OCH₂X^{75D}, -OCHX^{75D}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂,
 , -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
 NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{75D}₃, -OCHX^{75D}₂, R^{76D}-substituted or
 unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{76D}-substituted or unsubstituted heteroalkyl
 10 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{76D}-substituted or unsubstituted
 cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{76D}-substituted or unsubstituted heterocycloalkyl (e.g.,
 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{76D}-substituted or unsubstituted aryl
 (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{76D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10
 membered, 5 to 9 membered, or 5 to 6 membered). X^{75D} is halogen. In embodiments, X^{75D} is F.

- 15 [0402] R^{76D} is independently oxo,
 halogen, -CX^{76D}₃, -CHX^{76D}₂, -OCH₂X^{76D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{76D}₃, -OCHX^{76D}₂, R^{77D}-substituted or unsubstituted
 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{77D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 20 membered, 2 to 6 membered, or 2 to 4 membered), R^{77D}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{77D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{77D}-substituted or unsubstituted aryl (e.g.,
 C₆-C₁₀, C₁₀, or phenyl), or R^{77D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5
 to 9 membered, or 5 to 6 membered). X^{76D} is halogen. In embodiments, X^{76D} is F.

- 25 [0403] In embodiments, R^{17D} is independently hydrogen, oxo,
 halogen, -CX^{17D}₃, -CHX^{17D}₂, -OCH₂X^{17D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -
 SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
 NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{17D}₃, -OCHX^{17D}₂, R^{78D}-substituted or unsubstituted
 alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{78D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
 30 membered, 2 to 6 membered, or 2 to 4 membered), R^{78D}-substituted or unsubstituted cycloalkyl
 (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{78D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
 membered, 3 to 6 membered, or 5 to 6 membered), R^{78D}-substituted or unsubstituted aryl (e.g.,

C₆-C₁₀, C₁₀, or phenyl), or R^{78D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{17D} is halogen. In embodiments, X^{17D} is F.

[0404] R^{78D} is independently oxo,

halogen, -CX^{78D}₃, -CHX^{78D}₂, -OCH₂X^{78D}, -OCHX^{78D}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{78D}₃, -OCHX^{78D}₂, R^{79D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{79D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{79D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{79D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{79D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{79D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{78D} is halogen. In embodiments, X^{78D} is F.

[0405] R^{79D} is independently oxo,

halogen, -CX^{79D}₃, -CHX^{79D}₂, -OCH₂X^{79D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{79D}₃, -OCHX^{79D}₂, R^{80D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{80D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{80D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{80D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{80D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{80D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{79D} is halogen. In embodiments, X^{79D} is F.

[0406] In embodiments, R^{18D} is independently hydrogen, oxo,

halogen, -CX^{18D}₃, -CHX^{18D}₂, -OCH₂X^{18D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX^{18D}₃, -OCHX^{18D}₂, R^{81D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{81D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{81D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{81D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{81D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{81D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{18D} is halogen. In embodiments, X^{18D} is F.

[0407] R^{81D} is independently oxo,

halogen, $-CX^{81D}_3$, $-CHX^{81D}_2$, $-OCH_2X^{81D}$, $-OCHX^{81D}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{81D}_3$, $-OCHX^{81D}_2$, R^{82D} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{82D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{82D} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{82D} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{82D} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{82D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{81D} is halogen. In embodiments, X^{81D} is F.

[0408] R^{82D} is independently oxo,

halogen, $-CX^{82D}_3$, $-CHX^{82D}_2$, $-OCH_2X^{82D}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{82D}_3$, $-OCHX^{82D}_2$, R^{83D} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{83D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{83D} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{83D} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{83D} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{83D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{82D} is halogen. In embodiments, X^{82D} is F.

[0409] In embodiments, R^{19D} is independently hydrogen, oxo,

halogen, $-CX^{19D}_3$, $-CHX^{19D}_2$, $-OCH_2X^{19D}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{19D}_3$, $-OCHX^{19D}_2$, R^{84D} -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{84D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{84D} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{84D} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{84D} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{84D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{19D} is halogen. In embodiments, X^{19D} is F.

[0410] R^{84D} is independently oxo,

halogen, $-CX^{84D}_3$, $-CHX^{84D}_2$, $-OCH_2X^{84D}$, $-OCHX^{84D}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-$

NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{84D}₃, -OCHX^{84D}₂, R^{85D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{85D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{85D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{85D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{85D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{85D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{84D} is halogen. In embodiments, X^{84D} is F.

[0411] R^{85D} is independently oxo,

halogen, -CX^{85D}₃, -CHX^{85D}₂, -OCH₂X^{85D}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX^{85D}₃, -OCHX^{85D}₂, R^{86D}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R^{86D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{86D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R^{86D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{86D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R^{86D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{85D} is halogen. In embodiments, X^{85D} is F.

[0412] In embodiments, R²⁰ is independently hydrogen, oxo,

halogen, -CX²⁰₃, -CHX²⁰₂, -OCH₂X²⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX²⁰₃, -OCHX²⁰₂, R⁸⁷-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁷-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁷-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁰ is halogen. In embodiments, X²⁰ is F.

[0413] R⁸⁷ is independently oxo,

halogen, -CX⁸⁷₃, -CHX⁸⁷₂, -OCH₂X⁸⁷, -OCHX⁸⁷₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁷₃, -OCHX⁸⁷₂, R⁸⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁸-substituted or unsubstituted

cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸⁷ is halogen. In embodiments, X⁸⁷ is F.

- 5 **[0414]** R⁸⁸ is independently oxo, halogen, -CX⁸⁸₃, -CHX⁸⁸₂, -OCH₂X⁸⁸, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁸⁸₃, -OCHX⁸⁸₂, R⁸⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁸⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
- 10 membered, 2 to 6 membered, or 2 to 4 membered), R⁸⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁸⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁸⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁸⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁸⁸ is halogen. In embodiments, X⁸⁸ is F.
- 15 **[0415]** In embodiments, R²¹ is independently hydrogen, oxo, halogen, -CX²¹₃, -CHX²¹₂, -OCH₂X²¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²¹₃, -OCHX²¹₂, R⁹⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
- 20 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²¹ is halogen. In embodiments, X²¹ is F.
- 25 **[0416]** R⁹⁰ is independently oxo, halogen, -CX⁹⁰₃, -CHX⁹⁰₂, -OCH₂X⁹⁰, -OCHX⁹⁰₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁰₃, -OCHX⁹⁰₂, R⁹¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹¹-substituted or unsubstituted heteroalkyl
- 30 (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹¹-substituted or unsubstituted aryl

(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁰ is halogen. In embodiments, X⁹⁰ is F.

[0417] R⁹¹ is independently oxo,

halogen, -CX⁹¹₃, -CHX⁹¹₂, -OCH₂X⁹¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

5 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹¹₃, -OCHX⁹¹₂, R⁹²-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁹²-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
10 membered, 3 to 6 membered, or 5 to 6 membered), R⁹²-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁹²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X⁹¹ is halogen. In embodiments, X⁹¹ is F.

[0418] In embodiments, R²² is independently hydrogen, oxo,

halogen, -CX²²₃, -CHX²²₂, -OCH₂X²², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -

15 SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -
NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²²₃, -OCHX²²₂, R⁹³-substituted or unsubstituted alkyl
(e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹³-substituted or unsubstituted heteroalkyl (e.g., 2 to 8
membered, 2 to 6 membered, or 2 to 4 membered), R⁹³-substituted or unsubstituted cycloalkyl
(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹³-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8
20 membered, 3 to 6 membered, or 5 to 6 membered), R⁹³-substituted or unsubstituted aryl (e.g., C₆-
C₁₀, C₁₀, or phenyl), or R⁹³-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9
membered, or 5 to 6 membered). X²² is halogen. In embodiments, X²² is F.

[0419] R⁹³ is independently oxo,

halogen, -CX⁹³₃, -CHX⁹³₂, -OCH₂X⁹³, -OCHX⁹³₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -S

25 H, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -
NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹³₃, -OCHX⁹³₂, R⁹⁴-substituted or
unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁴-substituted or unsubstituted heteroalkyl
(e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁴-substituted or unsubstituted
cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁴-substituted or unsubstituted heterocycloalkyl (e.g.,
30 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁴-substituted or unsubstituted aryl
(e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁴-substituted or unsubstituted heteroaryl (e.g., 5 to 10
membered, 5 to 9 membered, or 5 to 6 membered). X⁹³ is halogen. In embodiments, X⁹³ is F.

[0420] R^{94} is independently oxo,

halogen, $-CX^{94}_3$, $-CHX^{94}_2$, $-OCH_2X^{94}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-$

$NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{94}_3$, $-OCHX^{94}_2$, R^{95} -substituted or unsubstituted alkyl

5 (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{95} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{95} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{95} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{95} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{95} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{94} is halogen. In embodiments, X^{94} is F.

[0421] In embodiments, R^{23} is independently hydrogen, oxo,

halogen, $-CX^{23}_3$, $-CHX^{23}_2$, $-OCH_2X^{23}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-$

$NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{23}_3$, $-OCHX^{23}_2$, R^{96} -substituted or unsubstituted alkyl

15 (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{96} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{96} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{96} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{96} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{96} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{23} is halogen. In embodiments, X^{23} is F.

[0422] R^{96} is independently oxo,

halogen, $-CX^{96}_3$, $-CHX^{96}_2$, $-OCH_2X^{96}$, $-OCHX^{96}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-$

$NHSO_2H$, $-NHC(=O)H$, $-NHC(O)-OH$, $-NHOH$, $-OCX^{96}_3$, $-OCHX^{96}_2$, R^{97} -substituted or

25 unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , or C_1-C_4), R^{97} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R^{97} -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , or C_5-C_6), R^{97} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R^{97} -substituted or unsubstituted aryl (e.g., C_6-C_{10} , C_{10} , or phenyl), or R^{97} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{96} is halogen. In embodiments, X^{96} is F.

[0423] R^{97} is independently oxo,

halogen, $-CX^{97}_3$, $-CHX^{97}_2$, $-OCH_2X^{97}$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(=O)NHNH_2$, $-NHC(=O)NH_2$, $-NHSO_2H$, $-$

NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁷₃, -OCHX⁹⁷₂, R⁹⁸-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁷ is halogen. In embodiments, X⁹⁷ is F.

[0424] In embodiments, R²⁴ is independently hydrogen, oxo, halogen, -CX²⁴₃, -CHX²⁴₂, -OCH₂X²⁴, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX²⁴₃, -OCHX²⁴₂, R⁹⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R⁹⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R⁹⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R⁹⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R⁹⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R⁹⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X²⁴ is halogen. In embodiments, X²⁴ is F.

[0425] R⁹⁹ is independently oxo, halogen, -CX⁹⁹₃, -CHX⁹⁹₂, -OCH₂X⁹⁹, -OCHX⁹⁹₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX⁹⁹₃, -OCHX⁹⁹₂, R¹⁰⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R¹⁰⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R¹⁰⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R¹⁰⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R¹⁰⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R¹⁰⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X⁹⁹ is halogen. In embodiments, X⁹⁹ is F.

[0426] R¹⁰⁰ is independently oxo, halogen, -CX¹⁰⁰₃, -CHX¹⁰⁰₂, -OCH₂X¹⁰⁰, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCX¹⁰⁰₃, -OCHX¹⁰⁰₂, R¹⁰¹-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), R¹⁰¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), R¹⁰¹-substituted or unsubstituted cycloalkyl

(e.g., C₃-C₈, C₃-C₆, or C₅-C₆), R¹⁰¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), R¹⁰¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or R¹⁰¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X¹⁰⁰ is halogen. In embodiments, X¹⁰⁰ is F.

- 5 **[0427]** R³², R³⁵, R³⁸, R⁴¹, R⁴⁴, R⁴⁷, R⁵⁰, R⁵³, R⁵⁶, R⁵⁹, R^{50A}, R^{53A}, R^{56A}, R^{59A}, R^{50B}, R^{53B}, R^{56B}, R^{59B}, R⁶², R⁶⁵, R⁶⁸, R⁷¹, R⁷⁴, R⁷⁷, R⁸⁰, R⁸³, R⁸⁶, R^{77A}, R^{80A}, R^{83A}, R^{86A}, R^{77B}, R^{80B}, R^{83B}, R^{86B}, R^{77C}, R^{80C}, R^{83C}, R^{86C}, R^{77D}, R^{80D}, R^{83D}, R^{86D}, R⁸⁹, R⁹², R⁹⁵, R⁹⁸, and R¹⁰¹ are independently hydrogen, oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
- 10 R³², R³⁵, R³⁸, R⁴¹, R⁴⁴, R⁴⁷, R⁵⁰, R⁵³, R⁵⁶, R⁵⁹, R^{50A}, R^{53A}, R^{56A}, R^{59A}, R^{50B}, R^{53B}, R^{56B}, R^{59B}, R⁶², R⁶⁵, R⁶⁸, R⁷¹, R⁷⁴, R⁷⁷, R⁸⁰, R⁸³, R⁸⁶, R^{77A}, R^{80A}, R^{83A}, R^{86A}, R^{77B}, R^{80B}, R^{83B}, R^{86B}, R^{77C}, R^{80C}, R^{83C}, R^{86C}, R^{77D}, R^{80D}, R^{83D}, R^{86D}, R⁸⁹, R⁹², R⁹⁵, R⁹⁸, and R¹⁰¹ are independently oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
- 15 R³², R³⁵, R³⁸, R⁴¹, R⁴⁴, R⁴⁷, R⁵⁰, R⁵³, R⁵⁶, R⁵⁹, R^{50A}, R^{53A}, R^{56A}, R^{59A}, R^{50B}, R^{53B}, R^{56B}, R^{59B}, R⁶², R⁶⁵, R⁶⁸, R⁷¹, R⁷⁴, R⁷⁷, R⁸⁰, R⁸³, R⁸⁶, R^{77A}, R^{80A}, R^{83A}, R^{86A}, R^{77B}, R^{80B}, R^{83B}, R^{86B}, R^{77C}, R^{80C}, R^{83C}, R^{86C}, R^{77D}, R^{80D}, R^{83D}, R^{86D}, R⁸⁹, R⁹², R⁹⁵, R⁹⁸, and R¹⁰¹ are independently oxo, halogen, -CF₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC=(O)NHNH₂, -NHC=(O)NH₂, -NHSO₂H, -NHC=(O)H, -NHC(O)-OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).
- 20 OH, -NHOH, -OCF₃, -OCHF₂, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

- 25 **[0428]** In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of all enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite stereoisomers. In embodiments, unless otherwise indicated, a compound described herein is a racemic mixture of two opposite enantiomers. In embodiments, unless otherwise indicated, a compound described herein is a single stereoisomer. In embodiments, unless otherwise indicated, a compound described herein is a single enantiomer.
- 30

[0429] In embodiments, the compound inhibits proliferation of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient

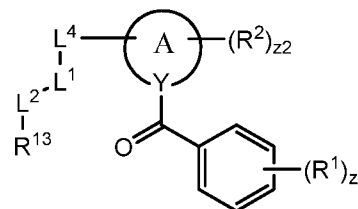
- 5 deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under conditions (e.g. local cell environment in a patient)
- 10 mimicking serum deprivation relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under conditions (e.g. local cell environment in a patient) mimicking serum deprivation relative to the absence of the compound.

[0430] In some embodiments, the compound is any one of the compounds described herein (e.g., in an aspect, embodiment, claim, figure, table, or example).

- 15 [0431] In some embodiments, a compound as described herein may include multiple instances of $R^1, R^2, R^7, R^8, R^9, R^{10}, X, X^1, X^2, m1, n1, v1, m2, n2, v2$, and/or other variables. In such embodiments, each variable may optional be different and be appropriately labeled to distinguish each group for greater clarity. For example, where each $R^1, R^2, R^7, R^8, R^9, R^{10}, X, X^1, X^2, m1, n1, v1, m2, n2$, and/or $v2$, is different, they may be referred to, for example, as $R^{1.1}, R^{1.2}, R^{1.3},$
- 20 $R^{1.4}, R^{1.5}, R^{1.6}, R^{1.7}, R^{2.1}, R^{2.2}, R^{2.3}, R^{2.4}, R^{2.5}, R^{2.6}, R^{2.7}, R^{2.8}, R^{2.9}, R^{2.10}, R^{7.1}, R^{7.2}, R^{7.3}, R^{7.4}, R^{7.5}, R^{7.6}, R^{7.7}, R^{8.1}, R^{8.2}, R^{8.3}, R^{8.4}, R^{8.5}, R^{8.6}, R^{8.7}, R^{9.1}, R^{9.2}, R^{9.3}, R^{9.4}, R^{9.5}, R^{9.6}, R^{9.7}, R^{10.1}, R^{10.2}, R^{10.3}, R^{10.4}, R^{10.5}, R^{10.6}, R^{10.7}, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^{1.1}, X^{1.2}, X^{1.3}, X^{1.4}, X^{1.5}, X^{1.6}, X^{2.1}, X^{2.2}, X^{2.3}, X^{2.4}, X^{2.5}, X^{2.6}, X^{2.7}, X^{2.8}, X^{2.9}, X^{2.10}, m^1, m^2, m^3, m^4, m^5, m^6, m^7, n^1, n^2, n^3, n^4, n^5, n^6, n^7, v^1, v^2, v^3, v^4, v^5, v^6, v^7, m1^1, m1^2, m1^3, m1^4, m1^5, m1^6, n1^1, n1^2, n1^3, n1^4, n1^5, n1^6, v1^1, v1^2, v1^3, v1^4,$
- 25 $v1^5, v1^6$, respectively, wherein the definition of R^1 is assumed by $R^{1.1}, R^{1.2}, R^{1.3}, R^{1.4}, R^{1.5}, R^{1.6}, R^{1.7}$, the definition of R^2 is assumed by $R^{2.1}, R^{2.2}, R^{2.3}, R^{2.4}, R^{2.5}, R^{2.6}, R^{2.7}, R^{2.8}, R^{2.9}, R^{2.10}$, the definition of R^7 is assumed by $R^{7.1}, R^{7.2}, R^{7.3}, R^{7.4}, R^{7.5}, R^{7.6}, R^{7.7}$, the definition of R^8 is assumed by $R^{8.1}, R^{8.2}, R^{8.3}, R^{8.4}, R^{8.5}, R^{8.6}, R^{8.7}$, the definition of R^9 is assumed by $R^{9.1}, R^{9.2}, R^{9.3}, R^{9.4}, R^{9.5}, R^{9.6}, R^{9.7}$, the definition of R^{10} is assumed by $R^{10.1}, R^{10.2}, R^{10.3}, R^{10.4}, R^{10.5}, R^{10.6}, R^{10.7}$, the
- 30 definition of X is assumed by $X^1, X^2, X^3, X^4, X^5, X^6, X^7$, the definition of X^1 is assumed by $X^{1.1}, X^{1.2}, X^{1.3}, X^{1.4}, X^{1.5}, X^{1.6}$, the definition of X^2 is assumed by $X^{2.1}, X^{2.2}, X^{2.3}, X^{2.4}, X^{2.5}, X^{2.6}, X^{2.7}, X^{2.8}, X^{2.9}, X^{2.10}$, the definition of m is assumed by $m^1, m^2, m^3, m^4, m^5, m^6, m^7$, the definition of n is assumed by $n^1, n^2, n^3, n^4, n^5, n^6, n^7$, the definition of v is assumed by $v^1, v^2, v^3, v^4, v^5, v^6$,

v^7 , the definition of $m1$ is assumed by $m1^1, m1^2, m1^3, m1^4, m1^5, m1^6$, the definition of $n1$ is assumed by $n1^1, n1^2, n1^3, n1^4, n1^5, n1^6$, the definition of $v1$ is assumed by $v1^1, v1^2, v1^3, v1^4, v1^5, v1^6$, the definition of $m2$ is assumed by $m2^1, m2^2, m2^3, m2^4, m2^5, m2^6, m2^7, m2^8, m2^9, m2^{10}$, the definition of $n2$ is assumed by $n2^1, n2^2, n2^3, n2^4, n2^5, n2^6, n2^7, n2^8, n2^9, n2^{10}$, the definition of $v2$ is assumed by $v2^1, v2^2, v2^3, v2^4, v2^5, v2^6, v2^7, v2^8, v2^9, v2^{10}$.

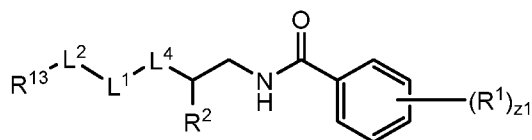
[0432] The variables used within a definition of $R^1, R^2, R^7, R^8, R^9, R^{10}, X, X^1, X^2, m1, n1, v1, m2, n2, v2$, and/or other variables that appear at multiple instances and are different may similarly be appropriately labeled to distinguish each group for greater clarity.



[0433] In an aspect is provided a compound having the formula:

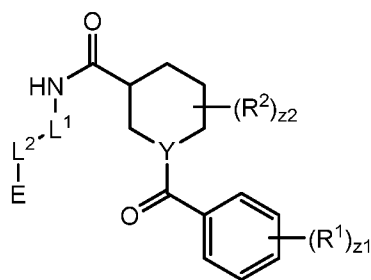
10 (IJ). Ring A, $R^1, z1, R^2, z2, L^1, L^2, L^4$, and R^{13} are as described herein. In embodiments, R^{13} is hydrogen. In embodiments, R^{13} is unsubstituted methyl. In embodiments, the compound is LB9. In embodiments, the compound is DB9.

[0434] In an aspect is provided, a compound having the formula:



15 $R^1, R^2, L^1, L^2, L^4, R^{13}$, and $z1$ are as described herein. In embodiments, R^{13} is hydrogen. In embodiments, R^{13} is unsubstituted methyl.

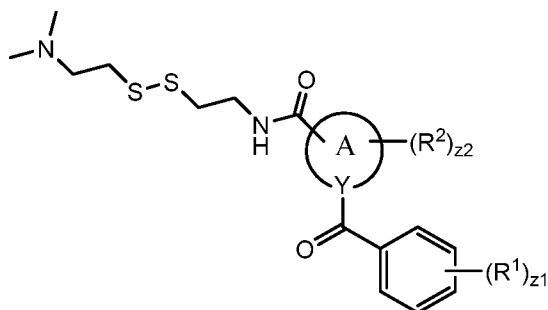
[0435] In embodiments, the compound does not have the formula:



$Y, R^1, z1, R^2, L^2, E$, and $z2$ are as described herein. In embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4

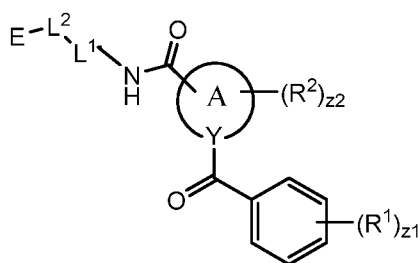
membered unsubstituted heteroalkyl. In embodiments, E is .

20 **[0436]** In embodiments, the compound does not have the formula:

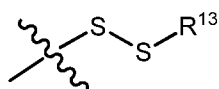


. Ring A, Y, R^1 , $z1$, R^2 , and $z2$ are as described herein. In embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, R^1 is halogen.

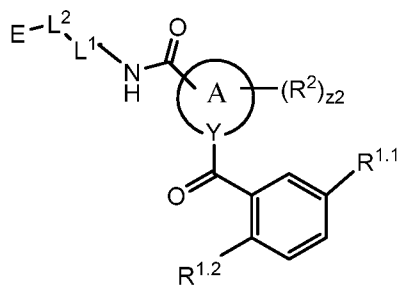
[0437] In embodiments, the compound does not have the formula:



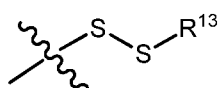
5 . Ring A, Y, R^1 , $z1$, R^2 , $z2$, L^1 , L^2 , and E are as described herein. In embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, R^1 is halogen. In embodiments, E is



[0438] In embodiments, the compound does not have the formula:

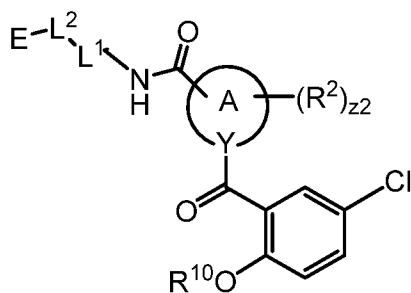


10 . Ring A, Y, $R^{1.1}$, $R^{1.2}$, R^2 , $z2$, L^1 , L^2 and E are as described herein. In embodiments, $R^{1.1}$ is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, $R^{1.2}$ is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments, $R^{1.1}$ is halogen. In embodiments, $R^{1.2}$ is halogen. In embodiments, E is



15

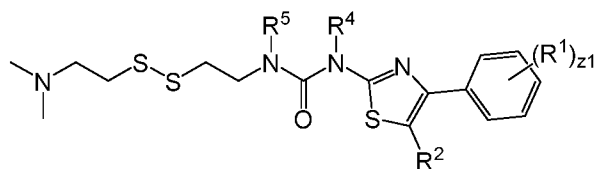
[0439] In embodiments, the compound does not have the formula:



. Ring A, Y, R², z₂, L¹, L², E, and R¹⁰ are as described herein.

In embodiments, E is .

[0440] In embodiments, the compound does not have the formula:

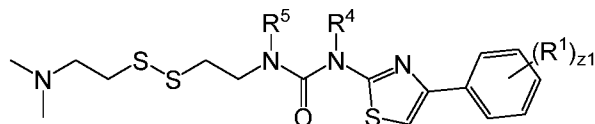


5

. R¹, z₁, R², R⁴, and R⁵ are as described herein.

In embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0441] In embodiments, the compound does not have the formula:

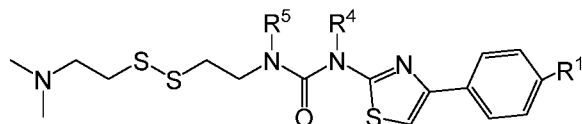


10

. R¹, z₁, R⁴, and R⁵ are as described herein. In

embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0442] In embodiments, the compound does not have the formula:

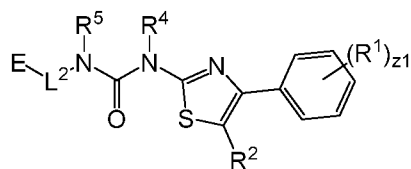


. R¹, R⁴, and R⁵ are as described herein. In

15

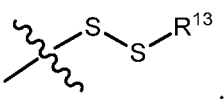
embodiments, R¹ is halogen, -OH, -COOH, -OCF₃, C₁-C₄ unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0443] In embodiments, the compound does not have the formula:



. R¹, z₁, L², E, R², R⁴, and R⁵ are as described herein. In

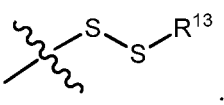
embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4

membered unsubstituted heteroalkyl. In embodiments, E is .

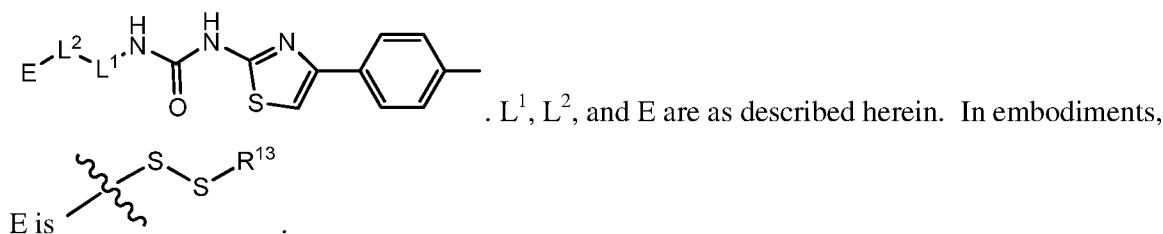
[0444] In embodiments, the compound does not have the formula:



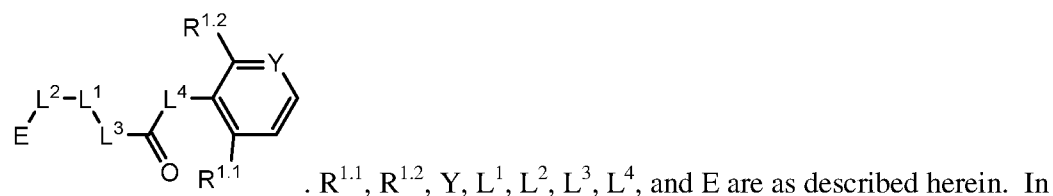
5 embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4

membered unsubstituted heteroalkyl. In embodiments, E is .

[0445] In embodiments, the compound does not have the formula:

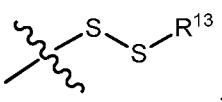


10 [0446] In embodiments, the compound does not have the formula:

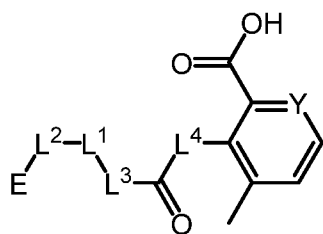


embodiments, $R^{1.1}$ is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4

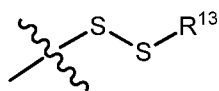
membered unsubstituted heteroalkyl. In embodiments, $R^{1.2}$ is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl. In embodiments

15 E is .

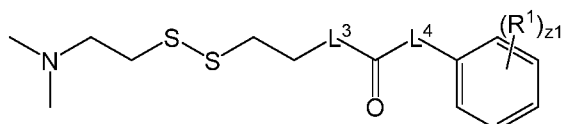
[0447] In embodiments, the compound does not have the formula:



. L^1 , L^2 , L^3 , L^4 , and E are as described herein. In embodiments, E is



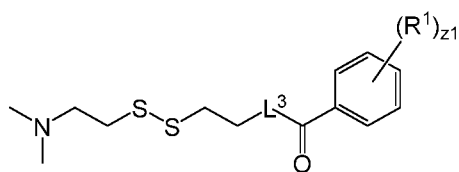
[0448] In embodiments, the compound does not have the formula:



. R^1 , $z1$, L^3 , and L^4 are as described herein. In

- 5 embodiments, R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

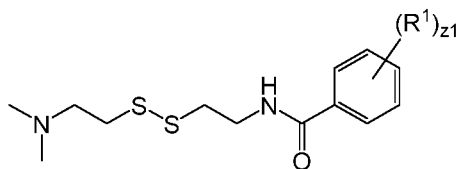
[0449] In embodiments, the compound does not have the formula:



. R^1 , $z1$, and L^3 are as described herein. In embodiments,

- 10 R^1 is halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

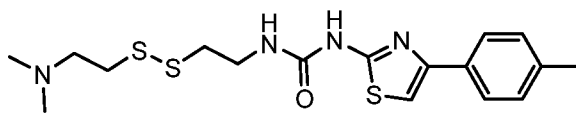
[0450] In embodiments, the compound does not have the formula:



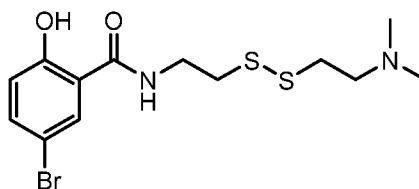
. R^1 and $z1$, are as described herein. In embodiments, R^1 is

- halogen, $-OH$, $-COOH$, $-OCF_3$, C_1 - C_4 unsubstituted alkyl, or 2 to 4 membered unsubstituted heteroalkyl.

[0451] In embodiments, the compound is not

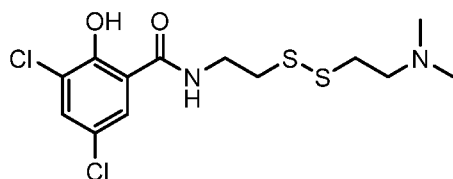


In embodiments, the compound is not

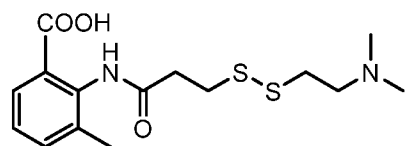


. In embodiments, the

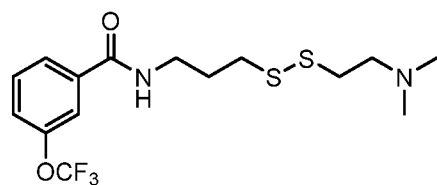
compound is not



. In embodiments, the compound is not

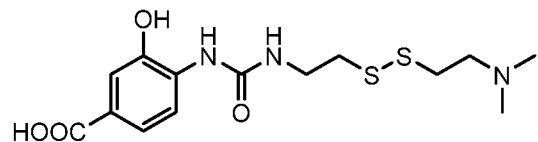


. In embodiments, the compound is not

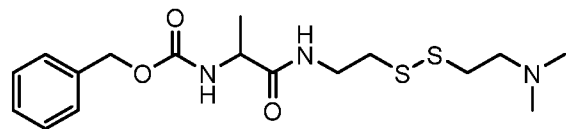


5

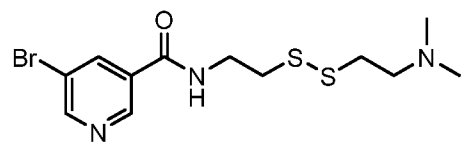
. In embodiments, the compound is not



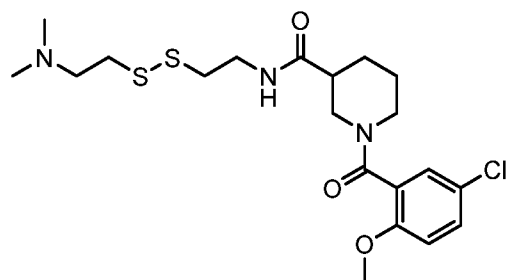
. In embodiments, the compound is not



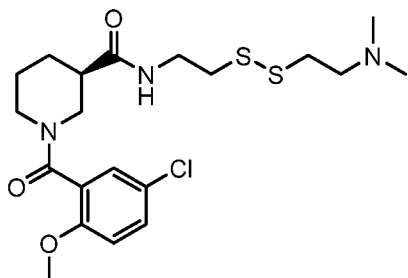
. In embodiments, the compound is not



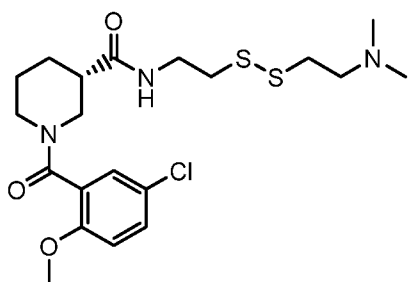
. In embodiments, the compound is not



. In embodiments, the compound is not

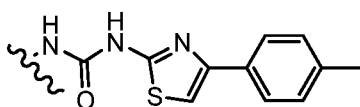


. In embodiments, the compound is not

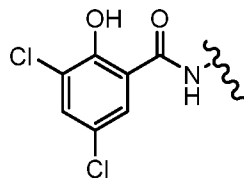
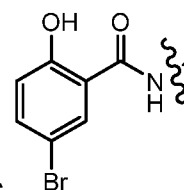


[0452] In embodiments, the compound is not a compound described herein, including in an example, figures, or table. In embodiments, the compound does not include

5

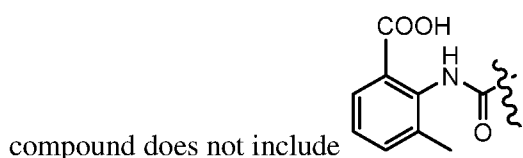


. In embodiments, the compound does not include

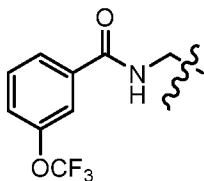


In embodiments, the compound does not include

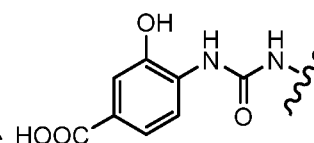
. In embodiments, the



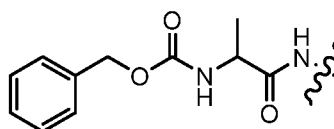
compound does not include . In embodiments, the compound does not include



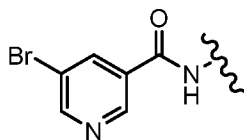
. In embodiments, the compound does not include



In embodiments, the compound does not include

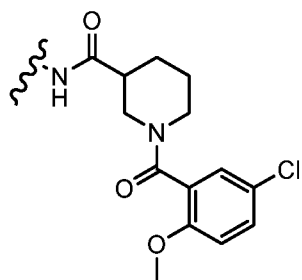


. In embodiments,



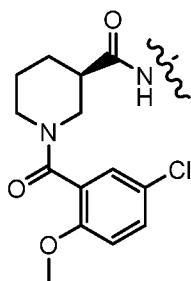
the compound does not include

. In embodiments, the compound does not

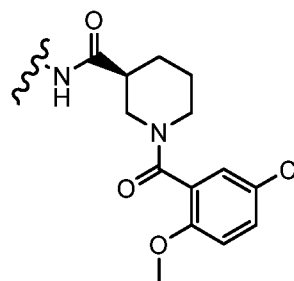


include

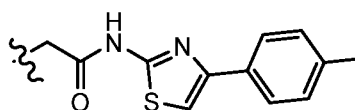
. In embodiments, the compound does not include



. In embodiments, the compound does not include

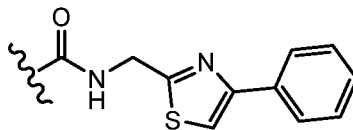


. In



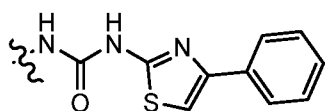
embodiments, the compound does not include

. In embodiments,



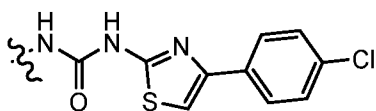
5 the compound does not include

. In embodiments, the compound

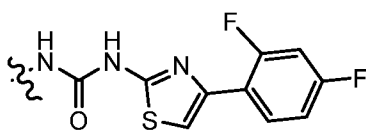


does not include

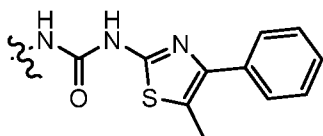
. In embodiments, the compound does not include



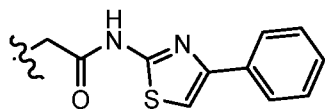
. In embodiments, the compound does not include



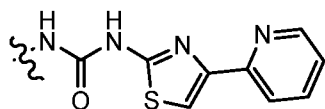
. In embodiments, the compound does not include



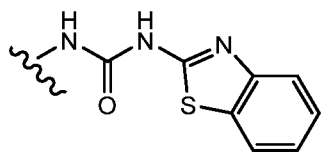
. In embodiments, the compound does not include



. In embodiments, the compound does not include



. In embodiments, the compound does not include



III. Pharmaceutical compositions

- 5 [0453] In an aspect is provided a pharmaceutical composition including a compound described herein and a pharmaceutically acceptable excipient.

- [0454] In embodiments, the pharmaceutical composition includes an effective amount of the compound. In embodiments, the pharmaceutical composition includes a therapeutically effective amount of the compound. In embodiments, the pharmaceutical composition includes a second agent (e.g., an anti-cancer agent). In embodiments of the pharmaceutical compositions, the pharmaceutical composition includes a second agent in a therapeutically effective amount. In
- 10 embodiments, the anti-cancer agent is an EGFR inhibitor (e.g. gefitinib (IressaTM), erlotinib (TarcevaTM), cetuximab (ErbixTM), lapatinib (TykerbTM), panitumumab (VectibixTM), vandetanib (CaprelsaTM), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788, pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, or BMS-599626). In embodiments, the anti-cancer agent is erlotinib. In embodiments, the anti-cancer agent is gefitinib. In embodiments, the anti-cancer agent is lapatinib. In embodiments, the anti-cancer agent is panitumumab. In
- 15 20 embodiments, the anti-cancer agent is panitumumab.

- [0455] The pharmaceutical compositions may include optical isomers, diastereomers, or pharmaceutically acceptable salts of the modulators disclosed herein. The compound included in the pharmaceutical composition may be covalently attached to a carrier moiety. Alternatively, the compound included in the pharmaceutical composition is not covalently linked to a carrier
- 25 moiety.

IV. Methods for Treating Diseases

[0456] In another aspect, a method of treating a disease in a subject in need of such treatment (patient) is provided. The method including administering a therapeutically effective amount of a compound described herein (including embodiments, examples, figures, tables) to the patient.

5 In some embodiments, the disease is cancer. In some embodiments, the cancer is lung cancer, colorectal cancer, colon cancer, pancreatic cancer, breast cancer, or leukemia. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is leukemia. In some embodiments, the cancer is pancreatic cancer. In some
10 embodiments, the cancer is a cancer associated with aberrant K-Ras. In some embodiments, the cancer is a cancer associated with a mutant K-Ras. In some embodiments, the cancer is a cancer associated with K-Ras G12C. In some embodiments, the cancer is a cancer associated with K-Ras G12D. In some embodiments, the cancer is a cancer associated with K-Ras G12V. In some
15 embodiments, the cancer is a cancer associated with K-Ras G12S. In some embodiments, the cancer is a cancer associated with K-Ras G13C. In some embodiments, the cancer is a cancer associated with K-Ras G13D.

[0457] In some embodiments, a method of treating a disorder in a subject in need thereof is provided, comprising a) determining the presence or absence of a mutation in a Ras protein (such
20 as in a K-Ras, N-Ras, or H-Ras protein) in a malignant or neoplastic cell isolated from the subject and b) if the mutation is determined to be present in the subject, administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of the invention. In some embodiments, the disorder is cancer.

[0458] The compounds of the invention (i.e. compounds described herein, including in
25 embodiments, examples, figures, tables) can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation or anti-cancer agents). In embodiments, the anti-cancer agent is an EGFR
30 inhibitor (e.g. gefitinib (IressaTM), erlotinib (TarcevaTM), cetuximab (ErbixTM), lapatinib (TykerbTM), panitumumab (VectibixTM), vandetanib (CaprelsaTM), afatinib/BIBW2992, CI-1033/canertinib, neratinib/HKI-272, CP-724714, TAK-285, AST-1306, ARRY334543, ARRY-380, AG-1478, dacomitinib/PF299804, OSI-420/desmethyl erlotinib, AZD8931, AEE788,

pelitinib/EKB-569, CUDC-101, WZ8040, WZ4002, WZ3146, AG-490, XL647, PD153035, or BMS-599626). In embodiments, the anti-cancer agent is erlotinib. In embodiments, the anti-cancer agent is gefitinib. In embodiments, the anti-cancer agent is lapatinib. In embodiments, the anti-cancer agent is panitumumab. In embodiments, the anti-cancer agent is panitumumab.

5 V. Methods of Modulating Activity

[0459] In an aspect is provided a method of reducing the level of activity of a K-Ras protein (e.g., human K-Ras 4B), the method including contacting the K-Ras protein with a compound described herein (including in embodiments, examples, figures, and tables). In some
 10 embodiments, the activity of the K-Ras protein is its GTPase activity, nucleotide exchange, differential GDP or GTP binding, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, K-Ras subcellular localization, K-Ras post-translational processing, K-Ras post-translational modifications, prenylation, or a GTP bound K-Ras signaling pathway. In some embodiments, the activity of the K-Ras protein is its GTPase activity,
 15 nucleotide exchange, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding, GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, or the activity of a GTP bound K-Ras signaling pathway. In some embodiments, the activity of the K-Ras protein is the activity of a signaling pathway activated by GTP bound K-Ras. In some embodiments, the modulating is increasing the activity of said K-
 20 Ras protein. In some embodiments, the modulating is reducing the activity of said K-Ras protein. In some embodiments, the K-Ras protein is a human K-Ras protein. In some embodiments, the human K-Ras protein contains a G12C mutation. In some embodiments, the human K-Ras protein contains a G12V mutation. In some embodiments, the human K-Ras protein contains a G12S mutation. In some embodiments, the human K-Ras protein contains a
 25 G12D mutation. In some embodiments, the human K-Ras protein contains a G13C mutation. In some embodiments, the human K-Ras protein contains a G13D mutation. In some embodiments, the K-Ras protein is a human K-Ras4A protein. In some embodiments, the K-Ras protein is a human K-Ras4B protein. In some embodiments, the K-Ras protein is a mutant K-Ras protein. In some embodiments, the K-Ras protein is an activated K-Ras protein. In some embodiments,
 30 the K-Ras protein is within a biological cell. In some embodiments, the biological cell forms part of an organism. In some embodiments of the method of modulating the activity of a K-Ras protein includes contacting the K-Ras protein with an effective amount of a compound described herein (including in embodiments, examples, figures, and tables), the compound is less effective

at modulating the activity of an H-Ras protein (e.g., compared to the level of modulation of K-Ras). In some embodiments of the method, the compound modulates the activity of K-Ras at least two-fold more than it modulates the activity of H-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least five-fold more than it modulates the activity of H-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least ten-fold more than it modulates the activity of H-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least fifty-fold more than it modulates the activity of H-Ras. In some embodiments of the method of modulating the activity of a K-Ras protein including contacting the K-Ras protein with an effective amount of a compound described herein (including embodiments, examples, figures, and tables), the compound is less effective at modulating the activity of an N-Ras protein. In some embodiments of the method, the compound modulates the activity of K-Ras at least two-fold more than it modulates the activity of N-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least five-fold more than it modulates the activity of N-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least ten-fold more than it modulates the activity of N-Ras. In some embodiments of the method, the compound modulates the activity of K-Ras at least fifty-fold more than it modulates the activity of N-Ras.

[0460] In another aspect, a method of modulating a K-Ras protein is provided. The method including contacting the K-Ras protein with an effective amount of a compound described herein (including in embodiments, examples, figures, and tables). In some embodiments, the K-Ras protein is modulated in K-Ras subcellular localization, K-Ras post-translational processing, K-Ras post-translational modifications, or a GTP bound K-Ras signaling pathway. In some embodiments, the modulating is increasing the post-translational processing or modifications of the K-Ras protein. In some embodiments, the modulating is reducing the post-translational processing or modifications of the K-Ras protein. In some embodiments, the K-Ras protein is a human K-Ras protein. In some embodiments, the human K-Ras protein contains a G12C mutation. In some embodiments, the human K-Ras protein contains a G12V mutation. In some embodiments, the human K-Ras protein contains a G12S mutation. In some embodiments, the human K-Ras protein contains a G12D mutation. In some embodiments, the human K-Ras protein contains a G13C mutation. In some embodiments, the human K-Ras protein contains a G13D mutation. In some embodiments, the K-Ras protein is a human K-Ras4A protein. In some embodiments, the K-Ras protein is a human K-Ras4B protein. In some embodiments, the K-Ras protein is a mutant K-Ras protein. In some embodiments, the K-Ras protein is an

activated K-Ras protein. In some embodiments, the K-Ras protein is within a biological cell. In some embodiments, the biological cell forms part of an organism. In embodiments, compound (e.g., compound described herein) modulates the stability of the K-Ras protein. In embodiments, compound (e.g., compound described herein) reduces the stability of the K-Ras protein relative to the absence of the compound. In embodiments, compound (e.g., compound described herein) increases the rate of degradation of the K-Ras protein relative to the absence of the compound.

[0461] In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to His95 in K-Ras (e.g., K-Ras 4B). In embodiments, the compound (e.g., compound described herein) reacts with His95 in K-Ras (K-Ras 4B). In embodiments, the compound (e.g., compound described herein) covalently binds to the amino acid corresponding to His95 in K-Ras (e.g., K-Ras 4B). In embodiments, the compound (e.g., compound described herein) covalently reacts with His95 in K-Ras (K-Ras 4B). In embodiments, the compound (e.g., compound described herein) is capable of binding to the amino acid corresponding to His95 or Cys185 in K-Ras (e.g., K-Ras 4B). In embodiments, the compound (e.g., compound described herein) is capable of reacting with His95 or Cys185 in K-Ras (K-Ras 4B).

[0462] In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to His95 in K-Ras (e.g., K-Ras 4B) protein when the K-Ras (e.g., K-Ras 4B) protein Cys185 (or amino acid corresponding to Cys185 of K-Ras 4B) is covalently modified (e.g., prenylated, farnesylated). In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to Cys185 in K-Ras (e.g., K-Ras 4B) protein when the K-Ras (e.g., K-Ras 4B) protein Cys185 (or amino acid corresponding to Cys185 of K-Ras 4B) is not covalently modified (e.g., prenylated, farnesylated). In embodiments, the compound (e.g., compound described herein) binds to the amino acid corresponding to Cys185 in K-Ras (e.g., K-Ras 4B) protein following protein synthesis, when the K-Ras (e.g., K-Ras 4B) protein Cys185 (or amino acid corresponding to Cys185 of K-Ras 4B) has not yet been covalently modified (e.g., prenylated, farnesylated).

[0463] In embodiments, the compound prevents productive folding of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound increases misfolding of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound increases unfolding of K-Ras protein (e.g., by

binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound increases degradation of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound reduces GTP binding to K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound decreases GDP release by K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound decreases interactions of a second protein (e.g., pathway component, effector) with K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound. In embodiments, the compound decreases prenylation (e.g., farnesylation, geranylgeranylation) of K-Ras protein (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound.

[0464] In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than about 1 hour (e.g., less than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 minutes). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than 1 hour (e.g., less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, or 50 minutes). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than about 1 day (e.g., less than about 1, 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 hours). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than 1 day (e.g., less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 hours). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than about 1 month (e.g., less than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days). In embodiments, the compound decreases (e.g., by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99%) the level of K-Ras function in a cell (e.g., by binding to K-Ras protein, by binding to the amino acid corresponding to His95 of K-Ras, by binding to the amino acid corresponding to Cys185 of K-Ras) relative to the absence of the compound, in less than 1 month (e.g., less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days). In embodiments, the compound binds to K-Ras (e.g., only K-Ras 4B, only K-Ras 4A, or both K-Ras 4A and K-Ras 4B).

VI. Compositions

[0465] In another aspect is provided, a K-Ras protein covalently (e.g., reversibly or irreversibly) bonded to a compound, for example a compound as described herein (including modulators, inhibitors, embodiments, examples, in figures, and in tables). In embodiments, the compound is a compound described herein. In embodiments, the compound is covalently bonded to a cysteine residue of the protein. In embodiments, the compound is irreversibly covalently bonded to a cysteine residue of the protein. In embodiments, the compound is covalently bonded to the residue corresponding to C185 of human K-Ras 4B. In embodiments, the compound is covalently bonded to a histidine residue of the protein. In embodiments, the compound is irreversibly covalently bonded to a histidine residue of the protein. In embodiments, the compound is covalently bonded to the residue corresponding to H95 of human K-Ras 4B.

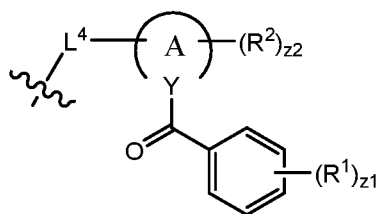
[0466] In embodiments, the covalently modified K-Ras protein has a modulated activity relative to a control, wherein the activity is selected from GTPase activity, nucleotide exchange, effector protein binding, effector protein activation, guanine exchange factor (GEF) binding,

GEF-facilitated nucleotide exchange, phosphate release, nucleotide release, nucleotide binding, K-Ras subcellular localization, K-Ras post-translational processing, and K- Ras post-translational modifications. In some embodiments, the covalently modified K-Ras protein is modulated in K-Ras subcellular localization, K-Ras post-translational processing, or K- Ras

5 post-translational modifications. In some embodiments, the covalently modified K-Ras protein contains a G12C mutation. In some embodiments, the covalently modified K-Ras protein contains a G12V mutation. In some embodiments, the covalently modified K-Ras protein contains a G12S mutation. In some embodiments, the compound is covalently bonded to

10 residue 95 (e.g., corresponding to H95 of K-Ras). In some embodiments, the covalently modified K-Ras protein contains a G13C mutation. In some embodiments, the K-Ras protein is bonded to a K-Ras inhibitor, a mutant K-Ras inhibitor, K-Ras H95 inhibitor, or a K-Ras C185 inhibitor. In some embodiments, the K-Ras protein is bonded to a K-Ras modulator, a mutant K-Ras modulator, K-Ras H95 inhibitor, or a K-Ras C185 modulator.

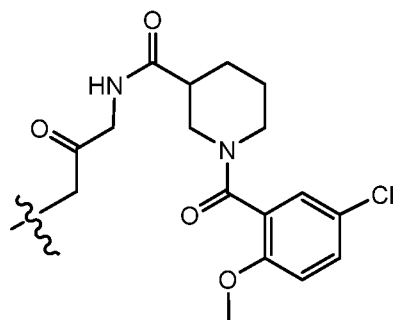
15 [0467] In an aspect is provided a K-Ras protein covalently bonded to a compound having the



formula:
herein.

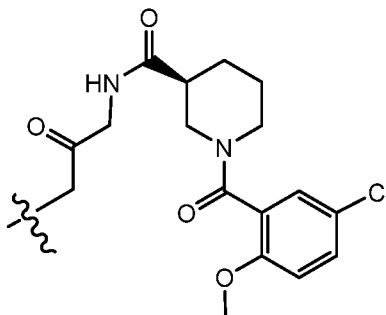
. R¹, R², Ring A, Y, L⁴, z1, and z2 are as described

[0468] In an aspect is provided a K-Ras protein covalently bonded to a compound having the



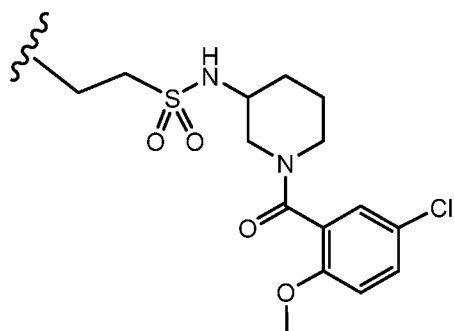
formula:

. In an embodiment, the K-Ras protein is covalently



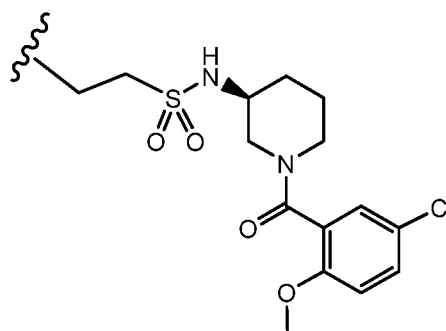
bonded to a compound having the formula:

[0469] In an aspect is provided a K-Ras protein covalently bonded to a compound having the



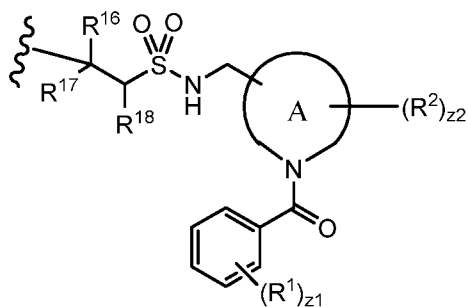
5 formula:

. In an embodiment, the K-Ras protein is

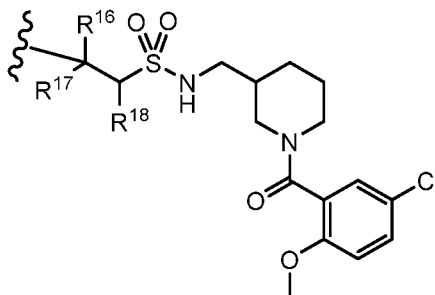


covalently bonded to a compound having the formula:

In an embodiment, the K-Ras protein is covalently bonded to a compound having the formula:

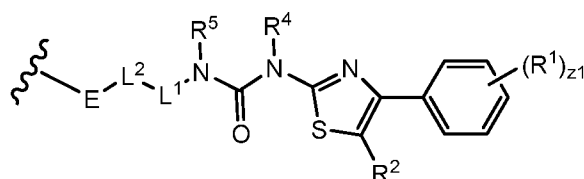
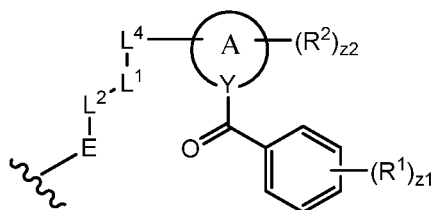


. In an embodiment, the K-Ras protein is covalently

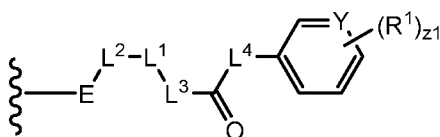


bonded to a compound having the formula:

embodiment, the K-Ras protein is covalently bonded to a compound having the formula:



, or



. E, R¹, R², R³, R⁴, R⁵, Ring A, Y, L¹, L², L³, L⁴, z1, and z2

are as described herein.

[0470] In embodiments, the compound is covalently bonded to a cysteine residue of the protein. In embodiments, the compound is covalently bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B. In embodiments, the compound is irreversibly covalently bonded to a cysteine (e.g., corresponding to C185 of human K-Ras-4B) of the protein. In embodiments, the compound is covalently bonded to a histidine residue of the protein. In embodiments, the compound is covalently bonded to a histidine residue of the protein corresponding to H95 of human K-Ras-4B. In embodiments, the compound is irreversibly covalently bonded to a histidine (e.g., corresponding to H95 of human K-Ras-4B) of the protein.

[0471] In another aspect, a Ras protein (e.g. K-Ras, N-Ras, H-Ras, or another Ras protein described herein) covalently bonded (e.g. reversibly or irreversibly) to a compound, for example

a compound as described herein (including modulators, inhibitors, embodiments, figures, examples, and tables), is provided. In some embodiments, the compound is a modulator. In some embodiments, the compound is a modulator such as an inhibitor. In some embodiments, the compound is a Ras modulator. In some embodiments, the compound is a Ras inhibitor.

5 **[0472]** In embodiments, the compound binds Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) at the CAAX box. In embodiments, the compound binds Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to the residue corresponding to C185 of human K-Ras
10 4B. In embodiments, the compound binds Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to the residue corresponding to H95 of human K-Ras 4B.

[0473] In embodiments, the compound modulates the conformation of the protein. In embodiments, the compound modulates the conformation of the CAAX box. In embodiments,
15 the compound modulates (e.g., reduces or inhibits) the prenylation of the protein at the CAAX box (e.g., residue corresponding to C185 of human K-Ras 4B). In embodiments, the compound inhibits (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000, 3000, 4000, 5000, 6000, 7000,
20 8000, 9000, 10000 fold or more) Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) activity relative to the absence of the compound. In embodiments, the compound inhibits (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or
25 100%) Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) activity relative to the absence of the compound. In embodiments, the compound inhibits (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) Ras (e.g. K-Ras, K-
30 Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) prenylation relative to the absence of the compound. In embodiments, the compound reduces (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40,

45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) the amount of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) protein (e.g., in a cell) relative to the absence of the compound. In embodiments, the compound reduces (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) production of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) protein (e.g., in a cell) relative to the absence of the compound. In embodiments, the compound increases (e.g. by about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%) the degradation of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) protein (e.g., in a cell) relative to the absence of the compound. In embodiments, the compound inhibits protein association with a membrane relative to the absence of the compound.

[0474] In embodiments, the compound inhibits proliferation of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under nutrient deficient conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under serum deprivation conditions relative to the absence of the compound. In embodiments, the compound inhibits growth of cancer cells under conditions (e.g. local cell environment in a patient) mimicking serum deprivation relative to the absence of the compound. In embodiments, the compound inhibits proliferation of cancer cells under conditions (e.g. local cell environment in a patient) mimicking serum deprivation relative to the absence of the compound.

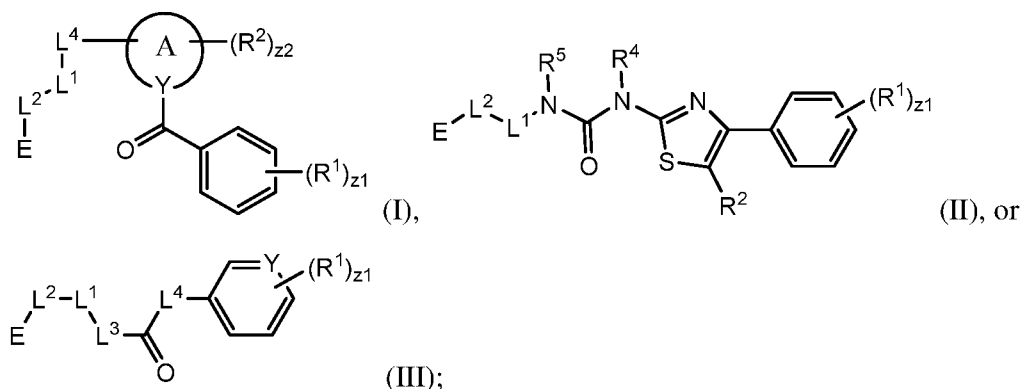
[0475] In embodiments, the compound increases the flexibility of the CAAX box (amino acid sequence at the C terminus of a protein wherein C is a cysteine that may be prenylated, A is an aliphatic amino acid, and X is an amino acid with variable sequence depending on the protein (e.g., M, S, Q, A, or C; L or E)) relative to the absence of the compound. In embodiments, the compound increases the disorder of the CAAX box relative to the absence of the compound. In embodiments, the compound inhibits the binding of Ras ((e.g. K-Ras, K-Ras 4B, human K-Ras

4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to another protein. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to another protein, wherein the binding is dependent on Ras prenylation. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to another protein, wherein the binding is dependent on Ras membrane association.

[0476] In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to Raf (e.g. Raf1). In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to SOS. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to a GEF. In embodiments, the compound inhibits the binding of Ras (e.g. K-Ras, K-Ras 4B, human K-Ras 4B, H-Ras, N-Ras, mutant Ras, K-Ras G12C, K-Ras G12V, K-Ras G12S, K-Ras G13C, K-Ras G12D, K-Ras G13D) to PI3K.

VII. Selected Embodiments

[0477] Embodiment P1. A compound having the formula:

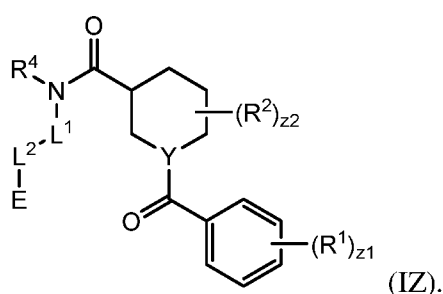


wherein, Y is N or CH; Ring A is a C₅-C₇ cycloalkyl or 5 to 7 membered heterocycloalkyl; R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHN⁷R⁸, -ONR⁷R⁸, -NHC(=O)NHN⁷R⁸, -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -

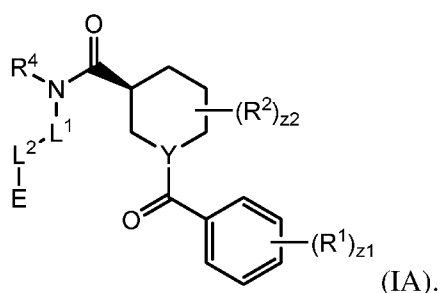
$\text{NR}^7\text{C}(\text{O})\text{R}^9$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^9$, $-\text{NR}^7\text{OR}^9$, $-\text{OCX}^1_3$, $-\text{OCHX}^1_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R^1 substituents may optionally be joined to form a substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L^2 is a bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{S}(\text{O})_2-$, $-\text{NR}^{7\text{B}}-$, $-\text{NR}^{7\text{B}}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^{7\text{B}}-$, $-\text{SO}_2\text{NR}^{7\text{B}}-$, $-\text{NR}^{7\text{B}}\text{SO}_2-$, $-\text{OC}(\text{O})\text{NR}^{7\text{B}}-$, $-\text{NR}^{7\text{B}}\text{C}(\text{O})\text{O}-$, $-\text{CR}^{9\text{B}}=\text{NO}-$, $-\text{ON}=\text{CR}^{9\text{B}}-$, $-\text{NR}^{8\text{B}}\text{C}(\text{O})\text{NR}^{7\text{B}}-$, $-\text{NR}^{8\text{B}}\text{C}(=\text{NR}^{10\text{B}})\text{NR}^{7\text{B}}-$, $-\text{NR}^{8\text{B}}\text{C}(=\text{NR}^{10\text{B}})-$, $-\text{C}(=\text{NR}^{10\text{B}})\text{NR}^{7\text{B}}-$, $-\text{OC}(=\text{NR}^{10\text{B}})-$, $-\text{C}(=\text{NR}^{10\text{B}})\text{O}-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L^3 is a bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{S}(\text{O})_2-$, $-\text{NR}^5-$, $-\text{NR}^5\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^5-$, $-\text{SO}_2\text{NR}^5-$, $-\text{NR}^5\text{SO}_2-$, $-\text{OC}(\text{O})\text{NR}^5-$, $-\text{NR}^5\text{C}(\text{O})\text{O}-$, substituted or unsubstituted C_1 - C_6 alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene; L^4 is a bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}-$, $-\text{SO}-$, $-\text{S}(\text{O})_2-$, $-\text{NR}^4-$, $-\text{NR}^4\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^4-$, $-\text{SO}_2\text{NR}^4-$, $-\text{NR}^4\text{SO}_2-$, $-\text{NR}^4\text{SO}_2-$, $-\text{OC}(\text{O})\text{NR}^4-$, $-\text{NR}^4\text{C}(\text{O})\text{O}-$, substituted or unsubstituted C_1 - C_3 alkylene, substituted or unsubstituted 2 to 3 membered heteroalkylene; E is a covalent cysteine modifier moiety; R^2 is independently oxo, halogen, CX^2_3 , $-\text{CHX}^2_2$, $-\text{CH}_2\text{X}^2$, $-\text{CN}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_2\text{R}^{14}$, $-\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $-\text{NHN}^{11}\text{R}^{12}$, $-\text{ONR}^{11}\text{R}^{12}$, $-\text{NHC}(\text{O})\text{NHN}^{11}\text{R}^{12}$, $-\text{NHC}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{N}(\text{O})_{\text{m}2}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{C}(\text{O})\text{R}^{14}$, $-\text{C}(\text{O})\text{OR}^{14}$, $-\text{C}(\text{O})\text{NR}^{11}\text{R}^{12}$, $-\text{OR}^{15}$, $-\text{NR}^{11}\text{SO}_2\text{R}^{15}$, $-\text{NR}^{11}\text{C}(\text{O})\text{R}^{14}$, $-\text{NR}^{11}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{11}\text{OR}^{14}$, $-\text{OCX}^2_3$, $-\text{OCHX}^2_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl; R^4 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^5 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^7 , R^8 , R^9 , R^{10} , R^{7B} , R^{8B} , R^{9B} , R^{10B} , R^{11} , R^{12} , R^{14} , and R^{15} are independently hydrogen, halogen, $-CX_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 and R^8 substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X, X^1 , and X^2 is independently $-F$, $-Cl$, $-Br$, or $-I$; n_1 , n_2 , v_1 , and v_2 are independently an integer from 0 to 4; m_1 and m_2 are independently an integer between 1 and 2; z_1 is independently an integer from 0 to 5; and z_2 is independently an integer from 0 to 10.

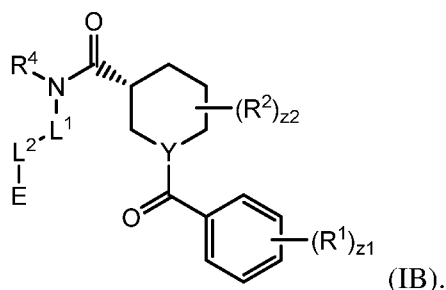
[0478] Embodiment P2. The compound of embodiment P1 having the formula:



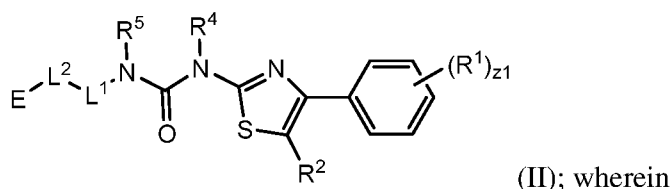
[0479] Embodiment P3. The compound of embodiment P1 having the formula:



[0480] Embodiment P4. The compound of embodiment P1 having the formula:

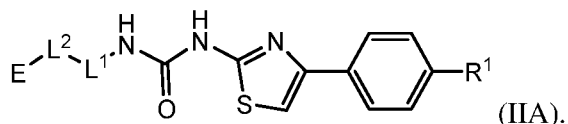


[0481] Embodiment P5. The compound of embodiment P1 having the formula:

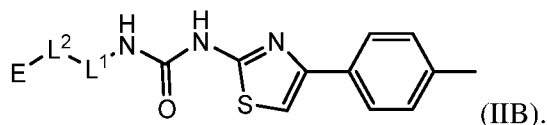


R^2 , R^4 , and R^5 are hydrogen.

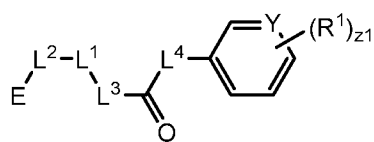
5 [0482] Embodiment P6. The compound of embodiment P5 having the formula:



[0483] Embodiment P7. The compound of embodiment P5 having the formula:



[0484] Embodiment P8. The compound of embodiment P1 having the formula:



bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(CH₃)C(O)NH-, or unsubstituted C₁-C₃ alkylene; and L^4 is a bond, -CH₂O-, -C(O)-, -NH-, or -O-.

[0485] Embodiment P9. The compound of one of embodiments P1 to P8, wherein Y is CH.

[0486] Embodiment P10. The compound of one of embodiments P1 to P8, wherein Y is N.

15 [0487] Embodiment P11. The compound of one of embodiments P1 to P10, wherein R^1 is independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -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, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0488] Embodiment P12. The compound of one of embodiments P1 to P10, wherein R¹ is independently

halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -COOH, -OCX¹₃, -OCHX¹₂, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃.

[0489] Embodiment P13. The compound of one of embodiments P1 to P12, wherein z₁ is 2.

[0490] Embodiment P14. The compound of one of embodiments P1 to P12, wherein z₁ is 3.

[0491] Embodiment P15. The compound of one of embodiments P1 to P14, wherein R² is independently oxo, halogen, CX²₃, -CHX²₂, -

CH₂X², -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, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0492] Embodiment P16. The compound of one of embodiments P1 to P14, wherein R² is independently oxo,

halogen, -CX²₃, -CHX²₂, -CH₂X², -OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃.

[0493] Embodiment P17. The compound of one of embodiments P1 to P16, wherein z₂ is 0.

[0494] Embodiment P18. The compound of one of embodiments P1 to P17, wherein R⁴ is hydrogen.

[0495] Embodiment P19. The compound of one of embodiments P1 to P18, wherein R⁵ is hydrogen.

[0496] Embodiment P20. The compound of one of embodiments P1 to P19, wherein L¹ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0497] Embodiment P21. The compound of one of embodiments P1 to P19, wherein L^1 is a bond, unsubstituted C_1 - C_4 alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

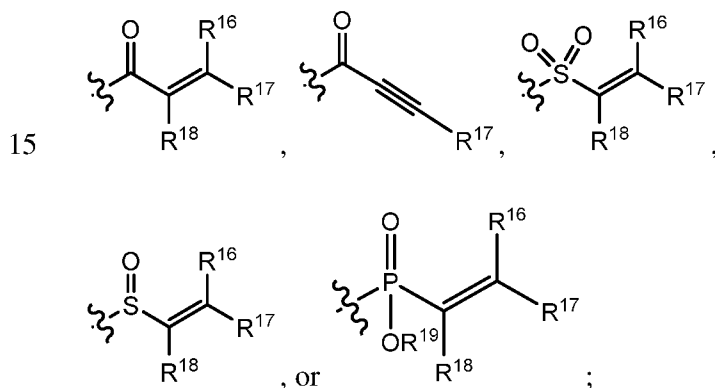
[0498] Embodiment P22. The compound of one of embodiments P1 to P19, wherein L^1 is a bond.

5 [0499] Embodiment P23. The compound of one of embodiments P1 to P22, wherein L^2 is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

10 [0500] Embodiment P24. The compound of one of embodiments P1 to P22, wherein L^2 is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C_1 - C_4 alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

[0501] Embodiment P25. The compound of one of embodiments P1 to P22, wherein L^2 is a bond.

[0502] Embodiment P26. The compound of one of embodiments P1 to P25, wherein E is



wherein R^{16} is independently hydrogen, halogen, CX^{16}_3 , $-CHX^{16}_2$, -

CH_2X^{16} , -CN, -SO₂Cl, -SO_{n16}R^{16D}, -SO_{v16}NR^{16A}R^{16B}, -NHN^{16A}R^{16B}, -ONR^{16A}R^{16B},

-NHC(=O)NHN^{16A}R^{16B},

20 -NHC(O)NR^{16A}R^{16B}, -N(O)_{m16}, -NR^{16A}R^{16B}, -C(O)R^{16C}, -C(O)-OR^{16C}, -C(O)NR^{16A}R^{16B}, -OR^{16D}, -NR^{16A}SO₂R^{16D}, -NR^{16A}C(O)R^{16C}, -NR^{16A}C(O)OR^{16C}, -NR^{16A}OR^{16C}, -OCX¹⁶₃, -OCHX¹⁶₂,

substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

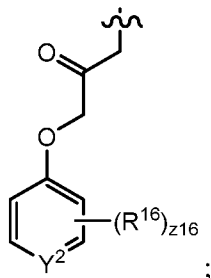
unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{17} is independently hydrogen,

25 halogen, CX^{17}_3 , $-CHX^{17}_2$, $-CH_2X^{17}$, -CN, -SO₂Cl, -SO_{n17}R^{17D}, -SO_{v17}NR^{17A}R^{17B}, -NHN^{17A}R^{17B},

- $-\text{ONR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{NHC}=\text{(O)NHN}\text{R}^{17\text{A}}\text{R}^{17\text{B}}$,
 $-\text{NHC(O)NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{N(O)}_{\text{m}17}$, $-\text{NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{C(O)R}^{17\text{C}}$, $-\text{C(O)-OR}^{17\text{C}}$, $-\text{C(O)NR}^{17\text{A}}\text{R}^{17\text{B}}$, $-\text{OR}^{17\text{D}}$,
 $-\text{NR}^{17\text{A}}\text{SO}_2\text{R}^{17\text{D}}$, $-\text{NR}^{17\text{A}}\text{C(O)R}^{17\text{C}}$, $-\text{NR}^{17\text{A}}\text{C(O)OR}^{17\text{C}}$, $-\text{NR}^{17\text{A}}\text{OR}^{17\text{C}}$, $-\text{OCX}^{17}_3$, $-\text{OCHX}^{17}_2$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 5 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen,
 halogen, CX^{18}_3 , $-\text{CHX}^{18}_2$, $-\text{CH}_2\text{X}^{18}$, $-\text{CN}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_{\text{n}18}\text{R}^{18\text{D}}$, $-\text{SO}_{\text{v}18}\text{NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{NHN}\text{R}^{18\text{A}}\text{R}^{18\text{B}}$,
 $-\text{ONR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{NHC}=\text{(O)NHN}\text{R}^{18\text{A}}\text{R}^{18\text{B}}$,
 $-\text{NHC(O)NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{N(O)}_{\text{m}18}$, $-\text{NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{C(O)R}^{18\text{C}}$, $-\text{C(O)-OR}^{18\text{C}}$, $-\text{C(O)NR}^{18\text{A}}\text{R}^{18\text{B}}$, $-\text{OR}^{18\text{D}}$,
 10 $-\text{NR}^{18\text{A}}\text{SO}_2\text{R}^{18\text{D}}$, $-\text{NR}^{18\text{A}}\text{C(O)R}^{18\text{C}}$, $-\text{NR}^{18\text{A}}\text{C(O)OR}^{18\text{C}}$, $-\text{NR}^{18\text{A}}\text{OR}^{18\text{C}}$, $-\text{OCX}^{18}_3$, $-\text{OCHX}^{18}_2$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{19} is independently hydrogen,
 halogen, CX^{19}_3 , $-\text{CHX}^{19}_2$, $-\text{CH}_2\text{X}^{19}$, $-\text{CN}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_{\text{n}19}\text{R}^{19\text{D}}$, $-\text{SO}_{\text{v}19}\text{NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{NHN}\text{R}^{19\text{A}}\text{R}^{19\text{B}}$,
 15 $-\text{ONR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{NHC}=\text{(O)NHN}\text{R}^{19\text{A}}\text{R}^{19\text{B}}$,
 $-\text{NHC(O)NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{N(O)}_{\text{m}19}$, $-\text{NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{C(O)R}^{19\text{C}}$, $-\text{C(O)-OR}^{19\text{C}}$, $-\text{C(O)NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{OR}^{19\text{D}}$,
 $-\text{NR}^{19\text{A}}\text{SO}_2\text{R}^{19\text{D}}$, $-\text{NR}^{19\text{A}}\text{C(O)R}^{19\text{C}}$, $-\text{NR}^{19\text{A}}\text{C(O)OR}^{19\text{C}}$, $-\text{NR}^{19\text{A}}\text{OR}^{19\text{C}}$, $-\text{OCX}^{19}_3$, $-\text{OCHX}^{19}_2$,
 substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
 20 unsubstituted aryl, substituted or unsubstituted heteroaryl; $\text{R}^{16\text{A}}$, $\text{R}^{16\text{B}}$, $\text{R}^{16\text{C}}$, $\text{R}^{16\text{D}}$, $\text{R}^{17\text{A}}$, $\text{R}^{17\text{B}}$,
 $\text{R}^{17\text{C}}$, $\text{R}^{17\text{D}}$, $\text{R}^{18\text{A}}$, $\text{R}^{18\text{B}}$, $\text{R}^{18\text{C}}$, $\text{R}^{18\text{D}}$, $\text{R}^{19\text{A}}$, $\text{R}^{19\text{B}}$, $\text{R}^{19\text{C}}$, $\text{R}^{19\text{D}}$, are independently hydrogen,
 halogen, $-\text{CX}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$,
 $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$,
 $-\text{NHOH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, substituted or unsubstituted alkyl,
 25 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted
 heteroaryl; $\text{R}^{16\text{A}}$ and $\text{R}^{16\text{B}}$ substituents bonded to the same nitrogen atom may optionally be
 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; $\text{R}^{17\text{A}}$ and $\text{R}^{17\text{B}}$ substituents bonded to the same nitrogen atom may optionally be
 30 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; $\text{R}^{18\text{A}}$ and $\text{R}^{18\text{B}}$ substituents bonded to the same nitrogen atom may optionally be
 joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted
 heteroaryl; $\text{R}^{19\text{A}}$ and $\text{R}^{19\text{B}}$ substituents bonded to the same nitrogen atom may optionally be

joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X, X¹⁶, X¹⁷, X¹⁸ and X¹⁹ is independently -F, -Cl, -Br, or -I; n₁₆, n₁₇, n₁₈, n₁₉, v₁₆, v₁₇, v₁₈, and v₁₉ are independently an integer from 0 to 4; and m₁₆, m₁₇, m₁₈, and m₁₉ are independently an integer from 1 to 2.

- 5 [0503] Embodiment P27. The compound of one of embodiments P1 to P25, wherein E is



wherein R¹⁶ is independently halogen, CX¹⁶₃, -CHX¹⁶₂, -

CH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂Cl, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -

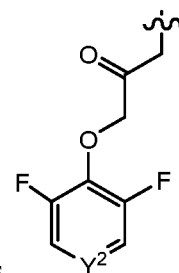
- 10 NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; Y² is N or CH; z₁₆ is an integer between 0 and 4; and each X¹⁶ is independently -F, -Cl, -Br, or -I.

- 15 [0504] Embodiment P28. The compound of embodiment P27 wherein R¹⁶ is independently halogen.

[0505] Embodiment P29. The compound of embodiment P27 wherein R¹⁶ is independently -F.

[0506] Embodiment P30. The compound of one of embodiments P27 to P29, wherein z₁₆ is 4.

- 20 [0507] Embodiment P31. The compound of one of embodiments P27 to P29, wherein z₁₆ is 2.

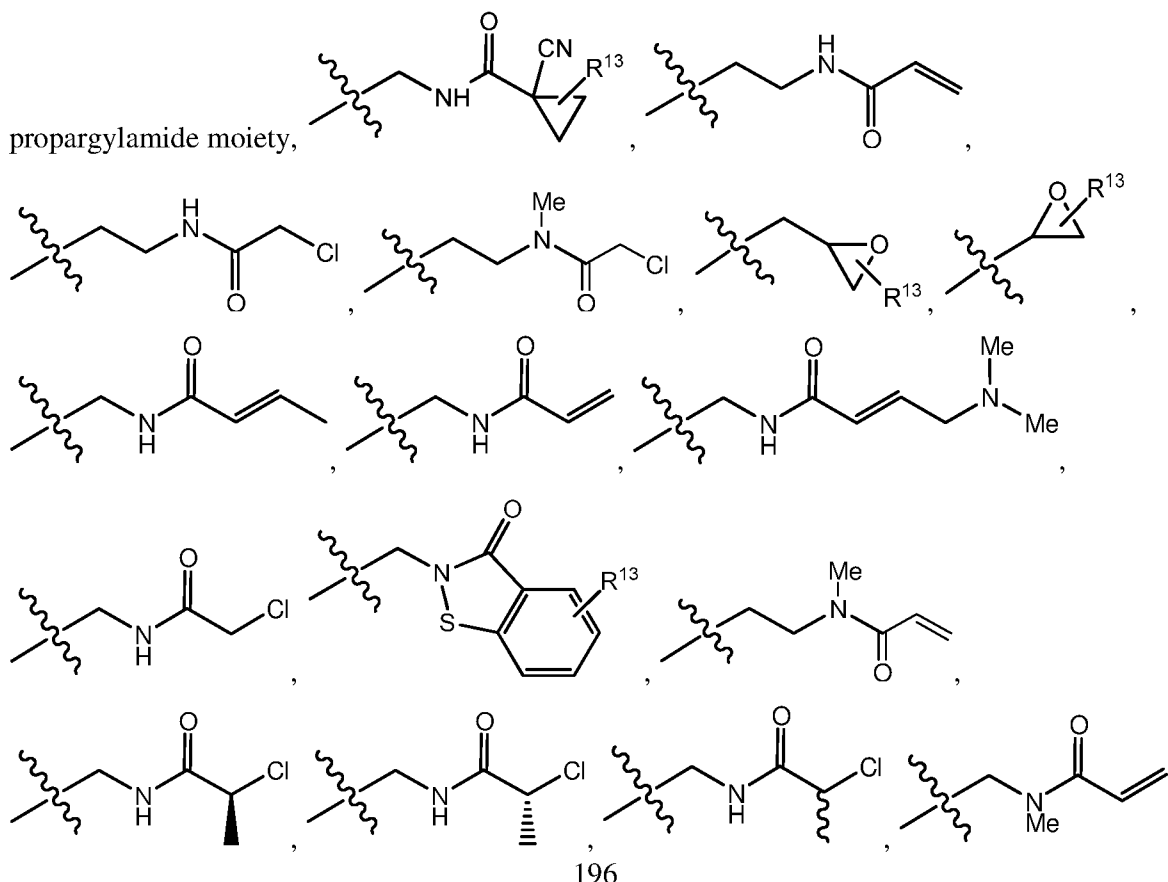


[0508] Embodiment P32. The compound of embodiment P31 wherein E is

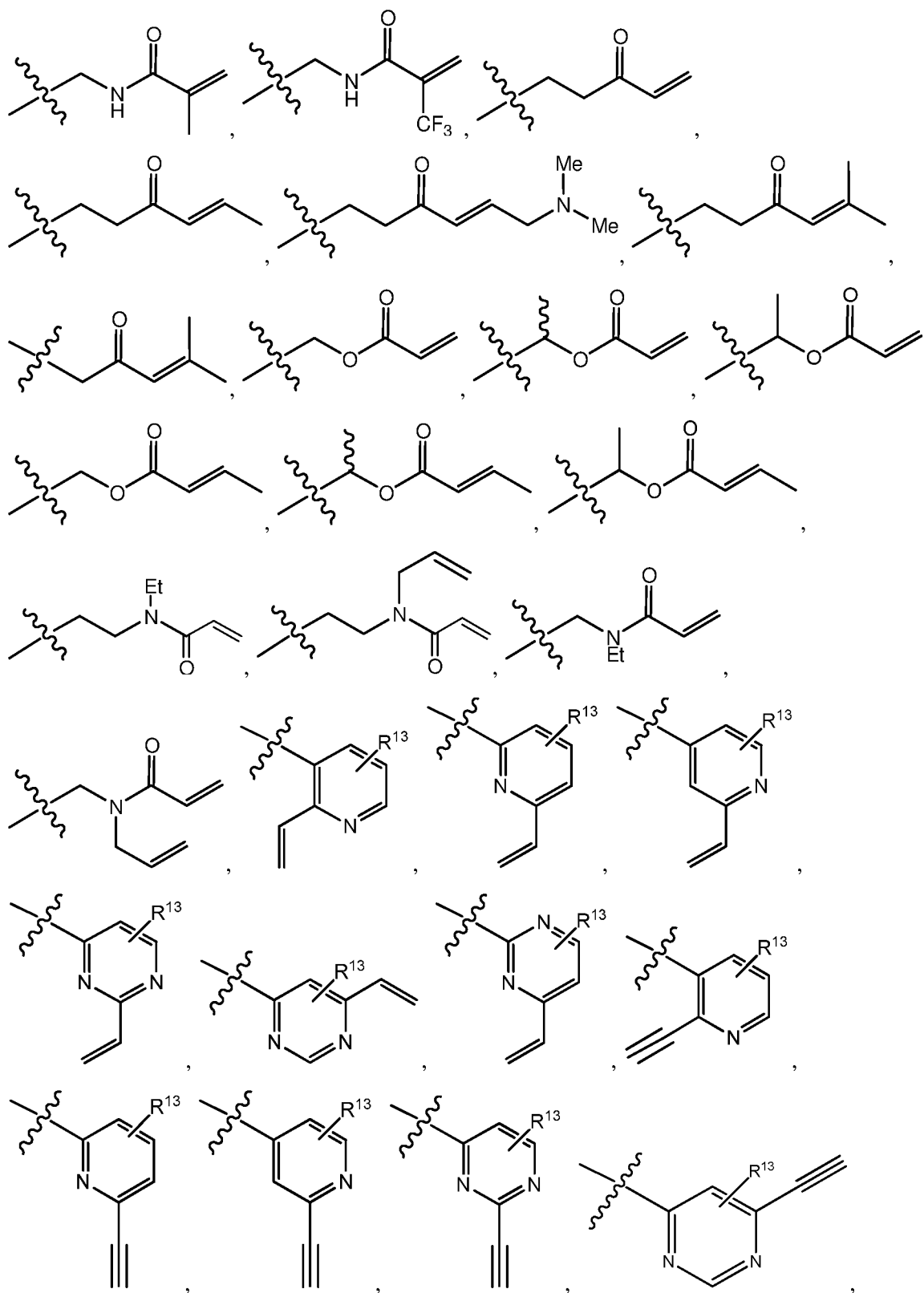
[0509] Embodiment P33. The compound of one of embodiments P27 to P32, wherein Y^2 is CH.

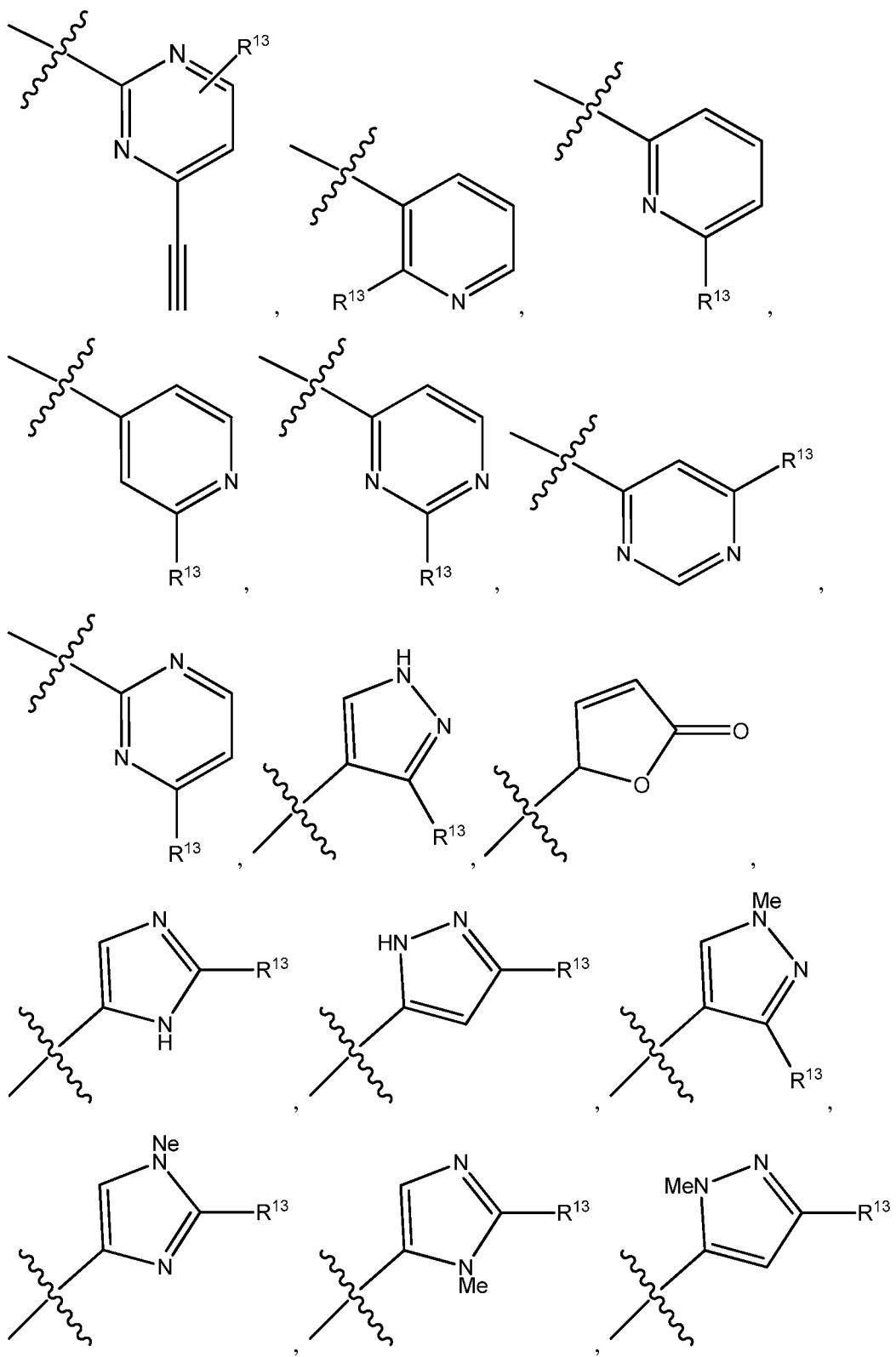
[0510] Embodiment P34. The compound of one of embodiments P27 to P32, wherein Y^2 is N.

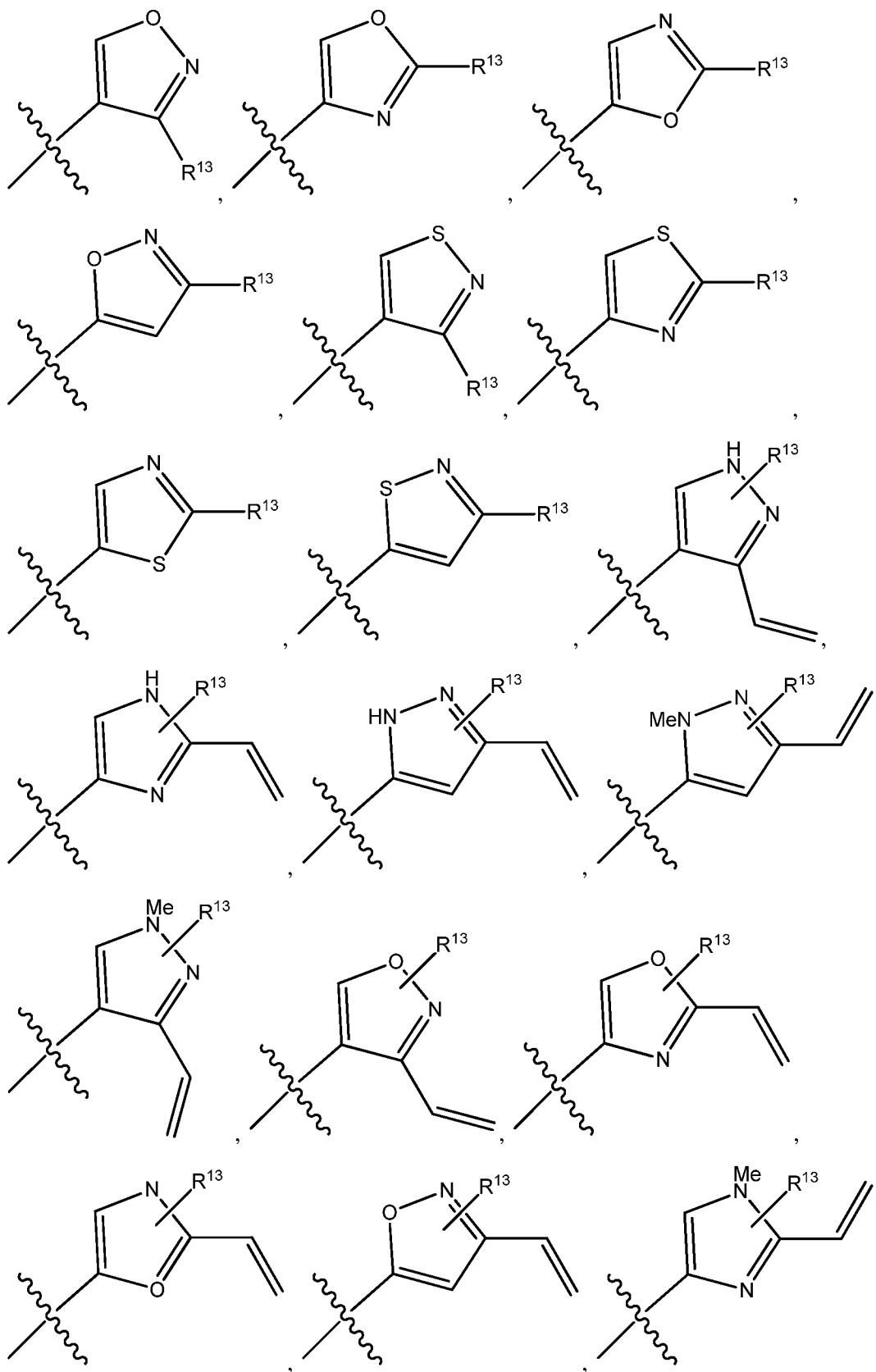
- 5 [0511] Embodiment P35. The compound of one of embodiments P1 to P25, wherein E comprises a substituted or unsubstituted vinyl sulfone moiety, substituted or unsubstituted vinyl sulfonamide moiety, substituted or unsubstituted fluoro(C_1 - C_4)alkylketone moiety, substituted or unsubstituted chloro(C_1 - C_4)alkylketone moiety, substituted or unsubstituted acrylamide moiety, substituted or unsubstituted disulfide moiety, substituted or unsubstituted thiol moiety,
- 10 substituted or unsubstituted phosphonate moiety, substituted or unsubstituted aldehyde moiety, substituted or unsubstituted enone moiety, substituted or unsubstituted diazomethylketone moiety, substituted or unsubstituted diazomethylamide moiety, substituted or unsubstituted cyanocyclopropyl carboxamide moiety, substituted or unsubstituted epoxide moiety, substituted or unsubstituted epoxyketone moiety, substituted or unsubstituted epoxyamide moiety,
- 15 substituted or unsubstituted aryl aldehyde moiety, substituted or unsubstituted aryl dialdehyde moiety, substituted or unsubstituted dialdehyde moiety, substituted or unsubstituted nitrogen mustard moiety, substituted or unsubstituted propargyl moiety, substituted or unsubstituted

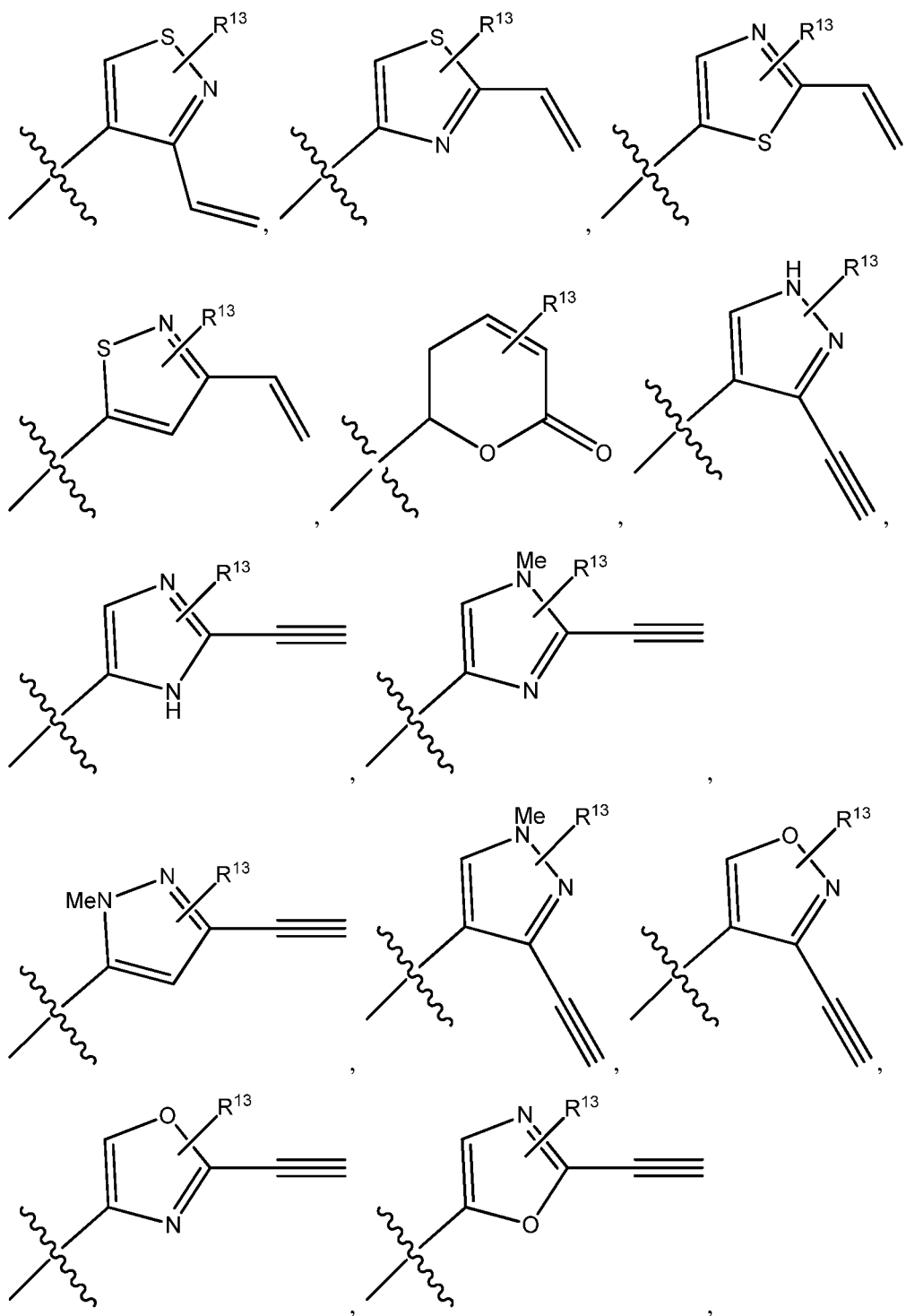


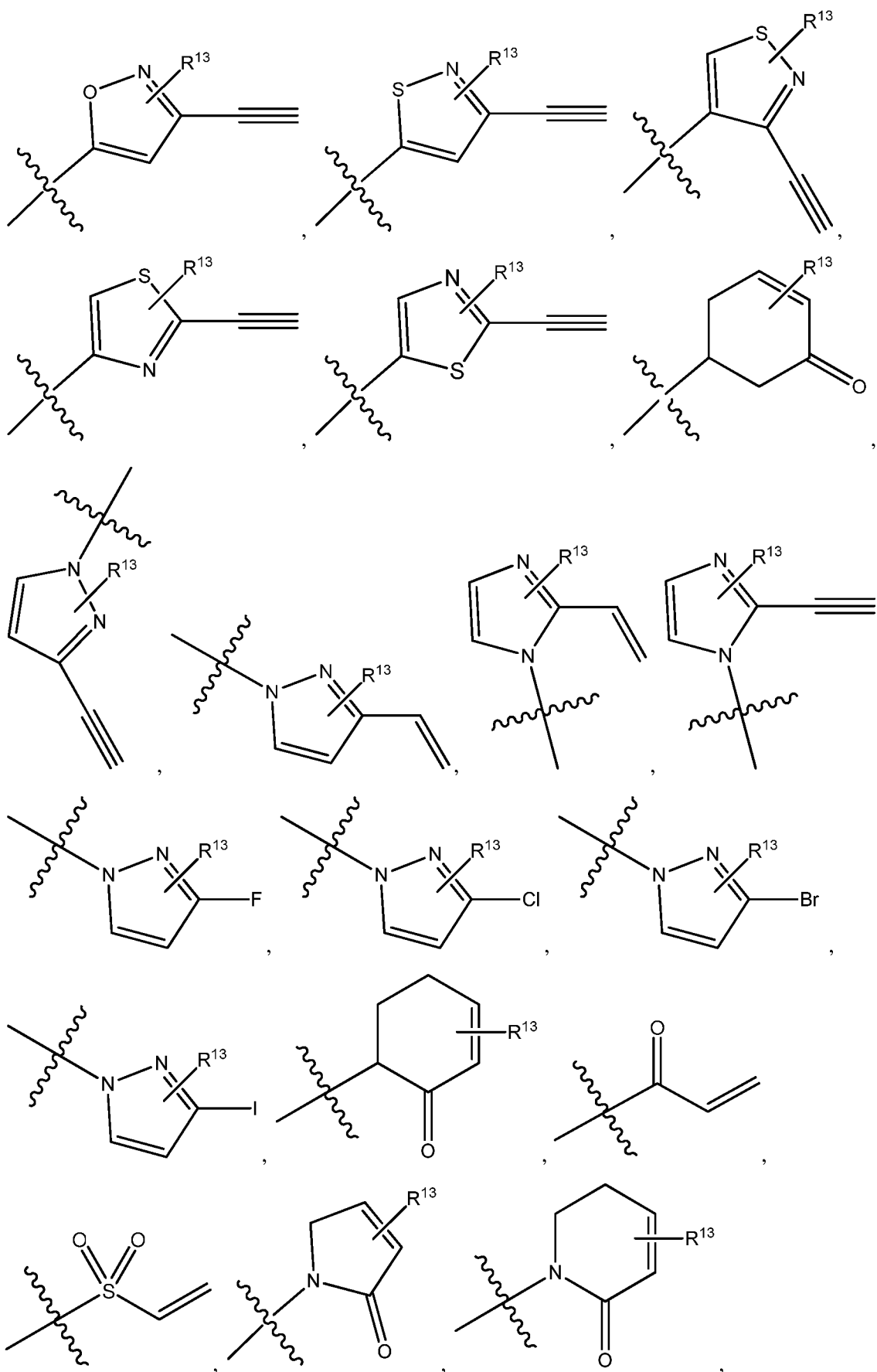
5

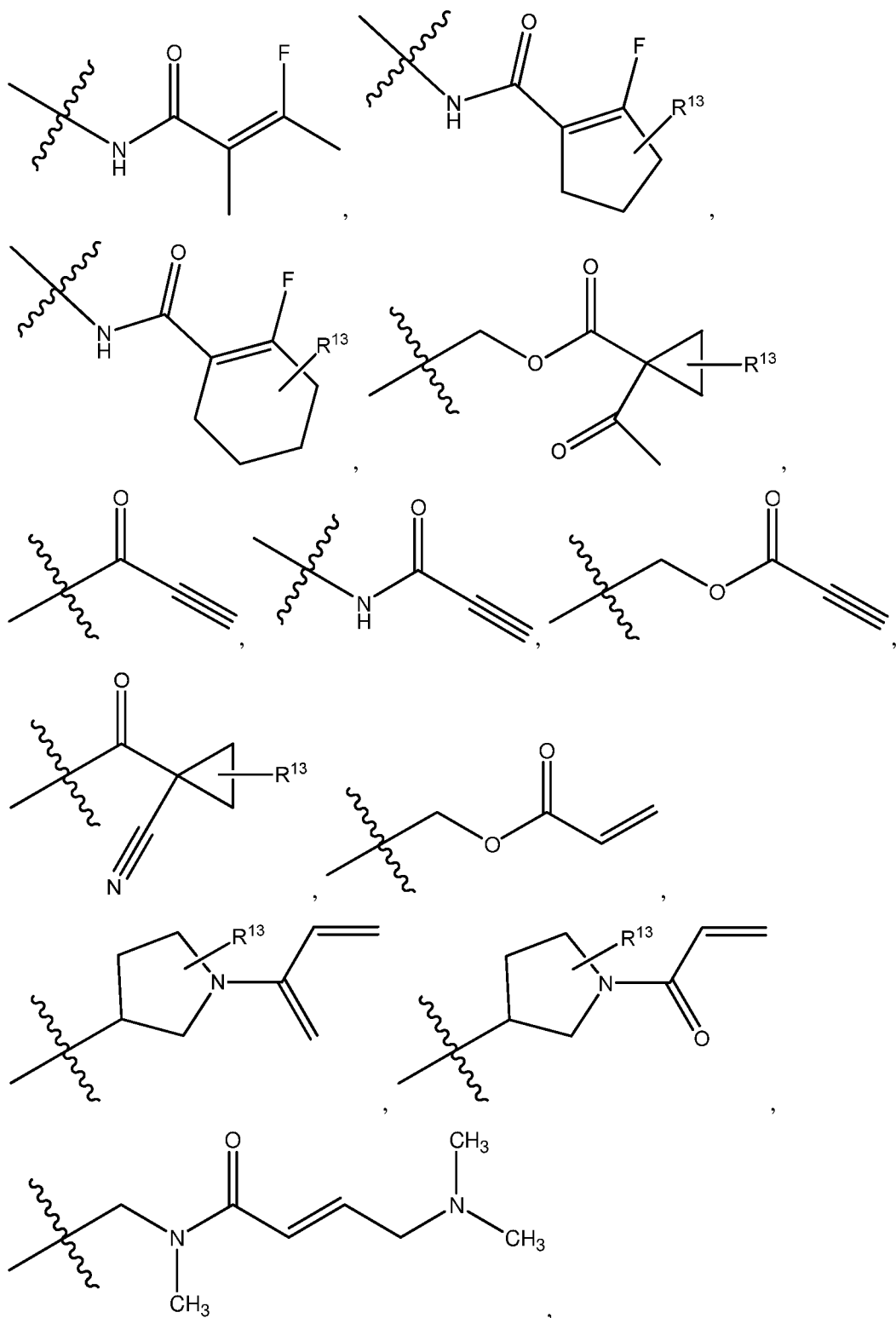


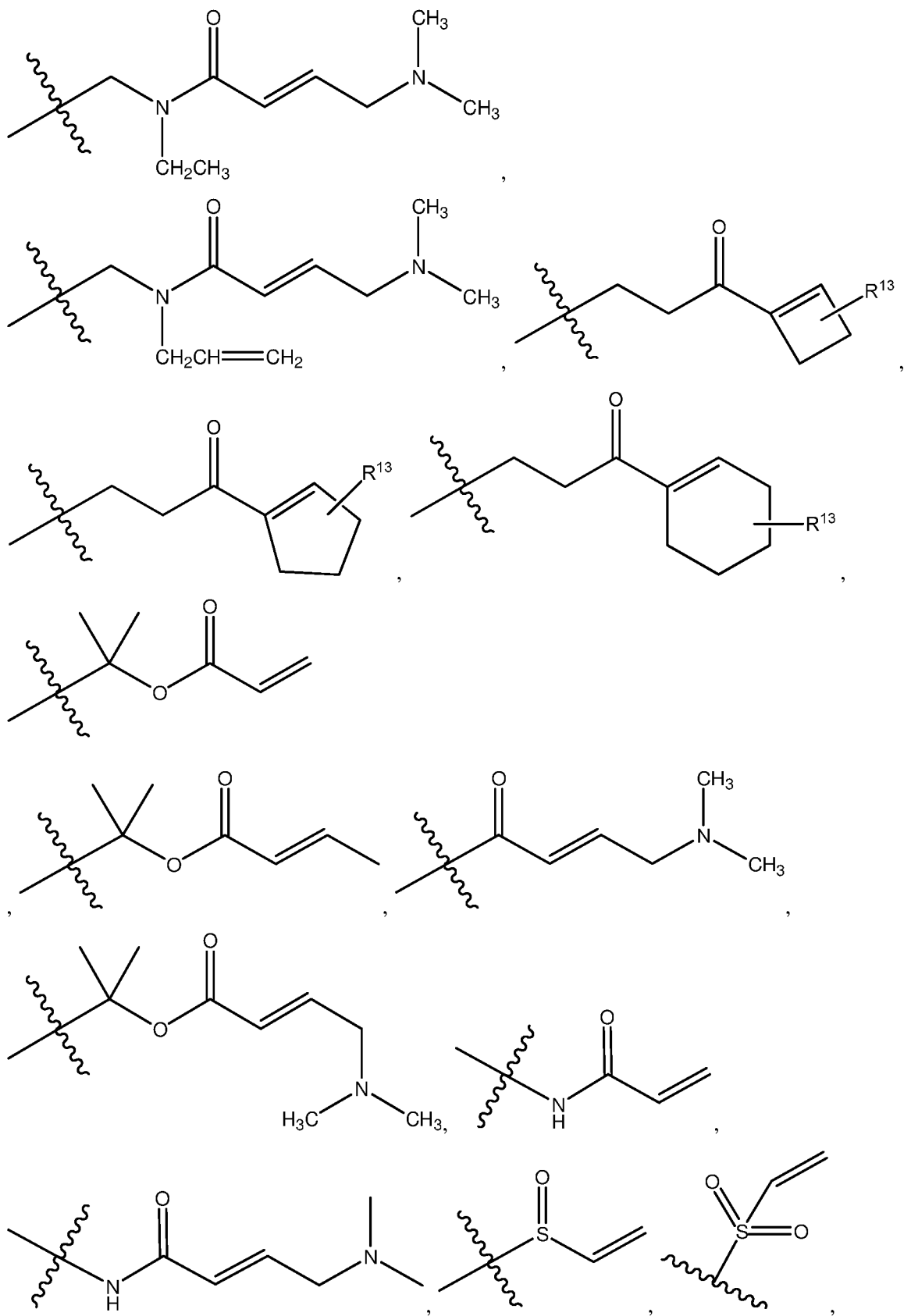


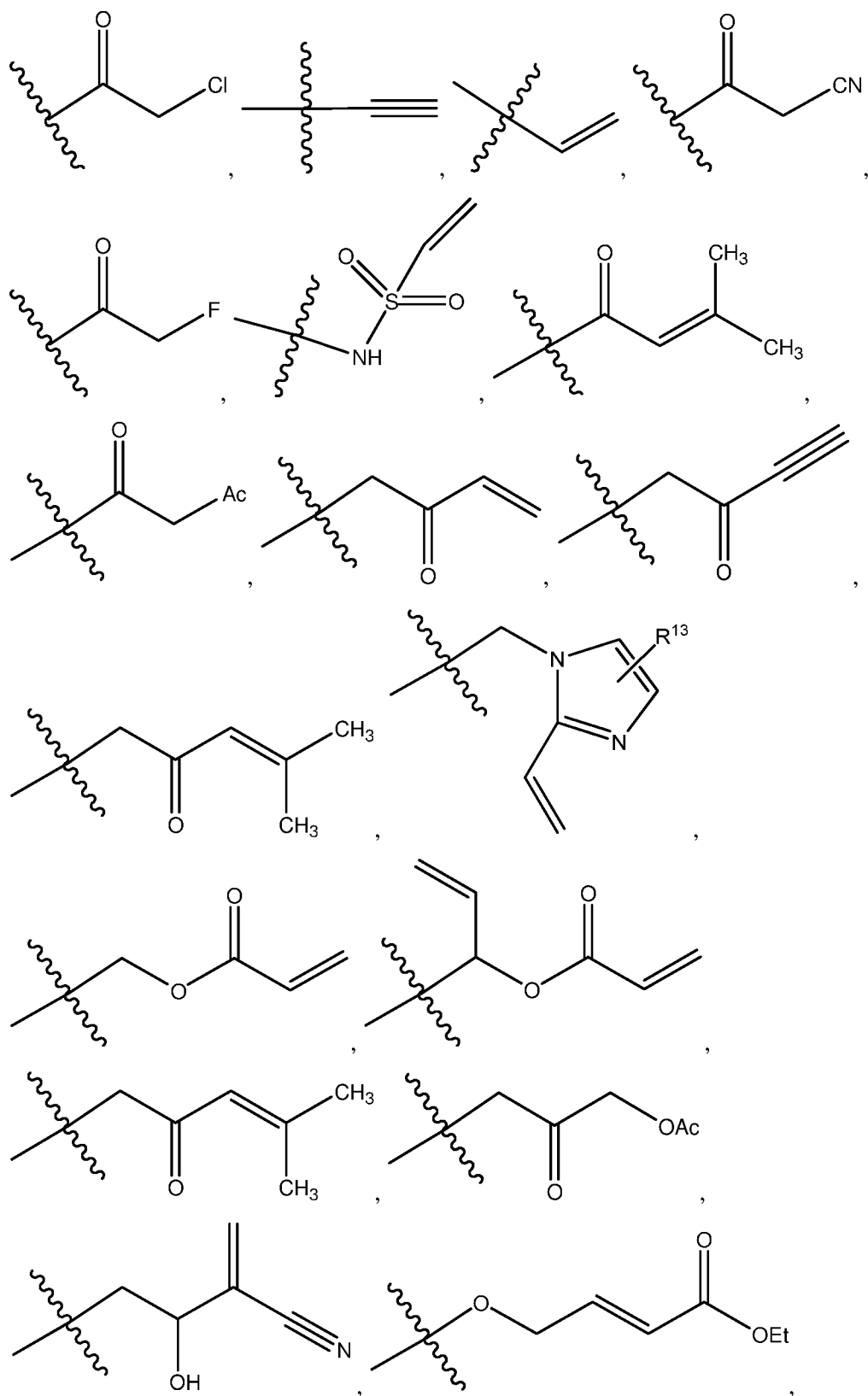


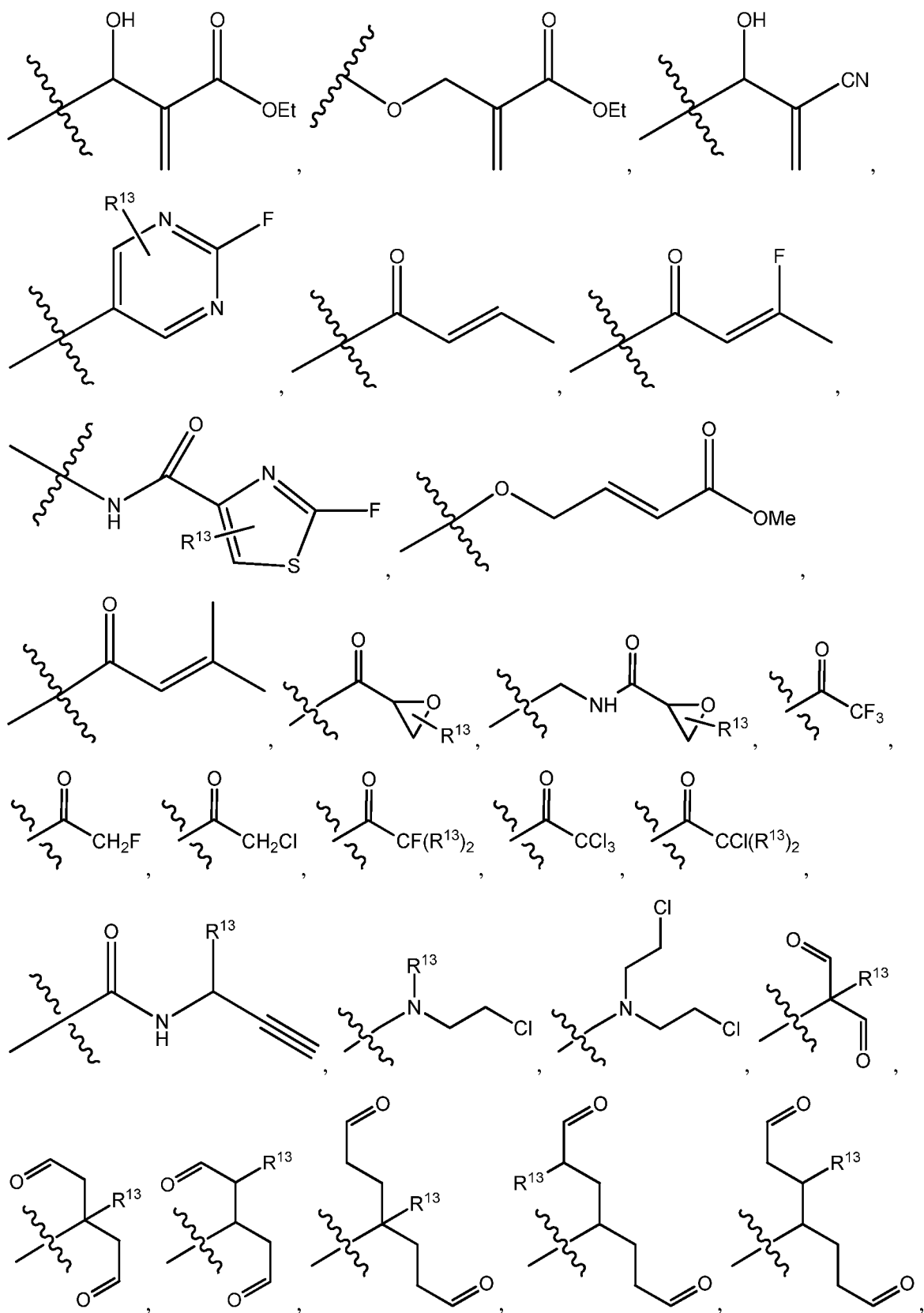


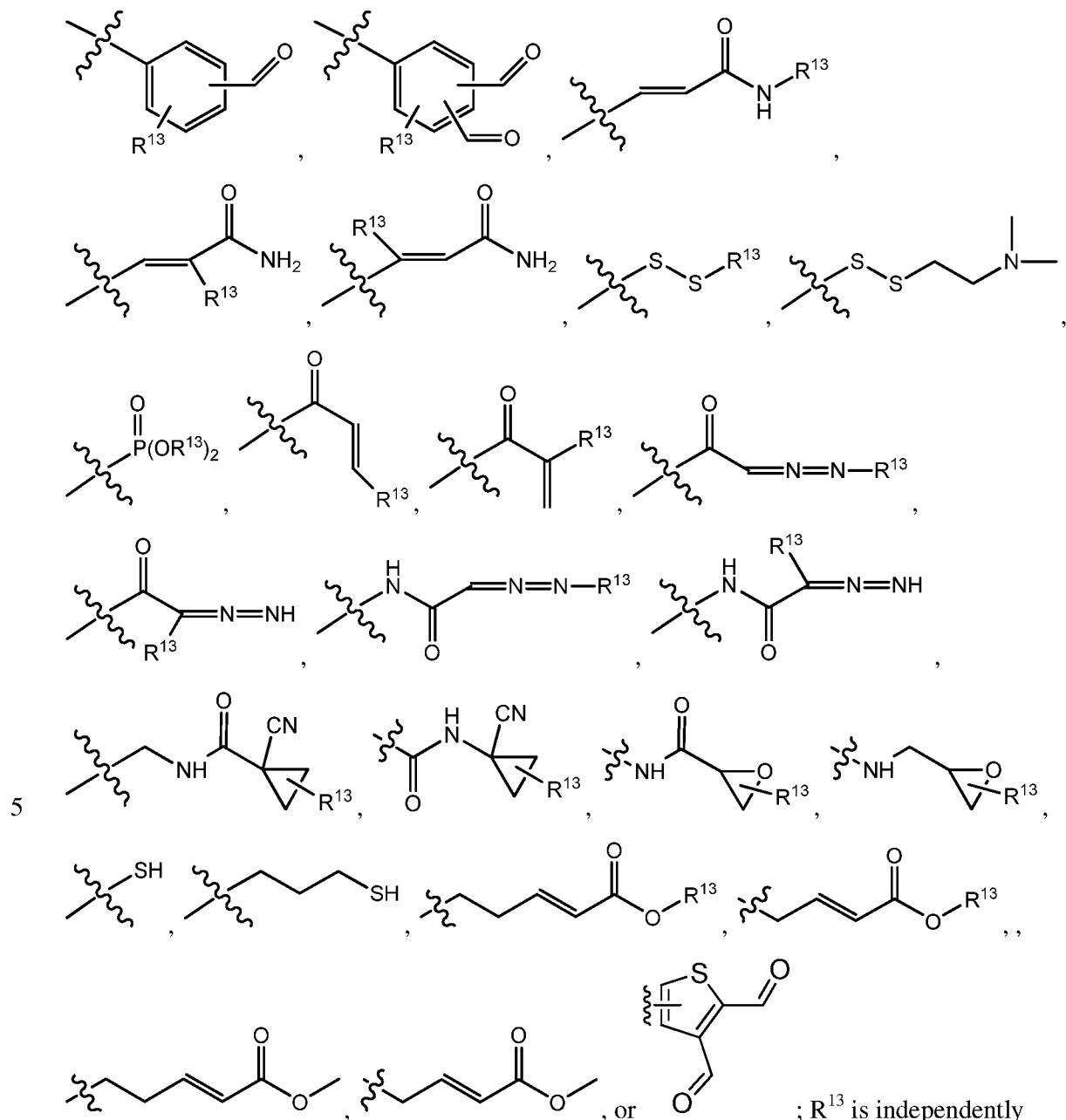












hydrogen, oxo, halogen, CX^{13}_3 , $-\text{CHX}^{13}_2$, $-\text{CH}_2\text{X}^{13}$, $-\text{CN}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_{\text{n}13}\text{R}^{22}$, $-\text{SO}_{\text{v}13}\text{NR}^{20}\text{R}^{21}$, $-\text{NHN}\text{R}^{20}\text{R}^{21}$, $-\text{ONR}^{20}\text{R}^{21}$, $-\text{NHC}(\text{O})\text{NHN}\text{R}^{20}\text{R}^{21}$,

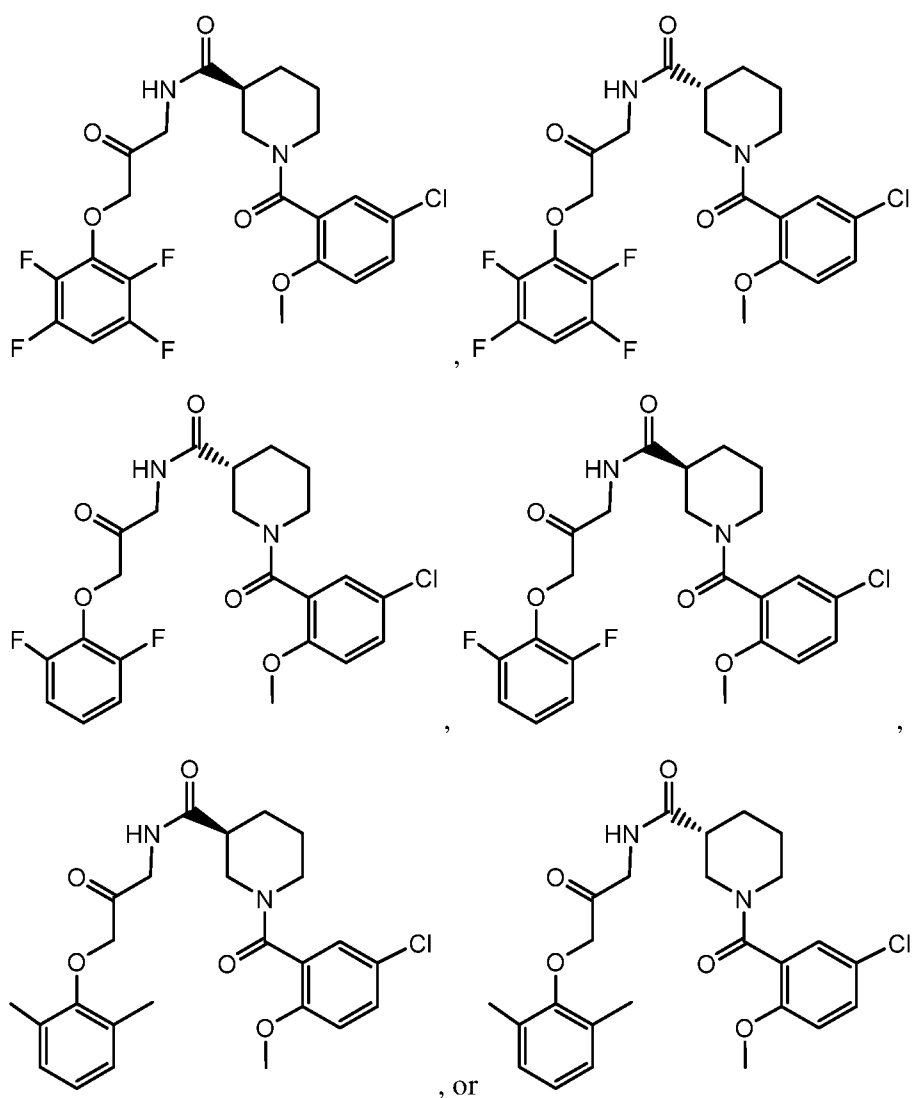
10 $-\text{NHC}(\text{O})\text{NR}^{20}\text{R}^{21}$, $-\text{N}(\text{O})_{\text{m}13}$, $-\text{NR}^{20}\text{R}^{21}$, $-\text{C}(\text{O})\text{R}^{22}$, $-\text{C}(\text{O})-\text{OR}^{22}$, $-\text{C}(\text{O})\text{NR}^{20}\text{R}^{21}$, $-\text{OR}^{23}$, $-\text{NR}^{20}\text{SO}_2\text{R}^{23}$, $-\text{NR}^{20}\text{C}(\text{O})\text{R}^{22}$, $-\text{NR}^{20}\text{C}(\text{O})\text{OR}^{22}$, $-\text{NR}^{20}\text{OR}^{22}$, $-\text{OCX}^{13}_3$, $-\text{OCHX}^{13}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents

15 bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl; R^{20} , R^{21} , R^{22} , and R^{23} are

independently hydrogen, halogen, $-CX^A_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^A_3$, $-OCHX^A_2$, $-CHX^A_2$, $-CH_2X^A$, substituted 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^{20} and R^{21} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X^A and X^{13} is independently $-F$, $-Cl$, $-Br$, or $-I$; n^{13} and v^{13} are independently an integer from 0 to 4; and m^{13} is independently an integer from 1 to

10 2.

[0512] Embodiment P36. A compound having the formula:



[0513] Embodiment P37. A pharmaceutical composition comprising the compound of any one of embodiments P1 to P36 and a pharmaceutically acceptable excipient.

[0514] Embodiment P38. A method of reducing the level of activity of a K-Ras protein, said method comprising contacting the K-Ras protein with a compound of one of embodiments P1 to P36.

[0515] Embodiment P39. A method of reducing the level of activity of a K-Ras-4B protein, said method comprising contacting the K-Ras-4B protein with a compound of one of embodiments P1 to P36.

[0516] Embodiment P40. A method for treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of one of embodiments P1 to P36.

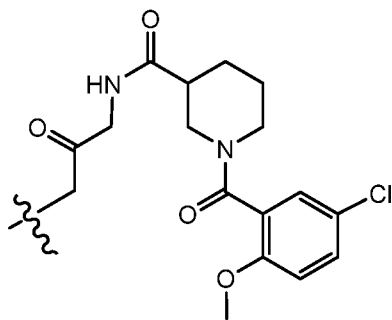
[0517] Embodiment P41. The method of embodiment P40, wherein said cancer is pancreatic cancer, lung cancer, or colorectal cancer.

[0518] Embodiment P42. A K-Ras protein covalently bonded to a compound of one of embodiments P1 to P36.

[0519] Embodiment P43. The K-Ras protein of embodiment P42, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0520] Embodiment P44. The K-Ras protein of embodiment P42, wherein the compound is irreversibly covalently bonded to a cysteine residue of the protein.

[0521] Embodiment P45. A K-Ras protein covalently bonded to a compound having the



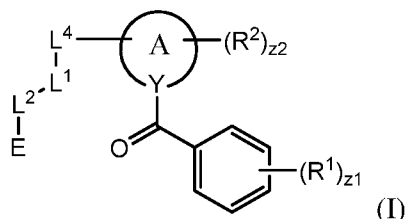
formula:

[0522] Embodiment P46. The K-Ras protein of embodiment P45, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0523] Embodiment P47. The K-Ras protein of embodiment P45, wherein the compound is covalently bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B.

VIII. Additional Embodiments

5 [0524] Embodiment 1. A compound having the formula:

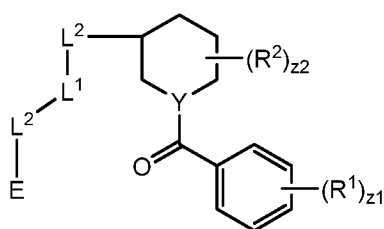


wherein, Y is N or CH; Ring A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl; R¹ is independently halogen, CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR⁷R⁸, -NHN⁷R⁸, -ONR⁷R⁸, -NHC(=O)NHN⁷R⁸,

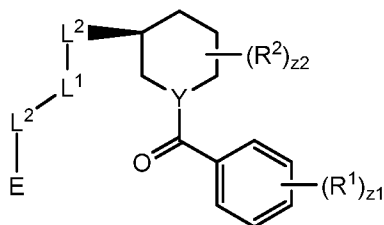
- 10 -NHC(O)NR⁷R⁸, -N(O)_{m1}, -NR⁷R⁸, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR⁷R⁸, -OR¹⁰, -NR⁷SO₂R¹⁰, -NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a substituted or
- 15 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted heteroarylene; L² is a
- 20 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-, -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
- 25 unsubstituted arylene, substituted or unsubstituted heteroarylene; L⁴ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-, substituted or unsubstituted C₁-C₃ alkylene, substituted or unsubstituted 2 to 3 membered heteroalkylene; E is an electrophilic moiety; R² is independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -SO₂Cl, -SO_{n2}R¹⁴, -SO_{v2}NR¹¹R¹², -NHN¹¹R¹²,

- $-\text{ONR}^{11}\text{R}^{12}$, $-\text{NHC}=\text{(O)NHNR}^{11}\text{R}^{12}$,
 $-\text{NHC(O)NR}^{11}\text{R}^{12}$, $-\text{N(O)}_{m2}$, $-\text{NR}^{11}\text{R}^{12}$, $-\text{C(O)R}^{14}$, $-\text{C(O)-OR}^{14}$, $-\text{C(O)NR}^{11}\text{R}^{12}$, $-\text{OR}^{15}$, $-\text{NR}^{11}\text{SO}_2\text{R}^{15}$, $-\text{NR}^{11}\text{C(O)R}^{14}$, $-\text{NR}^{11}\text{C(O)OR}^{14}$, $-\text{NR}^{11}\text{OR}^{14}$, $-\text{OCX}_3^2$, $-\text{OCHX}_2^2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents bonded to the same atom may optionally be joined to form a substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl; R^4 is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^7 , R^8 , R^9 , R^{10} , R^{7B} , R^{8B} , R^{9B} , R^{10B} , R^{11} , R^{12} , R^{14} , and R^{15} are independently hydrogen, halogen, $-\text{CX}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_2\text{Cl}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 and R^8 substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{11} and R^{12} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X , X^1 , and X^2 is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$; $n1$, $n2$, $v1$, and $v2$ are independently an integer from 0 to 4; $m1$ and $m2$ are independently an integer from 1 to 2; $z1$ is independently an integer from 0 to 5; and $z2$ is independently an integer from 0 to 10.

- 25 **[0525]** Embodiment 2. The compound of embodiment 1, having the formula:



- [0526]** Embodiment 3. The compound of embodiment 1, having the formula:



[0527] Embodiment 4. The compound of one of embodiments 1 to 3, wherein Y is CH.

[0528] Embodiment 5. The compound of one of embodiments 1 to 3, wherein Y is N.

[0529] Embodiment 6. The compound of one of embodiments 1 to 5, wherein R¹ is

- 5 independently halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or
10 unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0530] Embodiment 7. The compound of one of embodiments 1 to 5, wherein R¹ is independently

halogen, -CX¹₃, -CHX¹₂, -CH₂X¹, -OH, -SH, -COOH, -OCX¹₃, -OCHX¹₂, -CH₃, -CH₂CH₃, -OC
H₃, -OCH₂CH₃, -SCH₃, or -SCH₂CH₃.

- 15 [0531] Embodiment 8. The compound of one of embodiments 1 to 5, wherein R¹ is independently halogen or -OCH₃.

[0532] Embodiment 9. The compound of one of embodiments 1 to 8, wherein z₁ is 2.

[0533] Embodiment 10. The compound of one of embodiments 1 to 8, wherein z₁ is 3.

[0534] Embodiment 11. The compound of one of embodiments 1 to 10, wherein R² is

- 20 independently oxo, halogen, CX²₃, -CHX²₂, -CH₂X², -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈ cycloalkyl,

substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

[0535] Embodiment 12. The compound of one of embodiments 1 to 10, wherein R² is independently oxo,

5 halogen, -CX₃², -CHX₂², -CH₂X², --OH, -SH, -OCX₃², -OCHX₂², -CH₃, -CH₂CH₃, -OCH₃, -OC H₂CH₃, -SCH₃, or -SCH₂CH₃.

[0536] Embodiment 13. The compound of one of embodiments 1 to 12, wherein z₂ is 0.

[0537] Embodiment 14. The compound of one of embodiments 1 to 13, wherein L¹ is a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

10 [0538] Embodiment 15. The compound of one of embodiments 1 to 13, wherein L¹ is a bond, unsubstituted C₁-C₄ alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

[0539] Embodiment 16. The compound of one of embodiments 1 to 13, wherein L¹ is a bond.

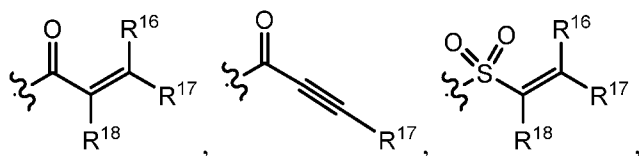
15 [0540] Embodiment 17. The compound of one of embodiments 1 to 16, wherein L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -NHSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

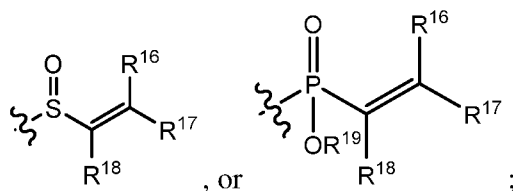
[0541] Embodiment 18. The compound of one of embodiments 1 to 16, wherein L² is a bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or
20 unsubstituted 2 to 4 membered heteroalkylene.

[0542] Embodiment 19. The compound of one of embodiments 1 to 16, wherein L² is -NH-.

[0543] Embodiment 20. The compound of one of embodiments 1 to 16, wherein L² is a bond.

25 [0544] Embodiment 21. The compound of one of embodiments 1 to 20, wherein E is





wherein R^{16} is independently hydrogen, halogen, CX^{16}_3 , $-CHX^{16}_2$, -

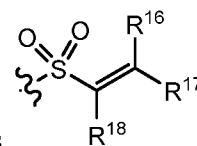
CH_2X^{16} , $-CN$, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHN R^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$,

$-NHC(=O)NHN R^{16A}R^{16B}$,

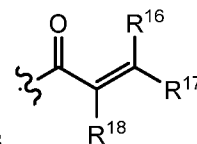
- 5 $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR^{16D}$, $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, $-NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{17} is independently hydrogen,
- 10 halogen, CX^{17}_3 , $-CHX^{17}_2$, $-CH_2X^{17}$, $-CN$, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHN R^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$, $-NHC(=O)NHN R^{17A}R^{17B}$, $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR^{17D}$, $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, $-NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
- 15 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{18} is independently hydrogen, halogen, CX^{18}_3 , $-CHX^{18}_2$, $-CH_2X^{18}$, $-CN$, $-SO_{n18}R^{18D}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHN R^{18A}R^{18B}$, $-ONR^{18A}R^{18B}$, $-NHC(=O)NHN R^{18A}R^{18B}$, $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18C}$, $-C(O)-OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, $-OR^{18D}$,
- 20 $-NR^{18A}SO_2R^{18D}$, $-NR^{18A}C(O)R^{18C}$, $-NR^{18A}C(O)OR^{18C}$, $-NR^{18A}OR^{18C}$, $-OCX^{18}_3$, $-OCHX^{18}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{19} is independently hydrogen, halogen, CX^{19}_3 , $-CHX^{19}_2$, $-CH_2X^{19}$, $-CN$, $-SO_{n19}R^{19D}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHN R^{19A}R^{19B}$,
- 25 $-ONR^{19A}R^{19B}$, $-NHC(=O)NHN R^{19A}R^{19B}$, $-NHC(O)NR^{19A}R^{19B}$, $-N(O)_{m19}$, $-NR^{19A}R^{19B}$, $-C(O)R^{19C}$, $-C(O)-OR^{19C}$, $-C(O)NR^{19A}R^{19B}$, $-OR^{19D}$, $-NR^{19A}SO_2R^{19D}$, $-NR^{19A}C(O)R^{19C}$, $-NR^{19A}C(O)OR^{19C}$, $-NR^{19A}OR^{19C}$, $-OCX^{19}_3$, $-OCHX^{19}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or
- 30 unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{16A} , R^{16B} , R^{16C} , R^{16D} , R^{17A} , R^{17B} ,

- R^{17C} , R^{17D} , R^{18A} , R^{18B} , R^{18C} , R^{18D} , R^{19A} , R^{19B} , R^{19C} , R^{19D} , are independently hydrogen, halogen, $-CX_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-CHX_2$, $-CH_2X$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{16A} and R^{16B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{17A} and R^{17B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{18A} and R^{18B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{19A} and R^{19B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; each X , X^{16} , X^{17} , X^{18} and X^{19} is independently $-F$, $-Cl$, $-Br$, or $-I$; n_{16} , n_{17} , n_{18} , n_{19} , v_{16} , v_{17} , v_{18} , and v_{19} are independently an integer from 0 to 4; and m_{16} , m_{17} , m_{18} , and m_{19} are independently an integer from 1 to 2.

[0545] Embodiment 22. The compound of embodiment 21, wherein E is



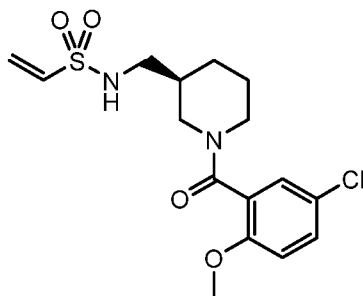
[0546] Embodiment 23. The compound of embodiment 21, wherein E is



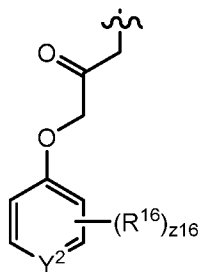
- [0547] Embodiment 24. The compound of one of embodiments 21 to 23, wherein R^{16} , R^{17} , and R^{18} are independently hydrogen, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2N(CH_3)_2$, or $-CH_2CH_2N(CH_3)_2$.

[0548] Embodiment 25. The compound of one of embodiments 21 to 24, wherein L^4 is a bond or $-CH_2-$.

- [0549] Embodiment 26. The compound of one of embodiments 21, 22, 24, or 25, having the formula:



[0550] Embodiment 27. The compound of one of embodiments 1 to 20, wherein E is



; wherein R^{16} is independently halogen, CX^{16}_3 , $-CHX^{16}_2$, -

CH_2X^{16} , $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$,

5 $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NH_2SO_2H$, $-NHC(O)H$, -

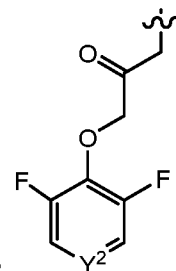
$NHC(O)OH$, $-NHOH$, $-OCX^{16}_3$, $-OCHX^{16}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; Y^2 is N or CH; z_{16} is an integer from 0 to 4; and each X^{16} is independently $-F$, $-Cl$, $-Br$, or $-I$.

10 [0551] Embodiment 28. The compound of embodiment 27 wherein R^{16} is independently halogen.

[0552] Embodiment 29. The compound of embodiment 27 wherein R^{16} is independently $-F$.

[0553] Embodiment 30. The compound of one of embodiments 27 to 29, wherein z_{16} is 4.

[0554] Embodiment 31. The compound of one of embodiments 27 to 29, wherein z_{16} is 2.



15 [0555] Embodiment 32. The compound of embodiment 31 wherein E is

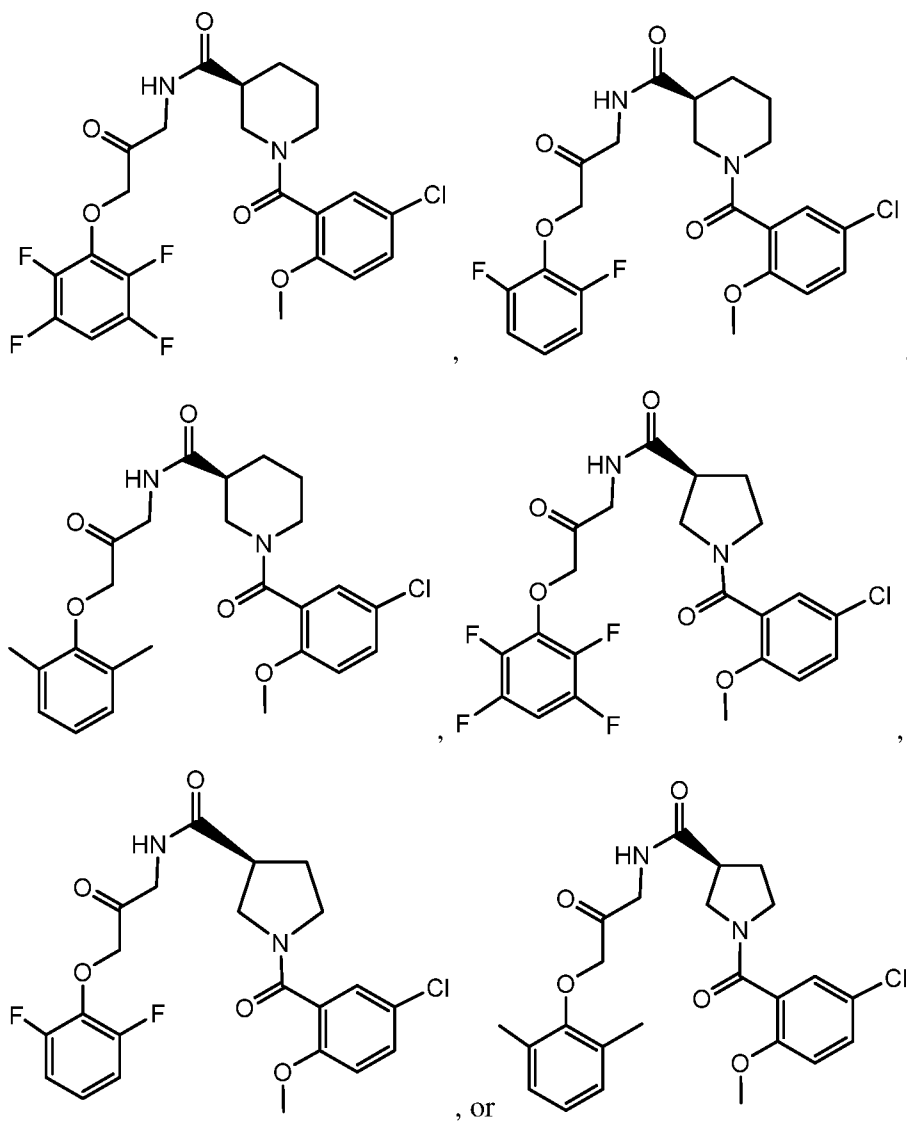
[0556] Embodiment 33. The compound of one of embodiments 27 to 32, wherein Y^2 is CH.

[0557] Embodiment 34. The compound of one of embodiments 27 to 32, wherein Y^2 is N.

[0558] Embodiment 35. The compound of one of embodiments 27 to 34, wherein L^4 is $-N(R^4)C(O)-$.

5 [0559] Embodiment 36. The compound of one of embodiments 27 to 35, wherein R^4 is hydrogen.

[0560] Embodiment 37. The compound of one of embodiments 27 to 36, having the formula:



[0561] Embodiment 38. A pharmaceutical composition comprising the compound of any one of embodiments 1 to 37 and a pharmaceutically acceptable excipient.

[0562] Embodiment 39. A method of reducing the level of activity of a K-Ras protein, said method comprising contacting the K-Ras protein with a compound of one of embodiments 1 to 37.

[0563] Embodiment 40. A method of reducing the level of activity of a K-Ras-4B protein, said method comprising contacting the K-Ras-4B protein with a compound of one of embodiments 1 to 37.

[0564] Embodiment 41. A method for treating cancer, said method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of one of embodiments 1 to 37.

[0565] Embodiment 42. The method of embodiment 41, wherein said cancer is pancreatic cancer, lung cancer, or colorectal cancer.

[0566] Embodiment 43. A K-Ras protein covalently bonded to a compound of one of embodiments 1 to 37.

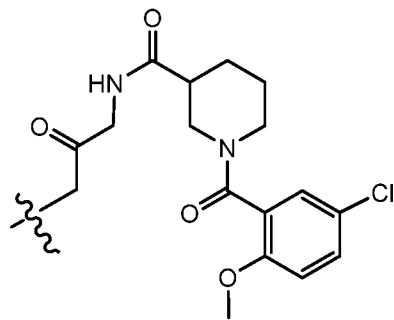
[0567] Embodiment 44. The K-Ras protein of embodiment 43, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0568] Embodiment 45. The K-Ras protein of embodiment 43, wherein the compound is irreversibly covalently bonded to a cysteine residue of the protein.

[0569] Embodiment 46. The K-Ras protein of embodiment 43, wherein the compound is covalently bonded to a histidine residue of the protein.

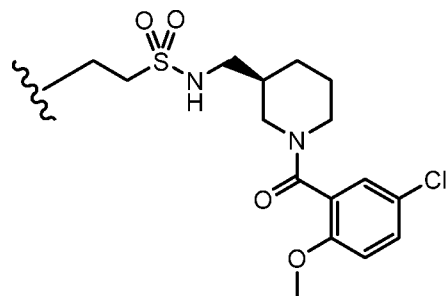
[0570] Embodiment 47. The K-Ras protein of embodiment 43, wherein the compound is irreversibly covalently bonded to a histidine residue of the protein.

[0571] Embodiment 48. A K-Ras protein covalently bonded to a compound having the



formula:

[0572] Embodiment 49. A K-Ras protein covalently bonded to a compound having the



formula:

5 **[0573]** Embodiment 50. The K-Ras protein of one of embodiments 48 to 49, wherein the compound is covalently bonded to a cysteine residue of the protein.

[0574] Embodiment 51. The K-Ras protein of embodiment 48, wherein the compound is covalently bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B.

10 **[0575]** Embodiment 52. The K-Ras protein of one of embodiments 48 to 49, wherein the compound is covalently bonded to a histidine residue of the protein.

[0576] Embodiment 53. The K-Ras protein of embodiment 48, wherein the compound is covalently bonded to a histidine residue of the protein corresponding to H95 of human K-Ras-4B.

15 IX. Examples

Example 1. Covalent modification of H95 residue in Kras using tethering small molecule compounds.

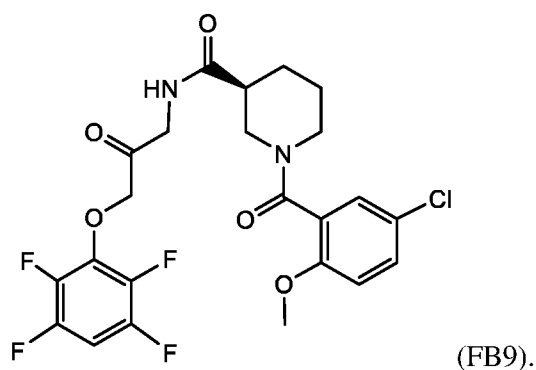
[0577] K-Ras is the most frequently mutated oncogene, with activating mutations in this small GTPase found in 30% of human cancers. Mutations in K-Ras are associated with resistance to chemotherapy or radiation. Patients whose tumors harbor these mutations are often excluded

from targeted therapies, and tend to have poor overall survival. Despite decades of research effort, there are no effective treatments for cancers with mutant K-Ras.

[0578] The development of small-molecule inhibitors that directly target Ras is highly desirable but has proven to be a major challenge. The isoforms of the Ras protein (H-Ras, N-Ras and K-Ras) play essential roles in normal cells. Therefore, the ideal Ras-targeting drug would specifically target the oncogenic form of the protein. However, targeting K-Ras (i.e. without distinguishing between wildtype and mutant protein) could be an effective approach, since all isoforms are redundant in normal tissues, and eliminating one is expected to be tolerable.

[0579] Considerable effort has been directed towards inhibiting Ras posttranslational processing. Inhibitors of farnesyl transferases (FTIs) have been investigated for their potential to attenuate C-terminal lipid modification of Ras required for correct plasma membrane localization and subsequent signaling. This approach is challenging since K-Ras was found to undergo alternative prenylation and remain oncogenically active.

[0580] The covalent modification of the CAAX-box cysteine of K-Ras may block prenylation at that site and inhibit the subsequent translocation/attachment of the K-Ras protein to the membrane that is necessary for its activity. This could be achieved with small molecule inhibitors designed for binding to the CAAX-box cysteine of K-Ras. The complication of alternative prenylation, inherent in alternative methods of inhibiting Ras prenylation, would be bypassed. Tethering compounds are composed of a fragment group that confers a non-covalent interaction with a potential pocket on the protein. Additionally, there is a disulfide moiety that interacts covalently with the CAAX-box cysteine under reducing conditions in a reversible fashion by disulfide exchange. The screen of recombinant His-tagged K-Ras G12D protein against the library of 1600 tethering compounds, followed by SAR, led to development of the FB9, depicted below:



[0581] In embodiments, compounds described herein (e.g., FB9) covalently labeled C185 in the full-length recombinant K-Ras4B. However, if FB9 is reacted with recombinant FME-Kras4B protein (farnesylated-carboxymethylated), where C185 is modified/blocked by farnesyl (as it is in the native, fully post-translationally processed K-Ras 4B *in vivo*), FB9 is not able to
5 displace the farnesyl from C185; instead, it covalently modifies other residues in the K-Ras4B protein.

[0582] Herein we show that in embodiments the recombinant FME-Kras4B, FB9 covalently modifies histidine 95 residue (H95), that is unique for Kras (Q in H-Ras or L in N-Ras). This residue is nucleophilic, making it vulnerable to electrophilic attack. This modification not only
10 was observed with recombinant FME-Kras4B protein; it was also detected in Kras4B G12V that was purified from cells treated with the compound.

[0583] **Chemical modification of unprocessed KRAS-4b at His-95** (protein G-Hs.KRAS4b(1-188), mass (average) 21481.59 Da.

[0584] KRAS4b (FIG. 43) was modified by FB9 *in vitro* (using 8.8-fold molar excess of FB9
15 for 1h at 37 °C, followed by 16 h at room temperature, 22 °C). MALDI-TOF MS analysis revealed that chemical modification of the protein was close to complete. Molecular species with 1 and 2 and 3 modification groups were present (FIG. 44).

[0585] To identify the modified amino acid residues, the protein preparation was digested by protease Glu-C. Analysis of the digest by MALDI-TOF MS revealed the presence of peptides
20 with m/z 2324 and 2674 with 2324 corresponding to unmodified peptide KMSKDGKKKKKKSKTKCVIM (SEQ ID NO:4) (170-189) and 2674 to the same peptide modified by FB9 at Cys-186 (FIG. 45) (confirmed by fragmentation). Peptide with m/z 1735 corresponds to sequence GKKKKKKKSKTKCVIM (SEQ ID NO: 3) (174-189) and m/z 2085 corresponds to the same peptide modified by FB9 at Cys-186 (confirmed by fragmentation).

[0586] To identify other potential residues modified by FB9, peptides obtained after digestion by Glu-C were further digested by trypsin (FIG. 46A). Fragmentation spectrum of a peptide with m/z 1320.614 revealed major fragment of 969, which is close to m/z of peptide DIHHYRE (SEQ ID NO:2) (expected m/z 969.4537, 93-99), suggesting that m/z 1320 corresponds to peptide DIHHYRE (SEQ ID NO:2) modified by FB9 (FIG. 45). Indeed, comparison of fragmentation
25 spectra of peptides 969.485 and 1320.614 demonstrated their relationship. Common fragments are indicated in FIG. 46B.

[0587] Modification of processed (farnesylated and carboxymethylated KRAS4b).

Protein prep GG-HsKRAS-4b, RP1151105092454 FmeKRAS4b (FIG. 47A) was modified by FB9 with 7.6-fold molar excess of FB9 for 1 h at 37 °C, followed by 16 h at room temperature (22 °C). MALDI-TOF MS analysis of chemical modification to the protein revealed that major
5 form represented species with 1 added modification group, less protein had 2 modification groups, and a little with 3 modification groups, some protein was left un-modified (FIG. 47B). To identify the modified amino acid residues protein preparation was digested by trypsin.

[0588] MALDI-TOF MS demonstrated that K-RAS tryptic peptides with m/z 1203

(SFEDIHHYR, SEQ ID NO:6), 1702 (SFEDIHHYREQIK, SEQ ID NO:8), 1858

10 (SFEDIHHYREQIKR, SEQ ID NO:7) are present also in modified form +(350-351) Da. During fragmentation, these modified peptides yielded intensive fragment corresponding to unmodified peptide and fragments of peptide (mostly without modification).

[0589] These peptides were modified on His residues. To identify which His was modified (i.e. 95 or 96 in the sequence of used recombinant KRAS) fragmentation spectra were analyzed
15 in BioTools when FB9 modification (C17H20Cl1N2O4, 350/351) was set on one of these His residues in Sequence Editor.

[0590] Analysis of fragmentation of m/z 1203.660 and 1554.856 observed in reflector mode (low intensity in reflector mode but well detected in linear mode as 1554.7) allowed to conclude that in peptide SFEDIHHYR (SEQ ID NO:6) His7 (i.e. H95 in the native protein) is modified. In
20 fragmentation spectrum of 1554 a fragment 825.409 was present but not in a spectrum of 1203. When FB9 modification was on His-7 this fragment was assigned by BioTools as modified y-3. Manual examination of the spectrum confirmed this conclusion.

[0591] Modification of H95 in Kras4B G12V in cells.

[0592] Mouse lung type II epithelial cell line E10 was transduced with HA-tagged KRas4B

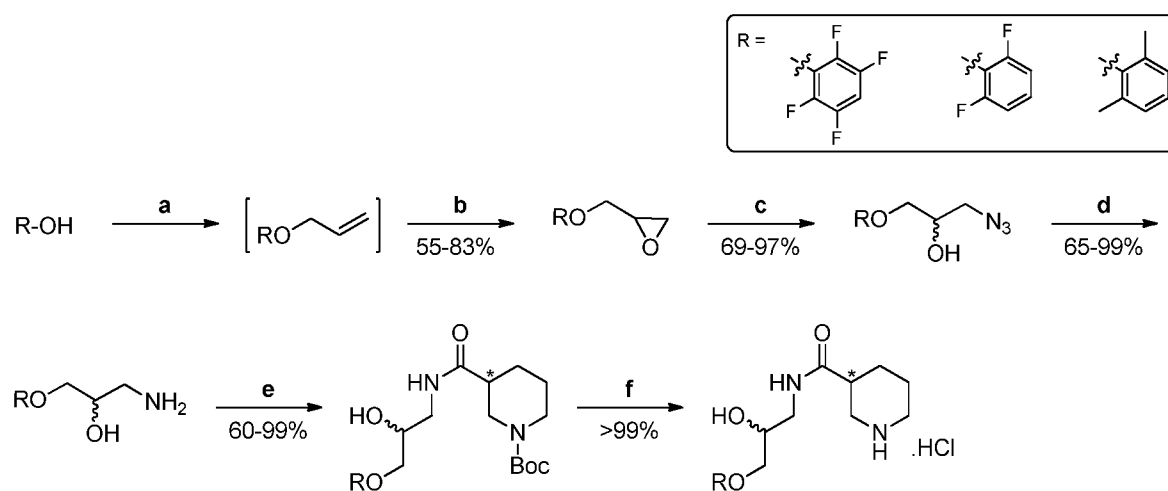
25 G12V, in a tetracycline-inducible retroviral expression vector. Individual clones were developed. Expression of the KRas4B transgene was induced with 500 ng/ml doxycycline for 48 h, then cells were treated with 20 µM of a close analogue of FB9, compound SMDC 993784, for 30 min. Cells homogenates were cleared by centrifugation, and Kras4B G12V was purified from lysates using HA-agarose immunoaffinity chromatography, resolved by SDS-PAGE, and
30 subjected to MALDI-TOF analysis of modification to Kras4B G12V. FIG. 42 shows the fragment of Kras4b peptide containing H95 modified with the compound. This fragment is not

present in the control sample (FIG. 41), obtained from cells that were not subjected to the drug treatment.

5

Example 2. Synthetic schemes

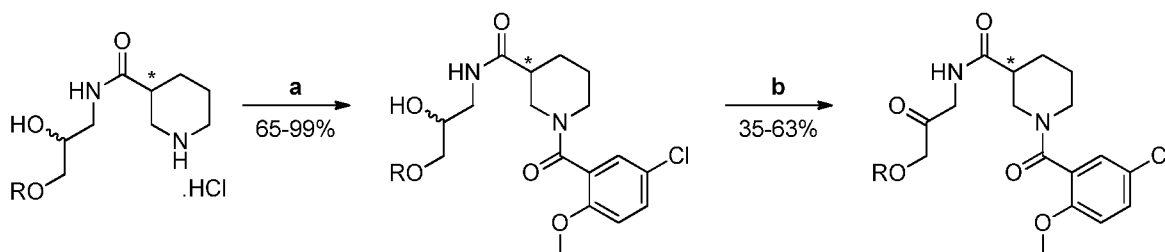
[0593] **Scheme 1.** Synthesis of covalent analogues of 6B9.



- 10 [0594] Conditions: (a) allyl bromide, K_2CO_3 , DMF, RT, 24 h; (b) *m*CPBA, DCM, RT, 24 h; (c) NaN_3 , NH_4Cl , MeOH/ H_2O (8:1), RT, 72 h; (d) 10% Pd/C, H_2 , MeOH, RT, 18 h; (e) (*R*)-Boc-nipecotic acid or (*S*)-Boc-nipecotic acid, HATU, DIPEA, DMF, RT, 18 h; (f) 4N dioxane HCl, RT, 3 h.

- 15 [0595] A six-step enantioselective synthesis of the electrophilic precursor group was devised starting from the appropriate phenol (scheme 1). Each step occurred in an acceptable yield and was well suited for performance on a gram scale.

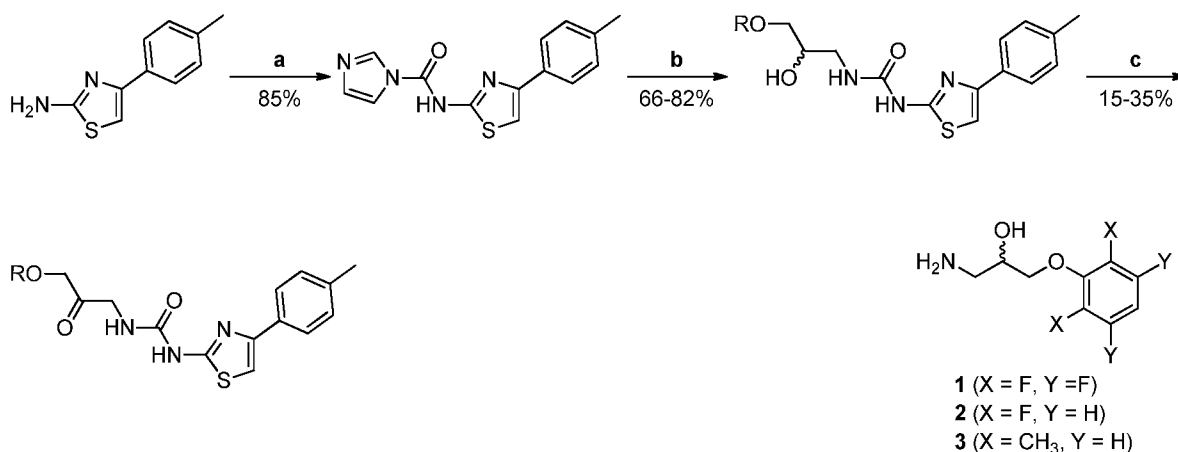
[0596] **Scheme 2.** Synthesis of covalent analogues of 6B9 (continued)



[0597] Conditions: (a) HATU, DIPEA, DMF, RT, 18 h; (b) Dess-Martin periodinane, DCM, 0°C – RT, 72 h.

[0598] The electrophilic precursor group was attached to the acid fragment in good yield using peptide coupling conditions (scheme 2a). In the final step of the reaction scheme the alcohol functionality was oxidized to the ketone using Dess-Martin periodinane, which formed the reactive covalent species. By varying the acid fragment in this synthetic route (scheme 2a) it was possible to prepare a small library of 6B9 analogues for use in future SAR studies.

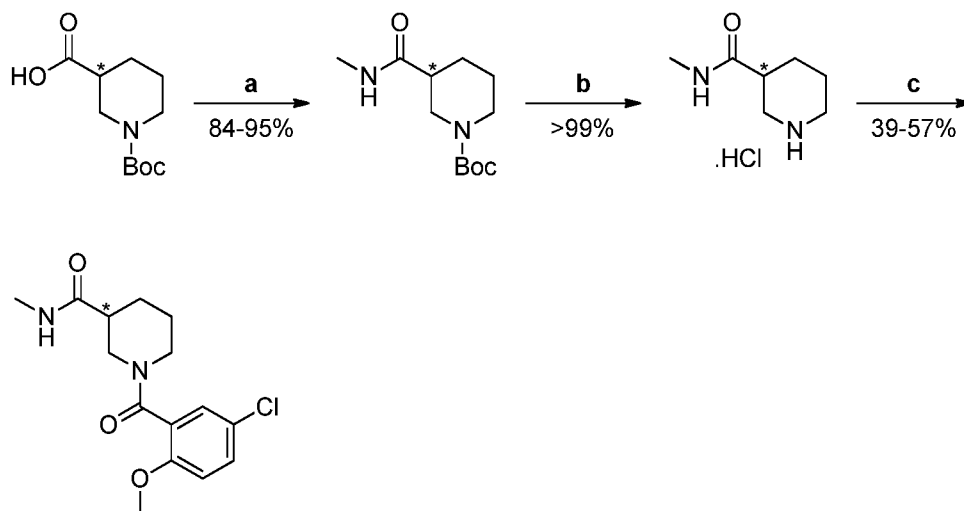
[0599] **Scheme 3.** Synthesis of covalent analogues of 3G4



[0600] Conditions: (a) CDI, THF, RT, 18 h; (b) **1,2**, or **3**, THF, RT, 18 h; (c) Dess-Martin periodinane, DCM, 0 °C - RT, 72 h.

[0601] Electrophilic derivatives of 3G4 were synthesized over three-steps following scheme 3. In contrast to the first two steps, which were were high yielding, a modest yield (15-35%) was obtained for the final reaction (scheme 3c), which was attributed to formation of multiple unidentified side products.

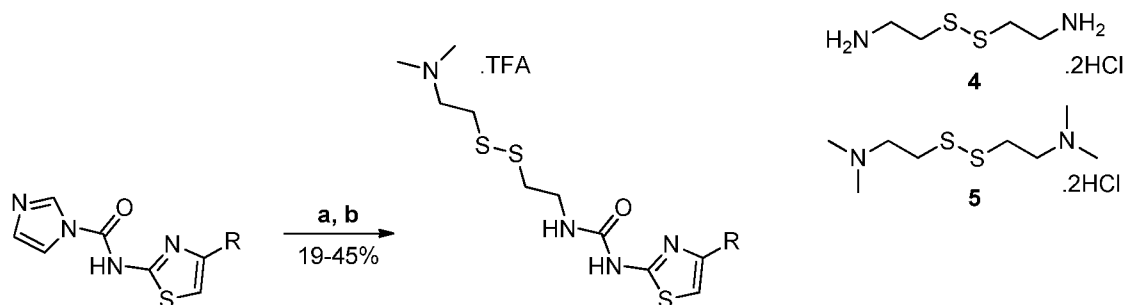
[0602] **Scheme 4.** Synthesis of non-covalent analogues of 6B9 for SPR studies



[0603] Conditions: (a) MeNH₂.HCl, EDC.HCl, HOBT, Et₃N, THF/DCM (1:3), RT, 18 h; (b) 4N dioxane HCl, RT, 3 h; (c) HATU, DIPEA, DMF, RT, 18 h.

[0604] Non-tethering analogues of 6B9 were prepared in satisfactory yield over three-steps following scheme 4. Boc-protected (*R*) or (*S*)-nipecotic acid was chosen as the starting material and allowed for enantioselective synthesis of the target molecule. This synthetic approach would likely be appropriate for future non-tethering derivatives, including the *N*-ethylamide and *N*-propylamide analogues of 6B9.

[0605] **Scheme 5.** Synthesis of 34G urea analogues

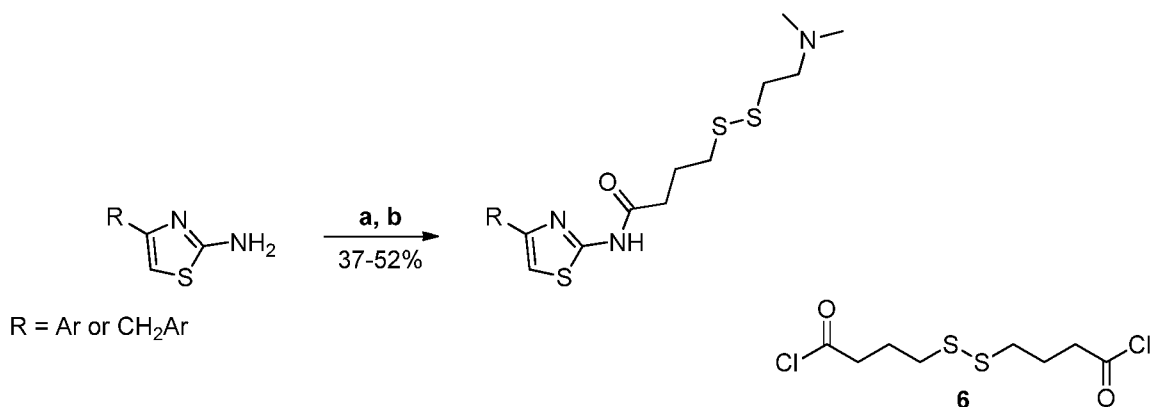


R = Ar or CH₂Ar

[0606] Conditions: (a) **4**, Et₃N, water/DMF (1:2); (b) **5**, TCEP (0.1 equiv.), Et₃N, water/DMF.

[0607] A simple two-step one-pot approach allowed the preparation of a small library of urea based analogues of 6B9 from their respective CDI adducts. Solubility issues of the urea product made purification problematic, which likely accounts of the modest yield.

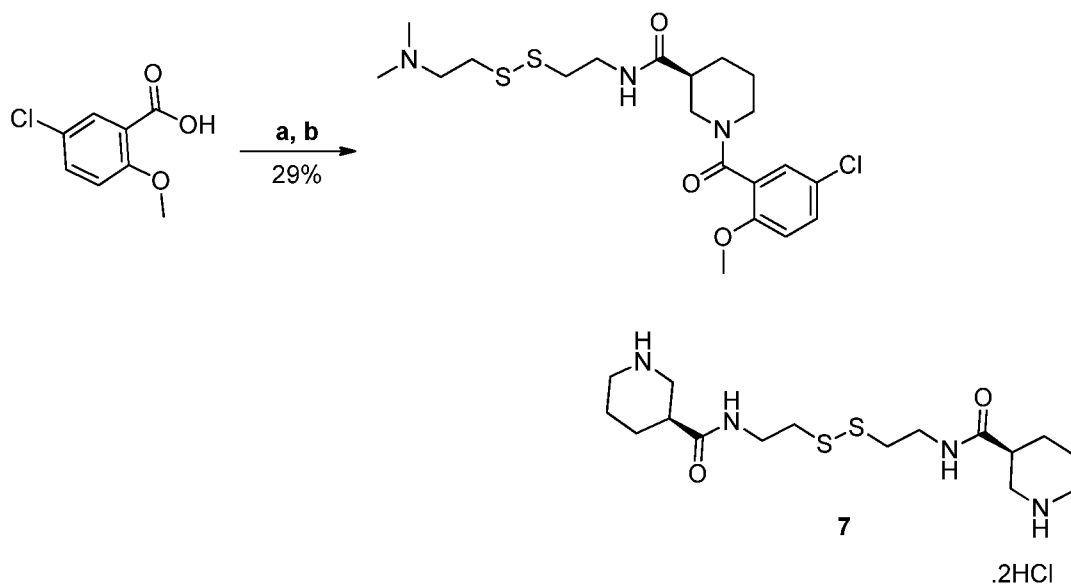
[0608] **Scheme 6.** Synthesis of 6B9 propylamide analogues



[0609] Conditions: (a) **6** (0.5 equiv.), DIPEA, DCM, RT, 3 h; (b) **5**, TCEP (0.1 equiv.), Et₃N, water/DMF, RT, 18 h.

[0610] A small library of propylamides were prepared *via* the reaction of 2-aminothiazoles with acid chloride **6** followed by disulfide exchange with dimethyl cystamine **5** in the presence of TCEP.

[0611] **Scheme 7.** Synthesis of disulfide tethering agent 6B9



[0612] Conditions: (a) **7** (0.5 equiv.), EDC.HCl, HOBT, Et₃N, DMF, RT, 18 h; (b) **5**, TCEP (0.1 equiv.), Et₃N, water/DMF, RT, 18 h

[0613] 5-Chloro-2-methoxybenzoic acid was coupled with amine **7** followed by disulfide exchange with cystamine **5** in the presence of TCEP using a method developed in-house for the preparation of disulfide fragment libraries.

[0614] QC Validation

[0615] ^1H -NMR and LC-MS analysis was performed upon all intermediates and target molecules to allow structural determination. Compounds submitted for biological evaluation were deemed to be in excess of 95% purity and were stored at $-80\text{ }^\circ\text{C}$ to prevent decomposition.

5 **[0616]** Equipment

[0617] ^1H -NMR spectra were obtained from samples dissolved in deuterated chloroform (CDCl_3) using a Bruker Avance III 300 MHz Spectrometer. Chemical shift values (δ) are reported in parts per million (ppm) with splitting patterns abbreviated to: s (singlet), br. s (broad singlet), d (doublet), t (triplet) and m (multiplet). The coupling constant (J) is given in Hz and
10 was calculated using the software package ACD LabsTM 12.0. Chemical shift values (δ) are reported in parts per million (ppm) with splitting patterns abbreviated to: s (singlet), br. s (broad singlet), d (doublet), t (triplet) and m (multiplet). The coupling constant (J) is given in Hz and was calculated using the software package ACD LabsTM 12.0.

[0618] LC-MS analysis was performed using a Waters Micromass ZQ mass spectrometer with
15 a Waters 2795 chromatography separations module, Waters 2996 photodiode array detector and Waters 2424 evaporative light scattering detector (ELSD) system controlled by MassLynx 4.1 software. The HPLC column used was a Waters XTerra MS C18 $5\mu\text{m}$ $4.6\times 50\text{ mm}$ column with a mobile phase of water (0.01% formic acid) / MeOH (0.01% formic acid).

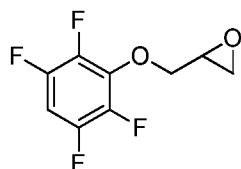
1,2,4,5-Tetrafluoro-3-(prop-2-en-1-yloxy)benzene



[0619] To a solution of 2,3,5,6-tetrafluorophenol (1.0g, 6.02 mmol) in DMF (15 mL) was added K_2CO_3 (1.66 g, 0.12 mol) followed by the dropwise addition of allyl bromide (547 μL , 6.32 mmol). The reaction mixture was stirred (RT, 3h), after which no starting material remained (observed by silica TLC, 1:9 EtOAc/Hexane). The reaction mixture was diluted with water (100
25 mL) then extracted with DCM (150 mL). The aqueous layer was removed and the remaining organic layer was washed with water (4 x 100 mL) and then dried (Na_2SO_4). The volume of solvent was reduced by half in-vacuo and the resulting DCM solution was used directly in the next reaction without further purification.

[0620] $R_f = 0.75$ (1:9 EtOAc/Hexane).

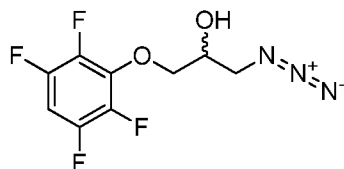
2-(2,3,5,6-Tetrafluorophenoxy)methyl)oxirane



[0621] To a solution of 1,2,4,5-tetrafluoro-3-(prop-2-en-1-yloxy)benzene (1.24g, 6.02 mmol) at 0 °C in DCM (50 mL) (prepared previously) was added 3-Chloroperbenzoic acid (2.7g, 12.0 mmol). The reaction was stirred at 0 °C then warmed to room temperature for an additional 3 days. The resulting solution was poured into a saturated aqueous solution of sodium thiosulfate (50 mL) and was allowed to stir for 30 minutes. The organic layer was removed then washed sequentially with saturated NaHCO_3 (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and purified by MPLC on silica (0-50% EtOAc/Hexane) to give 2-(2,3,5,6-tetrafluorophenoxy)methyl)oxirane (735 mg, 3.31 mmol, 55%) as a colorless oil.

[0622] $R_f = 0.28$ (1:9 EtOAc/Hexane); ^1H NMR (300 MHz, CDCl_3) δ 6.70-6.93 (m, 1H), 4.49 (dd, $J=2.92, 11.59$ Hz, 1H), 4.12-4.25 (m, 1H), 3.30-3.50 (m, 1H), 2.89 (dd, $J=3.70, 4.90$ Hz, 1H), 2.73 (dd, $J=2.64, 4.90$ Hz, 1H).

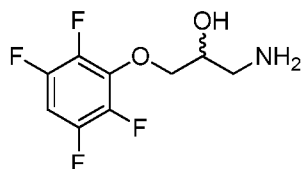
1-Azido-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol



[0623] A solution of 2-(2,3,5,6-tetrafluorophenoxy)methyl)oxirane (1.89 g, 8.5 mmol) in MeOH (30 mL) was added to a suspension of sodium azide (5.11 g, 78.6 mmol) in water (3.8 mL). Ammonium chloride (915 mg, 210 mmol) was added and reaction was stirred at room temperature for 24 hours. The reaction mixture was diluted with brine (100 mL) then extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (2 x 100 mL), dried (Na_2SO_4) and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (1:9 EtOAc:Hexane) to give the title compound (1.92 g, 7.3 mmol, 85%) as a colorless oil.

[0624] $R_f = 0.14$ (1:9 EtOAc/Hexane); ^1H NMR (300 MHz, CDCl_3) δ 6.72-6.93 (m, 1H), 4.22-4.36 (m, 2H), 4.07-4.22 (m, 1H), 3.45-3.65 (m, 2H), 2.56 (br. s., 1H).

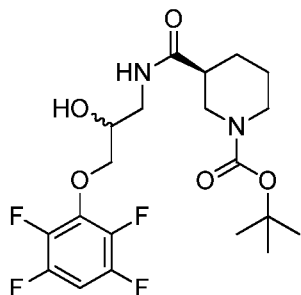
1-Amino-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol



[0625] To a solution of 1-azido-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol (1.9 g, 7.3 mmol) in MeOH (15 ml) was added 10% palladium on carbon (386 mg, 3.6 mmol). The reaction vessel was placed under an atmosphere of hydrogen and stirred overnight (RT, 18 h). The resulting mixture was filtered through Celite and the solvent was removed to give 1-amino-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol (1.2 g, 5.0 mmol, 69%) as a white solid.

[0626] ¹H NMR (300 MHz, MeOD) δ 7.01-7.21 (m, 1H), 4.22 (d, J=5.09 Hz, 2H), 3.85-3.99 (m, 1H), 2.90 (dd, J=3.96, 12.81 Hz, 1H), 2.77 (dd, J=7.70, 13.00 Hz, 1H); LRMS (ES+) m/z = 239.9 [M+H]⁺.

tert-Butyl (3S)-3-{[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]carbamoyl}piperidine-1-carboxylate

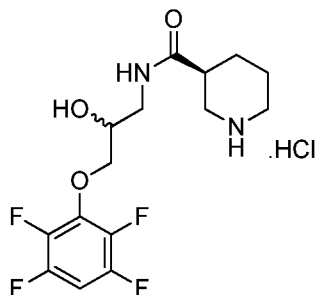


[0627] To a solution of 1-amino-3-(2,3,5,6-tetrafluorophenoxy)propan-2-ol (1.1 g, 4.6 mmol) in DMF (26 ml) was added hydroxybenzotriazole (HOBt) (59 mg, 0.4 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) (1.84 g, 11.9 mmol) and water (4.1 ml). Triethylamine (608 μ l, 4.4 mmol) was added and the resulting mixture was stirred (RT, 3h) resulting in consumption of the starting material (observed by TLC). The reaction was added to a saturated brine solution (100 mL) then extracted with EtOAc (150 mL). The organic layer was removed then washed sequentially with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL) then dried (MgSO₄) and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (0-10% MeOH/DCM) to give the title compound (1.94 g, 4.3 mmol, 99%) as a colorless oil.

[0628] $R_f = 0.45$ (1:9 MeOH/DCM); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 6.73-6.93 (m, 1H), 4.01-4.30 (m, 3H), 3.55-4.00 (m, 3H), 3.24-3.54 (m, 2H), 3.12 (m, 1H), 2.84-3.01 (m, 1H), 2.29-2.50 (m, 1H), 1.77-2.05 (m, 2H), 1.57-1.77 (m, 1H), 1.47 (s, 9H); LRMS (ES+) $m/z = 451.1$ $[\text{M}+\text{H}]^+$.

(3S)-N-[2-Hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide

5 hydrochloride

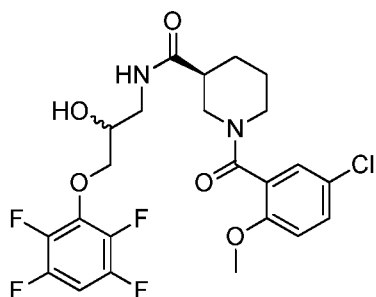


[0629] To a flask containing tert-butyl (3S)-3-{[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]carbamoyl} piperidine-1-carboxylate (50 mg, 0.1 mmol) was added 4N Hydrochloric acid in dioxane (500 μl , 2.0 mmol). The resulting solution was stirred at room temperature for 30 minutes then the solvent was removed in-vacuo to give the title compound (41 mg, 0.1 mmol, 96%) as a colorless oil.

[0630] $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.95 (br. s., 2H), 7.75-8.43 (m, 1H), 6.77 (br. s., 1H), 4.02-4.68 (m, 3H), 2.65-3.97 (m, 9H), 1.55-2.32 (m, 3H); LRMS (ES+) $m/z = 351.1$ $[\text{M}+\text{H}]^+$.

(3S)-1-[(5-Chloro-2-methoxyphenyl)carbonyl]-N-[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)

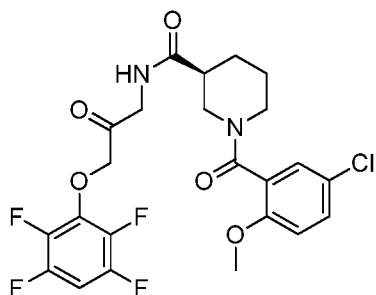
15 propyl]piperidine-3-carboxamide



[0631] To a solution of (3S)-N-[2-hydroxy-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide hydrochloride (155 mg, 0.40 mmol), (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) (168 mg, 0.44 mmol) and N,N-diisopropylethylamine (243 μl , 1.4 mmol) in DMF (2.3 ml) was added 5-chloro-2-methoxybenzoic acid (75 mg, 0.40 mmol). The reaction mixture was stirred overnight (RT, 18 h)

then added to saturated brine solution (25 mL). The aqueous mixture was extracted with EtOAc (2 x 25 mL) and the organic layers were combined, washed with brine (25 mL), dried (Na₂SO₄), and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (0-80% Hexane/EtOAc) to give the title product (206 mg, 0.40 mmol) as a colorless oil.

- 5 **[0632]** R_f = 0.40 (10% MeOH/DCM); ¹H NMR (300 MHz, CDCl₃) δ 7.32 (dd, J=2.45, 8.85 Hz, 1H), 7.13-7.21 (m, 1H), 6.86 (d, J=8.85 Hz, 1H), 6.68-6.79 (m, 1H), 4.16-4.30 (m, 1H), 3.99-4.16 (m, 2H), 3.80-3.87 (s, 3H), 3.66-3.76 (m, 1H), 3.43-3.65 (m, 1H), 3.07-3.43 (m, 3H), 2.67-2.78 (m, 1H), 2.55 (m, 1H), 1.96-2.31 (m, 1H), 1.71-1.95 (m, 1H), 1.41-1.69 (m, 2H); LRMS (ES⁺) m/z = 519.1 [M+H]⁺.
- 10 (3S)-1-[(5-Chloro-2-methoxyphenyl)carbonyl]-N-[2-oxo-3-(2,3,5,6-tetrafluorophenoxy)propyl]piperidine-3-carboxamide ('FB9')



- [0633]** To a solution of (3S)-1-[(5-chloro-2-methoxyphenyl)carbonyl]-N-[2-hydroxy-3-(2,3,5,6-tetrafluoro phenoxy)propyl]piperidine-3-carboxamide (17 mg, 3.4 x 10⁻² mmol) in
- 15 DCM (500 μl, 7.8 mmol) at 0 °C was added Dess-Martin periodinane (28 mg, 6.8 x 10⁻² mmol). The reaction mixture was stirred at 0 °C for 1 hour and was then allowed to warm to room temperature for an additional 72 hours. The crude product was diluted with DCM (2 mL) then added to a saturated solution of sodium thiosulfate in aqueous NaHCO₃ (3 mL). The resulting mixture was stirred rapidly for 1 hour at which point the aqueous layer was removed. The
- 20 remaining organic layer was washed sequentially with NaHCO₃ (3 mL) and brine (3 mL) then dried (Na₂SO₄) and the solvent was removed in-vacuo. The crude product was purified by MPLC on silica (0-10% MeOH/DCM) to give the title compound (12 mg, 2.3 x 10⁻² mmol, 69%) as a colorless oil.

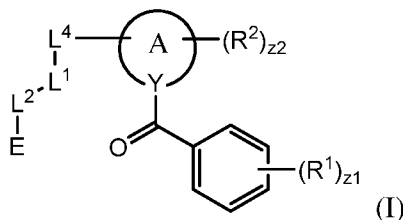
- [0634]** R_f = 0.43 (1:9 MeOH/DCM); ¹H NMR (300 MHz, CDCl₃) δ 7.31 (dd, J=2.64, 8.85 Hz, 1H), 7.16-7.25 (m, 1H), 6.75-6.92 (m, 2H), 4.80-4.97 (m, 2H), 4.17-4.59 (m, 2H), 3.75-3.95 (m, 3H), 3.51-3.74 (m, 1H), 3.11-3.38 (m, 2H), 2.52-2.72 (m, 2H), 2.00-2.22 (m, 1H), 1.89 (d,
- 25

J=11.87 Hz, 1H), 1.35-1.80 (m, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -138.0, -156.7; LRMS (ES+) m/z = 517.1 [M+H]⁺.

[0635] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein,

Y is N or CH

Ring A is a C₃-C₇ cycloalkyl or 3 to 7 membered heterocycloalkyl;

R¹ is independently halogen, CX¹₃, -CHX¹₂, -

CH₂X¹, -CN, -SO₂Cl, -SO_{n1}R¹⁰, -SO_{v1}NR^{7R8}, -NHN^{7R8}, -ONR^{7R8}, -NHC(=O)NHN^{7R8},
 -NHC(O)NR^{7R8}, -N(O)_{m1}, -NR^{7R8}, -C(O)R⁹, -C(O)-OR⁹, -C(O)NR^{7R8}, -OR¹⁰, -NR⁷SO₂R¹⁰,
 -NR⁷C(O)R⁹, -NR⁷C(O)OR⁹, -NR⁷OR⁹, -OCX¹₃, -OCHX¹₂, substituted or unsubstituted
 alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl,
 substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or
 unsubstituted heteroaryl; two adjacent R¹ substituents may optionally be joined to form a
 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl,
 substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

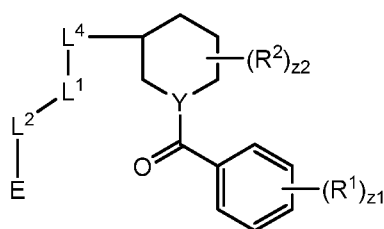
L¹ is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted
 heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted
 heterocycloalkylene, substituted or unsubstituted arylene, substituted or unsubstituted
 heteroarylene;

L² is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR^{7B}-, -
 NR^{7B}C(O)-, -C(O)NR^{7B}-, -SO₂NR^{7B}-, -NR^{7B}SO₂-, -OC(O)NR^{7B}-, -
 NR^{7B}C(O)O-, -CR^{9B}=NO-, -ON=CR^{9B}-, -NR^{8B}C(O)NR^{7B}-, -NR^{8B}C(=NR^{10B})NR^{7B}-,
 -NR^{8B}C(=NR^{10B})-, -C(=NR^{10B})NR^{7B}-, -OC(=NR^{10B})-, -C(=NR^{10B})O-, substituted or
 unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or
 unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or
 unsubstituted arylene, substituted or unsubstituted heteroarylene;

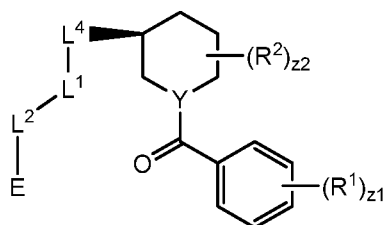
L⁴ is a bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NR⁴-, -
 NR⁴C(O)-, -C(O)NR⁴-, -SO₂NR⁴-, -NR⁴SO₂-, -NR⁴SO₂-, -OC(O)NR⁴-, -NR⁴C(O)O-,
 substituted or unsubstituted C₁-C₃ alkylene, substituted or unsubstituted 2 to 3 membered
 heteroalkylene;

30 E is an electrophilic moiety;
 31 R^2 is independently oxo, halogen, CX^2_3 , $-CHX^2_2$, -
 32 CH_2X^2 , $-CN$, $-SO_2Cl$, $-SO_{n2}R^{14}$, $-SO_{v2}NR^{11}R^{12}$, $-NHN R^{11}R^{12}$, $-ONR^{11}R^{12}$,
 33 $-NHC(=O)NHN R^{11}R^{12}$,
 34 $-NHC(O)NR^{11}R^{12}$, $-N(O)_{m2}$, $-NR^{11}R^{12}$, $-C(O)R^{14}$, $-C(O)-OR^{14}$, $-C(O)NR^{11}R^{12}$, $-OR^{15}$, -
 35 $NR^{11}SO_2R^{15}$, $-NR^{11}C(O)R^{14}$, $-NR^{11}C(O)OR^{14}$, $-NR^{11}OR^{14}$, $-OCX^2_3$, $-OCHX^2_2$, substituted or
 36 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 37 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl,
 38 substituted or unsubstituted heteroaryl; two adjacent R^2 substituents or two R^2 substituents
 39 bonded to the same atom may optionally be joined to form a substituted or unsubstituted
 40 cycloalkyl or substituted or unsubstituted heterocycloalkyl;
 41 R^4 is independently hydrogen, substituted or unsubstituted alkyl, substituted or
 42 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 43 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
 44 R^7 , R^8 , R^9 , R^{10} , R^{7B} , R^{8B} , R^{9B} , R^{10B} , R^{11} , R^{12} , R^{14} , and R^{15} are independently
 45 hydrogen, halogen, $-CX_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2Cl$, $-SO_3H$, -
 46 SO_4H , $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, -
 47 $NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX_3$, $-OCHX_2$, $-CHX_2$, $-CH_2X$, substituted or
 48 unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted
 49 cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or
 50 substituted or unsubstituted heteroaryl; R^7 and R^8 substituents bonded to the same nitrogen
 51 atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
 52 substituted or unsubstituted heteroaryl; R^{11} and R^{12} substituents bonded to the same nitrogen
 53 atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or
 54 substituted or unsubstituted heteroaryl;
 55 each X , X^1 , and X^2 is independently $-F$, $-Cl$, $-Br$, or $-I$;
 56 $n1$, $n2$, $v1$, and $v2$ are independently an integer from 0 to 4;
 57 $m1$ and $m2$ are independently an integer from 1 to 2;
 58 $z1$ is independently an integer from 0 to 5; and
 59 $z2$ is independently an integer from 0 to 10.

1 2. The compound of claim 1, having the formula:



3. The compound of claim 1, having the formula:



4. The compound of claim 1, wherein Y is CH.

5. The compound of claim 1, wherein Y is N.

6. The compound of claim 1, wherein R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^1_3$, $-OCHX^1_2$, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_8 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or unsubstituted C_6 aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

7. The compound of claim 1, wherein R^1 is independently halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OH$, $-SH$, $-COOH$, $-OCX^1_3$, $-OCHX^1_2$, $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-OCH_2CH_3$, $-SCH_3$, or $-SCH_2CH_3$.

8. The compound of claim 1, wherein R^1 is independently halogen or $-OCH_3$.

9. The compound of claim 1, wherein $z1$ is 2.

10. The compound of claim 1, wherein $z1$ is 3.

11. The compound of claim 1, wherein R^2 is independently oxo, halogen, CX^2_3 , $-CHX^2_2$, $-CH_2X^2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-$

3 SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -
 4 NHC(O)OH, -NHOH, -OCX²₃, -OCHX²₂, substituted or unsubstituted C₁-C₆ alkyl,
 5 substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₈
 6 cycloalkyl, substituted or unsubstituted 3 to 8 membered heterocycloalkyl, substituted or
 7 unsubstituted C₆ aryl, or substituted or unsubstituted 5 to 6 membered heteroaryl.

1 12. The compound of claim 1, wherein R² is independently oxo,
 2 halogen, -CX²₃, -CHX²₂, -CH₂X², -OH, -SH, -OCX²₃, -OCHX²₂, -CH₃, -CH₂CH₃, -OCH₃, -O
 3 CH₂CH₃, -SCH₃, or -SCH₂CH₃.

1 13. The compound of claim 1, wherein z₂ is 0.

1 14. The compound of claim 1, wherein L¹ is a bond, substituted or
 2 unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

1 15. The compound of claim 1, wherein L¹ is a bond, unsubstituted C₁-C₄
 2 alkylene, or unsubstituted 2 to 4 membered heteroalkylene.

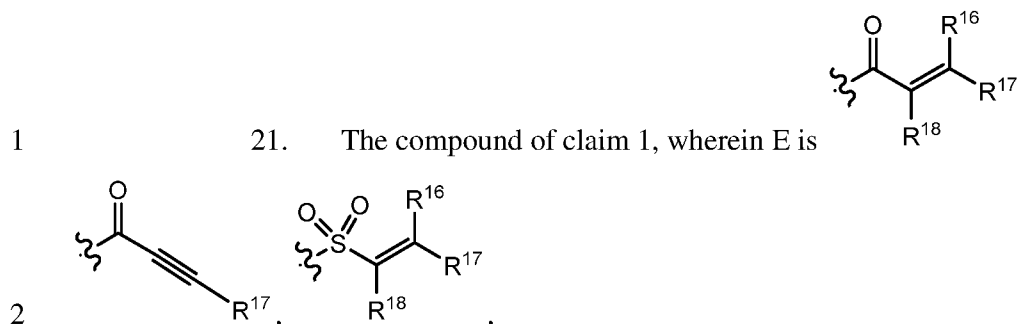
1 16. The compound of claim 1, wherein L¹ is a bond.

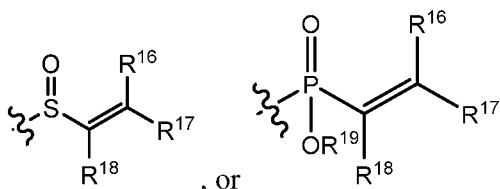
1 17. The compound of claim 1, wherein L² is a
 2 bond, -O-, -C(O)-, -S-, -SO-, -S(O)₂-, -NH-, -NHC(O)-, -C(O)NH-, -SO₂NH-, -
 3 NHSO₂-, -OC(O)NH-, -NHC(O)O-, -NHC(O)NH-, substituted or unsubstituted alkylene, or
 4 substituted or unsubstituted heteroalkylene.

1 18. The compound of claim 1, wherein L² is a
 2 bond, -O-, -C(O)-, -S-, -NH-, -NHC(O)-, -C(O)NH-, unsubstituted C₁-C₄ alkylene, or
 3 unsubstituted 2 to 4 membered heteroalkylene.

1 19. The compound of claim 1, wherein L² is -NH-.

1 20. The compound of claim 1, wherein L² is a bond.





3
4 wherein R^{16} is independently hydrogen, halogen, CX^{16}_3 , $-CHX^{16}_2$, -
5 CH_2X^{16} , $-CN$, $-SO_{n16}R^{16D}$, $-SO_{v16}NR^{16A}R^{16B}$, $-NHNR^{16A}R^{16B}$, $-ONR^{16A}R^{16B}$,
6 $-NHC(=O)NHNR^{16A}R^{16B}$,
7 $-NHC(O)NR^{16A}R^{16B}$, $-N(O)_{m16}$, $-NR^{16A}R^{16B}$, $-C(O)R^{16C}$, $-C(O)-OR^{16C}$, $-C(O)NR^{16A}R^{16B}$, $-OR$
8 ^{16D} , $-NR^{16A}SO_2R^{16D}$, $-NR^{16A}C(O)R^{16C}$, -
9 $NR^{16A}C(O)OR^{16C}$, $-NR^{16A}OR^{16C}$, $-OCX^{16}_3$, $-OCHX^{16}_2$, substituted or unsubstituted alkyl,
10 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
11 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
12 heteroaryl;

13 R^{17} is independently hydrogen, halogen, CX^{17}_3 , $-CHX^{17}_2$, -
14 CH_2X^{17} , $-CN$, $-SO_{n17}R^{17D}$, $-SO_{v17}NR^{17A}R^{17B}$, $-NHNR^{17A}R^{17B}$, $-ONR^{17A}R^{17B}$,
15 $-NHC(=O)NHNR^{17A}R^{17B}$,
16 $-NHC(O)NR^{17A}R^{17B}$, $-N(O)_{m17}$, $-NR^{17A}R^{17B}$, $-C(O)R^{17C}$, $-C(O)-OR^{17C}$, $-C(O)NR^{17A}R^{17B}$, $-OR$
17 ^{17D} , $-NR^{17A}SO_2R^{17D}$, $-NR^{17A}C(O)R^{17C}$, -
18 $NR^{17A}C(O)OR^{17C}$, $-NR^{17A}OR^{17C}$, $-OCX^{17}_3$, $-OCHX^{17}_2$, substituted or unsubstituted alkyl,
19 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
20 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
21 heteroaryl;

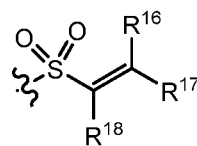
22 R^{18} is independently hydrogen, halogen, CX^{18}_3 , $-CHX^{18}_2$, -
23 CH_2X^{18} , $-CN$, $-SO_{n18}R^{18D}$, $-SO_{v18}NR^{18A}R^{18B}$, $-NHNR^{18A}R^{18B}$, $-ONR^{18A}R^{18B}$,
24 $-NHC(=O)NHNR^{18A}R^{18B}$,
25 $-NHC(O)NR^{18A}R^{18B}$, $-N(O)_{m18}$, $-NR^{18A}R^{18B}$, $-C(O)R^{18C}$, $-C(O)-OR^{18C}$, $-C(O)NR^{18A}R^{18B}$, $-OR$
26 ^{18D} , $-NR^{18A}SO_2R^{18D}$, $-NR^{18A}C(O)R^{18C}$, -
27 $NR^{18A}C(O)OR^{18C}$, $-NR^{18A}OR^{18C}$, $-OCX^{18}_3$, $-OCHX^{18}_2$, substituted or unsubstituted alkyl,
28 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
29 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
30 heteroaryl;

31 R^{19} is independently hydrogen, halogen, CX^{19}_3 , $-CHX^{19}_2$, -
32 CH_2X^{19} , $-CN$, $-SO_{n19}R^{19D}$, $-SO_{v19}NR^{19A}R^{19B}$, $-NHNR^{19A}R^{19B}$, $-ONR^{19A}R^{19B}$,
33 $-NHC(=O)NHNR^{19A}R^{19B}$,

34 $-\text{NHC(O)NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{N(O)}_{\text{m}19}$, $-\text{NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{C(O)R}^{19\text{C}}$, $-\text{C(O)-OR}^{19\text{C}}$, $-\text{C(O)NR}^{19\text{A}}\text{R}^{19\text{B}}$, $-\text{OR}$
 35 $^{19\text{D}}$, $-\text{NR}^{19\text{A}}\text{SO}_2\text{R}^{19\text{D}}$, $-\text{NR}^{19\text{A}}\text{C(O)R}^{19\text{C}}$, -
 36 $\text{NR}^{19\text{A}}\text{C(O)OR}^{19\text{C}}$, $-\text{NR}^{19\text{A}}\text{OR}^{19\text{C}}$, $-\text{OCX}^{19}$, $-\text{OCHX}^{19}$, substituted or unsubstituted alkyl,
 37 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 38 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted
 39 heteroaryl;
 40 $\text{R}^{16\text{A}}$, $\text{R}^{16\text{B}}$, $\text{R}^{16\text{C}}$, $\text{R}^{16\text{D}}$, $\text{R}^{17\text{A}}$, $\text{R}^{17\text{B}}$, $\text{R}^{17\text{C}}$, $\text{R}^{17\text{D}}$, $\text{R}^{18\text{A}}$, $\text{R}^{18\text{B}}$, $\text{R}^{18\text{C}}$, $\text{R}^{18\text{D}}$, $\text{R}^{19\text{A}}$,
 41 $\text{R}^{19\text{B}}$, $\text{R}^{19\text{C}}$, $\text{R}^{19\text{D}}$, are independently hydrogen,
 42 halogen, $-\text{CX}_3$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$,
 43 $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC(O)H}$, -
 44 NHC(O)OH , $-\text{NHOH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, substituted or unsubstituted alkyl,
 45 substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or
 46 unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or
 47 unsubstituted heteroaryl; $\text{R}^{16\text{A}}$ and $\text{R}^{16\text{B}}$ substituents bonded to the same nitrogen atom may
 48 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 49 unsubstituted heteroaryl; $\text{R}^{17\text{A}}$ and $\text{R}^{17\text{B}}$ substituents bonded to the same nitrogen atom may
 50 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 51 unsubstituted heteroaryl; $\text{R}^{18\text{A}}$ and $\text{R}^{18\text{B}}$ substituents bonded to the same nitrogen atom may
 52 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 53 unsubstituted heteroaryl; $\text{R}^{19\text{A}}$ and $\text{R}^{19\text{B}}$ substituents bonded to the same nitrogen atom may
 54 optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or
 55 unsubstituted heteroaryl;
 56 each X , X^{16} , X^{17} , X^{18} and X^{19} is independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$;
 57 n_{16} , n_{17} , n_{18} , n_{19} , v_{16} , v_{17} , v_{18} , and v_{19} are independently an integer from
 58 0 to 4; and
 59 m_{16} , m_{17} , m_{18} , and m_{19} are independently an integer from 1 to 2.

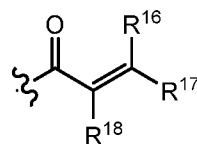
1

22. The compound of claim 21, wherein E is



1

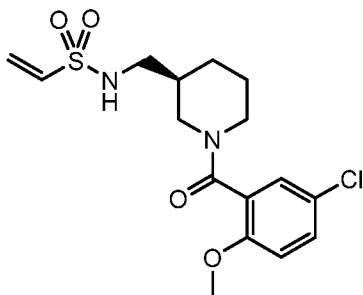
23. The compound of claim 21, wherein E is



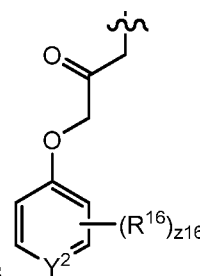
- 1 24. The compound of claim 21, wherein
 2 R¹⁶, R¹⁷, and R¹⁸ are independently hydrogen, -CH₂NH₂, -CH₂CH₂NH₂, -
 3 CH₂N(CH₃)₂, or -CH₂CH₂N(CH₃)₂.

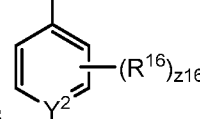
- 1 25. The compound of claim 21, wherein L⁴ is a bond or -CH₂-.

- 1 26. The compound of claim 21, having the formula:



2



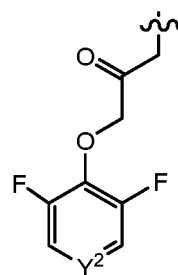
- 1 27. The compound of claim 1, wherein E is  ;
 2 wherein R¹⁶ is independently halogen, CX¹⁶₃, -CHX¹⁶₂, -
 3 CH₂X¹⁶, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂,
 4 -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -
 5 NHC(O)OH, -NHOH, -OCX¹⁶₃, -OCHX¹⁶₂, substituted or unsubstituted alkyl, substituted or
 6 unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted
 7 heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;
 8 Y² is N or CH;
 9 z₁₆ is an integer from 0 to 4; and
 10 each X¹⁶ is independently -F, -Cl, -Br, or -I.

- 1 28. The compound of claim 27 wherein R¹⁶ is independently halogen.

- 1 29. The compound of claim 27 wherein R¹⁶ is independently -F.

- 1 30. The compound of claim 27, wherein z₁₆ is 4.

- 1 31. The compound of claim 27, wherein z₁₆ is 2.



1 32. The compound of claim 31 wherein E is .

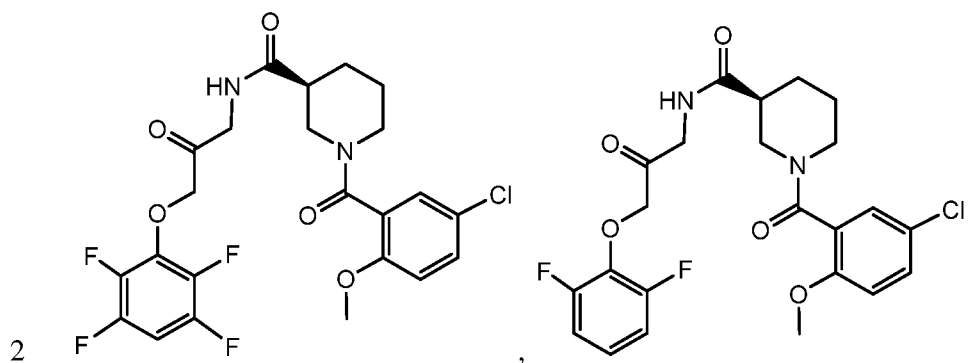
1 33. The compound of claim 27, wherein Y² is CH.

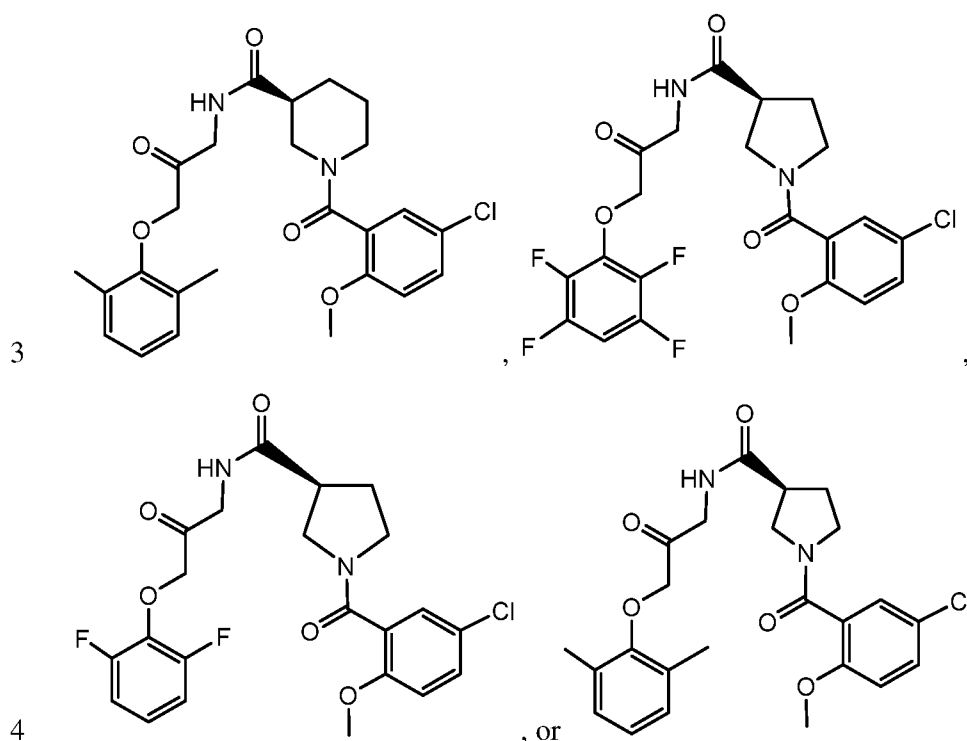
1 34. The compound of claim 27, wherein Y² is N.

1 35. The compound of claim 27, wherein L⁴ is -N(R⁴)C(O)-.

1 36. The compound of claim 27, wherein R⁴ is hydrogen.

1 37. The compound of claim 27, having the formula:





1 38. A pharmaceutical composition comprising the compound of any one of
2 claims 1 to 37 and a pharmaceutically acceptable excipient.

1 39. A method of reducing the level of activity of a K-Ras protein, said
2 method comprising contacting the K-Ras protein with a compound of one of claims 1 to 37.

1 40. A method of reducing the level of activity of a K-Ras-4B protein, said
2 method comprising contacting the K-Ras-4B protein with a compound of one of claims 1 to
3 37.

1 41. A method for treating cancer, said method comprising administering to
2 a subject in need thereof a therapeutically effective amount of a compound of one of claims 1
3 to 37.

1 42. The method of claim 41, wherein said cancer is pancreatic cancer, lung
2 cancer, or colorectal cancer.

1 43. A K-Ras protein covalently bonded to a compound of one of claims 1
2 to 37.

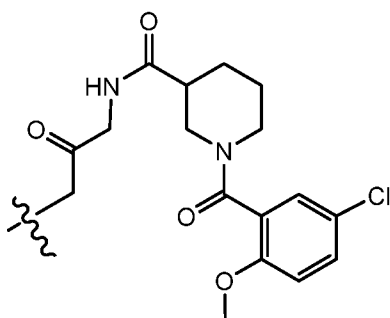
1 44. The K-Ras protein of claim 43, wherein the compound is covalently
2 bonded to a cysteine residue of the protein.

1 45. The K-Ras protein of claim 43, wherein the compound is irreversibly
2 covalently bonded to a cysteine residue of the protein.

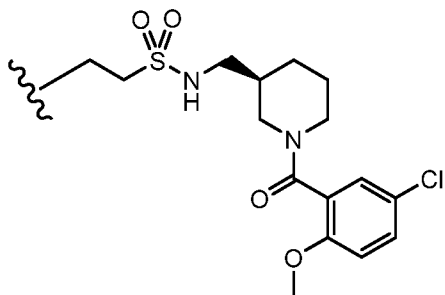
1 46. The K-Ras protein of claim 43, wherein the compound is covalently
2 bonded to a histidine residue of the protein.

1 47. The K-Ras protein of claim 43, wherein the compound is irreversibly
2 covalently bonded to a histidine residue of the protein.

1 48. A K-Ras protein covalently bonded to a compound having the formula:



1 49. A K-Ras protein covalently bonded to a compound having the formula:



1 50. The K-Ras protein of one of claims 48 to 49, wherein the compound is
2 covalently bonded to a cysteine residue of the protein.

1 51. The K-Ras protein of claim 48, wherein the compound is covalently
2 bonded to a cysteine residue of the protein corresponding to C185 of human K-Ras-4B.

1 52. The K-Ras protein of one of claims 48 to 49, wherein the compound is
2 covalently bonded to a histidine residue of the protein.

1 53. The K-Ras protein of claim 48, wherein the compound is covalently
2 bonded to a histidine residue of the protein corresponding to H95 of human K-Ras-4B.

1/47

FIG. 1A

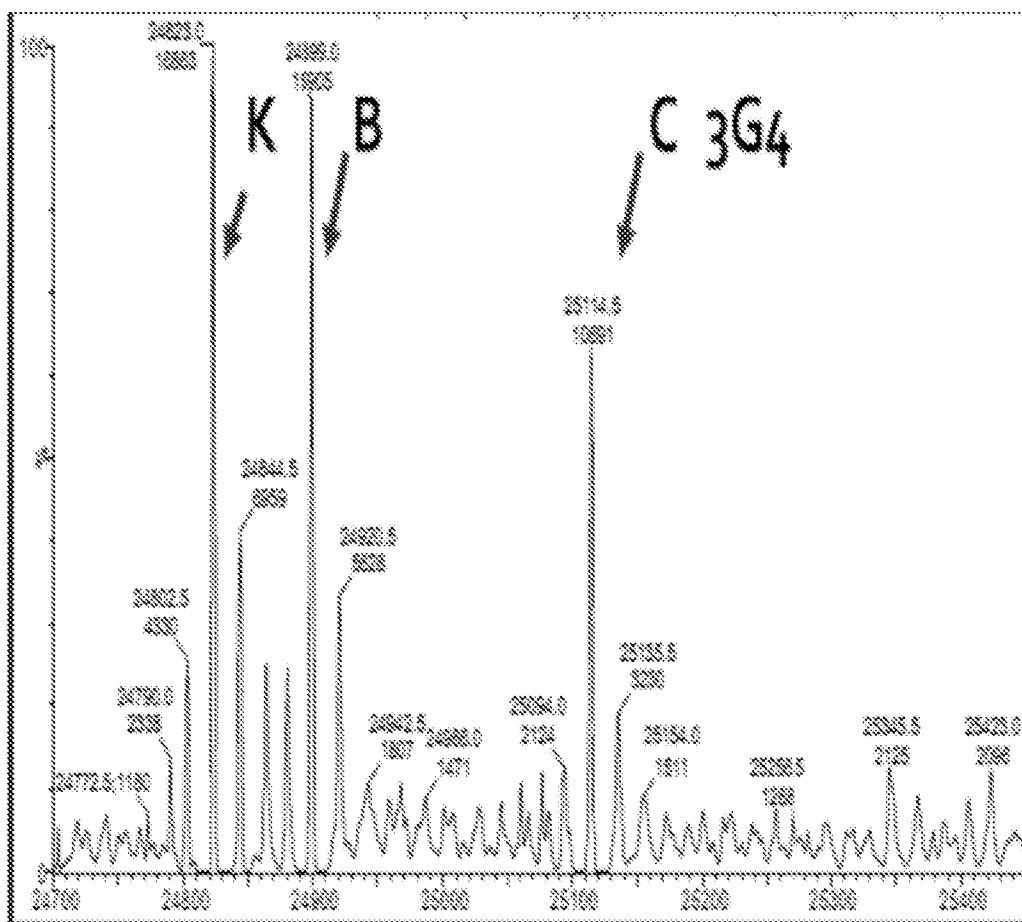


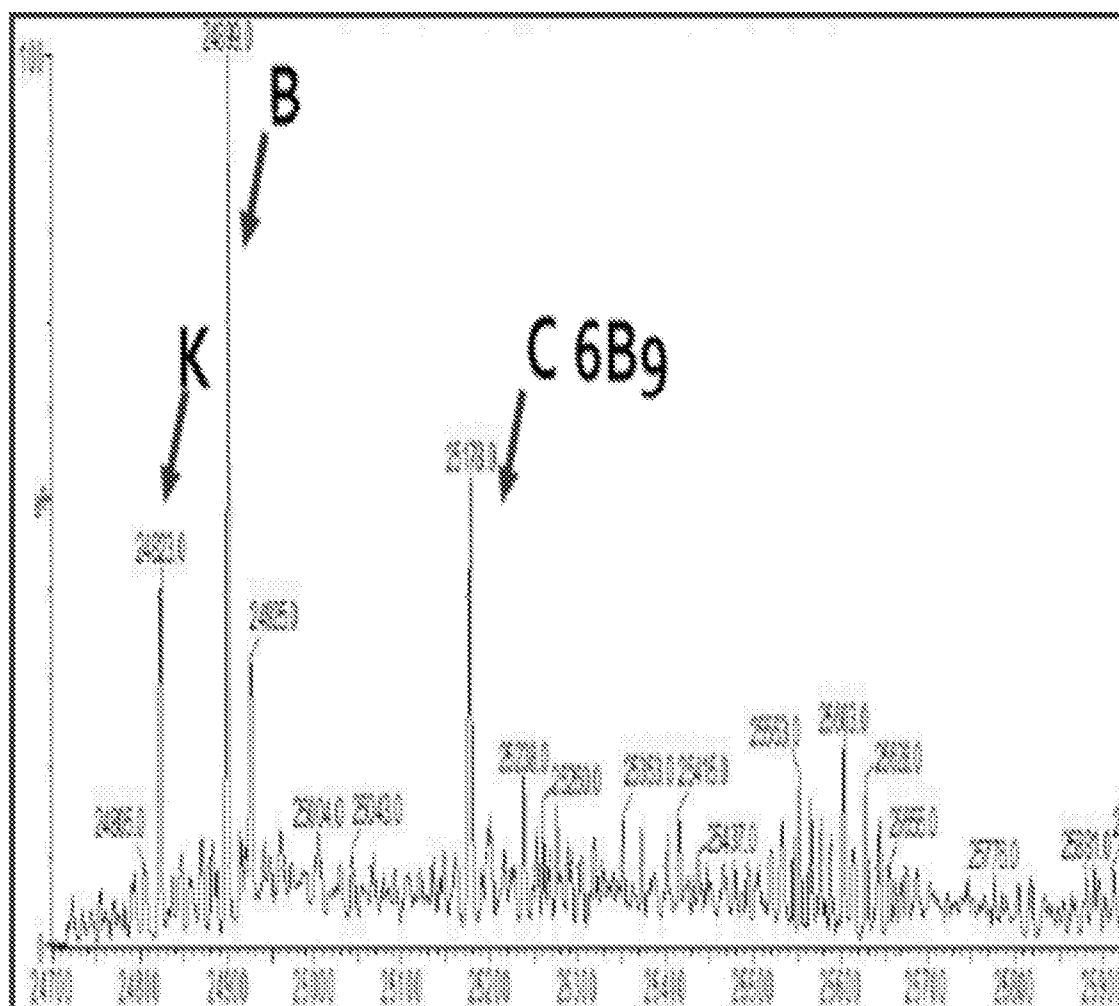
FIG. 1B

FIG. 1C

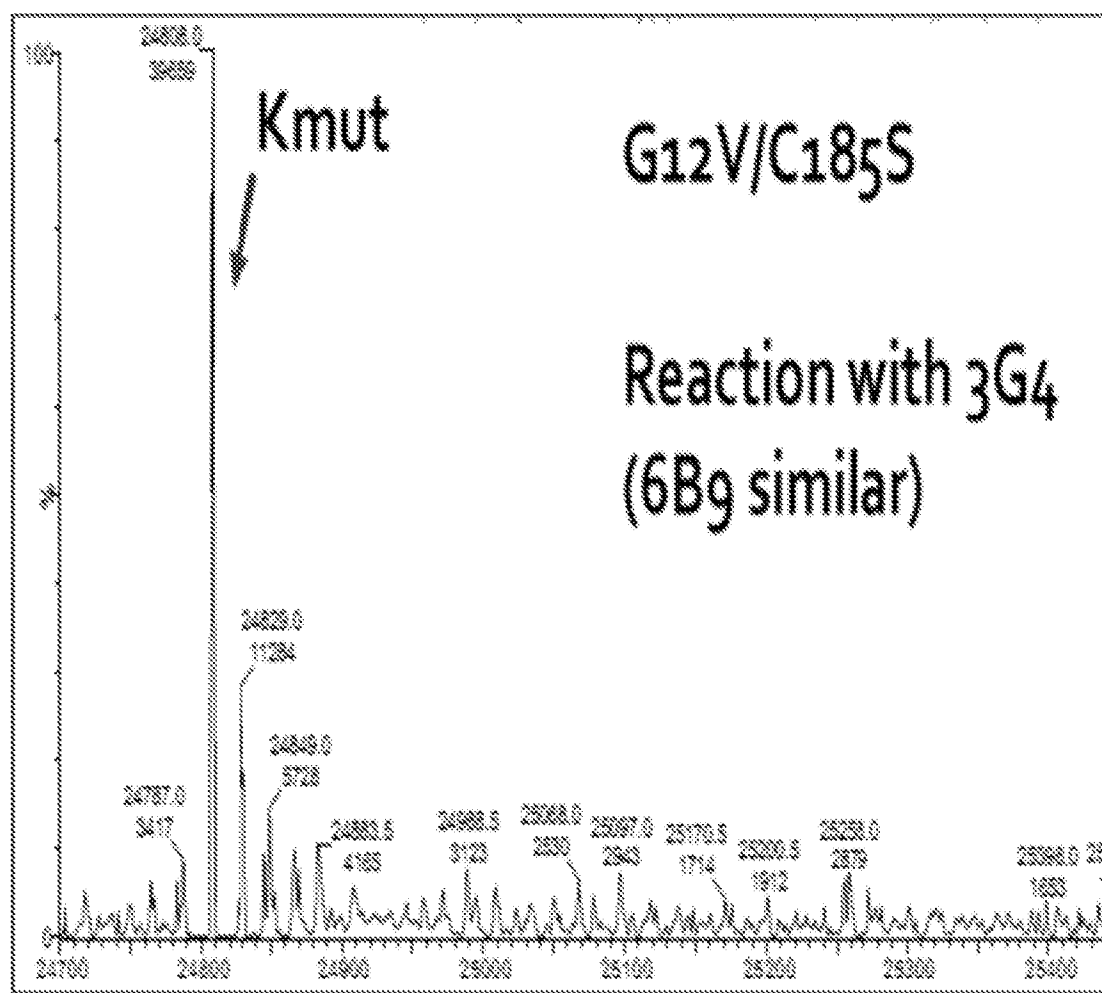
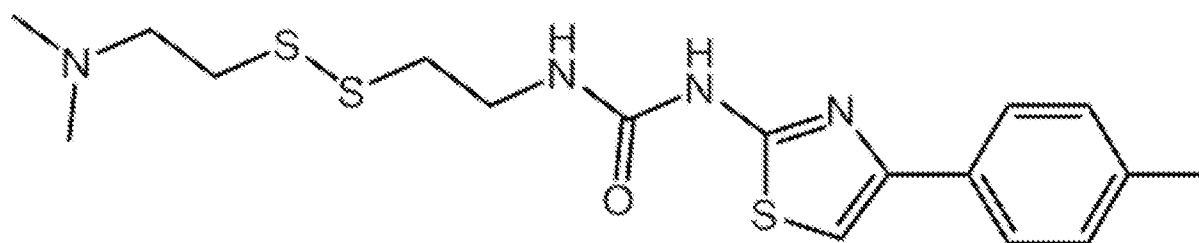
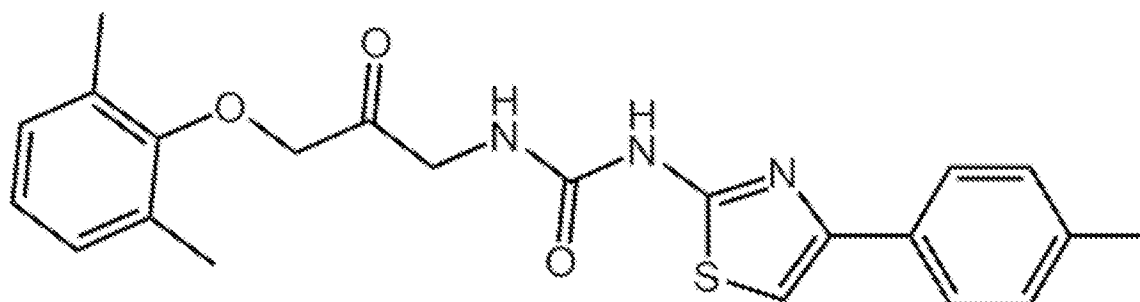


FIG. 2A

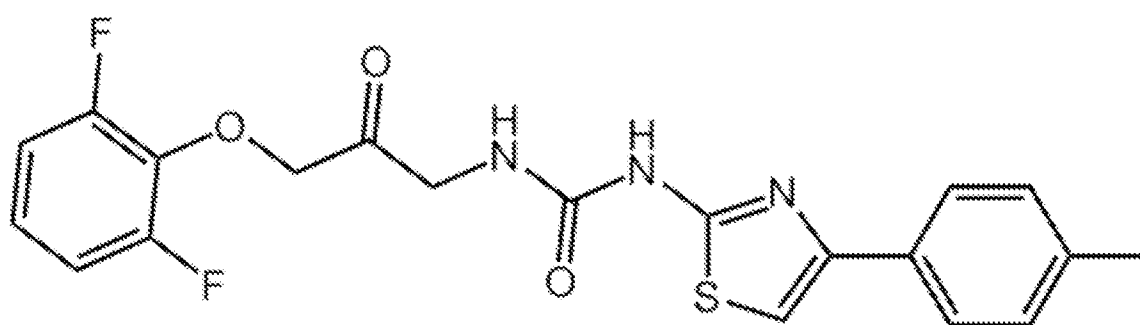


SMDC 917069 (also known as 3G4)

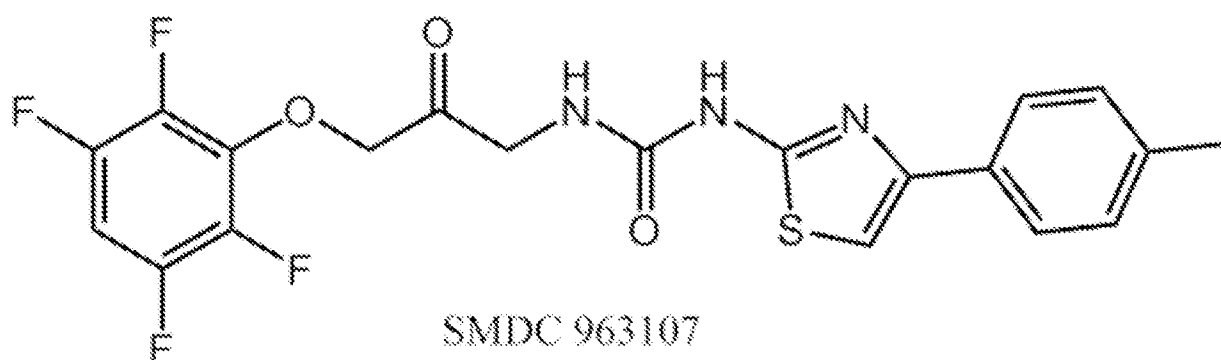
4/47

FIG. 2B

SMDC 963109

FIG. 2C

SMDC 963108

FIG. 2D

SMDC 963107

5/47

FIG. 3A

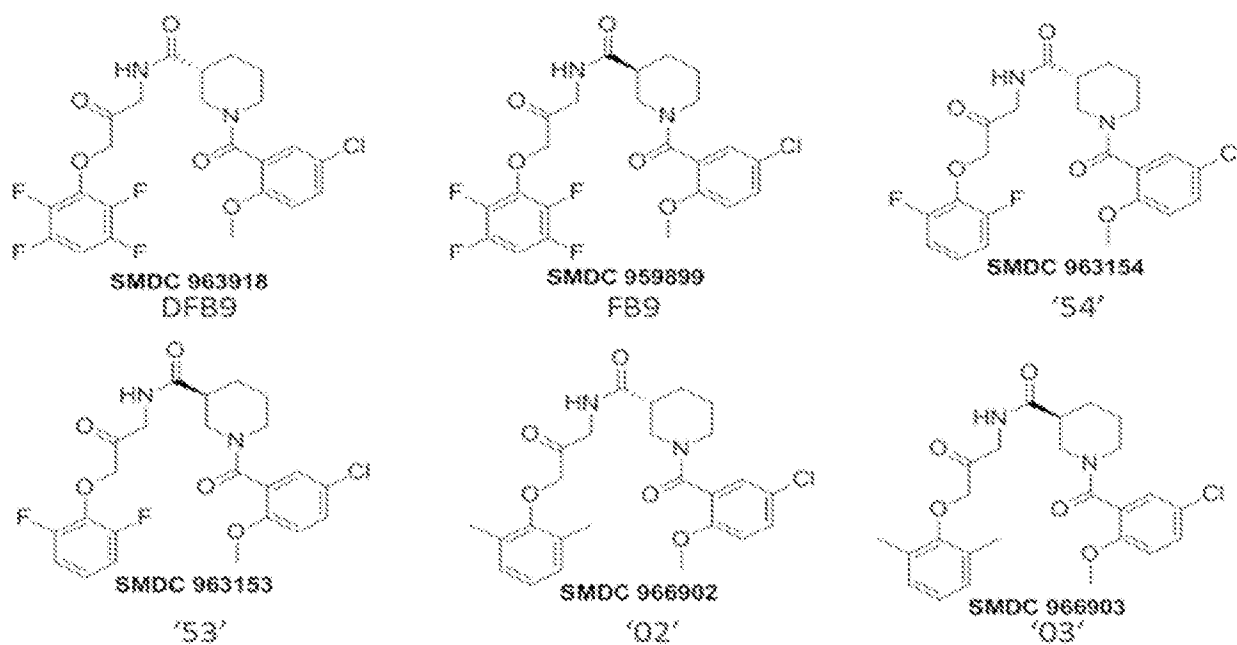


FIG. 3B

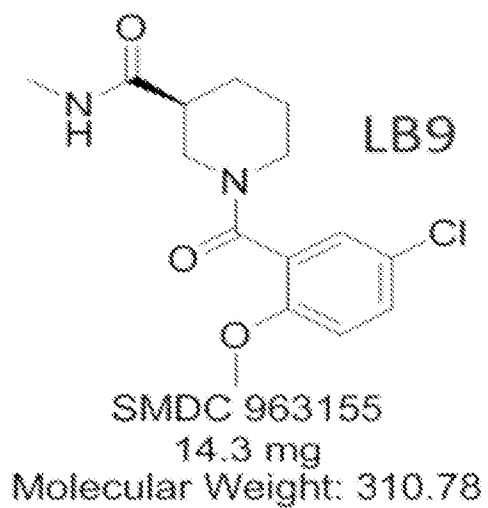
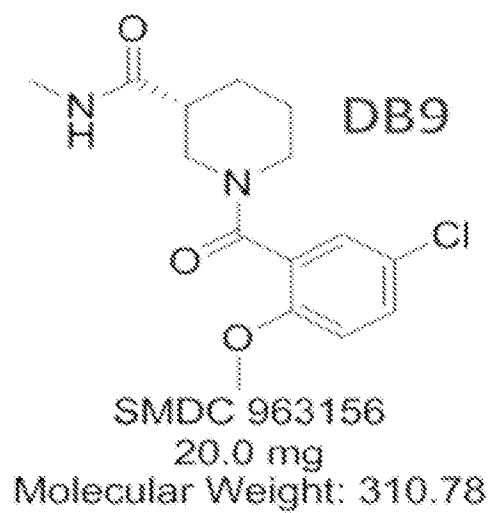
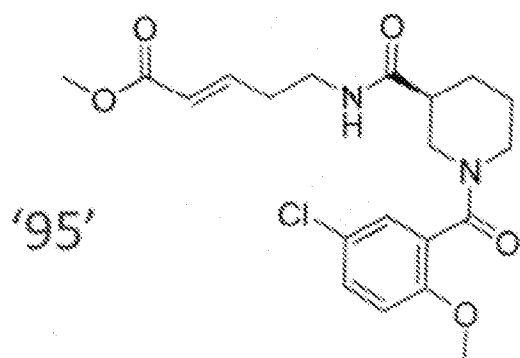


FIG. 3C



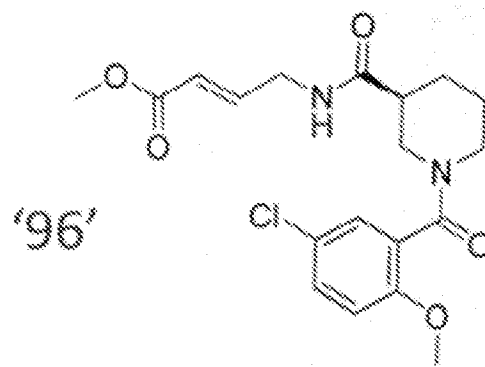
6/47

FIG. 4A



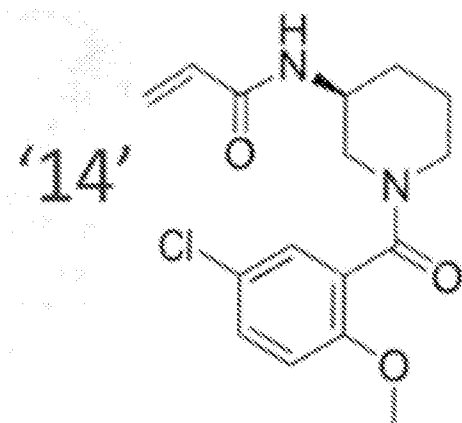
Molecular Weight: 408.88
SMDC 973195

FIG. 4B



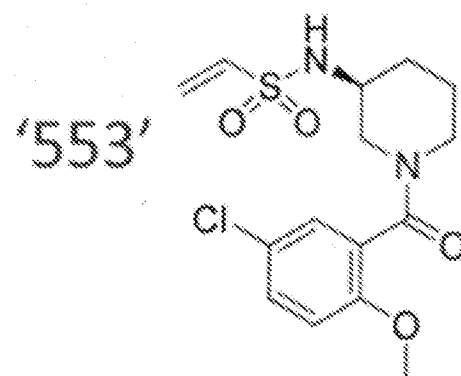
Molecular Weight: 394.85
SMDC 973196

FIG. 4C



Molecular Weight: 322.79
SMDC 973214

FIG. 4D



Molecular Weight: 358.84
SMDC 973553

7/47

FIG. 5A

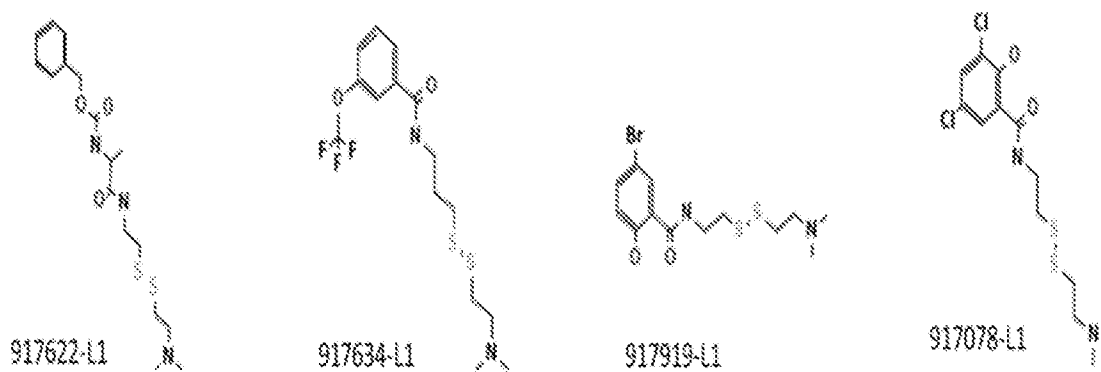


FIG. 5B

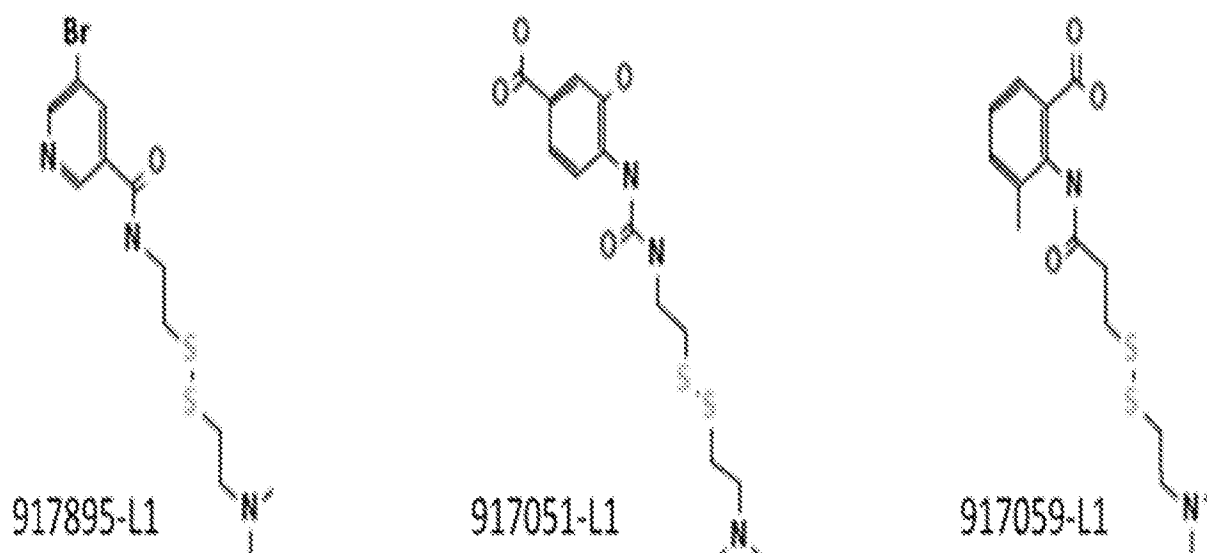
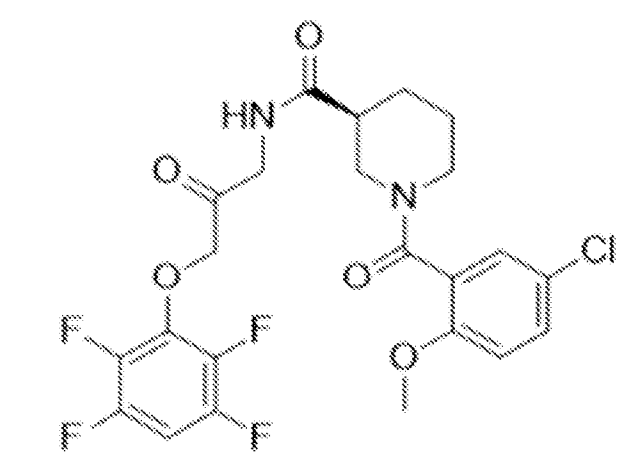
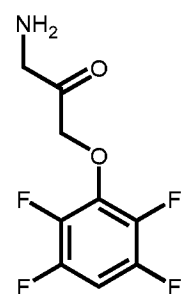
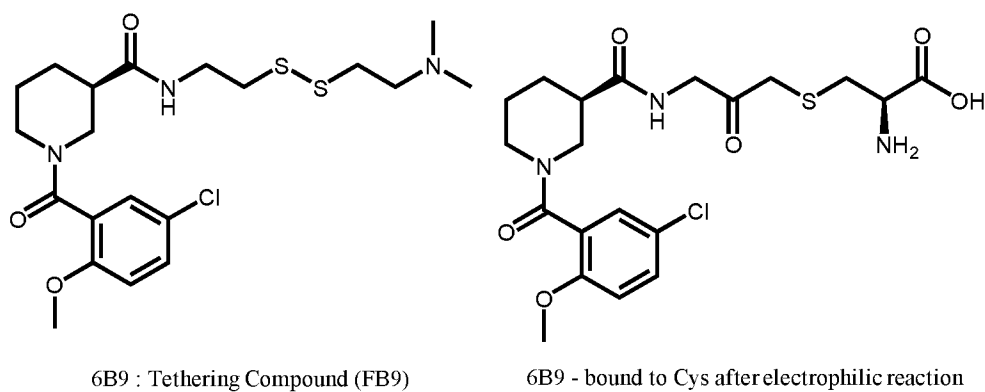


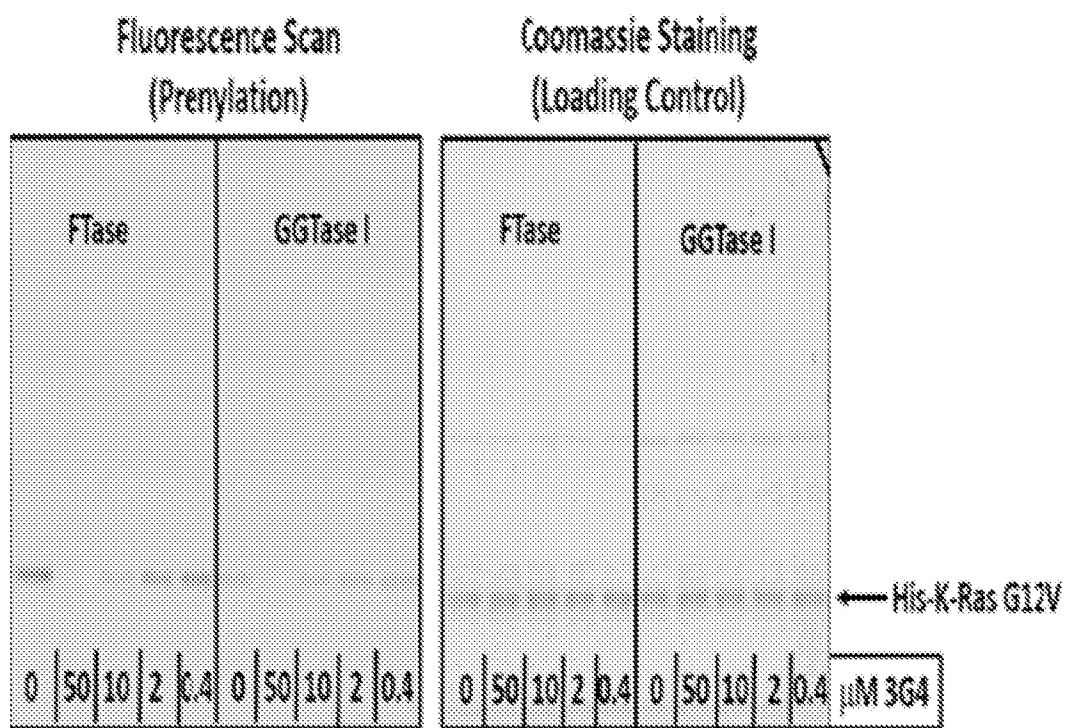
FIG. 6A



8/47

FIG. 6B

Electrophilic modification

FIG. 7A

9/47

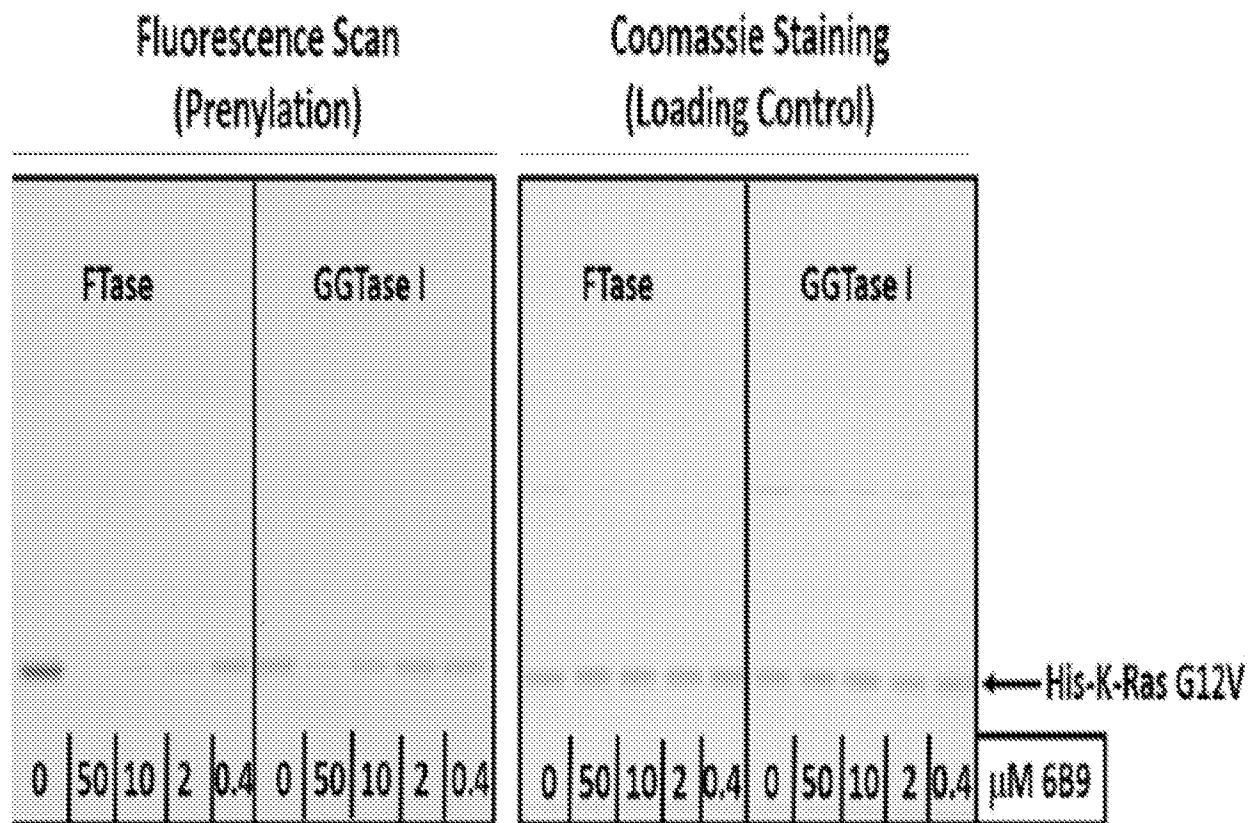
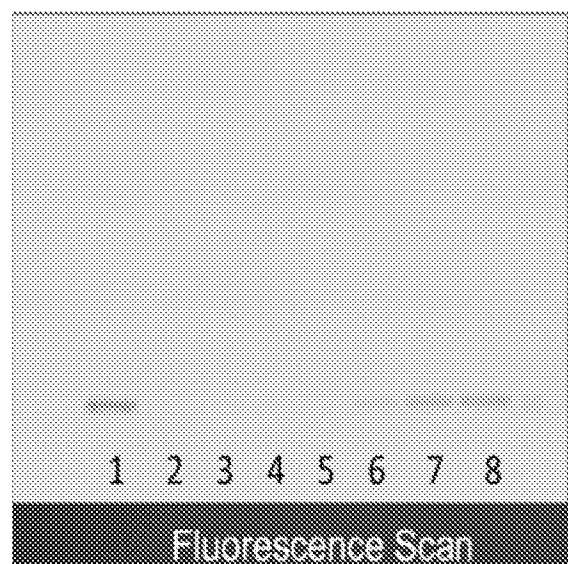
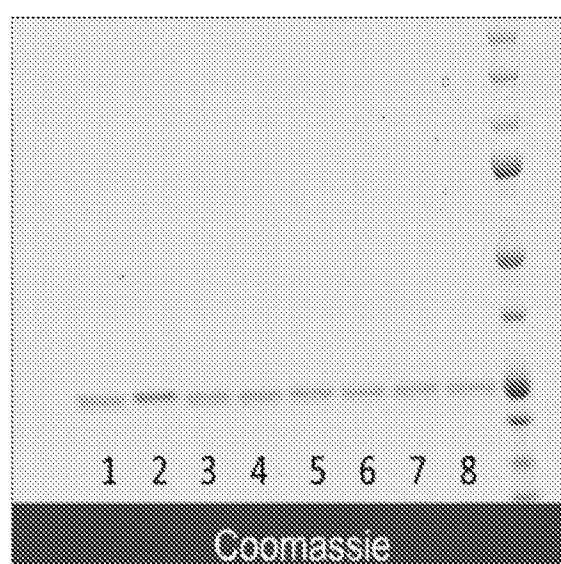
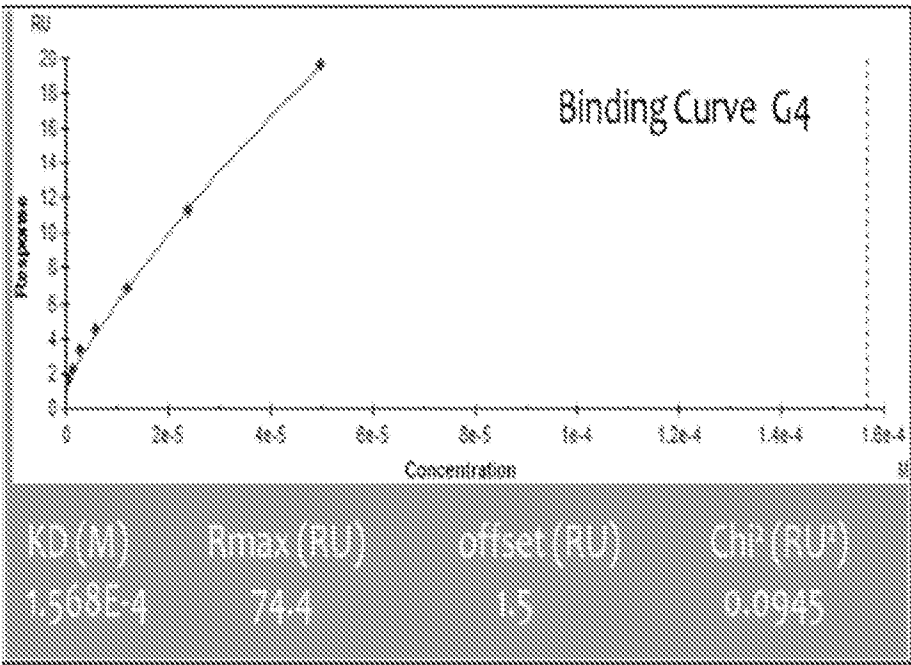
FIG. 7B**FIG. 8A****FIG. 8B**

FIG. 9

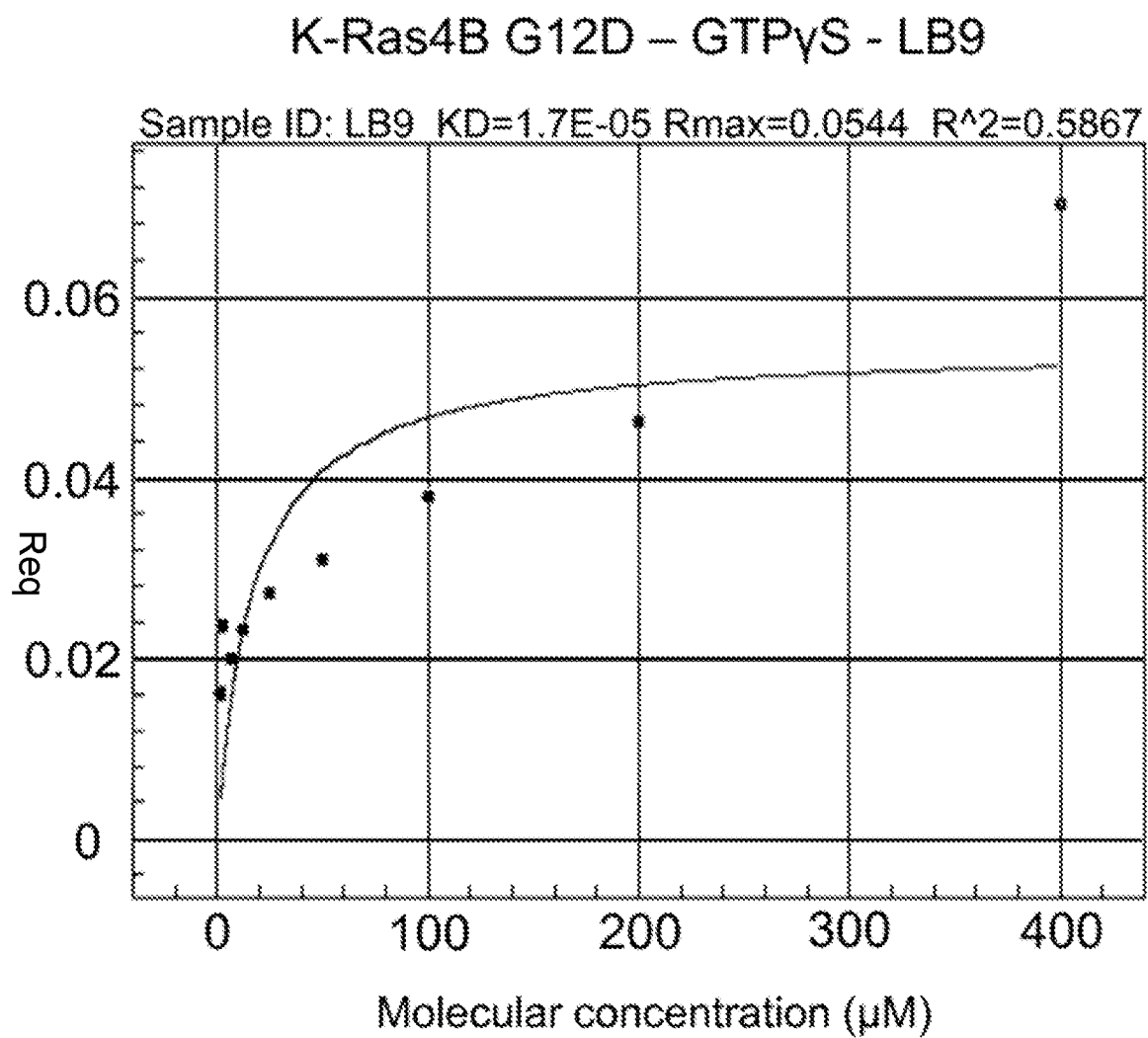


FIG. 10



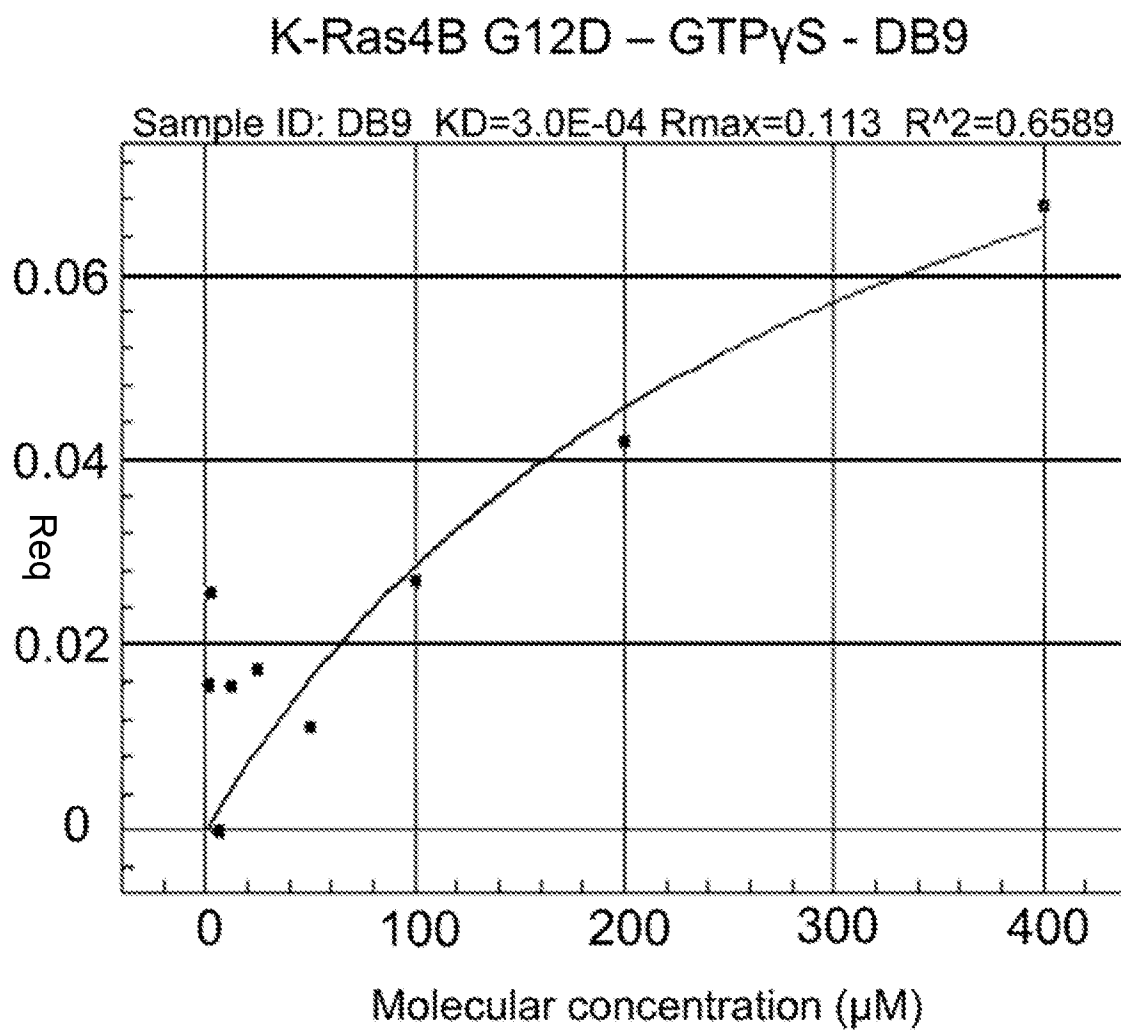
11/47

FIG. 11A



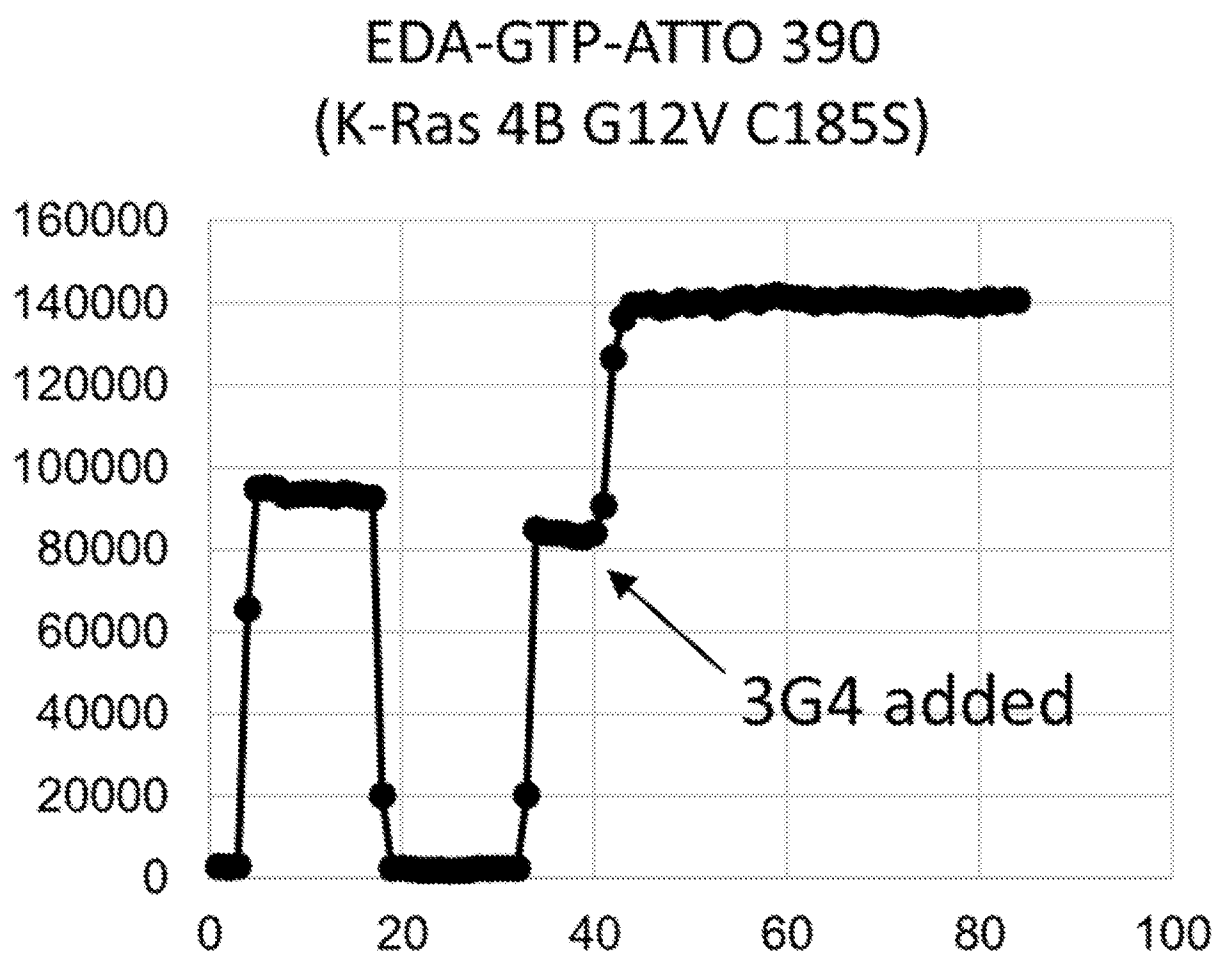
12/47

FIG. 11B

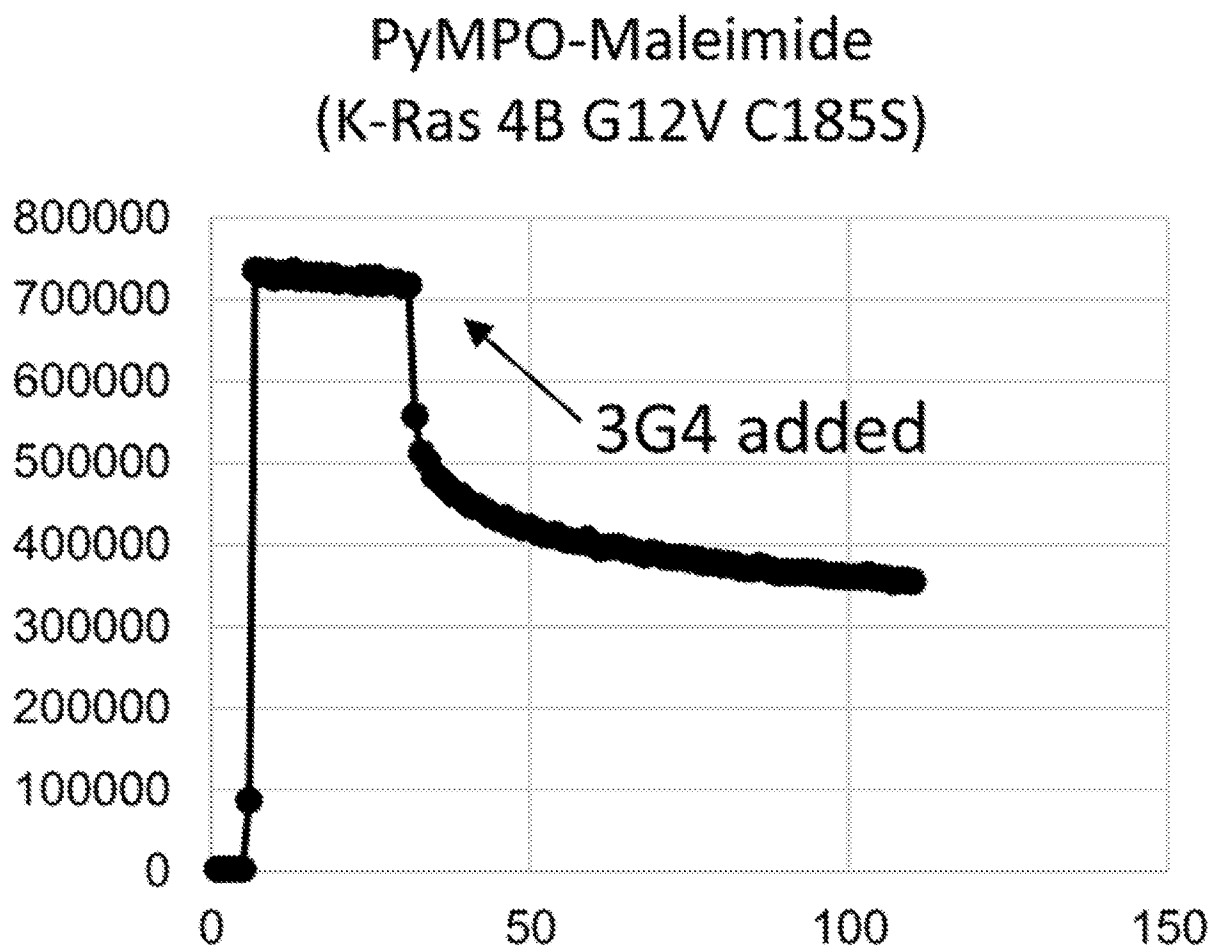


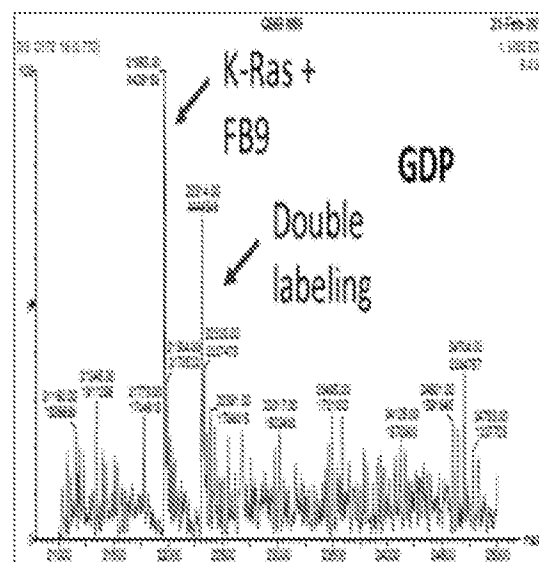
13/47

FIG. 12A



14/47

FIG. 12B



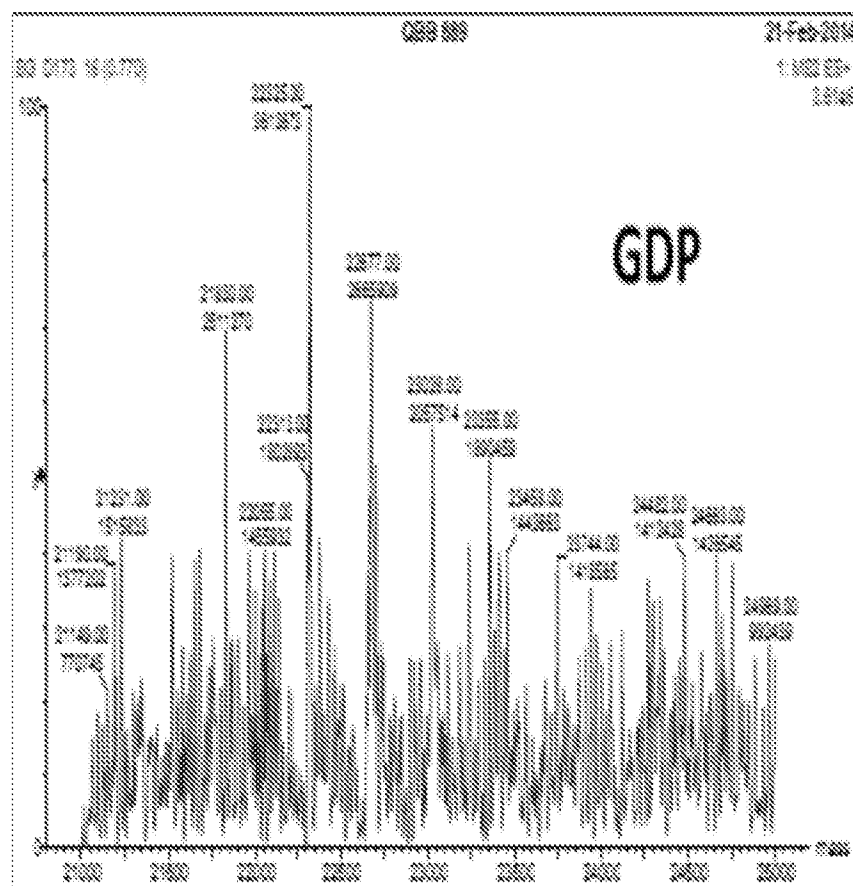
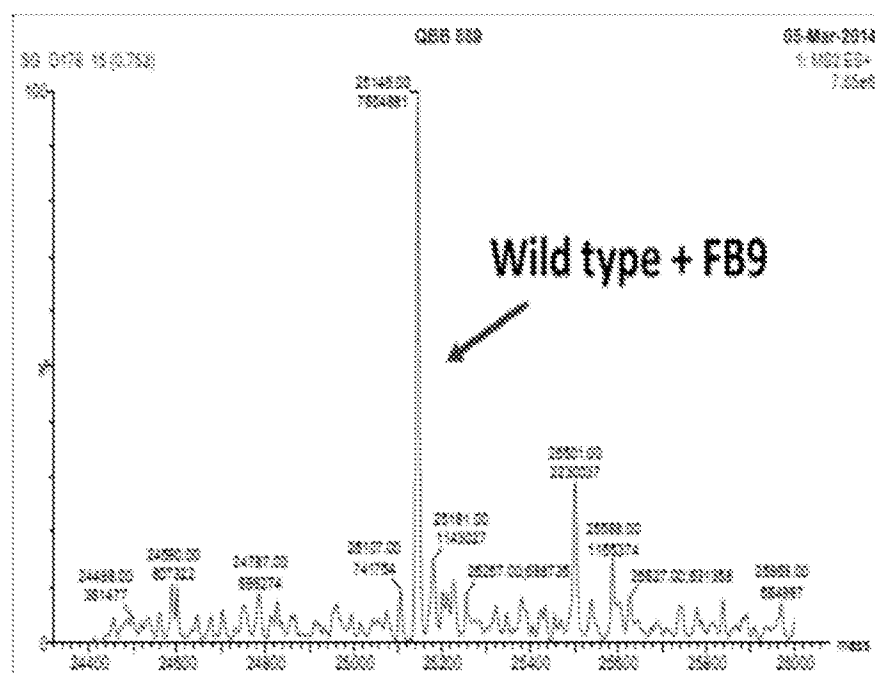


FIG. 14A



17/47

FIG. 14B

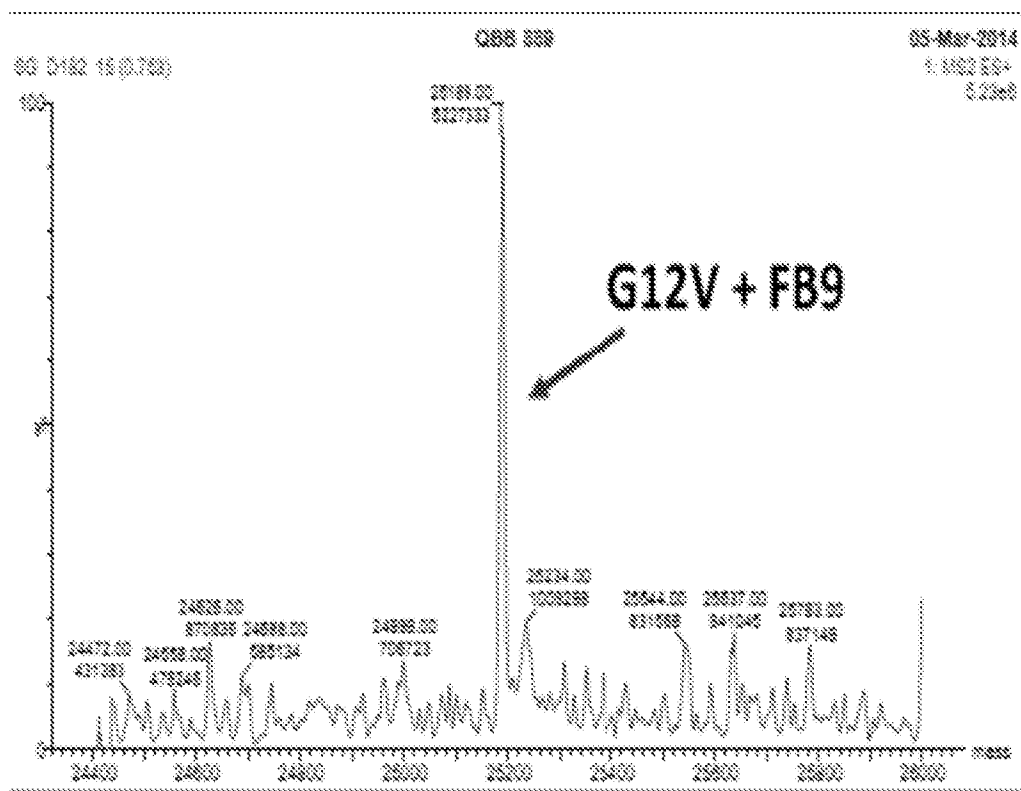


FIG. 14C

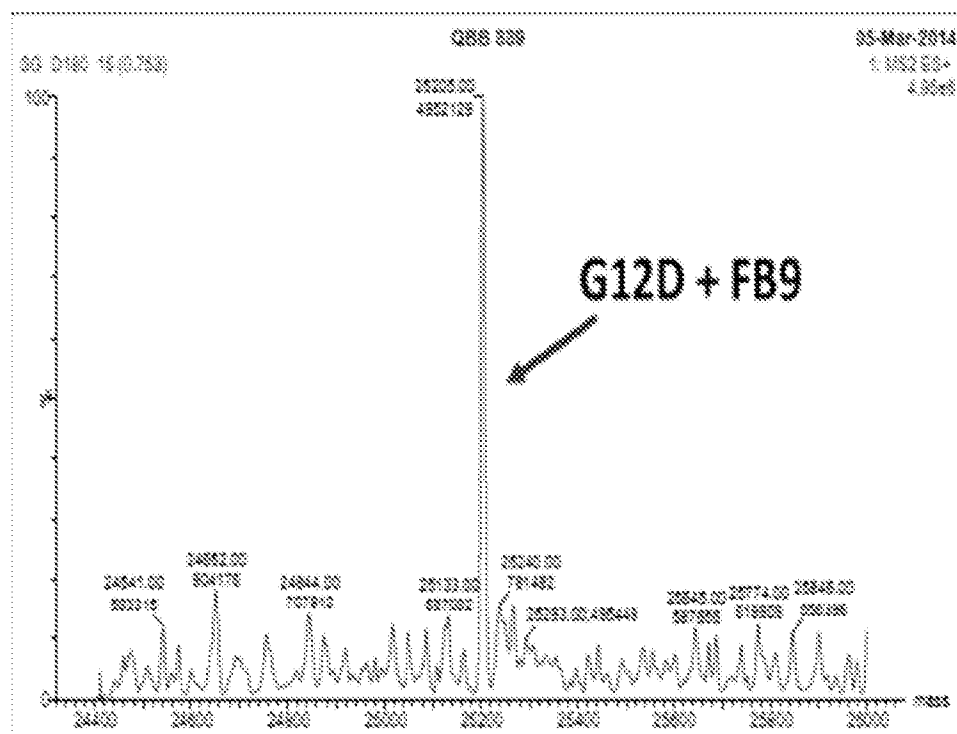


FIG. 14D

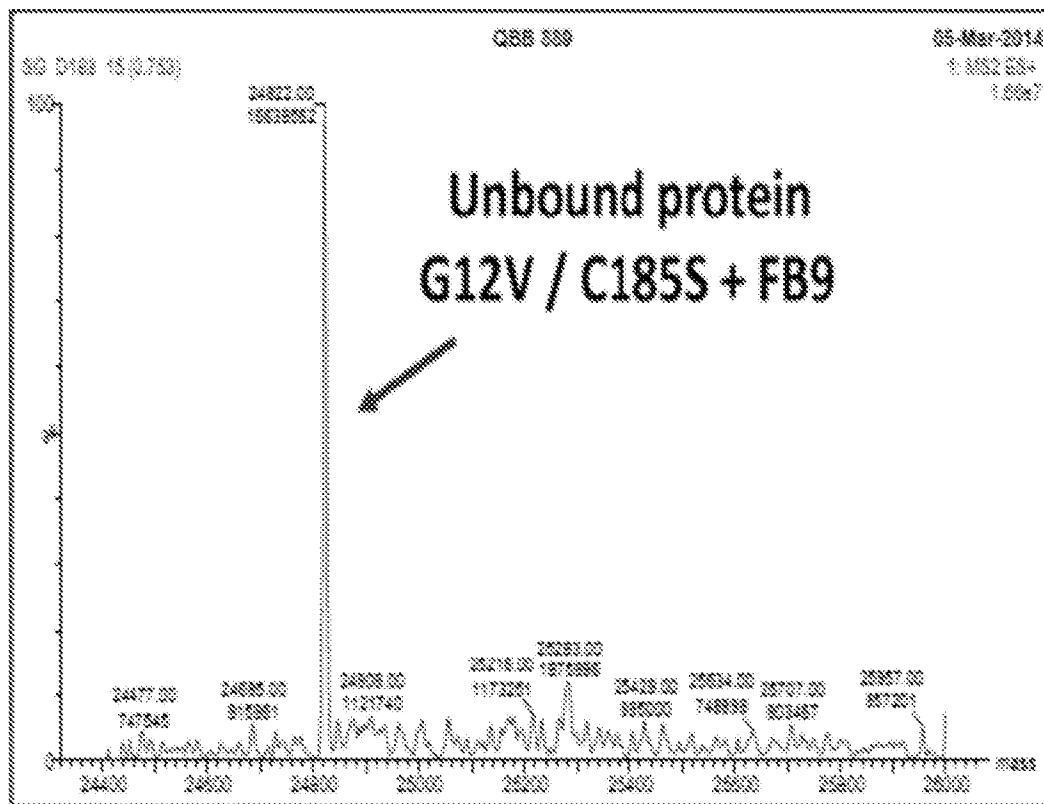


FIG. 15A

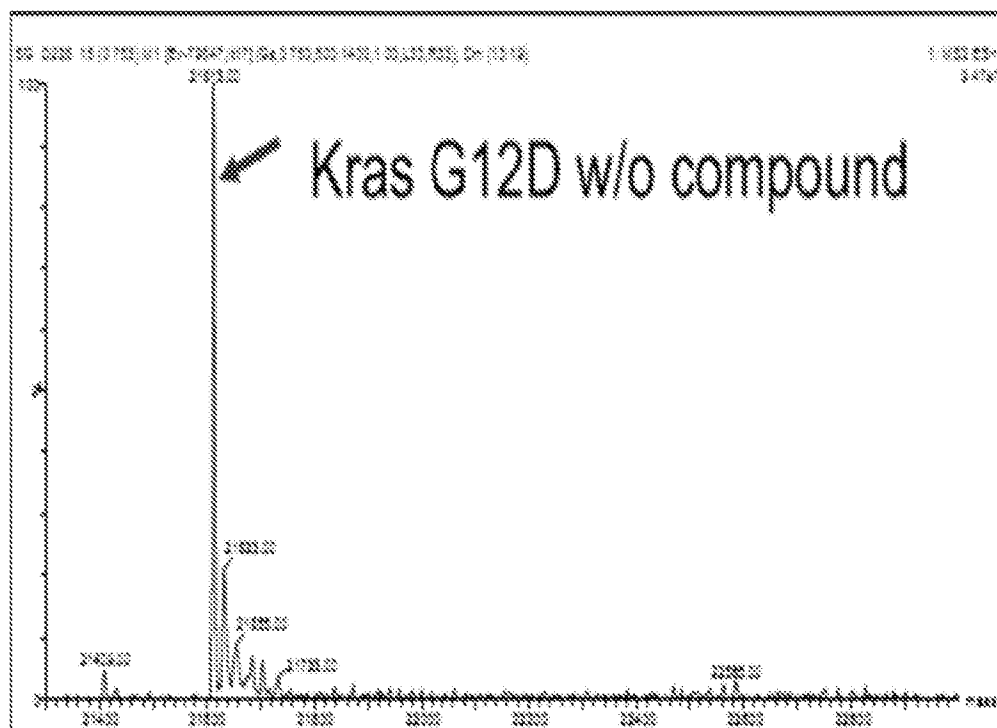


FIG. 15B

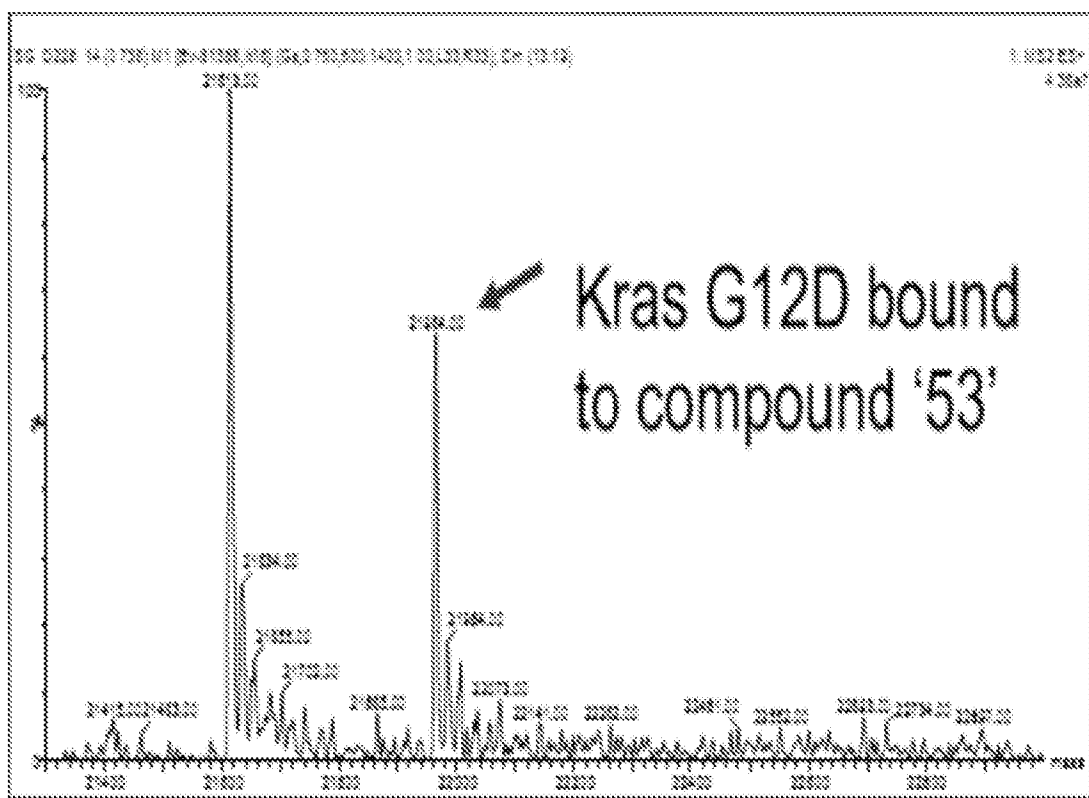
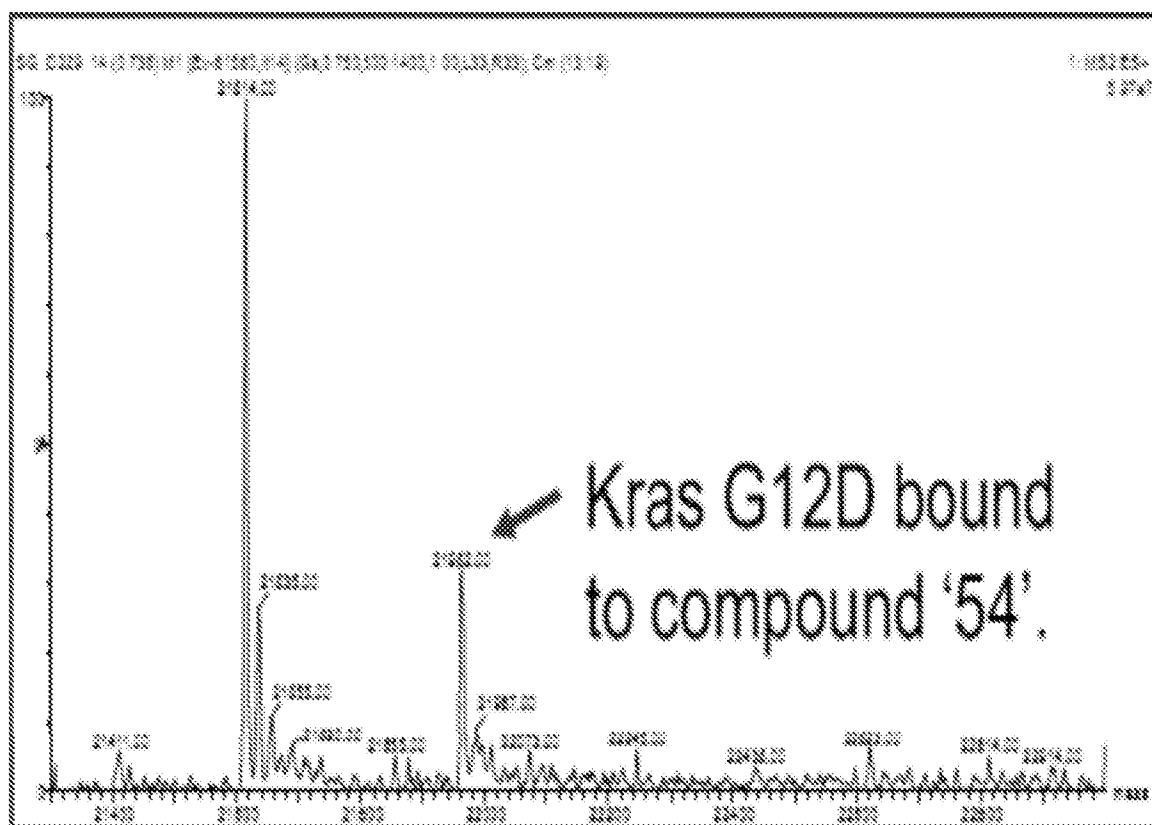
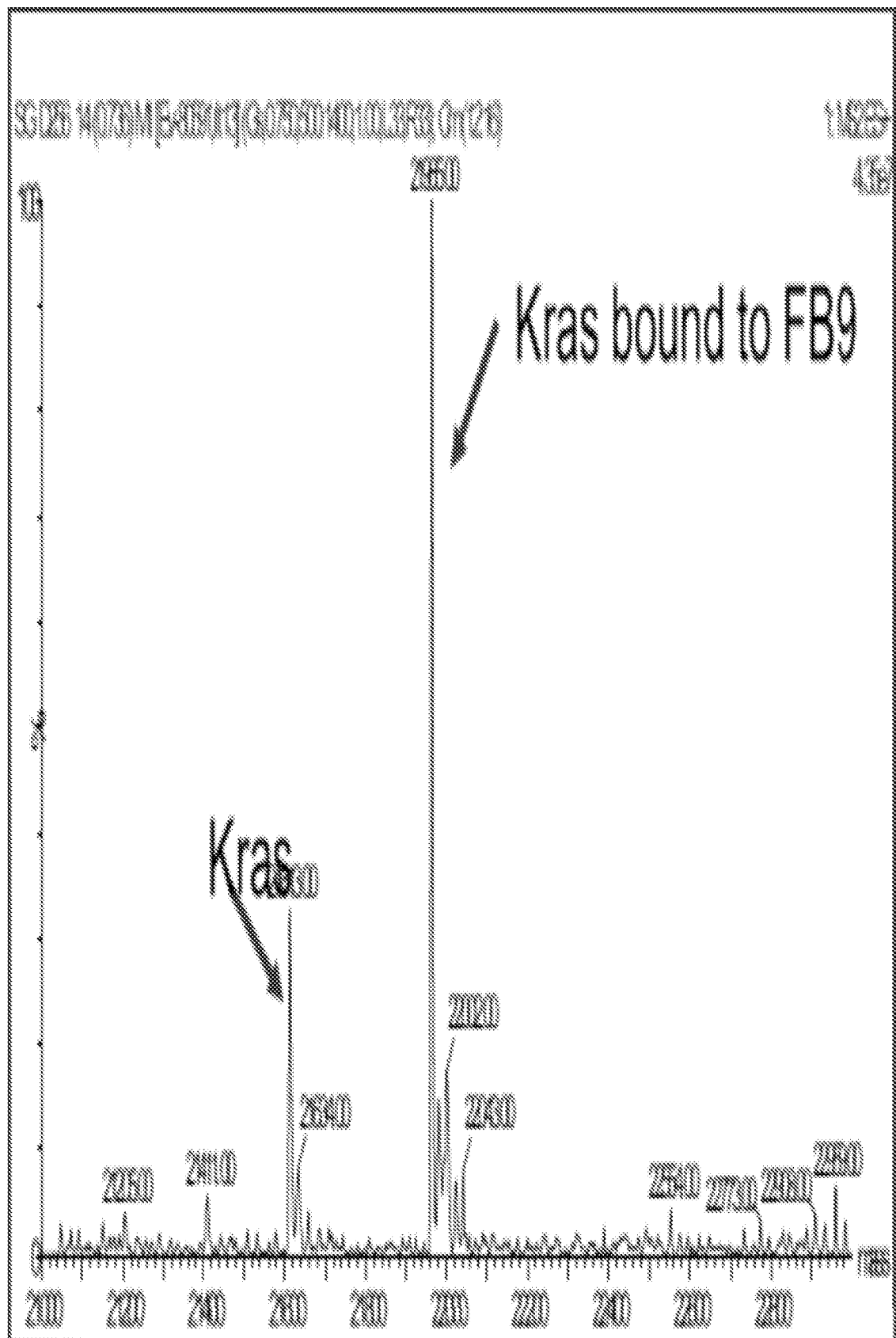


FIG. 15D



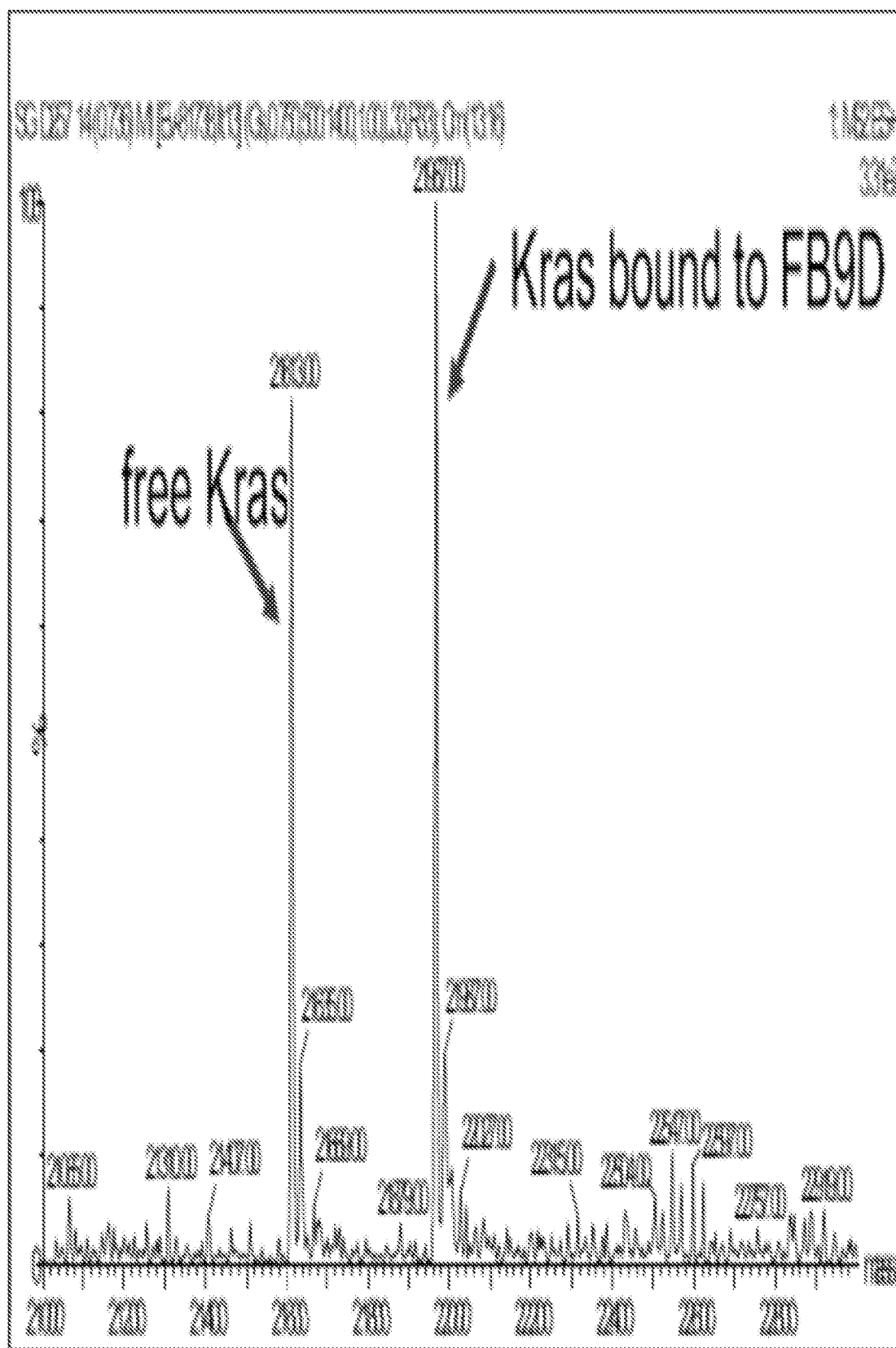
21/47

FIG. 16A



22/47

FIG. 16B



23/47

FIG. 17A

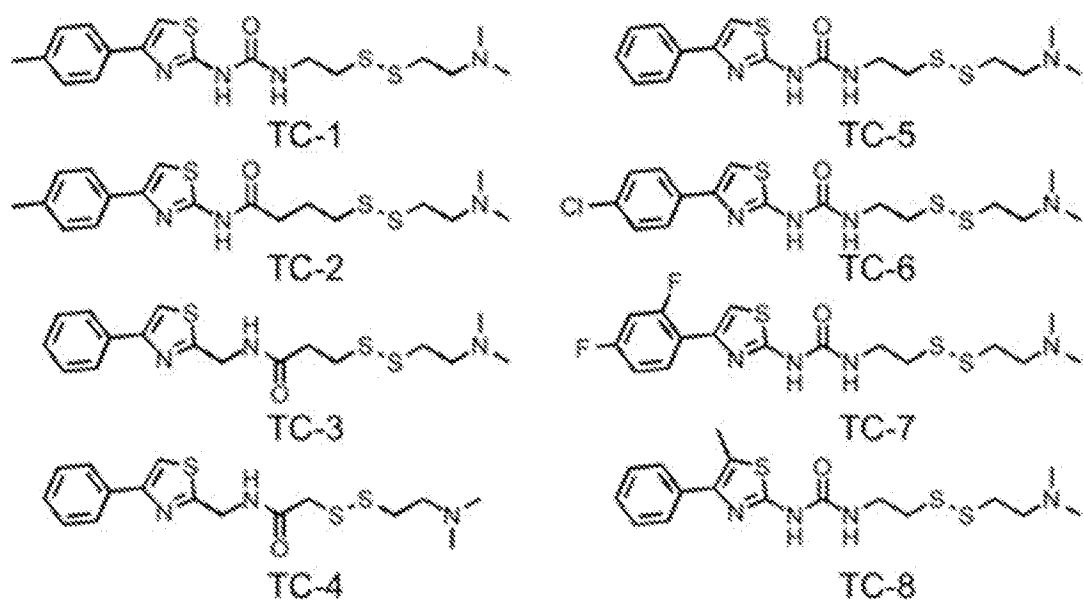
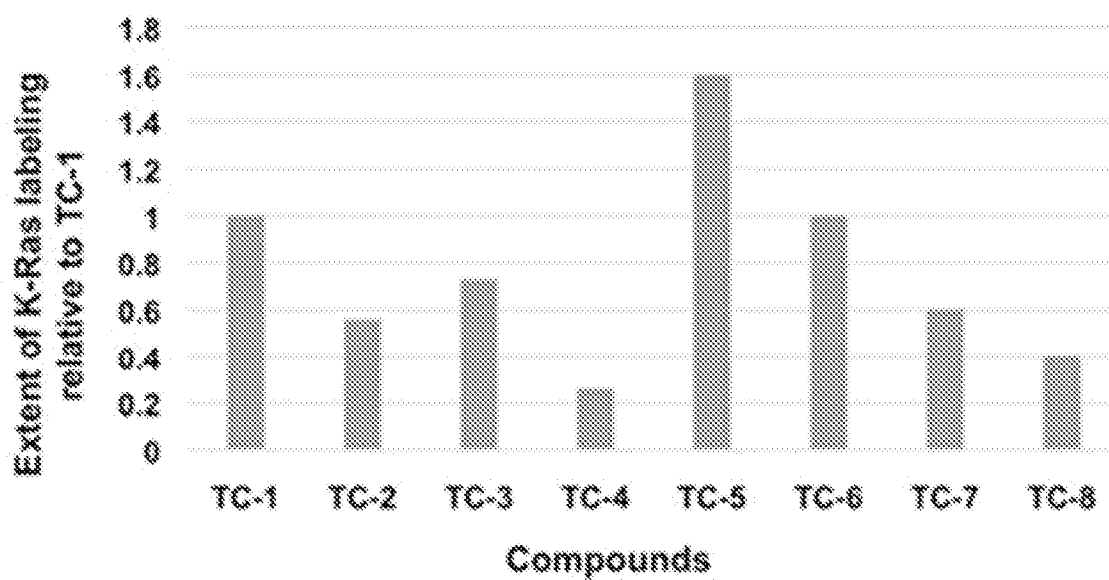
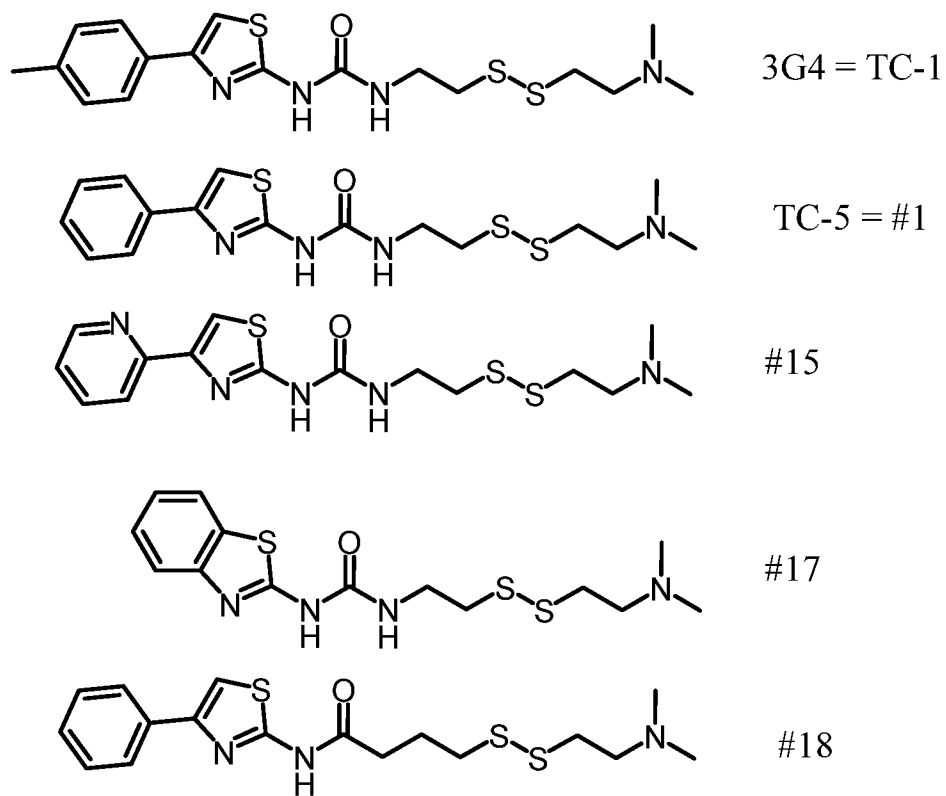


FIG. 17B



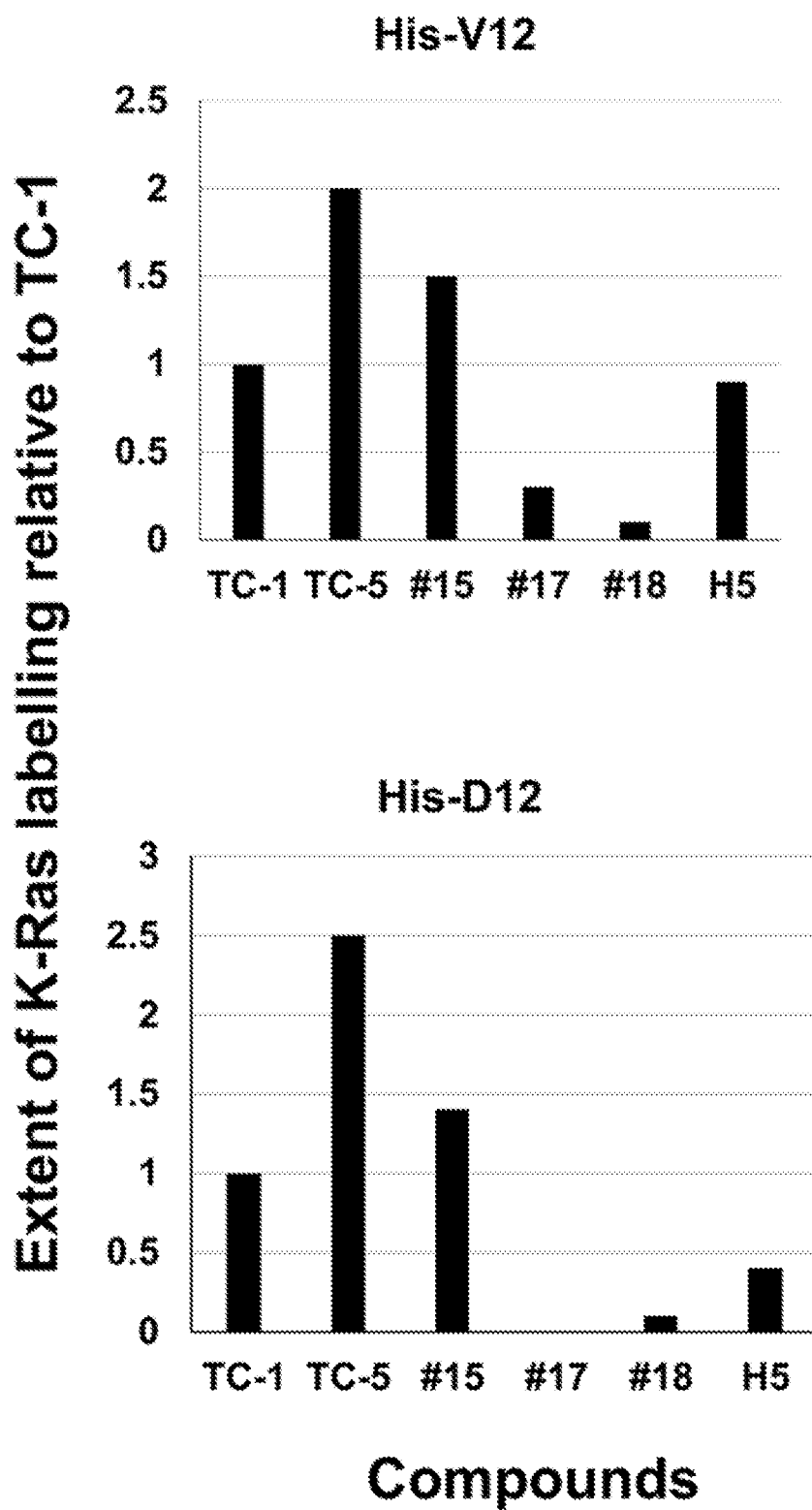
24/47

FIG. 18A

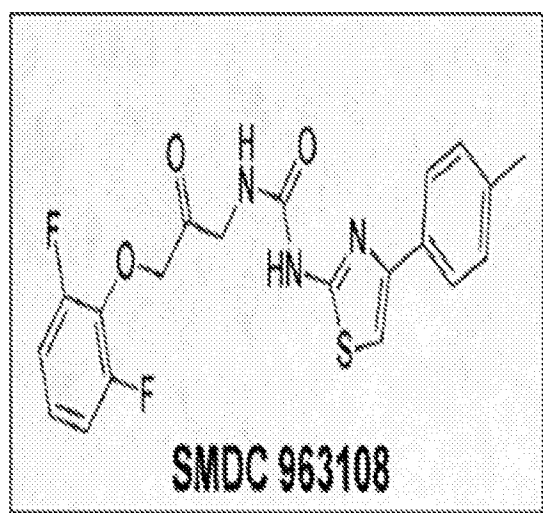
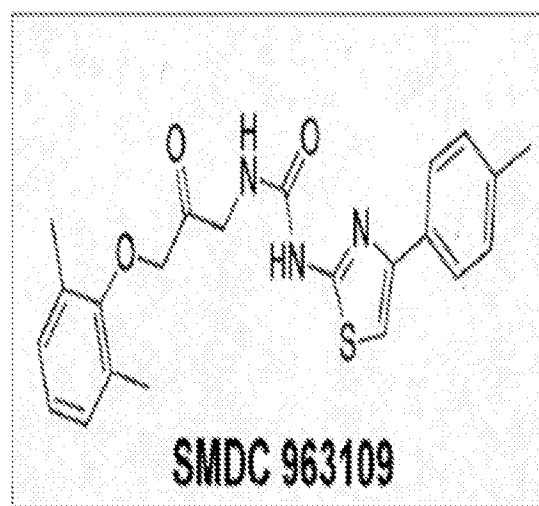
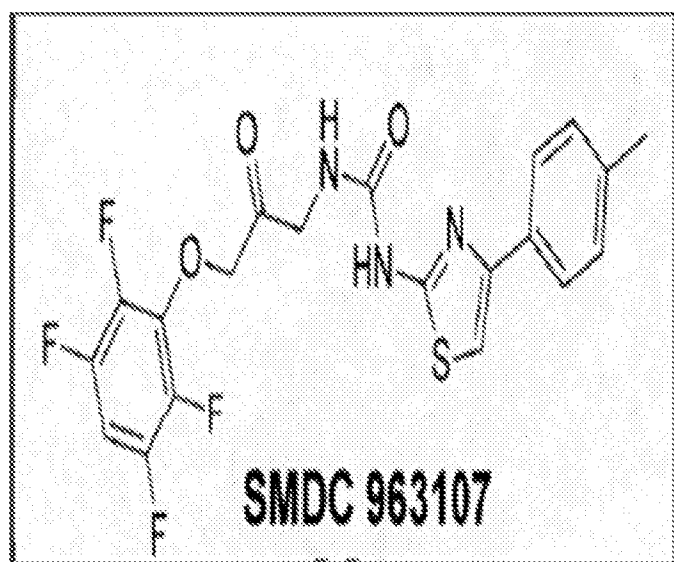


25/47

FIG. 18B



26/47

FIG. 19A**FIG. 19B****FIG. 19C**

27/47

FIG. 20A

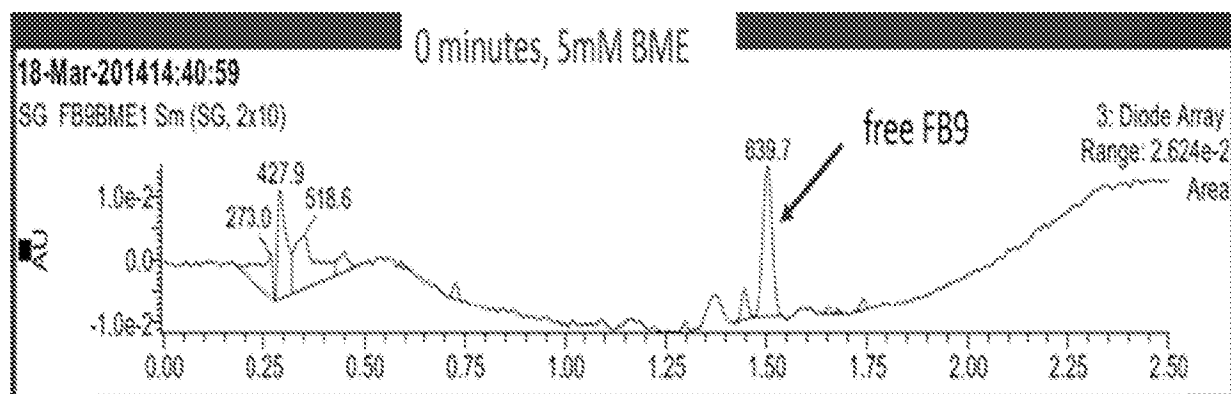


FIG. 20B

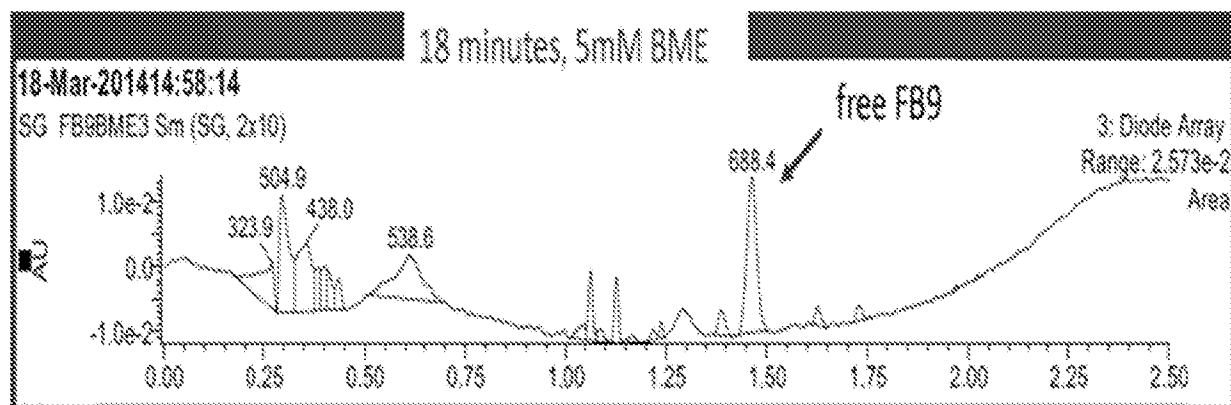
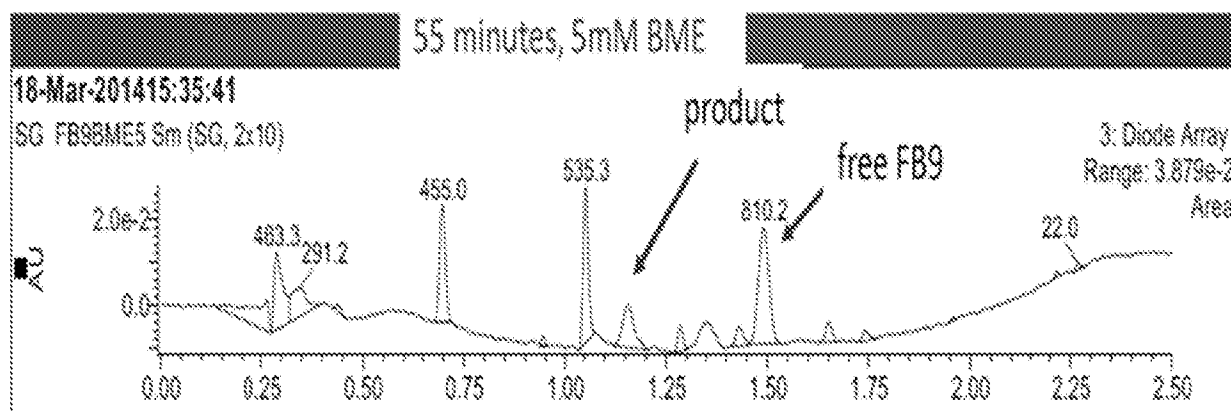


FIG. 20C



28/47

FIG. 21A

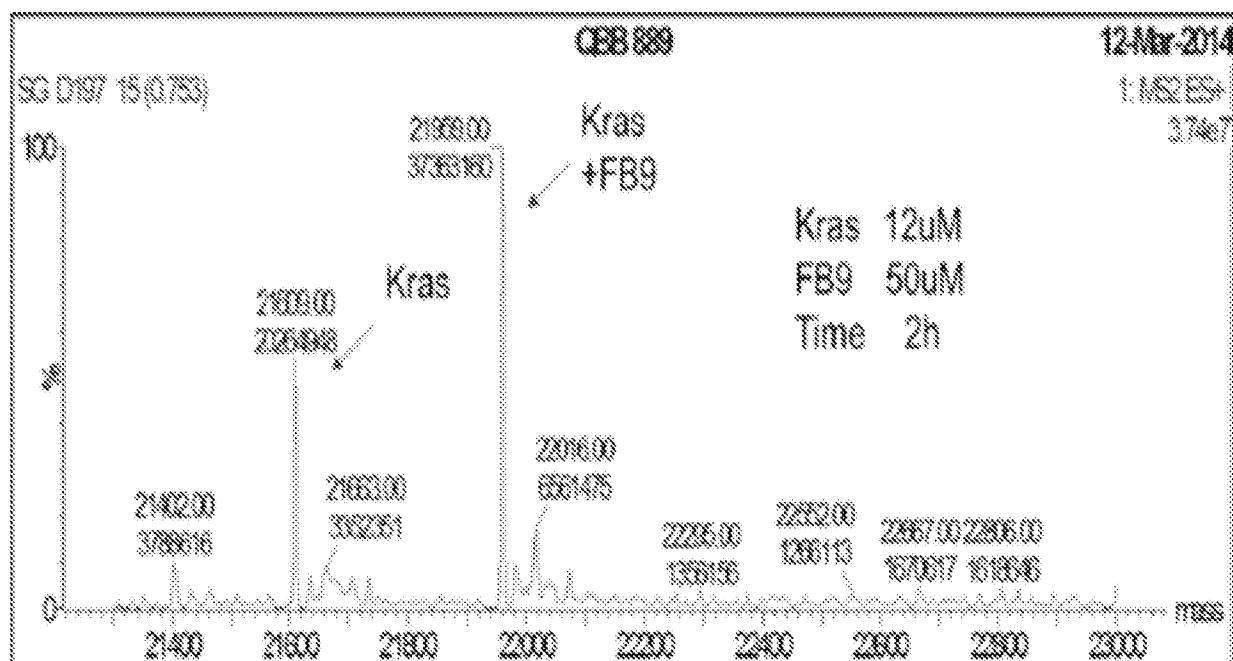
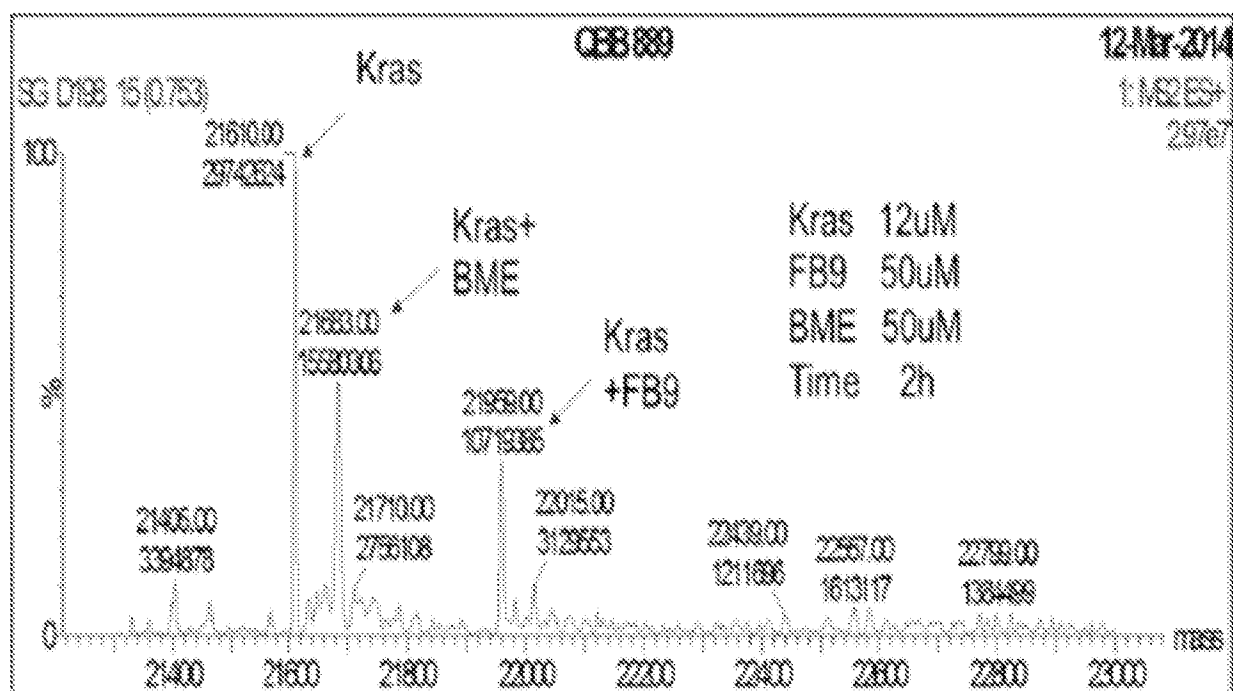


FIG. 21B



29/47

FIG. 21C

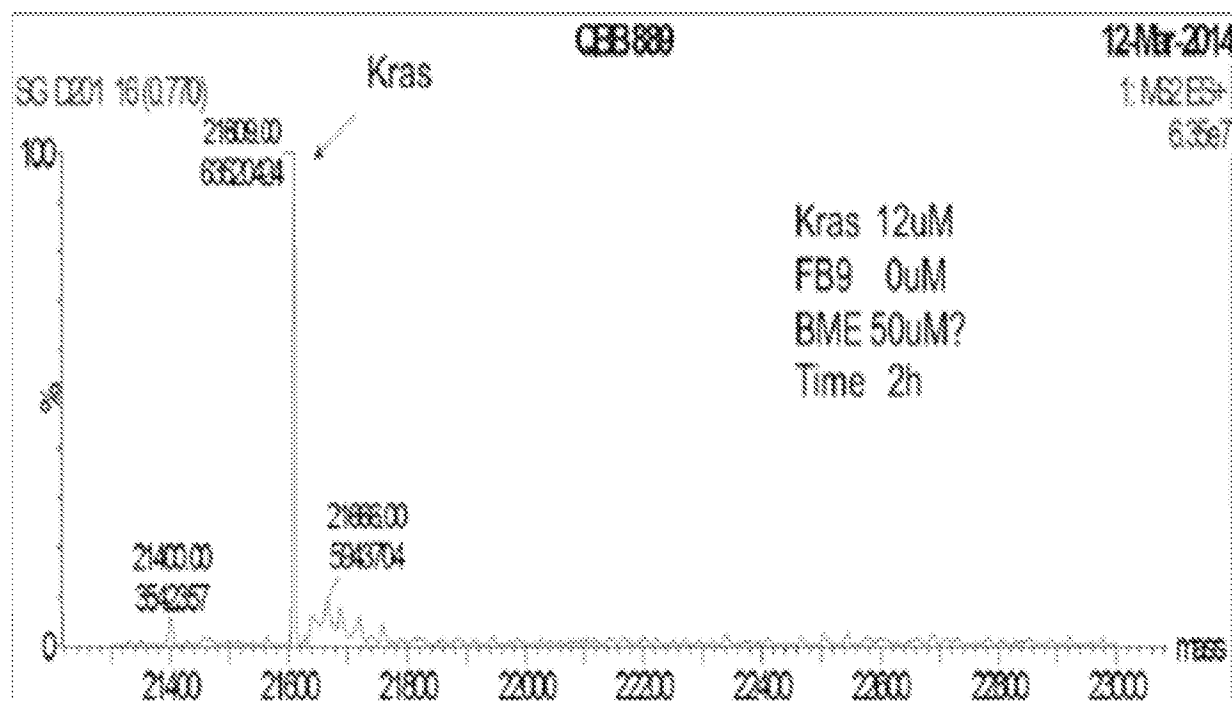
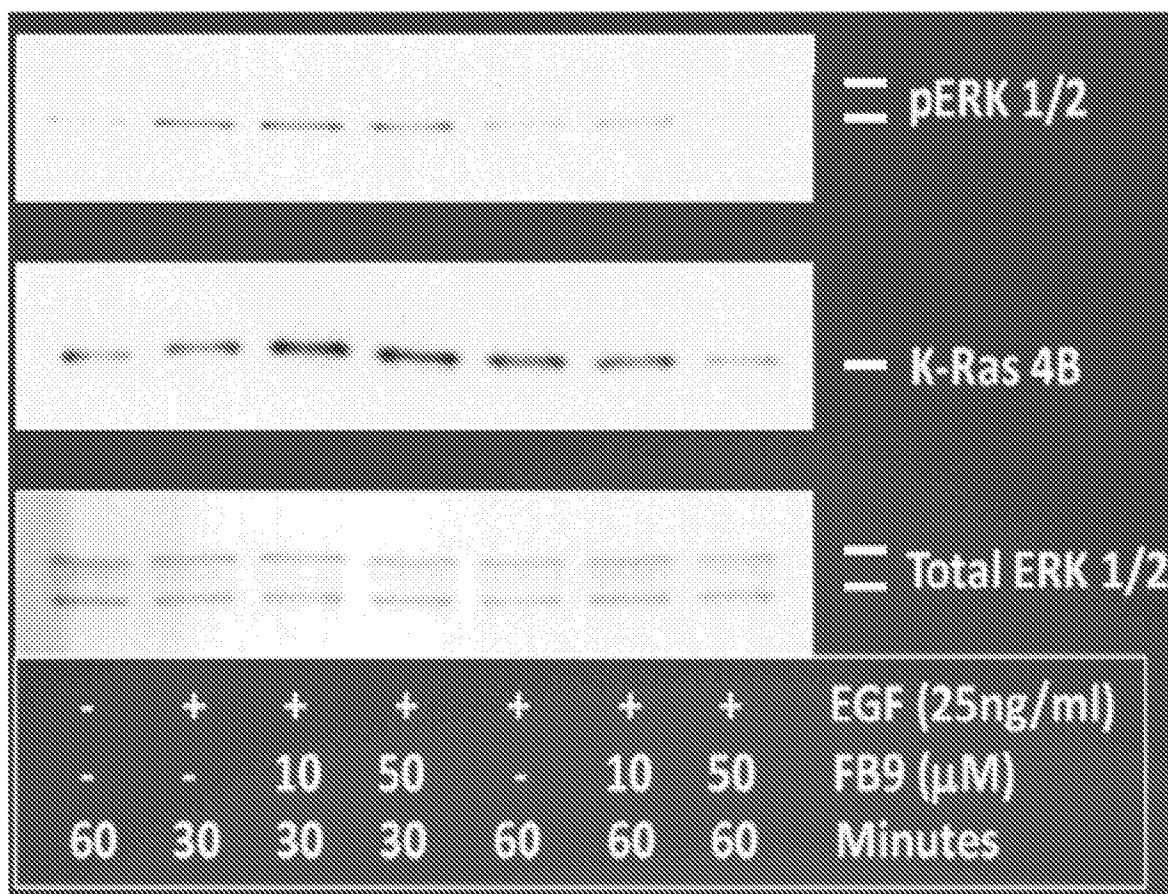
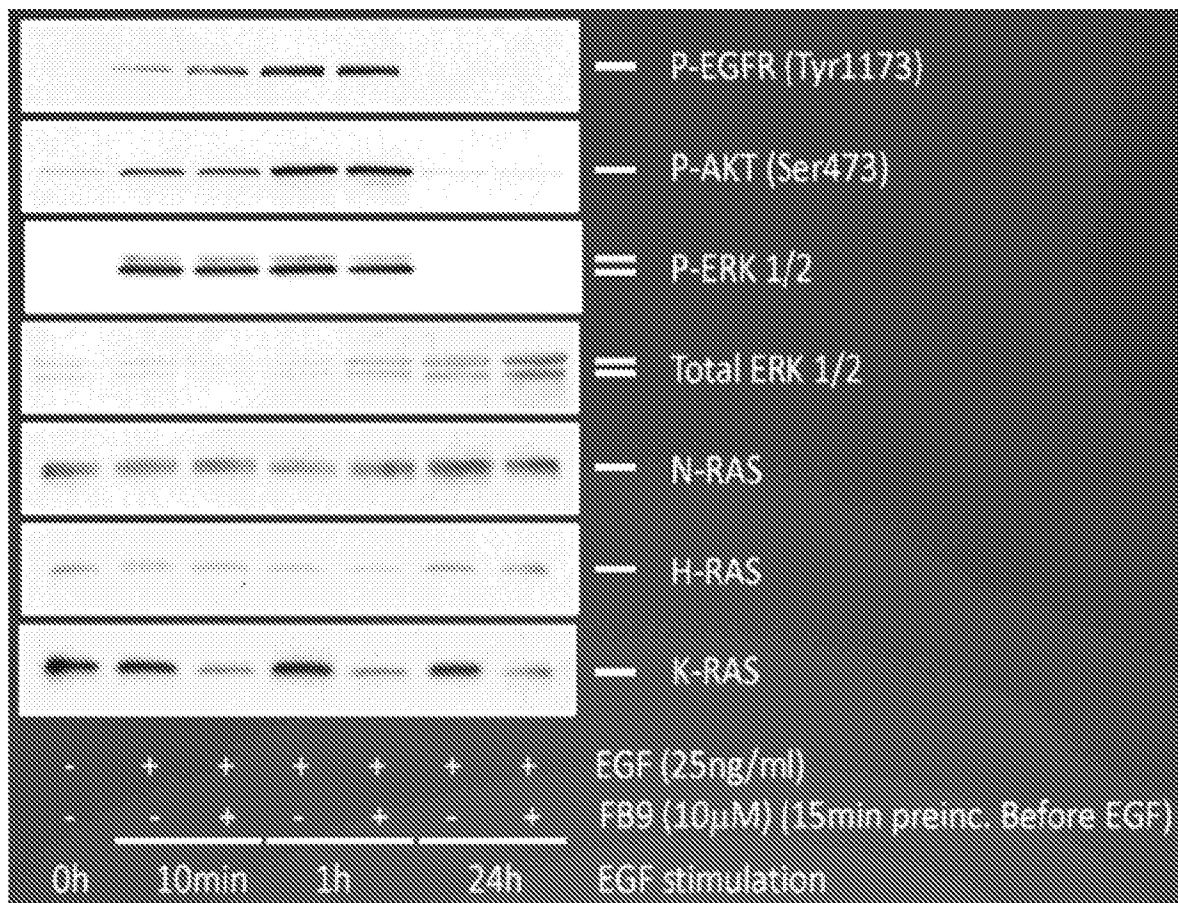


FIG. 22



30/47

FIG. 23

31/47

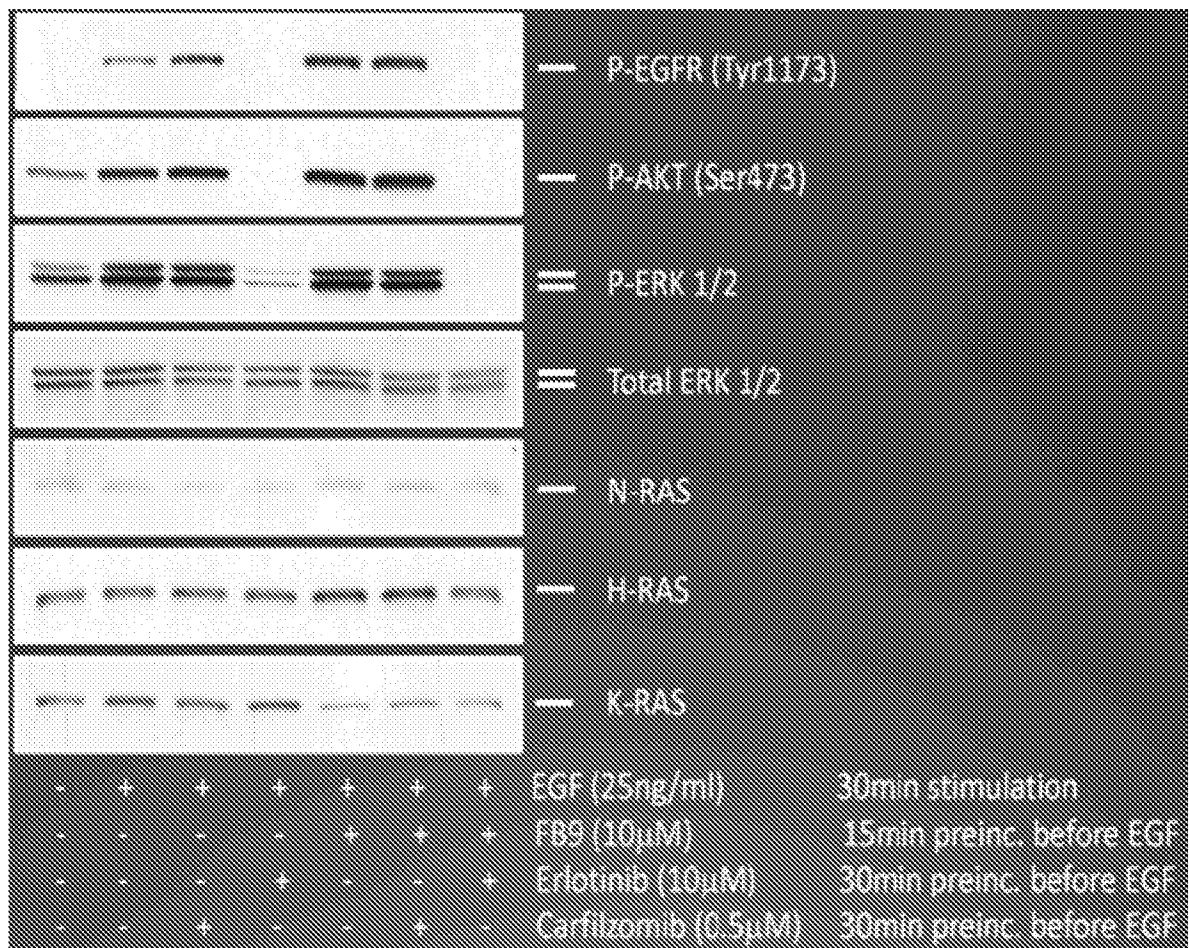
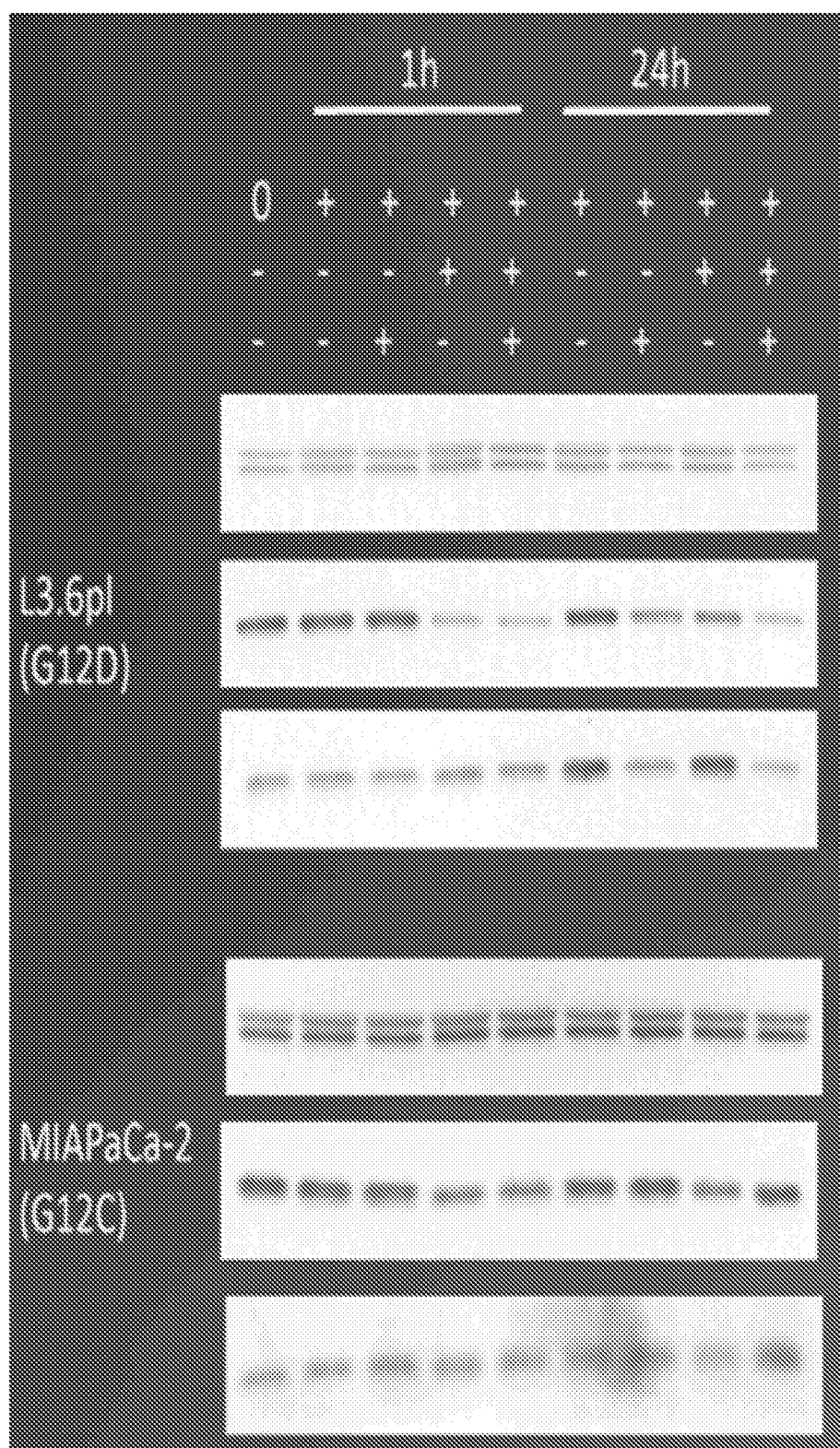
FIG. 24

FIG. 25A



33/47

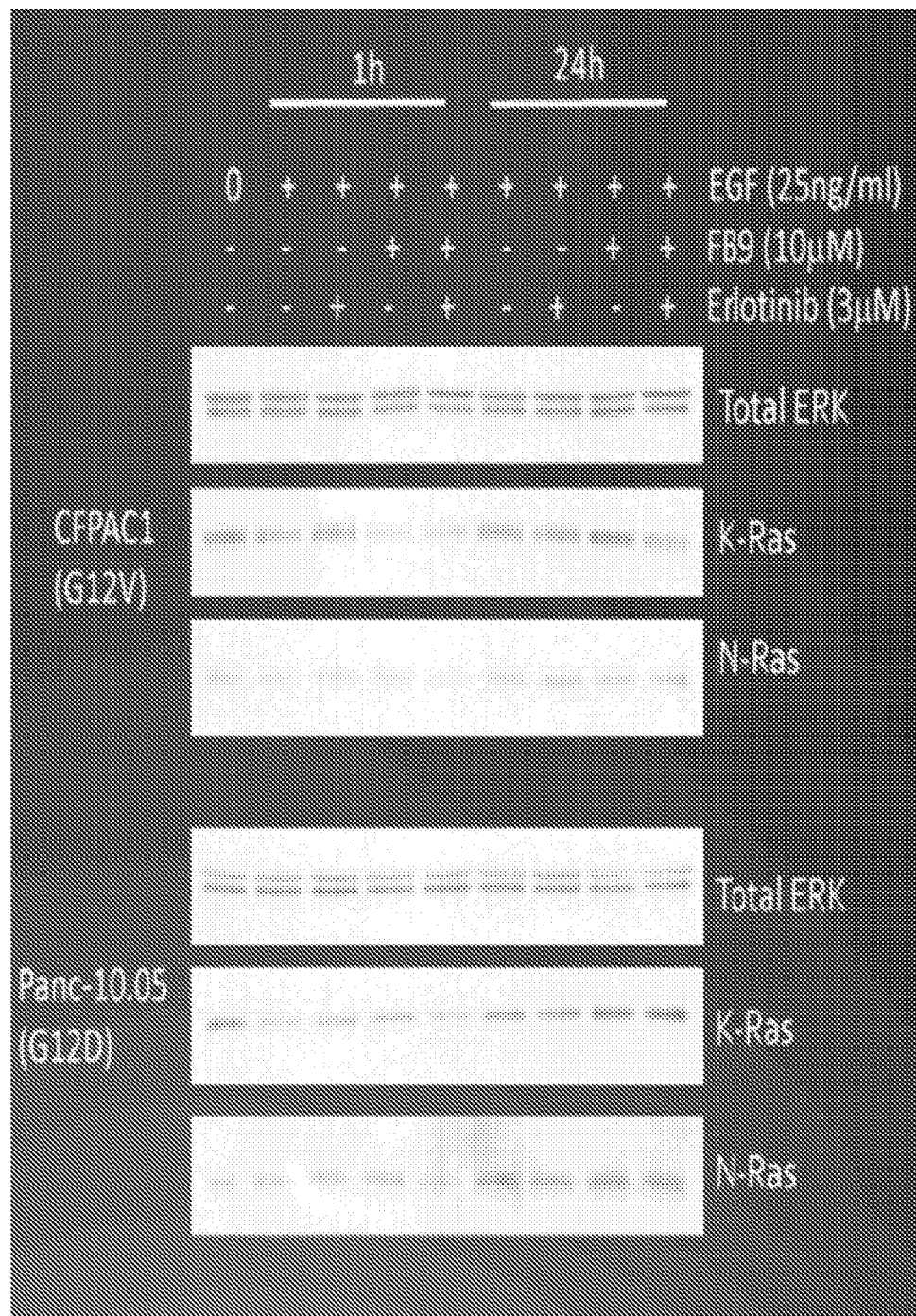
FIG. 25B

FIG. 28

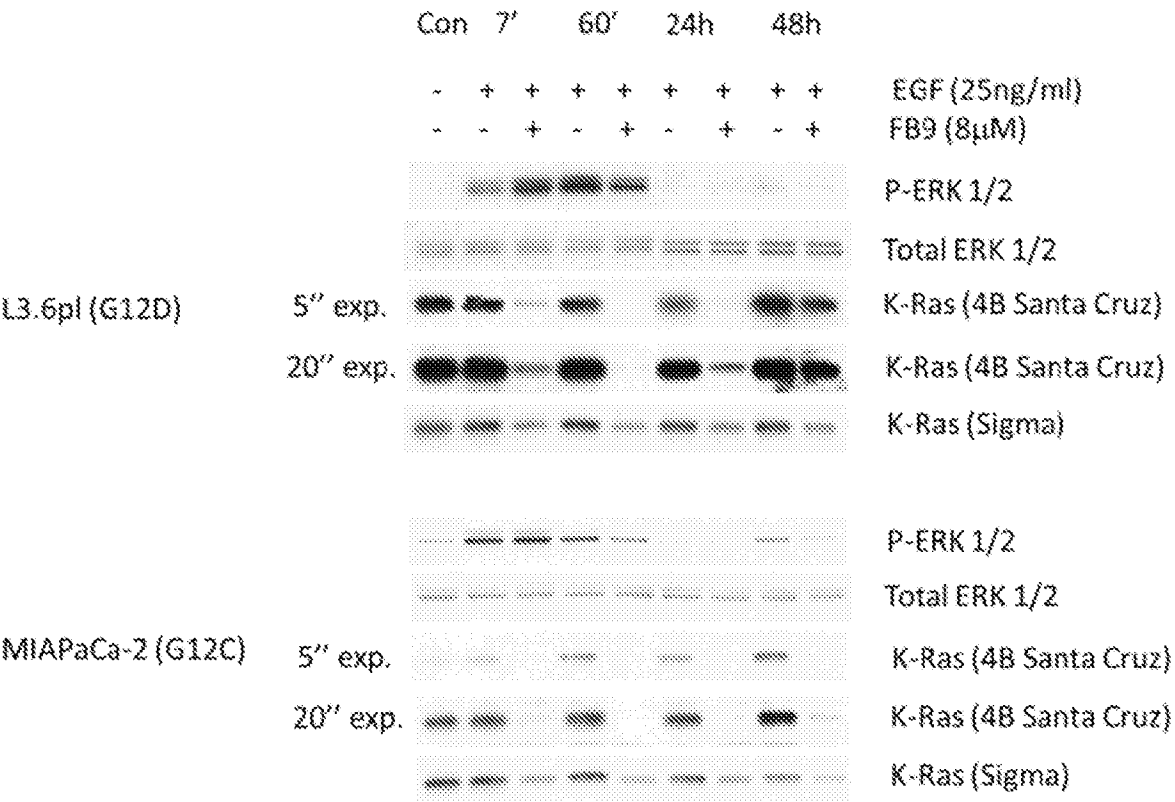
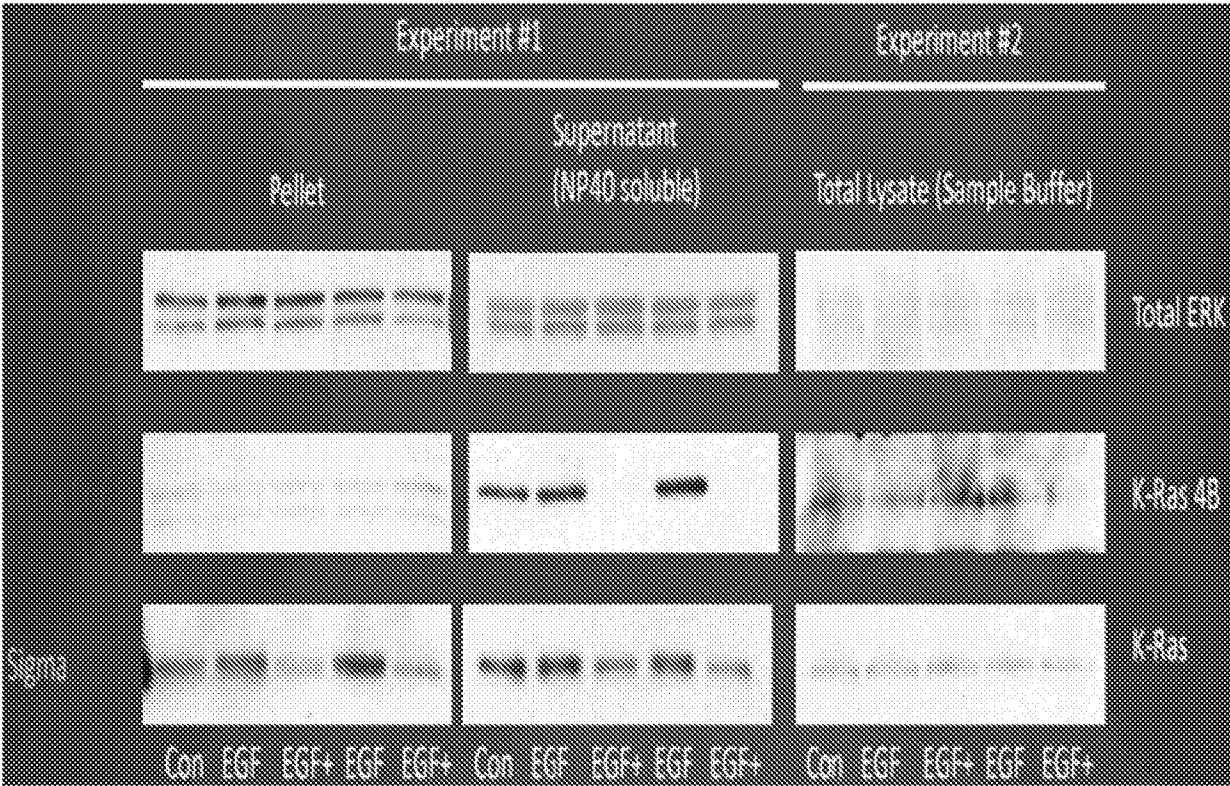
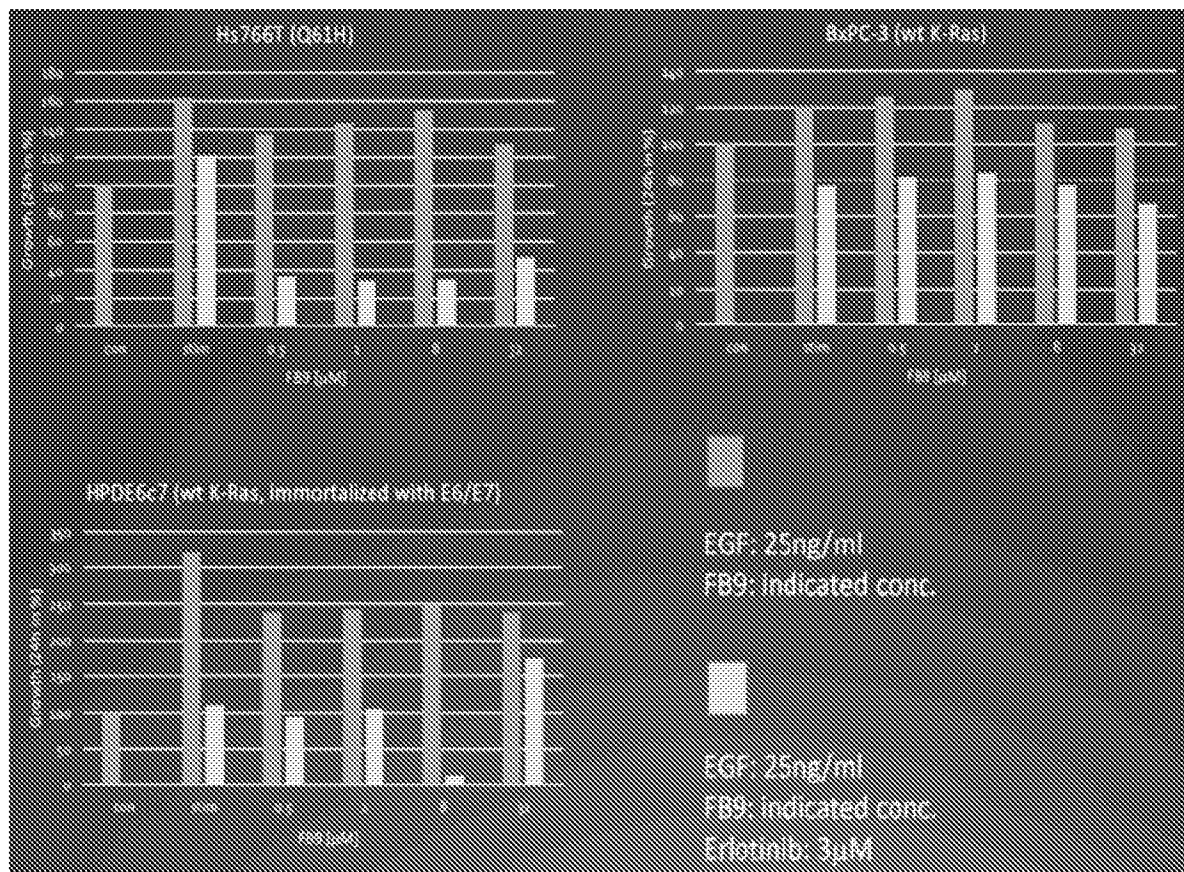


FIG. 29



37/47

FIG. 31



38/47

FIG. 32A

K-Ras 4B wild type C-terminus: Compound 3G4

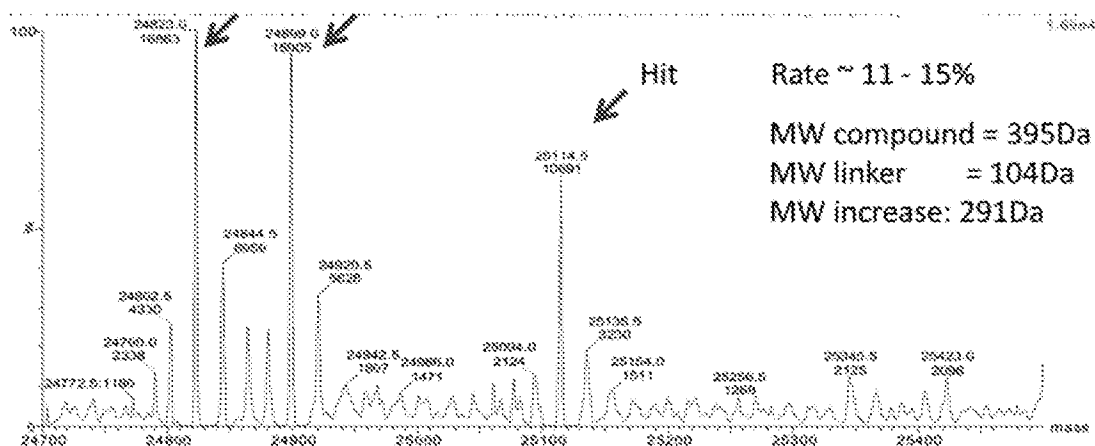


FIG. 32B

K-Ras 4B mutant C-terminus (C185S): Compound 3G4

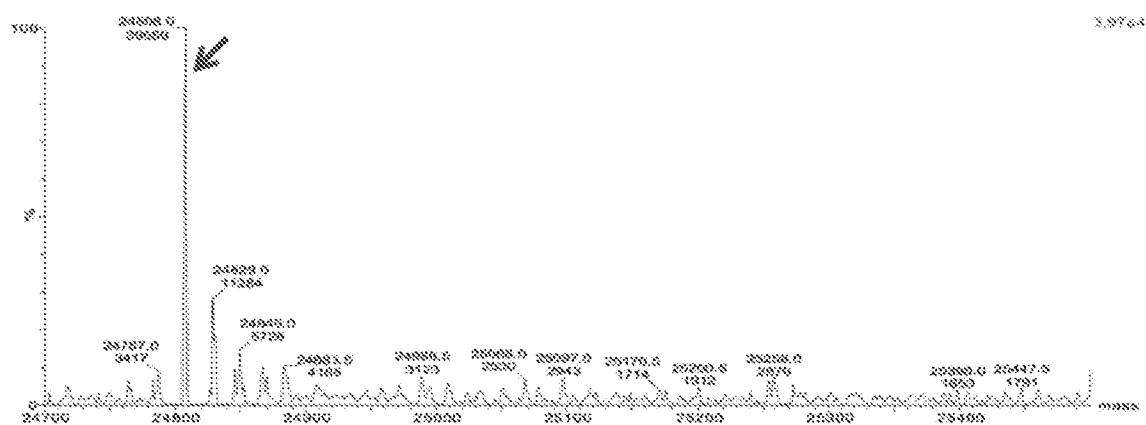


FIG. 33

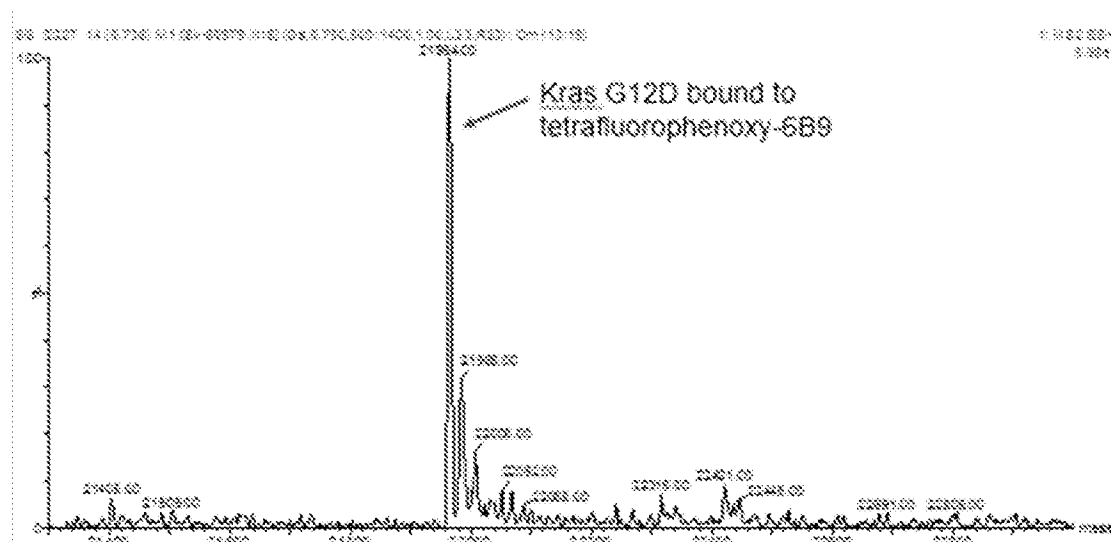


FIG. 34

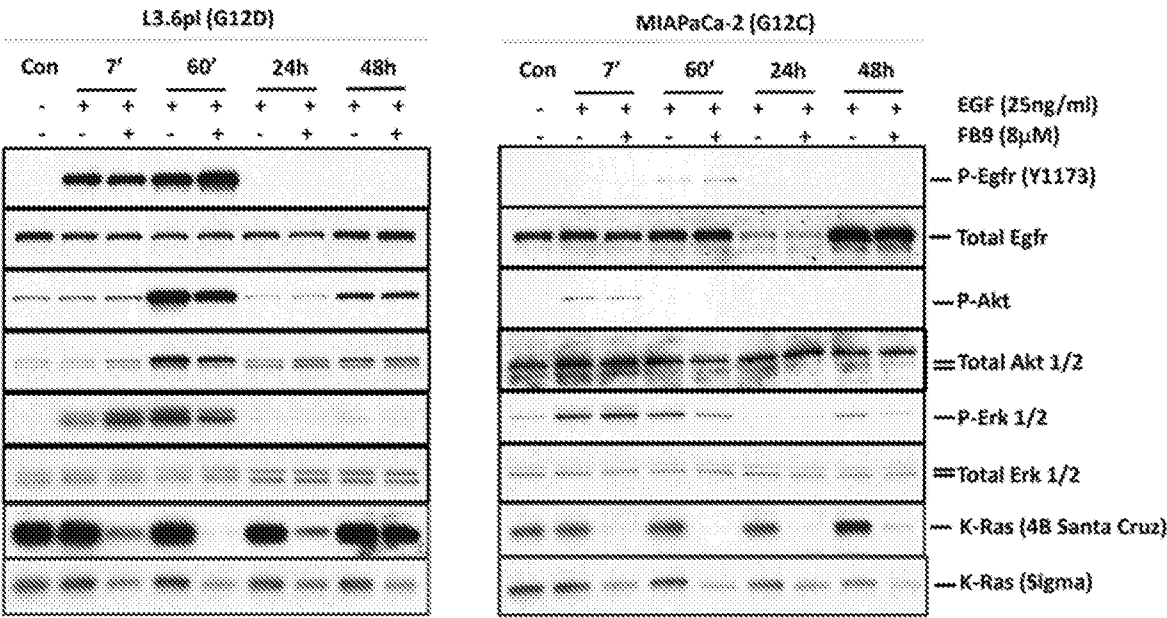


FIG. 35

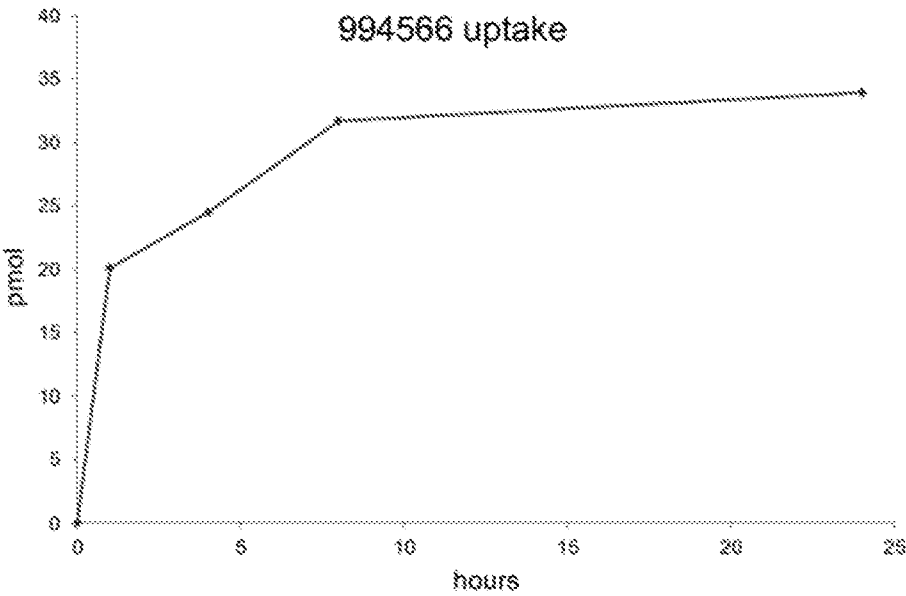


FIG. 36

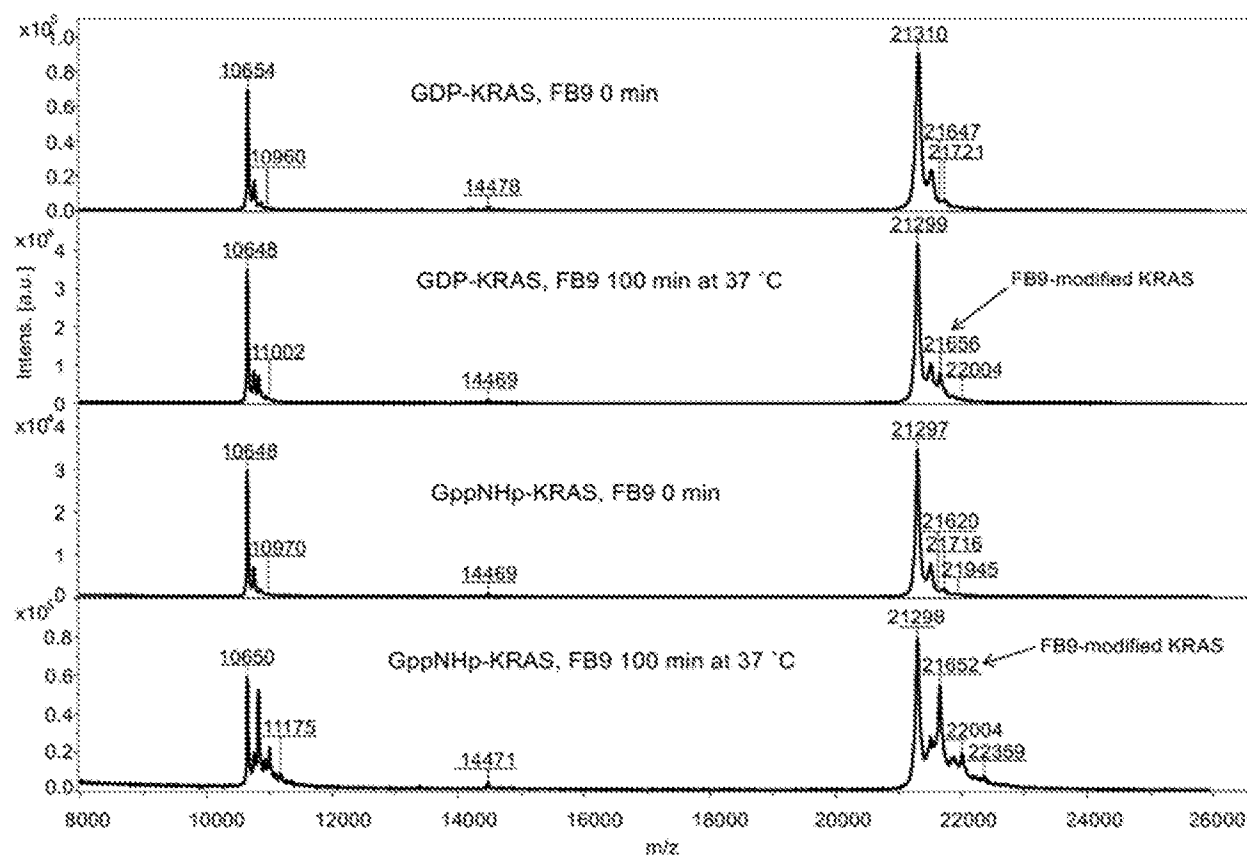
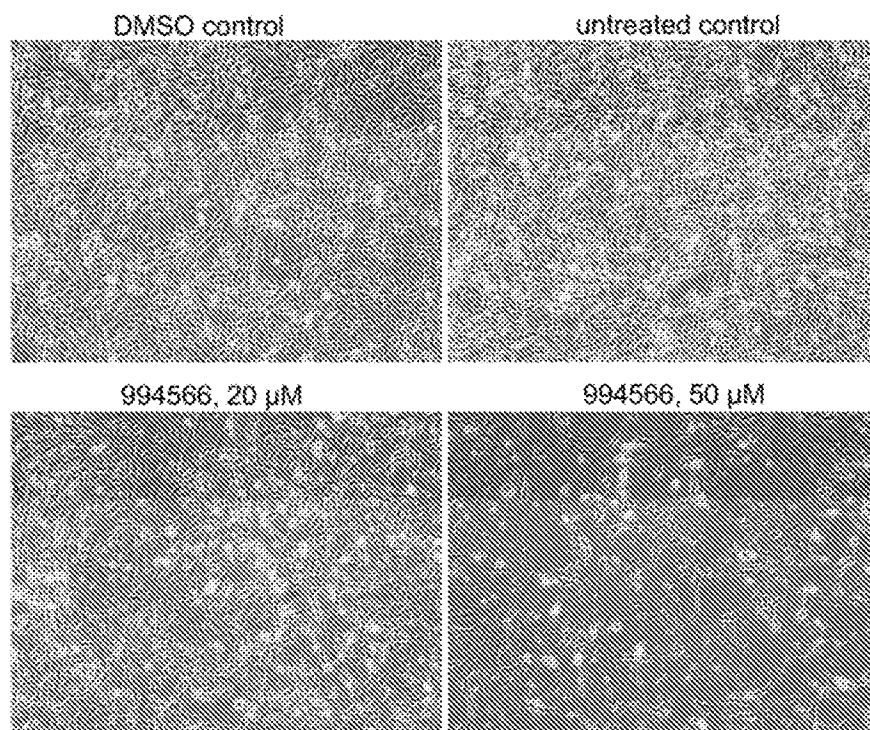
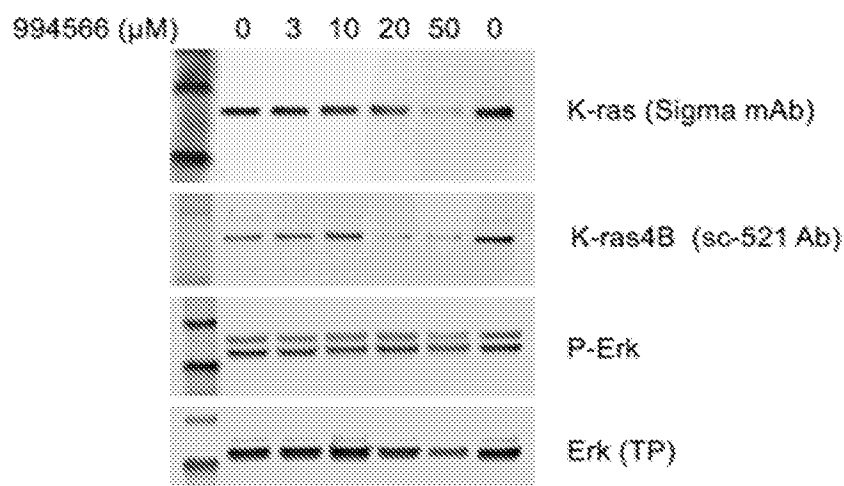
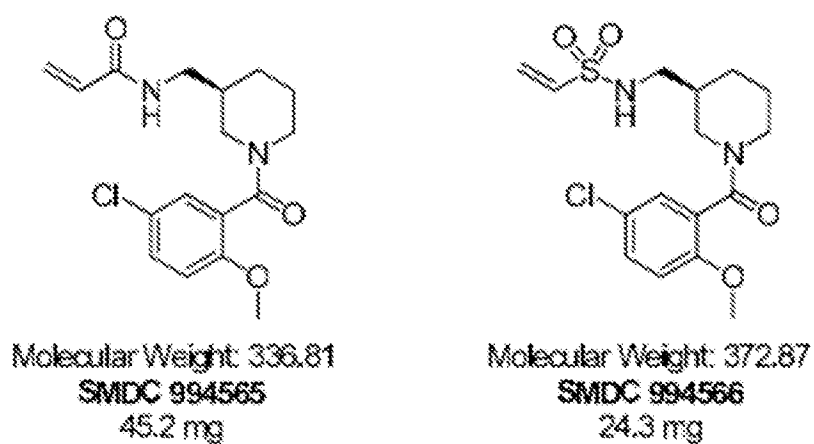
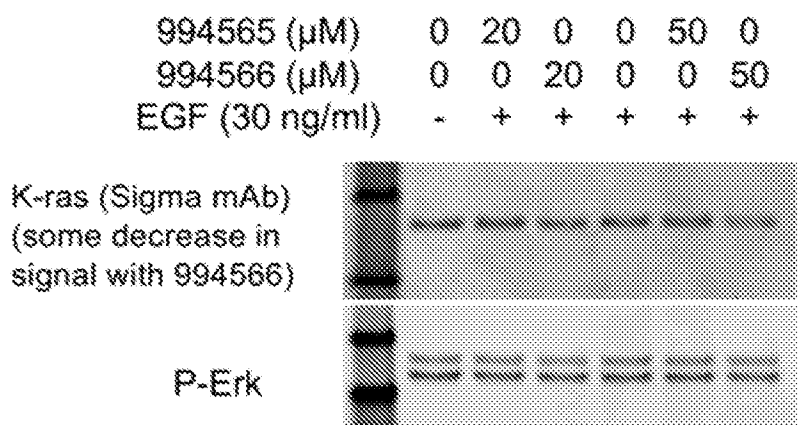


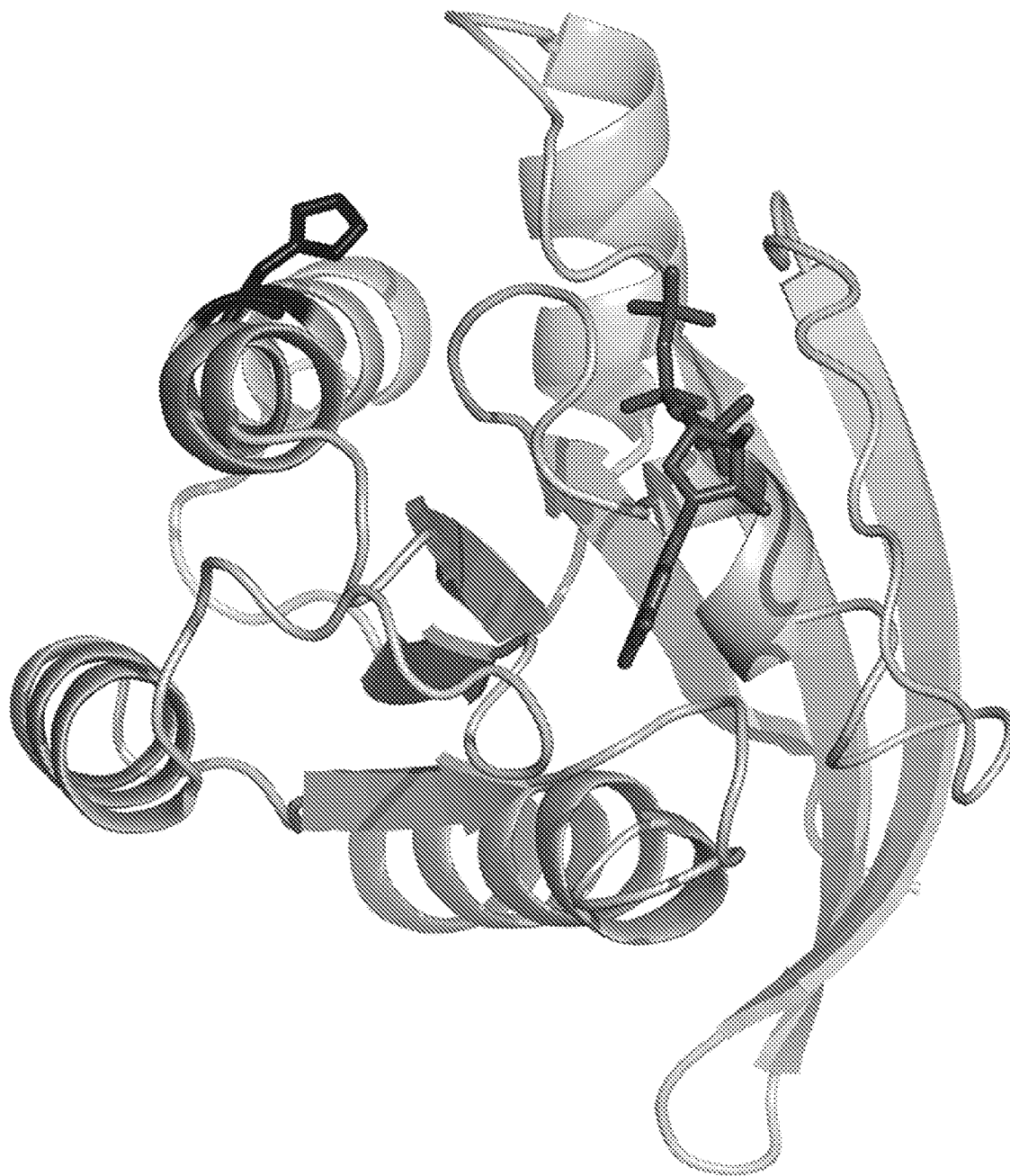
FIG. 37



41/47

FIG. 38A**FIG. 38B****FIG. 39**

42/47

FIG. 40

43/47

FIG. 41

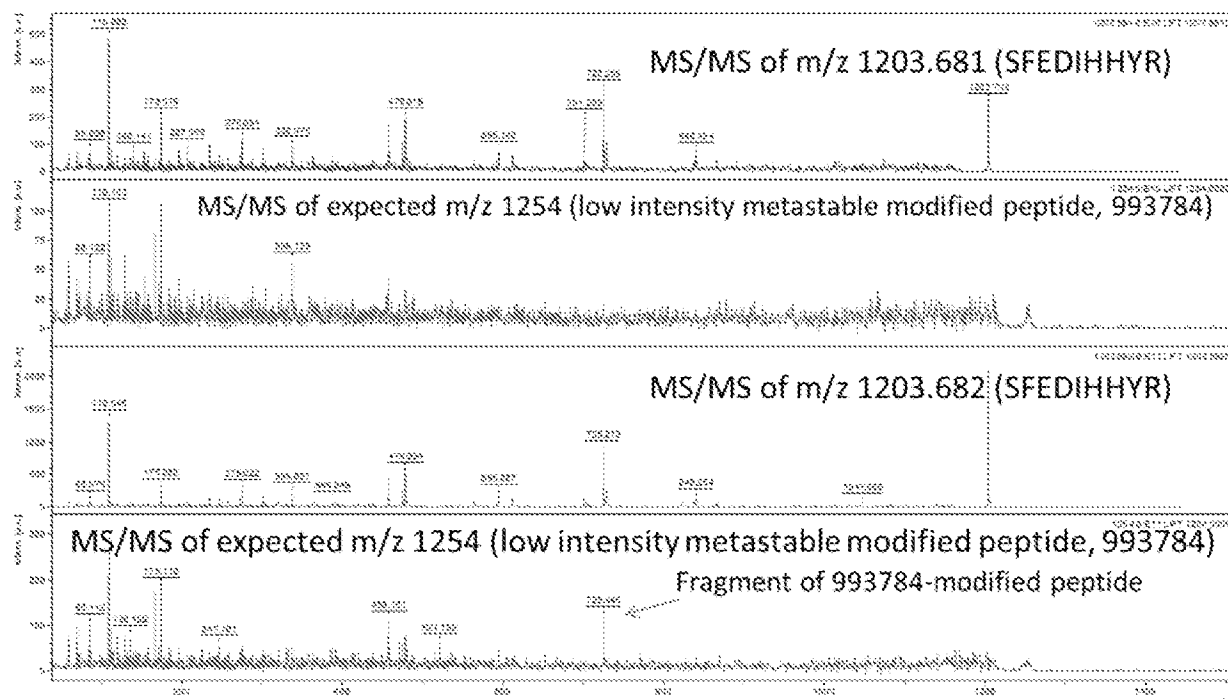


FIG. 42

Full-size KRAS (G-Hs.KRAS4b, 1-188); RPX150917.19; RP1150917140242
Average [M+H]⁺ 21482.5940

GMTEYKLVVVGAGGVGKSALTIQLIQNHVFDEYDPTIEDSYRKQVVIDGETCLLDILDITAGQEEYS
AMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDSQDVPMVLVGNKCDLPSRTVDTK
QAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEKMSKDGKKKKKSKTKCVIM

10	20	30	40	50	60
GMTEYKLVV	VVGAGGVGKS	ALTIQLIQNH	VFDEYDPTIE	DSYRKQVVID	GETCLLDILD
70	80	90	100	110	120
ITAGQEEYS	AMRDQYMRT	GEGFLCVFA	INNTKSFEDI	HHYREQIKRV	KDSQDVPMV
130	140	150	160	170	180
LPSRTVDTK	QAQDLARSY	GIPFIETSA	KTRQGVDDA	FYTLVREIR	KHKEKMSKD
					GKGGGGGSK
					TKTKCVIM

44/47

FIG. 43

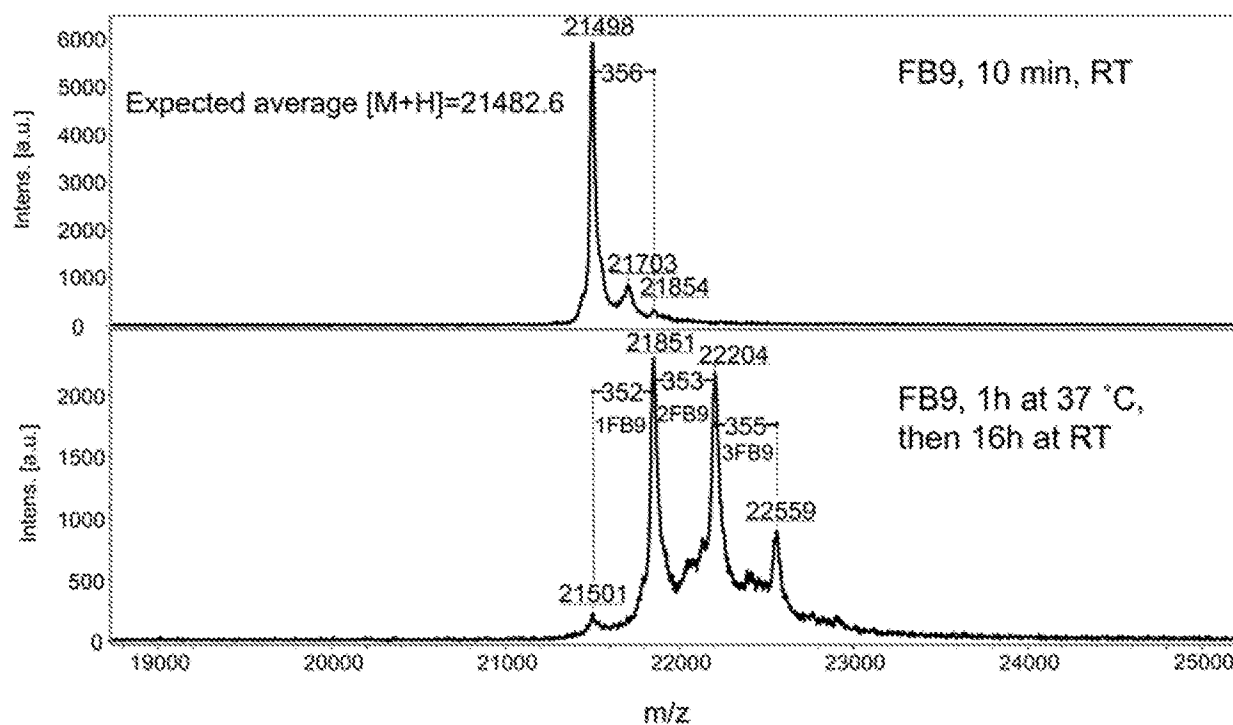
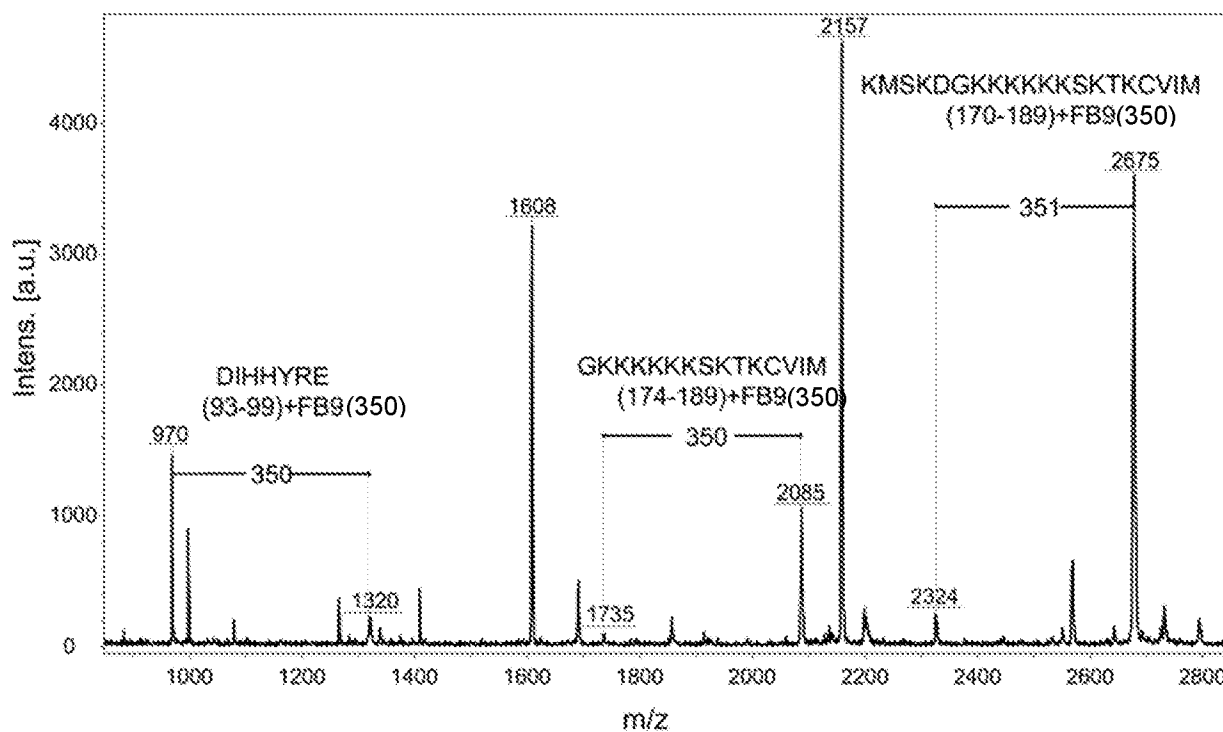


FIG. 44



45/47

FIG. 45A

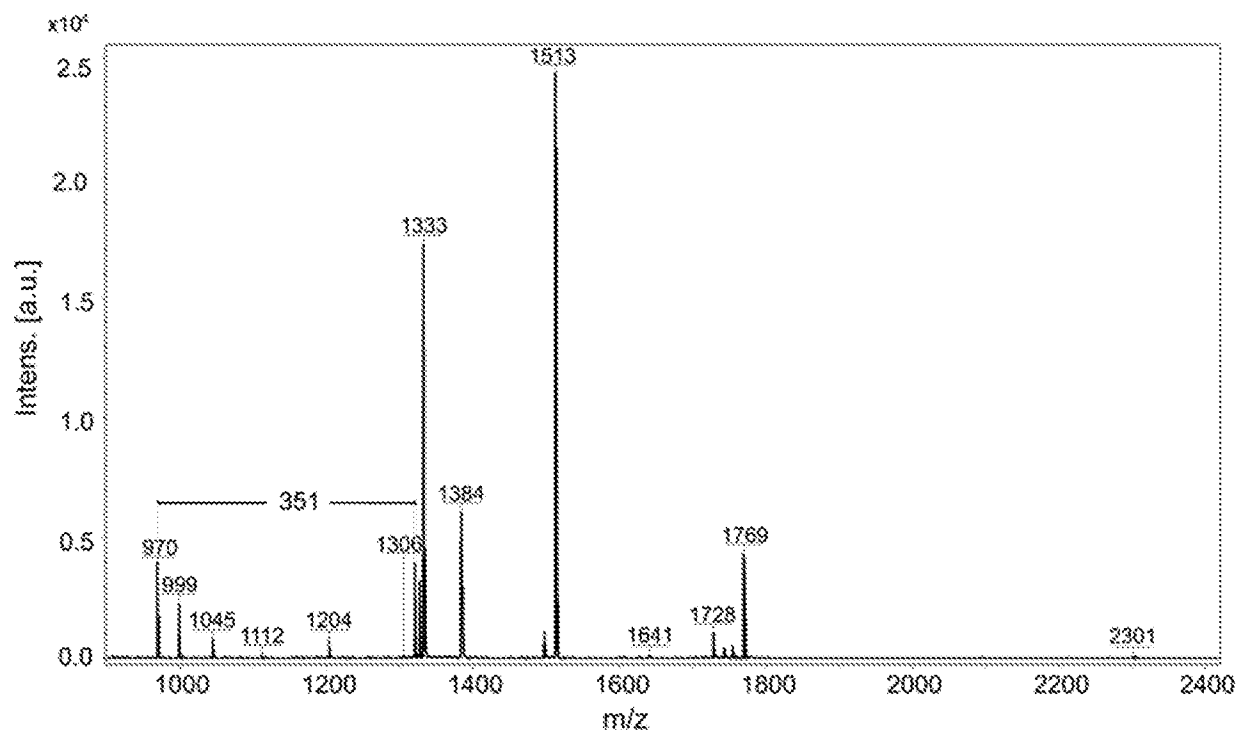
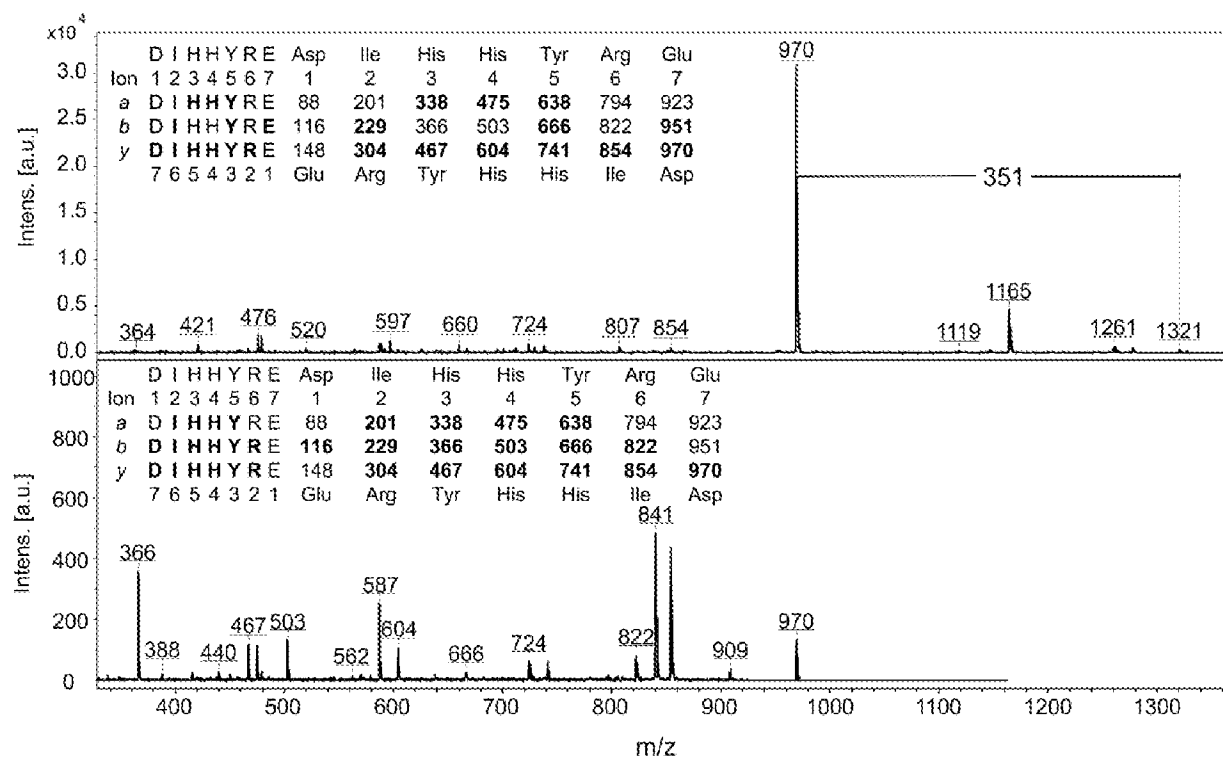


FIG. 45B

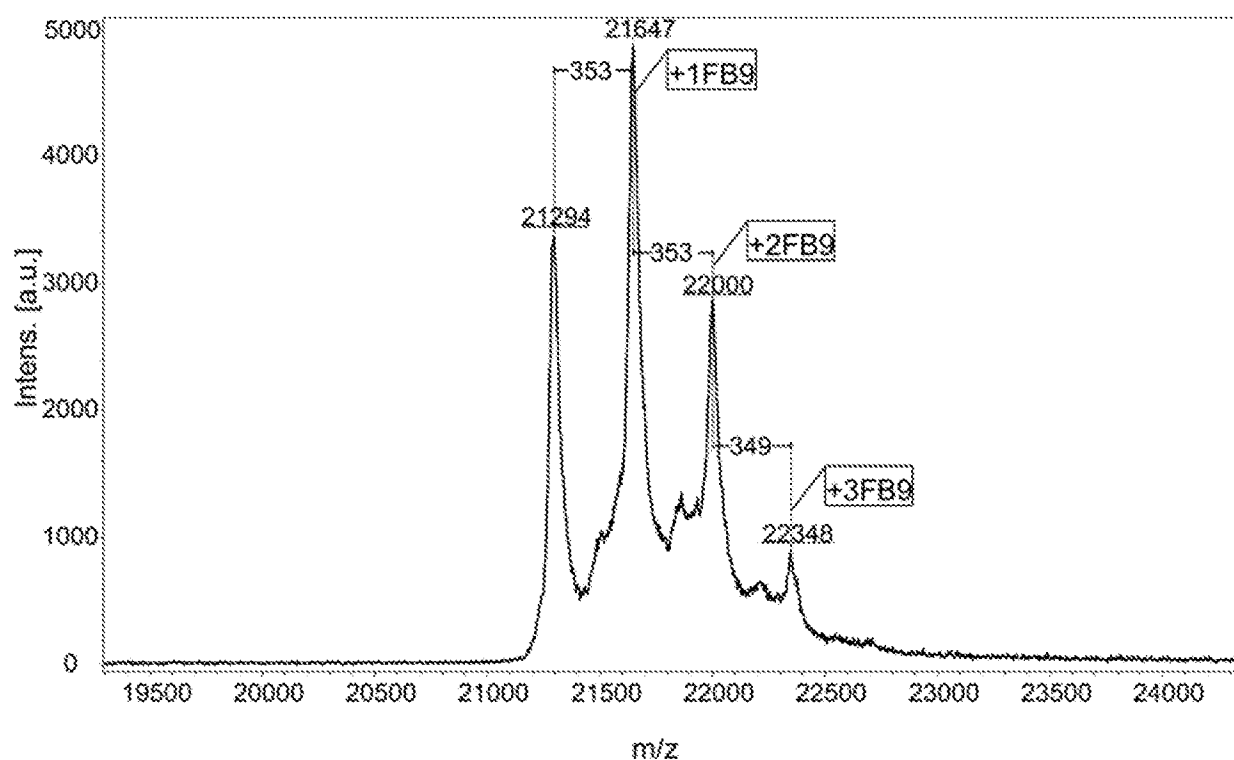


46/47

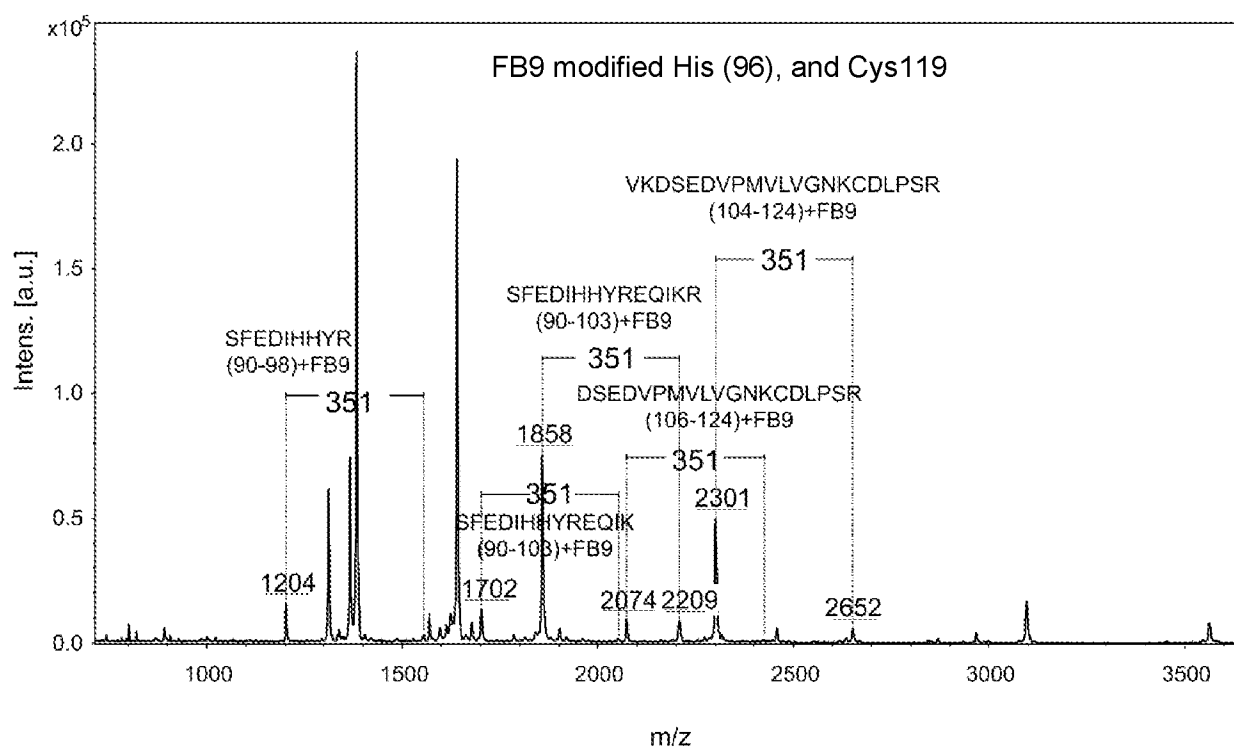
FIG. 46A

Farnesylated carboxymethylated KRAS4b GG-HsKRAS-4b,
RP1151105092454 Average [M+H]⁺ 21283.35

GGTEYKLVVVGAGGVGKSALTIQLIQNHVFVDEYDPTIEDSYRKQVVIDGET
CLLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIK
RVKDSIEDVPMVLVGNGKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQG
VDDAFYTLVREIRKHKEKMSKDGKKKKKKSKTKC-famMe

FIG. 46B

47/47

FIG. 47

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031344

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/44; A61K 31/445; A61K 31/451; A61K 31/4462 (2016.01)

CPC - A61K 31/44; A61K 31/445; C07D 213/75; C07D 401/12 (2016.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC - A61K 31/44; A61K 31/445; A61K 31/451; A61K 31/4462

CPC - A61K 31/44; A61K 31/445; C07D 213/75; C07D 401/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

IPC(8) - A61K 31/44; A61K 31/445; A61K 31/451; A61K 31/4462 (2016.01); CPC - A61K 31/44; A61K 31/445; C07D 213/75; C07D 401/12 (2016.05); USPC - 514/317; 546/194; 546/309 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, STN, PubChem, Google Patents, Google Scholar

Search terms used: benzamide cycloalkyl heterocycloalkyl cycloheteroalkyl electrophilic K Ras

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,475,109 A (SELNICK et al) 12 December 1995 (12.12.1995) entire document	1, 2, 5, 11, 14-18, 20, 21, 23, 25, 38 ----- 39, 41, 42
X	US 2007/0112000 A1 (BARTON et al) 17 May 2007 (17.05.2007) entire document	1, 3, 7, 8, 13
X	STRATMANN et al. Welwitindolinones, Unusual Alkaloids from the Blue-Green Algae Hapalosiphon welwitschii and Westiella intricata. Relationship to Fischerindoles and Hapalindoles. Journal of the American Chemical Society, 116(22), 9935-9942, 1994. supporting information. [retrieved on 11 July 2016]. Retrieved from the Internet. <http://pubs.acs.org/doi/suppl/10.1021/ja00101a015/suppl_file/ja00101a015_si_001.pdf> entire document	1, 4, 6
X	PUBCHEM, Substance Record for SID 110091647 Create Date: 2011-02-25. [retrieved on 08 July 2016]. retrieved from the internet: <https://pubchem.ncbi.nlm.nih.gov/substance/110091647>. entire document	1, 9
X	PUBCHEM, Substance Record for SID 74797094 Create Date: 2009-06-11. [retrieved on 08 July 2016]. retrieved from the internet: <https://pubchem.ncbi.nlm.nih.gov/substance/74797094>. entire document	1, 10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 July 2016

Date of mailing of the international search report

19 AUG 2016

Name and mailing address of the ISA/

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

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031344

Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
- a. ☒ forming part of the international application as filed:
- ☒ in the form of an Annex C/ST.25 text file.
- ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13*ter*. 1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
- ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*. 1(a)).
- ☐ on paper or in the form of an image file (Rule 13*ter*. 1(b) and Administrative Instructions, Section 713).
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/031344

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM, Substance Record for SID 223343680 Create Date: 2014-11-10. [retrieved on 08 July 2016]. retrieved from the internet: < https://pubchem.ncbi.nlm.nih.gov/substance/223343680 >. entire document	1, 12, 19
Y	US 2014/0288045 A1 (ARAXES PHARMA LLC) 25 September 2014 (25.09.2014) entire document	39, 41, 42
A	US 2015/087628 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 26 March 2015 (26.03.2015) entire document	1-53



(12)发明专利申请

(10)申请公布号 CN 107847495 A

(43)申请公布日 2018.03.27

(21)申请号 201680037365.9

D·特纳 S·吉森

(22)申请日 2016.05.06

A·E·玛西雅格 O·切尔托夫

(30)优先权数据

62/157,915 2015.05.06 US

62/158,356 2015.05.07 US

(74)专利代理机构 永新专利商标代理有限公司
72002

代理人 张晓威

(85)PCT国际申请进入国家阶段日

2017.12.25

(51)Int.Cl.

A61K 31/44(2006.01)

A61K 31/445(2006.01)

A61K 31/451(2006.01)

A61K 31/4462(2006.01)

(86)PCT国际申请的申请数据

PCT/US2016/031344 2016.05.06

(87)PCT国际申请的公布数据

W02016/179558 EN 2016.11.10

(71)申请人 加利福尼亚大学董事会

地址 美国加利福尼亚州

申请人 雷多思生物医学研究有限公司

权利要求书7页 说明书165页

序列表7页 附图48页

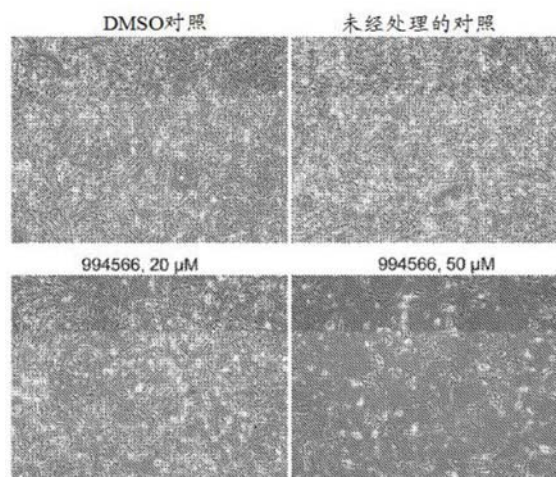
(72)发明人 F·麦考密克 A·R·伦斯洛

(54)发明名称

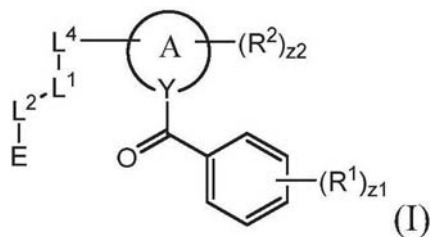
K-Ras调节剂

(57)摘要

本文尤其提供了用于抑制K-Ras和治疗癌症的方法和化合物。



1. 一种具有下式的化合物:



其中,

Y为N或CH

环A为C₃-C₇环烷基或3-7元杂环烷基;

R¹独立地为卤素、CX¹₃、-CHX¹₂、-CH₂X¹、-CN、-SO₂Cl、-SO_{n1}R¹⁰、-SO_{v1}NR⁷R⁸、-NHN⁷R⁸、-ONR⁷R⁸、-NHC(=O)NHN⁷R⁸、-NHC(=O)NR⁷R⁸、-N(O)_{m1}、-NR⁷R⁸、-C(O)R⁹、-C(O)-OR⁹、-C(O)NR⁷R⁸、-OR¹⁰、-NR⁷SO₂R¹⁰、-NR⁷C(O)R⁹、-NR⁷C(O)OR⁹、-NR⁷OR⁹、-OCX¹₃、-OCHX¹₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基;两个相邻的R¹取代基可任选地连接形成经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基;

L¹为键、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基;

L²为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7B}-、-NR^{7B}C(O)-、-C(O)NR^{7B}-、-SO₂NR^{7B}-、-NR^{7B}SO₂-、-OC(O)NR^{7B}-、-NR^{7B}C(O)O-、-CR^{9B}=NO-、-ON=CR^{9B}-、-NR^{8B}C(O)NR^{7B}-、-NR^{8B}C(=NR^{10B})NR^{7B}-、-NR^{8B}C(=NR^{10B})-、-C(=NR^{10B})NR^{7B}-、-OC(=NR^{10B})-、-C(=NR^{10B})O-、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基;

L⁴为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR⁴-、-NR⁴C(O)-、-C(O)NR⁴-、-SO₂NR⁴-、-NR⁴SO₂-、-NR⁴SO₂-、-OC(O)NR⁴-、-NR⁴C(O)O-、经取代或未取代的C₁-C₃亚烷基、经取代或未取代的2-3元杂亚烷基;

E为亲电子部分;

R²独立地为氧代、卤素、CX²₃、-CHX²₂、-CH₂X²、-CN、-SO₂Cl、-SO_{n2}R¹⁴、-SO_{v2}NR¹¹R¹²、-NHN¹¹R¹²、-ONR¹¹R¹²、-NHC(=O)NHN¹¹R¹²、-NHC(=O)NR¹¹R¹²、-N(O)_{m2}、-NR¹¹R¹²、-C(O)R¹⁴、-C(O)-OR¹⁴、-C(O)NR¹¹R¹²、-OR¹⁵、-NR¹¹SO₂R¹⁵、-NR¹¹C(O)R¹⁴、-NR¹¹C(O)OR¹⁴、-NR¹¹OR¹⁴、-OCX²₃、-OCHX²₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基;两个相邻的R²取代基或两个键合至相同原子的R²取代基可任选地连接形成经取代或未取代的环烷基或经取代或未取代的杂环烷基;

R⁴独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基;

R⁷、R⁸、R⁹、R¹⁰、R^{7B}、R^{8B}、R^{9B}、R^{10B}、R¹¹、R¹²、R¹⁴和R¹⁵独立地为氢、卤素、-CX₃、-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、-OCX₃、-OCHX₂、-CHX₂、-CH₂X、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的R⁷和R⁸取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的R¹¹和R¹²取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；

每个X、X¹和X²独立地为-F、-Cl、-Br或-I；

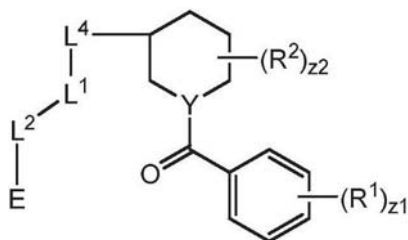
n₁、n₂、v₁和v₂独立地为0至4的整数；

m₁和m₂独立地为1至2的整数；

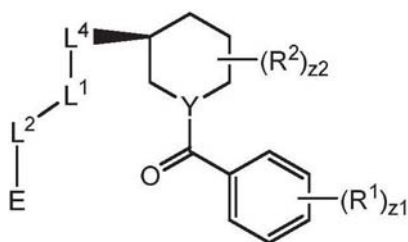
z₁独立地为0至5的整数；且

z₂独立地为0至10的整数。

2. 根据权利要求1所述的化合物，其具有下式：



3. 根据权利要求1所述的化合物，其具有下式：



4. 根据权利要求1所述的化合物，其中Y为CH。

5. 根据权利要求1所述的化合物，其中Y为N。

6. 根据权利要求1所述的化合物，其中R¹独立地为卤素、-CX¹₃、-CHX¹₂、-CH₂X¹、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC(O)NHNH₂、-NHC(O)NH₂、-NHSO₂H、-NHC(O)H、-NHC(O)OH、-NHOH、-OCX¹₃、-OCHX¹₂、经取代或未取代的C₁-C₆烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。

7. 根据权利要求1所述的化合物，其中R¹独立地为卤素、-CX¹₃、-CHX¹₂、-CH₂X¹、-OH、-SH、-COOH、-OCX¹₃、-OCHX¹₂、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。

8. 根据权利要求1所述的化合物，其中R¹独立地为卤素或-OCH₃。

9. 根据权利要求1所述的化合物，其中z₁为2。

10. 根据权利要求1所述的化合物，其中z₁为3。

11. 根据权利要求1所述的化合物，其中R²独立地为氧代、卤素、CX²₃、-CHX²₂、-CH₂X²、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC(O)

NHNH₂、-NHC(O)NH₂、-NHSO₂H、-NHC(O)H、-NHC(O)OH、-NHOH、-OCX₂³、-OCHX₂²、经取代或未取代的C₁-C₆烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。

12. 根据权利要求1所述的化合物,其中R²独立地为氧代、卤素、-CX₂³、-CHX₂²、-CH₂X²、-OH、-SH、-OCX₂³、-OCHX₂²、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。

13. 根据权利要求1所述的化合物,其中z₂为0。

14. 根据权利要求1所述的化合物,其中L¹为键、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。

15. 根据权利要求1所述的化合物,其中L¹为键、未取代的C₁-C₄亚烷基或未取代的2-4元杂亚烷基。

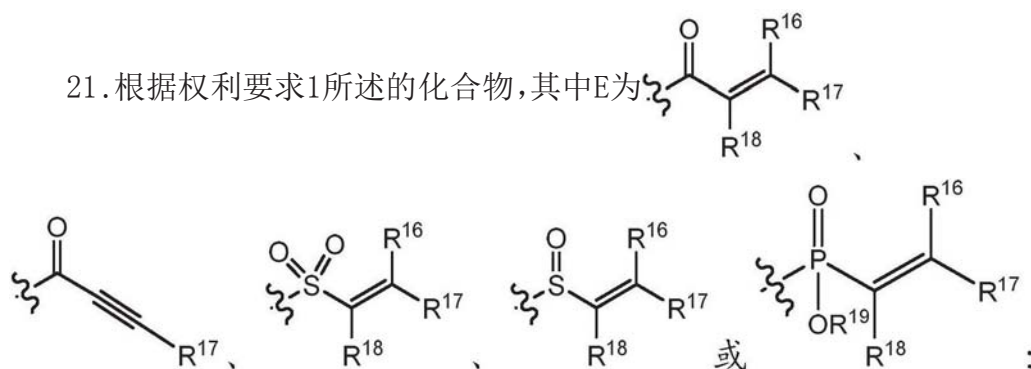
16. 根据权利要求1所述的化合物,其中L¹为键。

17. 根据权利要求1所述的化合物,其中L²为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHC(O)-、-C(O)NH-、-SO₂NH-、-NHSO₂-、-OC(O)NH-、-NHC(O)O-、-NHC(O)NH-、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。

18. 根据权利要求1所述的化合物,其中L²为键、-O-、-C(O)-、-S-、-NH-、-NHC(O)-、-C(O)NH-、未取代的C₁-C₄亚烷基或未取代的2-4元杂亚烷基。

19. 根据权利要求1所述的化合物,其中L²为-NH-。

20. 根据权利要求1所述的化合物,其中L²为键。



其中R¹⁶独立地为氢、卤素、CX₃¹⁶、-CHX₂¹⁶、-CH₂X¹⁶、-CN、-SO_{n16}R^{16D}、-SO_{v16}NR^{16A}R^{16B}、-NHNH^{16A}R^{16B}、-ONR^{16A}R^{16B}、-NHC(O)NHNH^{16A}R^{16B}、-NHC(O)NR^{16A}R^{16B}、-N(O)_{m16}、-NR^{16A}R^{16B}、-C(O)R^{16C}、-C(O)-OR^{16C}、-C(O)NR^{16A}R^{16B}、-OR^{16D}、-NR^{16A}SO₂R^{16D}、-NR^{16A}C(O)R^{16C}、-NR^{16A}C(O)OR^{16C}、-NR^{16A}OR^{16C}、-OCX₃¹⁶、-OCHX₂¹⁶、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；

R¹⁷独立地为氢、卤素、CX₃¹⁷、-CHX₂¹⁷、-CH₂X¹⁷、-CN、-SO_{n17}R^{17D}、-SO_{v17}NR^{17A}R^{17B}、-NHNH^{17A}R^{17B}、-ONR^{17A}R^{17B}、-NHC(O)NHNH^{17A}R^{17B}、-NHC(O)NR^{17A}R^{17B}、-N(O)_{m17}、-NR^{17A}R^{17B}、-C(O)R^{17C}、-C(O)-OR^{17C}、-C(O)NR^{17A}R^{17B}、-OR^{17D}、-NR^{17A}SO₂R^{17D}、-NR^{17A}C(O)R^{17C}、-NR^{17A}C(O)OR^{17C}、-NR^{17A}OR^{17C}、-OCX₃¹⁷、-OCHX₂¹⁷、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；

R¹⁸独立地为氢、卤素、CX₃¹⁸、-CHX₂¹⁸、-CH₂X¹⁸、-CN、-SO_{n18}R^{18D}、-SO_{v18}NR^{18A}R^{18B}、-

$\text{NHNr}^{18\text{A}}\text{R}^{18\text{B}}$ 、 $-\text{ONr}^{18\text{A}}\text{R}^{18\text{B}}$ 、 $-\text{NHC} = (\text{O})\text{NHNr}^{18\text{A}}\text{R}^{18\text{B}}$ 、 $-\text{NHC}(\text{O})\text{Nr}^{18\text{A}}\text{R}^{18\text{B}}$ 、 $-\text{N}(\text{O})_{\text{m}18}$ 、 $-\text{Nr}^{18\text{A}}\text{R}^{18\text{B}}$ 、 $-\text{C}(\text{O})\text{R}^{18\text{C}}$ 、 $-\text{C}(\text{O})-\text{OR}^{18\text{C}}$ 、 $-\text{C}(\text{O})\text{Nr}^{18\text{A}}\text{R}^{18\text{B}}$ 、 $-\text{OR}^{18\text{D}}$ 、 $-\text{Nr}^{18\text{A}}\text{SO}_2\text{R}^{18\text{D}}$ 、 $-\text{Nr}^{18\text{A}}\text{C}(\text{O})\text{R}^{18\text{C}}$ 、 $-\text{Nr}^{18\text{A}}\text{C}(\text{O})\text{OR}^{18\text{C}}$ 、 $-\text{Nr}^{18\text{A}}\text{OR}^{18\text{C}}$ 、 $-\text{OCX}^{18}_3$ 、 $-\text{OCHX}^{18}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；

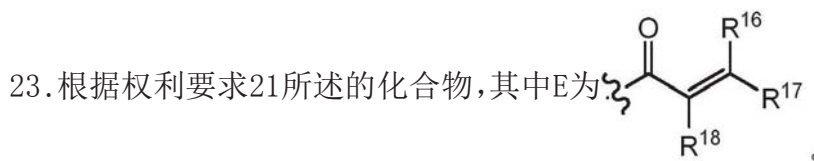
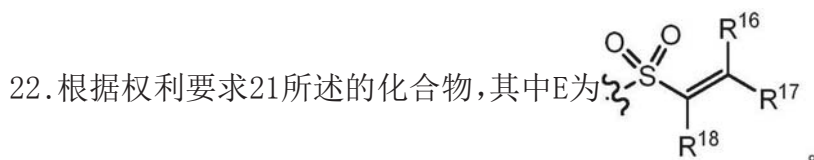
R^{19} 独立地为氢、卤素、 CX^{19}_3 、 $-CHX^{19}_2$ 、 $-CH_2X^{19}$ 、 $-CN$ 、 $-SO_{n19}R^{19D}$ 、 $-SO_{v19}NR^{19A}R^{19B}$ 、 $-NHNR^{19A}R^{19B}$ 、 $-ONR^{19A}R^{19B}$ 、 $-NHC=$ (O) $NHNR^{19A}R^{19B}$ 、 $-NHC$ (O) $NR^{19A}R^{19B}$ 、 $-N$ (O) $m19$ 、 $-NR^{19A}R^{19B}$ 、 $-C$ (O) R^{19C} 、 $-C$ (O) $-OR^{19C}$ 、 $-C$ (O) $NR^{19A}R^{19B}$ 、 $-OR^{19D}$ 、 $-NR^{19A}SO_2R^{19D}$ 、 $-NR^{19A}C$ (O) R^{19C} 、 $-NR^{19A}C$ (O) OR^{19C} 、 $-NR^{19A}OR^{19C}$ 、 $-OCX^{19}_3$ 、 $-OCHX^{19}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；

R^{16A} 、 R^{16B} 、 R^{16C} 、 R^{16D} 、 R^{17A} 、 R^{17B} 、 R^{17C} 、 R^{17D} 、 R^{18A} 、 R^{18B} 、 R^{18C} 、 R^{18D} 、 R^{19A} 、 R^{19B} 、 R^{19C} 、 R^{19D} 独立地为氢、卤素、 $-CX_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX_3$ 、 $-OCHX_2$ 、 $-CHX_2$ 、 $-CH_2X$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{16A} 和 R^{16B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{17A} 和 R^{17B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{18A} 和 R^{18B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{19A} 和 R^{19B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；

每个X、X¹⁶、X¹⁷、X¹⁸和X¹⁹独立地为-F、-Cl、-Br或-I；

$n_{16}, n_{17}, n_{18}, n_{19}, v_{16}, v_{17}, v_{18}$ 和 v_{19} 独立地为 0 至 4 的整数; 且

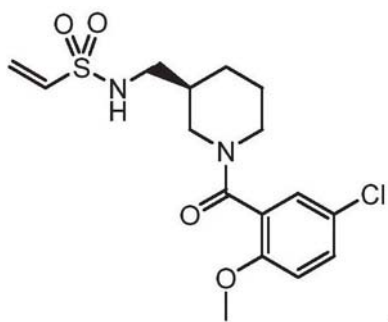
m16、m17、m18和m19独立地为1至2的整数。



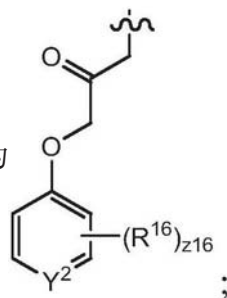
24. 根据权利要求21所述的化合物, 其中 R^{16} 、 R^{17} 和 R^{18} 独立地为氢、 $-CH_2NH_2$ 、 $-CH_2CH_2NH_2$ 、 $-CH_2N(CH_3)_2$ 或 $-CH_2CH_2N(CH_3)_2$ 。

25. 根据权利要求21所述的化合物, 其中 L^4 为键或 $-CH_2-$ 。

26. 根据权利要求21所述的化合物,其具有下式:



27. 根据权利要求1所述的化合物, 其中E为



其中 R^{16} 独立地为卤素、 CX^{16}_3 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_3H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基;

Y^2 为N或CH;

z_{16} 为0至4的整数; 且

每个 X^{16} 独立地为-F、-Cl、-Br或-I。

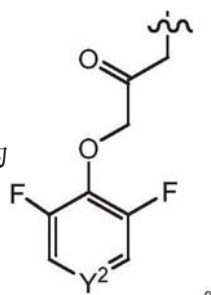
28. 根据权利要求27所述的化合物, 其中 R^{16} 独立地为卤素。

29. 根据权利要求27所述的化合物, 其中 R^{16} 独立地为-F。

30. 根据权利要求27所述的化合物, 其中 z_{16} 为4。

31. 根据权利要求27所述的化合物, 其中 z_{16} 为2。

32. 根据权利要求31所述的化合物, 其中E为



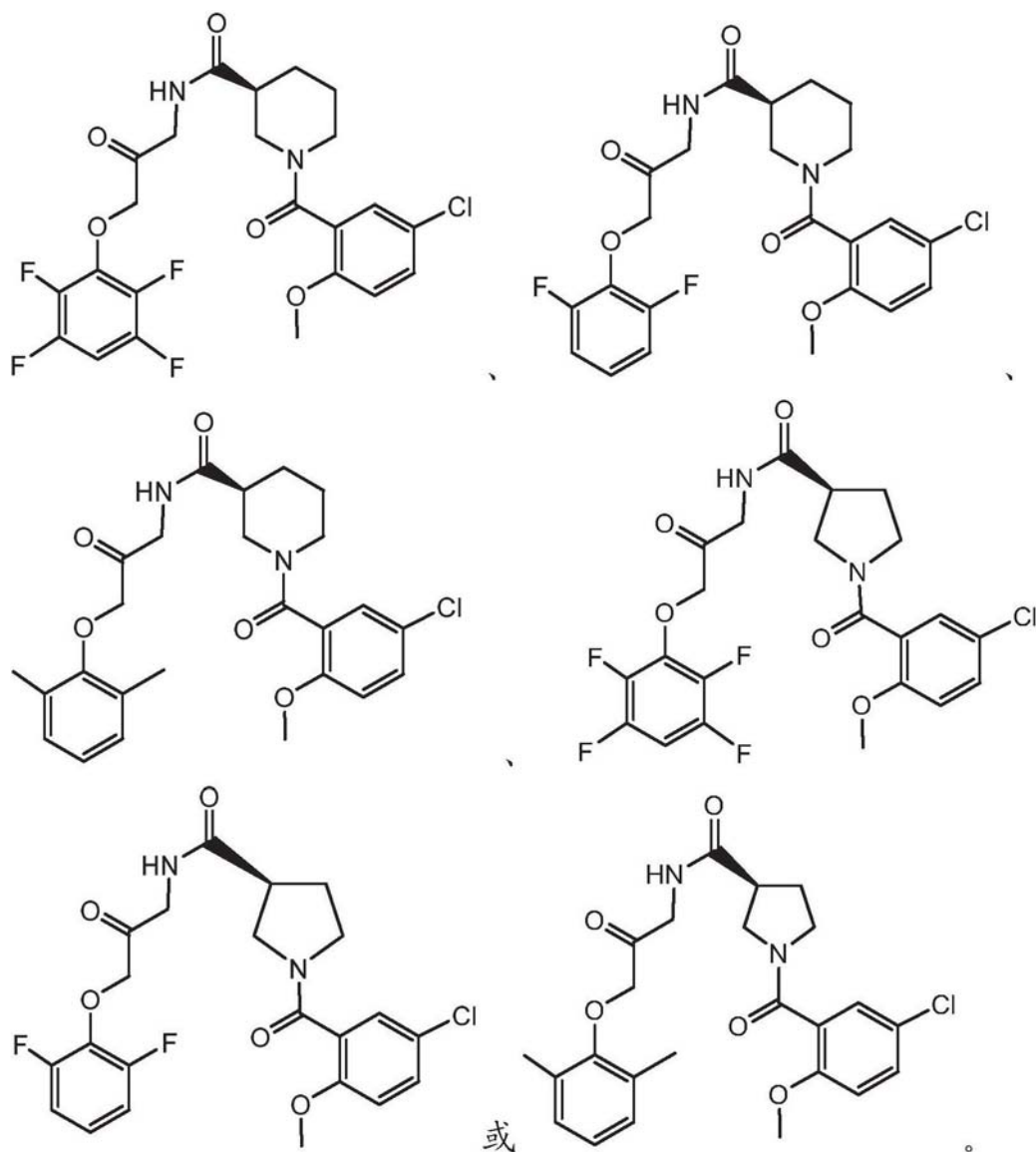
33. 根据权利要求27所述的化合物, 其中 Y^2 为CH。

34. 根据权利要求27所述的化合物, 其中 Y^2 为N。

35. 根据权利要求27所述的化合物, 其中 L^4 为 $-N(R^4)C(O)-$ 。

36. 根据权利要求27所述的化合物, 其中 R^4 为氢。

37. 根据权利要求27所述的化合物, 其具有下式:



38. 一种药物组合物,其包含根据权利要求1-37中任一项所述的化合物和药学上可接受的赋形剂。

39. 一种降低K-Ras蛋白的活性水平的方法,所述方法包括使所述K-Ras蛋白与根据权利要求1-37中的一项所述的化合物接触。

40. 一种降低K-Ras-4B蛋白的活性水平的方法,所述方法包括使所述K-Ras-4B蛋白与根据权利要求1-37中的一项所述的化合物接触。

41. 一种治疗癌症的方法,所述方法包括向有需要的受试者施用治疗有效量的根据权利要求1-37中的一项所述的化合物。

42. 根据权利要求41所述的方法,其中所述癌症为胰腺癌、肺癌或结直肠癌。

43. 一种K-Ras蛋白,其与根据权利要求1-37中的一项所述的化合物共价键合。

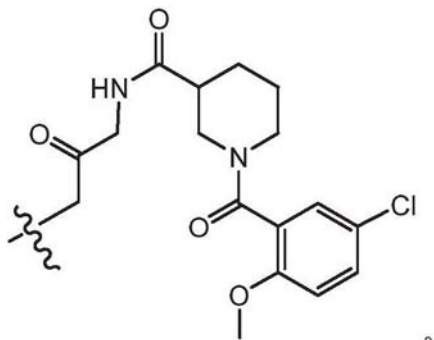
44. 根据权利要求43所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基共价键合。

45. 根据权利要求43所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基不可逆地共价键合。

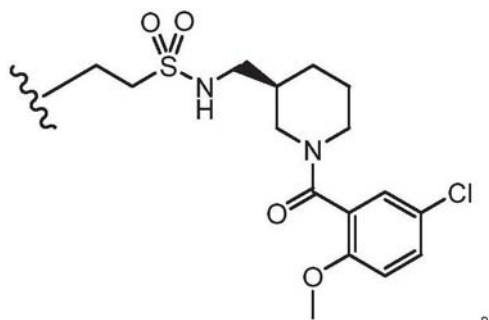
46. 根据权利要求43所述的K-Ras蛋白, 其中所述化合物与所述蛋白的组氨酸残基共价键合。

47. 根据权利要求43所述的K-Ras蛋白, 其中所述化合物与所述蛋白的组氨酸残基不可逆地共价键合。

48. 一种K-Ras蛋白, 其与具有下式的化合物共价键合:



49. 一种K-Ras蛋白, 其与具有下式的化合物共价键合:



50. 根据权利要求48-49中任一项所述的K-Ras蛋白, 其中所述化合物与所述蛋白的半胱氨酸残基共价键合。

51. 根据权利要求48所述的K-Ras蛋白, 其中所述化合物与所述蛋白对应于人K-Ras-4B的C185的半胱氨酸残基共价键合。

52. 根据权利要求48-49中任一项所述的K-Ras蛋白, 其中所述化合物与所述蛋白的组氨酸残基共价键合。

53. 根据权利要求48所述的K-Ras蛋白, 其中所述化合物与所述蛋白对应于人K-Ras-4B的H95的组氨酸残基共价键合。

K-Ras调节剂

[0001] 相关申请案的交叉引用

[0002] 本申请案要求2015年5月6日提交的美国临时申请案第62/157,915号和2015年5月7日提交的美国临时申请案第62/158,356号的权益,其以引用的方式整体并入本文并用于所有目的。

[0003] 对作为ASCII文件提交的“序列表”、表格、计算机程序列表附件的参考

[0004] 写入2016年5月3日创建的文件48536-569001W0_ST25.txt中,10,641字节、机器格式IBM-PC、MS Windows操作系统的序列表,据此以引用的方式并入。

[0005] 关于在联邦资助研究和开发下所做发明的权利的声明

[0006] 本发明是受政府支持在美国国家癌症研究所(National Cancer Institute)授予的合同编号HHSN261200800001E下进行的。政府享有本发明的某些权利。

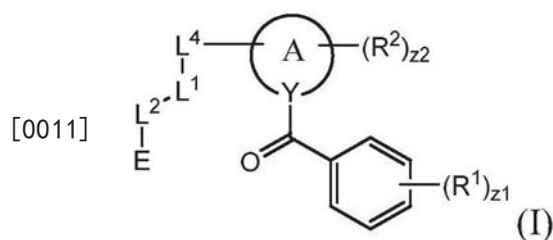
[0007] 发明背景

[0008] K-Ras是人类癌症中最常突变的致癌基因。过去尝试直接调节这种酶的活性尚未成功。Ras蛋白是通过在活性GTP结合构象和非活性GDP结合构象间循环而充当分子开关的小鸟嘌呤核苷酸结合蛋白。Ras蛋白在细胞增殖、分化和存活的调控中起关键作用。Ras信号传导途径调节异常几乎总是与疾病相关。Ras中高度活化体细胞突变是在人类癌症中发现的最常见的病变之一。虽然已经证实三种Ras亚型(K-Ras、N-Ras或H-Ras)中任一种的突变都会导致致癌性转化,但是到目前为止K-Ras突变是人类癌症中最常见的。例如,已知K-Ras突变常常与胰腺癌、结直肠癌和非小细胞肺癌相关。类似地,H-Ras突变是癌症如乳头状甲状腺癌、肺癌和皮肤癌中常见的。最后,N-Ras突变常发生于肝细胞癌中。在本领域中需要有效的Ras抑制剂和抗癌化合物。本文公开了本领域中这些和其它问题的解决方案。

发明内容

[0009] 本文尤其描述了共价(例如,可逆或不可逆)调节剂靶向Ras(例如,K-Ras)蛋白,包括但不限于致癌突变体的用途。

[0010] 一方面,提供了一种具有下式的化合物:



[0012] 其中,Y为N或CH;环A为C₃-C₇环烷基或3-7元杂环烷基;R¹独立地为卤素、CX¹₃、-CHX¹₂、-CH₂X¹、-CN、-SO₂Cl、-SO_{n1}R¹⁰、-SO_{v1}NR⁷R⁸、-NHN⁷R⁸、-ONR⁷R⁸、-NHC(=O)NHN⁷R⁸、-NHC(=O)NR⁷R⁸、-N(O)_{m1}、-NR⁷R⁸、-C(O)R⁹、-C(O)-OR⁹、-C(O)NR⁷R⁸、-OR¹⁰、-NR⁷SO₂R¹⁰、-NR⁷C(O)R⁹、-NR⁷C(O)OR⁹、-NR⁷OR⁹、-OCX¹₃、-OCHX¹₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基;两个相邻的R¹取代基可任选地连接形成经取代或未取代的环烷基、经取代

或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基； L^1 为键、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基； L^2 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7B}-、-NR^{7B}C(O)-、-C(O)NR^{7B}-、-SO₂NR^{7B}-、-NR^{7B}SO₂-、-OC(O)NR^{7B}-、-NR^{7B}C(O)O-、-CR^{9B}=NO-、-ON=CR^{9B}-、-NR^{8B}C(O)NR^{7B}-、-NR^{8B}C(=NR^{10B})NR^{7B}-、-NR^{8B}C(=NR^{10B})-、-C(=NR^{10B})NR^{7B}-、-OC(=NR^{10B})-、-C(=NR^{10B})O-、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基； L^4 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR⁴-、-NR⁴C(O)-、-C(O)NR⁴-、-SO₂NR⁴-、-NR⁴SO₂-、-NR⁴SO₂-、-OC(O)NR⁴-、-NR⁴C(O)O-、经取代或未取代的C₁-C₃亚烷基、经取代或未取代的2-3元杂亚烷基；E为亲电子部分；R²独立地为氧代、卤素、CX²₃、-CHX²₂、-CH₂X²、-CN、-SO₂Cl、-SO_{n2}R¹⁴、-SO_{v2}NR¹¹R¹²、-NHNH¹¹R¹²、-ONR¹¹R¹²、-NHC(=O)NHNH¹¹R¹²、-NHC(O)NR¹¹R¹²、-N(O)_{m2}、-NR¹¹R¹²、-C(O)R¹⁴、-C(O)OR¹⁴、-C(O)NR¹¹R¹²、-OR¹⁵、-NR¹¹SO₂R¹⁵、-NR¹¹C(O)R¹⁴、-NR¹¹C(O)OR¹⁴、-NR¹¹OR¹⁴、-OCX²₃、-OCHX²₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；两个相邻的R²取代基或两个键合至相同原子的R²取代基可任选地连接形成经取代或未取代的环烷基或经取代或未取代的杂环烷基；R⁴独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；R⁷、R⁸、R⁹、R¹⁰、R^{7B}、R^{8B}、R^{9B}、R^{10B}、R¹¹、R¹²、R¹⁴和R¹⁵独立地为氢、卤素、-CX₃、-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、-OCX₃、-OCHX₂、-CHX₂、-CH₂X、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的R⁷和R⁸取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的R¹¹和R¹²取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；每个X、X¹和X²独立地为-F、-Cl、-Br或-I；n₁、n₂、v₁和v₂独立地为0至4的整数；m₁和m₂独立地为1至2的整数；z₁独立地为0至5的整数；并且z₂独立地为0至10的整数。

[0013] 另一方面，提供了一种药物组合物，其包含本文描述的化合物和药学上可接受的赋形剂。

[0014] 另一方面，提供了一种治疗需要此类治疗的患者中的疾病的方法。在实施方案中，疾病为癌症。

[0015] 另一方面，提供了一种降低K-Ras蛋白（例如，人K-Ras 4B）的活性水平的方法，该方法包括使K-Ras蛋白与本文（包括在实施方案、实例、图和表中）描述的化合物接触。

[0016] 另一方面，提供了一种调节K-Ras蛋白的方法。该方法包括使K-Ras蛋白与有效量的本文（包括在实施方案、实例、图和表中）描述的化合物接触。

[0017] 另一方面，提供了一种K-Ras蛋白，其与化合物，例如本文描述的化合物（包括调节剂、抑制剂，或在实施方案、实例、图和表中）共价（例如，可逆地或不可逆地）键合。

附图说明

[0018] 图1A-1C.来自于用His-K-Ras 4B (G12V) 和 (G12V/C185S) 筛选的LC-MS数据。K是指未与化合物结合的His-K-Ras 4B (G12V) (24823 Da)。B是指与 β Me结合的His-K-Ras 4B (G12V) (24899 Da)。C:与系链(tethering)化合物结合的His-K-Ras 4B (G12V) (对于3G4而言25114.5 Da vs. 对于6B9而言25178Da)。Kmut是指未与化合物结合的His-K-Ras 4B (G12V/C185S) (24808 Da)。

[0019] 图2A-2D.来自筛选的示例性化合物及其衍生物,3G4 (含苯基噻唑的化合物) 和衍生物,其中3G4的二硫化物经替代性亲电子部分置换。图2A描绘了SMDC 917069 (本文也称为3G4) 的结构。图2B描绘了SMDC 963109的结构。图2C描绘了SMDC 963108的结构。图2D描绘了SMDC 963107的结构。

[0020] 图3A-3C.来自筛选的示例性化合物及其衍生物,包括6B9 (哌啶甲酸衍生物)、3G4 (含苯基噻唑的化合物);6B9的二硫化物部分经其它亲电子部分置换,包括四氟-苯氧基 (FB9,本文也称为SMDC 959899) 或二氟-苯氧基 (53,本文也称为SMDC 963153);3G4的二硫化物经替代性亲电子部分置换。

[0021] 图4A-4D.来自筛选的示例性化合物及其衍生物,包括6B9 (哌啶甲酸衍生物) 和其中6B9的二硫化物部分经其它亲电子部分,包括四氟-苯氧基 (FB9) 或二氟-苯氧基 (53) 置换的衍生物。6B9衍生物具有其它亲电子部分。

[0022] 图5A-5B.能够与K-Ras结合的示例性化合物。

[0023] 图6A-6B.化合物FB9;亲电体是四氟苯氧基-基团,其也是在FB9的半胱氨酸硫醇和其余部分之间的硫醚联键之后的离去基团,如图6B所描绘。

[0024] 图7A-7B.用纯化K-Ras和FT酶或GGT酶进行的体外异戊二烯化测定。法尼基转移酶的荧光底物,即3,7-二甲基-8-(7-硝基-苯并[1,2,5]噁二唑-4-基氨基)-辛-2,6-二烯-1-焦磷酸酯 (NBD-GPP),具有与法尼基焦磷酸的天然底物类似的动力学性质。图7A具有3G4的浓度。图7B具有6B9的浓度。

[0025] 图8A-8B.用6B9系链化合物进行的体外异戊二烯化。

[0026] 图9.将N-Ras与不同化合物做比较的体外异戊二烯化;1. KRAS4B wt CT;2. KRAS4B mut CT;3. 50 μ M 6B9;4. 20 μ M 6B9;5. 8 μ M 6B9;6. 3.2 μ M 6B9;7. 1.3 μ M 6B9;及8. 0.5 μ M 6B9。法尼基转移酶的荧光底物,即3,7-二甲基-8-(7-硝基-苯并[1,2,5]噁二唑-4-基氨基)-辛-2,6-二烯-1-焦磷酸酯 (NBD-GPP),具有与法尼基焦磷酸的天然底物类似的动力学性质。

[0027] 图10.用3G4对K-Ras 4B进行的BIACore实验;表面等离子体共振 (SPR) 和 ForteBio/Octet实验显示3G4和6B9片段 (LB9) 在K-Ras 4B是否具有次级非共价相互作用位点;实验应显示化合物是否与K-Ras 4B在2个位点 (例如,为CAAX-盒半胱氨酸的共价位点和非共价位点) 相互作用;用K-Ras 4B G12V/C185S进行的SPR实验,使得仅可能非共价相互作用;3G4与K-Ras 4B G12V/C185S的结合曲线;化合物3G4与K-Ras C186S的结合曲线,证明潜在的非共价相互作用。

[0028] 图11A-11B.ForteBio/Octet测定;测量化合物与蛋白质的结合:缔合相对于解离,稳态;用FB9和FB9D片段 (产生非共价相互作用的FB9/FB9D部分) 测试Avi标记的Kras G12D;LB9:FB9的片段;DB9:FB9D的片段;Avi标记的Kras G12D负载有GTPyS/Mg;用LB9的曲线比用DB9更佳;LB9的Kd为17 μ M左右。

[0029] 图12A-12B. 测量因添加3G4诱导的构象变化; 二次谐波发生 (SHG) 实验; 设计SHG实验以便了解化合物3G4是否诱导K-Ras 4B中的任何构象变化; 经FPLC纯化的K-Ras标记有EDA-GTP-ATTO390 (荧光GTP类似物) 或PyMPO-马来酰亚胺 (标记半胱氨酸的荧光染料) 或PyMPO-SE (标记胺的另一种荧光染料); 经标记的K-Ras 4B经由His-标签固定在芯片表面并且在DMSO或3G4化合物的存在下进行实验; 用标记有EDA-GTP-ATTO 390或PyMPO-马来酰亚胺的K-Ras 4B G12V/C185S进行2次实验。使用具有二次谐波发生活性的荧光染料, EDA-GTP-ATTO 390和PyMPO-马来酰亚胺。

[0030] 图13A-13E. FB9与GTPyS或GDP结合的K-Ras G12D的结合测定; 比较FB9与His标记的K-Ras wt、G12D、G12V和His标记的K-Ras G12V/C185S的结合; 蛋白质负载有GTPyS/Mg; 与FB9的结合反应在室温下进行4小时; Rec全长G12D变成负载有GDP或GTPyS和Mg²⁺; 在室温下~10 μ M蛋白与100 μ M亲电子化合物结合并且在5和23小时后取时间点; 化合物6B9具有四氟-苯氧基亲电子修饰 (FB9); 当K-Ras与GTPyS/Mg²⁺复合时化合物结合更好; 在K-Ras/GDP/Mg²⁺的情况下, 5小时后蛋白在第二位点得到明显标记。图13B和图13D是在5小时后完成的。图13C和图13E是在23小时时完成的。

[0031] 图14A-14D. 亲电子6B9衍生物 (FB9) 与不同致癌His-K-Ras 4B的结合。

[0032] 图15A-15D. 用二氟苯氧基-6B9的立体异构体进行的实验; Kras G12D/GTPyS/Mg²⁺、DMSO对照, 在室温下温育2小时; 将FB9与Kras G12D的结合与二氟苯氧基-6B9的立体异构体 (53、54) 做比较; 温育2小时后FB9 100%结合; 在相同条件下与FB9相比, 二氟苯氧基-6B9 (化合物 '53') 与约62%结合; 与FB9相比, 化合物 '53' 的立体异构体 ('54') 与大致35%结合, FB9大致为化合物 '53' 的50%; 局部立体定向相互作用。

[0033] 图16A-16B. FB9和FB9D与K-Ras (G12D)、GTPyS/Mg的结合比较; 原始化合物 (FB9): 50 μ M, 在室温下2.5小时; 还比较了FB9与其对映异构体FB9D的结合; 比FB9D多结合约25-30%的FB9, 显示出局部立体选择性。

[0034] 图17A-17B. 3G4 (苯基噻唑) 的修饰及通过质谱法测定的相对结合。图17B描绘了KRas标记相对于化合物TC-1的程度。

[0035] 图18A-18B. 3G4的附加修饰和质谱结合测定。

[0036] 图19A-19C. 化合物3G4的不同亲电体 (四氟-苯氧基-3G4、二氟-苯氧基-3G4、二甲基-苯氧基-3G4); 某些亲电子修饰导致在当前测定中的结合减少; 3G4可以找到不同于6B9的口袋 (例如, 产生不同的接触或相互作用)。

[0037] 图20A-20C. 四氟苯氧基-6B9 (FB9) 与BME的反应性; 用1mM FB9并减去或加上5mM BME在37 $^{\circ}$ C下进行实验。在0、18和55分钟取时间点; 图表显示曲线下面积vs时间; 游离化合物峰值减小的分析显示约25%产物出现在55分钟后。

[0038] 图21A-21C. 在BME不存在或存在的情况下FB9与Kras的相互作用; 处于室温下指定时间; 在BME中的滴定导致化合物的反应性降低; BME本身不与蛋白质反应。

[0039] 图22. 用表达G12D的RAS较少的MEFS进行的基于细胞的测定; 用EGF刺激外源性表达K-Ras G12D的Ras较少的细胞30和60分钟。附带地按不同浓度添加FB9。用表达各种致癌性突变的胰腺细胞系进行类似实验。K-Ras蛋白水平的变化可见。还完成了生长曲线。

[0040] 图23. 与FB9处理 (L3.6p1 G12D) 组合的EGF刺激的时程。

[0041] 图24. 用EGF与FB9、厄洛替尼、卡非佐米组合处理 (L3.6p1 G12D) 进行刺激。

[0042] 图25A-25B. 与FB9处理 (L3.6p1 G12D) 组合的EGF刺激的时程。

[0043] 图26. 与FB9处理 (L3.6p1 G12D) 组合的EGF刺激的时程。

[0044] 图27. 比较不同的纯化K-Ras 4B形式的凝胶迁移率和抗体反应性。大肠杆菌 (E.Coli): 从大肠杆菌纯化的未加工的K-ras 4B.Fme: 从SF9细胞纯化的经加工的K-ras 4B.FB9: 经FB9标记达到约70%的未加工的K-ras 4B。

[0045] 图28. 时程: 短和长。

[0046] 图29. 不同提取技术和抗体比较。同时并且在相同介质溶液和细胞 (L3.6p1 (G12D)) 中进行实验#1和#2; 团块成分未完全进入溶液。Santa Cruz抗体所识别的团块成分显示两个条带。上部条带为K-Ras。

[0047] 图30. 人胰腺癌细胞系在24小时内的生长曲线: EGF加上FB9, 或EGF加上FB9加上厄洛替尼。

[0048] 图31. 人胰腺癌细胞系在24小时内的生长曲线: EGF加上FB9, 或EGF加上FB9加上厄洛替尼。

[0049] 图32A-32B. 图32A: K-ras 4B野生型C-末端: 化合物3G4. 图32B: K-ras 4B突变体C-末端 (C185S): 化合物3G4。

[0050] 图33. 与四氟苯氧基-6B9结合的Kras G12D的鉴定。

[0051] 图34. 时程: 短和长。

[0052] 图35. 显示24小时内994566在MiaPaCa-2细胞中的稳定性的细胞摄取实验。在完全培养基中用994566处理 1×10^6 个接种于皮氏培养皿 (Petri dish) 上的细胞。将细胞收集到200 μ l乙腈中, 15,000g x离心裂解物15分钟, 过滤到HPLC小瓶中并通过LC/MS分析母体化合物的存在。

[0053] 图36. FB9对fmeKRAS4b的修饰。重组fmeKRAS4b负载GDP或GppNHp (非水解GTP类似物), 然后与FB9在37 $^{\circ}$ C下反应100分钟。MALDI-TOF分析揭示FB9对蛋白质的共价修饰 (质量增加350Da) 在存在GTP类似物时更明显。

[0054] 图37. FB9的乙烯基磺酰胺类似物, 即化合物994566, 抑制表达Kras4B G12D的小鼠胚胎成纤维细胞 (MEF) 增殖。使细胞血清饥饿过夜, 接着用994566和EGF (30ng/ml) 处理。8小时后将培养基换成完全培养基 (10% FBS), 然后再次添加化合物。培养72小时后采集图像。

[0055] 图38A-38B. 图38A: FB9的乙烯基磺酰胺类似物, 即化合物994566, 减少表达Kras4B G12D的小鼠胚胎成纤维细胞 (MEF) 中的Kras蛋白质表达。使细胞血清饥饿过夜, 接着用994566和EGF (30ng/ml) 处理。8小时后将培养基换成完全培养基 (10% FBS), 然后再次添加化合物。培养96小时后收集细胞裂解物。图38B: FB9的乙烯基丙烯酰胺 (左) 和乙烯基磺酰胺 (右) 类似物的结构。

[0056] 图39. FB9的乙烯基磺酰胺类似物, 即化合物994566, 在处理24小时后减少表达Kras4B G12D的小鼠胚胎成纤维细胞 (MEF) 中的Kras蛋白质表达。使细胞血清饥饿过夜, 接着用994566或994565处理, 之后立即用EGF (30ng/ml) 处理。加工24小时后收获的细胞用于Western印迹分析。

[0057] 图40. 显示H95的蛋白质构象是在表面上并且暴露为药物可进入。

[0058] 图41. 对样品。在这项实验中使用经HA标记的Kras4B G12V稳定转导的小鼠肺上皮细胞系。用多西环素 (doxycycline) 诱导HA-Kras4BG12V表达48小时, 然后用FB9的精密类

似物,即化合物993784处理细胞。使用免疫亲和色谱法从细胞裂解物纯化Kras蛋白,接着进行SDS-PAGE,然后进行对Kras蛋白的修饰的MALDI-TOF分析。检测经化合物修饰的肽的特征片段(下图)。该片段在对照样品中不存在(从上往下的第二张图)。

[0059] 图42.用于MALDI-TOF实验中的KRAS4b的序列GMTEYKLVVVGAGGVGKSALTIQLIQNHFVD EYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDSE DVPMLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEKMSKDGKKKKKSKTK CVIM (SEQ ID NO:1)。

[0060] 图43.经FB9修饰的KRAS4B (SEQ ID NO:1)的MALDI-TOF光谱。

[0061] 图44.FB9修饰的全尺寸(1-188) KRAS4b的Glu-C消化(室温,过夜)的MALDI-TOF MS(线性模式)。图44中列出的序列是DIHHYRE (SEQ ID NO:2)、GKKKKKSKTKCVIM (SEQ ID NO:3)和KMSKDGKKKKKSKTKCVIM (SEQ ID NO:4)。

[0062] 图45A-45B.KRAS 4b上经FB9修饰的残基的鉴定。图45A:Glu-C消化后获得的肽进一步用胰蛋白酶消化。图45B:肽969.485和1320.614的常见片段和片段化光谱的比较。

[0063] 图46A-46B.图46A:用于实验的蛋白质的序列,特别是GGTEYKLVVVGAGGVGKSALTIQL IQNHFVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQI KRVKDSVDPMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEKMSKDGKKK KKKSKTKC (SEQ ID NO:5)。图46B:经FB9修饰的FME-Kras4b蛋白质的MALDI-TOF光谱。

[0064] 图47.Kras4b中经FB9修饰的肽的MALDI-TOF分析。图47中列出的序列是SFEDIHHYR (SEQ ID NO:6)、SFEDIHHYREQIKR (SEQ ID NO:7)、SFEDIHHYREQIK (SEQ ID NO:8)和 DSEDVPMVLVGNKCDLPSR (SEQ ID NO:9)。

[0065] I.定义

[0066] 本文所用的缩写具有其在化学和生物学领域中的常规含义。本文阐述的化学结构和化学式根据化学领域已知的化学价标准规则构造。

[0067] 取代基团用其常规化学式指定,从左到右书写时,其同样涵盖从右到左书写结构将产生的化学上相同的取代基,例如, $-\text{CH}_2\text{O}-$ 相当于 $-\text{OCH}_2-$ 。

[0068] 除非另有规定,否则术语“烷基”,本身或作为另一取代基的一部分,意指直链(即,未分支)或分支碳链(或碳),或其组合,其可为完全饱和、单或多不饱和并且可包括单价、二价或多价基,具有指定碳原子数(即, C_1 - C_{10} 意指一至十个碳)。烷基为未环化链。饱和烃基的实例包括但不限于以下基团,例如甲基、乙基、正丙基、异丙基、正丁基、叔丁基、异丁基、仲丁基、(环己基)甲基、(例如)正戊基、正己基、正庚基、正辛基等的同系物和异构体。不饱和烷基是具有一个或多个双键或三键的烷基。不饱和烷基的实例包括但不限于乙烯基、2-丙烯基、巴豆基、2-异戊烯基、2-(丁二烯基)、2,4-戊二烯基、3-(1,4-戊二烯基)、乙炔基、1-和3-丙炔基、3-丁炔基及高级同系物和异构体。烷氧基是经由氧接头($-\text{O}-$)附连到分子其余部分的烷基。

[0069] 除非另有规定,否则术语“亚烷基”,本身或作为另一取代基的一部分,意指源自烷基的二价基,例如但不限于 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ 。通常,烷基(或亚烷基)将具有1至24个碳原子,本文优选具有10个或更少碳原子的那些基团。“低级烷基”或“低级亚烷基”是短链烷基或亚烷基,通常具有8个或更少的碳原子。除非另有规定,否则术语“亚烯基”,本身或作为另一取代基的一部分,意指源自烯烃的二价基。

[0070] 除非另有规定,否则术语“杂烷基”,本身或与另一术语组合,意指稳定的直链或支链,或其组合,包括至少一个碳原子和至少一个杂原子(例如,选自由O、N、P、Si和S组成的组,并且其中氮和硫原子可任选地经氧化,并且氮杂原子可任选地季铵化)。杂原子(例如,O、N、P、S、B、As或Si)可位于杂烷基的任一内部位置或烷基附连到分子其余部分的位置。杂烷基为未环化链。实例包括但不限于: $-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_3$ 、 $-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_3$ 、 $-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_3$ 、 $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_3$ 、 $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})-\text{CH}_3$ 、 $-\text{CH}_2-\text{CH}_2-\text{S}(\text{O})_2-\text{CH}_3$ 、 $-\text{CH}=\text{CH}-\text{O}-\text{CH}_3$ 、 $-\text{Si}(\text{CH}_3)_3-$ 、 $-\text{CH}_2-\text{CH}=\text{N}-\text{OCH}_3$ 、 $-\text{CH}=\text{CH}-\text{N}(\text{CH}_3)-\text{CH}_3$ 、 $-\text{O}-\text{CH}_3$ 、 $-\text{O}-\text{CH}_2-\text{CH}_3$ 和 $-\text{CN}$ 。多达两个或三个杂原子可以是连续的,例如, $-\text{CH}_2-\text{NH}-\text{OCH}_3$ 和 $-\text{CH}_2-\text{O}-\text{Si}(\text{CH}_3)_3$ 。

[0071] 类似地,除非另有规定,否则术语“杂亚烷基”,本身或作为另一取代基的一部分,意指源自杂烷基的二价基,例如但不限于 $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ 和 $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$ 。对于杂亚烷基而言,杂原子也可占用任一或两个链末端(例如,亚烷基氧基、亚烷基二氧基、亚烷基氨基、亚烷基二氨基等)。再进一步地,对于亚烷基和杂亚烷基连接基团而言,书写连接基团公式的方向并不暗示连接基团的取向。例如,式 $-\text{C}(\text{O})_2\text{R}'-$ 表示 $-\text{C}(\text{O})_2\text{R}'-$ 和 $-\text{R}'\text{C}(\text{O})_2-$ 。如上所述,杂烷基,如本文所用,包括通过杂原子附连到分子其余部分的那些基团,例如 $-\text{C}(\text{O})\text{R}'$ 、 $-\text{C}(\text{O})\text{NR}'$ 、 $-\text{NR}'\text{R}''$ 、 $-\text{OR}'$ 、 $-\text{SR}'$ 和/或 $-\text{SO}_2\text{R}'$ 。叙述“杂烷基”,接着叙述具体的杂烷基,例如 $-\text{NR}'\text{R}''$ 等时,应理解术语杂烷基和 $-\text{NR}'\text{R}''$ 不是冗余的或互相排斥的。相反,叙述具体的杂烷基是为了更加清楚。因此,本文不应将术语“杂烷基”解释为除去了具体的杂烷基,例如 $-\text{NR}'\text{R}''$ 等。

[0072] 除非另有规定,否则术语“环烷基”和“杂环烷基”,本身或与其它术语组合,分别意指“烷基”和“杂烷基”的环状形式。环烷基和杂烷基不是芳香族。另外,对于杂环烷基而言,杂原子可占据杂环附连到分子其余部分的位置。环烷基的实例包括但不限于环丙基、环丁基、环戊基、环己基、1-环己烯基、3-环己烯基、环庚基等。杂环烷基的实例包括但不限于1-(1,2,5,6-四氢吡啶基)、1-哌啶基、2-哌啶基、3-哌啶基、4-吗啉基、3-吗啉基、四氢呋喃-2-基、四氢呋喃-3-基、四氢噻吩-2-基、四氢噻吩-3-基、1-哌嗪基、2-哌嗪基等。“亚环烷基”和“杂亚环烷基”,单独地或作为另一取代基的一部分,分别意指源自环烷基和杂环烷基的二价基。

[0073] 除非另有规定,否则术语“卤代”或“卤素”,本身或作为另一取代基的一部分,意指氟、氯、溴或碘原子。另外,术语如“卤代烷基”意在包括单卤代烷基和多卤代烷基。例如,术语“卤代(C_1-C_4)烷基”包括但不限于氟甲基、二氟甲基、三氟甲基、2,2,2-三氟乙基、4-氯丁基、3-溴丙基等。

[0074] 除非另有规定,否则术语“酰基”意指 $-\text{C}(\text{O})\text{R}$,其中R为经取代或未取代的烷基、经取代或未取代的环烷基、经取代或未取代的杂烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基。

[0075] 除非另有规定,否则术语“芳基”意指多不饱和、芳香族、烃取代基,其可以是单环或稠合在一起(即,稠环芳基)或共价连接的多个环(优选1至3个环)。稠环芳基是指稠合在一起的多个环,其中至少一个稠环为芳基环。术语“杂芳基”是指含有至少一个杂原子例如N、O或S的芳基(或环),其中氮和硫原子任选地经氧化,并且氮原子任选地季铵化。因此,术语“杂芳基”包括稠环杂芳基(即,稠合在一起的多个环,其中至少一个稠环为芳杂环)。5,6-稠环杂亚芳基是指稠合在一起的两个环,其中一个环具有5元而另一个环具有6元,并且其

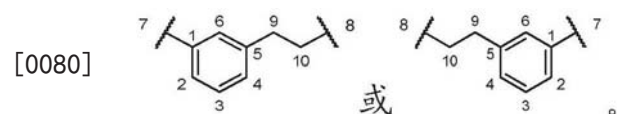
中至少一个环为杂芳基环。同样,6,6-稠环杂亚芳基是指稠合在一起的两个环,其中一个环具有6元且另一个环具有6元,并且其中至少一个环为杂芳基环。并且6,5-稠环杂亚芳基是指稠合在一起的两个环,其中一个环具有6元而另一个环具有5元,并且其中至少一个环为杂芳基环。杂芳基可通过碳或杂原子附连到分子其余部分。芳基和杂芳基的非限制性实例包括苯基、萘基、吡咯基、吡唑基、哒嗪基、三嗪基、嘧啶基、咪唑基、吡嗪基、嘌呤基、噁唑基、异噁唑基、噻唑基、呋喃基、噻吩基、吡啶基、嘧啶基、苯并噻唑基、苯并噁唑基、苯并咪唑基、苯并呋喃基、异苯并呋喃基、吲哚基、异吲哚基、苯并噻吩基、异喹啉基、喹啉基、喹啉基、1-萘基、2-萘基、4-联苯基、1-吡咯基、2-吡咯基、3-吡咯基、3-吡唑基、2-咪唑基、4-咪唑基、吡嗪基、2-噁唑基、4-噁唑基、2-苯基-4-噁唑基、5-噁唑基、3-异噁唑基、4-异噁唑基、5-异噁唑基、2-噻唑基、4-噻唑基、5-噻唑基、2-呋喃基、3-呋喃基、2-噻吩基、3-噻吩基、2-吡啶基、3-吡啶基、4-吡啶基、2-嘧啶基、4-嘧啶基、5-苯并噻唑基、嘌呤基、2-苯并咪唑基、5-吲哚基、1-异喹啉基、5-异喹啉基、2-喹啉基、5-喹啉基、3-喹啉基和6-喹啉基。上面提到的每个芳基和杂芳基环系的取代基选自下面描述的可接受的取代基的组。“亚芳基”和“杂亚芳基”,单独地或作为另一取代基的一部分,分别意指源自芳基和杂芳基的二价基。杂芳基取代基可-O-键合至环杂原子氮上。

[0076] 螺环是两个或更多个环,其中相邻环通过单个原子附连。螺环内的单个环可以相同或不同。螺环内的单个环可以经取代或未取代并且可具有不同于一组螺环内其它单个环的取代基。螺环内单个环的可能取代基,在不是螺环的一部分时,是相同环的可能取代基(例如,环烷基或杂环烷基环的取代基)。螺环可以是经取代或未取代的环烷基、经取代或未取代的亚环烷基、经取代或未取代的杂环烷基或经取代或未取代的杂亚环烷基并且螺环基团内的单个环可以是前一列表中的任一种,包括具有一种类型的所有环(例如,所有环均为经取代的杂亚环烷基,其中每个环可以是相同或不同的经取代的杂亚环烷基)。当提到螺环环系时,杂环螺环意指其中至少一个环为杂环并且其中每个环可以是不同环的螺环。当提到螺环环系时,经取代的螺环意指至少一个环经取代并且每个取代基可以任选地不同。

[0077] 符号“”表示一个化学部分与分子或化学式的其余部分的附连点。

[0078] 如本文中所用,术语“氧”意指与碳原子双键键合的氧。

[0079] 术语“烷基亚芳基”作为与亚烷基部分(本文也称为亚烷基接头)共价键合的亚芳基部分。在实施方案中,烷基亚芳基具有下式:



[0081] 烷基亚芳基部分可以在亚烷基部分或亚芳基接头上(例如,在2、3、4或6碳处)经卤素、氧代、-N₃、-CF₃、-CCl₃、-CBr₃、-CI₃、-CN、-CHO、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₂CH₃-SO₃H、-OSO₃H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC(O)NHNH₂、经取代或未取代的C₁-C₅烷基或经取代或未取代的2-5元杂烷基)取代(例如经取代基取代)。在实施方案中,烷基亚芳基未经取代。

[0082] 以上每个术语(例如,“烷基”、“杂烷基”、“芳基”和“杂芳基”)包括指定基团的取代和未取代形式两种。下面提供了每种类型的基团的优选取代基。

[0083] 烷基和杂烷基(包括常常称为亚烷基、烯基、杂亚烷基、杂烯基、炔基、环烷基、杂环

烷基、环烯基和杂环烯基的那些基团)的取代基可以是选自但不限于以下的各种基团中的一种或多种: $-\text{OR}'$ 、 $=\text{O}$ 、 $=\text{NR}'$ 、 $=\text{N}-\text{OR}''$ 、 $-\text{NR}''\text{R}''$ 、 $-\text{SR}'$ 、-卤素、 $-\text{SiR}'\text{R}''\text{R}'''$ 、 $-\text{OC}(\text{O})\text{R}'$ 、 $-\text{C}(\text{O})\text{R}'$ 、 $-\text{CO}_2\text{R}'$ 、 $-\text{CONR}''\text{R}''$ 、 $-\text{OC}(\text{O})\text{NR}''\text{R}''$ 、 $-\text{NR}''\text{C}(\text{O})\text{R}'$ 、 $-\text{NR}'-\text{C}(\text{O})\text{NR}''\text{R}''$ 、 $-\text{NR}''\text{C}(\text{O})_2\text{R}'$ 、 $-\text{NR}-\text{C}(\text{NR}'\text{R}''\text{R}''')=\text{NR}''''$ 、 $-\text{NR}-\text{C}(\text{NR}'\text{R}''')=\text{NR}''''$ 、 $-\text{S}(\text{O})\text{R}'$ 、 $-\text{S}(\text{O})_2\text{R}'$ 、 $-\text{S}(\text{O})_2\text{NR}'\text{R}''$ 、 $-\text{NRSO}_2\text{R}'$ 、 $-\text{NR}'\text{NR}''\text{R}''$ 、 $-\text{ONR}'\text{R}''$ 、 $-\text{NR}'\text{C}(\text{O})\text{NR}''\text{R}''$ 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、 $-\text{NR}'\text{SO}_2\text{R}''$ 、 $-\text{NR}'\text{C}(\text{O})\text{R}''$ 、 $-\text{NR}'\text{C}(\text{O})-\text{OR}''$ 、 $-\text{NR}'\text{OR}''$, 数量范围从零至 $(2m'+1)$, 其中 m' 是此类基团中碳原子的总数。 R 、 R' 、 R'' 、 R''' 和 R'''' 各自优选独立地指氢、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基(例如, 经1-3个卤素取代的芳基)、经取代或未取代的杂芳基、经取代或未取代的烷基、烷氧基或硫代烷氧基或芳烷基。当本文描述的化合物包括一个以上的R基团时, 例如, 如同每个 R 、 R' 、 R'' 、 R''' 和 R'''' 基团一样(当这些基团中的一个以上存在时)独立地选择每个R基团。当 R' 和 R'' 附连到相同氮原子上时, 它们可与氮原子组合形成4-、5-、6-或7-元环。例如, $-\text{NR}'\text{R}''$ 包括但不限于1-吡咯烷基和4-吗啉基。从上面对取代基的讨论看, 本领域的技术人员将理解术语“烷基”意在包括含有与除氢基以外的基团结合的碳原子的基团, 例如卤代烷基(例如, $-\text{CF}_3$ 和 $-\text{CH}_2\text{CF}_3$)和酰基(例如, $-\text{C}(\text{O})\text{CH}_3$ 、 $-\text{C}(\text{O})\text{CF}_3$ 、 $-\text{C}(\text{O})\text{CH}_2\text{CH}_3$ 等)。

[0084] 与针对烷基描述的取代基类似, 芳基和杂芳基的取代基是变化的并且选自, 例如: $-\text{OR}'$ 、 $-\text{NR}'\text{R}''$ 、 $-\text{SR}'$ 、-卤素、 $-\text{SiR}'\text{R}''\text{R}'''$ 、 $-\text{OC}(\text{O})\text{R}'$ 、 $-\text{C}(\text{O})\text{R}'$ 、 $-\text{CO}_2\text{R}'$ 、 $-\text{CONR}''\text{R}''$ 、 $-\text{OC}(\text{O})\text{NR}''\text{R}''$ 、 $-\text{NR}''\text{C}(\text{O})\text{R}'$ 、 $-\text{NR}'-\text{C}(\text{O})\text{NR}''\text{R}''$ 、 $-\text{NR}''\text{C}(\text{O})_2\text{R}'$ 、 $-\text{NR}-\text{C}(\text{NR}'\text{R}''\text{R}''')=\text{NR}''''$ 、 $-\text{NR}-\text{C}(\text{NR}'\text{R}''')=\text{NR}''''$ 、 $-\text{S}(\text{O})\text{R}'$ 、 $-\text{S}(\text{O})_2\text{R}'$ 、 $-\text{S}(\text{O})_2\text{NR}'\text{R}''$ 、 $-\text{NRSO}_2\text{R}'$ 、 $-\text{NR}'\text{NR}''\text{R}''$ 、 $-\text{ONR}'\text{R}''$ 、 $-\text{NR}'\text{C}(\text{O})\text{NR}''\text{R}''$ 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、 $-\text{R}'$ 、 $-\text{N}_3$ 、 $-\text{CH}(\text{Ph})_2$ 、氟(C_1 - C_4)烷氧基和氟(C_1 - C_4)烷基、 $-\text{NR}'\text{SO}_2\text{R}''$ 、 $-\text{NR}'\text{C}(\text{O})\text{R}''$ 、 $-\text{NR}'\text{C}(\text{O})-\text{OR}''$ 、 $-\text{NR}'\text{OR}''$, 数量范围从零到芳香环系上开放化合价的总数; 并且其中 R' 、 R'' 、 R''' 和 R'''' 优选独立地选自氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基和经取代或未取代的杂芳基。当本文描述的化合物包括一个以上的R基团时, 例如, 如同每个 R 、 R' 、 R'' 、 R''' 和 R'''' 基团一样(当这些基团中的一个以上存在时)独立地选择每个R基团。

[0085] 环(例如环烷基、杂环烷基、芳基、杂芳基、亚环烷基、杂亚环烷基、亚芳基或杂亚芳基)的取代基可描绘为环上, 而不是环的特定原子上的取代基(通常称为浮动取代基)。在这种情况下, 取代基可附连到任一环原子(遵照化学价规则)并且在稠环或螺环的情况下, 描绘为与稠环或螺环的一个成员相关的取代基(单环上的浮动取代基), 可以是任一稠环或螺环上的取代基(多个环上的浮动取代基)。当取代基附连到环上, 而不是特定原子上(浮动取代基), 并且取代基的下标是大于一的整数时, 多个取代基可以在相同原子、相同环、不同原子、不同稠环、不同螺环上, 并且每个取代基可任选地不同。环与分子其余部分的附连点不限于单个原子时(浮动取代基), 附连点可以是环的任一原子并且在稠环或螺环的情况下, 任一稠环或螺环的任一原子同时遵照化学价规则。环, 稠环或螺环含有一个或多个环杂原子并且显示该环, 稠环或螺环具有一个或多个浮动取代基(包括但不限于, 与分子其余部分的附连点)时, 浮动取代基可与杂原子键合。当具有浮动取代基的公式的结构中显示环杂原子与一个或多个氢结合时(环氮具有两个至环原子的键和至氢的第三键), 当杂原子与浮动取代基键合时, 取代基将被理解为置换氢, 同时遵照化学价规则。

[0086] 两个或更多个取代基可任选地连接形成芳基、杂芳基、环烷基或杂环烷基。此类所

谓的成环取代基,虽然不一定但通常,发现与环状基础结构附连。在一个实施方案中,成环取代基与基础结构的相邻成员附连。例如,与环状基础结构的相邻成员附连的两个成环取代基产生稠环结构。在另一个实施方案中,成环取代基与基础结构的单个成员附连。例如,与环状基础结构的单个成员附连的两个成环取代基产生螺环结构。再一个实施方案中,成环取代基与基础结构的非相邻成员附连。

[0087] 芳基或杂芳基环的相邻原子上的两个取代基可任选地形成式 $-T-C(O)-(CRR')_q-U$ 的环,其中T和U独立地为 $-NR-$ 、 $-O-$ 、 $-CRR'-$ 或单键,并且q为0至3的整数。可选地,芳基或杂芳基环的相邻原子上的两个取代基可任选地经式 $-A-(CH_2)_r-B-$ 的取代基置换,其中A和B独立地为 $-CRR'-$ 、 $-O-$ 、 $-NR-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 、 $-S(O)_2NR'-$ 或单键,并且r为1至4的整数。这样形成的新环的一个单键可任选地经双键置换。可选地,芳基或杂芳基环的相邻原子上的两个取代基可任选地经式 $-(CRR')_s-X'-(C''R''R''')_d-$ 的取代基置换,其中s和d独立地为0至3的整数,并且X'为 $-O-$ 、 $-NR'-$ 、 $-S-$ 、 $-S(O)-$ 、 $-S(O)_2-$ 或 $-S(O)_2NR'-$ 。取代基R、R'、R''和R'''优选独立地选自氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基和经取代或未取代的杂芳基。

[0088] 如本文中所用,术语“杂原子”或“环杂原子”意在包括氧(O)、氮(N)、硫(S)、磷(P)和硅(Si)。

[0089] 如本文中所用,“取代基”意指选自以下部分的基团:

[0090] (A) 氧代、卤素、 $-CF_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCF_3$ 、 $-OCHF_2$ 、未取代的烷基、未取代的杂烷基、未取代的环烷基、未取代的杂环烷基、未取代的芳基、未取代的杂芳基,及

[0091] (B) 烷基、杂烷基、环烷基、杂环烷基、芳基、杂芳基,其经选自以下的至少一个取代基取代:

[0092] (i) 氧代、卤素、 $-CF_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCF_3$ 、 $-OCHF_2$ 、未取代的烷基、未取代的杂烷基、未取代的环烷基、未取代的杂环烷基、未取代的芳基、未取代的杂芳基,及

[0093] (ii) 烷基、杂烷基、环烷基、杂环烷基、芳基、杂芳基,其经选自以下的至少一个取代基取代:

[0094] (a) 氧代、卤素、 $-CF_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCF_3$ 、 $-OCHF_2$ 、未取代的烷基、未取代的杂烷基、未取代的环烷基、未取代的杂环烷基、未取代的芳基、未取代的杂芳基,及

[0095] (b) 烷基、杂烷基、环烷基、杂环烷基、芳基、杂芳基,其经选自以下的至少一个取代基取代:氧代、卤素、 $-CF_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCF_3$ 、 $-OCHF_2$ 、未取代的烷基、未取代的杂烷基、未取代的环烷基、未取代的杂环烷基、未取代的芳基、未取代的杂芳基。

[0096] 如本文中所用,“大小受限的取代基”或“大小受限的取代基基团”意指选自以上针

对“取代基基团”所描述的所有取代基的基团,其中每个经取代或未取代的烷基是经取代或未取代的C₁-C₂₀烷基,每个经取代或未取代的杂烷基是经取代或未取代的2-20元杂烷基,每个经取代或未取代的环烷基是经取代或未取代的C₃-C₈环烷基,每个经取代或未取代的杂环烷基是经取代或未取代的3-8元杂环烷基,每个经取代或未取代的芳基是经取代或未取代的C₆-C₁₀芳基,并且每个经取代或未取代的杂芳基是经取代或未取代的5-10元杂芳基。

[0097] 如本文中所用,“低级取代基”或“低级取代基基团”,意指选自以上针对“取代基基团”所描述的所有取代基的基团,其中每个经取代或未取代的烷基是经取代或未取代的C₁-C₈烷基,每个经取代或未取代的杂烷基是经取代或未取代的2-8元杂烷基,每个经取代或未取代的环烷基是经取代或未取代的C₃-C₇环烷基,每个经取代或未取代的杂环烷基是经取代或未取代的3-7元杂环烷基,每个经取代或未取代的芳基是经取代或未取代的C₆-C₁₀芳基,并且每个经取代或未取代的杂芳基是经取代或未取代的5-9元杂芳基。

[0098] 在一些实施方案中,在本文化合物中描述的每个经取代的基团是经至少一个取代基基团取代。更具体地,在一些实施方案中,在本文化合物中描述的每个经取代的烷基、经取代的杂烷基、经取代的环烷基、经取代的杂环烷基、经取代的芳基、经取代的杂芳基、经取代的亚烷基、经取代的杂亚烷基、经取代的亚环烷基、经取代的杂亚环烷基、经取代的亚芳基和/或经取代的杂亚芳基是经至少一个取代基基团取代。在其它实施方案中,这些基团中的至少一个或全部经至少一个大小受限的取代基基团取代。在其它实施方案中,这些基团中的至少一个或全部经至少一个低级取代基基团取代。

[0099] 在本文化合物的其它实施方案中,每个经取代或未取代的烷基可以是经取代或未取代的C₁-C₂₀烷基,每个经取代或未取代的杂烷基是经取代或未取代的2-20元杂烷基,每个经取代或未取代的环烷基是经取代或未取代的C₃-C₈环烷基,每个经取代或未取代的杂环烷基是经取代或未取代的3-8元杂环烷基,每个经取代或未取代的芳基是经取代或未取代的C₆-C₁₀芳基,和/或每个经取代或未取代的杂芳基是经取代或未取代的5-10元杂芳基。在本文化合物的一些实施方案中,每个经取代或未取代的亚烷基可以是经取代或未取代的C₁-C₂₀亚烷基,每个经取代或未取代的杂亚烷基是经取代或未取代的2-20元杂亚烷基,每个经取代或未取代的亚环烷基是经取代或未取代的C₃-C₈亚环烷基,每个经取代或未取代的杂亚环烷基是经取代或未取代的3-8元杂亚环烷基,每个经取代或未取代的亚芳基是经取代或未取代的C₆-C₁₀亚芳基,和/或每个经取代或未取代的杂亚芳基是经取代或未取代的5-10元杂亚芳基。

[0100] 在一些实施方案中,每个经取代或未取代的烷基是经取代或未取代的C₁-C₈烷基,每个经取代或未取代的杂烷基是经取代或未取代的2-8元杂烷基,每个经取代或未取代的环烷基是经取代或未取代的C₃-C₇环烷基,每个经取代或未取代的杂环烷基是经取代或未取代的3-7元杂环烷基,每个经取代或未取代的芳基是经取代或未取代的C₆-C₁₀芳基,和/或每个经取代或未取代的杂芳基是经取代或未取代的5-9元杂芳基。在一些实施方案中,每个经取代或未取代的亚烷基是经取代或未取代的C₁-C₈亚烷基,每个经取代或未取代的杂亚烷基是经取代或未取代的2-8元杂亚烷基,每个经取代或未取代的亚环烷基是经取代或未取代的C₃-C₇亚环烷基,每个经取代或未取代的杂亚环烷基是经取代或未取代的3-7元杂亚环烷基,每个经取代或未取代的亚芳基是经取代或未取代的C₆-C₁₀亚芳基,和/或每个经取代或未取代的杂亚芳基是经取代或未取代的5-9元杂亚芳基。在一些实施方案中,化合物是下面

实例部分、附图或表中阐述的化学物类。

[0101] 本发明的某些化合物具有不对称碳原子(光学或手性中心)或双键;依据绝对立体化学,对于氨基酸和单个异构体而言可以定义为(R)-或(S)-,或(D)-或(L)-的对映异构体、外消旋物、非对映异构体、互变异构体、几何异构体、立体异构体形式涵盖在本发明的范围内。本发明的化合物不包括本领域中已知太不稳定而无法合成和/或分离的那些。本发明意在包括呈外消旋和光学纯形式的化合物。光学活性的(R)-和(S)-或(D)-和(L)-异构体可以使用手性合成子或手性试剂制备,或使用常规技术分解。当本文描述的化合物含有烯键或其它几何不对称中心,并且除非另有说明时,意图是所述化合物包括E和Z几何异构体两种。

[0102] 如本文中所用,术语“异构体”是指具有相同数量和种类的源自,并因此具有相同分子量,但是关于原子的结构排列或构型不同的化合物。

[0103] 如本文中所用,术语“互变异构体”是指平衡存在并且易于从一种异构体形式转化为另一种的两种或更多种结构异构体中的一种。

[0104] 本领域的技术人员将显而易见的是,本发明的某些化合物可呈互变异构体形式存在,化合物的所有此类互变异构体形式均在本发明范围内。

[0105] 除非另有规定,否则本文描绘的结构也意在包括该结构的所有立体化学形式;即,每个不对称中心的R和S构型。因此,本化合物的单个立体化学异构体以及对映异构体和非对映异构体混合物在本发明的范围内。

[0106] 除非另有规定,否则本文描绘的结构也意在包括仅在一个或多个富含同位素的原子的存在上不同的化合物。例如,除了氢被氘或氚置换,或碳被富含 ^{13}C 或 ^{14}C 的原子置换以外,具有本结构的化合物在本发明的范围内。

[0107] 本发明的化合物也可在构成此类化合物的一个或多个原子处含有非天然比例的原子同位素。例如,化合物可用放射性同位素,例如氚(^3H)、碘-125(^{125}I)或碳-14(^{14}C)进行放射性标记。本发明化合物的所有同位素变型,不管是否是放射性的,都涵盖在本发明的范围内。

[0108] 应当指出的是在整个申请案中,以马库西群组(Markush group)撰写替代方案,例如,含有一种以上可能的氨基酸的每个氨基酸位置。特别考虑到马库西群组的每个成员都应单独考虑,从而包括另一实施方案,并且马库西群组不应作为单个单元进行阅读。

[0109] “类似物”根据其在化学和生物学中的简单普通含义使用并且是指结构上与另一种化合物(即,所谓的“参考”化合物)类似,但在组成上不同,例如一个原子被不同元素的原子置换,或在特定官能团的存在上,或一个官能团被另一个官能团置换,或参考化合物的一个或多个手性中心的绝对立体化学上不同的化学化合物。因此,类似物是在功能和外观上而不是在结构或来源上与参考化合物相似或同等的化合物。

[0110] 如本文中所用,术语“一”或“一种(一个)”意指一个或多个。另外,如本文中所用,短语“经一个……取代”意指指定基团可以被任何或所有命名取代基中的一个或多个取代。例如,当基团,如烷基或杂烷基,“被未取代的 $\text{C}_1\text{-C}_{20}$ 烷基或未取代的2-20元杂烷基取代”时,该基团可含一个或多个未取代的 $\text{C}_1\text{-C}_{20}$ 烷基和/或一个或多个未取代的2-20元杂烷基。

[0111] 而且,当一个部分被R取代基取代时,该基团可以称为“经R取代”。当一个部分经R取代时,该部分是经至少一个R取代基取代并且每个R取代基任选地不同。在化学种类的描述(例如式(I))中存在特定R基团时,可以使用罗马字母符号或附加数字来区分该特定R基

团的每种外观。例如,存在多个 R^{13} 取代基时,可将每个 R^{13} 取代基区分为 R^{13A} 、 R^{13B} 、 R^{13C} 、 R^{13D} 等,其中 R^{13A} 、 R^{13B} 、 R^{13C} 、 R^{13D} 等中的每一个在 R^{13} 的定义范围内定义并且任选地不同。

[0112] 如本文中所用的“可检测部分”是指可与化合物或生物分子共价或非共价附连,可以例如使用本领域已知的技术检测的部分。在实施方案中,可检测部分共价附连。可检测部分可以提供附连化合物或生物分子的成像。可检测部分可以指示两种化合物之间的接触。示例性可检测部分为荧光团、抗体、反应性染料、放射性标记部分、磁性造影剂和量子点。示例性荧光团包括荧光素、若丹明、GFP、香豆素、FITC、Alexa fluor、Cy3、Cy5、BODIPY和花青染料。示例性放射性核素包括氟-18、镓-68和铜-64。示例性磁性造影剂包括钆、氧化铁和铁铂及锰。

[0113] 对本发明化合物的描述受本领域技术人员已知的化学键合原理限制。因此,基团可以被许多取代基中的一种或多种取代时,可以选择此类取代基以便遵从化学键合原理并产生并非本来就不稳定和/或将为本领域普通技术人员称为很可能在环境条件下(例如水性、中性和几种已知的生理条件下)不稳定的化合物。例如,杂环烷基或杂芳基依照本领域技术人员已知的化学键合原理经由环杂原子与分子其余部分附连,从而避免有本来就不稳定的化合物。

[0114] 术语“药学上可接受的盐”意在包括根据本文描述的化合物上发现的特定取代基而定,用相对无毒的酸或碱制备的活性化合物的盐。当本发明化合物含有相对酸性的官能团时,可以通过使中性形式的此类化合物与足量的所需碱(纯的或在合适的惰性溶剂中)接触而获得碱加成盐。药学上可接受的碱加成盐的实例包括钠、钾、钙、铵、有机氨基或镁盐或类似的盐。当本发明化合物含有相对碱性的官能团时,可以通过使中性形式的此类化合物与足量的所需酸(纯的或在合适的惰性溶剂中)接触而获得酸加成盐。药学上可接受的酸加成盐的实例包括源自无机酸的那些盐,所述无机酸如盐酸、氢溴酸、硝酸、碳酸、一氢碳酸、磷酸、一氢磷酸、二氢磷酸、硫酸、一氢硫酸、氢碘酸或亚磷酸等,以及源自相对无毒的有机酸的盐,所述有机酸如乙酸、丙酸、异丁酸、马来酸、丙二酸、苯甲酸、琥珀酸、辛二酸、富马酸、乳酸、扁桃酸、邻苯二甲酸、苯磺酸、对甲苯磺酸、枸橼酸、酒石酸、草酸、甲磺酸等。还包括氨基酸的盐如精氨酸盐等,以及有机酸如葡糖醛酸或半乳糖醛酸等的盐(参见,例如Berge等人,“Pharmaceutical Salts”, Journal of Pharmaceutical Science, 1977, 66, 1-19)。本发明的某些特定化合物含有碱性及酸性官能团两者,这允许化合物转变为碱或酸加成盐。

[0115] 因此,本发明的化合物可作为例如用药学上可接受的酸形成的盐存在。本发明包括此类盐。此类盐的非限制性实例包括盐酸盐、氢溴酸盐、磷酸盐、硫酸盐、甲磺酸盐、硝酸盐、马来酸盐、乙酸盐、枸橼酸盐、富马酸盐、丙酸盐、酒石酸盐(例如(+)-酒石酸盐、(-)-酒石酸盐或其混合物,包括外消旋混合物)、琥珀酸盐、苯甲酸盐以及用氨基酸如谷氨酸形成的盐和季铵盐(例如碘甲烷、碘乙烷等)。这些盐可以通过本领域技术人员已知的方法来制备。

[0116] 中性形式的化合物优选通过使盐与碱或酸接触并且以常规方式分离母体化合物而再生。母体形式的化合物在某些物理特性上,例如在极性溶剂中的溶解度上不同于各种盐形式。

[0117] 除盐形式以外,本发明还提供了呈前药形式的化合物。本文描述的化合物的前药

是易于在生理条件下发生化学变化以提供本发明化合物的那些化合物。本文描述的化合物的前药可以在施用后在体内转化。另外,前药可通过化学或生物化学方法在离体环境中,例如,在接触合适的酶或化学试剂时转化为本发明的化合物。

[0118] 本发明的某些化合物可以呈非溶剂化形式以及溶剂化形式(包括水合形式)存在。一般而言,溶剂化形式与非溶剂化形式等效并且涵盖在本发明的范围内。本发明的某些化合物可以呈多晶形或无定形形式存在。一般而言,所有物理形式对于本发明所考虑的用途是等效的并且旨在属于本发明的范围之内。

[0119] 术语“多肽”、“肽”和“蛋白质”在本文中可互换用于指氨基酸残基的聚合物,其中所述聚合物可任选地与不是由氨基酸组成的部分偶联。该术语适用于其中一个或多个氨基酸残基为相应天然存在的氨基酸的人工化学模拟物的氨基酸聚合物,以及天然存在的氨基酸聚合物和非天然存在的氨基酸聚合物。

[0120] 多肽或细胞是人工的或经工程化的,或源自或含有人工或工程化蛋白或核酸(例如非天然或非野生型)时,是“重组的”。例如,插入载体或任何其它异源位置,例如重组生物的基因组中,使其不与像在自然界中发现时那样通常侧接多核苷酸的核苷酸序列缔合的多核苷酸为重组多核苷酸。在体外或体内由重组多核苷酸表达的蛋白质是重组多肽的实例。同样,自然界中未出现的多核苷酸序列,例如天然存在的基因的变体,是重组的。

[0121] “联合施用”意指在施用一种或多种附加疗法的同时、就在之前或就在之后施用本文描述的组合物。本发明的化合物可以单独施用或可以向患者联合施用。联合施用意在包括化合物单独地或呈组合(一种以上化合物)同时或依次施用。因此,需要时,也可将制剂与其它活性物质组合(例如以减少代谢降解)。本发明的组合物可通过局部途径经皮递送,或配制成涂药棒、溶液、混悬液、乳液、凝胶、乳膏、软膏、糊剂、凝胶剂、涂剂、粉剂和气溶胶。

[0122] 如本文中所用的“细胞”,是指执行足以保护或复制其基因组DNA的代谢或其它功能的细胞。可通过本领域的公知方法鉴定细胞,包括例如,完整膜的存在,用特定染料染色,产生子代的能力,或在配子的情况下,与第二配子组合以产生可以存活的后代的能力。细胞可包括原核和真核细胞。原核细胞包括但不限于细菌。真核细胞包括但不限于酵母细胞及源自植物和动物的细胞,例如哺乳动物、昆虫(例如夜蛾)和人类细胞。细胞在天然非粘附性或已处理(例如通过胰蛋白酶处理)而不粘附到表面时,可以是有用的。

[0123] 术语“治疗”是指成功治疗或改善损伤、疾病、病理或病状的任何标记,包括任何客观或主观参数,如症状的减轻;缓解;减少或者使得损伤、病理或病状更为患者所耐受;退化或衰退速率减缓;使得退化终点衰弱程度较小;改善患者的身体或精神健康。症状的治疗或改善可以基于客观或主观参数;包括身体检查、神经精神检查和/或精神病学评价的结果。例如,本文所提出的某些方法通过降低癌症的发病率和或致使癌症缓解而成功地治疗癌症。在本文描述的组合物或方法的一些实施方案中,治疗癌症包括减缓癌细胞的生长或扩散速率,减少转移,或降低转移性肿瘤的生长。术语“治疗”及其变形包括预防损伤、病理、病状或疾病。

[0124] “有效量”是对于化合物而言相对于该化合物不存在的情况,足以实现规定目的(例如达到施用其的效果,治疗疾病,降低酶活性,增加酶活性,减少信号传导途径,减轻疾病或病状的一种或多种症状(例如减少GTP结合的Ras(例如K-Ras)刺激的信号传导途径,降低Ras的信号传导途径活性,降低K-Ras的信号传导途径活性,降低K-Ras4A的信号传导途径

活性,降低K-Ras4B的信号传导途径活性,降低H-Ras的信号传导途径活性,降低N-Ras的信号传导途径活性,降低突变K-Ras的信号传导途径活性,抑制K-Ras与SOS的结合,抑制K-Ras与GEF的结合,减少K-Ras向膜的定位,减少K-Ras的异戊二烯化,抑制K-Ras向膜的定位,抑制K-Ras的异戊二烯化)的量。“有效量”的实例是足以促进疾病的一种或多种症状的治疗、预防或减轻的量,也可称为“治疗有效量”。一种或多种症状的“减轻”(以及该短语的语法同等成分)意指降低症状的严重程度或频率,或消除症状。药物的“预防有效量”是药物向受试者施用时将具有预期的预防效果的量,所述预防效果例如预防或延迟损伤、疾病、病理或病状的发作(或复发),或降低损伤、疾病、病理或病状或其症状发作(或复发)的可能性。完全的预防效果不一定通过施用一个剂量而出现,并且可能只有在施用一系列剂量之后出现。因此,预防有效量可以分一次或多次施用来施用。“活性降低量”,如本文中所用,是指相对于拮抗剂不存在的情况,降低酶活性所需的拮抗剂的量。“功能破坏量”,如本文中所用,是指相对于拮抗剂不存在的情况,破坏酶或蛋白质的功能(例如破坏K-Ras和信号传导途径结合蛋白如PI3K之间的蛋白质-蛋白质相互作用,破坏K-Ras和GEF的相互作用,破坏K-Ras和SOS的相互作用,破坏K-Ras与Raf的相互作用,破坏K-Ras向膜的定位,破坏K-Ras的异戊二烯化)所需的拮抗剂的量。确切的量将取决于治疗目的,并且将可由本领域技术人员使用已知技术确定(参见,例如,Lieberman, *Pharmaceutical Dosage Forms* (第1-3卷,1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); 及Remington: *The Science and Practice of Pharmacy*, 第20版,2003, Gennaro, Ed., Lippincott, Williams&Wilkins)。

[0125] “对照”或“对照实验”根据其简单普通含义使用并且是指除了省略实验程序、试剂或变量外,如同在平行实验中那样处理实验的受试者或试剂的实验。在一些情况下,对照作为比较标准用于评价实验效果。在一些实施方案中,对照是在本文所述化合物不存在的情况下,对蛋白质(例如Ras、K-Ras、突变K-Ras、K-Ras G12C、K-Ras G12D、K-Ras G13C、K-Ras G13D、K-Ras G12V、K-Ras G12S)活性(例如信号传导途径)的测量。

[0126] “接触”根据其简单普通含义使用并且是指使至少两种不同的物类(例如化学化合物,包括生物分子或细胞)变得足够接近以便反应、相互作用或物理性触碰的过程。然而,应认识到,所得反应产物可直接由所加试剂之间的反应生成或由反应混合物中可生成的来自一种或多种所加试剂的中间产物生成。

[0127] 术语“接触”可包括使两种物类反应、相互作用或物理性触碰,其中两种物类可以是本文描述的化合物和蛋白质或酶(例如Ras、K-Ras、H-Ras、N-Ras、K-Ras4A、K-Ras4B、突变Ras、突变K-Ras、K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)。在一些实施方案中,蛋白质可为K-Ras。在一些实施方案中,蛋白质可为突变K-Ras(例如K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)。在一些实施方案中,蛋白质可为K-Ras4A。在一些实施方案中,蛋白质可为K-Ras4B。在一些实施方案中接触包括使本文描述的化合物与信号传导途径中所涉及的蛋白质或酶相互作用。

[0128] 如本文中所定义,关于蛋白质-抑制剂相互作用的术语“抑制”意指相对于抑制剂不存在的情况下蛋白质的活性或功能,负面影响(例如降低)蛋白质的活性或功能(例如减少GTP结合的Ras(例如K-Ras、K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)刺激的信号传导途径、核苷酸交换、效应蛋白结合、效应蛋白活化、鸟嘌呤

呤交换因子 (GEF) 结合、SOS结合、GEF促进的核苷酸交换、磷酸释放、核苷酸释放、核苷酸结合、膜定位、蛋白质异戊二烯化)。在一些实施方案中抑制是指疾病或疾病症状的减轻。在一些实施方案中,抑制是指信号转导途径或信号传导途径的活性的降低(例如涉及GTP结合的Ras(例如K-Ras、K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)的途径的降低,涉及突变K-Ras(例如K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)的途径的降低)。因此,抑制包括,至少部分、局部或完全阻滞刺激,减少、防止或延迟活化,或灭活、脱敏化或下调信号传导途径或酶活性或蛋白质(例如K-Ras、K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)的量。在一些实施方案中,抑制是指对Ras(K-Ras、K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G13D、K-Ras G12V、K-Ras G12S)于信号传导途径结合伴侣(例如PI3K、SOS、Raf)的相互作用的抑制。在一些实施方案中,抑制是指对Ras与GEF(例如SOS)的相互作用的抑制。在一些实施方案中,抑制是指对Ras异戊二烯化的抑制。在一些实施方案中,抑制是指对Ras定位的抑制。在一些实施方案中,抑制是指对Ras膜定位的抑制。

[0129] 术语“调节剂”是指相对于组合物不存在的情况,增加或降低靶分子的水平或靶分子的功能(例如,效应蛋白结合、效应蛋白活化、鸟嘌呤交换因子 (GEF) 结合、SOS结合、异戊二烯化、定位)或分子靶标(例如靶标可为K-Ras并且功能可为水解GTP或活化受GTP结合的K-Ras活化的信号传导途径、K-Ras与蛋白质结合伴侣(例如PI3K、SOS、Raf)的相互作用)的物理状态(例如Ras亚细胞定位、Ras翻译后加工、Ras翻译后修饰(异戊二烯化))的组合物。在一些实施方案中,K-Ras疾病调节剂是相对于化合物不存在的情况,降低与K-Ras相关的疾病(例如癌症、转移癌)的一种或多种症状的严重程度的化合物。K-Ras调节剂是相对于化合物不存在的情况,增加或降低K-Ras的活性或功能或活性水平或功能水平或K-Ras水平或处于特定物理状态的K-Ras的水平的化合物。突变K-Ras调节剂是相对于化合物不存在的情况,增加或降低突变K-Ras的活性或功能或活性水平或功能水平或突变K-Ras水平或处于特定物理状态的突变K-Ras的水平的化合物。K-Ras G12C调节剂、K-Ras G12D调节剂、K-Ras G13C调节剂、K-Ras G12V调节剂、K-Ras G12S调节剂或K-Ras G13D调节剂是相对于化合物不存在的情况,增加或降低该特定突变K-Ras的活性或功能或活性水平或功能水平或该特定突变K-Ras的水平或处于特定物理状态的该特定突变K-Ras的水平的化合物。K-Ras抑制剂是相对于化合物不存在的情况,降低K-Ras的活性或功能或活性水平或功能水平或K-Ras水平或处于特定物理状态的K-Ras的水平的化合物。突变K-Ras抑制剂是相对于化合物不存在的情况,降低突变K-Ras的活性或功能或活性水平或功能水平或突变K-Ras水平或处于特定物理状态的突变K-Ras的水平的化合物。K-Ras G12C抑制剂、K-Ras G12D抑制剂、K-Ras G13C抑制剂、K-Ras G12V抑制剂、K-Ras G12S抑制剂或K-Ras G13D抑制剂是相对于化合物不存在的情况,降低该特定突变K-Ras的活性或功能或活性水平或功能水平或该特定突变K-Ras的水平或处于特定物理状态的该特定突变K-Ras的水平的化合物。

[0130] 术语“调节”根据其简单普通含义使用并且是指变化或改变一种或多种性质的作用。“调节”是指变化或改变一种或多种性质的过程。例如,应用于调节剂对靶蛋白的影响,调节意指通过增加或降低靶分子的性质或功能或靶分子的量来变化。

[0131] “患者”或“有需要的受试者”是指患有或易患可通过施用本文所提供的药物组合物来治疗的疾病或病状的活生物体。非限制性实例包括人、其它哺乳动物、牛、大鼠、小鼠、

狗、猴子、山羊、绵羊、奶牛、鹿和其它非哺乳类动物。在一些实施方案中，患者为人。

[0132] “疾病”或“病状”是指患者或受试者的能够用本文提供的化合物或方法治疗的生存状态或健康状况。在一些实施方案中，疾病是与Ras有关(例如由其引起)的疾病。在一些实施方案中，疾病是与K-Ras(例如K-Ras G12C、G13C、G12D、G12V、G12S或G13D)或异常的K-Ras信号传导途径活性有关(例如由其引起)的疾病(例如肺癌、乳腺癌、结肠癌、结直肠癌、胰腺癌、白血病)。疾病、病症或病状的实例包括但不限于癌症。疾病、病症或病状的实例包括但不限于MYH相关的息肉病。在一些情况下，“疾病”或“病状”是指癌症。在一些情况下，“疾病”或“病状”是指MYH相关的息肉病。在一些另外的情况下，“癌症”是指人类癌症和癌、肉瘤、腺癌、淋巴瘤、白血病等，包括实体癌和淋巴瘤、肾癌、乳腺癌、肺癌、膀胱癌、结肠癌、卵巢癌、前列腺癌、胰腺癌、胃癌、脑癌、头颈癌、皮肤癌、子宫癌、睾丸癌、神经胶质瘤、食道癌和肝脏癌(包括肝癌)、淋巴瘤(包括B-急性淋巴母细胞性淋巴瘤、非霍奇金淋巴瘤(non-Hodgkin's lymphoma)(例如伯基特淋巴瘤(Burkitt's)、小细胞和大细胞淋巴瘤)、霍奇金淋巴瘤)、白血病(包括AML、ALL和CML)或多发性骨髓瘤。

[0133] 如本文中所用，术语“癌症”是指在哺乳动物中发现的所有类型的癌症、赘生物或恶性肿瘤，包括白血病、癌和肉瘤。可用本文提供的化合物或方法治疗的示例性癌症包括甲状腺癌、内分泌系统癌、脑癌、乳腺癌、宫颈癌、结肠癌、头颈癌、肝癌、肾癌、肺癌、非小细胞肺癌、黑素瘤、间皮瘤、卵巢癌、肉瘤、胃癌、子宫癌、成神经管细胞瘤、结直肠癌、胰腺癌。另外的实例包括霍奇金病(Hodgkin's Disease)、非霍奇金淋巴瘤、多发性骨髓瘤、成神经细胞瘤、神经胶质瘤、多形性成胶质细胞瘤、卵巢癌、横纹肌肉瘤、原发性血小板增多、原发性巨球蛋白血症、原发性脑瘤、癌症、恶性胰腺胰岛素瘤、恶性类癌、膀胱癌、恶性前皮肤病变、睾丸癌、淋巴瘤、甲状腺癌、成神经细胞瘤、食道癌、泌尿生殖道癌、恶性高钙血症、子宫内膜癌、肾上腺皮质癌、内分泌或外分泌胰腺赘生物、甲状腺髓样癌症、甲状腺髓样癌、黑素瘤、结直肠癌、乳头状甲状腺癌、肝细胞癌或前列腺癌。

[0134] 术语“白血病”广泛地指造血器官的进行性、恶性疾病并且通常特征在于血液和骨髓中的白细胞及其前体的畸变增殖和发育。白血病通常在临床上基于以下进行分类：(1)急性或慢性疾病的持续时间和特征；(2)所涉细胞的类型；骨髓(骨髓性)、淋巴(淋巴源性)或单核细胞性；及(3)血液中异常细胞数量的增加或不增加-白血性或非白血性(亚白血病)。可用本文提供的化合物或方法治疗的示例性白细胞包括，例如急性非淋巴细胞性白血病、慢性淋巴细胞性白血病、急性粒细胞性白血病、慢性粒细胞性白血病、急性早幼粒细胞白血病、成人T细胞白血病、非白血性白血病、白血球血症性白血病、嗜碱细胞性白血病、母细胞白血病、牛白血病、慢性髓细胞性白血病、皮肤白血病、干细胞性白血病、嗜酸细胞性白血病、格罗斯白血病(Gross' leukemia)、毛细胞白血病、成血细胞性白血病、血胚细胞性白血病、组织细胞性白血病、干细胞白血病、急性单核细胞白血病、白细胞减少性白血病、淋巴性白血病、成淋巴细胞性白血病、淋巴细胞性白血病、淋巴源性白血病、淋巴样白血病、淋巴瘤细胞白血病、肥大细胞白血病、巨核细胞性白血病、小原粒型白血病、单核细胞性白血病、成髓细胞性白血病、髓细胞性白血病、髓样粒细胞性白血病、髓单核细胞白血病、内格利氏白血病(Naegeli leukemia)、浆细胞白血病、多发性骨髓瘤、浆细胞性白血病、早幼粒细胞性白血病、里德尔氏细胞性白血病(Rieder cell leukemia)、希林氏白血病(Schilling's leukemia)、干细胞白血病、亚白血性白血病以及未分化细胞白血病。

[0135] 术语“肉瘤”通常是指由如同胚性结缔组织等物质构成并且通常由嵌入纤维或均质物质中的密集细胞组成的肿瘤。可用本文提供的化合物或方法治疗的肉瘤包括软骨肉瘤、纤维肉瘤、淋巴肉瘤、黑素肉瘤、粘液肉瘤、骨肉瘤、艾伯内西氏肉瘤(Abemethy's sarcoma)、脂肪肉瘤、脂肉瘤、腺泡状软组织肉瘤、成釉细胞性肉瘤、葡萄样肉瘤、绿色瘤肉瘤、绒毛膜癌、胚胎性肉瘤、韦尔姆斯氏肿瘤肉瘤(Wilms'tumor sarcoma)、子宫内膜肉瘤、基质肉瘤、尤因氏肉瘤(Ewing's sarcoma)、筋膜肉瘤、纤维母细胞性肉瘤、巨细胞肉瘤、粒细胞性肉瘤、霍奇金氏肉瘤(Hodgkin's sarcoma)、特发性多发性色素沉着出血性肉瘤、B细胞的免疫母细胞性肉瘤、淋巴瘤、T细胞的免疫母细胞性肉瘤、詹森氏肉瘤(Jensen's sarcoma)、卡波西肉瘤(Kaposi's sarcoma)、库普弗细胞肉瘤(Kupffer cell sarcoma)、血管肉瘤、白血病性肉瘤、恶性间质瘤肉瘤、骨膜外肉瘤、网织红细胞性肉瘤、劳斯肉瘤(Rous sarcoma)、浆液囊性肉瘤、滑膜肉瘤或毛细血管扩张性肉瘤。

[0136] 术语“黑素瘤”用于意指由皮肤和其它器官的黑素细胞系统产生的肿瘤。可用本文提供的化合物或方法治疗的黑素瘤包括例如肢端雀斑样痣黑素瘤、无黑色素性黑素瘤、良性青少年黑素瘤、克劳德曼氏黑素瘤(Cloudman's melanoma)、S91黑素瘤、哈丁-帕西黑素瘤(Harding-Passey melanoma)、青少年黑素瘤、恶性小痣黑素瘤、恶性黑素瘤、结节性黑素瘤、甲下黑素瘤和浅表扩散性黑素瘤。

[0137] 术语“癌”是指由倾向于浸润周围组织并引起转移的上皮细胞组成的恶性新生物。可用本文提供的化合物或方法治疗的恶性癌瘤包括例如甲状腺髓样癌、家族性甲状腺髓样癌、腺泡癌、腺泡状癌、囊性腺样癌、腺样囊性癌、腺癌、肾上腺皮质癌、肺泡癌、肺泡细胞癌、基底细胞癌、基底上皮细胞癌、基底细胞样癌、基底鳞状细胞癌、细支气管肺泡癌、细支气管癌、支气管癌、脑样癌、胆管细胞癌、绒毛膜癌、胶质性癌、粉刺癌、子宫体癌、筛状癌、胸廓癌、皮肤癌、柱状癌、柱状细胞癌、导管癌、硬癌、胚性癌、髓样癌、表皮样癌、腺样上皮细胞癌、外植癌、溃疡癌、纤维癌、胶样癌(gelatiniform carcinoma)、胶状癌(gelatinous carcinoma)、巨细胞癌(giant cell carcinoma)、巨细胞癌(carcinoma gigantocellulare)、腺癌、颗粒细胞癌、发母质癌、多血癌、肝细胞癌、许特尔细胞癌(Hurthle cell carcinoma)、透明癌、肾上腺样癌、幼稚性胚胎性癌、原位癌、表皮内癌、上皮内癌、克龙派切尔皮肤癌(Krompecher's carcinoma)、库尔契茨基底细胞癌(Kulchitzky-cell carcinoma)、大细胞癌、豆状癌(lenticular carcinoma)、豆状癌(carcinoma lenticulare)、脂瘤样癌、淋巴上皮癌、髓样癌(carcinoma medullare)、髓样癌(medullary carcinoma)、黑色素癌、软癌、粘液癌(mucinous carcinoma)、粘液癌(carcinoma muciparum)、粘液细胞癌(carcinoma mucocellulare)、粘液表皮样癌、粘液癌(carcinoma mucosum)、粘液癌(mucous carcinoma)、粘液瘤样癌(carcinoma myxomatodes)、鼻咽癌、燕麦细胞癌、骨样癌(carcinoma ossificans)、骨样癌(osteoid carcinoma)、乳头状癌、门静脉周癌、浸润前癌、棘细胞癌(prickle cell carcinoma)、髓样癌、肾脏肾细胞癌、贮备细胞癌、肉瘤样癌、施奈德癌(schneiderian carcinoma)、硬癌、阴囊癌、印戒细胞癌、单纯癌、小细胞癌、马铃薯状癌(solanoid carcinoma)、球状细胞癌、梭形细胞癌、髓样癌、鳞状癌、鳞状细胞癌(squamous cell carcinoma)、绳捆癌(string carcinoma)、血管扩张性癌(carcinoma telangiectaticum)、血管扩张性癌(carcinoma telangiectodes)、移行细胞癌、结节性皮癌(carcinoma tuberosum)、结节性皮癌

(tuberous carcinoma)、疣状癌或绒毛状癌。

[0138] “Ras相关癌症”(本文也称为“Ras有关癌症”)是指由异常的Ras活性或信号传导引起的癌症。“与异常K-Ras活性相关的癌症”(本文也称为“K-Ras有关癌症”)是由异常的K-Ras活性或信号传导(例如突变K-Ras)引起的癌症。K-Ras有关癌症可包括肺癌、非小细胞肺癌、乳腺癌、白血病、胰腺癌、结肠癌、结直肠癌。与Ras、K-Ras、H-Ras、N-Ras、突变K-Ras(包括K-Ras G12C、K-Ras G13C、K-Ras G12D、K-Ras G12V、K-Ras G12S、K-Ras G13D突变体)、突变N-Ras和突变H-Ras中的一种或多种的异常活性相关的其它癌症是本领域公知的并且确定此类癌症是在本领域技术人员的技术范围之内。

[0139] “药学上可接受的赋形剂”和“药学上可接受的载体”是指有助于向受试者施用活性剂并被受试者吸收,并且可以包括在本发明的组合物中,而不会对患者引起显著不良毒性作用的物质。药学上可接受的赋形剂的非限制性实例包括水、NaCl、生理盐溶液、乳酸林格氏液(lactated Ringer's)、普通蔗糖、普通葡萄糖、粘合剂、填充剂、崩解剂、润滑剂、包衣、甜味剂、调味剂、盐溶液(如林格氏液)、醇、油、明胶、碳水化合物(如乳糖、直链淀粉或淀粉)、脂肪酸酯、羟甲基纤维素、聚乙烯吡咯烷和色素等。此类制剂可灭菌,并且若需要,可与不会与本发明的化合物发生有害反应的助剂如润滑剂、防腐剂、稳定剂、润湿剂、乳化剂、用于影响渗透压的盐、缓冲剂、着色和/或芳香物质等混合。本领域的技术人员将认识到药物赋形剂在本发明中有用。

[0140] 术语“制剂”旨在包括活性化合物与作为载体提供胶囊的封装材料的调配物,在胶囊中有或无其它载体的活性组分被载体包围,因此载体与之缔合。类似地,包括扁囊剂和锭剂。片剂、粉剂、胶囊、丸剂、扁囊剂和锭剂可作为适于口服施用的固体剂型使用。

[0141] 如本文中所用,术语“施用”意指口服施用、作为栓剂施用、局部接触、静脉内、腹膜内、肌肉内、病灶内、鞘内、鼻内或皮下施用,或向受试者植入缓释装置,例如微量渗透泵。通过任何途径施用,包括肠胃外和经粘膜(例如,口腔、舌下、腭、牙龈、鼻部、阴道、直肠或经皮)。肠胃外施用包括,例如静脉内、肌肉内、小动脉内、皮内、皮下、腹膜内、心室内和颅内。其它递送模式包括但不限于使用脂质体调配物、静脉输注、透皮贴剂等。用“联合施用”意指在施用一种或多种附加疗法的同时、就在之前或就在之后施用本文描述的组合物,所述附加疗法例如癌症疗法,如化学疗法、激素疗法、放射疗法或免疫疗法。本发明的化合物可以单独施用或可以向患者联合施用。联合施用意在包括化合物单独地或呈组合(一种以上化合物)同时或依次施用。因此,需要时,也可将制剂与其它活性物质组合(例如以减少代谢降解)。本发明的组合物可通过局部途径经皮递送,配制成涂药棒、溶液、混悬液、乳液、凝胶、乳膏、软膏、糊剂、凝胶剂、涂剂、粉剂和气溶胶。

[0142] 术语“施用Ras抑制剂”意指向受试者施用抑制一种或多种Ras蛋白的活性或水平(例如量)或信号传导途径水平的化合物(例如Ras抑制剂、K-Ras抑制剂、N-Ras抑制剂、H-Ras抑制剂、突变K-Ras抑制剂、K-Ras G12C抑制剂、K-Ras G12V抑制剂、K-Ras G12S抑制剂、K-Ras G13C抑制剂、K-Ras G12D抑制剂、K-Ras G13D抑制剂)。施用可包括(但不受机理限制)允许足够时间以便Ras抑制剂降低一种或多种Ras蛋白的活性或以便Ras抑制剂减轻疾病的一种或多种症状(例如癌症,其中Ras抑制剂可以阻止细胞循环,减缓细胞循环,减少DNA复制,减少细胞复制,减少细胞生长,减少转移或引起细胞死亡)。术语“施用K-Ras抑制剂”意指施用抑制一种或多种K-Ras蛋白(K-Ras、突变K-Ras、K-Ras G12C、K-Ras G12V、K-

Ras G12S、K-Ras G12D、K-Ras G13C、K-Ras G13D) 的活性或水平 (例如量) 或信号传导途径水平的化合物。

[0143] 本文描述的化合物可相互组合, 与已知在治疗与表达特定Ras、K-Ras、突变K-Ras的细胞相关的疾病 (例如癌症) 中有用的其它活性剂组合, 或与可能单独无效但可有助于活性剂的功效的辅助剂组合使用。

[0144] 在一些实施方案中, 联合施用包括在第二活性剂0.5、1、2、4、6、8、10、12、16、20或24小时内施用一种活性剂。联合施用包括同时、大约同时 (例如, 在彼此约1、5、10、15、20或30分钟内) 或以任何顺序依次施用两种活性剂。在一些实施方案中, 联合施用可通过共同配制实现, 即制备包括两种活性剂的单一药物组合物。在其它实施方案中, 活性剂可单独配制。在另一实施方案中, 活性剂和/或辅助剂可相互连接或偶联。

[0145] 作为非限制性实例, 本文描述的化合物可与常规化学治疗剂联合施用, 所述化学治疗剂包括烷化剂 (例如, 环磷酰胺、异环磷酰胺、苯丁酸氮芥、白消安、美法仑、二氯甲二乙胺 (mechlorethamine)、乌拉莫司汀、塞替派、亚硝基脲等)、抗代谢物 (例如, 5-氟尿嘧啶、硫唑嘌呤、甲氨蝶呤、甲酰四氢叶酸、卡培他滨、阿糖胞苷、氟尿苷、氟达拉滨、吉西他滨、培美曲塞、雷替曲塞等)、植物碱 (例如, 长春新碱、长春碱、长春瑞滨、长春地辛、鬼臼毒素、紫杉醇、多西他赛等)、拓扑异构酶抑制剂 (例如, 伊立替康、托泊替康、安吡啶、依托泊苷 (VP16)、磷酸依托泊苷、替尼泊苷等)、抗肿瘤抗生素 (例如, 多柔比星、阿霉素 (adriamycin)、柔红霉素、表柔比星、放线菌素、博来霉素、丝裂霉素、米托蒽醌、普卡霉素等)、铂基化合物 (例如顺铂、奥沙利铂 (oxaloplatin)、卡铂等) 及类似物。

[0146] 本文描述的化合物也可与常规激素治疗剂联合施用, 所述激素治疗剂包括但不限于类固醇 (例如, 地塞米松)、非那雄胺、芳香酶抑制剂、他莫昔芬和促性腺激素释放激素激动剂 (GnRH) 如戈舍瑞林。

[0147] 另外, 本文描述的化合物可与常规免疫治疗剂联合施用, 所述免疫治疗剂包括但不限于免疫刺激剂 (例如, 卡介苗 (*Bacillus Calmette-Guérin*) (BCG)、左旋咪唑、白细胞介素-2、 α -干扰素等)、单克隆抗体 (例如, 抗CD20、抗HER2、抗CD52、抗HLA-DR和抗VEGF单克隆抗体)、免疫毒素 (例如, 抗CD33单克隆抗体-卡奇霉素 (calicheamicin) 偶联物、抗CD22单克隆抗体-假单胞菌外毒素偶联物等) 和放射免疫疗法 (例如, 与 ^{111}In 、 ^{90}Y 或 ^{131}I 偶联的抗CD20单克隆抗体等)。

[0148] 在另一实施方案中, 本文描述的化合物可与常规放射性治疗剂联合施用, 所述放射性治疗剂包括但不限于任选与针对肿瘤抗原的抗体偶联的放射性核素如 ^{47}Sc 、 ^{64}Cu 、 ^{67}Cu 、 ^{89}Sr 、 ^{86}Y 、 ^{87}Y 、 ^{90}Y 、 ^{105}Rh 、 ^{111}Ag 、 ^{111}In 、 $^{117\text{m}}\text{Sn}$ 、 ^{149}Pm 、 ^{153}Sm 、 ^{166}Ho 、 ^{177}Lu 、 ^{186}Re 、 ^{188}Re 、 ^{211}At 和 ^{212}Bi 。

[0149] 在用于癌症治疗的治疗性用途中, 本发明药物组合物中利用的化合物可按每天约0.001mg/kg至约1000mg/kg的初始剂量施用。可以使用约0.01mg/kg至约500mg/kg, 或约0.1mg/kg至约200mg/kg, 或约1mg/kg至约100mg/kg, 或约10mg/kg至约50mg/kg的日剂量范围。然而, 剂量可根据患者的需求、所治病状的严重程度及和所采用的化合物或药物而改变。例如, 可以考虑在特定患者中诊断出的癌症类型和分期, 根据经验确定剂量。在本发明的背景下, 向患者施用的量, 应足以随时间推移影响患者中的有益治疗反应。剂量大小也将由特定患者中伴随化合物施用的任何不良副作用的存在、特性和程度来决定。特定情形的适当剂量的确定在从业者的技术范围之内。通常, 以低于化合物最佳剂量的较小剂量开始

治疗。之后,以小增量增加剂量,直至达到情况下的最佳效果。为了方便起见,若需要,可在当天将每日总剂量分开并逐份施用。

[0150] 本文描述的化合物可相互组合,与已知在治疗癌症中有用的其它活性剂组合,或与可能单独无效但可有助于活性剂的功效的辅助剂组合使用。

[0151] 在与疾病(例如蛋白质相关疾病、与异常Ras活性相关的癌症、K-Ras相关癌症、突变K-Ras相关癌症、活化K-Ras相关癌症、K-RasG12C相关癌症、K-Ras G12V相关癌症、K-Ras G12S相关癌症、K-RasG13C相关癌症、K-Ras G12D相关癌症、K-Ras G13D相关癌症)相关的物质或物质活性或功能的背景下,术语“相关”或“与……相关”意指该疾病(例如癌症)由(完全或部分),或该疾病的症状由(完全或部分)所述物质或物质活性或功能引起。例如,与异常Ras活性或功能相关的癌症可以是由异常Ras活性或功能(例如酶活性、蛋白质-蛋白质相互作用、信号传导途径)引起的癌症或其中疾病的特定症状由(完全或部分)异常Ras活性或功能引起的癌症。如本文中所用,描述为与疾病相关的要素,如果是病原体,则可为疾病治疗的靶标。例如,在增强的Ras活性或功能(例如信号传导途径活性)引起癌症的情况下,与异常Ras活性或功能相关的癌症或Ras相关癌症,可用Ras调节剂或Ras抑制剂治疗。例如,与K-Ras G12V相关的癌症可以是有K-Ras G12V的受试者与无K-Ras G12V的受试者相比处于更高的发展风险的癌症。

[0152] 如本文中所述的术语“异常”是指不同于正常。当用于描述酶活性时,异常是指活性高于或低于正常对照或正常非患病对照样品的平均值。异常活性可指产生疾病的活性的量,其中使异常活性恢复至正常或非疾病相关的量(例如通过施用化合物或使用本文描述的方法),引起疾病或一种或多种疾病症状减轻。

[0153] “抗癌剂”根据其简单普通含义使用并且是指具有抗肿瘤性质或抑制细胞生长或增殖的能力的组合物(例如化合物、药物、拮抗剂、抑制剂、调节剂)。在一些实施方案中,抗癌剂为化学治疗剂。在一些实施方案中,抗癌剂是本文鉴定的在治疗癌症的方法中具有实用性的试剂。在一些实施方案中,抗癌剂是FDA或除USA以外的国家的类似监管结构批准用于治疗癌症的药剂。抗癌剂的实例包括但不限于MEK(例如MEK1、MEK2或MEK1和MEK2)抑制剂(例如XL518、CI-1040、PD035901、司美替尼/AZD6244、GSK1120212/曲美替尼、GDC-0973、ARRY-162、ARRY-300、AZD8330、PD0325901、U0126、PD98059、TAK-733、PD318088、AS703026、BAY 869766)、烷化剂(例如,环磷酰胺、异环磷酰胺、苯丁酸氮芥、白消安、美法仑、二氯甲二乙胺、乌拉莫司汀、塞替派、亚硝基脲、氮芥(例如,二氯甲二乙胺、环磷酰胺、苯丁酸氮芥、美法仑)、乙烯亚胺和甲基三聚氰胺(例如,六甲基三聚氰胺、塞替派)、烷基磺酸盐(例如,白消安)、亚硝基脲(例如,卡莫司汀、洛莫司汀、司莫司汀、链佐星)、三氮烯(氮烯咪胺)、抗代谢物(例如,5-硫唑嘌呤、甲酰四氢叶酸、卡培他滨、氟达拉滨、吉西他滨、培美曲塞、雷替曲塞、叶酸类似物(例如,甲氨蝶呤)或嘧啶类似物(例如,氟尿嘧啶、氟尿苷、阿糖胞苷)、嘌呤类似物(例如,巯基嘌呤、硫鸟嘌呤、戊糖苷)等)、植物碱(例如,长春新碱、长春碱、长春瑞滨、长春地辛、鬼臼毒素、紫杉醇、多西他赛等)、拓扑异构酶抑制剂(例如,伊立替康、托泊替康、安吡啶、依托泊苷(VP16)、磷酸依托泊苷、替尼泊苷等)、抗肿瘤抗生素(例如,多柔比星、阿霉素、柔红霉素、表柔比星、放线菌素、博来霉素、丝裂霉素、米托蒽醌、普卡霉素等)、铂基化合物(例如顺铂、奥沙利铂、卡铂)、蒽醌(例如,米托蒽醌)、经取代的脲(例如,羟基脲)、甲基胍衍生物(例如,丙卡巴肼)、肾上腺皮质抑制剂(例如,米托坦、氨鲁米特)、表鬼臼毒素(例如,

依托泊苷)、抗生素(例如,柔红霉素、多柔比星、博来霉素)、酶(例如,L-门冬酰胺酶)、丝裂原活化蛋白激酶信号传导抑制剂(例如U0126、PD98059、PD184352、PD0325901、ARRY-142886、SB239063、SP600125、BAY 43-9006、渥曼青霉素或LY294002、Syk抑制剂、mTOR抑制剂、抗体(例如,利妥昔单抗(美罗华(rituxan)))、棉子酚(gossypol)、根纳三思(genasense)、多酚E、Chlorofusin、全反式视黄酸(ATRA)、苔藓抑素、肿瘤坏死因子相关的凋亡诱导配体(TRAIL)、5-氮杂-2'-脱氧胞苷、全反式视黄酸、多柔比星、长春新碱、依托泊苷、吉西他滨、伊马替尼(Gleevec.RTM.)、格尔德霉素、17-N-丙烯胺-17-去甲氧格尔德霉素(17-AAG)、夫拉平度、LY294002、硼替佐米、曲妥珠单抗、BAY 11-7082、PKC412、PD184352、20-表-1,25二羟维生素D3;5-乙炔尿嘧啶;阿比特龙;阿柔比星;酰基富烯(acylfulvene);腺环戊醇(adecypenol);阿多来新;阿地白介素;ALL-TK拮抗剂;六甲蜜胺;氨莫司汀;艾美多(amidox);氨磷汀;氨基乙酰丙酸;氨柔比星;安吡啶;阿那格雷;阿那曲唑;穿心莲内酯;血管生成抑制剂;拮抗剂D;拮抗剂G;安雷利克斯(antarelix);抗背部化形态发生蛋白-1;前列腺癌抗雄激素药;抗雌激素药;抗瘤酮;反义寡核苷酸;甘氨酸阿非科林;凋亡基因调节剂;凋亡调控剂;脱嘌呤核酸;ara-CDP-DL-PTBA;精氨酸脱氨酶;奥沙那宁(asulacrine);阿他美坦;阿莫司汀;阿新司坦汀1(axinastatin 1);阿新司坦汀2;阿新司坦汀3;阿扎司琼;阿扎毒素;重氮酪氨酸;浆果赤霉素(baccatin) III衍生物;巴拉诺(balanol);巴马司他;BCR/ABL拮抗剂;苯并二氢卟吩(benzochlorins);苯甲酰十字孢碱(benzoylstauroporine);β内酰胺衍生物;β-阿立辛(beta-alethine);倍他克拉霉素B(betaclamycin B);桦木酸(betulinic acid);bFGF抑制剂;比卡鲁胺;比生群;双氮丙啶基精胺(bisaziridinylspermine);双奈法德;双特拉汀A(bistratene A);比折来新;比锐来特(breflate);溴匹立明;布度钛;丁硫胺磺酰亚胺(buthionine sulfoximine);卡泊三醇;卡弗他丁C(calphostin C);喜树碱衍生物;金丝雀痘IL-2;卡培他滨;氮甲酰-氨基-三唑;羧胺三唑;CaRest M3;CARN 700;软骨源性抑制剂;卡折来新;酪蛋白激酶抑制剂(ICOS);栗树精胺(castanospermine);杀菌肽B;西曲瑞克;绿素类(chlorins);氯喹啉磺酰胺;西卡前列素;顺式-卟啉;克拉屈滨;氯米芬类似物;克霉唑;克立霉素A(collismycin A);克立霉素B;考布他汀A4(combretastatin A4);考布他汀类似物;康纳京尼(conagenin);克拉昔汀816(crambescidin 816);克立那托;念珠藻素8(cryptophycin 8);念珠藻素A衍生物;库拉欣A(curacin A);环戊蒽醌(cyclopentantraquinones);环普兰姆(cycloplatam);西匹霉素(cypemycin);阿糖胞苷十八烷基磷酸盐(cytarabine ocfosfate);溶细胞因子;细胞抑素(cytostatin);达昔单抗;地西他滨;脱氢膜海鞘素B(dehydrodidemnin B);地洛瑞林;地塞米松;右异环磷酰胺(dexifosfamide);右雷佐生;右维拉帕米;地吡酮;膜海鞘素B(didemnin B);地多西(didox);二乙基去甲精胺(diethylnorspermine);二氢-5-氮杂胞苷;9-二噻霉素(9-dioxamycin);二苯基螺莫司汀;二十二醇;多拉司琼;去氧氟尿苷;屈洛昔芬;屈大麻酚;倍癌霉素SA(duocarmycin SA);依布硒;依考莫司汀;依地福新;依决洛单抗;依氟鸟氨酸;榄香烯;乙嘧替氟;表柔比星;爱普列特;雌莫司汀类似物;雌激素激动剂;雌激素拮抗剂;依他硝唑;磷酸依托泊苷;依西美坦;法倔唑;法扎拉滨;芬维A胺(fenretinide);非格司亭;非那雄胺;夫拉平度;氟卓斯汀;氟斯特酮(flusterone);氟达拉滨;盐酸氟道诺欣(fluorodaunorubicin hydrochloride);福酚美克;福美坦;福司曲星;福莫司汀;德克萨卟啉钆(gadolinium texaphyrin);硝酸镓;加

洛他滨;加尼瑞克;明胶酶抑制剂;吉西他滨;谷胱甘肽抑制剂;海普法姆(hepsulfam);海瑞古林(hereregulin);六亚甲基二乙酰胺;金丝桃素;伊班膦酸;伊达比星;艾多昔芬;伊决孟酮;伊莫福新;伊洛马司他;咪唑并吡啶酮(imidazoacridones);咪唑莫特;免疫刺激肽;胰岛素样生长因子-1受体抑制剂;干扰素激动剂;干扰素类;白介素;碘苄胍;碘阿霉素;4-甘露苦醇;伊罗普拉;伊索拉定;异苯胍唑(isobengazole);异高软海绵素B(isohomohalicondrin B);伊他司琼;伽斯利德(jasplakinolide);卡哈利德F(kahalalide F);三醋酸片螺素-N(lamellarin-N triacetate);兰瑞肽;雷那霉素(leinamycin);来格司亭;硫酸香菇多糖;立托斯坦汀(leptolstatin);来曲唑;白血病抑制因子;白细胞 α 干扰素;亮丙瑞林+雌激素+孕酮;亮丙瑞林;左旋咪唑;利阿唑;直链多元胺类似物;亲脂性双糖肽;亲脂性铂化合物;立索克林酰胺7(lissoclinamide 7);洛铂;蚯蚓磷脂;洛美曲索;氯尼达明;洛索萘醌;洛伐他汀;洛索立宾;勒托替康;德克萨卜啉钬(lutetium texaphyrin);里斯福林(lysofylline);裂解肽;美坦新;麦洛坦汀A(mannostatin A);马立马司他;马索罗酚;乳腺丝抑蛋白(maspin);基质溶解因子抑制剂;基质金属蛋白酶抑制剂;美诺立尔;麦尔巴隆(merbarone);美替瑞林;甲硫氨酸酶;甲氧氯普胺;MIF抑制剂;米非司酮;米替福新;米立司亭;错配双链RNA;米托胍脲;二溴卫矛醇;丝裂霉素类似物;米托蒽胺;米托毒素成纤维细胞生长因子-皂草素;米托萘醌;莫法罗汀;莫拉司亭;单克隆抗体;人绒毛膜促性腺激素;人类绒毛膜促性腺激素;单磷酸脂质A+分枝杆菌细胞壁sk;莫哌达醇;多重耐药基因抑制剂;基于多肿瘤抑制基因1的疗法;氮芥抗癌剂;印度洋海绵B(mycaperoxide B);分枝杆菌细胞壁提取物;美瑞普仁(myriaporone);N-乙酰地那林(N-acetyldinaline);N-取代的苯甲酰胺;那法瑞林;纳格瑞替(nagrestip);纳洛酮+喷他佐辛;纳帕维(napavin);奈帕特林(naphterpin);那托司亭;奈达铂;奈莫柔比星;奈立膦酸;中性肽链内切酶;尼鲁米特;尼撒霉素(nisamycin);一氧化氮调节剂;硝基氧抗氧化剂;纽崔林(nitrullyn);06-苄基鸟嘌呤;奥曲肽;奥克恩(okicenone);寡核苷酸;奥那司酮;昂丹司琼;昂丹司琼;奥拉新(oracin);口服细胞因子诱导剂;奥马铂;奥沙特隆;奥沙利铂;厄诺霉素(oxaunomycin);巴拉乌胺(palauamine);棕榈酰根霉素(palmitoylrhizoxin);帕米膦酸;人参炔三醇(panaxytriol);帕诺米芬;副球菌素(parabactin);帕折普汀;培门冬酶;培得星(peldesine);戊聚糖聚硫酸钠;喷司他丁;泮托唑(pentozole);全氟溴烷;培磷酰胺;紫苏醇;苯连氮霉素(phenazinomycin);苯乙酸盐(phenylacetate);磷酸酶抑制剂;毕西巴尼(picibanil);盐酸毛果芸香碱;吡柔比星;吡曲克辛;普拉汀A(placetin A);普拉汀B;纤溶酶原活化因子抑制剂;铂络合物;铂化合物;铂-三胺络合物;吡吩姆钠;泊非霉素;泼尼松;丙基双吡啶酮;前列腺素J2;蛋白酶体抑制剂;基于蛋白A的免疫调节剂;蛋白激酶C抑制剂;微藻蛋白激酶C抑制剂;蛋白质酪氨酸磷酸酶抑制剂;嘌呤核苷磷酸化酶抑制剂;紫红素(purpurin);吡唑啉吡啶(pyrazoloacridine);吡醇羟乙酯血红蛋白聚氧乙烯共轭物;raf拮抗剂;雷替曲塞;雷莫司琼;ras法尼基蛋白转移酶抑制剂;ras抑制剂;ras-GAP抑制剂;脱甲基化瑞替普汀;依替膦酸铈Re 186;根霉素;核酶;RII维甲酰胺;罗谷亚胺;罗希吐碱(rohitukine);罗莫肽;罗喹美克;卢比基酮B1(rubiginone B1);卢伯西(ruboxyl);沙芬戈(safingol);圣特平(saintopin);SarCNU;肌肉叶绿醇A(sarcophytol A);沙格司亭;Sdi 1模拟物;司莫司汀;衰老源抑制剂1;有义寡核苷酸;信号转导抑制剂;信号转导调节剂;单链抗原结合蛋白;西佐喃(sizofuran);索布佐生;硼卡钠(sodium borocaptate);苯乙酸钠;

索维洛(solverol);生长介素结合蛋白;索纳明(sonermin);膦门冬酸(sparfosic acid);斯卡霉素D(spicamycin D);螺莫司汀;脾脏五肽(splenopentin);海绵抑素1(spongistatin 1);角鲨胺(squalamine);干细胞抑制剂;干细胞分裂抑制剂;斯蒂酰胺(stipiamide);基质溶素抑制剂(stromelysin inhibitors);斯菲诺辛(sulfinosine);强效血管活性肠肽拮抗剂;苏拉斯塔(suradista);舒拉明;苦马豆素;合成葡萄糖胺聚糖;他莫司汀;他莫昔芬甲碘化物;牛磺莫司汀;他扎罗汀;替可加兰钠;替加氟;tellurapyrylium;端粒末端转移酶抑制剂(telomerase inhibitor);替莫泊芬;替莫唑胺;替尼泊苷;四氯癸氧化物;四唑明(tetrazomine);噻立拉斯汀(thaliblastine);噻可拉林;促血小板生成素;促血小板生成素模拟物;胸腺法新;胸腺生长素受体激动剂;胸腺曲南;促甲状腺激素;本紫红素乙酯锡(tin ethyl etiopurpurin);替拉扎明;二氯二茂钛(titanocene bichloride);特西汀(topsentin);托瑞米芬;全能干细胞因子;翻译抑制剂;维A酸(tretinoin);三乙酰尿苷;曲西立滨;三甲曲沙;曲普瑞林;托烷司琼;妥罗雄脲;酪氨酸激酶抑制剂;酪氨酸磷酸化抑制剂(tyrphostin);UBC抑制剂;乌苯美司;尿殖窦源生长抑制因子;尿激酶受体拮抗剂;伐普肽;维洛林B(variolin B);载体系统红细胞基因治疗剂;维拉雷琐;藜芦胺(veramine);维尔丁(verdin);维替泊芬;长春瑞滨;维夏汀(vinxaltine);维他欣(vitaxin);伏氯唑;扎诺特隆;折尼铂;亚苾维C(zilascorb);净司他丁斯酯;阿霉素;放线菌素D(Dactinomycin);博来霉素;长春碱;顺铂;阿西维辛;阿柔比星;盐酸阿考达唑;阿克罗宁;阿多来新;阿地白介素;六甲蜜胺;安波霉素;醋酸阿美茵醌;氨鲁米特;安吡啶;阿那曲唑;氨茴霉素;门冬酰胺酶;曲林菌素;阿扎胞苷;阿扎替派;阿佐霉素;巴马司他;苯佐替派;比卡鲁胺;盐酸比生群;二甲磺酸双奈法德;比折来新;硫酸博来霉素;布喹那钠;溴匹立明;白消安;放线菌素C(cactinomycin);卡普睾酮;卡醋酸;卡贝替姆;卡铂;卡莫司汀;盐酸卡柔比星;卡折来新;西地芬戈;苯丁酸氮芥;西罗霉素;克拉屈滨;甲磺酸克立那托;环磷酰胺;阿糖胞苷;达卡巴嗪;盐酸柔红霉素;地西他滨;右奥马铂;地扎胍宁;甲磺酸地扎胍宁;地吡醌;多柔比星;盐酸多柔比星;屈洛昔芬;枸橼酸屈洛昔芬;丙酸屈他雄酮;达佐霉素;依达曲沙;盐酸依氟鸟氨酸;依沙芦星;恩洛铂;恩普氨酯;依匹哌啶;盐酸表柔比星;厄布洛唑;盐酸依索比星;雌莫司汀;雌莫司汀磷酸钠;依他硝唑;依托泊苷;磷酸依托泊苷;艾托卜宁(etoprine);盐酸法倔唑;法扎拉滨;芬维A胺;氟尿苷;磷酸氟达拉滨;氟尿嘧啶;氟西他滨(fluorocitabine);磷喹酮;福司曲星钠;吉西他滨;盐酸吉西他滨;羟基脲;盐酸伊达比星;异环磷酰胺;伊莫福新(iimofosine);白介素II(包括重组白介素II或r1L2)、干扰素 α -2a;干扰素 α -2b;干扰素 α -n1;干扰素 α -n3;干扰素 β -1a;干扰素 γ -1b;异丙铂;盐酸伊立替康;醋酸兰瑞肽;来曲唑;醋酸亮丙瑞林;盐酸利阿唑;洛美曲索钠;洛莫司汀;盐酸洛索茵醌;马索罗酚;美坦辛;盐酸二氯甲二乙胺;醋酸甲地孕酮;醋酸美仑孕酮;美法仑;美诺立尔;巯基嘌呤;甲氨蝶呤;甲氨蝶呤钠;氯苯氨啶;美妥替哌;米丁度胺;米托卡星(mitocarcin);丝裂红素;米托洁林;米托马星;丝裂霉素;米托司培;米托坦;盐酸米托蒽醌;麦考酚酸;诺考达唑;诺拉霉素;奥马铂;奥昔舒仑;培门冬酶;培利霉素;戊氮芥;硫酸培洛霉素;培磷酰胺;哌泊溴烷;哌泊舒凡;盐酸吡罗茵醌;普卡霉素;普洛美坦;吡吩姆钠;泊非霉素;泼尼莫司汀;盐酸丙卡巴肼;嘌罗霉素;盐酸嘌罗霉素;吡唑咪喃菌素(pyrazofurin);利波腺苷;罗谷亚胺;沙芬戈;盐酸沙芬戈;司莫司汀;辛曲秦;磷乙酰天冬氨酸钠(sparfosate sodium);司帕霉素;盐酸螺旋胺;螺莫司汀;螺铂;链黑菌素;链佐星;

磺氯苯脲;他利霉素;替可加兰钠;替加氟;盐酸替洛萸醌;替莫泊芬;替尼泊昔;替罗昔隆;鞣内酯;硫咪嘌呤(thiamiprine);硫鸟嘌呤;塞替派;噻唑呋啉(tiazofurin);替拉扎明;枸橼酸托瑞米芬;醋酸曲托龙;磷酸曲西立滨;三甲曲沙;葡糖醛酸三甲曲沙;曲普瑞林;盐酸妥布氯唑;尿嘧啶氮芥;乌瑞替派;伐普肽;维替泊芬;硫酸长春碱;硫酸长春新碱;长春地辛;硫酸长春地辛;硫酸长春匹定;硫酸长春甘酯;硫酸长春罗新;酒石酸长春瑞滨;硫酸长春罗定;硫酸长春利定;伏氯唑;折尼铂;净司他丁;盐酸佐柔比星,使细胞停滞在G2-M期和/或调节微管形成或稳定性的试剂,(例如Taxol.TM(即紫杉醇)、Taxotere.TM、包含紫杉烷骨架的化合物、厄布洛唑(即R-55104)、多拉司他汀10(即DLS-10和NSC-376128)、米伏布林羟乙基磺酸盐(Mivobulin isethionate)(即作为CI-980)、长春新碱、NSC-639829、圆皮海绵内酯(Discodermolide)、(即作为NVP-XX-A-296)、ABT-751(Abbott,即E-7010)、奥图海汀(Altorhyrtin)(例如奥图海汀A和奥图海汀C)、海绵抑素(Spongistatin)(例如海绵抑素1、海绵抑素2、海绵抑素3、海绵抑素4、海绵抑素5、海绵抑素6、海绵抑素7、海绵抑素8和海绵抑素9)、盐酸西马多丁(即LU-103793和NSC-D-669356)、埃博霉素(例如埃博霉素A、埃博霉素B、埃博霉素C(即脱氧埃博霉素A或dEpoA)、埃博霉素D(即KOS-862、dEpoB和脱氧埃博霉素B)、埃博霉素E、埃博霉素F、埃博霉素B N-氧化物、埃博霉素AN-氧化物、16-氮杂-埃博霉素B、21-氨基埃博霉素B(即BMS-310705)、21-羟基埃博霉素D(即脱氧埃博霉素F和dEpoF)、26-氟埃博霉素)、类固醇(例如,地塞米松)、非那雄胺、芳香酶抑制剂、促性腺激素释放激素激动剂(GnRH)(如戈舍瑞林或亮丙瑞林)、肾上腺皮质类固醇(例如,泼尼松)、孕酮(例如,己酸羟孕酮、醋酸甲地孕酮、醋酸甲羟孕酮)、雌激素(例如,己烯雌酚、炔雌醇)、抗雌激素(例如,他莫昔芬)、雄激素(例如,丙酸睾酮、氟甲睾酮)、抗雄激素(例如,氟他胺)、免疫刺激剂(例如,卡介苗(BCG)、左旋咪唑、白细胞介素-2、 α -干扰素等)、单克隆抗体(例如,抗CD20、抗HER2、抗CD52、抗HLA-DR和抗VEGF单克隆抗体)、免疫毒素(例如,抗CD33单克隆抗体-卡奇霉素偶联物、抗CD22单克隆抗体-假单胞菌外毒素偶联物等)、放射免疫疗法(例如,与 ^{111}In 、 ^{90}Y 或 ^{131}I 偶联的抗CD20单克隆抗体等)、雷公藤内酯(triptolide)、高三尖杉酯碱、放射菌素D、多柔比星、表柔比星、托泊替康、伊曲康唑、长春地辛、西立伐他汀、长春新碱、脱氧腺苷、舍曲林、匹伐他汀、伊立替康、氯法齐明、5-壬基氧基色胺、威罗菲尼、达拉菲尼、厄洛替尼、吉非替尼、EGFR抑制剂、表皮生长因子受体(EGFR)靶向疗法或治疗剂(例如,吉非替尼(IressaTM)、厄洛替尼(TarcevaTM)、西妥昔单抗(ErbixTM)、拉帕替尼(TykerbTM)、帕尼单抗(VectibixTM)、凡德他尼(CaprelsaTM)、阿法替尼/BIBW2992、CI-1033/卡奈替尼、来那替尼/HKI-272、CP-724714、TAK-285、AST-1306、ARRY334543、ARRY-380、AG-1478、达克替尼/PF299804、OSI-420/去甲基厄洛替尼、AZD8931、AEE788、培利替尼/EKB-569、CUDC-101、WZ8040、WZ4002、WZ3146、AG-490、XL647、PD153035、BMS-599626)、索拉非尼、伊马替尼、舒尼替尼、达沙替尼、Ras抑制剂等。

[0154] “化学治疗剂”根据其简单普通含义使用并且是指具有抗肿瘤性质或抑制细胞生长或增殖的能力的化学组合物或化合物。

[0155] 如本文中所述的术语“亲电子”是指化学基团能够接收电子密度。“亲电子取代基”、“亲电子化学部分”或“亲电子部分”是指缺电子的化学基团、取代基或部分(单价化学基团),其可以通过接受电子对或电子密度形成键与供电子基团如亲核试剂反应。在一些实施方案中,化合物的亲电子取代基能够与半胱氨酸残基反应。在一些实施方案中,亲电子取

代基能够与半胱氨酸残基(例如,K-ras半胱氨酸残基,对应人K-Ras 4B的C185的残基)形成共价键并且可以称为“共价半胱氨酸修饰部分”或“共价半胱氨酸修饰取代基”。亲电子取代基和半胱氨酸的巯基之间形成的共价键可为可逆或不可逆键。在一些实施方案中,亲电子取代基能够与组氨酸残基(例如,K-ras组氨酸残基,对应人K-Ras 4B的H95的残基)形成共价键并且可以称为“共价组氨酸修饰部分”或“共价组氨酸修饰取代基”。亲电子取代基和组氨酸之间形成的共价键可为可逆或不可逆键。

[0156] 如本文中所述的“亲核”是指能够给予电子密度的化学基团。

[0157] 术语“Ras”是指人Ras GTP酶蛋白家族(例如K-Ras、H-Ras、N-Ras)中的一种或多种。术语“K-Ras”是指人K-Ras(例如人K-Ras4A(NP_203524.1)、人K-Ras4B(NP_004976.2),或K-Ras4A和K-Ras4B)的核苷酸序列或蛋白。术语“K-Ras”包括野生型核苷酸序列或蛋白质形式及其任何突变体。在一些实施方案中,“K-Ras”为野生型K-Ras。在一些实施方案中,“K-Ras”为一种或多种突变体形式。术语“K-Ras”XYZ是指突变体K-Ras的核苷酸序列或蛋白,其中在野生型中具有X氨基酸的K-Ras的Y编号氨基酸在突变体中改为具有Z氨基酸(例如K-Ras G12C在野生型蛋白中具有G,但在K-Ras G12C突变体蛋白中具有C)。在一些实施方案中K-Ras是指K-Ras4A和K-Ras4B。在一些实施方案中,K-Ras是指K-Ras4A。在一些实施方案中,K-Ras是指K-Ras4B。在实施方案中K-Ras是指具有本文描述的氨基酸序列的蛋白质。

[0158] 如本文中所述的术语“Ras抑制剂试验化合物”是指在测定中表征其抑制Ras蛋白活性、功能或水平(例如量)的能力的化合物。如本文中所述的术语“K-Ras抑制剂试验化合物”是指在测定中表征其抑制K-Ras蛋白活性、功能或水平(例如量)的能力的化合物。

[0159] 如本文中所述的术语“信号传导途径”是指细胞和任选胞外组分(例如蛋白质、核酸、小分子、离子、脂质)之间的一系列相互作用,所述相互作用将一种组分的变化传送到一种或多种其它组分,这又可将变化传送到另外的组分,任选地传播到其它信号传导途径组分。例如,K-Ras与本文所述化合物的结合引起K-Ras的一种或多种蛋白质-蛋白质相互作用或K-Ras与膜之间的相互作用的变化,从而引起细胞生长、增殖或存活的变化。

[0160] 蛋白质中的氨基酸残基在占据蛋白质中与给定残基相同的基本结构位置时,与给定残基“对应”。例如,当选定残基占据人K-Ras4A或人K-Ras4B或两者中与Gly 12相同的基本空间或其它结构关系时,选定蛋白中的选定残基与人K-Ras4A或人K-Ras4B或两者的Gly 12对应。在一些实施方案中,比对选定蛋白与人K-Ras4A或人K-Ras4B蛋白的最大同源性时,称所比对的选定蛋白中与Gly 12相符的位置与Gly 12对应。代替一级序列比对,也可以使用三维结构比对,例如,其中,比对选定蛋白的结构与人K-Ras4A或人K-Ras4B蛋白的最大对应性并比较整体结构。在这种情况下,在结构模型中占据与Gly 12相同的基本位置的氨基酸被称为与Gly 12残基对应。另一实例是其中当选定残基(例如,半胱氨酸残基)占据蛋白质中与人K-Ras4B中的C185相同的序列、空间或其它结构关系时,选定蛋白中的选定残基与人K-Ras4B的C185对应。

[0161] 术语“未取代的乙烯砜部分”、“未取代的乙烯基磺酰胺部分”、“未取代的氟(C₁-C₄)烷基酮部分”、“未取代的氯(C₁-C₄)烷基酮部分”、“未取代的丙烯酰胺部分”、“未取代的二硫化物部分”、“未取代的硫醇部分”、“未取代的磷酸酯部分”、“未取代的醛部分”、“未取代的烯酮部分”、“未取代的重氮甲基酮部分”、“未取代的重氮甲酰胺部分”、“未取代的氰基环丙基羧酰胺部分”、“未取代的环氧化物部分”、“未取代的环氧酮部分”、“未取代的环氧酰胺部

分”、“未取代的芳醛部分”、“未取代的芳二醛部分”、“未取代的二醛部分”、“未取代的氮芥部分”、“未取代的炔丙基部分”或“未取代的炔丙基酰胺部分”根据其简单普通的化学含义使用并且是指在遵照化学价规则的同时,对于每个此类基团而言具有最低分子量的那些命名的单价化学基团。所命名基团之一的经取代形式可以在遵照化学价规则的同时,经本文描述的任何取代基基团中的一个或多个取代。

[0162] 人野生型H-Ras

[0163]

MTEYKLVVVG AGGVGKSALT IQLIQNHFVD EYDPTIEDSY
RKQVVIDGET CLLDILDTAG QEEYSAMRDQ YMRTGEGFLC
VFAINNTKSF EDIHQYREQI KRVKDSDDVP MVLVGNKCDL

[0164]

AARTVESRQA QDLARSYGIP YIETSAKTRQ GVEDAFYTLV
REIRQHKLRL LNPPDESGPG CMSCKCVLS (SEQ ID NO:10)

[0165] 人野生型K-Ras 4A

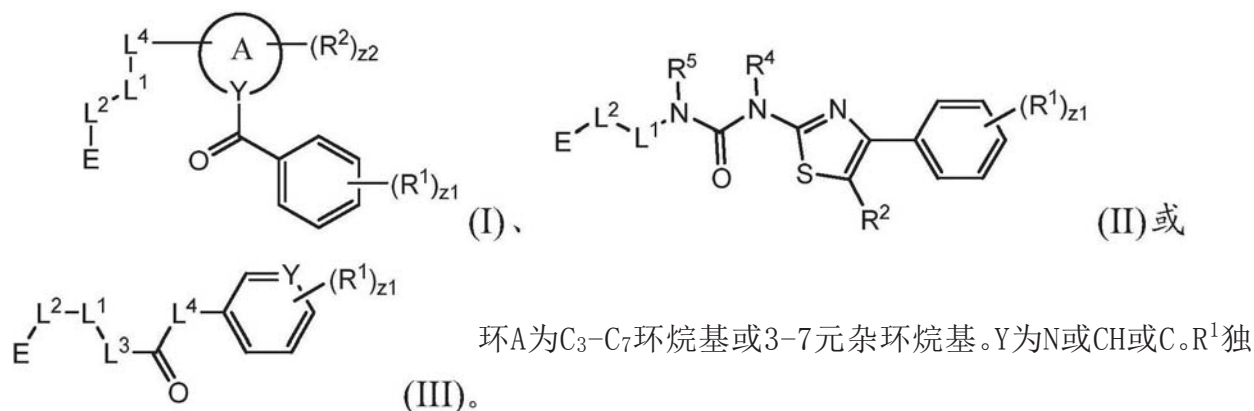
[0166] mteyklvvvg aggvvgksalt iqliqnhfvd eydptiedsy rkqvvidget clldiltdtag
qeaysamrdq ymrtgegflc vfainntksf edihhyreqi krkvdsedvp mvlvgnkcdl psrtvtdkqa
qdlarsygip fietsaktrq rvedafytlv reirqyrlkk iskeektpgc vkikkciim (SEQ ID NO:
11)

[0167] 人野生型K-Ras 4B

[0168] mteyklvvvg aggvvgksalt iqliqnhfvd eydptiedsy rkqvvidget clldiltdtag
qeaysamrdq ymrtgegflc vfainntksf edihhyreqi krkvdsedvp mvlvgnkcdl psrtvtdkqa
qdlarsygip fietsaktrq gvddafytlv reirkhkekm skdgkkkkkk sktkcvim (SEQ ID NO:12)

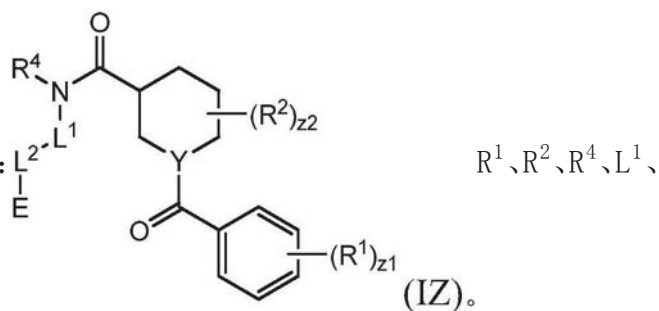
[0169] II. 化合物

[0170] 一方面,提供了一种具有下式的化合物:



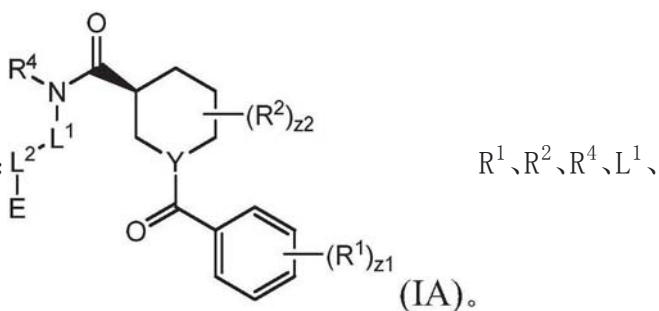
未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基； L^1 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NR^{7A}-$ 、 $-NR^{7A}C(O)-$ 、 $-C(O)NR^{7A}-$ 、 $-SO_2NR^{7A}-$ 、 $-NR^{7A}SO_2-$ 、 $-OC(O)NR^{7A}-$ 、 $-NR^{7A}C(O)O-$ 、 $-CR^{9A}=NO-$ 、 $-ON=CR^{9A}-$ 、 $-NR^{8A}C(O)NR^{7A}-$ 、 $-NR^{8A}C(=NR^{10A})NR^{7A}-$ 、 $-NR^{8A}C(=NR^{10A})-$ 、 $-C(=NR^{10A})NR^{7A}-$ 、 $-OC(=NR^{10A})-$ 、 $-C(=NR^{10A})O-$ 、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基。 L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NR^{7B}-$ 、 $-NR^{7B}C(O)-$ 、 $-C(O)NR^{7B}-$ 、 $-SO_2NR^{7B}-$ 、 $-NR^{7B}SO_2-$ 、 $-OC(O)NR^{7B}-$ 、 $-NR^{7B}C(O)O-$ 、 $-CR^{9B}=NO-$ 、 $-ON=CR^{9B}-$ 、 $-NR^{8B}C(O)NR^{7B}-$ 、 $-NR^{8B}C(=NR^{10B})NR^{7B}-$ 、 $-NR^{8B}C(=NR^{10B})-$ 、 $-C(=NR^{10B})NR^{7B}-$ 、 $-OC(=NR^{10B})-$ 、 $-C(=NR^{10B})O-$ 、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基。 L^3 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NR^5-$ 、 $-NR^5C(O)-$ 、 $-C(O)NR^5-$ 、 $-SO_2NR^5-$ 、 $-NR^5SO_2-$ 、 $-OC(O)NR^5-$ 、 $-NR^5C(O)O-$ 、经取代或未取代的 C_1-C_6 亚烷基、经取代或未取代的2-6元杂亚烷基。 L^4 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NR^4-$ 、 $-NR^4C(O)-$ 、 $-C(O)NR^4-$ 、 $-SO_2NR^4-$ 、 $-NR^4SO_2-$ 、 $-NR^4SO_2-$ 、 $-OC(O)NR^4-$ 、 $-NR^4C(O)O-$ 、经取代或未取代的 C_1-C_3 亚烷基、经取代或未取代的2-3元杂亚烷基。 E 为亲电子部分。 R^2 独立地为氢、氧代、卤素、 CX^2_3 、 $-CHX^2_2$ 、 $-CH_2X^2$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n2}R^{14}$ 、 $-SO_{v2}NR^{11}R^{12}$ 、 $-NHNH^{11}R^{12}$ 、 $-ONR^{11}R^{12}$ 、 $-NHC(=O)NHNH^{11}R^{12}$ 、 $-NHC(O)NR^{11}R^{12}$ 、 $-N(O)_{m2}$ 、 $-NR^{11}R^{12}$ 、 $-C(O)R^{14}$ 、 $-C(O)-OR^{14}$ 、 $-C(O)NR^{11}R^{12}$ 、 $-OR^{15}$ 、 $-NR^{11}SO_2R^{15}$ 、 $-NR^{11}C(O)R^{14}$ 、 $-NR^{11}C(O)OR^{14}$ 、 $-NR^{11}OR^{14}$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；两个相邻的 R^2 取代基或两个键合至相同原子的 R^2 取代基可任选地连接形成经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基。 R^4 独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。 R^5 独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。 R^7 、 R^8 、 R^9 、 R^{10} 、 R^{7A} 、 R^{8A} 、 R^{9A} 、 R^{10A} 、 R^{7B} 、 R^{8B} 、 R^{9B} 、 R^{10B} 、 R^{11} 、 R^{12} 、 R^{14} 和 R^{15} 独立地为氢、卤素、 $-CX_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX_3$ 、 $-OCHX_2$ 、 $-CHX_2$ 、 $-CH_2X$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^7 和 R^8 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{11} 和 R^{12} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基。每个 X 、 X^1 和 X^2 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ 。符号 $n1$ 、 $n2$ 、 $v1$ 和 $v2$ 独立地为0至4的整数。符号 $m1$ 和 $m2$ 独立地为1至2的整数。符号 $z1$ 独立地为0至5的整数。符号 $z2$ 独立地为0至10的整数。

[0171] 在实施方案中,化合物具有下式:



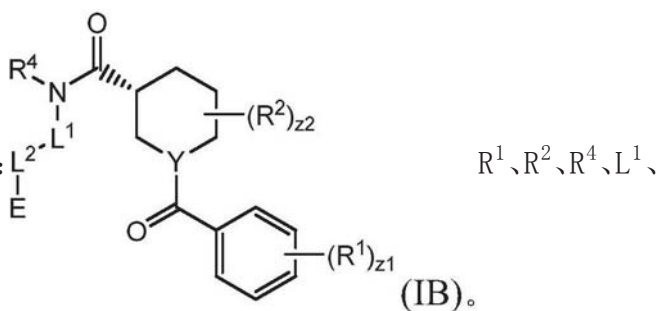
$L^2, E, Y, z1$ 和 $z2$ 如本文所述。

[0172] 在实施方案中,化合物具有下式:



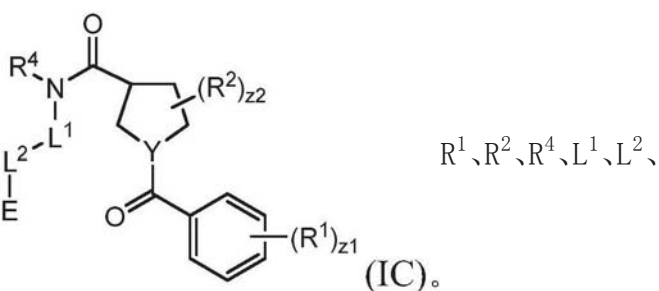
$L^2, E, Y, z1$ 和 $z2$ 如本文所述。

[0173] 在实施方案中,化合物具有下式:



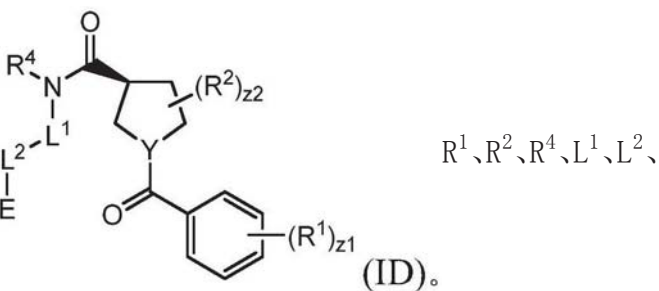
$L^2, E, Y, z1$ 和 $z2$ 如本文所述。

[0174] 在实施方案中,化合物具有下式:



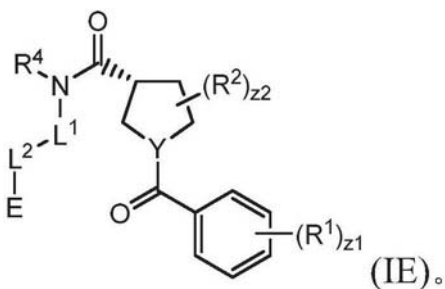
$E, Y, z1$ 和 $z2$ 如本文所述。

[0175] 在实施方案中,化合物具有下式:



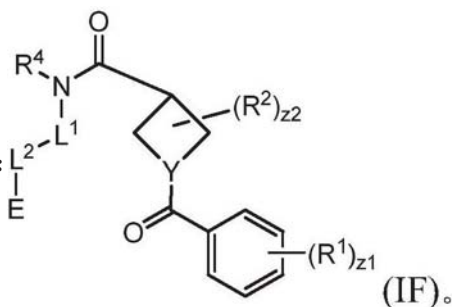
$E, Y, z1$ 和 $z2$ 如本文所述。

[0176] 在实施方案中,化合物具有下式: $R^1, R^2, R^4, L^1, L^2,$



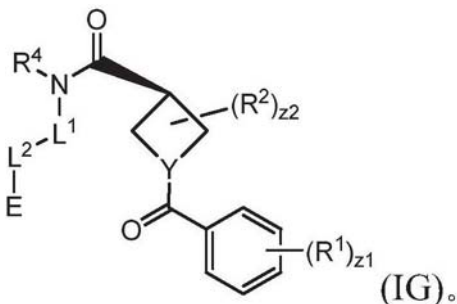
E、Y、z1和z2如本文所述。

[0177] 在实施方案中,化合物具有下式: $R^1, R^2, R^4, L^1, L^2,$



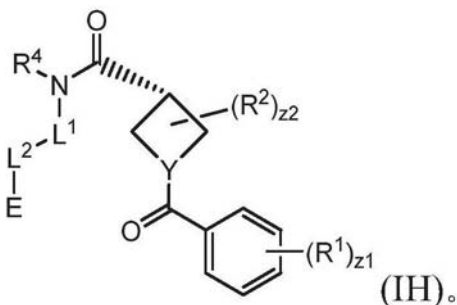
E、Y、z1和z2如本文所述。

[0178] 在实施方案中,化合物具有下式: $R^1, R^2, R^4, L^1,$



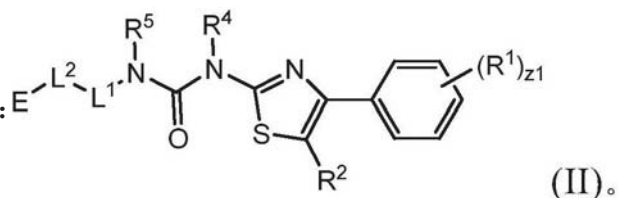
L^2 、E、Y、z1和z2如本文所述。

[0179] 在实施方案中,化合物具有下式: $R^1, R^2, R^4, L^1,$



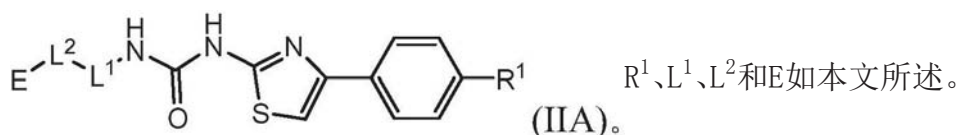
L^2 、E、Y、z1和z2如本文所述。

[0180] 在实施方案中,化合物具有下式: $R^1,$

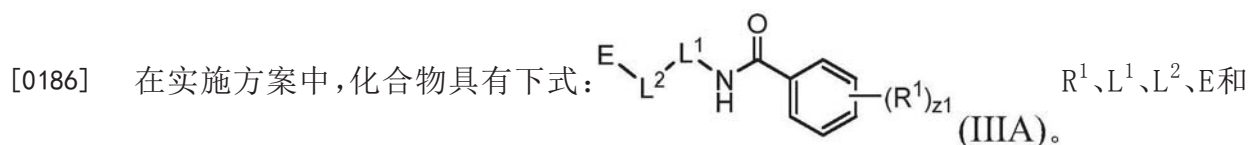
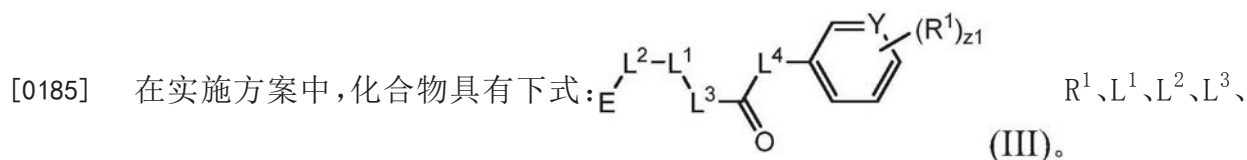
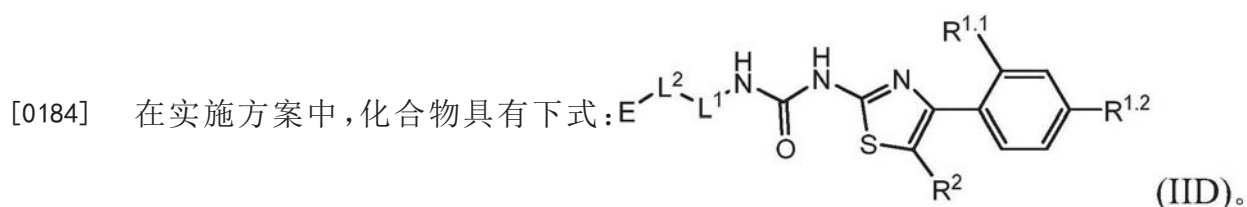
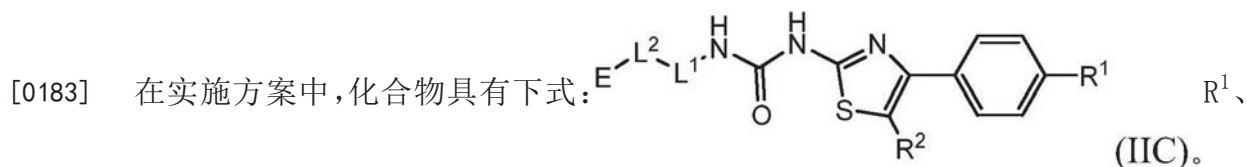


$R^2, R^4, R^5, L^1, L^2, E$ 和z1如本文所述。

[0181] 在式II化合物的实施方案中, R^2, R^4 和 R^5 为氢。在实施方案中,化合物具有下式:



[0182] 在实施方案中, 化合物具有下式: $\text{E}-\text{L}^2-\text{L}^1-\text{NH}-\text{C}(=\text{O})-\text{NH}-\text{C}_5\text{H}_3\text{N}_2-\text{C}_6\text{H}_4-$ L^1, L^2 和 E 如本文所述 (例如, 对于式 I、II、III、VI, 及其实施方案而言或在实例、图、表或权利要求书中)。



[0187] 在实施方案中, L^3 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHCH(CH₃)C(O)NH- 或未取代的 C₁-C₃ 亚烷基。在实施方案中, L^4 为键、-CH₂O-、-C(O)-、-NH- 或 -O-。在实施方案中, L^3 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHC(CH₃)C(O)NH- 或未取代的 C₁-C₃ 亚烷基且 L^4 为键、-CH₂O-、-C(O)-、-NH- 或 -O-。在实施方案中, L^3 为键。在实施方案中, L^3 为 -O-。在实施方案中, L^3 为 -C(O)-。在实施方案中, L^3 为 -S-。在实施方案中, L^3 为 -SO-。在实施方案中, L^3 为 -S(O)₂-。在实施方案中, L^3 为 -NR⁵-。在实施方案中, L^3 为 -NH-。在实施方案中, L^3 为 -NR⁵C(O)-。在实施方案中, L^3 为 -NHC(O)-。在实施方案中, L^3 为 -C(O)NR⁵-。在实施方案中, L^3 为 -C(O)NH-。在实施方案中, L^3 为 -SO₂NR⁵-。在实施方案中, L^3 为 -

SO₂NH-。在实施方案中, L³为-NR⁵SO₂-。在实施方案中, L³为-NHSO₂-。在实施方案中, L³为-OC(O)NR⁵-。在实施方案中, L³为-OC(O)NH-。在实施方案中, L³为-NR⁵C(O)O-。在实施方案中, L³为-NHC(O)O-。在实施方案中, L³为经取代或未取代的C₁-C₆亚烷基。在实施方案中, L³为经取代或未取代的2-6元杂亚烷基。在实施方案中, L³为未取代的亚甲基。在实施方案中, L³为键。

[0188] 在实施方案中, L⁴为键。在实施方案中, L⁴为-O-。在实施方案中, L⁴为-C(O)-。在实施方案中, L⁴为-S-。在实施方案中, L⁴为-SO-。在实施方案中, L⁴为-S(O)₂-。在实施方案中, L⁴为-NR⁴-。在实施方案中, L⁴为-NR⁴C(O)-。在实施方案中, L⁴为-C(O)NR⁴-。在实施方案中, L⁴为-SO₂NR⁴-。在实施方案中, L⁴为-NR⁴SO₂-。在实施方案中, L⁴为-OC(O)NR⁴-。在实施方案中, L⁴为-NR⁴C(O)O-。在实施方案中, L⁴为经取代或未取代的C₁-C₃亚烷基。在实施方案中, L⁴为经取代或未取代的2-3元杂亚烷基。在实施方案中, L⁴为-NH-。在实施方案中, L⁴为-NHC(O)-。在实施方案中, L⁴为-C(O)NH-。在实施方案中, L⁴为-SO₂NH-。在实施方案中, L⁴为-NHSO₂-。在实施方案中, L⁴为-NHSO₂-。在实施方案中, L⁴为-OC(O)NH-。在实施方案中, L⁴为-NHC(O)O-。在实施方案中, L⁴为未取代的C₁-C₃亚烷基。在实施方案中, L⁴为未取代的2-3元杂亚烷基。在实施方案中, L⁴为-CH₂NH-。在实施方案中, L⁴为未取代的亚甲基。

[0189] 在实施方案中, 环A为C₃-C₇环烷基。在实施方案中, 环A为3-7元杂环烷基。在实施方案中, 环A为C₅-C₇环烷基。在实施方案中, 环A为5-7元杂环烷基。在实施方案中, 环A为C₃环烷基。在实施方案中, 环A为C₄环烷基。在实施方案中, 环A为C₅环烷基。在实施方案中, 环A为C₆环烷基。在实施方案中, 环A为C₇环烷基。在实施方案中, 环A为饱和C₃环烷基。在实施方案中, 环A为饱和C₄环烷基。在实施方案中, 环A为饱和C₅环烷基。在实施方案中, 环A为饱和C₆环烷基。在实施方案中, 环A为饱和C₇环烷基。在实施方案中, 环A为不饱和C₃环烷基。在实施方案中, 环A为不饱和C₄环烷基。在实施方案中, 环A为不饱和C₅环烷基。在实施方案中, 环A为不饱和C₆环烷基。在实施方案中, 环A为不饱和C₇环烷基。在实施方案中, 环A为3元杂环烷基。在实施方案中, 环A为4元杂环烷基。在实施方案中, 环A为5元杂环烷基。在实施方案中, 环A为6元杂环烷基。在实施方案中, 环A为7元杂环烷基。在实施方案中, 环A为饱和3元杂环烷基。在实施方案中, 环A为饱和4元杂环烷基。在实施方案中, 环A为饱和5元杂环烷基。在实施方案中, 环A为饱和6元杂环烷基。在实施方案中, 环A为饱和7元杂环烷基。在实施方案中, 环A为不饱和3元杂环烷基。在实施方案中, 环A为不饱和4元杂环烷基。在实施方案中, 环A为不饱和5元杂环烷基。在实施方案中, 环A为不饱和6元杂环烷基。在实施方案中, 环A为不饱和7元杂环烷基。在实施方案中, 环A为氮丙啶基。在实施方案中, 环A为吡丙因基(aziriny1)。在实施方案中, 环A为二氮丙啶基。在实施方案中, 环A为二吡丙因基。在实施方案中, 环A为氮杂环丁烷基。在实施方案中, 环A为氮杂环丁二烯基(azety1)。在实施方案中, 环A为二氮杂环丁烷基。在实施方案中, 环A为二氮杂环丁二烯基(adiazety1)。在实施方案中, 环A为哌啶基。在实施方案中, 环A为吡咯烷基。在实施方案中, 环A为氮杂环庚烷基(azepany1)。在实施方案中, 环A为N-哌啶基。在实施方案中, 环A为N-吡咯烷基。在实施方案中, 环A为N-氮杂环庚烷基。在实施方案中, 环A为1-哌啶基。在实施方案中, 环A为1-吡咯烷基。在实施方案中, 环A为1-氮杂环庚烷基。在实施方案中, 环A为哌嗪基。在实施方案中, 环A为咪唑烷基。在实施方案中, 环A为吡唑烷基。在实施方案中, 环A为噁唑烷基。在实施方案中, 环A为异噁唑烷基。在实施方案中, 环A为噻唑烷基。在实施方案中, 环A为异噻唑烷基。在实施方案中, 环A为吡啶基。在实施方案中, 环A为吡喃基。在实施方案中, 环A为噻喃基。在实施方案中, 环A为氧杂环己

烷基 (oxanylyl)。在实施方案中,环A为噻烷基。在实施方案中,环A为吗啉基。在实施方案中,环A为硫代吗啉基。在实施方案中,环A为二噁烷基。在实施方案中,环A为二噻烷基。在实施方案中,环A为二嗪基。在实施方案中,环A为噁嗪基。在实施方案中,环A为噻嗪基。在实施方案中,环A为二氧杂环己烯基 (dioxinylyl)。在实施方案中,环A为二硫杂环己二烯基 (dithiinylyl)。

[0190] 在实施方案中,Y为CH。在实施方案中,Y为N。在实施方案中,Y为C。

[0191] 在实施方案中, R^1 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、经取代或未取代的 C_1 - C_6 烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的5-6元杂芳基。在实施方案中, R^1 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-OH$ 、 $-SH$ 、 $-COOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。在实施方案中, R^1 独立地为卤素或 $-OCH_3$ 。在实施方案中, R^1 为经取代或未取代的 C_1 - C_6 烷基。在实施方案中, R^1 为经取代或未取代的2-6元杂烷基。在实施方案中, R^1 为经取代或未取代的 C_3 - C_8 环烷基。在实施方案中, R^1 为经取代或未取代的3-8元杂环烷基。在实施方案中, R^1 为经取代或未取代的 C_6 芳基。在实施方案中, R^1 为经取代或未取代的5-6元杂芳基。在实施方案中, R^1 独立地为卤素。在实施方案中, R^1 独立地为 $-CX^1_3$ 。在实施方案中, R^1 独立地为 $-CHX^1_2$ 。在实施方案中, R^1 独立地为 $-CH_2X^1$ 。在实施方案中, R^1 独立地为 $-OH$ 。在实施方案中, R^1 独立地为 $-SH$ 。在实施方案中, R^1 独立地为 $-COOH$ 。在实施方案中, R^1 独立地为 $-OCX^1_3$ 。在实施方案中, R^1 独立地为 $-OCHX^1_2$ 。在实施方案中, R^1 独立地为 $-CH_3$ 。在实施方案中, R^1 独立地为 $-CH_2CH_3$ 。在实施方案中, R^1 独立地为 $-OCH_3$ 。在实施方案中, R^1 独立地为 $-OCH_2CH_3$ 。在实施方案中, R^1 独立地为 $-SCH_3$ 。在实施方案中, R^1 独立地为 $-SCH_2CH_3$ 。在实施方案中, R^1 独立地为 $-Cl$ 或 $-OCH_3$ 。在实施方案中, R^1 独立地为卤素、 $-CX^1_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、经取代或未取代的 C_1 - C_8 烷基或经取代或未取代的2-8元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的苯基或经取代或未取代的5-6元杂芳基。在实施方案中, R^1 独立地为卤素、 $-CX^1_3$ 、 $-CN$ 、未取代的 C_1 - C_4 烷基或未取代的2-4元杂烷基。在实施方案中, R^1 独立地为未取代的甲基、未取代的乙基、未取代的异丙基或未取代的叔丁基。在实施方案中, R^1 独立地为未取代的甲基。在实施方案中, R^1 独立地为未取代的乙基。在实施方案中, R^1 独立地为未取代的丙基。在实施方案中, R^1 独立地为未取代的正丙基。在实施方案中, R^1 独立地为未取代的异丙基。在实施方案中, R^1 独立地为未取代的丁基。在实施方案中, R^1 独立地为未取代的正丁基。在实施方案中, R^1 独立地为未取代的异丁基。在实施方案中, R^1 独立地为未取代的叔丁基。在实施方案中, R^1 独立地为未取代的戊基。在实施方案中, R^1 独立地为未取代的己基。在实施方案中, R^1 独立地为未取代的庚基。在实施方案中, R^1 独立地为未取代的辛基。在实施方案中, R^1 独立地为 $-F$ 。在实施方案中, R^1 独立地为 $-Cl$ 。在实施方案中, R^1 独立地为 $-Br$ 。在实施方案中, R^1 独立地为 $-I$ 。在实施方案中, R^1 独立地为未取代的甲氧基。在实施方案中, R^1 独立地为未取代的乙氧基。在实施方案中, R^1 独立地为 $-CF_3$ 。在实施方案中, R^1 独立地为 $-CCl_3$ 。在实施方案中, R^1 为未取代的异丙基。在实施方案中, R^1 为未取代的苯基。在实施方案中, R^1 为未取代的吡啶基。在实施方案中, R^1 独立地为卤素。在实施方案中, R^1 独立地为 $-CX^1_3$ 。在实施方案

[illegible]

芳基。

[0192] 在实施方案中, $R^{1.1}$ 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、经取代或未取代的 C_1 - C_6 烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的5-6元杂芳基。在实施方案中, $R^{1.1}$ 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-OH$ 、 $-SH$ 、 $-COOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。在实施方案中, $R^{1.1}$ 独立地为卤素或 $-OCH_3$ 。在实施方案中, $R^{1.1}$ 为经取代或未取代的 C_1 - C_6 烷基。在实施方案中, $R^{1.1}$ 为经取代或未取代的2-6元杂烷基。在实施方案中, $R^{1.1}$ 为经取代或未取代的 C_3 - C_8 环烷基。在实施方案中, $R^{1.1}$ 为经取代或未取代的3-8元杂环烷基。在实施方案中, $R^{1.1}$ 为经取代或未取代的 C_6 芳基。在实施方案中, $R^{1.1}$ 为经取代或未取代的5-6元杂芳基。在实施方案中, $R^{1.1}$ 独立地为卤素。在实施方案中, $R^{1.1}$ 独立地为 $-CX^1_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CHX^1_2$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CH_2X^1$ 。在实施方案中, $R^{1.1}$ 独立地为 $-OH$ 。在实施方案中, $R^{1.1}$ 独立地为 $-SH$ 。在实施方案中, $R^{1.1}$ 独立地为 $-COOH$ 。在实施方案中, $R^{1.1}$ 独立地为 $-OCX^1_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-OCHX^1_2$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CH_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CH_2CH_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-OCH_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-OCH_2CH_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-SCH_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-SCH_2CH_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-Cl$ 或 $-OCH_3$ 。在实施方案中, $R^{1.1}$ 独立地为卤素、 $-CX^1_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、经取代或未取代的 C_1 - C_8 烷基、or经取代或未取代的2-8元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的苯基或经取代或未取代的5-6元杂芳基。在实施方案中, $R^{1.1}$ 独立地为卤素、 $-CX^1_3$ 、 $-CN$ 、未取代的 C_1 - C_4 烷基或未取代的2-4元杂烷基。在实施方案中, $R^{1.1}$ 独立地为未取代的甲基、未取代的乙基、未取代的异丙基或未取代的叔丁基。在实施方案中, $R^{1.1}$ 独立地为未取代的甲基。在实施方案中, $R^{1.1}$ 独立地为未取代的乙基。在实施方案中, $R^{1.1}$ 独立地为未取代的丙基。在实施方案中, $R^{1.1}$ 独立地为未取代的正丙基。在实施方案中, $R^{1.1}$ 独立地为未取代的异丙基。在实施方案中, $R^{1.1}$ 独立地为未取代的丁基。在实施方案中, $R^{1.1}$ 独立地为未取代的正丁基。在实施方案中, $R^{1.1}$ 独立地为未取代的异丁基。在实施方案中, $R^{1.1}$ 独立地为未取代的叔丁基。在实施方案中, $R^{1.1}$ 独立地为未取代的戊基。在实施方案中, $R^{1.1}$ 独立地为未取代的己基。在实施方案中, $R^{1.1}$ 独立地为未取代的庚基。在实施方案中, $R^{1.1}$ 独立地为未取代的辛基。在实施方案中, $R^{1.1}$ 独立地为 $-F$ 。在实施方案中, $R^{1.1}$ 独立地为 $-Cl$ 。在实施方案中, $R^{1.1}$ 独立地为 $-Br$ 。在实施方案中, $R^{1.1}$ 独立地为 $-I$ 。在实施方案中, $R^{1.1}$ 独立地为未取代的甲氧基。在实施方案中, $R^{1.1}$ 独立地为未取代的乙氧基。在实施方案中, $R^{1.1}$ 独立地为 $-CF_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CCl_3$ 。在实施方案中, $R^{1.1}$ 为未取代的异丙基。在实施方案中, $R^{1.1}$ 为未取代的苯基。在实施方案中, $R^{1.1}$ 为未取代的吡啶基。在实施方案中, $R^{1.1}$ 独立地为卤素。在实施方案中, $R^{1.1}$ 独立地为 $-CX^1_3$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CHX^1_2$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CH_2X^1$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CN$ 。在实施方案中, $R^{1.1}$ 独立地为 $-OH$ 。在实施方案中, $R^{1.1}$ 独立地为 $-NH_2$ 。在实施方案中, $R^{1.1}$ 独立地为 $-COOH$ 。在实施方案中, $R^{1.1}$ 独立地为 $-CONH_2$ 。在实施方案中, $R^{1.1}$ 独立地为 $-NO_2$ 。在实施方案中, $R^{1.1}$ 独立地为 $-SH$ 。在实施方案中, $R^{1.1}$ 独立地为 $-SO_2Cl$ 。在实施方案中, $R^{1.1}$ 独立地为-

SO₃H。在实施方案中, R^{1.1}独立地为-SO₄H。在实施方案中, R^{1.1}独立地为-SO₂NH₂。在实施方案中, R^{1.1}独立地为-NHNH₂。在实施方案中, R^{1.1}独立地为-ONH₂。在实施方案中, R^{1.1}独立地为-NHC (O) NHNH₂。在实施方案中, R^{1.1}独立地为-NHC (O) NH₂。在实施方案中, R^{1.1}独立地为-NHSO₂H。在实施方案中, R^{1.1}独立地为-NHC (O) H。在实施方案中, R^{1.1}独立地为-NHC (O) OH。在实施方案中, R^{1.1}独立地为-NHOH。在实施方案中, R^{1.1}独立地为-OCX¹₃。在实施方案中, R^{1.1}独立地为-OCHX¹₂。在实施方案中, R^{1.1}独立地为经取代或未取代的烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的杂烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的环烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的杂环烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的芳基。在实施方案中, R^{1.1}独立地为经取代或未取代的杂芳基。在实施方案中, R^{1.1}独立地为经取代的烷基。在实施方案中, R^{1.1}独立地为经取代的杂烷基。在实施方案中, R^{1.1}独立地为经取代的环烷基。在实施方案中, R^{1.1}独立地为经取代的杂环烷基。在实施方案中, R^{1.1}独立地为经取代的芳基。在实施方案中, R^{1.1}独立地为经取代的杂芳基。在实施方案中, R^{1.1}独立地为未取代的烷基。在实施方案中, R^{1.1}独立地为未取代的杂烷基。在实施方案中, R^{1.1}独立地为未取代的环烷基。在实施方案中, R^{1.1}独立地为未取代的杂环烷基。在实施方案中, R^{1.1}独立地为未取代的芳基。在实施方案中, R^{1.1}独立地为未取代的杂芳基。在实施方案中, R^{1.1}独立地为经取代或未取代的C₁-C₈烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的2-8元杂烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的C₃-C₈环烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的3-8元杂环烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的C₆-C₁₀芳基。在实施方案中, R^{1.1}独立地为经取代或未取代的5-10元杂芳基。在实施方案中, R^{1.1}独立地为经取代的C₁-C₈烷基。在实施方案中, R^{1.1}独立地为经取代的2-8元杂烷基。在实施方案中, R^{1.1}独立地为经取代的C₃-C₈环烷基。在实施方案中, R^{1.1}独立地为经取代的3-8元杂环烷基。在实施方案中, R^{1.1}独立地为经取代的C₆-C₁₀芳基。在实施方案中, R^{1.1}独立地为经取代的5-10元杂芳基。在实施方案中, R^{1.1}独立地为未取代的C₁-C₈烷基。在实施方案中, R^{1.1}独立地为未取代的2-8元杂烷基。在实施方案中, R^{1.1}独立地为未取代的C₃-C₈环烷基。在实施方案中, R^{1.1}独立地为未取代的3-8元杂环烷基。在实施方案中, R^{1.1}独立地为未取代的C₆-C₁₀芳基。在实施方案中, R^{1.1}独立地为未取代的5-10元杂芳基。在实施方案中, R^{1.1}独立地为经取代或未取代的C₁-C₄烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的2-4元杂烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的C₃-C₆环烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的3-6元杂环烷基。在实施方案中, R^{1.1}独立地为经取代或未取代的苯基。在实施方案中, R^{1.1}独立地为经取代或未取代的5-6元杂芳基。在实施方案中, R^{1.1}独立地为经取代的C₁-C₄烷基。在实施方案中, R^{1.1}独立地为经取代的2-4元杂烷基。在实施方案中, R^{1.1}独立地为经取代的C₃-C₆环烷基。在实施方案中, R^{1.1}独立地为经取代的3-6元杂环烷基。在实施方案中, R^{1.1}独立地为经取代的苯基。在实施方案中, R^{1.1}独立地为经取代的5-6元杂芳基。在实施方案中, R^{1.1}独立地为未取代的C₁-C₄烷基。在实施方案中, R^{1.1}独立地为未取代的2-4元杂烷基。在实施方案中, R^{1.1}独立地为未取代的C₃-C₆环烷基。在实施方案中, R^{1.1}独立地为未取代的3-6元杂环烷基。在实施方案中, R^{1.1}独立地为未取代的苯基。在实施方案中, R^{1.1}独立地为未取代的5-6元杂芳基。在实施方案中, R^{1.1}独立地为氢。

[0193] 在实施方案中, R^{1.2}独立地为卤素、-CX¹₃、-CHX¹₂、-CH₂X¹、-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、-OCX¹₃、-OCHX¹₂、经取代或未取代的C₁-C₆烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。在实施方案中，R^{1,2}独立地为卤素、-CX¹₃、-CHX¹₂、-CH₂X¹、-OH、-SH、-COOH、-OCX¹₃、-OCHX¹₂、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。在实施方案中，R^{1,2}独立地为卤素或-OCH₃。在实施方案中，R^{1,2}为经取代或未取代的C₁-C₆烷基。在实施方案中，R^{1,2}为经取代或未取代的2-6元杂烷基。在实施方案中，R^{1,2}为经取代或未取代的C₃-C₈环烷基。在实施方案中，R^{1,2}为经取代或未取代的3-8元杂环烷基。在实施方案中，R^{1,2}为经取代或未取代的C₆芳基。在实施方案中，R^{1,2}为经取代或未取代的5-6元杂芳基。在实施方案中，R^{1,2}独立地为卤素。在实施方案中，R^{1,2}独立地为-CX¹₃。在实施方案中，R^{1,2}独立地为-CHX¹₂。在实施方案中，R^{1,2}独立地为-CH₂X¹。在实施方案中，R^{1,2}独立地为-OH。在实施方案中，R^{1,2}独立地为-SH。在实施方案中，R^{1,2}独立地为-COOH。在实施方案中，R^{1,2}独立地为-OCX¹₃。在实施方案中，R^{1,2}独立地为-OCHX¹₂。在实施方案中，R^{1,2}独立地为-CH₃。在实施方案中，R^{1,2}独立地为-CH₂CH₃。在实施方案中，R^{1,2}独立地为-OCH₃。在实施方案中，R^{1,2}独立地为-OCH₂CH₃。在实施方案中，R^{1,2}独立地为-SCH₃。在实施方案中，R^{1,2}独立地为-SCH₂CH₃。在实施方案中，R^{1,2}独立地为-Cl或-OCH₃。在实施方案中，R^{1,2}独立地为卤素、-CX¹₃、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-OCX¹₃、-OCHX¹₂、-CHX¹₂、-CH₂X¹、经取代或未取代的C₁-C₈烷基或经取代或未取代的2-8元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的苯基或经取代或未取代的5-6元杂芳基。在实施方案中，R^{1,2}独立地为卤素、-CX¹₃、-CN、未取代的C₁-C₄烷基或未取代的2-4元杂烷基。在实施方案中，R^{1,2}独立地为未取代的甲基、未取代的乙基、未取代的异丙基或未取代的叔丁基。在实施方案中，R^{1,2}独立地为未取代的甲基。在实施方案中，R^{1,2}独立地为未取代的乙基。在实施方案中，R^{1,2}独立地为未取代的丙基。在实施方案中，R^{1,2}独立地为未取代的正丙基。在实施方案中，R^{1,2}独立地为未取代的异丙基。在实施方案中，R^{1,2}独立地为未取代的丁基。在实施方案中，R^{1,2}独立地为未取代的正丁基。在实施方案中，R^{1,2}独立地为未取代的异丁基。在实施方案中，R^{1,2}独立地为未取代的叔丁基。在实施方案中，R^{1,2}独立地为未取代的戊基。在实施方案中，R^{1,2}独立地为未取代的己基。在实施方案中，R^{1,2}独立地为未取代的庚基。在实施方案中，R^{1,2}独立地为未取代的辛基。在实施方案中，R^{1,2}独立地为-F。在实施方案中，R^{1,2}独立地为-Cl。在实施方案中，R^{1,2}独立地为-Br。在实施方案中，R^{1,2}独立地为-I。在实施方案中，R^{1,2}独立地为未取代的甲氧基。在实施方案中，R^{1,2}独立地为未取代的乙氧基。在实施方案中，R^{1,2}独立地为-CF₃。在实施方案中，R^{1,2}独立地为-CCl₃。在实施方案中，R^{1,2}为未取代的异丙基。在实施方案中，R^{1,2}为未取代的苯基。在实施方案中，R^{1,2}为未取代的吡啶基。在实施方案中，R^{1,2}独立地为卤素。在实施方案中，R^{1,2}独立地为-CX¹₃。在实施方案中，R^{1,2}独立地为-CHX¹₂。在实施方案中，R^{1,2}独立地为-CH₂X¹。在实施方案中，R^{1,2}独立地为-CN。在实施方案中，R^{1,2}独立地为-OH。在实施方案中，R^{1,2}独立地为-NH₂。在实施方案中，R^{1,2}独立地为-COOH。在实施方案中，R^{1,2}独立地为-CONH₂。在实施方案中，R^{1,2}独立地为-NO₂。在实施方案中，R^{1,2}独立地为-SH。在实施方案中，R^{1,2}独立地为-SO₂Cl。在实施方案中，R^{1,2}独立地为-SO₃H。在实施方案中，R^{1,2}独立地为-SO₄H。在实施方案中，R^{1,2}独立地为-SO₂NH₂。在实施方案中，R^{1,2}独立地为-NHNH₂。在实施方案中，R^{1,2}独立地为-ONH₂。在实施方案中，R^{1,2}独立地为-NHC(O)NHNH₂。在实施方案中，R^{1,2}独立地为-NHC(O)NH₂。在实施方案中，R^{1,2}独立地为-

NHSO₂H。在实施方案中，R^{1.2}独立地为-NHC(O)H。在实施方案中，R^{1.2}独立地为-NHC(O)OH。在实施方案中，R^{1.2}独立地为-NHOH。在实施方案中，R^{1.2}独立地为-OCX¹₃。在实施方案中，R^{1.2}独立地为-OCHX¹₂。在实施方案中，R^{1.2}独立地为经取代或未取代的烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的杂烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的环烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的杂环烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的芳基。在实施方案中，R^{1.2}独立地为经取代或未取代的杂芳基。在实施方案中，R^{1.2}独立地为经取代的烷基。在实施方案中，R^{1.2}独立地为经取代的杂烷基。在实施方案中，R^{1.2}独立地为经取代的环烷基。在实施方案中，R^{1.2}独立地为经取代的杂环烷基。在实施方案中，R^{1.2}独立地为经取代的芳基。在实施方案中，R^{1.2}独立地为经取代的杂芳基。在实施方案中，R^{1.2}独立地为未取代的烷基。在实施方案中，R^{1.2}独立地为未取代的杂烷基。在实施方案中，R^{1.2}独立地为未取代的环烷基。在实施方案中，R^{1.2}独立地为未取代的杂环烷基。在实施方案中，R^{1.2}独立地为未取代的芳基。在实施方案中，R^{1.2}独立地为未取代的杂芳基。在实施方案中，R^{1.2}独立地为经取代或未取代的C₁-C₈烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的2-8元杂烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的C₃-C₈环烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的3-8元杂环烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的C₆-C₁₀芳基。在实施方案中，R^{1.2}独立地为经取代或未取代的5-10元杂芳基。在实施方案中，R^{1.2}独立地为经取代的C₁-C₈烷基。在实施方案中，R^{1.2}独立地为经取代的2-8元杂烷基。在实施方案中，R^{1.2}独立地为经取代的C₃-C₈环烷基。在实施方案中，R^{1.2}独立地为经取代的3-8元杂环烷基。在实施方案中，R^{1.2}独立地为经取代的C₆-C₁₀芳基。在实施方案中，R^{1.2}独立地为经取代的5-10元杂芳基。在实施方案中，R^{1.2}独立地为未取代的C₁-C₈烷基。在实施方案中，R^{1.2}独立地为未取代的2-8元杂烷基。在实施方案中，R^{1.2}独立地为未取代的C₃-C₈环烷基。在实施方案中，R^{1.2}独立地为未取代的3-8元杂环烷基。在实施方案中，R^{1.2}独立地为未取代的C₆-C₁₀芳基。在实施方案中，R^{1.2}独立地为未取代的5-10元杂芳基。在实施方案中，R^{1.2}独立地为经取代或未取代的C₁-C₄烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的2-4元杂烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的C₃-C₆环烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的3-6元杂环烷基。在实施方案中，R^{1.2}独立地为经取代或未取代的苯基。在实施方案中，R^{1.2}独立地为经取代或未取代的5-6元杂芳基。在实施方案中，R^{1.2}独立地为经取代的C₁-C₄烷基。在实施方案中，R^{1.2}独立地为经取代的2-4元杂烷基。在实施方案中，R^{1.2}独立地为经取代的C₃-C₆环烷基。在实施方案中，R^{1.2}独立地为经取代的3-6元杂环烷基。在实施方案中，R^{1.2}独立地为经取代的苯基。在实施方案中，R^{1.2}独立地为经取代的5-6元杂芳基。在实施方案中，R^{1.2}独立地为未取代的C₁-C₄烷基。在实施方案中，R^{1.2}独立地为未取代的2-4元杂烷基。在实施方案中，R^{1.2}独立地为未取代的C₃-C₆环烷基。在实施方案中，R^{1.2}独立地为未取代的3-6元杂环烷基。在实施方案中，R^{1.2}独立地为未取代的苯基。在实施方案中，R^{1.2}独立地为未取代的5-6元杂芳基。在实施方案中，R^{1.2}独立地为氢。

[0194] 在实施方案中，z1为2。在实施方案中，z1为3。在实施方案中，z1为0。在实施方案中，z1为1。在实施方案中，z1为4。在实施方案中，z1为5。

[0195] 在实施方案中，R²独立地为氢、氧代、卤素、CX²₃、-CHX²₂、-CH₂X²、-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、-OCX²₃、-OCHX²₂、经取代或未取代的C₁-C₆烷

基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。在实施方案中,R²独立地为氧代、卤素、-CX²₃、-CHX²₂、-CH₂X²、-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、-OCX²₃、-OCHX²₂、经取代或未取代的C₁-C₆烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。在实施方案中,R²独立地为氢、卤素、-CX²₃、-CHX²₂、-CH₂X²、-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、-OCX²₃、-OCHX²₂、经取代或未取代的C₁-C₆烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。在实施方案中,R²独立地为氧代、卤素、-CX²₃、-CHX²₂、-CH₂X²、-OH、-SH、-OCX²₃、-OCHX²₂、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。在实施方案中,R²独立地为氢、卤素、-CX²₃、-CHX²₂、-CH₂X²、-OH、-SH、-OCX²₃、-OCHX²₂、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。在实施方案中,R²独立地为氢。在实施方案中,R²独立地为卤素。在实施方案中,R²独立地为未取代的甲基。在实施方案中,两个相邻的R²取代基或两个键合至相同原子的R²取代基可任选地连接形成经取代或未取代的环烷基或经取代或未取代的杂环烷基。在实施方案中,两个相邻的R²取代基可任选地连接形成经取代或未取代的环烷基或经取代或未取代的杂环烷基或经取代或未取代的芳基或经取代或未取代的杂芳基。在实施方案中,R²独立地为卤素、-CX²₃、-CHX²₂、-CH₂X²、-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、-OCX²₃、-OCHX²₂、经取代或未取代的C₁-C₆烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。在实施方案中,R²独立地为卤素、-CX²₃、-CHX²₂、-CH₂X²、-OH、-SH、-COOH、-OCX²₃、-OCHX²₂、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。在实施方案中,R²独立地为卤素或-OCH₃。在实施方案中,R²为经取代或未取代的C₁-C₆烷基。在实施方案中,R²为经取代或未取代的2-6元杂烷基。在实施方案中,R²为经取代或未取代的C₃-C₈环烷基。在实施方案中,R²为经取代或未取代的3-8元杂环烷基。在实施方案中,R²为经取代或未取代的C₆芳基。在实施方案中,R²为经取代或未取代的5-6元杂芳基。在实施方案中,R²独立地为卤素。在实施方案中,R²独立地为-CX²₃。在实施方案中,R²独立地为-CHX²₂。在实施方案中,R²独立地为-CH₂X²。在实施方案中,R²独立地为-OH。在实施方案中,R²独立地为-SH。在实施方案中,R²独立地为-COOH。在实施方案中,R²独立地为-OCX²₃。在实施方案中,R²独立地为-OCHX²₂。在实施方案中,R²独立地为-CH₃。在实施方案中,R²独立地为-CH₂CH₃。在实施方案中,R²独立地为-OCH₃。在实施方案中,R²独立地为-OCH₂CH₃。在实施方案中,R²独立地为-SCH₃。在实施方案中,R²独立地为-SCH₂CH₃。在实施方案中,R²独立地为-Cl或-OCH₃。在实施方案中,R²独立地为卤素、-CX²₃、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-OCX²₃、-OCHX²₂、-CHX²₂、-CH₂X²、经取代或未取代的C₁-C₈烷基或经取代或未取代的2-8元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的苯基或经取代或未取代的5-6元杂芳基。在实施方案中,R²独立地为卤素、-CX²₃、-CN、未取代的C₁-C₄烷基或未

取代的2-4元杂烷基。在实施方案中, R^2 独立地为未取代的甲基、未取代的乙基、未取代的异丙基或未取代的叔丁基。在实施方案中, R^2 独立地为未取代的甲基。在实施方案中, R^2 独立地为未取代的乙基。在实施方案中, R^2 独立地为未取代的丙基。在实施方案中, R^2 独立地为未取代的正丙基。在实施方案中, R^2 独立地为未取代的异丙基。在实施方案中, R^2 独立地为未取代的丁基。在实施方案中, R^2 独立地为未取代的正丁基。在实施方案中, R^2 独立地为未取代的异丁基。在实施方案中, R^2 独立地为未取代的叔丁基。在实施方案中, R^2 独立地为未取代的戊基。在实施方案中, R^2 独立地为未取代的己基。在实施方案中, R^2 独立地为未取代的庚基。在实施方案中, R^2 独立地为未取代的辛基。在实施方案中, R^2 独立地为-F。在实施方案中, R^2 独立地为-Cl。在实施方案中, R^2 独立地为-Br。在实施方案中, R^2 独立地为-I。在实施方案中, R^2 独立地为未取代的甲氧基。在实施方案中, R^2 独立地为未取代的乙氧基。在实施方案中, R^2 独立地为-CF₃。在实施方案中, R^2 独立地为-CCl₃。在实施方案中, R^2 为未取代的异丙基。在实施方案中, R^2 为未取代的苯基。在实施方案中, R^2 为未取代的吡啶基。在实施方案中, R^2 独立地为卤素。在实施方案中, R^2 独立地为-CX₃。在实施方案中, R^2 独立地为-CHX₂。在实施方案中, R^2 独立地为-CH₂X²。在实施方案中, R^2 独立地为-CN。在实施方案中, R^2 独立地为-OH。在实施方案中, R^2 独立地为-NH₂。在实施方案中, R^2 独立地为-COOH。在实施方案中, R^2 独立地为-CONH₂。在实施方案中, R^2 独立地为-NO₂。在实施方案中, R^2 独立地为-SH。在实施方案中, R^2 独立地为-SO₂Cl。在实施方案中, R^2 独立地为-SO₃H。在实施方案中, R^2 独立地为-SO₄H。在实施方案中, R^2 独立地为-SO₂NH₂。在实施方案中, R^2 独立地为-NHNH₂。在实施方案中, R^2 独立地为-ONH₂。在实施方案中, R^2 独立地为-NHC(O)NHNH₂。在实施方案中, R^2 独立地为-NHC(O)NH₂。在实施方案中, R^2 独立地为-NHSO₂H。在实施方案中, R^2 独立地为-NHC(O)H。在实施方案中, R^2 独立地为-NHC(O)OH。在实施方案中, R^2 独立地为-NHOH。在实施方案中, R^2 独立地为-OCX₃。在实施方案中, R^2 独立地为-OCHX₂。在实施方案中, R^2 独立地为经取代或未取代的烷基。在实施方案中, R^2 独立地为经取代或未取代的杂烷基。在实施方案中, R^2 独立地为经取代或未取代的环烷基。在实施方案中, R^2 独立地为经取代或未取代的杂环烷基。在实施方案中, R^2 独立地为经取代或未取代的芳基。在实施方案中, R^2 独立地为经取代或未取代的杂芳基。在实施方案中, R^2 独立地为经取代的烷基。在实施方案中, R^2 独立地为经取代的杂烷基。在实施方案中, R^2 独立地为经取代的环烷基。在实施方案中, R^2 独立地为经取代的杂环烷基。在实施方案中, R^2 独立地为经取代的芳基。在实施方案中, R^2 独立地为经取代的杂芳基。在实施方案中, R^2 独立地为未取代的烷基。在实施方案中, R^2 独立地为未取代的杂烷基。在实施方案中, R^2 独立地为未取代的环烷基。在实施方案中, R^2 独立地为未取代的杂环烷基。在实施方案中, R^2 独立地为未取代的芳基。在实施方案中, R^2 独立地为未取代的杂芳基。在实施方案中, R^2 独立地为经取代或未取代的C₁-C₈烷基。在实施方案中, R^2 独立地为经取代或未取代的2-8元杂烷基。在实施方案中, R^2 独立地为经取代或未取代的C₃-C₈环烷基。在实施方案中, R^2 独立地为经取代或未取代的3-8元杂环烷基。在实施方案中, R^2 独立地为经取代或未取代的C₆-C₁₀芳基。在实施方案中, R^2 独立地为经取代或未取代的5-10元杂芳基。在实施方案中, R^2 独立地为经取代的C₁-C₈烷基。在实施方案中, R^2 独立地为经取代的2-8元杂烷基。在实施方案中, R^2 独立地为经取代的C₃-C₈环烷基。在实施方案中, R^2 独立地为经取代的3-8元杂环烷基。在实施方案中, R^2 独立地为经取代的C₆-C₁₀芳基。在实施方案中, R^2 独立地为经取代的5-10元杂芳基。在实施方案中, R^2 独立地为未取代的C₁-C₈烷基。在实施方案中, R^2 独立地为未取代的2-8

元杂烷基。在实施方案中, R^2 独立地为未取代的 C_3 - C_8 环烷基。在实施方案中, R^2 独立地为未取代的 3-8 元杂环烷基。在实施方案中, R^2 独立地为未取代的 C_6 - C_{10} 芳基。在实施方案中, R^2 独立地为未取代的 5-10 元杂芳基。在实施方案中, R^2 独立地为经取代或未取代的 C_1 - C_4 烷基。在实施方案中, R^2 独立地为经取代或未取代的 2-4 元杂烷基。在实施方案中, R^2 独立地为经取代或未取代的 C_3 - C_6 环烷基。在实施方案中, R^2 独立地为经取代或未取代的 3-6 元杂环烷基。在实施方案中, R^2 独立地为经取代或未取代的苯基。在实施方案中, R^2 独立地为经取代或未取代的 5-6 元杂芳基。在实施方案中, R^2 独立地为经取代的 C_1 - C_4 烷基。在实施方案中, R^2 独立地为经取代的 2-4 元杂烷基。在实施方案中, R^2 独立地为经取代的 C_3 - C_6 环烷基。在实施方案中, R^2 独立地为经取代的 3-6 元杂环烷基。在实施方案中, R^2 独立地为经取代的苯基。在实施方案中, R^2 独立地为经取代的 5-6 元杂芳基。在实施方案中, R^2 独立地为未取代的 C_1 - C_4 烷基。在实施方案中, R^2 独立地为未取代的 2-4 元杂烷基。在实施方案中, R^2 独立地为未取代的 C_3 - C_6 环烷基。在实施方案中, R^2 独立地为未取代的 3-6 元杂环烷基。在实施方案中, R^2 独立地为未取代的苯基。在实施方案中, R^2 独立地为未取代的 5-6 元杂芳基。

[0196] 在实施方案中, z_2 为 0。在实施方案中, z_2 为 1。在实施方案中, z_2 为 2。在实施方案中, z_2 为 3。在实施方案中, z_2 为 4。在实施方案中, z_2 为 5。在实施方案中, z_2 为 6。在实施方案中, z_2 为 7。在实施方案中, z_2 为 8。在实施方案中, z_2 为 9。在实施方案中, z_2 为 10。

[0197] 在实施方案中, R^4 为氢。在实施方案中, R^5 为氢。在实施方案中, R^4 为未取代的甲基。在实施方案中, R^4 为未取代的乙基。在实施方案中, R^4 为未取代的丙基。在实施方案中, R^4 为未取代的丁基。在实施方案中, R^5 为未取代的甲基。在实施方案中, R^5 为未取代的乙基。在实施方案中, R^5 为未取代的丙基。在实施方案中, R^5 为未取代的丁基。在实施方案中, R^4 为经取代或未取代的烷基。在实施方案中, R^4 为经取代或未取代的杂烷基。在实施方案中, R^4 为经取代或未取代的环烷基。在实施方案中, R^4 为经取代或未取代的杂环烷基。在实施方案中, R^4 为经取代或未取代的芳基。在实施方案中, R^4 为经取代或未取代的杂芳基。在实施方案中, R^5 为经取代或未取代的烷基。在实施方案中, R^5 为经取代或未取代的杂烷基。在实施方案中, R^5 为经取代或未取代的环烷基。在实施方案中, R^5 为经取代或未取代的杂环烷基。在实施方案中, R^5 为经取代或未取代的芳基。在实施方案中, R^5 为经取代或未取代的杂芳基。

[0198] 在实施方案中, L^1 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7A}-、-NR^{7A}C(O)-、-C(O)NR^{7A}-、-SO₂NR^{7A}-、-NR^{7A}SO₂-、-OC(O)NR^{7A}-、-NR^{7A}C(O)O-、-CR^{9A}=NO-、-ON=CR^{9A}-、-NR^{8A}C(O)NR^{7A}-、-NR^{8A}C(=NR^{10A})NR^{7A}-、-NR^{8A}C(=NR^{10A})-、-C(=NR^{10A})NR^{7A}-、-OC(=NR^{10A})-、-C(=NR^{10A})O-、经取代或未取代的亚烷基(例如 C_1 - C_8 、 C_1 - C_6 或 C_1 - C_4)、经取代或未取代的杂亚烷基(例如 2-8 元、2-6 元或 2-4 元)、经取代或未取代的亚环烷基(例如 C_3 - C_8 、 C_3 - C_6 、或 C_5 - C_6)、经取代或未取代的杂亚环烷基(例如 3-8 元、3-6 元或 5-6 元)、经取代或未取代的亚芳基(例如 C_6 - C_{10} 、 C_{10} 或亚苯基)或经取代或未取代的杂亚芳基(例如 5-10 元、5-9 元或 5-6 元)。

[0199] 在实施方案中, L^1 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHC(O)-、-C(O)NH-、-SO₂NH-、-NHSO₂-、-OC(O)NH-、-NHC(O)O-、-CH=NO-、-ON=CH-、-NHC(O)NH-、-NHC(=NH)NH-、-NHC(=NH)-、-C(=NH)NH-、-OC(=NH)-、-C(=NH)O-、经取代或未取代的亚烷基(例如, C_1 - C_8 、 C_1 - C_6 或 C_1 - C_4)、经取代或未取代的杂亚烷基(例如, 2-8 元、2-6 元或 2-4 元)、经取代或未取代的亚环烷基(例如, C_3 - C_8 、 C_3 - C_6 或 C_5 - C_6)、经取代或未取代的杂亚环烷基(例如, 3-8 元、3-6 元或 5-6 元)、经取代或未取代的亚芳基(例如, C_6 - C_{10} 、 C_{10} 或亚苯基)或经取代

或未取代的杂亚芳基(例如,5-10元、5-9元或5-6元)。

[0200] 在实施方案中, L^1 为键、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。在实施方案中, L^1 为键、未取代的 C_1 - C_4 亚烷基或未取代的2-4元杂亚烷基。在实施方案中, L^1 为键。在实施方案中, L^1 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHC(O)-、-C(O)NH-、-SO₂NH-、-NHSO₂-、-OC(O)NH-、-NHC(O)O-、-CH=NO-、-ON=CH-、-NHC(O)NH-、-NHC(=NH)NH-、-NHC(=NH)-、-C(=NH)NH-、-OC(=NH)-、-C(=NH)O-、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基。在实施方案中, L^1 为键、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基。在实施方案中, L^1 为键。在实施方案中, L^1 为键、-O-、-C(O)-、-S-、-NH-、-NHC(O)-、-C(O)NH-、未取代的 C_1 - C_4 亚烷基或未取代的2-4元杂亚烷基。在实施方案中, L^1 为-NH-。在实施方案中, L^1 为-CH(CH₂C₁)CH₂-。在实施方案中, L^1 为-C(O)CH(CH₂C₁)CH₂-。在实施方案中, L^1 为-NHC(O)CH(CH₂C₁)CH₂-。在实施方案中, L^1 为卤素取代的 C_1 - C_4 亚烷基。在实施方案中, L^1 为卤素取代的 C_2 - C_4 亚烷基。在实施方案中, L^1 为卤素取代的 C_3 - C_4 亚烷基。在实施方案中, L^1 为卤素取代的 C_3 亚烷基。在实施方案中, L^1 为键。在实施方案中, L^1 为-O-。在实施方案中, L^1 为-C(O)-。在实施方案中, L^1 为-S-。在实施方案中, L^1 为-SO-。在实施方案中, L^1 为-S(O)₂-。在实施方案中, L^1 为-NH-。在实施方案中, L^1 为-NHC(O)-。在实施方案中, L^1 为-C(O)NH-。在实施方案中, L^1 为-SO₂NH-。在实施方案中, L^1 为-NHSO₂-。在实施方案中, L^1 为-OC(O)NH-。在实施方案中, L^1 为-NHC(O)O-。在实施方案中, L^1 为-CH=NO-。在实施方案中, L^1 为-ON=CH-。在实施方案中, L^1 为-NHC(O)NH-。在实施方案中, L^1 为-NHC(=NH)NH-。在实施方案中, L^1 为-NHC(=NH)-。在实施方案中, L^1 为-C(=NH)NH-。在实施方案中, L^1 为-OC(=NH)-。在实施方案中, L^1 为-C(=NH)O-

[0201] 在实施方案中, L^1 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7A}-、-NR^{7A}C(O)-、-C(O)NR^{7A}-、-SO₂NR^{7A}-、-NR^{7A}SO₂-、-OC(O)NR^{7A}-、-NR^{7A}C(O)O-、-CR^{9A}=NO-、-ON=CR^{9A}-、-NR^{8A}C(O)NR^{7A}-、-NR^{8A}C(=NR^{10A})NR^{7A}-、-NR^{8A}C(=NR^{10A})-、-C(=NR^{10A})NR^{7A}-、-OC(=NR^{10A})-、-C(=NR^{10A})O-、R^{7A}-取代的或未取代的亚烷基(例如, C_1 - C_8 、 C_1 - C_6 或 C_1 - C_4)、R^{7A}-取代的或未取代的杂亚烷基(例如,2-8元、2-6元或2-4元)、R^{7A}-取代的或未取代的亚环烷基(例如, C_3 - C_8 、 C_3 - C_6 或 C_5 - C_6)、R^{7A}-取代的或未取代的杂亚环烷基(例如,3-8元、3-6元或5-6元)、R^{7A}-取代的或未取代的亚芳基(例如, C_6 - C_{10} 、 C_{10} 或亚苯基)或R^{7A}-取代的或未取代的杂亚芳基(例如,5-10元、5-9元或5-6元)。

[0202] 在实施方案中, L^1 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHC(O)-、-C(O)NH-、-SO₂NH-、-NHSO₂-、-OC(O)NH-、-NHC(O)O-、-CH=NO-、-ON=CH-、-NHC(O)NH-、-NHC(=NH)NH-、-NHC(=NH)-、-C(=NH)NH-、-OC(=NH)-、-C(=NH)O-、R^{7A}-取代的或未取代的亚烷基(例如, C_1 - C_8 、 C_1 - C_6 或 C_1 - C_4)、R^{7A}-取代的或未取代的杂亚烷基(例如,2-8元、2-6元或2-4元)、R^{7A}-取代的或未取代的亚环烷基(例如, C_3 - C_8 、 C_3 - C_6 或 C_5 - C_6)、R^{7A}-取代的或未取代的杂亚环烷基(例如,3-8元、3-6元或5-6元)、R^{7A}-取代的或未取代的亚芳基(例如, C_6 - C_{10} 、 C_{10} 或亚苯基)或R^{7A}-取代的或未取代的杂亚芳基(例如,5-10元、5-9元或5-6元)。

[0203] 在实施方案中, L^2 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7B}-、-NR^{7B}C(O)-、-C(O)NR^{7B}-、-SO₂NR^{7B}-、-NR^{7B}SO₂-、-OC(O)NR^{7B}-、-NR^{7B}C(O)O-、-CR^{9B}=NO-、-ON=CR^{9B}-、-NR^{8B}C(O)

NR^{7B}-、-NR^{8B}C(=NR^{10B})NR^{7B}-、-NR^{8B}C(=NR^{10B})-、-C(=NR^{10B})NR^{7B}-、-OC(=NR^{10B})-、-C(=NR^{10B})O-、经取代或未取代的亚烷基(例如,C₁-C₈、C₁-C₆或C₁-C₄)、经取代或未取代的杂亚烷基(例如,2-8元、2-6元或2-4元)、经取代或未取代的亚环烷基(例如,C₃-C₈、C₃-C₆或C₅-C₆)、经取代或未取代的杂亚环烷基(例如,3-8元、3-6元或5-6元)、经取代或未取代的亚芳基(例如,C₆-C₁₀、C₁₀或亚苯基)或经取代或未取代的杂亚芳基(例如,5-10元、5-9元或5-6元)。

[0204] 在实施方案中, L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、 $-SO_2NH-$ 、 $-NHSO_2-$ 、 $-OC(O)NH-$ 、 $-NHC(O)O-$ 、 $-CH=NO-$ 、 $-ON=CH-$ 、 $-NHC(O)NH-$ 、 $-NHC(=NH)NH-$ 、 $-NHC(=NH)-$ 、 $-C(=NH)NH-$ 、 $-OC(=NH)-$ 、 $-C(=NH)O-$ 、经取代或未取代的亚烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、经取代或未取代的杂亚烷基 (例如, 2-8元、2-6元或2-4元)、经取代或未取代的亚环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、经取代或未取代的杂亚环烷基 (例如, 3-8元、3-6元或5-6元)、经取代或未取代的亚芳基 (例如, C_6-C_{10} 、 C_{10} 或亚苯基) 或经取代或未取代的杂亚芳基 (例如, 5-10元、5-9元或5-6元)。

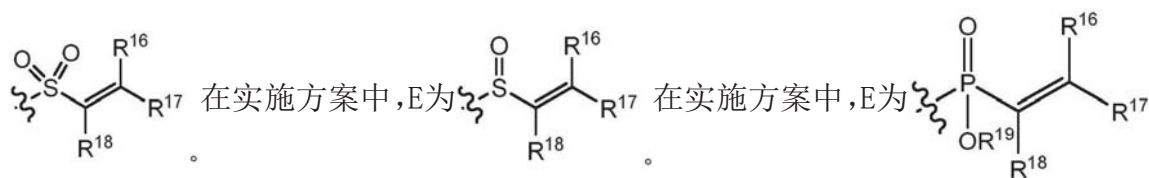
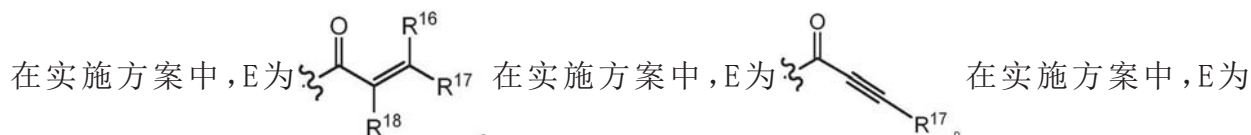
[0205] 在实施方案中, L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、 $-SO_2NH-$ 、 $-NHSO_2-$ 、 $-OC(O)NH-$ 、 $-NHC(O)O-$ 、 $-CH=NO-$ 、 $-ON=CH-$ 、 $-NHC(O)NH-$ 、 $-NHC(=NH)NH-$ 、 $-NHC(=NH)-$ 、 $-C(=NH)NH-$ 、 $-OC(=NH)-$ 、 $-C(=NH)O-$ 、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基。在实施方案中, L^2 为键、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基。在实施方案中, L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、 $-SO_2NH-$ 、 $-NHSO_2-$ 、 $-OC(O)NH-$ 、 $-NHC(O)O-$ 、 $-NHC(O)NH-$ 、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。在实施方案中, L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、未取代的 C_1 - C_4 亚烷基或未取代的 2-4 元杂亚烷基。在实施方案中, L^2 为键。在实施方案中, L^2 为 $-NH-$ 。在实施方案中, L^2 为 $-CH(CH_2Cl)CH_2-$ 。在实施方案中, L^2 为 $-C(O)CH(CH_2Cl)CH_2-$ 。在实施方案中, L^2 为 $-NHC(O)CH(CH_2Cl)CH_2-$ 。在实施方案中, L^2 为 $-NHC(O)-$ 。在实施方案中, L^2 为 $-NH-$ 。在实施方案中, L^2 为卤素取代的 C_1 - C_4 亚烷基。在实施方案中, L^2 为卤素取代的 C_2 - C_4 亚烷基。在实施方案中, L^2 为卤素取代的 C_3 - C_4 亚烷基。在实施方案中, L^2 为卤素取代的 C_3 亚烷基。

[0206] 在实施方案中, L^2 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7B}-、-NR^{7B}C(O)-、-C(O)NR^{7B}-、-SO₂NR^{7B}-、-NR^{7B}SO₂-、-OC(O)NR^{7B}-、-NR^{7B}C(O)O-、-CR^{9B}=NO-、-ON=CR^{9B}-、-NR^{8B}C(O)NR^{7B}-、-NR^{8B}C(=NR^{10B})NR^{7B}-、-NR^{8B}C(=NR^{10B})-、-C(=NR^{10B})NR^{7B}-、-OC(=NR^{10B})-、-C(=NR^{10B})O-、R^{7B}-取代的或未取代的亚烷基(例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{7B}-取代的或未取代的杂亚烷基(例如, 2-8元、2-6元或2-4元)、R^{7B}-取代的或未取代的亚环烷基(例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{7B}-取代的或未取代的杂亚环烷基(例如, 3-8元、3-6元或5-6元)、R^{7B}-取代的或未取代的亚芳基(例如, C₆-C₁₀、C₁₀或亚苯基)或R^{7B}-取代的或未取代的杂亚芳基(例如, 5-10元、5-9元或5-6元)。在实施方案中, L^2 为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NH-、-NHC(O)-、-C(O)NH-、-SO₂NH-、-NHSO₂-、-OC(O)NH-、-NHC(O)O-、-CH=NO-、-ON=CH-、-NHC(O)NH-、-NHC(=NH)NH-、-NHC(=NH)-、-C(=NH)NH-、-OC(=NH)-、-C(=NH)O-、R^{7B}-取代的或未取代的亚烷基(例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{7B}-取代的或未取代的杂亚烷基(例如, 2-8元、2-6元或2-4元)、R^{7B}-取代的或未取代的亚环烷基(例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{7B}-取代的或未

取代的杂亚环烷基(例如,3-8元、3-6元或5-6元)、 R^{7B} -取代的或未取代的亚芳基(例如, C_6 - C_{10} 、 C_{10} 或亚苯基)或 R^{7B} -取代的或未取代的杂亚芳基(例如,5-10元、5-9元或5-6元)。

[0207] 在实施方案中,L2为环C为经取代或未取代的杂亚环烷基或经取代或未取代的杂亚芳基。在实施方案中,环C为经取代或未取代的5-6元杂亚环烷基或经取代或未取代的5-6元杂亚芳基。在实施方案中,环C为 R^{7B} -经取代或未取代的杂亚环烷基或 R^{7B} -取代的或未取代的杂亚芳基。在实施方案中,环C为 R^{7B} -取代的或未取代的5-6元杂亚环烷基或 R^{7B} -经取代或未取代的5-6元杂亚芳基。

[0208] 在实施方案中,E为共价半胱氨酸修饰部分。在实施方案中,E为共价组氨酸修饰部分。



[0209] R^{16} 独立地为氢、卤素、 CX^{16}_3 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n16}R^{16D}$ 、 $-SO_{v16}NR^{16A}R^{16B}$ 、 $-NHNr^{16A}R^{16B}$ 、 $-ONR^{16A}R^{16B}$ 、 $-NHC(=O)NHNr^{16A}R^{16B}$ 、 $-NHC(=O)NR^{16A}R^{16B}$ 、 $-N(O)_{m16}$ 、 $-NR^{16A}R^{16B}$ 、 $-C(O)R^{16C}$ 、 $-C(O)OR^{16C}$ 、 $-C(O)NR^{16A}R^{16B}$ 、 $-OR^{16D}$ 、 $-NR^{16A}SO_2R^{16D}$ 、 $-NR^{16A}C(O)R^{16C}$ 、 $-NR^{16A}C(O)OR^{16C}$ 、 $-NR^{16A}OR^{16C}$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。 R^{17} 独立地为氢、卤素、 CX^{17}_3 、 $-CHX^{17}_2$ 、 $-CH_2X^{17}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n17}R^{17D}$ 、 $-SO_{v17}NR^{17A}R^{17B}$ 、 $-NHNr^{17A}R^{17B}$ 、 $-ONR^{17A}R^{17B}$ 、 $-NHC(=O)NHNr^{17A}R^{17B}$ 、 $-NHC(=O)NR^{17A}R^{17B}$ 、 $-N(O)_{m17}$ 、 $-NR^{17A}R^{17B}$ 、 $-C(O)R^{17C}$ 、 $-C(O)OR^{17C}$ 、 $-C(O)NR^{17A}R^{17B}$ 、 $-OR^{17D}$ 、 $-NR^{17A}SO_2R^{17D}$ 、 $-NR^{17A}C(O)R^{17C}$ 、 $-NR^{17A}C(O)OR^{17C}$ 、 $-NR^{17A}OR^{17C}$ 、 $-OCX^{17}_3$ 、 $-OCHX^{17}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。 R^{18} 独立地为氢、卤素、 CX^{18}_3 、 $-CHX^{18}_2$ 、 $-CH_2X^{18}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n18}R^{18D}$ 、 $-SO_{v18}NR^{18A}R^{18B}$ 、 $-NHNr^{18A}R^{18B}$ 、 $-ONR^{18A}R^{18B}$ 、 $-NHC(=O)NHNr^{18A}R^{18B}$ 、 $-NHC(=O)NR^{18A}R^{18B}$ 、 $-N(O)_{m18}$ 、 $-NR^{18A}R^{18B}$ 、 $-C(O)R^{18C}$ 、 $-C(O)OR^{18C}$ 、 $-C(O)NR^{18A}R^{18B}$ 、 $-OR^{18D}$ 、 $-NR^{18A}SO_2R^{18D}$ 、 $-NR^{18A}C(O)R^{18C}$ 、 $-NR^{18A}C(O)OR^{18C}$ 、 $-NR^{18A}OR^{18C}$ 、 $-OCX^{18}_3$ 、 $-OCHX^{18}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。 R^{19} 独立地为氢、卤素、 CX^{19}_3 、 $-CHX^{19}_2$ 、 $-CH_2X^{19}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n19}R^{19D}$ 、 $-SO_{v19}NR^{19A}R^{19B}$ 、 $-NHNr^{19A}R^{19B}$ 、 $-ONR^{19A}R^{19B}$ 、 $-NHC(=O)NHNr^{19A}R^{19B}$ 、 $-NHC(=O)NR^{19A}R^{19B}$ 、 $-N(O)_{m19}$ 、 $-NR^{19A}R^{19B}$ 、 $-C(O)R^{19C}$ 、 $-C(O)OR^{19C}$ 、 $-C(O)NR^{19A}R^{19B}$ 、 $-OR^{19D}$ 、 $-NR^{19A}SO_2R^{19D}$ 、 $-NR^{19A}C(O)R^{19C}$ 、 $-NR^{19A}C(O)OR^{19C}$ 、 $-NR^{19A}OR^{19C}$ 、 $-OCX^{19}_3$ 、 $-OCHX^{19}_2$ 、经取代或未取代的烷基、经取代或未取

代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。 R^{16A} 、 R^{16B} 、 R^{16C} 、 R^{16D} 、 R^{17A} 、 R^{17B} 、 R^{17C} 、 R^{17D} 、 R^{18A} 、 R^{18B} 、 R^{18C} 、 R^{18D} 、 R^{19A} 、 R^{19B} 、 R^{19C} 、 R^{19D} 独立地为氢、卤素、 $-CX_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_3H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX_3$ 、 $-OCHX_2$ 、 $-CHX_2$ 、 $-CH_2X$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{16A} 和 R^{16B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{17A} 和 R^{17B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{18A} 和 R^{18B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{19A} 和 R^{19B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基。每个 X 、 X^{16} 、 X^{17} 、 X^{18} 和 X^{19} 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ 。符号 n_{16} 、 n_{17} 、 n_{18} 、 n_{19} 、 v_{16} 、 v_{17} 、 v_{18} 和 v_{19} 独立地为0至4的整数。符号 m_{16} 、 m_{17} 、 m_{18} 和 m_{19} 独立地为1至2的整数。在实施方案中， R^{18} 为 $-CN$ 。在实施方案中， R^{16} 为未取代的甲基。在实施方案中， R^{17} 为未取代的甲基。在实施方案中， R^{19} 为未取代的甲基。在实施方案中， R^{18} 为氢。在实施方案中， R^{16} 为氢。在实施方案中， R^{17} 为氢。在实施方案中， R^{19} 为氢。

[0210] X 可独立地为 $-F$ 。 X 可独立地为 $-Cl$ 。 X 可独立地为 $-Br$ 。 X 可独立地为 $-I$ 。 X^{16} 可独立地为 $-F$ 。 X^{16} 可独立地为 $-Cl$ 。 X^{16} 可独立地为 $-Br$ 。 X^{16} 可独立地为 $-I$ 。 X^{17} 可独立地为 $-F$ 。 X^{17} 可独立地为 $-Cl$ 。 X^{17} 可独立地为 $-Br$ 。 X^{17} 可独立地为 $-I$ 。 X^{18} 可独立地为 $-F$ 。 X^{18} 可独立地为 $-Cl$ 。 X^{18} 可独立地为 $-Br$ 。 X^{18} 可独立地为 $-I$ 。 X^{19} 可独立地为 $-F$ 。 X^{19} 可独立地为 $-Cl$ 。 X^{19} 可独立地为 $-Br$ 。 X^{19} 可独立地为 $-I$ 。

[0211] n_{16} 可独立地为0。 n_{16} 可独立地为1。 n_{16} 可独立地为2。 n_{16} 可独立地为3。 n_{16} 可独立地为4。 n_{17} 可独立地为0。 n_{17} 可独立地为1。 n_{17} 可独立地为2。 n_{17} 可独立地为3。 n_{17} 可独立地为4。 n_{18} 可独立地为0。 n_{18} 可独立地为1。 n_{18} 可独立地为2。 n_{18} 可独立地为3。 n_{18} 可独立地为4。 n_{19} 可独立地为0。 n_{19} 可独立地为1。 n_{19} 可独立地为2。 n_{19} 可独立地为3。 n_{19} 可独立地为4。

[0212] v_{16} 可独立地为0。 v_{16} 可独立地为1。 v_{16} 可独立地为2。 v_{16} 可独立地为3。 v_{16} 可独立地为4。 v_{17} 可独立地为0。 v_{17} 可独立地为1。 v_{17} 可独立地为2。 v_{17} 可独立地为3。 v_{17} 可独立地为4。 v_{18} 可独立地为0。 v_{18} 可独立地为1。 v_{18} 可独立地为2。 v_{18} 可独立地为3。 v_{18} 可独立地为4。 v_{19} 可独立地为0。 v_{19} 可独立地为1。 v_{19} 可独立地为2。 v_{19} 可独立地为3。 v_{19} 可独立地为4。

[0213] m_{16} 可独立地为1。 m_{16} 可独立地为2。 m_{17} 可独立地为1。 m_{17} 可独立地为2。 m_{18} 可独立地为1。 m_{18} 可独立地为2。 m_{19} 可独立地为1。 m_{19} 可独立地为2。

[0214] 在实施方案中， R^{16} 为氢。在实施方案中， R^{16} 为卤素。在实施方案中， R^{16} 为 CX^{16}_3 。在实施方案中， R^{16} 为 $-CHX^{16}_2$ 。在实施方案中， R^{16} 为 $-CH_2X^{16}$ 。在实施方案中， R^{16} 为 $-CN$ 。在实施方案中， R^{16} 为 $-SO_{n_{16}}R^{16D}$ 。在实施方案中， R^{16} 为 $-SO_{v_{16}}NR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-NHNR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-ONR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-NHC(O)NHNR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-NHC(O)NR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-N(O)_{m_{16}}$ 。在实施方案中， R^{16} 为 $-NR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-C(O)R^{16C}$ 。在实施方案中， R^{16} 为 $-C(O)-OR^{16C}$ 。在实施方案中， R^{16} 为 $-C(O)NR^{16A}R^{16B}$ 。在实施方案中， R^{16} 为 $-OR^{16D}$ 。在实施方案中， R^{16} 为 $-NR^{16A}SO_2R^{16D}$ 。在实施方案中， R^{16} 为 $-NR^{16A}C(O)R^{16C}$ 。在实施方案中， R^{16} 为 $-NR^{16A}C(O)OR^{16C}$ 。在实施方案中， R^{16} 为 $-NR^{16A}OR^{16C}$ 。在实施方案

中, R^{16} 为 $-OCX^{16}_3$ 。在实施方案中, R^{16} 为 $-OCHX^{16}_2$ 。在实施方案中, R^{16} 为经取代或未取代的烷基。在实施方案中, R^{16} 为经取代或未取代的杂烷基。在实施方案中, R^{16} 为经取代或未取代的环烷基。在实施方案中, R^{16} 为经取代或未取代的杂环烷基。在实施方案中, R^{16} 为经取代或未取代的芳基。在实施方案中, R^{16} 为经取代或未取代的杂芳基。在实施方案中, R^{16} 为经取代的烷基。在实施方案中, R^{16} 为经取代的杂烷基。在实施方案中, R^{16} 为经取代的环烷基。在实施方案中, R^{16} 为经取代的杂环烷基。在实施方案中, R^{16} 为经取代的芳基。在实施方案中, R^{16} 为经取代的杂芳基。在实施方案中, R^{16} 为未取代的烷基。在实施方案中, R^{16} 为未取代的杂烷基。在实施方案中, R^{16} 为未取代的环烷基。在实施方案中, R^{16} 为未取代的杂环烷基。在实施方案中, R^{16} 为未取代的芳基。在实施方案中, R^{16} 为未取代的杂芳基。在实施方案中, R^{16} 为未取代的甲基。在实施方案中, R^{16} 为未取代的乙基。在实施方案中, R^{16} 为未取代的丙基。在实施方案中, R^{16} 为未取代的异丙基。在实施方案中, R^{16} 为未取代的丁基。在实施方案中, R^{16} 为未取代的叔丁基。在实施方案中, R^{16} 为 $-CH_2Ph$ 。在实施方案中, R^{16} 独立地为卤素、 $-CX^{16}_3$ 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的 C_1 - C_6 烷基、经取代或未取代的 2-6 元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的 3-8 元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的 5-6 元杂芳基。在实施方案中, R^{16} 独立地为卤素、 $-CX^{16}_3$ 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-OH$ 、 $-SH$ 、 $-COOH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。在实施方案中, R^{16} 独立地为卤素或 $-OCH_3$ 。在实施方案中, R^{16} 为经取代或未取代的 C_1 - C_6 烷基。在实施方案中, R^{16} 为经取代或未取代的 2-6 元杂烷基。在实施方案中, R^{16} 为经取代或未取代的 C_3 - C_8 环烷基。在实施方案中, R^{16} 为经取代或未取代的 3-8 元杂环烷基。在实施方案中, R^{16} 为经取代或未取代的 C_6 芳基。在实施方案中, R^{16} 为经取代或未取代的 5-6 元杂芳基。在实施方案中, R^{16} 独立地为卤素。在实施方案中, R^{16} 独立地为 $-CX^{16}_3$ 。在实施方案中, R^{16} 独立地为 $-CHX^{16}_2$ 。在实施方案中, R^{16} 独立地为 $-CH_2X^{16}$ 。在实施方案中, R^{16} 独立地为 $-OH$ 。在实施方案中, R^{16} 独立地为 $-SH$ 。在实施方案中, R^{16} 独立地为 $-COOH$ 。在实施方案中, R^{16} 独立地为 $-OCX^{16}_3$ 。在实施方案中, R^{16} 独立地为 $-OCHX^{16}_2$ 。在实施方案中, R^{16} 独立地为 $-CH_3$ 。在实施方案中, R^{16} 独立地为 $-CH_2CH_3$ 。在实施方案中, R^{16} 独立地为 $-OCH_3$ 。在实施方案中, R^{16} 独立地为 $-OCH_2CH_3$ 。在实施方案中, R^{16} 独立地为 $-SCH_3$ 。在实施方案中, R^{16} 独立地为 $-SCH_2CH_3$ 。在实施方案中, R^{16} 独立地为 $-Cl$ 或 $-OCH_3$ 。在实施方案中, R^{16} 独立地为卤素、 $-CX^{16}_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、经取代或未取代的 C_1 - C_8 烷基或经取代或未取代的 2-8 元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的 3-8 元杂环烷基、经取代或未取代的苯基或经取代或未取代的 5-6 元杂芳基。在实施方案中, R^{16} 独立地为卤素、 $-CX^{16}_3$ 、 $-CN$ 、未取代的 C_1 - C_4 烷基或未取代的 2-4 元杂烷基。在实施方案中, R^{16} 独立地为未取代的甲基、未取代的乙基、未取代的异丙基或未取代的叔丁基。在实施方案中, R^{16} 独立地为未取代的甲基。在实施方案中, R^{16} 独立地为未取代的乙基。在实施方案中, R^{16} 独立地为未取代的丙基。在实施方案中, R^{16} 独立地为未取代的正丙基。在实施方案中, R^{16} 独立地为未取代的异丙基。在实施方案中, R^{16} 独立地为未取代的丁基。在实施方案中, R^{16} 独立地为未取代的正丁基。在实施方案中, R^{16} 独立地为未取代的异丁基。在实施方案中, R^{16} 独立地为未取代的叔丁基。在实施方案中, R^{16} 独立地为未取代的戊基。在实施方案中, R^{16} 独立地为未取代的己基。在实施方案中, R^{16} 独立

地为未取代的庚基。在实施方案中, R^{16} 独立地为未取代的辛基。在实施方案中, R^{16} 独立地为-F。在实施方案中, R^{16} 独立地为-Cl。在实施方案中, R^{16} 独立地为-Br。在实施方案中, R^{16} 独立地为-I。在实施方案中, R^{16} 独立地为未取代的甲氧基。在实施方案中, R^{16} 独立地为未取代的乙氧基。在实施方案中, R^{16} 独立地为-CF₃。在实施方案中, R^{16} 独立地为-CCl₃。在实施方案中, R^{16} 为未取代的异丙基。在实施方案中, R^{16} 为未取代的苯基。在实施方案中, R^{16} 为未取代的吡啶基。在实施方案中, R^{16} 独立地为卤素。在实施方案中, R^{16} 独立地为-CX¹⁶₃。在实施方案中, R^{16} 独立地为-CHX¹⁶₂。在实施方案中, R^{16} 独立地为-CH₂X¹⁶。在实施方案中, R^{16} 独立地为-CN。在实施方案中, R^{16} 独立地为-OH。在实施方案中, R^{16} 独立地为-NH₂。在实施方案中, R^{16} 独立地为-COOH。在实施方案中, R^{16} 独立地为-CONH₂。在实施方案中, R^{16} 独立地为-NO₂。在实施方案中, R^{16} 独立地为-SH。在实施方案中, R^{16} 独立地为-SO₂Cl。在实施方案中, R^{16} 独立地为-SO₃H。在实施方案中, R^{16} 独立地为-SO₄H。在实施方案中, R^{16} 独立地为-SO₂NH₂。在实施方案中, R^{16} 独立地为-NHNH₂。在实施方案中, R^{16} 独立地为-ONH₂。在实施方案中, R^{16} 独立地为-NHC(O)NHNH₂。在实施方案中, R^{16} 独立地为-NHC(O)NH₂。在实施方案中, R^{16} 独立地为-NHSO₂H。在实施方案中, R^{16} 独立地为-NHC(O)H。在实施方案中, R^{16} 独立地为-NHC(O)OH。在实施方案中, R^{16} 独立地为-NHOH。在实施方案中, R^{16} 独立地为-OCX¹⁶₃。在实施方案中, R^{16} 独立地为-OCHX¹⁶₂。在实施方案中, R^{16} 独立地为经取代或未取代的烷基。在实施方案中, R^{16} 独立地为经取代或未取代的杂烷基。在实施方案中, R^{16} 独立地为经取代或未取代的环烷基。在实施方案中, R^{16} 独立地为经取代或未取代的杂环烷基。在实施方案中, R^{16} 独立地为经取代或未取代的芳基。在实施方案中, R^{16} 独立地为经取代或未取代的杂芳基。在实施方案中, R^{16} 独立地为经取代的烷基。在实施方案中, R^{16} 独立地为经取代的杂烷基。在实施方案中, R^{16} 独立地为经取代的环烷基。在实施方案中, R^{16} 独立地为经取代的杂环烷基。在实施方案中, R^{16} 独立地为经取代的芳基。在实施方案中, R^{16} 独立地为经取代的杂芳基。在实施方案中, R^{16} 独立地为未取代的烷基。在实施方案中, R^{16} 独立地为未取代的杂烷基。在实施方案中, R^{16} 独立地为未取代的环烷基。在实施方案中, R^{16} 独立地为未取代的杂环烷基。在实施方案中, R^{16} 独立地为未取代的芳基。在实施方案中, R^{16} 独立地为未取代的杂芳基。在实施方案中, R^{16} 独立地为经取代或未取代的C₁-C₈烷基。在实施方案中, R^{16} 独立地为经取代或未取代的2-8元杂烷基。在实施方案中, R^{16} 独立地为经取代或未取代的C₃-C₈环烷基。在实施方案中, R^{16} 独立地为经取代或未取代的3-8元杂环烷基。在实施方案中, R^{16} 独立地为经取代或未取代的C₆-C₁₀芳基。在实施方案中, R^{16} 独立地为经取代或未取代的5-10元杂芳基。在实施方案中, R^{16} 独立地为经取代的C₁-C₈烷基。在实施方案中, R^{16} 独立地为经取代的2-8元杂烷基。在实施方案中, R^{16} 独立地为经取代的C₃-C₈环烷基。在实施方案中, R^{16} 独立地为经取代的3-8元杂环烷基。在实施方案中, R^{16} 独立地为经取代的C₆-C₁₀芳基。在实施方案中, R^{16} 独立地为经取代的5-10元杂芳基。在实施方案中, R^{16} 独立地为未取代的C₁-C₈烷基。在实施方案中, R^{16} 独立地为未取代的2-8元杂烷基。在实施方案中, R^{16} 独立地为未取代的C₃-C₈环烷基。在实施方案中, R^{16} 独立地为未取代的3-8元杂环烷基。在实施方案中, R^{16} 独立地为未取代的C₆-C₁₀芳基。在实施方案中, R^{16} 独立地为未取代的5-10元杂芳基。在实施方案中, R^{16} 独立地为经取代或未取代的C₁-C₄烷基。在实施方案中, R^{16} 独立地为经取代或未取代的2-4元杂烷基。在实施方案中, R^{16} 独立地为经取代或未取代的C₃-C₆环烷基。在实施方案中, R^{16} 独立地为经取代或未取代的3-6元杂环烷基。在实施方案中, R^{16} 独立地为经取代或未取代的苯基。在实施方案中, R^{16} 独立地为经取代或未

取代的5-6元杂芳基。在实施方案中， R^{16} 独立地为经取代的 C_1 - C_4 烷基。在实施方案中， R^{16} 独立地为经取代的2-4元杂烷基。在实施方案中， R^{16} 独立地为经取代的 C_3 - C_6 环烷基。在实施方案中， R^{16} 独立地为经取代的3-6元杂环烷基。在实施方案中， R^{16} 独立地为经取代的苯基。在实施方案中， R^{16} 独立地为经取代的5-6元杂芳基。在实施方案中， R^{16} 独立地为未取代的 C_1 - C_4 烷基。在实施方案中， R^{16} 独立地为未取代的2-4元杂烷基。在实施方案中， R^{16} 独立地为未取代的 C_3 - C_6 环烷基。在实施方案中， R^{16} 独立地为未取代的3-6元杂环烷基。在实施方案中， R^{16} 独立地为未取代的苯基。在实施方案中， R^{16} 独立地为未取代的5-6元杂芳基。

[0215] 在实施方案中， R^{16A} 为氢。在实施方案中， R^{16A} 为 $-CX_3$ 。在实施方案中， R^{16A} 为 $-CN$ 。在实施方案中， R^{16A} 为 $-COOH$ 。在实施方案中， R^{16A} 为 $-CONH_2$ 。在实施方案中， R^{16A} 为 $-CHX_2$ 。在实施方案中， R^{16A} 为 $-CH_2X$ 。在实施方案中， R^{16A} 为未取代的甲基。在实施方案中， R^{16A} 为未取代的乙基。在实施方案中， R^{16A} 为未取代的丙基。在实施方案中， R^{16A} 为未取代的异丙基。在实施方案中， R^{16A} 为未取代的丁基。在实施方案中， R^{16A} 为未取代的叔丁基。

[0216] 在实施方案中， R^{16B} 为氢。在实施方案中， R^{16B} 为 $-CX_3$ 。在实施方案中， R^{16B} 为 $-CN$ 。在实施方案中， R^{16B} 为 $-COOH$ 。在实施方案中， R^{16B} 为 $-CONH_2$ 。在实施方案中， R^{16B} 为 $-CHX_2$ 。在实施方案中， R^{16B} 为 $-CH_2X$ 。在实施方案中， R^{16B} 为未取代的甲基。在实施方案中， R^{16B} 为未取代的乙基。在实施方案中， R^{16B} 为未取代的丙基。在实施方案中， R^{16B} 为未取代的异丙基。在实施方案中， R^{16B} 为未取代的丁基。在实施方案中， R^{16B} 为未取代的叔丁基。

[0217] 在实施方案中， R^{16C} 为氢。在实施方案中， R^{16C} 为 $-CX_3$ 。在实施方案中， R^{16C} 为 $-CN$ 。在实施方案中， R^{16C} 为 $-COOH$ 。在实施方案中， R^{16C} 为 $-CONH_2$ 。在实施方案中， R^{16C} 为 $-CHX_2$ 。在实施方案中， R^{16C} 为 $-CH_2X$ 。在实施方案中， R^{16C} 为未取代的甲基。在实施方案中， R^{16C} 为未取代的乙基。在实施方案中， R^{16C} 为未取代的丙基。在实施方案中， R^{16C} 为未取代的异丙基。在实施方案中， R^{16C} 为未取代的丁基。在实施方案中， R^{16C} 为未取代的叔丁基。

[0218] 在实施方案中， R^{16D} 为氢。在实施方案中， R^{16D} 为 $-CX_3$ 。在实施方案中， R^{16D} 为 $-CN$ 。在实施方案中， R^{16D} 为 $-COOH$ 。在实施方案中， R^{16D} 为 $-CONH_2$ 。在实施方案中， R^{16D} 为 $-CHX_2$ 。在实施方案中， R^{16D} 为 $-CH_2X$ 。在实施方案中， R^{16D} 为未取代的甲基。在实施方案中， R^{16D} 为未取代的乙基。在实施方案中， R^{16D} 为未取代的丙基。在实施方案中， R^{16D} 为未取代的异丙基。在实施方案中， R^{16D} 为未取代的丁基。在实施方案中， R^{16D} 为未取代的叔丁基。

[0219] 在实施方案中， R^{17} 为氢。在实施方案中， R^{17} 为卤素。在实施方案中， R^{17} 为 CX^{17}_3 。在实施方案中， R^{17} 为 $-CHX^{17}_2$ 。在实施方案中， R^{17} 为 $-CH_2X^{17}$ 。在实施方案中， R^{17} 为 $-CN$ 。在实施方案中， R^{17} 为 $-SO_{n17}R^{17D}$ 。在实施方案中， R^{17} 为 $-SO_{v17}NR^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-NHN R^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-ONR^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-NHC(O)NHN R^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-NHC(O)NR^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-N(O)_{m17}$ 。在实施方案中， R^{17} 为 $-NR^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-C(O)R^{17C}$ 。在实施方案中， R^{17} 为 $-C(O)-OR^{17C}$ 。在实施方案中， R^{17} 为 $-C(O)NR^{17A}R^{17B}$ 。在实施方案中， R^{17} 为 $-OR^{17D}$ 。在实施方案中， R^{17} 为 $-NR^{17A}SO_2R^{17D}$ 。在实施方案中， R^{17} 为 $-NR^{17A}C(O)R^{17C}$ 。在实施方案中， R^{17} 为 $-NR^{17A}C(O)OR^{17C}$ 。在实施方案中， R^{17} 为 $-NR^{17A}OR^{17C}$ 。在实施方案中， R^{17} 为 $-OCX^{17}_3$ 。在实施方案中， R^{17} 为 $-OCHX^{17}_2$ 。在实施方案中， R^{17} 为经取代或未取代的烷基。在实施方案中， R^{17} 为经取代或未取代的杂烷基。在实施方案中， R^{17} 为经取代或未取代的环烷基。在实施方案中， R^{17} 为经取代或未取代的杂环烷基。在实施方案中， R^{17} 为经取代或未取代的芳基。在实施方案中， R^{17} 为经取代或未取代的杂芳基。在实施方案中， R^{17} 为经取代的

烷基。在实施方案中, R^{17} 为经取代的杂烷基。在实施方案中, R^{17} 为经取代的环烷基。在实施方案中, R^{17} 为经取代的杂环烷基。在实施方案中, R^{17} 为经取代的芳基。在实施方案中, R^{17} 为经取代的杂芳基。在实施方案中, R^{17} 为未取代的烷基。在实施方案中, R^{17} 为未取代的杂烷基。在实施方案中, R^{17} 为未取代的环烷基。在实施方案中, R^{17} 为未取代的杂环烷基。在实施方案中, R^{17} 为未取代的芳基。在实施方案中, R^{17} 为未取代的杂芳基。在实施方案中, R^{17} 为未取代的甲基。在实施方案中, R^{17} 为未取代的乙基。在实施方案中, R^{17} 为未取代的丙基。在实施方案中, R^{17} 为未取代的异丙基。在实施方案中, R^{17} 为未取代的丁基。在实施方案中, R^{17} 为未取代的叔丁基。在实施方案中, R^{17} 为 $-\text{CH}_2\text{Ph}$ 。

[0220] 在实施方案中, R^{17A} 为氢。在实施方案中, R^{17A} 为 $-\text{CX}_3$ 。在实施方案中, R^{17A} 为 $-\text{CN}$ 。在实施方案中, R^{17A} 为 $-\text{COOH}$ 。在实施方案中, R^{17A} 为 $-\text{CONH}_2$ 。在实施方案中, R^{17A} 为 $-\text{CHX}_2$ 。在实施方案中, R^{17A} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{17A} 为未取代的甲基。在实施方案中, R^{17A} 为未取代的乙基。在实施方案中, R^{17A} 为未取代的丙基。在实施方案中, R^{17A} 为未取代的异丙基。在实施方案中, R^{17A} 为未取代的丁基。在实施方案中, R^{17A} 为未取代的叔丁基。

[0221] 在实施方案中, R^{17B} 为氢。在实施方案中, R^{17B} 为 $-\text{CX}_3$ 。在实施方案中, R^{17B} 为 $-\text{CN}$ 。在实施方案中, R^{17B} 为 $-\text{COOH}$ 。在实施方案中, R^{17B} 为 $-\text{CONH}_2$ 。在实施方案中, R^{17B} 为 $-\text{CHX}_2$ 。在实施方案中, R^{17B} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{17B} 为未取代的甲基。在实施方案中, R^{17B} 为未取代的乙基。在实施方案中, R^{17B} 为未取代的丙基。在实施方案中, R^{17B} 为未取代的异丙基。在实施方案中, R^{17B} 为未取代的丁基。在实施方案中, R^{17B} 为未取代的叔丁基。

[0222] 在实施方案中, R^{17C} 为氢。在实施方案中, R^{17C} 为 $-\text{CX}_3$ 。在实施方案中, R^{17C} 为 $-\text{CN}$ 。在实施方案中, R^{17C} 为 $-\text{COOH}$ 。在实施方案中, R^{17C} 为 $-\text{CONH}_2$ 。在实施方案中, R^{17C} 为 $-\text{CHX}_2$ 。在实施方案中, R^{17C} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{17C} 为未取代的甲基。在实施方案中, R^{17C} 为未取代的乙基。在实施方案中, R^{17C} 为未取代的丙基。在实施方案中, R^{17C} 为未取代的异丙基。在实施方案中, R^{17C} 为未取代的丁基。在实施方案中, R^{17C} 为未取代的叔丁基。

[0223] 在实施方案中, R^{17D} 为氢。在实施方案中, R^{17D} 为 $-\text{CX}_3$ 。在实施方案中, R^{17D} 为 $-\text{CN}$ 。在实施方案中, R^{17D} 为 $-\text{COOH}$ 。在实施方案中, R^{17D} 为 $-\text{CONH}_2$ 。在实施方案中, R^{17D} 为 $-\text{CHX}_2$ 。在实施方案中, R^{17D} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{17D} 为未取代的甲基。在实施方案中, R^{17D} 为未取代的乙基。在实施方案中, R^{17D} 为未取代的丙基。在实施方案中, R^{17D} 为未取代的异丙基。在实施方案中, R^{17D} 为未取代的丁基。在实施方案中, R^{17D} 为未取代的叔丁基。

[0224] 在实施方案中, R^{18} 为氢。在实施方案中, R^{18} 为卤素。在实施方案中, R^{18} 为 CX^{18}_3 。在实施方案中, R^{18} 为 $-\text{CHX}^{18}_2$ 。在实施方案中, R^{18} 为 $-\text{CH}_2\text{X}^{18}$ 。在实施方案中, R^{18} 为 $-\text{CN}$ 。在实施方案中, R^{18} 为 $-\text{SO}_{n18}\text{R}^{18D}$ 。在实施方案中, R^{18} 为 $-\text{SO}_{v18}\text{NR}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{NHN}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{ONR}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{NHC} = (\text{O})\text{NHN}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{NHC}(\text{O})\text{NR}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{N}(\text{O})_{m18}$ 。在实施方案中, R^{18} 为 $-\text{NR}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{C}(\text{O})\text{R}^{18C}$ 。在实施方案中, R^{18} 为 $-\text{C}(\text{O})-\text{OR}^{18C}$ 。在实施方案中, R^{18} 为 $-\text{C}(\text{O})\text{NR}^{18A}\text{R}^{18B}$ 。在实施方案中, R^{18} 为 $-\text{OR}^{18D}$ 。在实施方案中, R^{18} 为 $-\text{NR}^{18A}\text{SO}_2\text{R}^{18D}$ 。在实施方案中, R^{18} 为 $-\text{NR}^{18A}\text{C}(\text{O})\text{R}^{18C}$ 。在实施方案中, R^{18} 为 $-\text{NR}^{18A}\text{C}(\text{O})\text{OR}^{18C}$ 。在实施方案中, R^{18} 为 $-\text{NR}^{18A}\text{OR}^{18C}$ 。在实施方案中, R^{18} 为 $-\text{OCX}^{18}_3$ 。在实施方案中, R^{18} 为 $-\text{OCHX}^{18}_2$ 。在实施方案中, R^{18} 为经取代或未取代的烷基。在实施方案中, R^{18} 为经取代或未取代的杂烷基。在实施方案中, R^{18} 为经取代或未取代的环烷基。在实施方案中, R^{18} 为经取代或未取代的杂环烷基。在实施方案中, R^{18} 为经取代或未

取代的芳基。在实施方案中, R^{18} 为经取代或未取代的杂芳基。在实施方案中, R^{18} 为经取代的烷基。在实施方案中, R^{18} 为经取代的杂烷基。在实施方案中, R^{18} 为经取代的环烷基。在实施方案中, R^{18} 为经取代的杂环烷基。在实施方案中, R^{18} 为经取代的芳基。在实施方案中, R^{18} 为经取代的杂芳基。在实施方案中, R^{18} 为未取代的烷基。在实施方案中, R^{18} 为未取代的杂烷基。在实施方案中, R^{18} 为未取代的环烷基。在实施方案中, R^{18} 为未取代的杂环烷基。在实施方案中, R^{18} 为未取代的芳基。在实施方案中, R^{18} 为未取代的杂芳基。在实施方案中, R^{18} 为未取代的甲基。在实施方案中, R^{18} 为未取代的乙基。在实施方案中, R^{18} 为未取代的丙基。在实施方案中, R^{18} 为未取代的异丙基。在实施方案中, R^{18} 为未取代的丁基。在实施方案中, R^{18} 为未取代的叔丁基。在实施方案中, R^{18} 为 $-\text{CH}_2\text{Ph}$ 。

[0225] 在实施方案中, R^{18A} 为氢。在实施方案中, R^{18A} 为 $-\text{CX}_3$ 。在实施方案中, R^{18A} 为 $-\text{CN}$ 。在实施方案中, R^{18A} 为 $-\text{COOH}$ 。在实施方案中, R^{18A} 为 $-\text{CONH}_2$ 。在实施方案中, R^{18A} 为 $-\text{CHX}_2$ 。在实施方案中, R^{18A} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{18A} 为未取代的甲基。在实施方案中, R^{18A} 为未取代的乙基。在实施方案中, R^{18A} 为未取代的丙基。在实施方案中, R^{18A} 为未取代的异丙基。在实施方案中, R^{18A} 为未取代的丁基。在实施方案中, R^{18A} 为未取代的叔丁基。

[0226] 在实施方案中, R^{18B} 为氢。在实施方案中, R^{18B} 为 $-\text{CX}_3$ 。在实施方案中, R^{18B} 为 $-\text{CN}$ 。在实施方案中, R^{18B} 为 $-\text{COOH}$ 。在实施方案中, R^{18B} 为 $-\text{CONH}_2$ 。在实施方案中, R^{18B} 为 $-\text{CHX}_2$ 。在实施方案中, R^{18B} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{18B} 为未取代的甲基。在实施方案中, R^{18B} 为未取代的乙基。在实施方案中, R^{18B} 为未取代的丙基。在实施方案中, R^{18B} 为未取代的异丙基。在实施方案中, R^{18B} 为未取代的丁基。在实施方案中, R^{18B} 为未取代的叔丁基。

[0227] 在实施方案中, R^{18C} 为氢。在实施方案中, R^{18C} 为 $-\text{CX}_3$ 。在实施方案中, R^{18C} 为 $-\text{CN}$ 。在实施方案中, R^{18C} 为 $-\text{COOH}$ 。在实施方案中, R^{18C} 为 $-\text{CONH}_2$ 。在实施方案中, R^{18C} 为 $-\text{CHX}_2$ 。在实施方案中, R^{18C} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{18C} 为未取代的甲基。在实施方案中, R^{18C} 为未取代的乙基。在实施方案中, R^{18C} 为未取代的丙基。在实施方案中, R^{18C} 为未取代的异丙基。在实施方案中, R^{18C} 为未取代的丁基。在实施方案中, R^{18C} 为未取代的叔丁基。

[0228] 在实施方案中, R^{18D} 为氢。在实施方案中, R^{18D} 为 $-\text{CX}_3$ 。在实施方案中, R^{18D} 为 $-\text{CN}$ 。在实施方案中, R^{18D} 为 $-\text{COOH}$ 。在实施方案中, R^{18D} 为 $-\text{CONH}_2$ 。在实施方案中, R^{18D} 为 $-\text{CHX}_2$ 。在实施方案中, R^{18D} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{18D} 为未取代的甲基。在实施方案中, R^{18D} 为未取代的乙基。在实施方案中, R^{18D} 为未取代的丙基。在实施方案中, R^{18D} 为未取代的异丙基。在实施方案中, R^{18D} 为未取代的丁基。在实施方案中, R^{18D} 为未取代的叔丁基。

[0229] 在实施方案中, R^{19} 为氢。在实施方案中, R^{19} 为卤素。在实施方案中, R^{19} 为 CX^{19}_3 。在实施方案中, R^{19} 为 $-\text{CHX}^{19}_2$ 。在实施方案中, R^{19} 为 $-\text{CH}_2\text{X}^{19}$ 。在实施方案中, R^{19} 为 $-\text{CN}$ 。在实施方案中, R^{19} 为 $-\text{SO}_{n19}\text{R}^{19D}$ 。在实施方案中, R^{19} 为 $-\text{SO}_{v19}\text{NR}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{NHN}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{ONR}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{NHC}=\text{(O)}\text{NHN}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{NHC}(\text{O})\text{NR}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{N}(\text{O})_{m19}$ 。在实施方案中, R^{19} 为 $-\text{NR}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{C}(\text{O})\text{R}^{19C}$ 。在实施方案中, R^{19} 为 $-\text{C}(\text{O})-\text{OR}^{19C}$ 。在实施方案中, R^{19} 为 $-\text{C}(\text{O})\text{NR}^{19A}\text{R}^{19B}$ 。在实施方案中, R^{19} 为 $-\text{OR}^{19D}$ 。在实施方案中, R^{19} 为 $-\text{NR}^{19A}\text{SO}_2\text{R}^{19D}$ 。在实施方案中, R^{19} 为 $-\text{NR}^{19A}\text{C}(\text{O})\text{R}^{19C}$ 。在实施方案中, R^{19} 为 $-\text{NR}^{19A}\text{C}(\text{O})\text{OR}^{19C}$ 。在实施方案中, R^{19} 为 $-\text{NR}^{19A}\text{OR}^{19C}$ 。在实施方案中, R^{19} 为 $-\text{OCX}^{19}_3$ 。在实施方案中, R^{19} 为 $-\text{OCHX}^{19}_2$ 。在实施方案中, R^{19} 为经取代或未取代的烷基。在实施方案中, R^{19} 为经取代或未取代的杂烷基。在实施方案中, R^{19} 为经取代或未取代的

环烷基。在实施方案中, R^{19} 为经取代或未取代的杂环烷基。在实施方案中, R^{19} 为经取代或未取代的芳基。在实施方案中, R^{19} 为经取代或未取代的杂芳基。在实施方案中, R^{19} 为经取代的烷基。在实施方案中, R^{19} 为经取代的杂烷基。在实施方案中, R^{19} 为经取代的环烷基。在实施方案中, R^{19} 为经取代的杂环烷基。在实施方案中, R^{19} 为经取代的芳基。在实施方案中, R^{19} 为经取代的杂芳基。在实施方案中, R^{19} 为未取代的烷基。在实施方案中, R^{19} 为未取代的杂烷基。在实施方案中, R^{19} 为未取代的环烷基。在实施方案中, R^{19} 为未取代的杂环烷基。在实施方案中, R^{19} 为未取代的芳基。在实施方案中, R^{19} 为未取代的杂芳基。在实施方案中, R^{19} 为未取代的甲基。在实施方案中, R^{19} 为未取代的乙基。在实施方案中, R^{19} 为未取代的丙基。在实施方案中, R^{19} 为未取代的异丙基。在实施方案中, R^{19} 为未取代的丁基。在实施方案中, R^{19} 为未取代的叔丁基。在实施方案中, R^{19} 为 $-\text{CH}_2\text{Ph}$ 。

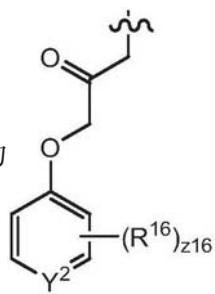
[0230] 在实施方案中, R^{19A} 为氢。在实施方案中, R^{19A} 为 $-\text{CX}_3$ 。在实施方案中, R^{19A} 为 $-\text{CN}$ 。在实施方案中, R^{19A} 为 $-\text{COOH}$ 。在实施方案中, R^{19A} 为 $-\text{CONH}_2$ 。在实施方案中, R^{19A} 为 $-\text{CHX}_2$ 。在实施方案中, R^{19A} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{19A} 为未取代的甲基。在实施方案中, R^{19A} 为未取代的乙基。在实施方案中, R^{19A} 为未取代的丙基。在实施方案中, R^{19A} 为未取代的异丙基。在实施方案中, R^{19A} 为未取代的丁基。在实施方案中, R^{19A} 为未取代的叔丁基。

[0231] 在实施方案中, R^{19B} 为氢。在实施方案中, R^{19B} 为 $-\text{CX}_3$ 。在实施方案中, R^{19B} 为 $-\text{CN}$ 。在实施方案中, R^{19B} 为 $-\text{COOH}$ 。在实施方案中, R^{19B} 为 $-\text{CONH}_2$ 。在实施方案中, R^{19B} 为 $-\text{CHX}_2$ 。在实施方案中, R^{19B} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{19B} 为未取代的甲基。在实施方案中, R^{19B} 为未取代的乙基。在实施方案中, R^{19B} 为未取代的丙基。在实施方案中, R^{19B} 为未取代的异丙基。在实施方案中, R^{19B} 为未取代的丁基。在实施方案中, R^{19B} 为未取代的叔丁基。

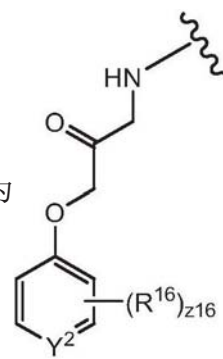
[0232] 在实施方案中, R^{19C} 为氢。在实施方案中, R^{19C} 为 $-\text{CX}_3$ 。在实施方案中, R^{19C} 为 $-\text{CN}$ 。在实施方案中, R^{19C} 为 $-\text{COOH}$ 。在实施方案中, R^{19C} 为 $-\text{CONH}_2$ 。在实施方案中, R^{19C} 为 $-\text{CHX}_2$ 。在实施方案中, R^{19C} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{19C} 为未取代的甲基。在实施方案中, R^{19C} 为未取代的乙基。在实施方案中, R^{19C} 为未取代的丙基。在实施方案中, R^{19C} 为未取代的异丙基。在实施方案中, R^{19C} 为未取代的丁基。在实施方案中, R^{19C} 为未取代的叔丁基。

[0233] 在实施方案中, R^{19D} 为氢。在实施方案中, R^{19D} 为 $-\text{CX}_3$ 。在实施方案中, R^{19D} 为 $-\text{CN}$ 。在实施方案中, R^{19D} 为 $-\text{COOH}$ 。在实施方案中, R^{19D} 为 $-\text{CONH}_2$ 。在实施方案中, R^{19D} 为 $-\text{CHX}_2$ 。在实施方案中, R^{19D} 为 $-\text{CH}_2\text{X}$ 。在实施方案中, R^{19D} 为未取代的甲基。在实施方案中, R^{19D} 为未取代的乙基。在实施方案中, R^{19D} 为未取代的丙基。在实施方案中, R^{19D} 为未取代的异丙基。在实施方案中, R^{19D} 为未取代的丁基。在实施方案中, R^{19D} 为未取代的叔丁基。

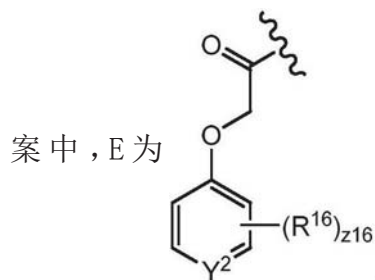
[0234] 在实施方案中, E 为



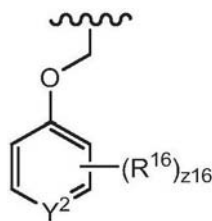
在实施方案中, E 为



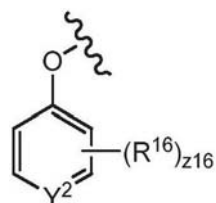
在实施方案中, E 为



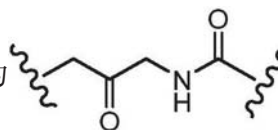
在实施方案中, E 为



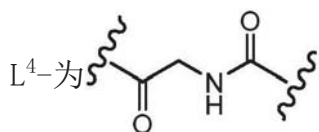
在实施方案中, E 为



在实施方案中, $-L^2-L^1-L^4-$ 为



在实施方案中, $-L^2-L^1-$



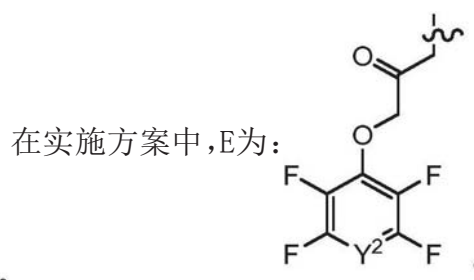
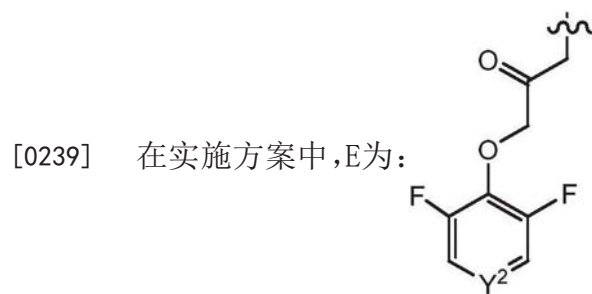
在实施方案中, $-L^2-L^1-L^4-$ 为 $-\text{CH}_2\text{NHC(O)}-$ 。

[0235] 在实施方案中, R^{16} 独立地为卤素、 CX^{16}_3 、 $-\text{CHX}^{16}_2$ 、 $-\text{CH}_2\text{X}^{16}$ 、 $-\text{CN}$ 、 $-\text{OH}$ 、 $-\text{NH}_2$ 、 $-\text{COOH}$ 、 $-\text{CONH}_2$ 、 $-\text{NO}_2$ 、 $-\text{SH}$ 、 $-\text{SO}_2\text{Cl}$ 、 $-\text{SO}_3\text{H}$ 、 $-\text{SO}_4\text{H}$ 、 $-\text{SO}_2\text{NH}_2$ 、 $-\text{NHNH}_2$ 、 $-\text{ONH}_2$ 、 $-\text{NHC(O)NHNH}_2$ 、 $-\text{NHC(O)NH}_2$ 、 $-\text{NHSO}_2\text{H}$ 、 $-\text{NHC(O)H}$ 、 $-\text{NHC(O)OH}$ 、 $-\text{NHOH}$ 、 $-\text{OCX}^{16}_3$ 、 $-\text{OCHX}^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。在实施方案中, R^{16} 独立地为卤素。在实施方案中, R^{16} 独立地为 $-\text{F}$ 。

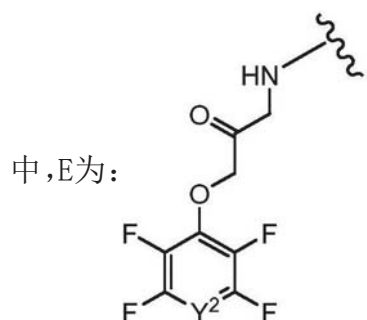
[0236] Y^2 为 N 或 CH 。在实施方案中, Y^2 为 CH 。在实施方案中, Y^2 为 N 。

[0237] 符号 z_{16} 为 0 至 4 的整数。每个 X^{16} 独立地为 $-\text{F}$ 、 $-\text{Cl}$ 、 $-\text{Br}$ 或 $-\text{I}$ 。

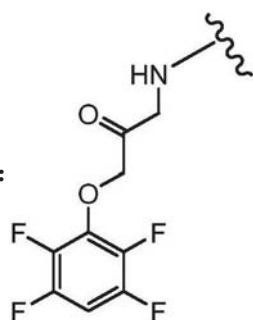
[0238] 在实施方案中, z_{16} 为 4。在实施方案中, z_{16} 为 2。在实施方案中, z_{16} 为 1。在实施方案中, z_{16} 为 0。在实施方案中, z_{16} 为 3。



在实施方案

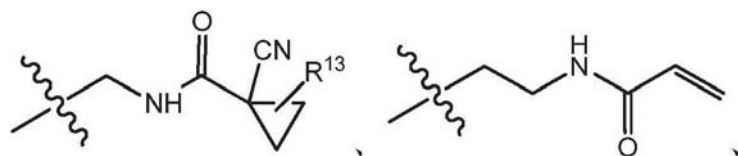


在实施方案中, E 为:

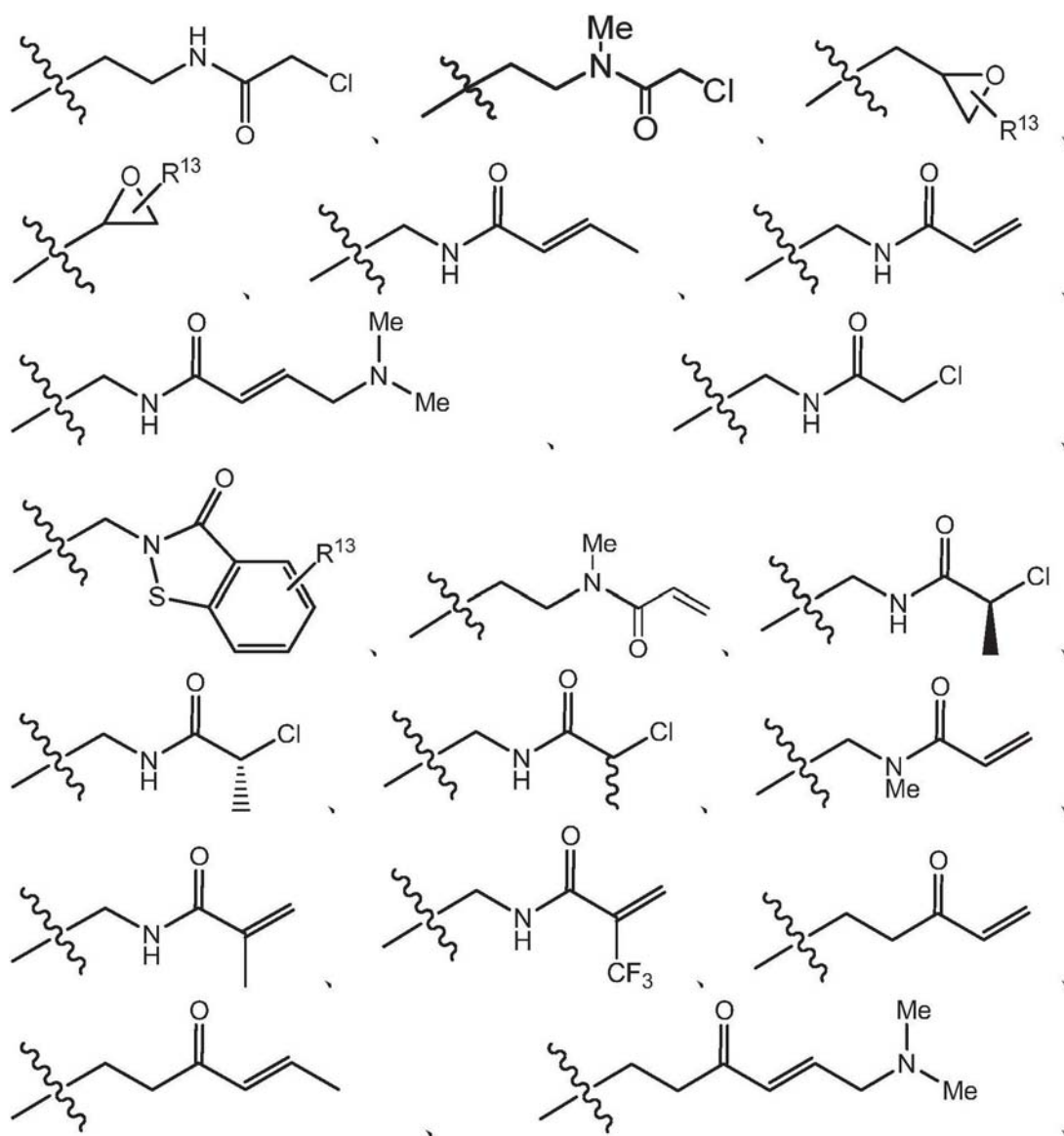


[0240] 在实施方案中, E 包含经取代或未取代的乙烯砜部分、经取代或未取代的乙烯基磺

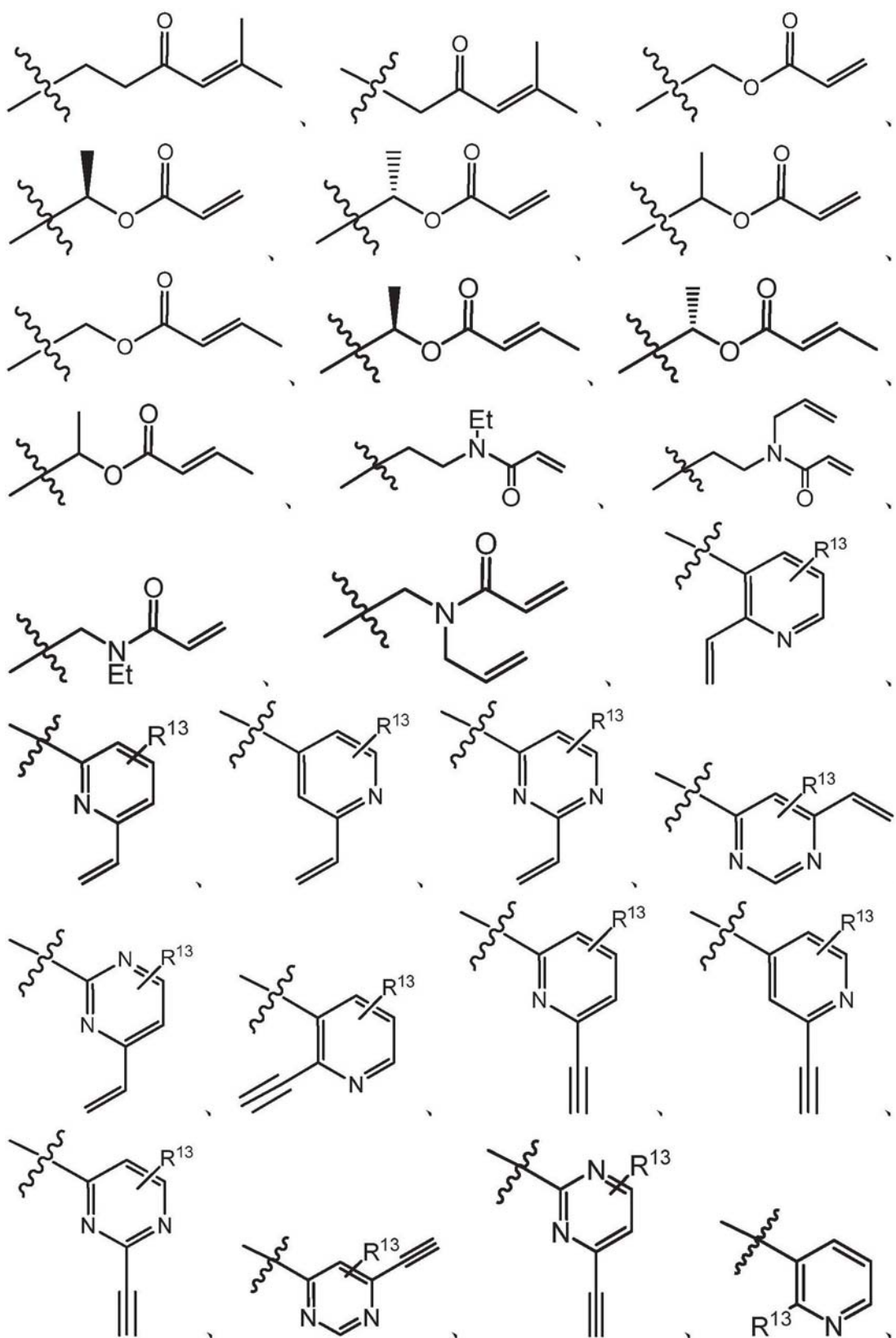
酰胺部分、经取代或未取代的氟 (C₁-C₄) 烷基酮部分、经取代或未取代的氯 (C₁-C₄) 烷基酮部分、经取代或未取代的丙烯酰胺部分、经取代或未取代的二硫化物部分、经取代或未取代的硫醇部分、经取代或未取代的磷酸酯部分、经取代或未取代的醛部分、经取代或未取代的烯酮部分、经取代或未取代的重氮甲基酮部分、经取代或未取代的重氮甲酰胺部分、经取代或未取代的氰基环丙基羧酰胺部分、经取代或未取代的环氧化物部分、经取代或未取代的环氧酮部分、经取代或未取代的环氧酰胺部分、经取代或未取代的芳醛部分、经取代或未取代的芳二醛部分、经取代或未取代的二醛部分、经取代或未取代的氮芥部分、经取代或未取代的炔丙基部分、经取代或未取代的炔丙基酰胺部分、

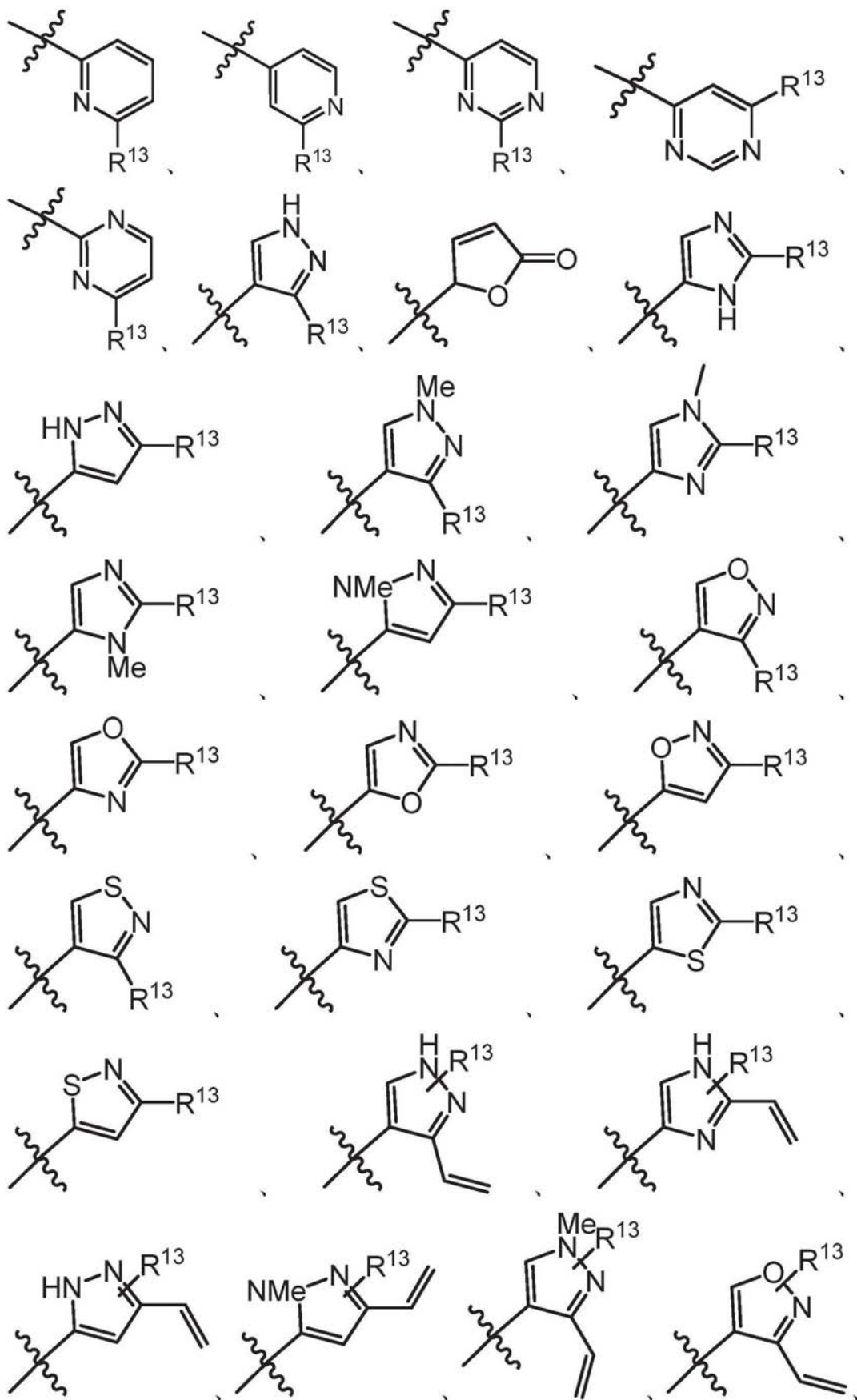


[0241]

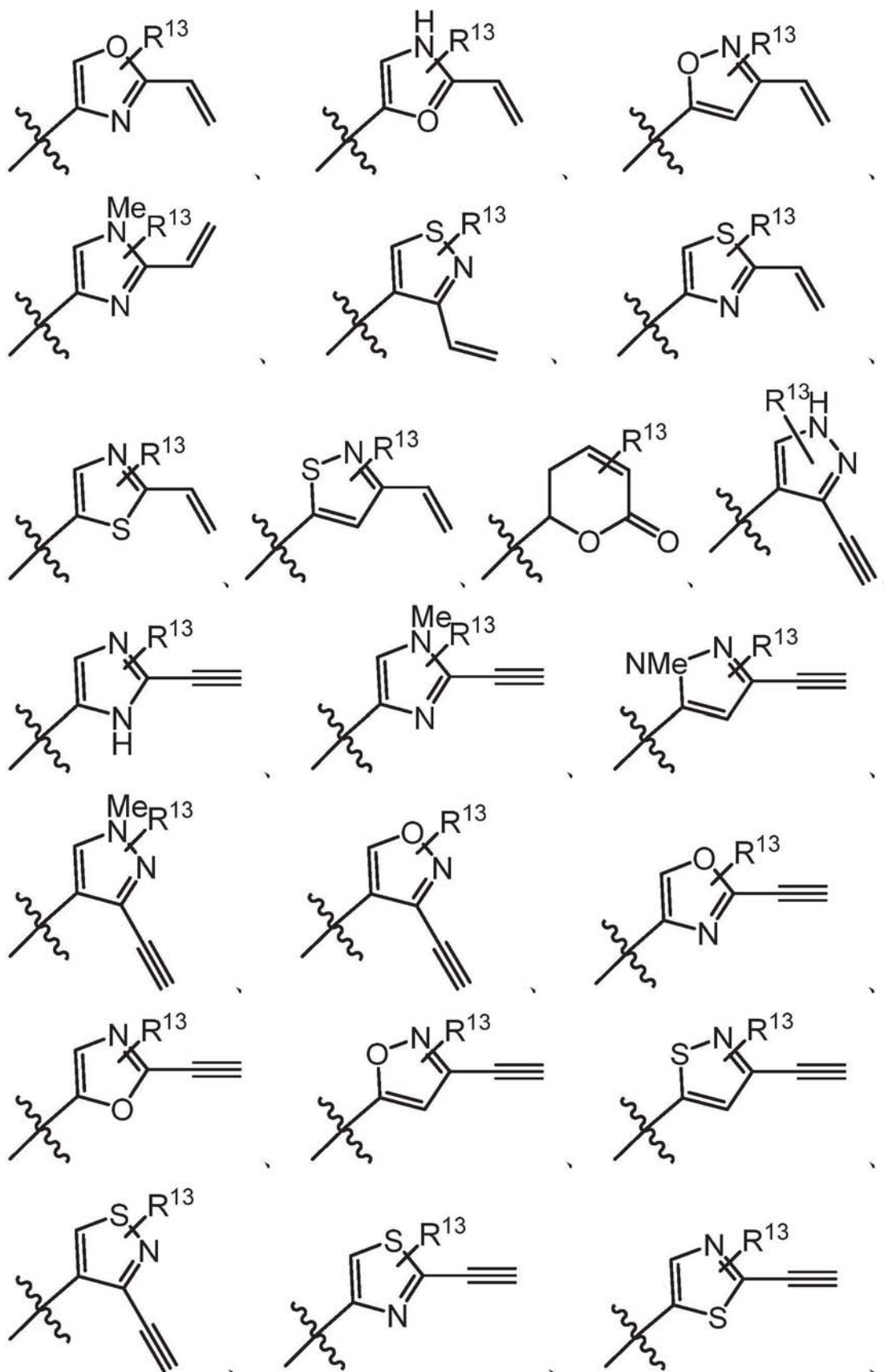


[0242]

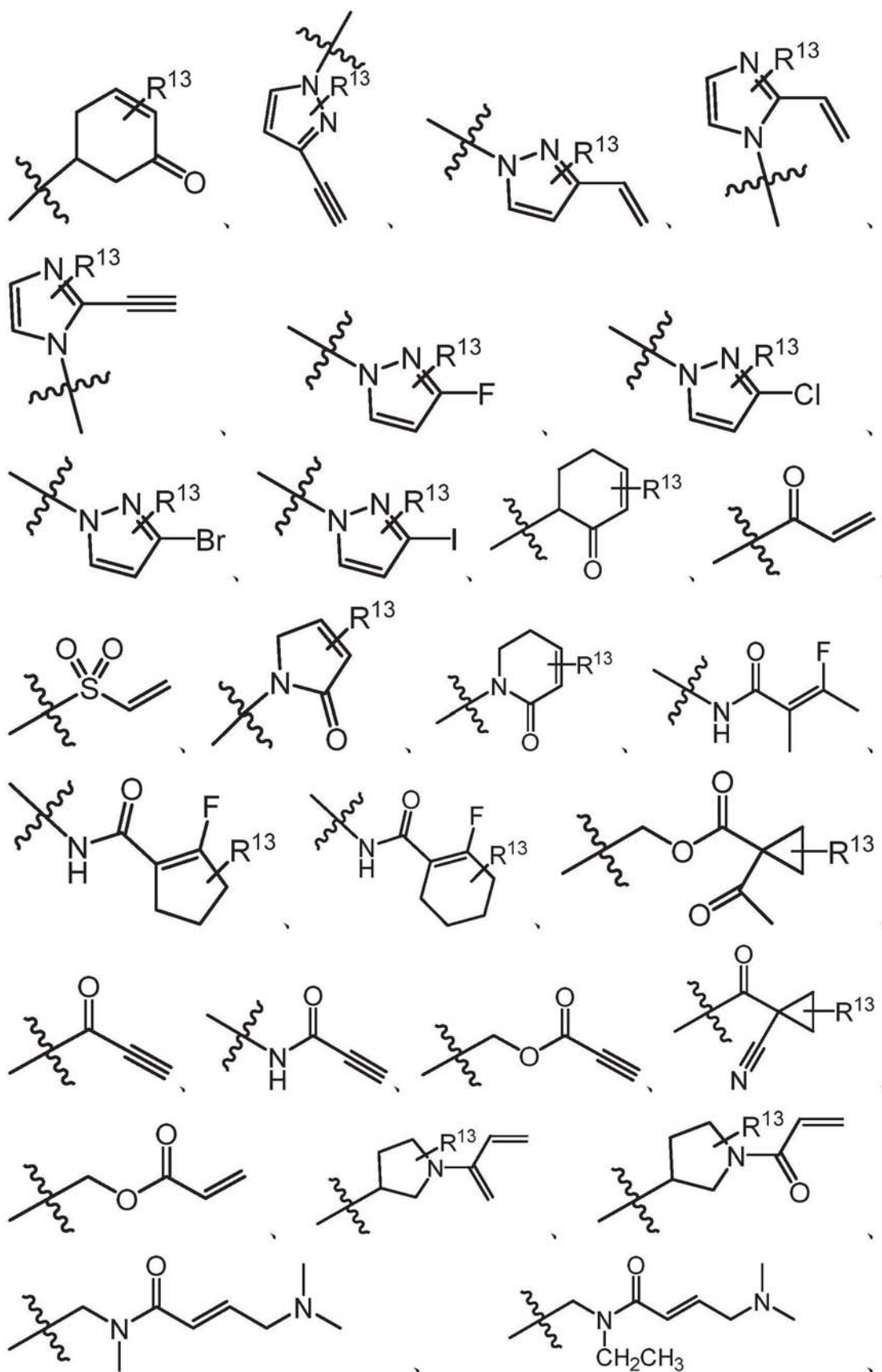




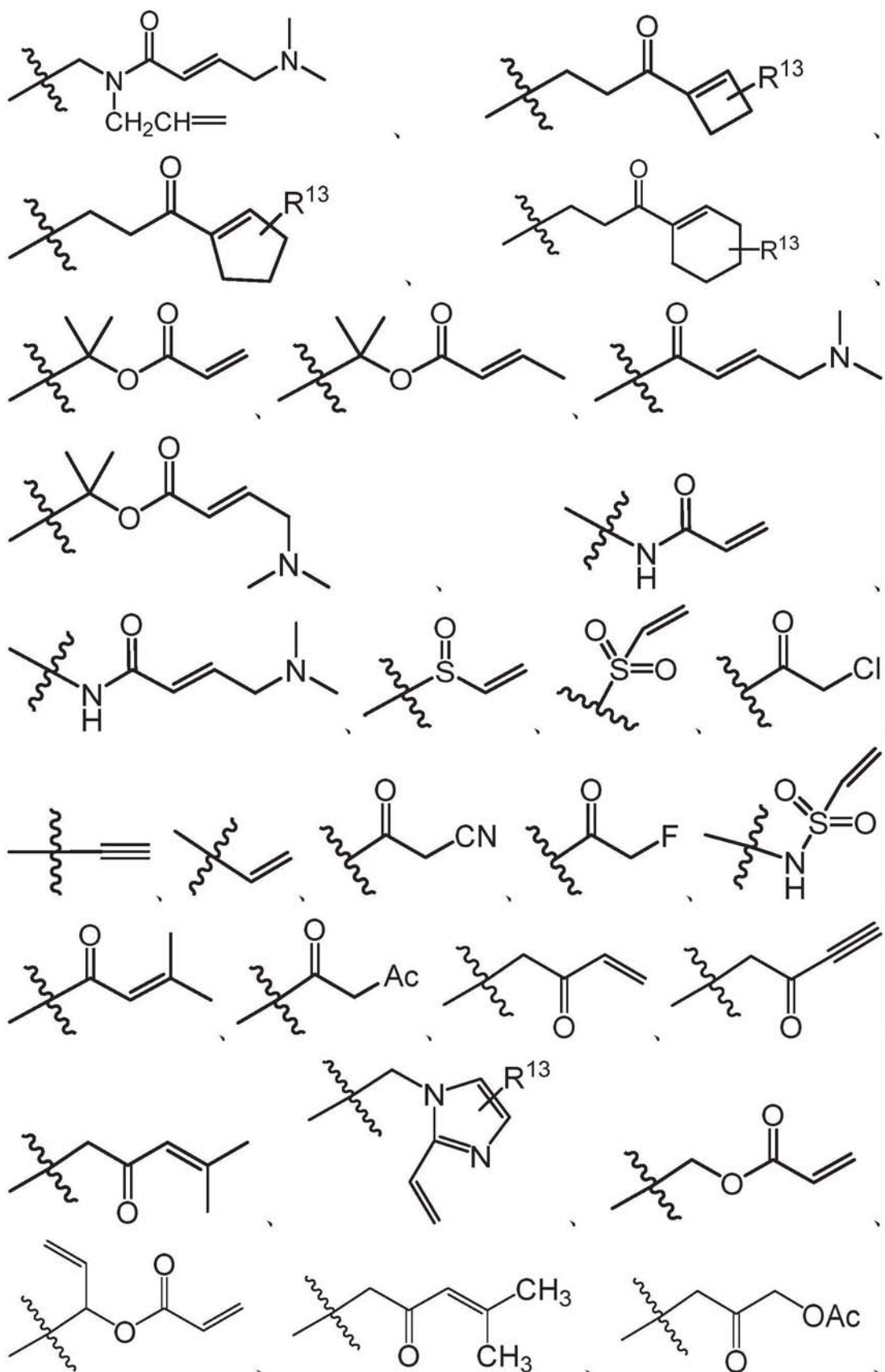
[0244]



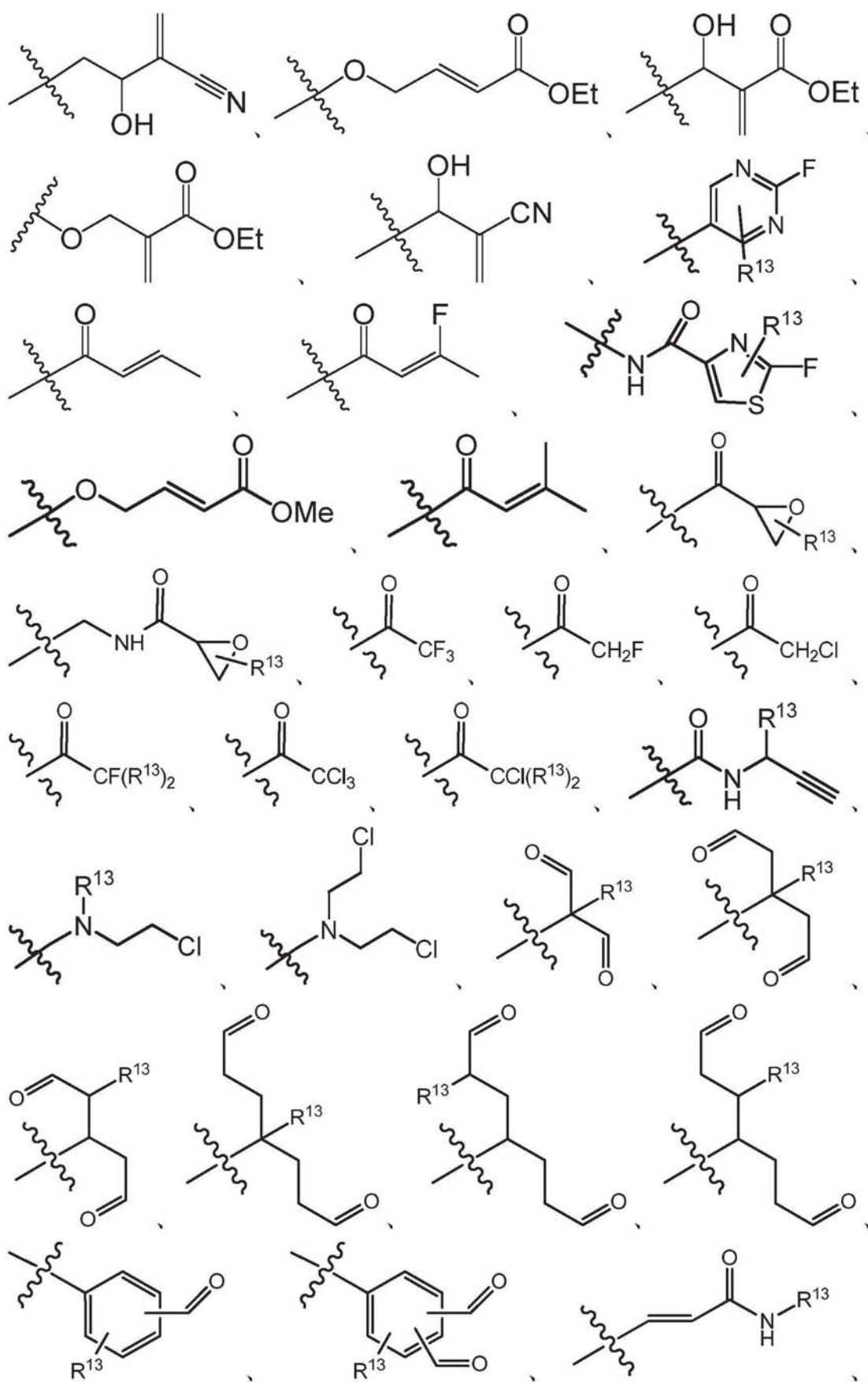
[0245]

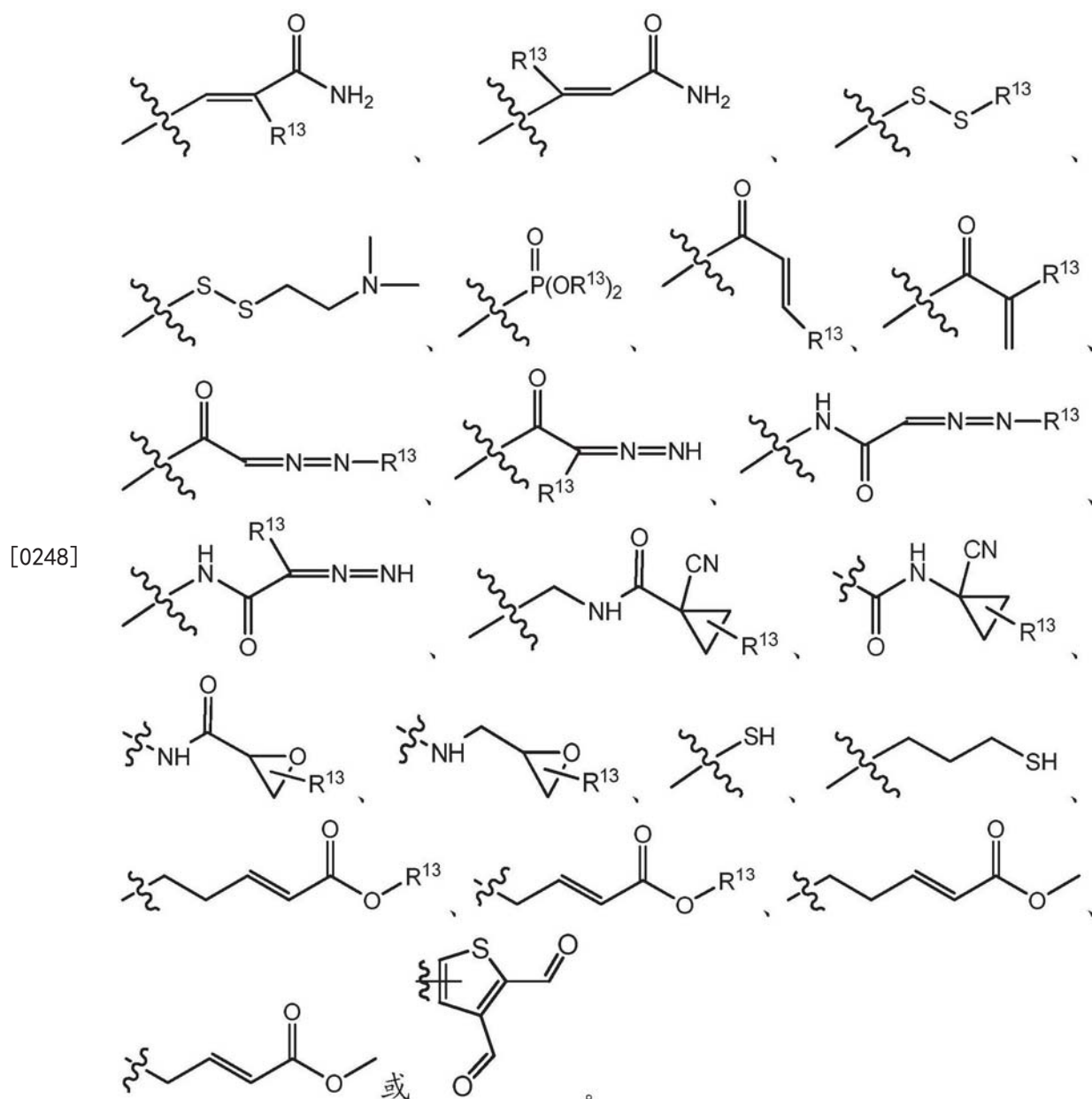


[0246]

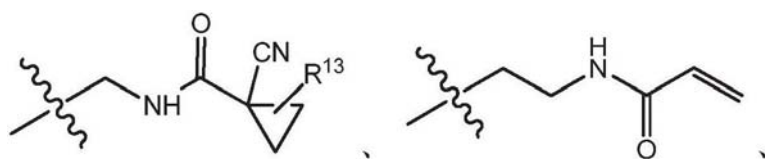


[0247]

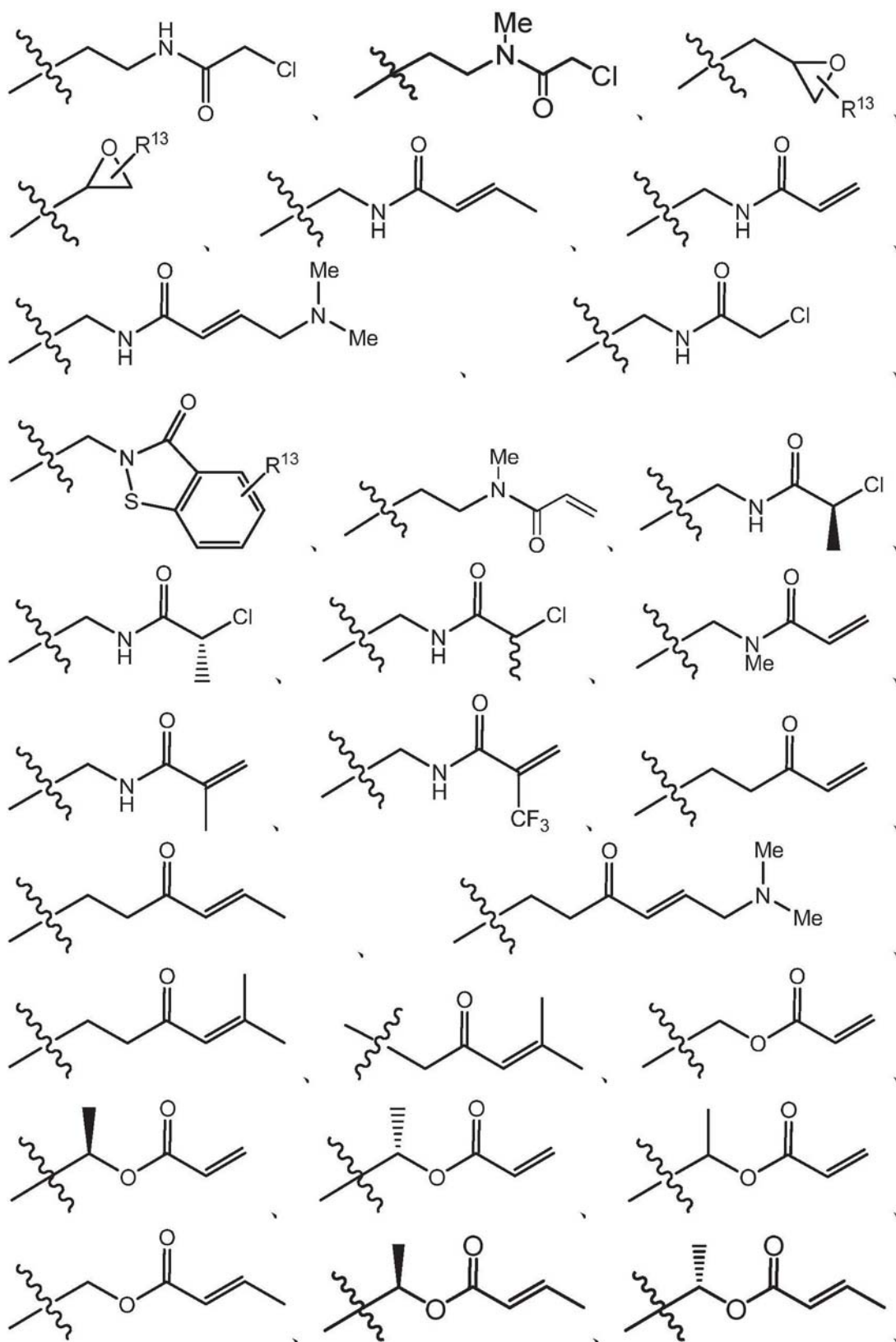




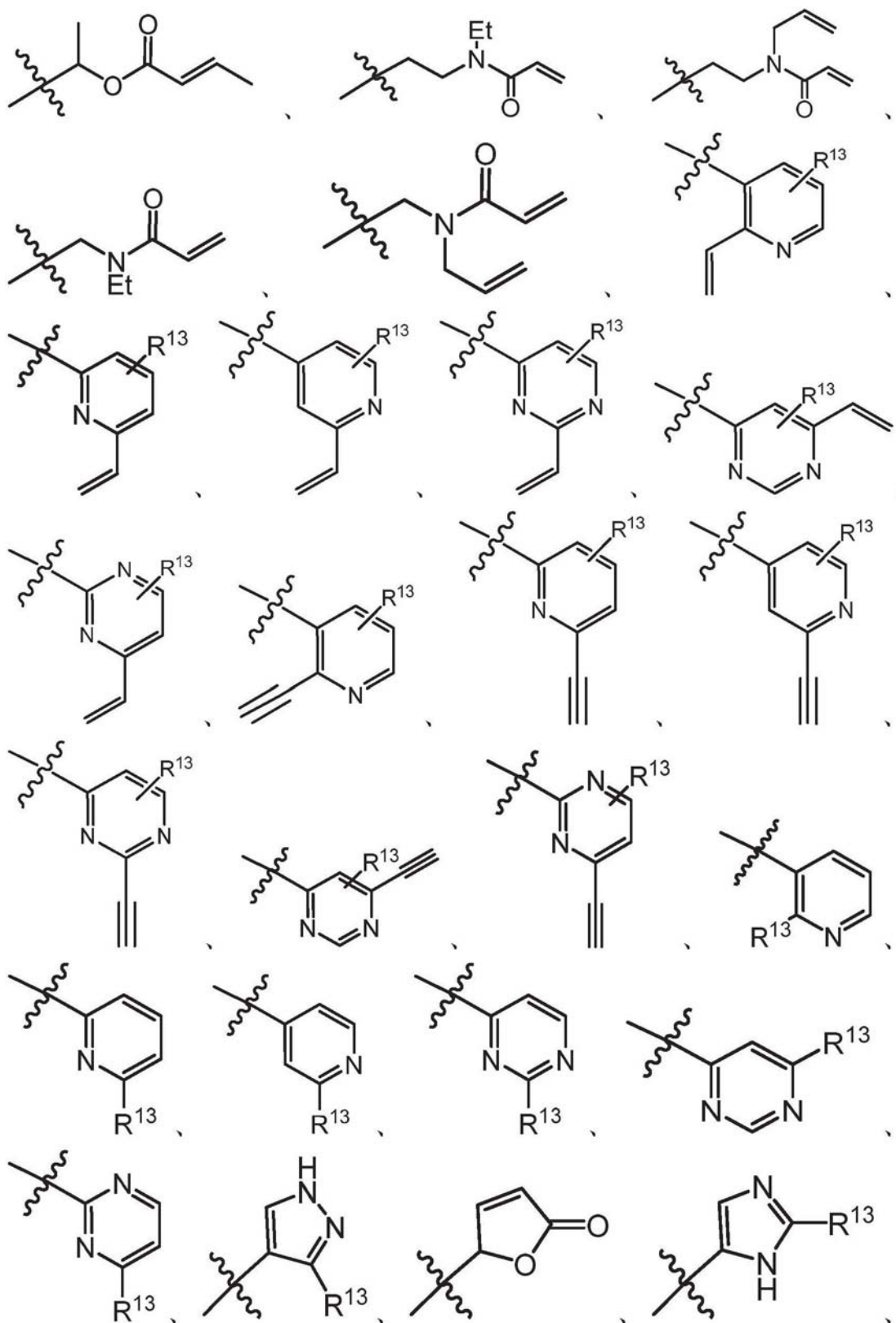
[0249] 在实施方案中,E为经取代或未取代的乙烯砜部分、经取代或未取代的乙烯基磺酰胺部分、经取代或未取代的氟(C₁-C₄)烷基酮部分、经取代或未取代的氯(C₁-C₄)烷基酮部分、经取代或未取代的丙烯酰胺部分、经取代或未取代的二硫化物部分、经取代或未取代的硫醇部分、经取代或未取代的膦酸酯部分、经取代或未取代的醛部分、经取代或未取代的烯酮部分、经取代或未取代的重氮甲基酮部分、经取代或未取代的重氮甲酰胺部分、经取代或未取代的氰基环丙基羧酰胺部分、经取代或未取代的环氧化物部分、经取代或未取代的环氧酮部分、经取代或未取代的环氧酰胺部分、经取代或未取代的芳醛部分、经取代或未取代的芳二醛部分、经取代或未取代的二醛部分、经取代或未取代的氮芥部分、经取代或未取代的炔丙基部分、经取代或未取代的炔丙基酰胺部分、

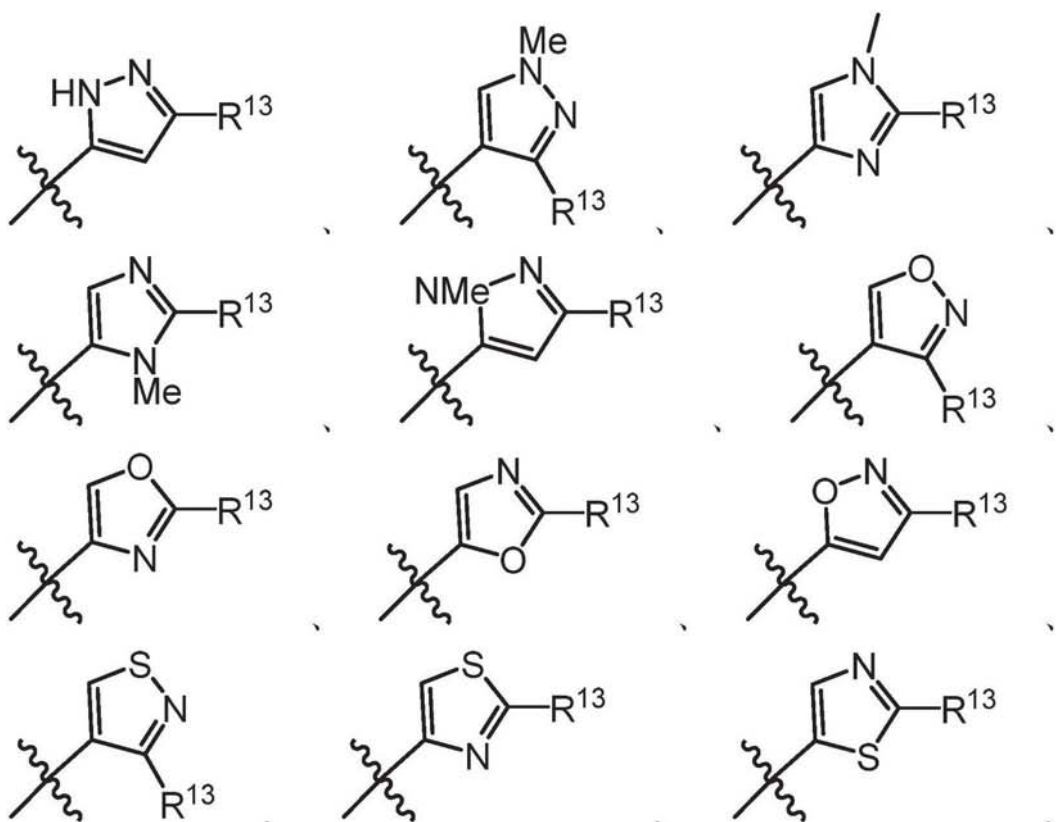


[0250]

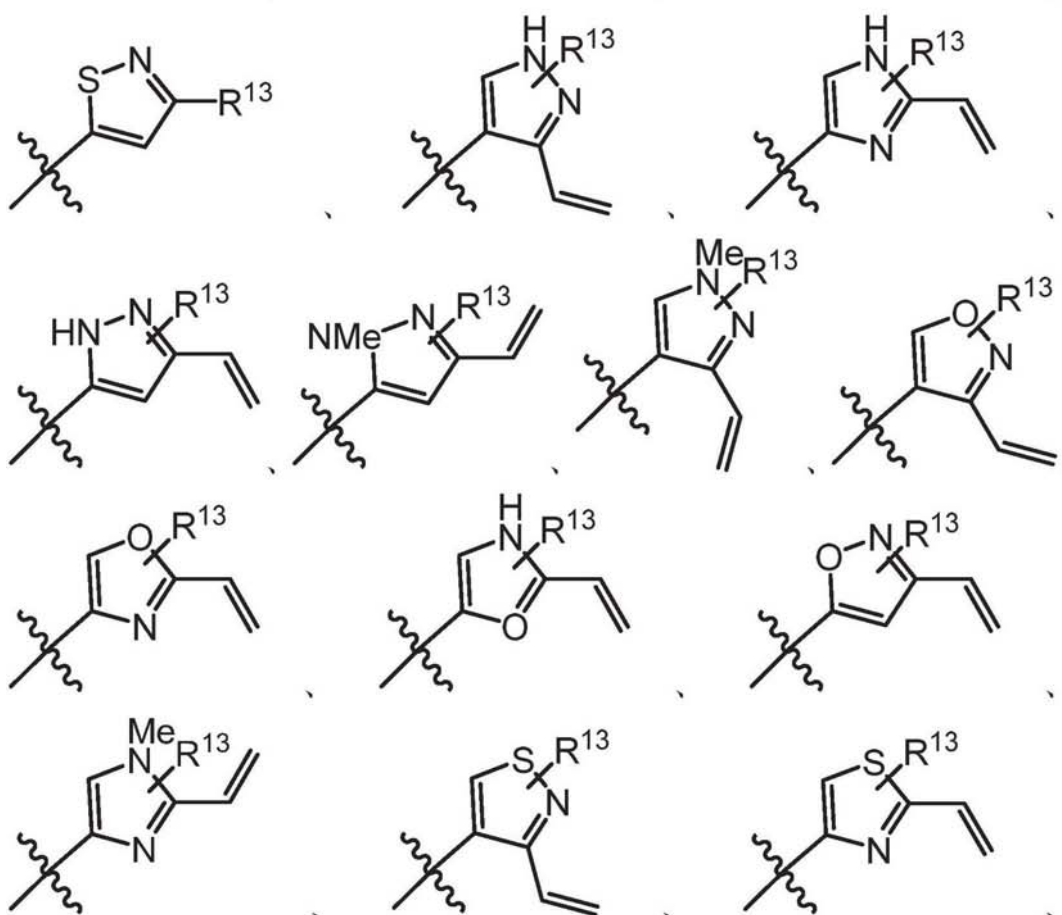


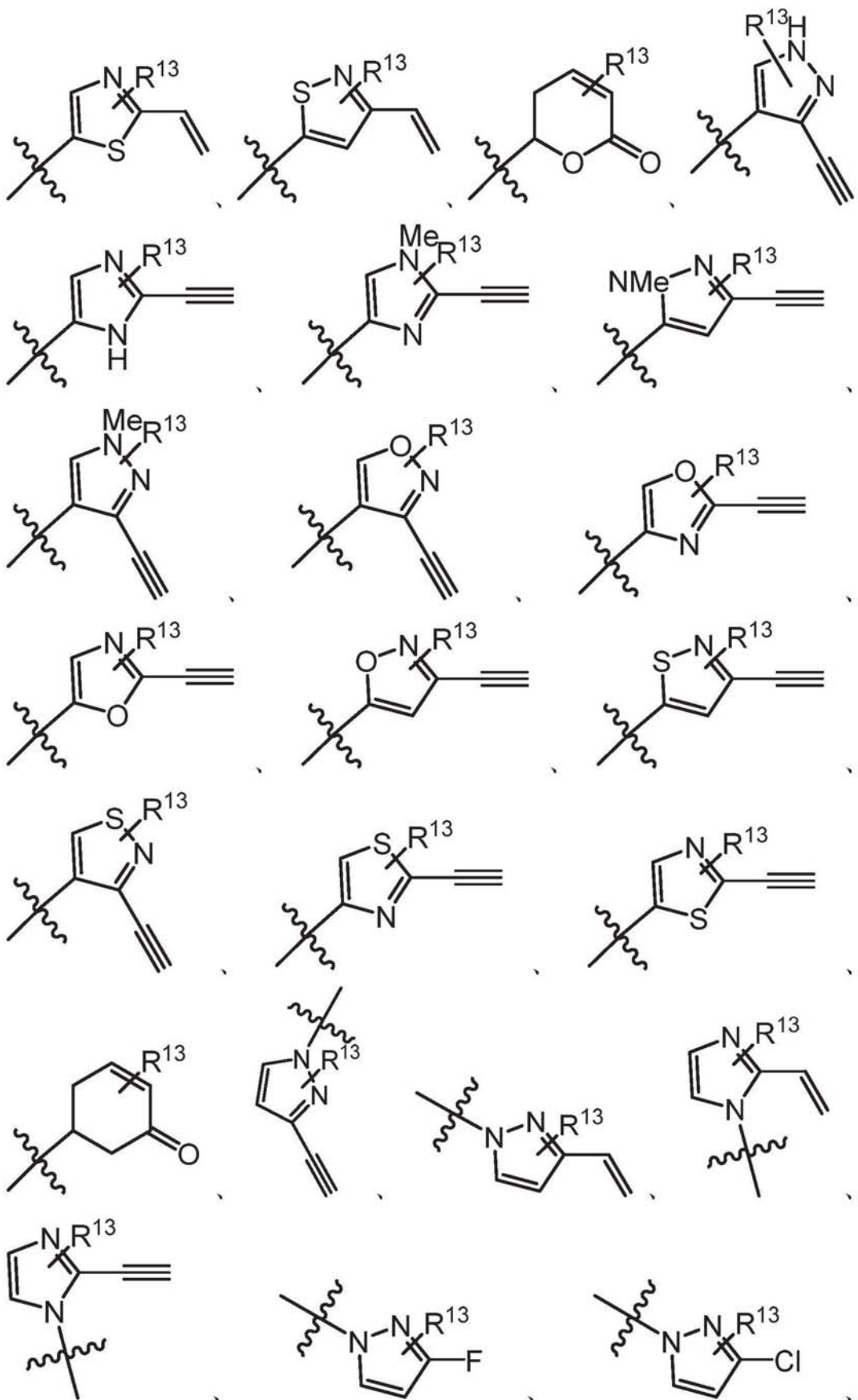
[0251]

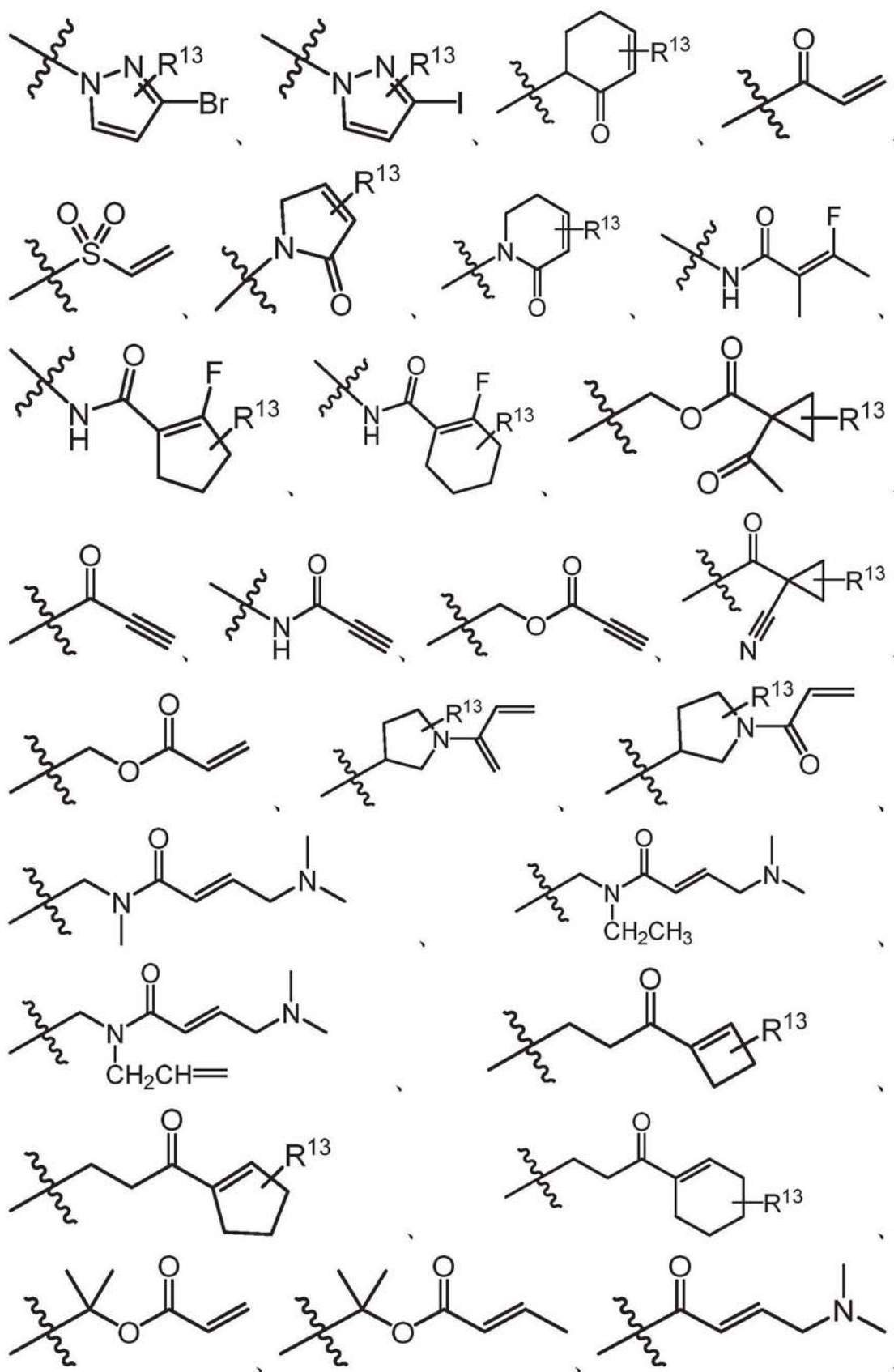




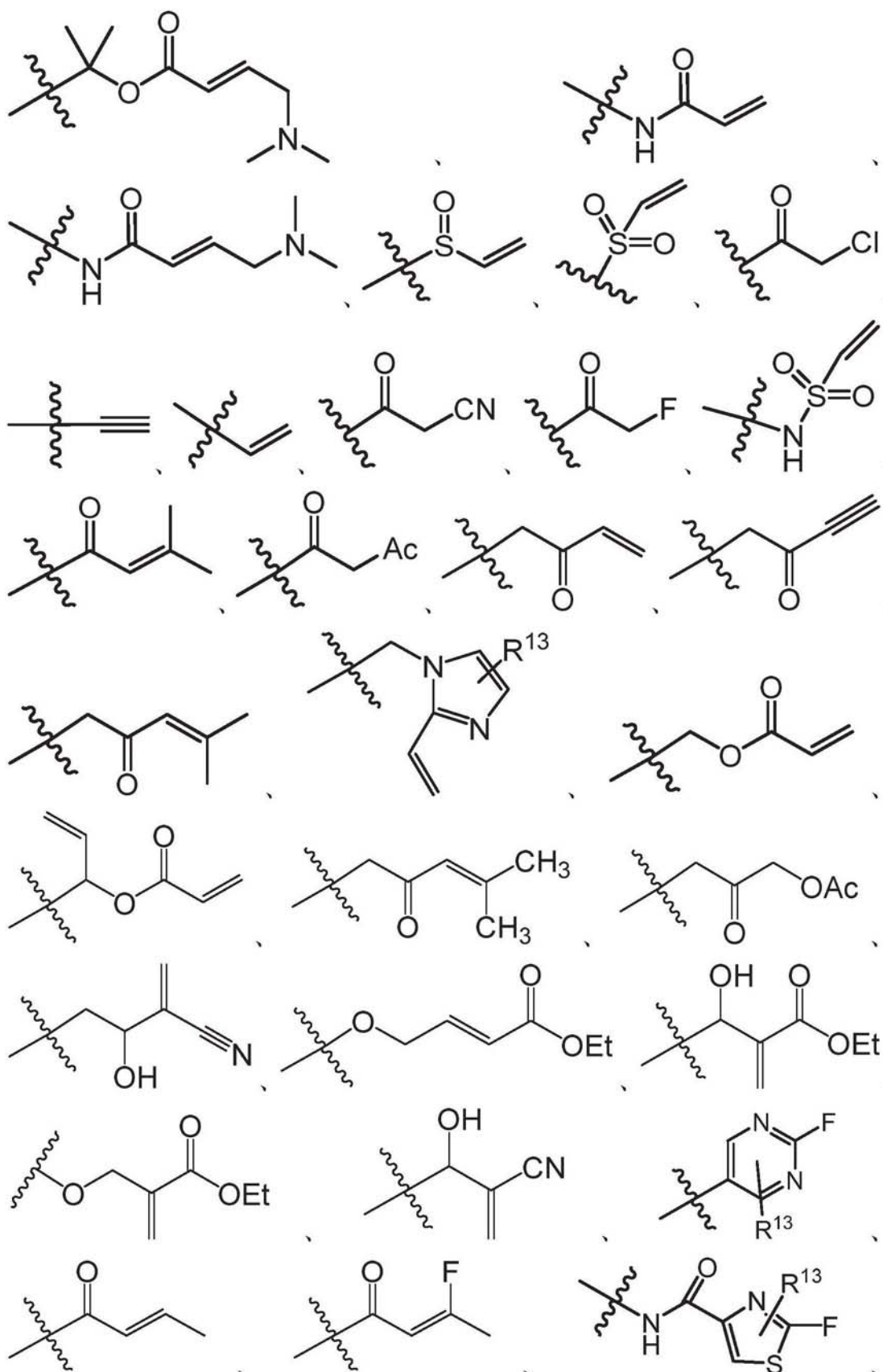
[0252]



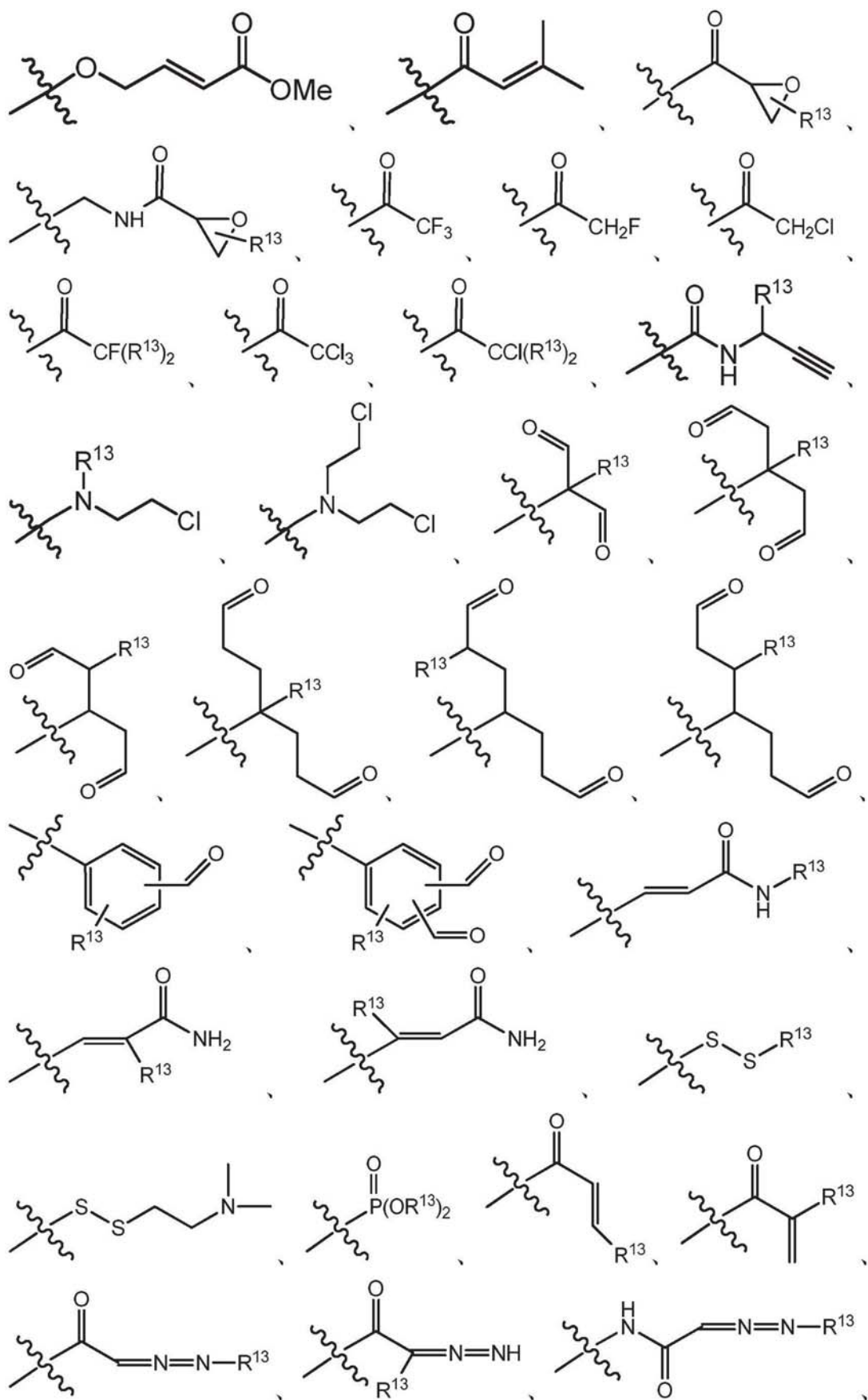


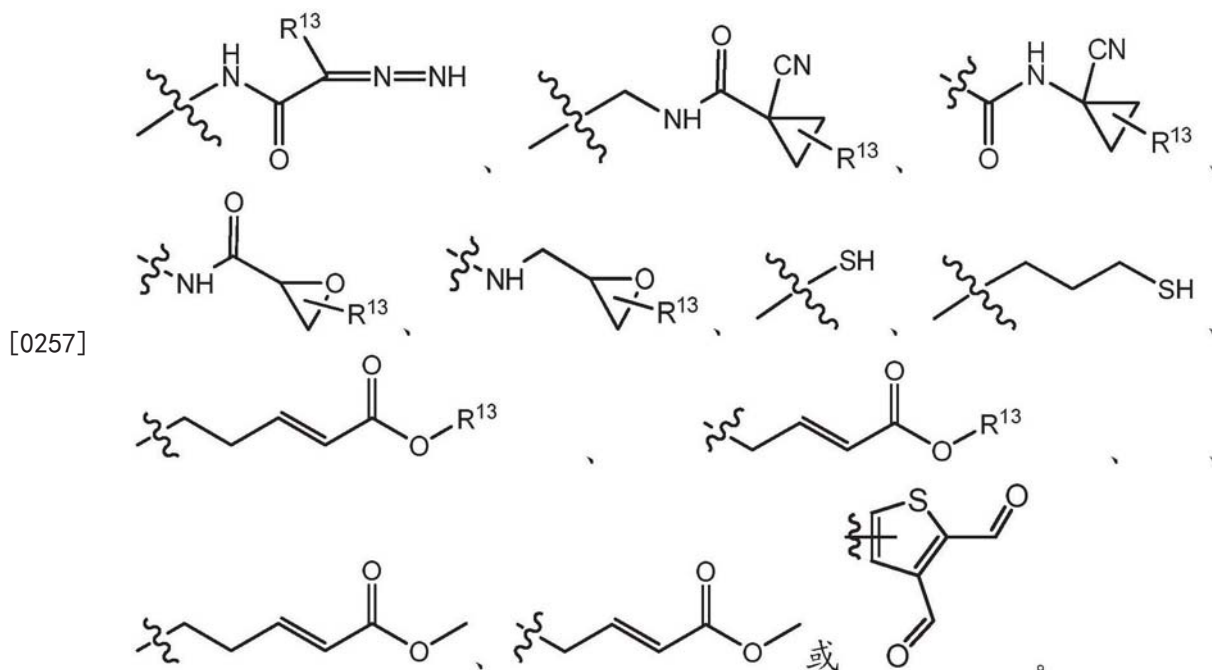


[0255]



[0256]





[0258] 在实施方案中,E为未取代的乙烯砜部分、未取代的乙烯基磺酰胺部分、未取代的氟(C₁-C₄)烷基酮部分、未取代的氯(C₁-C₄)烷基酮部分、未取代的丙烯酰胺部分、未取代的二硫化物部分、未取代的硫醇部分、未取代的膦酸酯部分、未取代的醛部分、未取代的烯酮部分、未取代的重氮甲基酮部分、未取代的重氮甲酰胺部分、未取代的氰基环丙基羧酰胺部分、未取代的环氧化物部分、未取代的环氧酮部分、未取代的环氧酰胺部分、未取代的芳醛部分、未取代的芳二醛部分、未取代的二醛部分、未取代的氮芥部分、未取代的炔丙基部分或未取代的炔丙基酰胺部分。

[0259] R^{13} 独立地为氢、氧代、卤素、 CX^{13}_3 、 $-\text{CHX}^{13}_2$ 、 $-\text{CH}_2\text{X}^{13}$ 、 $-\text{CN}$ 、 $-\text{SO}_{n13}\text{R}^{22}$ 、 $-\text{SO}_{v13}\text{NR}^{20}\text{R}^{21}$ 、 $-\text{NHNR}^{20}\text{R}^{21}$ 、 $-\text{ONR}^{20}\text{R}^{21}$ 、 $-\text{NHC}=(\text{O})\text{NHNR}^{20}\text{R}^{21}$ 、 $-\text{NHC}(\text{O})\text{NR}^{20}\text{R}^{21}$ 、 $-\text{N}(\text{O})_{m13}$ 、 $-\text{NR}^{20}\text{R}^{21}$ 、 $-\text{C}(\text{O})\text{R}^{22}$ 、 $-\text{C}(\text{O})-\text{OR}^{22}$ 、 $-\text{C}(\text{O})\text{NR}^{20}\text{R}^{21}$ 、 $-\text{OR}^{23}$ 、 $-\text{NR}^{20}\text{SO}_2\text{R}^{23}$ 、 $-\text{NR}^{20}\text{C}(\text{O})\text{R}^{22}$ 、 $-\text{NR}^{20}\text{C}(\text{O})\text{OR}^{22}$ 、 $-\text{NR}^{20}\text{OR}^{22}$ 、 $-\text{OCX}^{13}_3$ 、 $-\text{OCHX}^{13}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；键合至相同原子的 R^{20} 和 R^{21} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基。在实施方案中, R^{13} 独立地为氢。在实施方案中, R^{13} 独立地为经取代或未取代的烷基。在实施方案中, R^{13} 独立地为氧代、卤素、 CX^{13}_3 、 $-\text{CHX}^{13}_2$ 、 $-\text{CH}_2\text{X}^{13}$ 、 $-\text{CN}$ 、 $-\text{SO}_{n13}\text{R}^{22}$ 、 $-\text{SO}_{v13}\text{NR}^{20}\text{R}^{21}$ 、 $-\text{NHNR}^{20}\text{R}^{21}$ 、 $-\text{ONR}^{20}\text{R}^{21}$ 、 $-\text{NHC}=(\text{O})\text{NHNR}^{20}\text{R}^{21}$ 、 $-\text{NHC}(\text{O})\text{NR}^{20}\text{R}^{21}$ 、 $-\text{N}(\text{O})_{m13}$ 、 $-\text{NR}^{20}\text{R}^{21}$ 、 $-\text{C}(\text{O})\text{R}^{22}$ 、 $-\text{C}(\text{O})-\text{OR}^{22}$ 、 $-\text{C}(\text{O})\text{NR}^{20}\text{R}^{21}$ 、 $-\text{OR}^{23}$ 、 $-\text{NR}^{20}\text{SO}_2\text{R}^{23}$ 、 $-\text{NR}^{20}\text{C}(\text{O})\text{R}^{22}$ 、 $-\text{NR}^{20}\text{C}(\text{O})\text{OR}^{22}$ 、 $-\text{NR}^{20}\text{OR}^{22}$ 、 $-\text{OCX}^{13}_3$ 、 $-\text{OCHX}^{13}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。在实施方案中, R^{13} 独立地为经取代或未取代的杂烷基。在实施方案中, R^{13} 独立地为经取代或未取代的环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的杂环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的芳基。在实施方案中, R^{13} 独立地为经取代或未取代的杂芳基。在实施方案中, R^{13} 独立地为卤素、 $-\text{CX}^{13}_3$ 、 $-\text{CHX}^{13}_2$ 、 $-\text{CH}_2\text{X}^{13}$ 、 $-\text{CN}$ 、 $-\text{OH}$ 、 $-\text{NH}_2$ 、 $-\text{COOH}$ 、 $-\text{CONH}_2$ 、 $-\text{NO}_2$ 、 $-\text{SH}$ 、 $-\text{SO}_2\text{Cl}$ 、 $-\text{SO}_3\text{H}$ 、 $-\text{SO}_4\text{H}$ 、 $-\text{SO}_2\text{NH}_2$ 、 $-\text{NHNH}_2$ 、 $-\text{ONH}_2$ 、 $-\text{NHC}(\text{O})\text{NHNH}_2$ 、 $-\text{NHC}(\text{O})\text{NH}_2$ 、 $-\text{NHSO}_2\text{H}$ 、 $-\text{NHC}(\text{O})\text{H}$ 、 $-\text{NHC}(\text{O})\text{OH}$ 、 $-\text{NHOH}$ 、 $-\text{OCX}^{13}_3$ 、 $-\text{OCHX}^{13}_2$ 、经取代或未取代的C₁-C₆烷基、经取

代或未取代的2-6元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的C₆芳基或经取代或未取代的5-6元杂芳基。在实施方案中，R¹³独立地为卤素、-CX¹³₃、-CHX¹³₂、-CH₂X¹³、-OH、-SH、-COOH、-OCX¹³₃、-OCHX¹³₂、-CH₃、-CH₂CH₃、-OCH₃、-OCH₂CH₃、-SCH₃或-SCH₂CH₃。在实施方案中，R¹³独立地为卤素或-OCH₃。在实施方案中，R¹³为经取代或未取代的C₁-C₆烷基。在实施方案中，R¹³为经取代或未取代的2-6元杂烷基。在实施方案中，R¹³为经取代或未取代的C₃-C₈环烷基。在实施方案中，R¹³为经取代或未取代的3-8元杂环烷基。在实施方案中，R¹³为经取代或未取代的C₆芳基。在实施方案中，R¹³为经取代或未取代的5-6元杂芳基。在实施方案中，R¹³独立地为卤素。在实施方案中，R¹³独立地为-CX¹³₃。在实施方案中，R¹³独立地为-CHX¹³₂。在实施方案中，R¹³独立地为-CH₂X¹³。在实施方案中，R¹³独立地为-OH。在实施方案中，R¹³独立地为-SH。在实施方案中，R¹³独立地为-COOH。在实施方案中，R¹³独立地为-OCX¹³₃。在实施方案中，R¹³独立地为-OCHX¹³₂。在实施方案中，R¹³独立地为-CH₃。在实施方案中，R¹³独立地为-CH₂CH₃。在实施方案中，R¹³独立地为-OCH₃。在实施方案中，R¹³独立地为-OCH₂CH₃。在实施方案中，R¹³独立地为-SCH₃。在实施方案中，R¹³独立地为-SCH₂CH₃。在实施方案中，R¹³独立地为-Cl或-OCH₃。在实施方案中，R¹³独立地为卤素、-CX¹³₃、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-OCX¹³₃、-OCHX¹³₂、-CHX¹³₂、-CH₂X¹³、经取代或未取代的C₁-C₈烷基、or经取代或未取代的2-8元杂烷基、经取代或未取代的C₃-C₈环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的苯基或经取代或未取代的5-6元杂芳基。在实施方案中，R¹³独立地为卤素、-CX¹³₃、-CN、未取代的C₁-C₄烷基、or未取代的2-4元杂烷基。在实施方案中，R¹³独立地为未取代的甲基、未取代的乙基、未取代的异丙基或未取代的叔丁基。在实施方案中，R¹³独立地为未取代的甲基。在实施方案中，R¹³独立地为未取代的乙基。在实施方案中，R¹³独立地为未取代的丙基。在实施方案中，R¹³独立地为未取代的正丙基。在实施方案中，R¹³独立地为未取代的异丙基。在实施方案中，R¹³独立地为未取代的丁基。在实施方案中，R¹³独立地为未取代的正丁基。在实施方案中，R¹³独立地为未取代的异丁基。在实施方案中，R¹³独立地为未取代的叔丁基。在实施方案中，R¹³独立地为未取代的戊基。在实施方案中，R¹³独立地为未取代的己基。在实施方案中，R¹³独立地为未取代的庚基。在实施方案中，R¹³独立地为未取代的辛基。在实施方案中，R¹³独立地为-F。在实施方案中，R¹³独立地为-Cl。在实施方案中，R¹³独立地为-Br。在实施方案中，R¹³独立地为-I。在实施方案中，R¹³独立地为未取代的甲氧基。在实施方案中，R¹³独立地为未取代的乙氧基。在实施方案中，R¹³独立地为-CF₃。在实施方案中，R¹³独立地为-CCl₃。在实施方案中，R¹³为未取代的异丙基。在实施方案中，R¹³为未取代的苯基。在实施方案中，R¹³为未取代的吡啶基。在实施方案中，R¹³独立地为卤素。在实施方案中，R¹³独立地为-CX¹³₃。在实施方案中，R¹³独立地为-CHX¹³₂。在实施方案中，R¹³独立地为-CH₂X¹³。在实施方案中，R¹³独立地为-CN。在实施方案中，R¹³独立地为-OH。在实施方案中，R¹³独立地为-NH₂。在实施方案中，R¹³独立地为-COOH。在实施方案中，R¹³独立地为-CONH₂。在实施方案中，R¹³独立地为-NO₂。在实施方案中，R¹³独立地为-SH。在实施方案中，R¹³独立地为-SO₂Cl。在实施方案中，R¹³独立地为-SO₃H。在实施方案中，R¹³独立地为-SO₄H。在实施方案中，R¹³独立地为-SO₂NH₂。在实施方案中，R¹³独立地为-NHNH₂。在实施方案中，R¹³独立地为-ONH₂。在实施方案中，R¹³独立地为-NHC(O)NHNH₂。在实施方案中，R¹³独立地为-NHC(O)NH₂。在实施方案中，R¹³独立地为-NHSO₂H。在实施方案中，R¹³独立地为-NHC(O)H。在实施方案中，R¹³独立地为-NHC(O)OH。在实施方案中，R¹³独立地为-NHOH。在实施方案中，

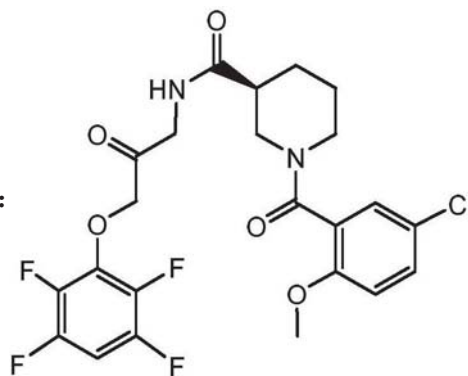
R^{13} 独立地为 $-OCX^{13}_3$ 。在实施方案中, R^{13} 独立地为 $-OCHX^{13}_2$ 。在实施方案中, R^{13} 独立地为经取代或未取代的烷基。在实施方案中, R^{13} 独立地为经取代或未取代的杂烷基。在实施方案中, R^{13} 独立地为经取代或未取代的环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的杂环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的芳基。在实施方案中, R^{13} 独立地为经取代或未取代的杂芳基。在实施方案中, R^{13} 独立地为经取代的烷基。在实施方案中, R^{13} 独立地为经取代的杂烷基。在实施方案中, R^{13} 独立地为经取代的环烷基。在实施方案中, R^{13} 独立地为经取代的杂环烷基。在实施方案中, R^{13} 独立地为经取代的芳基。在实施方案中, R^{13} 独立地为经取代的杂芳基。在实施方案中, R^{13} 独立地为未取代的烷基。在实施方案中, R^{13} 独立地为未取代的杂烷基。在实施方案中, R^{13} 独立地为未取代的环烷基。在实施方案中, R^{13} 独立地为未取代的杂环烷基。在实施方案中, R^{13} 独立地为未取代的芳基。在实施方案中, R^{13} 独立地为未取代的杂芳基。在实施方案中, R^{13} 独立地为经取代或未取代的 C_1 - C_8 烷基。在实施方案中, R^{13} 独立地为经取代或未取代的2-8元杂烷基。在实施方案中, R^{13} 独立地为经取代或未取代的 C_3 - C_8 环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的3-8元杂环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的 C_6 - C_{10} 芳基。在实施方案中, R^{13} 独立地为经取代或未取代的5-10元杂芳基。在实施方案中, R^{13} 独立地为经取代的 C_1 - C_8 烷基。在实施方案中, R^{13} 独立地为经取代的2-8元杂烷基。在实施方案中, R^{13} 独立地为经取代的 C_3 - C_8 环烷基。在实施方案中, R^{13} 独立地为经取代的3-8元杂环烷基。在实施方案中, R^{13} 独立地为经取代的 C_6 - C_{10} 芳基。在实施方案中, R^{13} 独立地为经取代的5-10元杂芳基。在实施方案中, R^{13} 独立地为未取代的 C_1 - C_8 烷基。在实施方案中, R^{13} 独立地为未取代的2-8元杂烷基。在实施方案中, R^{13} 独立地为未取代的 C_3 - C_8 环烷基。在实施方案中, R^{13} 独立地为未取代的3-8元杂环烷基。在实施方案中, R^{13} 独立地为未取代的 C_6 - C_{10} 芳基。在实施方案中, R^{13} 独立地为未取代的5-10元杂芳基。在实施方案中, R^{13} 独立地为经取代或未取代的 C_1 - C_4 烷基。在实施方案中, R^{13} 独立地为经取代或未取代的2-4元杂烷基。在实施方案中, R^{13} 独立地为经取代或未取代的 C_3 - C_6 环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的3-6元杂环烷基。在实施方案中, R^{13} 独立地为经取代或未取代的苯基。在实施方案中, R^{13} 独立地为经取代或未取代的5-6元杂芳基。在实施方案中, R^{13} 独立地为经取代的 C_1 - C_4 烷基。在实施方案中, R^{13} 独立地为经取代的2-4元杂烷基。在实施方案中, R^{13} 独立地为经取代的 C_3 - C_6 环烷基。在实施方案中, R^{13} 独立地为经取代的3-6元杂环烷基。在实施方案中, R^{13} 独立地为经取代的苯基。在实施方案中, R^{13} 独立地为经取代的5-6元杂芳基。在实施方案中, R^{13} 独立地为未取代的 C_1 - C_4 烷基。在实施方案中, R^{13} 独立地为未取代的2-4元杂烷基。在实施方案中, R^{13} 独立地为未取代的 C_3 - C_6 环烷基。在实施方案中, R^{13} 独立地为未取代的3-6元杂环烷基。在实施方案中, R^{13} 独立地为未取代的苯基。在实施方案中, R^{13} 独立地为未取代的5-6元杂芳基。

[0260] R^{20} 、 R^{21} 、 R^{22} 和 R^{23} 独立地为氢、卤素、 $-CX^A_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^A_3$ 、 $-OCHX^A_2$ 、 $-CHX^A_2$ 、 $-CH_2X^A$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{20} 和 R^{21} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基。

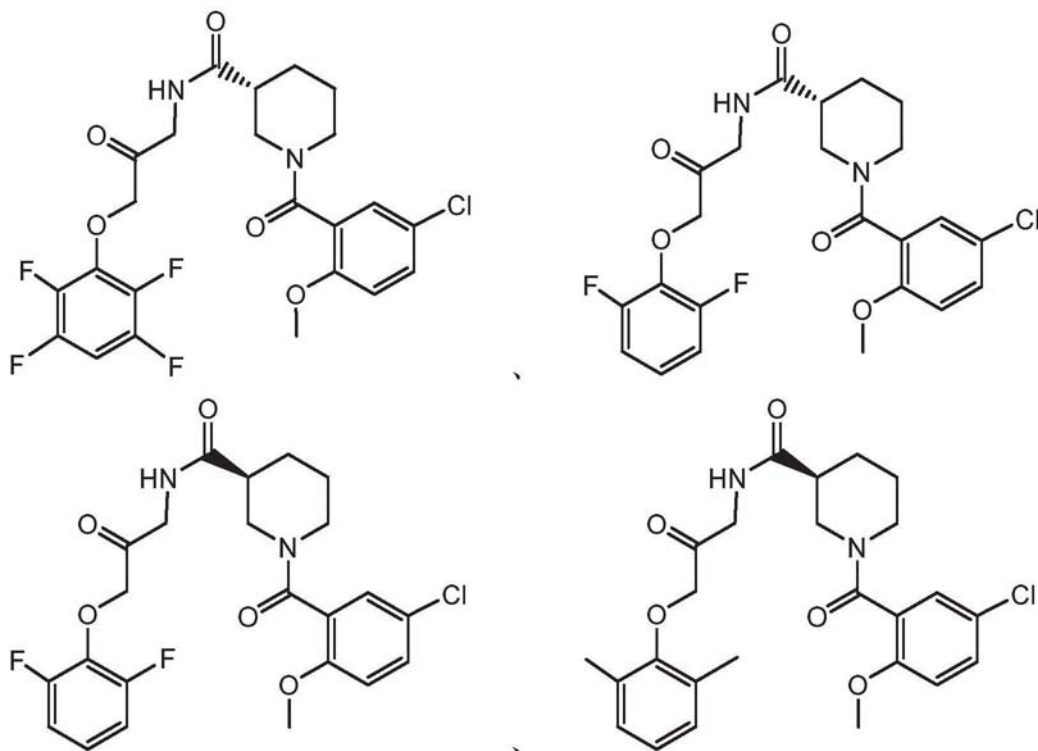
[0261] 每个 X^A 和 X^{13} 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ 。符号 n_{13} 和 v_{13} 独立地为0至4的整数。符号

m13独立地为1至2的整数。

[0262] 在实施方案中,化合物具有下式:

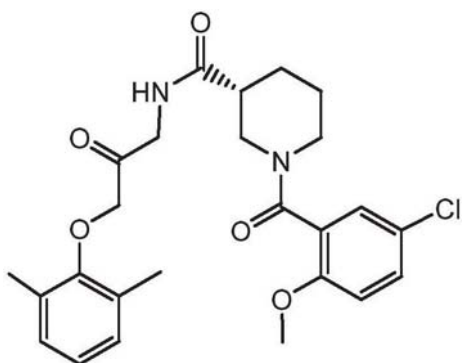


[0263]

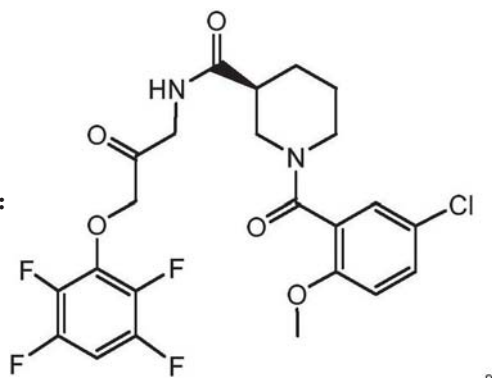


或

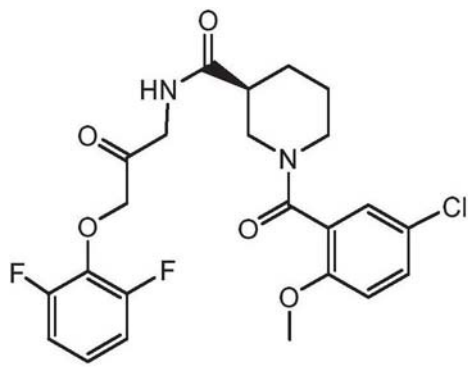
[0264]



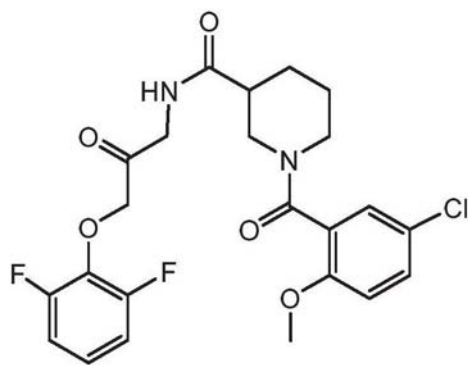
在实施方案中,化合物具有下式:



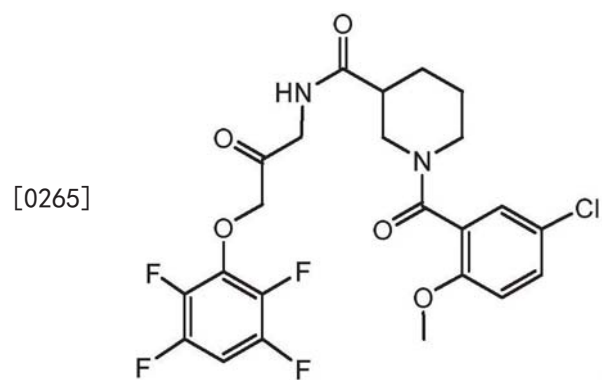
在实施方案中,化合物具有下式:



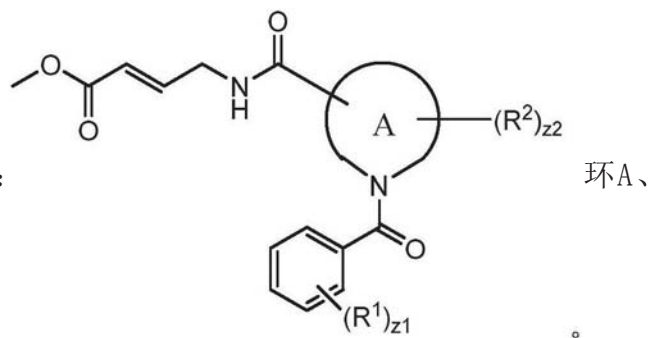
在实施方案中,化合物具有下式:



在实施方案中,化合物具有下式:

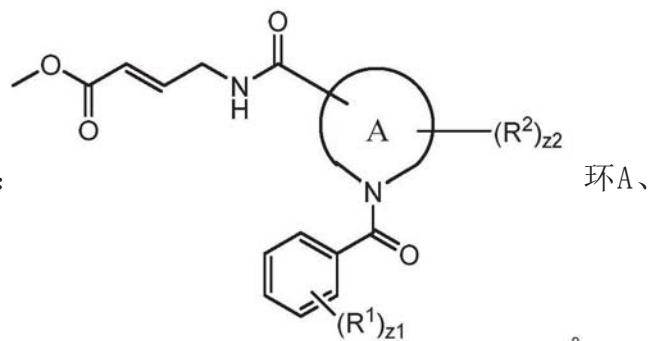


[0266] 在实施方案中,化合物具有下式:



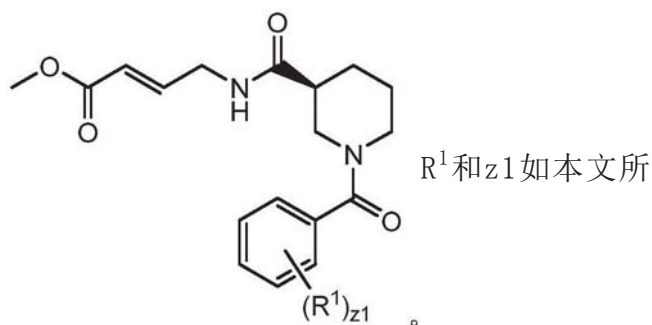
R^1 、 z_1 、 R^2 和 z_2 如本文所述。

[0267] 在实施方案中,化合物具有下式:



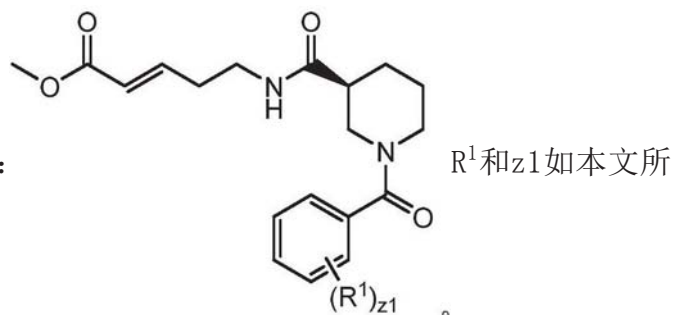
R^1 、 z_1 、 R^2 和 z_2 如本文所述。

[0268] 在实施方案中,化合物具有下式:



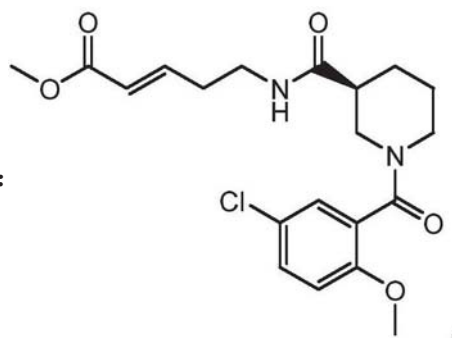
述。

[0269] 在实施方案中,化合物具有下式:

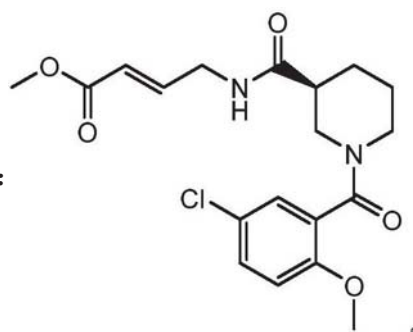


述。

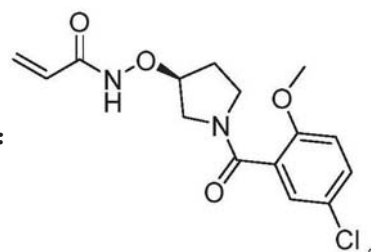
[0270] 在实施方案中,化合物具有下式:



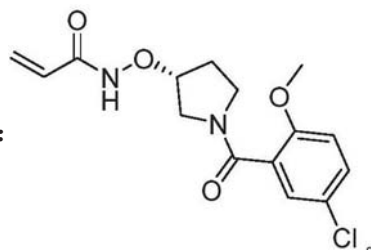
[0271] 在实施方案中,化合物具有下式:



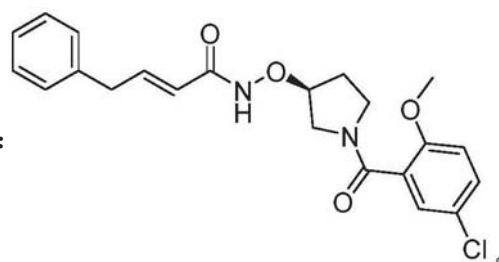
[0272] 在实施方案中,化合物具有下式:



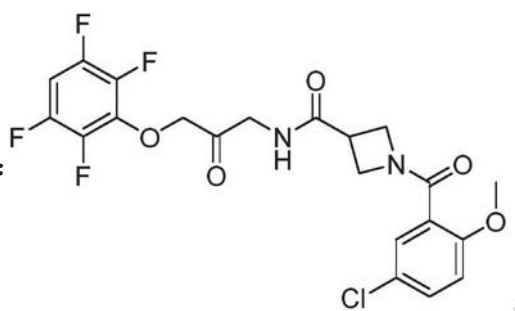
[0273] 在实施方案中,化合物具有下式:



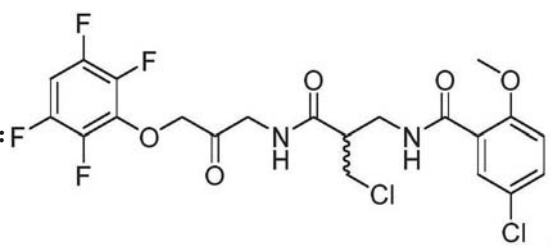
[0274] 在实施方案中,化合物具有下式:



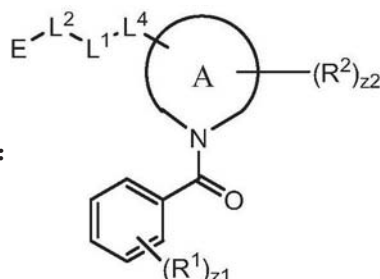
[0275] 在实施方案中,化合物具有下式:



[0276] 在实施方案中,化合物具有下式:



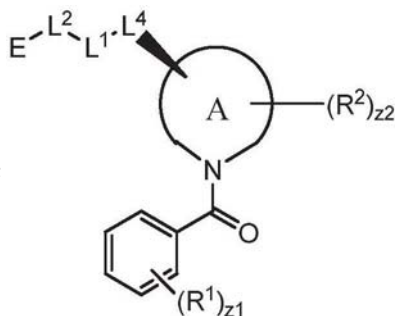
[0277] 在实施方案中,化合物具有下式:



环A、 R^1 、 z_1 、 R^2 、 z_2 、

L^1 、 L^2 、 L^4 和E如本文所述。

[0278] 在实施方案中,化合物具有下式:



环A、 R^1 、 z_1 、 R^2 、 z_2 、

L^1 、 L^2 、 L^4 和E如本文所述。

[0279] 在实施方案中,环A为5-7元杂环烷基。在实施方案中,环A为3-5元杂环烷基。在实施方案中,环A为吡咯烷基。在实施方案中,环A为哌啶基。在实施方案中,环A为氮杂环丁烷基。在实施方案中,Y为N。

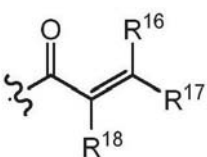
[0280] 在实施方案中, R^1 独立地为卤素、 CX^1_3 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-CN$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(=O)NHNH_2$ 、 $-NHC(=O)NH_2$ 、 $-N(O)_2$ 、 $-NH_2$ 、 $-C(=O)H$ 、 $-C(=O)OH$ 、 $-C(=O)NH_2$ 、 $-OH$ 、 $-NHSO_2H$ 、 $-NHC(=O)H$ 、 $-NHC(=O)OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。在实施方案中, R^1 独立地为卤素、 $-CF_3$ 、 $-NH_2$ 、 $-C(=O)H$ 、 $-C(=O)OH$ 、 $-C(=O)NH_2$ 、 $-OH$ 、经取代或未取代的 C_1 - C_4 烷基或经取代或未取代的2-4元杂烷基。在实施方案中, R^1 独立地为卤素、 $-CF_3$ 、 $-NH_2$ 、 $-C(=O)H$ 、 $-C(=O)OH$ 、 $-C(=O)NH_2$ 、 $-OH$ 、未取代的 C_1 - C_4 烷基或未取代的2-4元杂烷基。

[0281] 在实施方案中, L^1 为键。在实施方案中, L^1 为 $-NH-$ 。

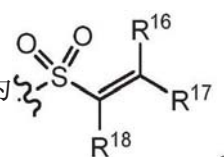
[0282] 在实施方案中, L^2 为键。在实施方案中, L^2 为 $-NH-$ 。

[0283] 在实施方案中, L^4 为键。在实施方案中, L^4 为经取代或未取代的 C_1 - C_3 亚烷基。在实施方案中, L^4 为未取代的亚甲基。

[0284] 在实施方案中,E为



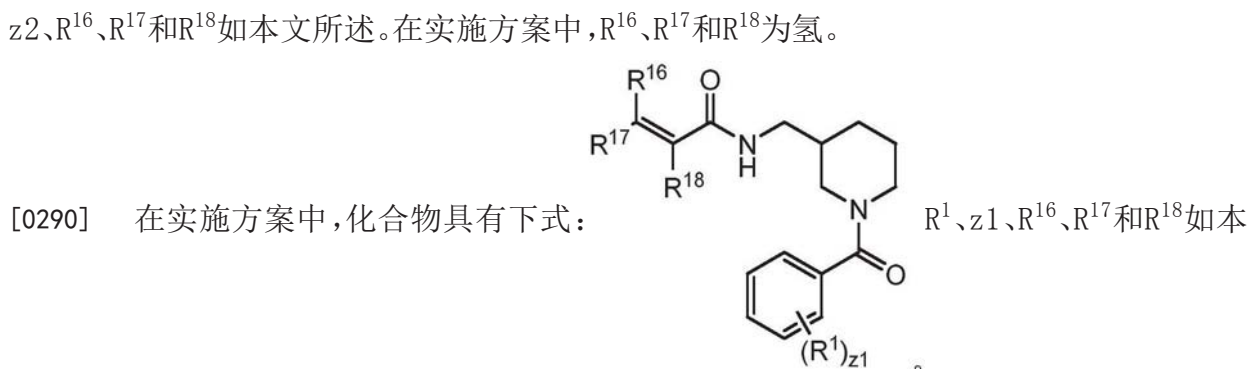
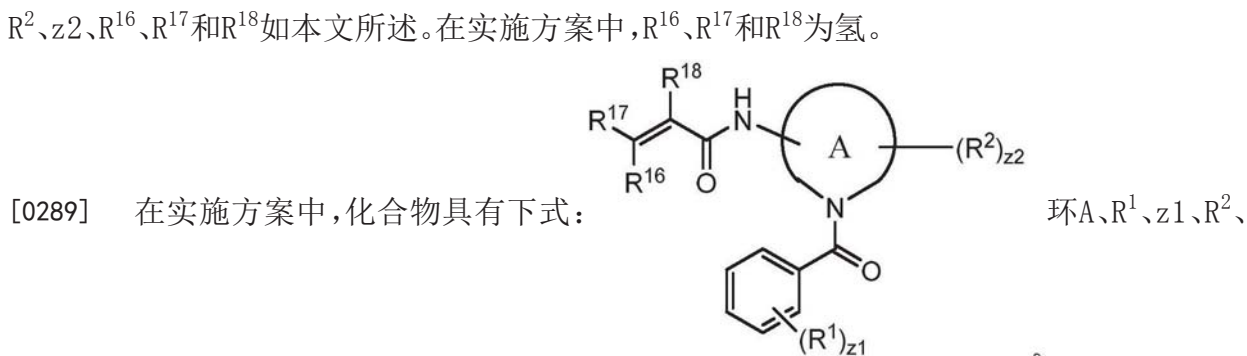
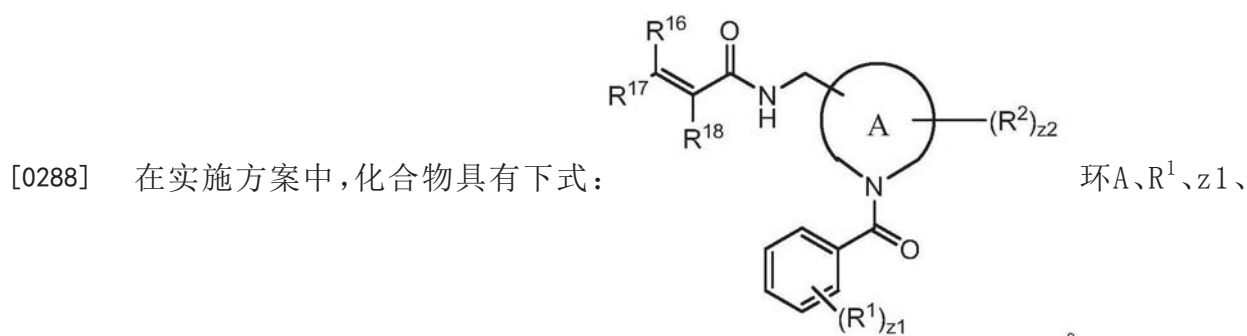
在实施方案中,E为



[0285] 在实施方案中, R^{16} 为未取代的甲基。在实施方案中, R^{17} 为未取代的甲基。在实施方案中, R^{18} 为未取代的甲基。在实施方案中, R^{16} 为氢。在实施方案中, R^{17} 为氢。在实施方案中, R^{18} 为氢。在实施方案中, R^{16} 为 $-\text{CH}_2\text{N}(\text{CH}_3)_2$ 。在实施方案中, R^{17} 为 $-\text{CH}_2\text{N}(\text{CH}_3)_2$ 。在实施方案中, R^{18} 为 $-\text{CH}_2\text{N}(\text{CH}_3)_2$ 。在实施方案中, R^{16} 为 $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ 。在实施方案中, R^{17} 为 $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ 。在实施方案中, R^{18} 为 $-\text{CH}_2\text{Ph}$ 。在实施方案中, R^{18} 为 $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ 。

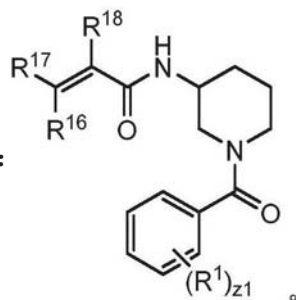
[0286] 在实施方案中, R^2 独立地为卤素、 CX^2_3 、 $-\text{CHX}^2_2$ 、 $-\text{CH}_2\text{X}^2$ 、 $-\text{CN}$ 、 $-\text{SO}_3\text{H}$ 、 $-\text{SO}_4\text{H}$ 、 $-\text{SO}_2\text{NH}_2$ 、 $-\text{NHNH}_2$ 、 $-\text{ONH}_2$ 、 $-\text{NHC}=\text{O}$ 、 NHNH_2 、 $-\text{NHC}(\text{O})\text{NH}_2$ 、 $-\text{N}(\text{O})_2$ 、 $-\text{NH}_2$ 、 $-\text{C}(\text{O})\text{H}$ 、 $-\text{C}(\text{O})\text{OH}$ 、 $-\text{C}(\text{O})\text{NH}_2$ 、 $-\text{OH}$ 、 $-\text{NHSO}_2\text{H}$ 、 $-\text{NHC}(\text{O})\text{H}$ 、 $-\text{NHC}(\text{O})\text{OH}$ 、 $-\text{NHOH}$ 、 $-\text{OCX}^2_3$ 、 $-\text{OCHX}^2_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。在实施方案中, R^2 独立地为卤素、 $-\text{CF}_3$ 、 $-\text{NH}_2$ 、 $-\text{C}(\text{O})\text{H}$ 、 $-\text{C}(\text{O})\text{OH}$ 、 $-\text{C}(\text{O})\text{NH}_2$ 、 $-\text{OH}$ 、经取代或未取代的 C_1 - C_4 烷基或经取代或未取代的 2-4 元杂烷基。在实施方案中, R^2 独立地为卤素、 $-\text{CF}_3$ 、 $-\text{NH}_2$ 、 $-\text{C}(\text{O})\text{H}$ 、 $-\text{C}(\text{O})\text{OH}$ 、 $-\text{C}(\text{O})\text{NH}_2$ 、 $-\text{OH}$ 、未取代的 C_1 - C_4 烷基或未取代的 2-4 元杂烷基。在实施方案中, R^2 独立地为 $-\text{Cl}$ 。在实施方案中, R^2 独立地为 $-\text{F}$ 。在实施方案中, R^2 独立地为 $-\text{Br}$ 。在实施方案中, R^2 独立地为 $-\text{I}$ 。在实施方案中, R^2 独立地为 $-\text{OCH}_3$ 。在实施方案中, R^2 独立地为 $-\text{OCH}_2\text{CH}_3$ 。

[0287] 在实施方案中, z_1 为 2。在实施方案中, z_2 为 0。



文所述。在实施方案中， R^{16} 、 R^{17} 和 R^{18} 为氢。

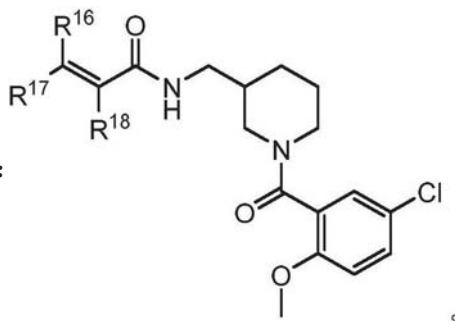
[0291] 在实施方案中，化合物具有下式：



R^1 、 $z1$ 、 R^{16} 、 R^{17} 和 R^{18} 如本文

所述。在实施方案中， R^{16} 、 R^{17} 和 R^{18} 为氢。

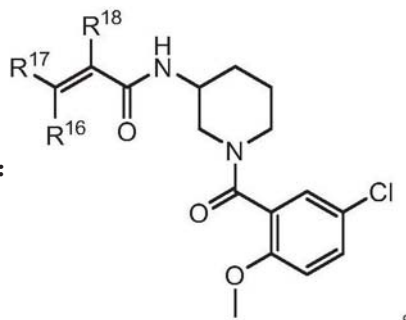
[0292] 在实施方案中，化合物具有下式：



R^{16} 、 R^{17} 和 R^{18} 如

本文所述。在实施方案中， R^{16} 、 R^{17} 和 R^{18} 为氢。

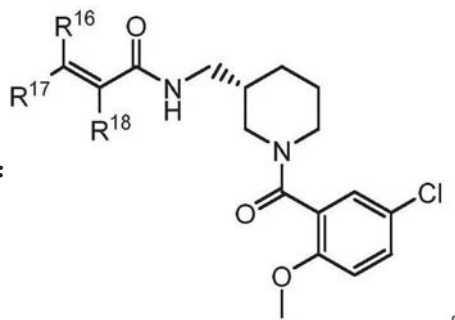
[0293] 在实施方案中，化合物具有下式：



R^{16} 、 R^{17} 和 R^{18} 如本文

所述。在实施方案中， R^{16} 、 R^{17} 和 R^{18} 为氢。

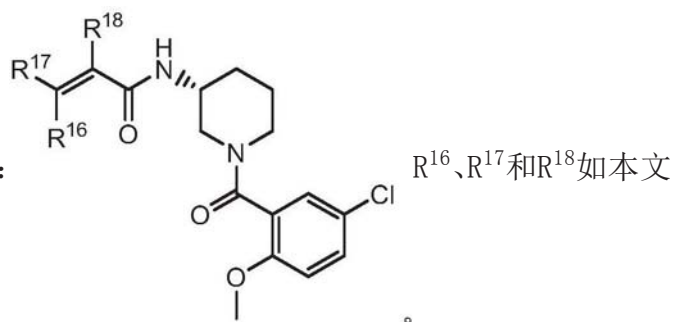
[0294] 在实施方案中，化合物具有下式：



R^{16} 、 R^{17} 和 R^{18} 如

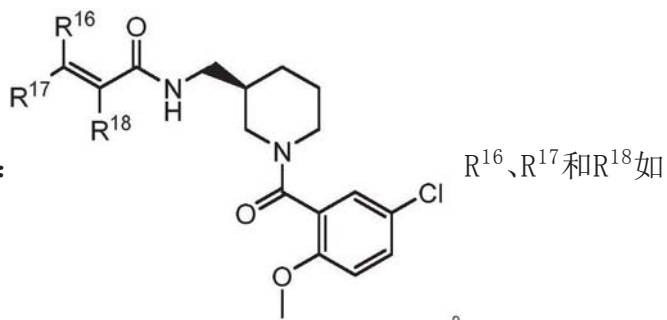
本文所述。在实施方案中， R^{16} 、 R^{17} 和 R^{18} 为氢。

[0295] 在实施方案中,化合物具有下式:



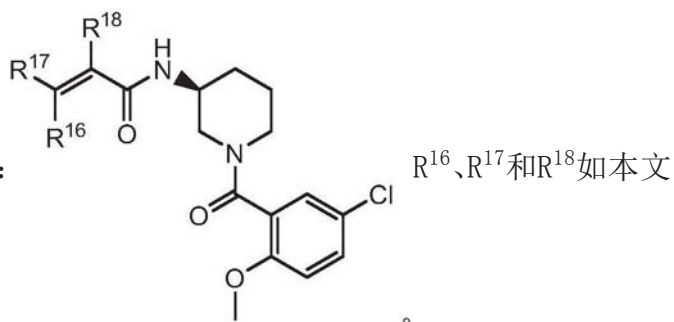
所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0296] 在实施方案中,化合物具有下式:



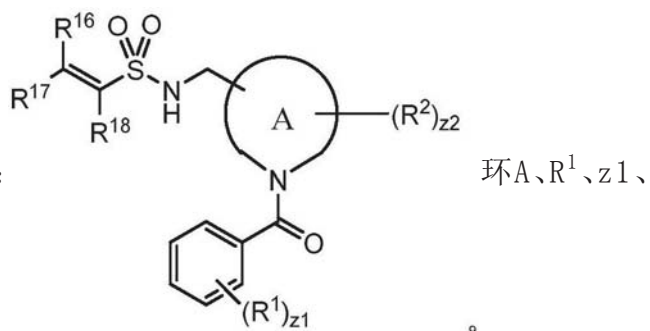
本文所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0297] 在实施方案中,化合物具有下式:



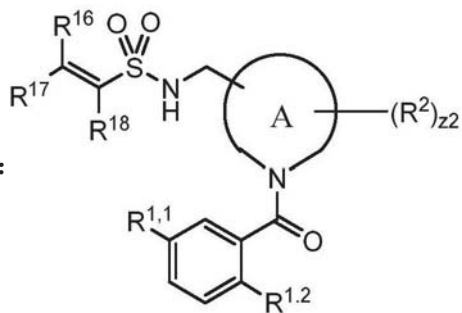
所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0298] 在实施方案中,化合物具有下式:



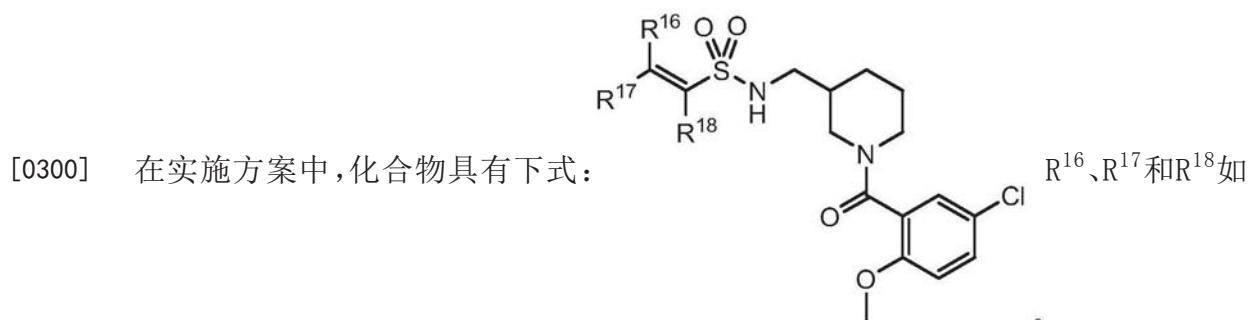
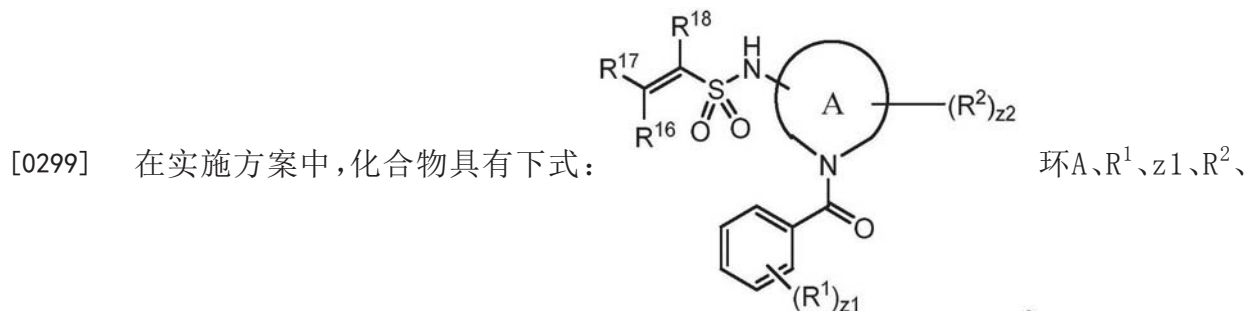
R²、z2、R¹⁶、R¹⁷和R¹⁸如本文所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。在实施方案中,化合物具

有下式:

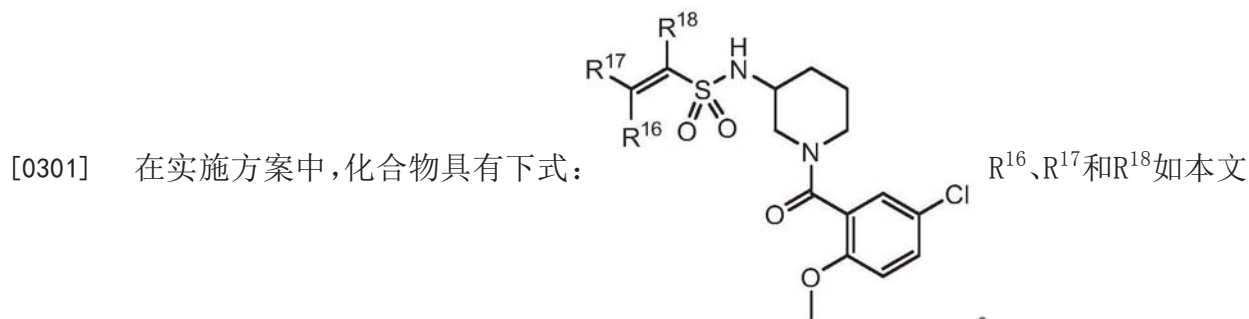
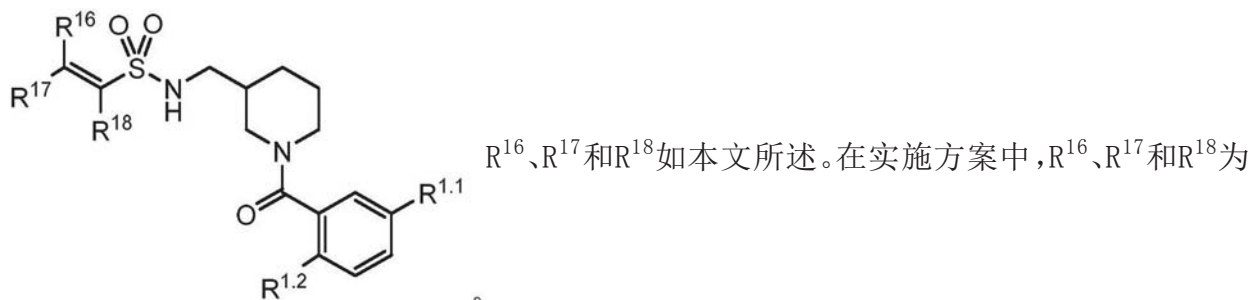


环A、R²、z2、R¹⁶、R¹⁷和R¹⁸如本文所述。在实施方案

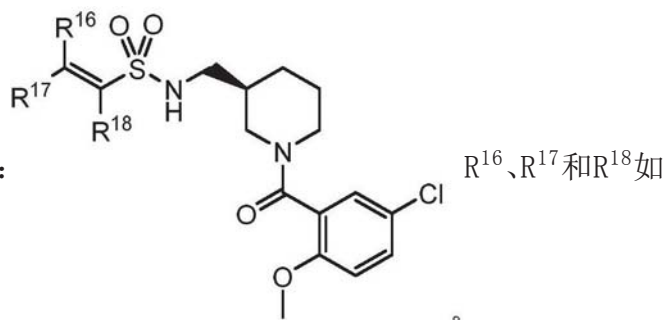
中, R^{16} 、 R^{17} 和 R^{18} 为氢。 $R^{1.1}$ 和 $R^{1.2}$ 具有 R^1 的值。 $R^{1.1}$ 可为卤素。 $R^{1.1}$ 可为氢。 $R^{1.1}$ 可为-Cl。 $R^{1.2}$ 可为氢。 $R^{1.2}$ 可为未取代的2-4元杂烷基。 $R^{1.2}$ 可为未取代的2-3元杂烷基。 $R^{1.2}$ 可为未取代的甲氧基。 $R^{1.2}$ 可为未取代的乙氧基。 $R^{1.2}$ 可为未取代的丙氧基。



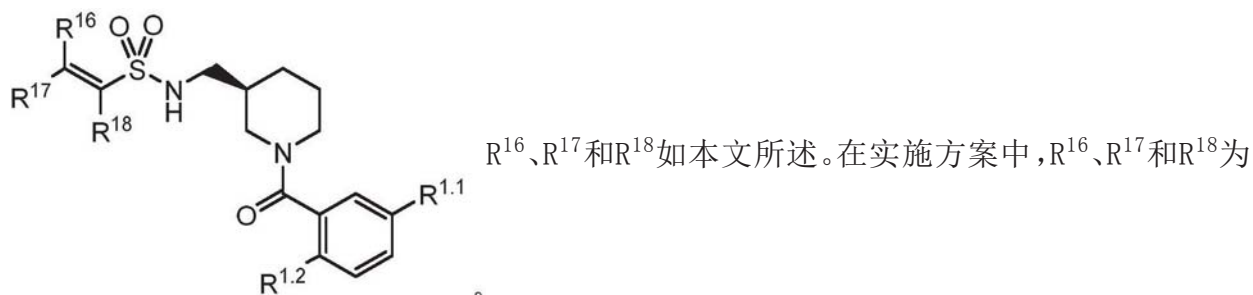
在实施方案中, 化合物具有下式:



[0302] 在实施方案中,化合物具有下式:

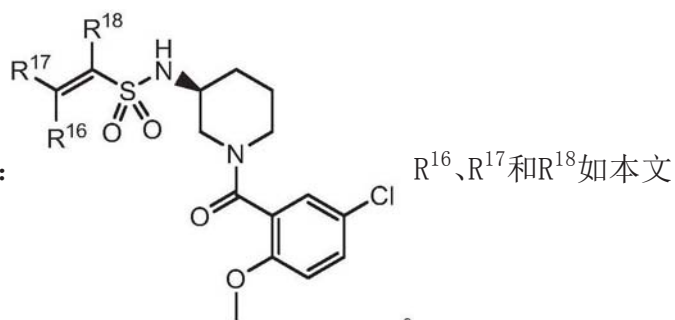


本文所述。在实施方案中, R¹⁶、R¹⁷和R¹⁸为氢。在实施方案中, 化合物具有下式:



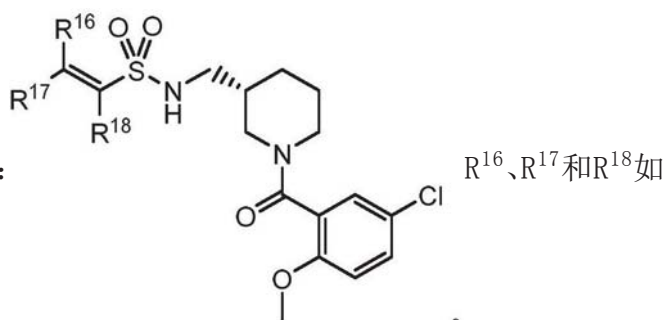
氢。R^{1.1}和R^{1.2}具有R¹的值。R^{1.1}可为卤素。R^{1.1}可为氢。R^{1.1}可为-Cl。R^{1.2}可为氢。R^{1.2}可为未取代的2-4元杂烷基。R^{1.2}可为未取代的2-3元杂烷基。R^{1.2}可为未取代的甲氧基。R^{1.2}可为未取代的乙氧基。R^{1.2}可为未取代的丙氧基。

[0303] 在实施方案中,化合物具有下式:



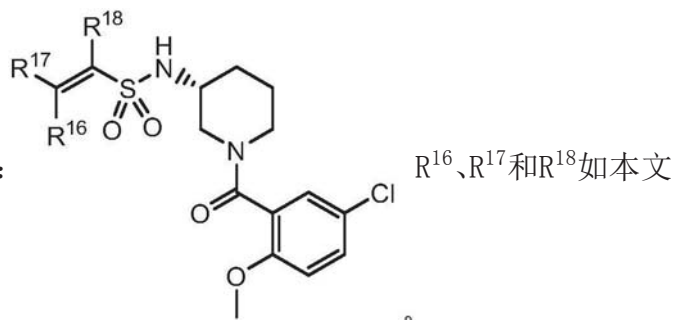
所述。在实施方案中, R¹⁶、R¹⁷和R¹⁸为氢。

[0304] 在实施方案中,化合物具有下式:



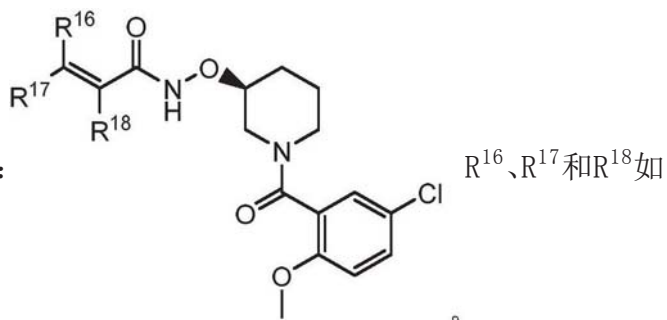
本文所述。在实施方案中, R¹⁶、R¹⁷和R¹⁸为氢。

[0305] 在实施方案中,化合物具有下式:



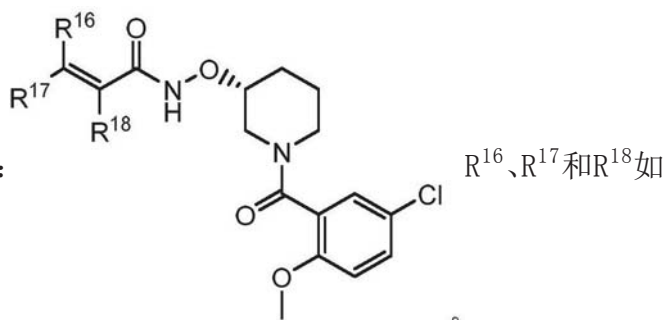
所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0306] 在实施方案中,化合物具有下式:



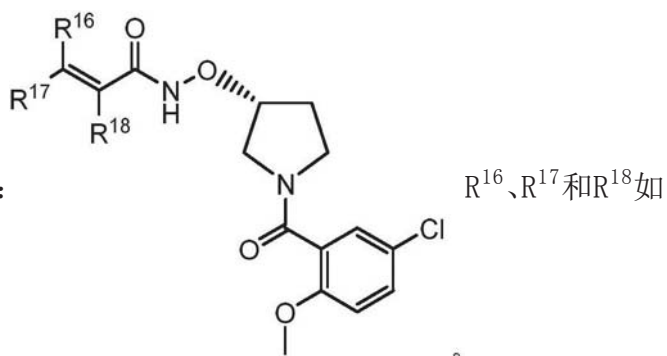
本文所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0307] 在实施方案中,化合物具有下式:



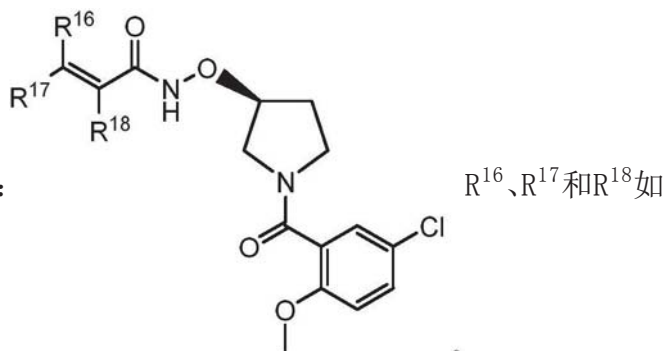
本文所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0308] 在实施方案中,化合物具有下式:



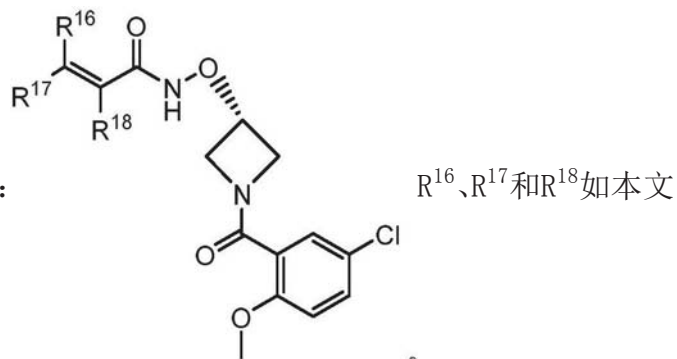
本文所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0309] 在实施方案中,化合物具有下式:



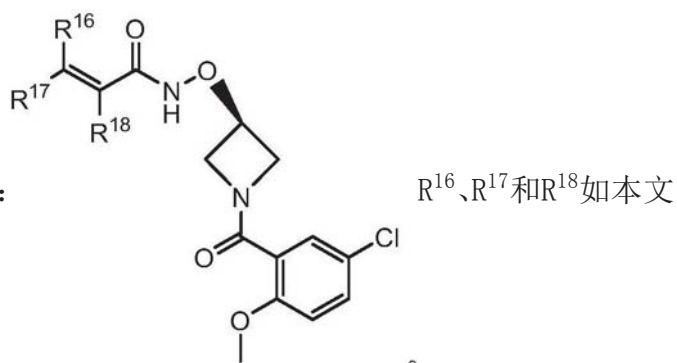
本文所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。在实施方案中,R¹⁶和R¹⁸为氢而R¹⁷为-CH₂Ph。

[0310] 在实施方案中,化合物具有下式:



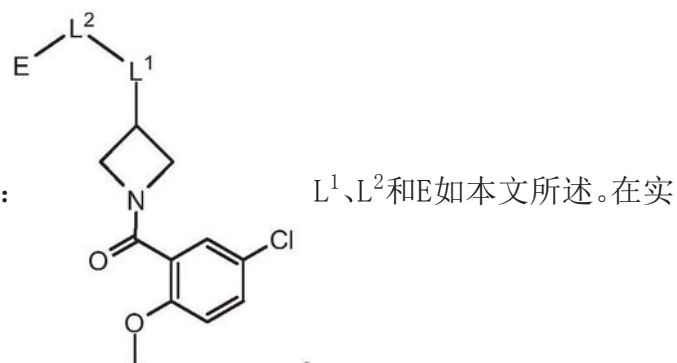
所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0311] 在实施方案中,化合物具有下式:

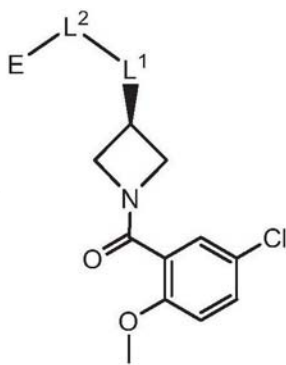


所述。在实施方案中,R¹⁶、R¹⁷和R¹⁸为氢。

[0312] 在实施方案中,化合物具有下式:

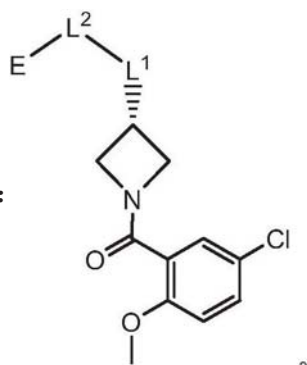


实施方案中,化合物具有下式:



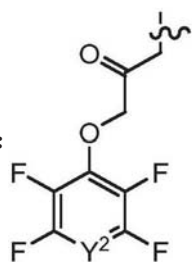
L^1 、 L^2 和E如本文所述。在实施方案中,化

合物具有下式:

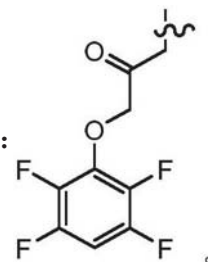


L^1 、 L^2 和E如本文所述。在实施方案中, R^{16} 、 R^{17} 和 R^{18} 为

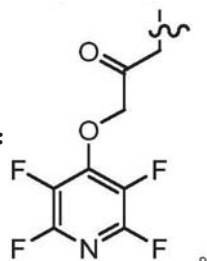
氢。在实施方案中,E为:



且 Y^2 如本文所述。在实施方案中,E为:

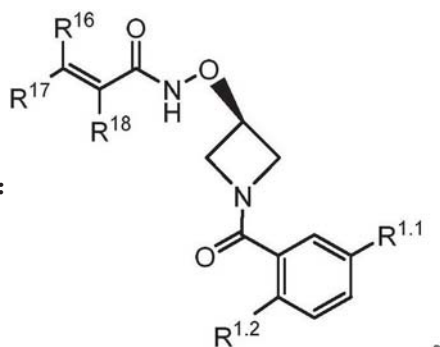


在实施方案中,E为:



在实施方案中, L^1 为 $-C(O)-$ 。在实施方案中, L^2 为 $-NH-$ 。在

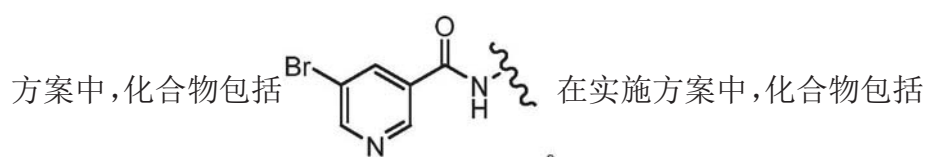
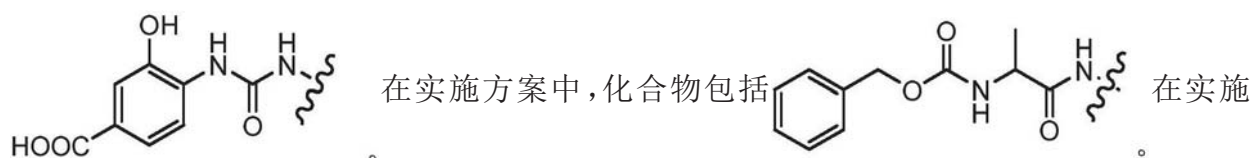
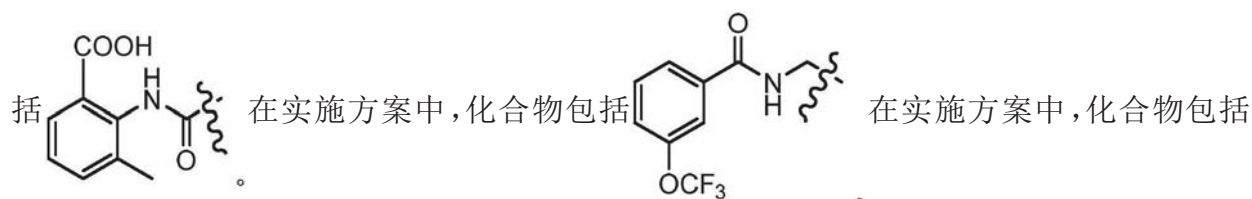
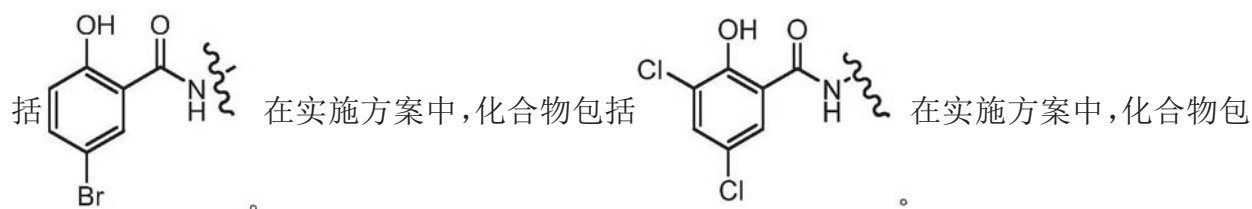
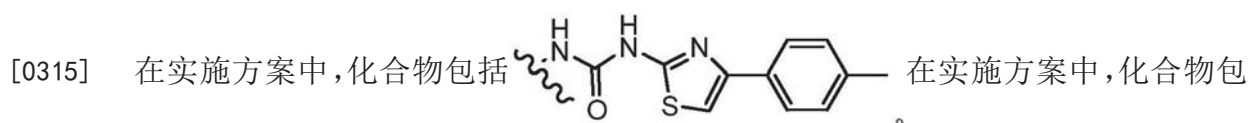
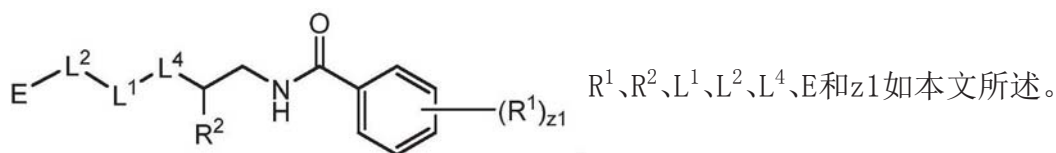
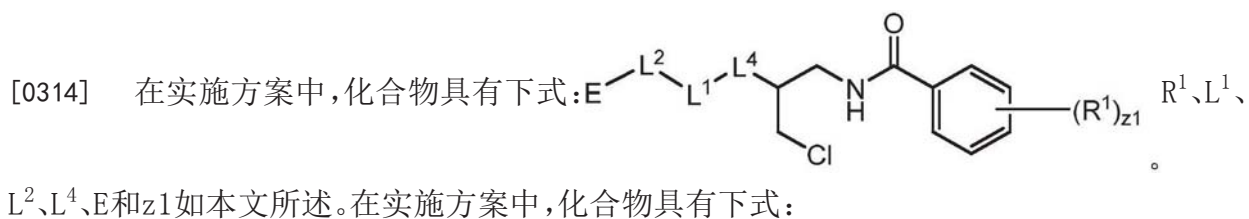
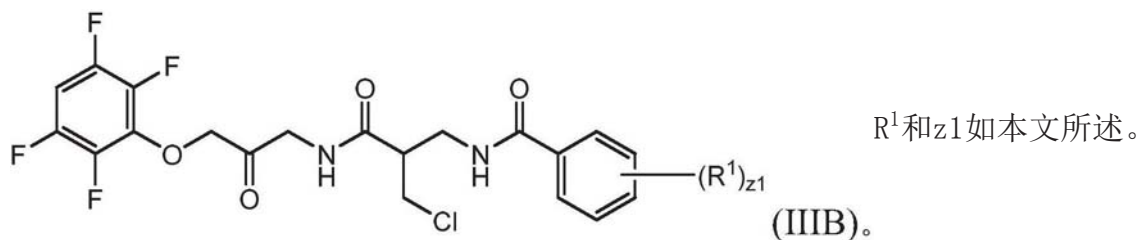
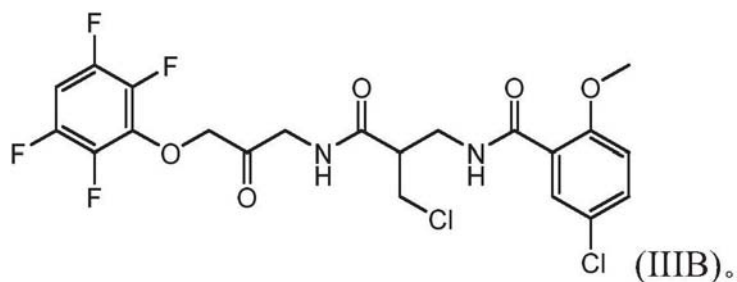
实施方案中,化合物具有下式:

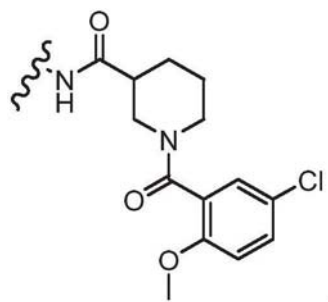


R^{16} 、 R^{17} 和 R^{18} 如本文所述。在

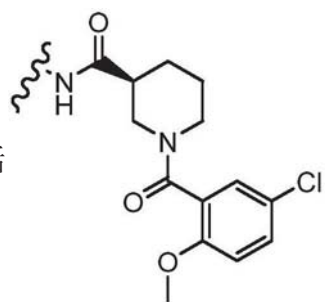
实施方案中, R^{16} 、 R^{17} 和 R^{18} 为氢。 $R^{1.1}$ 和 $R^{1.2}$ 具有 R^1 的值。 $R^{1.1}$ 可为卤素。 $R^{1.1}$ 可为氢。 $R^{1.1}$ 可为 $-Cl$ 。 $R^{1.2}$ 可为氢。 $R^{1.2}$ 可为未取代的2-4元杂烷基。 $R^{1.2}$ 可为未取代的2-3元杂烷基。 $R^{1.2}$ 可为未取代的甲氧基。 $R^{1.2}$ 可为未取代的乙氧基。 $R^{1.2}$ 可为未取代的丙氧基。

[0313] 在实施方案中,化合物具有下式:





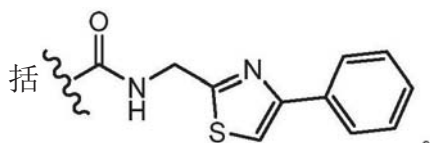
在实施方案中,化合物包括



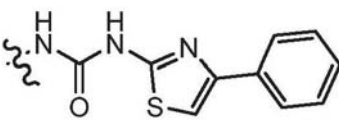
在实施方案

中,化合物是本文,包括在实例、图或表中描述的化合物。

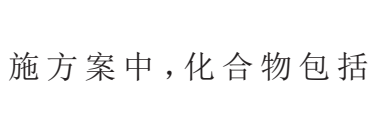
[0316] 在实施方案中,化合物包括 在实施方案中,化合物包



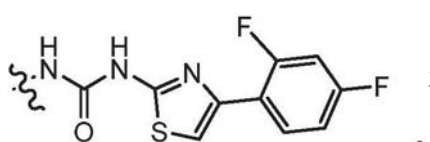
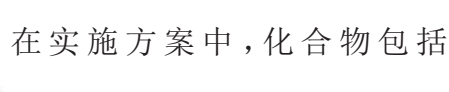
在实施方案中,化合物包括



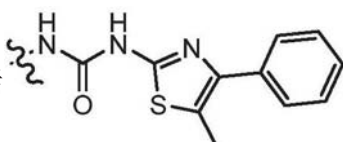
在实



在实施方案中,化合物包括



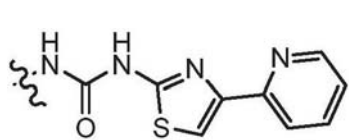
在实施方案中,化合物包括



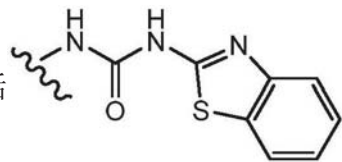
在实



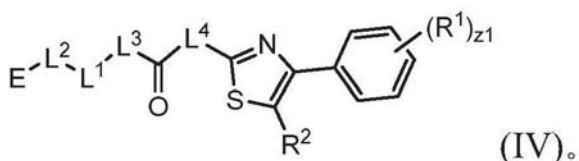
在实施方案中,化合物包括



在实施方案中,化合物包括



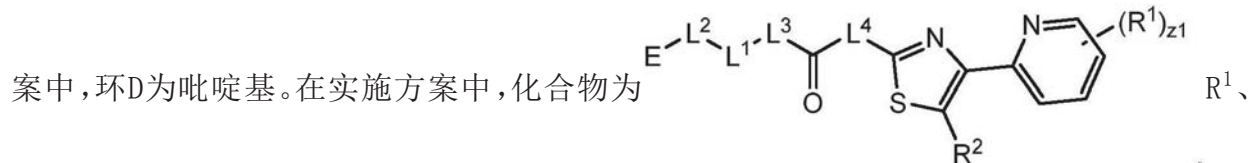
[0317] 一方面,提供了一种具有下式的化合物:



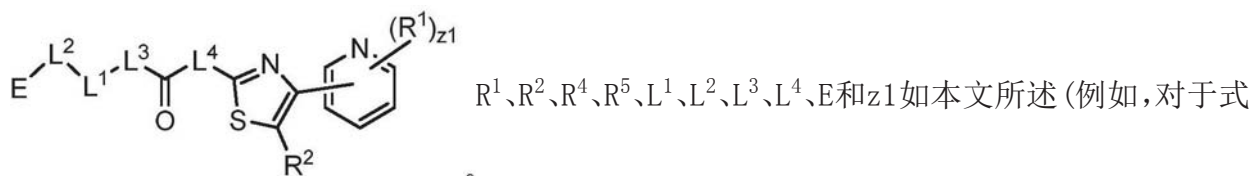
R^1 、 R^2 、 R^4 、 R^5 、 L^1 、 L^2 、 L^3 、 L^4 、 E 和 $z1$ 如本文所述(例如,对于式I、II、III及其实施方案而言或在实例、图、表或权利要求书中)。 L^4 可为 $-N(R^4)-$ 。 L^4 可为 $-CH_2N(R^4)-$ 。 L^3 可为 $-N(R^5)-$ 。 L^3 可为键。 L^4 可为键。 R^4 和 R^5 可为氢。 L^3 可为未取代的亚甲基。 L^3 可为未取代的乙烯基。 L^3 可为未取代的正-丙烯基。 L^3 可为未取代的正-丁烯基。 R^2 可为未取代的甲基。 R^2 可为氢。

[0318] 一方面,提供了一种具有下式的化合物: (V)。

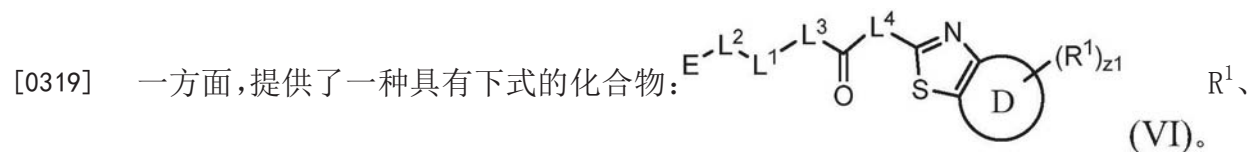
R^1 、 R^2 、 R^4 、 R^5 、 L^1 、 L^2 、 L^3 、 L^4 、E和 $z1$ 如本文所述(例如,对于式I、II、III、VI及其实施方案而言或在实例、图、表或权利要求书中)。 L^4 可为 $-N(R^4)-$ 。 L^4 可为 $-N(H)-$ 。 L^4 可为 $-CH_2N(R^4)-$ 。 L^3 可为 $-N(R^5)-$ 。 L^4 可为 $-N(H)-$ 。 L^3 可为键。 L^4 可为键。 R^4 和 R^5 可为氢。 L^3 可为未取代的亚甲基。 L^3 可为未取代的乙烯基。 L^3 可为未取代的正-丙烯基。 L^3 可为未取代的正-丁烯基。 R^2 可为未取代的甲基。 R^2 可为氢。环D为环烷基、杂环烷基、芳基或杂芳基。在实施方案中,环D为 C_3 - C_8 环烷基、3-8元杂环烷基、 C_6 - C_{10} 芳基或5-10元杂芳基。在实施方案中,环D为 C_3 - C_8 环烷基。在实施方案中,环D为3-8元杂环烷基。在实施方案中,环D为 C_6 - C_{10} 芳基。在实施方案中,环D为5-10元杂芳基。在实施方案中,环D为苯基。在实施方案中,环D为5-9元杂芳基。在实施方案中,环D为5-6元杂芳基。在实施方案中,环D为5元杂芳基。在实施方案中,环D为6元杂芳基。在实施方案中,环D为吡啶基。在实施方案中,化合物为



R^2 、 R^4 、 R^5 、 L^1 、 L^2 、 L^3 、 L^4 、E和 $z1$ 如本文所述(例如,对于式I、II、III、VI及其实施方案而言或在实例、图、表或权利要求书中)。在实施方案中, $z1$ 为0。在实施方案中,化合物为



I、II、III、VI及其实施方案而言或在实例、图、表或权利要求书中)。



R^2 、 R^4 、 R^5 、 L^1 、 L^2 、 L^3 、 L^4 、E和 $z1$ 如本文所述(例如,对于式I、II、III、IV、V及其实施方案而言或在实例、图、表或权利要求书中)。 L^4 可为 $-N(R^4)-$ 。 L^4 可为 $-N(H)-$ 。 L^4 可为 $-CH_2N(R^4)-$ 。 L^3 可为 $-N(R^5)-$ 。 L^3 可为 $-N(H)-$ 。 L^3 可为键。 L^4 可为键。 R^4 和 R^5 可为氢。 L^3 可为未取代的亚甲基。 L^3 可为未取代的乙烯基。 L^3 可为未取代的正-丙烯基。 L^3 可为未取代的正-丁烯基。 R^2 可为未取代的甲基。 R^2 可为氢。环D为环烷基、杂环烷基、芳基或杂芳基。在实施方案中,环D为 C_3 - C_8 环烷基、3-8元杂环烷基、 C_6 - C_{10} 芳基或5-10元杂芳基。在实施方案中,环D为 C_3 - C_8 环烷基。在实施方案中,环D为3-8元杂环烷基。在实施方案中,环D为 C_6 - C_{10} 芳基。在实施方案中,环D为5-10元杂芳基。在实施方案中,环D为苯基。在实施方案中,环D为5-9元杂芳基。在实施方案中,环D为5-6元杂芳基。在实施方案中,环D为5元杂芳基。在实施方案中,环D为6元杂芳基。在实施方案中,环D为吡啶基。

[0320] 在实施方案中, R^1 独立地为氢、氧代、卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-OCH_2X^1$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(=O)NHNH_2$ 、 $-NHC(=O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(=O)H$ 、 $-NHC(=O)OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 R^{30} -取代的或未取代的烷基(例如, C_1 - C_8 、 C_1 - C_6 或 C_1 - C_4)、 R^{30} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{30} -取代的或未取代的环烷基(例如, C_3 - C_8 、 C_3 - C_6 或 C_5 - C_6)、 R^{30} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{30} -取代的或未取代的芳基(例如, C_6 - C_{10} 、 C_{10} 或苯基)或 R^{30} -

经取代或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。在实施方案中, R^1 独立地为氧代、卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-OCH_2X^1$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 R^{30} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{30} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{30} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{30} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{30} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{30} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^1 为卤素。在实施方案中, X^1 为F。

[0321] R^{30} 独立地为氧代、卤素、 $-CX^{30}_3$ 、 $-CHX^{30}_2$ 、 $-OCH_2X^{30}$ 、 $-OCHX^{30}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{30}_3$ 、 $-OCHX^{30}_2$ 、 R^{31} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{31} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{31} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{31} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{31} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{31} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{30} 为卤素。在实施方案中, X^{30} 为F。

[0322] R^{31} 独立地为氧代、卤素、 $-CX^{31}_3$ 、 $-CHX^{31}_2$ 、 $-OCH_2X^{31}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{31}_3$ 、 $-OCHX^{31}_2$ 、 R^{32} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{32} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{32} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{32} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{32} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{32} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{31} 为卤素。在实施方案中, X^{31} 为F。

[0323] 在实施方案中, R^2 独立地为氢、氧代、卤素、 $-CX^2_3$ 、 $-CHX^2_2$ 、 $-OCH_2X^2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、 R^{33} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{33} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{33} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{33} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{33} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{33} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。在实施方案中, R^2 独立地为氧代、卤素、 $-CX^2_3$ 、 $-CHX^2_2$ 、 $-OCH_2X^2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、 R^{33} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{33} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{33} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{33} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{33} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{33} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^2 为卤素。在实施方案中, X^2 为F。

[0324] R^{33} 独立地为氧代、卤素、 $-CX^{33}_3$ 、 $-CHX^{33}_2$ 、 $-OCH_2X^{33}$ 、 $-OCHX^{33}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=O$ 、 $NHNH_2$ 、 $-NHC=O$ 、 NH_2 、 $-NHSO_2H$ 、 $-NHC=O$ 、 H 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{33}_3$ 、 $-OCHX^{33}_2$ 、 R^{34} -取代的或未取代的烷基(例

如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{34} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{34} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{34} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{34} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{34} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X³³为卤素。在实施方案中, X³³为F。

[0325] R^{34} 独立地为氧代、卤素、 $-CX^{34}_3$ 、 $-CHX^{34}_2$ 、 $-OCH_2X^{34}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{34}_3$ 、 $-OCHX^{34}_2$ 、 R^{35} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{35} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{35} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{35} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{35} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{35} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X³⁴为卤素。在实施方案中, X³⁴为F。

[0326] 在实施方案中, R^3 独立地为氢、氧代、卤素、 $-CX^3_3$ 、 $-CHX^3_2$ 、 $-OCH_2X^3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^3_3$ 、 $-OCHX^3_2$ 、 R^{36} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{36} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{36} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{36} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{36} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{36} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X³为卤素。在实施方案中, X³为F。

[0327] R^{36} 独立地为氧代、卤素、 $-CX^{36}_3$ 、 $-CHX^{36}_2$ 、 $-OCH_2X^{36}$ 、 $-OCHX^{36}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{36}_3$ 、 $-OCHX^{36}_2$ 、 R^{37} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{37} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{37} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{37} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{37} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{37} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X³⁶为卤素。在实施方案中, X³⁶为F。

[0328] R^{37} 独立地为氧代、卤素、 $-CX^{37}_3$ 、 $-CHX^{37}_2$ 、 $-OCH_2X^{37}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{37}_3$ 、 $-OCHX^{37}_2$ 、 R^{38} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{38} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{38} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{38} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{38} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{38} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X³⁷为卤素。在实施方案中, X³⁷为F。

[0329] 在实施方案中, R^4 独立地为氢、氧代、卤素、 $-CX^4_3$ 、 $-CHX^4_2$ 、 $-OCH_2X^4$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^4_3$ 、 $-OCHX^4_2$ 、 R^{39} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{39} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{39} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{39} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{39} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{39} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X⁴为卤素。在实施方案中, X⁴为F。

[0330] R^{39} 独立地为氧代、卤素、 $-CX^{39}_3$ 、 $-CHX^{39}_2$ 、 $-OCH_2X^{39}$ 、 $-OCHX^{39}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{39}_3$ 、 $-OCHX^{39}_2$ 、 R^{40} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{40} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{40} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{40} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{40} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{40} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{39} 为卤素。在实施方案中, X^{39} 为F。

[0331] R^{40} 独立地为氧代、卤素、 $-CX^{40}_3$ 、 $-CHX^{40}_2$ 、 $-OCH_2X^{40}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{40}_3$ 、 $-OCHX^{40}_2$ 、 R^{41} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{41} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{41} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{41} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{41} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{41} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{40} 为卤素。在实施方案中, X^{40} 为F。

[0332] 在实施方案中, R^5 独立地为氢、氧代、卤素、 $-CX^5_3$ 、 $-CHX^5_2$ 、 $-OCH_2X^5$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^5_3$ 、 $-OCHX^5_2$ 、 R^{42} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{42} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{42} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{42} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{42} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{42} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^5 为卤素。在实施方案中, X^5 为F。

[0333] R^{42} 独立地为氧代、卤素、 $-CX^{42}_3$ 、 $-CHX^{42}_2$ 、 $-OCH_2X^{42}$ 、 $-OCHX^{42}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{42}_3$ 、 $-OCHX^{42}_2$ 、 R^{43} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{43} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{43} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{43} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{43} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{43} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{42} 为卤素。在实施方案中, X^{42} 为F。

[0334] R^{43} 独立地为氧代、卤素、 $-CX^{43}_3$ 、 $-CHX^{43}_2$ 、 $-OCH_2X^{43}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{43}_3$ 、 $-OCHX^{43}_2$ 、 R^{44} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{44} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{44} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{44} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{44} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{44} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{43} 为卤素。在实施方案中, X^{43} 为F。

[0335] 在实施方案中, R^6 独立地为氢、氧代、卤素、 $-CX^6_3$ 、 $-CHX^6_2$ 、 $-OCH_2X^6$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^6_3$ 、 $-OCHX^6_2$ 、 R^{45} -取代的或未取代的alkyl(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{45} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、

R^{45} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{45} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{45} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{45} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^6 为卤素。在实施方案中, X^6 为F。

[0336] R^{45} 独立地为氧代、卤素、 $-CX^{45}_3$ 、 $-CHX^{45}_2$ 、 $-OCH_2X^{45}$ 、 $-OCHX^{45}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{45}_3$ 、 $-OCHX^{45}_2$ 、 R^{46} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{46} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{46} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{46} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{46} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{46} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{45} 为卤素。在实施方案中, X^{45} 为F。

[0337] R^{46} 独立地为氧代、卤素、 $-CX^{46}_3$ 、 $-CHX^{46}_2$ 、 $-OCH_2X^{46}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{46}_3$ 、 $-OCHX^{46}_2$ 、 R^{47} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{47} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{47} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{47} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{47} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{47} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{46} 为卤素。在实施方案中, X^{46} 为F。

[0338] 在实施方案中, R^7 独立地为氢、氧代、卤素、 $-CX^7_3$ 、 $-CHX^7_2$ 、 $-OCH_2X^7$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^7_3$ 、 $-OCHX^7_2$ 、 R^{48} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{48} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{48} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{48} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{48} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{48} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^7 为卤素。在实施方案中, X^7 为F。

[0339] R^{48} 独立地为氧代、卤素、 $-CX^{48}_3$ 、 $-CHX^{48}_2$ 、 $-OCH_2X^{48}$ 、 $-OCHX^{48}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{48}_3$ 、 $-OCHX^{48}_2$ 、 R^{49} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{49} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{49} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{49} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{49} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{49} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{48} 为卤素。在实施方案中, X^{48} 为F。

[0340] R^{49} 独立地为氧代、卤素、 $-CX^{49}_3$ 、 $-CHX^{49}_2$ 、 $-OCH_2X^{49}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{49}_3$ 、 $-OCHX^{49}_2$ 、 R^{50} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{50} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{50} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{50} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{50} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{50} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{49} 为卤素。在实施方案中, X^{49} 为F。

[0341] 在实施方案中, R^8 独立地为氢、氧代、卤素、 $-CX^8_3$ 、 $-CHX^8_2$ 、 $-OCH_2X^8$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-$

COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁸₃、-OCHX⁸₂、R⁵¹-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁵¹-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁵¹-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁵¹-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁵¹-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁵¹-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁸为卤素。在实施方案中, X⁸为F。

[0342] R⁵¹独立地为氧代、卤素、-CX⁵¹₃、-CHX⁵¹₂、-OCH₂X⁵¹、-OCHX⁵¹₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁵¹₃、-OCHX⁵¹₂、R⁵²-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁵²-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁵²-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁵²-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁵²-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁵²-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁵¹为卤素。在实施方案中, X⁵¹为F。

[0343] R⁵²独立地为氧代、卤素、-CX⁵²₃、-CHX⁵²₂、-OCH₂X⁵²、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁵²₃、-OCHX⁵²₂、R⁵³-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁵³-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁵³-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁵³-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁵³-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁵³-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁵²为卤素。在实施方案中, X⁵²为F。

[0344] 在实施方案中, R⁹独立地为氢、氧代、卤素、-CX⁹₃、-CHX⁹₂、-OCH₂X⁹、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁹₃、-OCHX⁹₂、R⁵⁴-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁵⁴-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁵⁴-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁵⁴-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁵⁴-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁵⁴-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁹为卤素。在实施方案中, X⁹为F。

[0345] R⁵⁴独立地为氧代、卤素、-CX⁵⁴₃、-CHX⁵⁴₂、-OCH₂X⁵⁴、-OCHX⁵⁴₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁵⁴₃、-OCHX⁵⁴₂、R⁵⁵-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁵⁵-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁵⁵-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁵⁵-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁵⁵-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁵⁵-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁵⁴为卤素。在实施方案中, X⁵⁴为F。

[0346] R⁵⁵独立地为氧代、卤素、-CX⁵⁵₃、-CHX⁵⁵₂、-OCH₂X⁵⁵、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁵⁵₃、-OCHX⁵⁵₂、R⁵⁶-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁵⁶-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁵⁶-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁵⁶-取代的或未取代的杂环烷基 (例如, 3-8元、3-

6元或5-6元)、 R^{56} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{56} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{55} 为卤素。在实施方案中, X^{55} 为F。

[0347] 在实施方案中, R^{10} 独立地为氢、氧代、卤素、 $-CX^{10}_3$ 、 $-CHX^{10}_2$ 、 $-OCH_2X^{10}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{10}_3$ 、 $-OCHX^{10}_2$ 、 R^{57} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{57} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{57} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{57} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{57} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{57} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{10} 为卤素。在实施方案中, X^{10} 为F。

[0348] R^{57} 独立地为氧代、卤素、 $-CX^{57}_3$ 、 $-CHX^{57}_2$ 、 $-OCH_2X^{57}$ 、 $-OCHX^{57}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{57}_3$ 、 $-OCHX^{57}_2$ 、 R^{58} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{58} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{58} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{58} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{58} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{58} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{57} 为卤素。在实施方案中, X^{57} 为F。

[0349] R^{58} 独立地为氧代、卤素、 $-CX^{58}_3$ 、 $-CHX^{58}_2$ 、 $-OCH_2X^{58}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{58}_3$ 、 $-OCHX^{58}_2$ 、 R^{59} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{59} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{59} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{59} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{59} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{59} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{58} 为卤素。在实施方案中, X^{58} 为F。

[0350] 在实施方案中, R^{7A} 独立地为氢、氧代、卤素、 $-CX^{7A}_3$ 、 $-CHX^{7A}_2$ 、 $-OCH_2X^{7A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{7A}_3$ 、 $-OCHX^{7A}_2$ 、 R^{48A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{48A} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{48A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{48A} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{48A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{48A} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。在实施方案中, R^{7A} 独立地为氧代、卤素、 $-CX^{7A}_3$ 、 $-CHX^{7A}_2$ 、 $-OCH_2X^{7A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{7A}_3$ 、 $-OCHX^{7A}_2$ 、 R^{48A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{48A} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{48A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{48A} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{48A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{48A} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{7A} 为卤素。在实施方案中, X^{7A} 为F。

[0351] R^{48A} 独立地为氧代、卤素、 $-CX^{48A}_3$ 、 $-CHX^{48A}_2$ 、 $-OCH_2X^{48A}$ 、 $-OCHX^{48A}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-$

COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{48A}₃、-OCHX^{48A}₂、R^{49A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{49A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{49A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{49A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{49A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{49A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{48A}为卤素。在实施方案中, X^{48A}为F。

[0352] R^{49A}独立地为氧代、卤素、-CX^{49A}₃、-CHX^{49A}₂、-OCH₂X^{49A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{49A}₃、-OCHX^{49A}₂、R^{50A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{50A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{50A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{50A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{50A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{50A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{49A}为卤素。在实施方案中, X^{49A}为F。

[0353] 在实施方案中, R^{8A}独立地为氢、氧代、卤素、-CX^{8A}₃、-CHX^{8A}₂、-OCH₂X^{8A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{8A}₃、-OCHX^{8A}₂、R^{51A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{51A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{51A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{51A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{51A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{51A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{8A}为卤素。在实施方案中, X^{8A}为F。

[0354] R^{51A}独立地为氧代、卤素、-CX^{51A}₃、-CHX^{51A}₂、-OCH₂X^{51A}、-OCHX^{51A}₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{51A}₃、-OCHX^{51A}₂、R^{52A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{52A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{52A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{52A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{52A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{52A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{51A}为卤素。在实施方案中, X^{51A}为F。

[0355] R^{52A}独立地为氧代、卤素、-CX^{52A}₃、-CHX^{52A}₂、-OCH₂X^{52A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{52A}₃、-OCHX^{52A}₂、R^{53A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{53A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{53A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{53A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{53A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{53A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{52A}为卤素。在实施方案中, X^{52A}为F。

[0356] 在实施方案中, R^{9A} 独立地为氢、氧代、卤素、 $-CX^{9A}_3$ 、 $-CHX^{9A}_2$ 、 $-OCH_2X^{9A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{9A}_3$ 、 $-OCHX^{9A}_2$ 、 R^{54A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{54A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{54A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{54A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{54A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{54A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{9A} 为卤素。在实施方案中, X^{9A} 为F。

[0357] R^{54A} 独立地为氧代、卤素、 $-CX^{54A}_3$ 、 $-CHX^{54A}_2$ 、 $-OCH_2X^{54A}$ 、 $-OCHX^{54A}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{54A}_3$ 、 $-OCHX^{54A}_2$ 、 R^{55A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{55A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{55A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{55A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{55A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{55A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{54A} 为卤素。在实施方案中, X^{54A} 为F。

[0358] R^{55A} 独立地为氧代、卤素、 $-CX^{55A}_3$ 、 $-CHX^{55A}_2$ 、 $-OCH_2X^{55A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{55A}_3$ 、 $-OCHX^{55A}_2$ 、 R^{56A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{56A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{56A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{56A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{56A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{56A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{55A} 为卤素。在实施方案中, X^{55A} 为F。

[0359] 在实施方案中, R^{10A} 独立地为氢、氧代、卤素、 $-CX^{10A}_3$ 、 $-CHX^{10A}_2$ 、 $-OCH_2X^{10A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{10A}_3$ 、 $-OCHX^{10A}_2$ 、 R^{57A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{57A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{57A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{57A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{57A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{57A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{10A} 为卤素。在实施方案中, X^{10A} 为F。

[0360] R^{57A} 独立地为氧代、卤素、 $-CX^{57A}_3$ 、 $-CHX^{57A}_2$ 、 $-OCH_2X^{57A}$ 、 $-OCHX^{57A}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{57A}_3$ 、 $-OCHX^{57A}_2$ 、 R^{58A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{58A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{58A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{58A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{58A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{58A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{57A} 为卤素。在实施方案

中, X^{57A} 为 F。

[0361] R^{58A} 独立地为氧代、卤素、 $-CX^{58A}_3$ 、 $-CHX^{58A}_2$ 、 $-OCH_2X^{58A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{58A}_3$ 、 $-OCHX^{58A}_2$ 、 R^{59A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{59A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{59A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{59A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{59A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{59A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{58A} 为卤素。在实施方案中, X^{58A} 为 F。

[0362] 在实施方案中, R^{7B} 独立地为氢、氧代、卤素、 $-CX^{7B}_3$ 、 $-CHX^{7B}_2$ 、 $-OCH_2X^{7B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{7B}_3$ 、 $-OCHX^{7B}_2$ 、 R^{48B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{48B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{48B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{48B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{48B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{48B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。在实施方案中, R^{7B} 独立地为氧代、卤素、 $-CX^{7B}_3$ 、 $-CHX^{7B}_2$ 、 $-OCH_2X^{7B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{7B}_3$ 、 $-OCHX^{7B}_2$ 、 R^{48B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{48B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{48B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{48B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{48B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{48B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{7B} 为卤素。在实施方案中, X^{7B} 为 F。

[0363] R^{48B} 独立地为氧代、卤素、 $-CX^{48B}_3$ 、 $-CHX^{48B}_2$ 、 $-OCH_2X^{48B}$ 、 $-OCHX^{48B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{48B}_3$ 、 $-OCHX^{48B}_2$ 、 R^{49B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{49B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{49B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{49B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{49B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{49B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{48B} 为卤素。在实施方案中, X^{48B} 为 F。

[0364] R^{49B} 独立地为氧代、卤素、 $-CX^{49B}_3$ 、 $-CHX^{49B}_2$ 、 $-OCH_2X^{49B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{49B}_3$ 、 $-OCHX^{49B}_2$ 、 R^{50B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{50B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{50B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{50B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{50B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{50B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{49B} 为卤素。在实施方案中, X^{49B} 为 F。

[0365] 在实施方案中, R^{8B} 独立地为氢、氧代、卤素、 $-CX^{8B}_3$ 、 $-CHX^{8B}_2$ 、 $-OCH_2X^{8B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{8B}_3$ 、 $-OCHX^{8B}_2$ 、 R^{51B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{51B} -取代的或未取代的杂烷基 (例如, 2-8 元、2-6 元或 2-4 元)、 R^{51B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{51B} -取代的或未取代的杂环烷基 (例如, 3-8 元、3-6 元或 5-6 元)、 R^{51B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{51B} -取代的或未取代的杂芳基 (例如, 5-10 元、5-9 元或 5-6 元)。 X^{8B} 为卤素。在实施方案中, X^{8B} 为 F。

[0366] R^{51B} 独立地为氧代、卤素、 $-CX^{51B}_3$ 、 $-CHX^{51B}_2$ 、 $-OCH_2X^{51B}$ 、 $-OCHX^{51B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{51B}_3$ 、 $-OCHX^{51B}_2$ 、 R^{52B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{52B} -取代的或未取代的杂烷基 (例如, 2-8 元、2-6 元或 2-4 元)、 R^{52B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{52B} -取代的或未取代的杂环烷基 (例如, 3-8 元、3-6 元或 5-6 元)、 R^{52B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{52B} -取代的或未取代的杂芳基 (例如, 5-10 元、5-9 元或 5-6 元)。 X^{51B} 为卤素。在实施方案中, X^{51B} 为 F。

[0367] R^{52B} 独立地为氧代、卤素、 $-CX^{52B}_3$ 、 $-CHX^{52B}_2$ 、 $-OCH_2X^{52B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{52B}_3$ 、 $-OCHX^{52B}_2$ 、 R^{53B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{53B} -取代的或未取代的杂烷基 (例如, 2-8 元、2-6 元或 2-4 元)、 R^{53B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{53B} -取代的或未取代的杂环烷基 (例如, 3-8 元、3-6 元或 5-6 元)、 R^{53B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{53B} -取代的或未取代的杂芳基 (例如, 5-10 元、5-9 元或 5-6 元)。 X^{52B} 为卤素。在实施方案中, X^{52B} 为 F。

[0368] 在实施方案中, R^{9B} 独立地为氢、氧代、卤素、 $-CX^{9B}_3$ 、 $-CHX^{9B}_2$ 、 $-OCH_2X^{9B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{9B}_3$ 、 $-OCHX^{9B}_2$ 、 R^{54B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{54B} -取代的或未取代的杂烷基 (例如, 2-8 元、2-6 元或 2-4 元)、 R^{54B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{54B} -取代的或未取代的杂环烷基 (例如, 3-8 元、3-6 元或 5-6 元)、 R^{54B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{54B} -取代的或未取代的杂芳基 (例如, 5-10 元、5-9 元或 5-6 元)。 X^{9B} 为卤素。在实施方案中, X^{9B} 为 F。

[0369] R^{54B} 独立地为氧代、卤素、 $-CX^{54B}_3$ 、 $-CHX^{54B}_2$ 、 $-OCH_2X^{54B}$ 、 $-OCHX^{54B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{54B}_3$ 、 $-OCHX^{54B}_2$ 、 R^{55B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{55B} -取代的或未取代的杂烷基 (例如, 2-8 元、2-6 元或 2-4 元)、 R^{55B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{55B} -取代的或未取代的杂环烷基 (例如, 3-8 元、3-6 元或 5-6 元)、 R^{55B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{55B} -取代的或未取代的杂芳基 (例如, 5-10 元、5-9 元或 5-6 元)。 X^{54B} 为卤素。在实施方案

中, X^{54B} 为 F。

[0370] R^{55B} 独立地为氧代、卤素、 $-CX^{55B}_3$ 、 $-CHX^{55B}_2$ 、 $-OCH_2X^{55B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{55B}_3$ 、 $-OCHX^{55B}_2$ 、 R^{56B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{56B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{56B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{56B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{56B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{56B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{55B} 为卤素。在实施方案中, X^{55B} 为F。

[0371] 在实施方案中, R^{10B} 独立地为氢、氧代、卤素、 $-CX^{10B}_3$ 、 $-CHX^{10B}_2$ 、 $-OCH_2X^{10B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{10B}_3$ 、 $-OCHX^{10B}_2$ 、 R^{57B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{57B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{57B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{57B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{57B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{57B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{10B} 为卤素。在实施方案中, X^{10B} 为F。

[0372] R^{57B} 独立地为氧代、卤素、 $-CX^{57B}_3$ 、 $-CHX^{57B}_2$ 、 $-OCH_2X^{57B}$ 、 $-OCHX^{57B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{57B}_3$ 、 $-OCHX^{57B}_2$ 、 R^{58B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{58B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{58B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{58B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{58B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{58B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{57B} 为卤素。在实施方案中, X^{57B} 为F。

[0373] R^{58B} 独立地为氧代、卤素、 $-CX^{58B}_3$ 、 $-CHX^{58B}_2$ 、 $-OCH_2X^{58B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{58B}_3$ 、 $-OCHX^{58B}_2$ 、 R^{59B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{59B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{59B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{59B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{59B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{59B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{58B} 为卤素。在实施方案中, X^{58B} 为F。

[0374] 在实施方案中, R^{11} 独立地为氢、氧代、卤素、 $-CX^{11}_3$ 、 $-CHX^{11}_2$ 、 $-OCH_2X^{11}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{11}_3$ 、 $-OCHX^{11}_2$ 、 R^{60} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{60} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{60} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{60} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{60} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或

R^{60} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{11} 为卤素。在实施方案中, X^{11} 为F。

[0375] R^{60} 独立地为氧代、卤素、 $-CX^{60}_3$ 、 $-CHX^{60}_2$ 、 $-OCH_2X^{60}$ 、 $-OCHX^{60}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{60}_3$ 、 $-OCHX^{60}_2$ 、 R^{61} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{61} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{61} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{61} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{61} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{61} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{60} 为卤素。在实施方案中, X^{60} 为F。

[0376] R^{61} 独立地为氧代、卤素、 $-CX^{61}_3$ 、 $-CHX^{61}_2$ 、 $-OCH_2X^{61}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{61}_3$ 、 $-OCHX^{61}_2$ 、 R^{62} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{62} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{62} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{62} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{62} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{62} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{61} 为卤素。在实施方案中, X^{61} 为F。

[0377] 在实施方案中, R^{12} 独立地为氢、氧代、卤素、 $-CX^{12}_3$ 、 $-CHX^{12}_2$ 、 $-OCH_2X^{12}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{12}_3$ 、 $-OCHX^{12}_2$ 、 R^{63} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{63} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{63} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{63} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{63} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{63} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{12} 为卤素。在实施方案中, X^{12} 为F。

[0378] R^{63} 独立地为氧代、卤素、 $-CX^{63}_3$ 、 $-CHX^{63}_2$ 、 $-OCH_2X^{63}$ 、 $-OCHX^{63}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{63}_3$ 、 $-OCHX^{63}_2$ 、 R^{64} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{64} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{64} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{64} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{64} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{64} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{63} 为卤素。在实施方案中, X^{63} 为F。

[0379] R^{64} 独立地为氧代、卤素、 $-CX^{64}_3$ 、 $-CHX^{64}_2$ 、 $-OCH_2X^{64}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{64}_3$ 、 $-OCHX^{64}_2$ 、 R^{65} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{65} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{65} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{65} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{65} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{65} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{64} 为卤素。在实施方案中, X^{64} 为F。

[0380] 在实施方案中, R^{13} 独立地为氢、氧代、卤素、 $-CX^{13}_3$ 、 $-CHX^{13}_2$ 、 $-OCH_2X^{13}$ 、 $-CN$ 、 $-OH$ 、

C_1-C_6 或 C_1-C_4)、 R^{71} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{71} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{71} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{71} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{71} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{70} 为卤素。在实施方案中, X^{70} 为F。

[0386] 在实施方案中, R^{15} 独立地为氢、氧代、卤素、 $-CX^{15}_3$ 、 $-CHX^{15}_2$ 、 $-OCH_2X^{15}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{15}_3$ 、 $-OCHX^{15}_2$ 、 R^{72} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{72} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{72} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{72} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{72} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{72} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{15} 为卤素。在实施方案中, X^{15} 为F。

[0387] R^{72} 独立地为氧代、卤素、 $-CX^{72}_3$ 、 $-CHX^{72}_2$ 、 $-OCH_2X^{72}$ 、 $-OCHX^{72}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{72}_3$ 、 $-OCHX^{72}_2$ 、 R^{73} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{73} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{73} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{73} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{73} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{73} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{72} 为卤素。在实施方案中, X^{72} 为F。

[0388] R^{73} 独立地为氧代、卤素、 $-CX^{73}_3$ 、 $-CHX^{73}_2$ 、 $-OCH_2X^{73}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{73}_3$ 、 $-OCHX^{73}_2$ 、 R^{74} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{74} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{74} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{74} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{74} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{74} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{73} 为卤素。在实施方案中, X^{73} 为F。

[0389] 在实施方案中, R^{16} 独立地为氢、氧代、卤素、 $-CX^{16}_3$ 、 $-CHX^{16}_2$ 、 $-OCH_2X^{16}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、 R^{75} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{75} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{75} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{75} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{75} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{75} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{16} 为卤素。在实施方案中, X^{16} 为F。

[0390] R^{75} 独立地为氧代、卤素、 $-CX^{75}_3$ 、 $-CHX^{75}_2$ 、 $-OCH_2X^{75}$ 、 $-OCHX^{75}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=(O)NHNH_2$ 、 $-NHC=(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC=(O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{75}_3$ 、 $-OCHX^{75}_2$ 、 R^{76} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{76} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{76} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{76} -取代的或未取代的杂环烷基(例

如,3-8元、3-6元或5-6元)、 R^{76} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{76} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{75} 为卤素。在实施方案中, X^{75} 为F。

[0391] R^{76} 独立地为氧代、卤素、 $-CX^{76}_3$ 、 $-CHX^{76}_2$ 、 $-OCH_2X^{76}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{76}_3$ 、 $-OCHX^{76}_2$ 、 R^{77} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{77} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{77} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{77} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{77} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{77} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{76} 为卤素。在实施方案中, X^{76} 为F。

[0392] 在实施方案中, R^{17} 独立地为氢、氧代、卤素、 $-CX^{17}_3$ 、 $-CHX^{17}_2$ 、 $-OCH_2X^{17}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{17}_3$ 、 $-OCHX^{17}_2$ 、 R^{78} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{78} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{78} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{78} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{78} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{78} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{17} 为卤素。在实施方案中, X^{17} 为F。

[0393] R^{78} 独立地为氧代、卤素、 $-CX^{78}_3$ 、 $-CHX^{78}_2$ 、 $-OCH_2X^{78}$ 、 $-OCHX^{78}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{78}_3$ 、 $-OCHX^{78}_2$ 、 R^{79} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{79} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{79} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{79} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{79} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{79} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{78} 为卤素。在实施方案中, X^{78} 为F。

[0394] R^{79} 独立地为氧代、卤素、 $-CX^{79}_3$ 、 $-CHX^{79}_2$ 、 $-OCH_2X^{79}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{79}_3$ 、 $-OCHX^{79}_2$ 、 R^{80} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{80} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{80} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{80} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{80} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{80} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{79} 为卤素。在实施方案中, X^{79} 为F。

[0395] 在实施方案中, R^{18} 独立地为氢、氧代、卤素、 $-CX^{18}_3$ 、 $-CHX^{18}_2$ 、 $-OCH_2X^{18}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{18}_3$ 、 $-OCHX^{18}_2$ 、 R^{81} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{81} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{81} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{81} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{81} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{81} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{18} 为卤素。在实施方案中, X^{18} 为F。

[0396] R^{81} 独立地为氧代、卤素、 $-CX^{81}_3$ 、 $-CHX^{81}_2$ 、 $-OCH_2X^{81}$ 、 $-OCHX^{81}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{81}_3$ 、 $-OCHX^{81}_2$ 、 R^{82} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{82} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{82} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{82} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{82} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{82} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{81} 为卤素。在实施方案中, X^{81} 为F。

[0397] R^{82} 独立地为氧代、卤素、 $-CX^{82}_3$ 、 $-CHX^{82}_2$ 、 $-OCH_2X^{82}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{82}_3$ 、 $-OCHX^{82}_2$ 、 R^{83} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{83} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{83} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{83} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{83} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{83} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{82} 为卤素。在实施方案中, X^{82} 为F。

[0398] 在实施方案中, R^{19} 独立地为氢、氧代、卤素、 $-CX^{19}_3$ 、 $-CHX^{19}_2$ 、 $-OCH_2X^{19}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{19}_3$ 、 $-OCHX^{19}_2$ 、 R^{84} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{84} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{84} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{84} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{84} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{84} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{19} 为卤素。在实施方案中, X^{19} 为F。

[0399] R^{84} 独立地为氧代、卤素、 $-CX^{84}_3$ 、 $-CHX^{84}_2$ 、 $-OCH_2X^{84}$ 、 $-OCHX^{84}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{84}_3$ 、 $-OCHX^{84}_2$ 、 R^{85} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{85} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{85} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{85} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{85} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{85} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{84} 为卤素。在实施方案中, X^{84} 为F。

[0400] R^{85} 独立地为氧代、卤素、 $-CX^{85}_3$ 、 $-CHX^{85}_2$ 、 $-OCH_2X^{85}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{85}_3$ 、 $-OCHX^{85}_2$ 、 R^{86} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{86} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{86} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{86} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{86} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{86} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{85} 为卤素。在实施方案中, X^{85} 为F。

[0401] 在实施方案中, R^{16A} 独立地为氢、氧代、卤素、 $-CX^{16A}_3$ 、 $-CHX^{16A}_2$ 、 $-OCH_2X^{16A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{16A}_3$ 、 $-OCHX^{16A}_2$ 、 R^{75A} -取代的或未取代

的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{75A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{75A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{75A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{75A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{75A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X^{16A}为卤素。在实施方案中, X^{16A}为F。

[0402] R^{75A} 独立地为氧代、卤素、 $-CX^{75A}_3$ 、 $-CHX^{75A}_2$ 、 $-OCH_2X^{75A}$ 、 $-OCHX^{75A}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{75A}_3$ 、 $-OCHX^{75A}_2$ 、 R^{76A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{76A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{76A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{76A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{76A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{76A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X^{75A}为卤素。在实施方案中, X^{75A}为F。

[0403] R^{76A} 独立地为氧代、卤素、 $-CX^{76A}_3$ 、 $-CHX^{76A}_2$ 、 $-OCH_2X^{76A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{76A}_3$ 、 $-OCHX^{76A}_2$ 、 R^{77A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{77A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{77A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{77A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{77A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{77A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X^{76A}为卤素。在实施方案中, X^{76A}为F。

[0404] 在实施方案中, R^{17A} 独立地为氢、氧代、卤素、 $-CX^{17A}_3$ 、 $-CHX^{17A}_2$ 、 $-OCH_2X^{17A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{17A}_3$ 、 $-OCHX^{17A}_2$ 、 R^{78A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{78A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{78A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{78A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{78A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{78A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X^{17A}为卤素。在实施方案中, X^{17A}为F。

[0405] R^{78A} 独立地为氧代、卤素、 $-CX^{78A}_3$ 、 $-CHX^{78A}_2$ 、 $-OCH_2X^{78A}$ 、 $-OCHX^{78A}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{78A}_3$ 、 $-OCHX^{78A}_2$ 、 R^{79A} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{79A} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{79A} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{79A} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{79A} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{79A} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。X^{78A}为卤素。在实施方案中, X^{78A}为F。

[0406] R^{79A} 独立地为氧代、卤素、 $-CX^{79A}_3$ 、 $-CHX^{79A}_2$ 、 $-OCH_2X^{79A}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、

NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{79A}₃、-OCHX^{79A}₂、R^{80A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{80A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{80A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{80A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{80A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{80A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{79A}为卤素。在实施方案中, X^{79A}为F。

[0407] 在实施方案中, R^{18A}独立地为氢、氧代、卤素、-CX^{18A}₃、-CHX^{18A}₂、-OCH₂X^{18A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{18A}₃、-OCHX^{18A}₂、R^{81A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{81A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{81A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{81A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{81A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{81A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{18A}为卤素。在实施方案中, X^{18A}为F。

[0408] R^{81A}独立地为氧代、卤素、-CX^{81A}₃、-CHX^{81A}₂、-OCH₂X^{81A}、-OCHX^{81A}₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{81A}₃、-OCHX^{81A}₂、R^{82A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{82A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{82A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{82A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{82A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{82A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{81A}为卤素。在实施方案中, X^{81A}为F。

[0409] R^{82A}独立地为氧代、卤素、-CX^{82A}₃、-CHX^{82A}₂、-OCH₂X^{82A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{82A}₃、-OCHX^{82A}₂、R^{83A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{83A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{83A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{83A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{83A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{83A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{82A}为卤素。在实施方案中, X^{82A}为F。

[0410] 在实施方案中, R^{19A}独立地为氢、氧代、卤素、-CX^{19A}₃、-CHX^{19A}₂、-OCH₂X^{19A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{19A}₃、-OCHX^{19A}₂、R^{84A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{84A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{84A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{84A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{84A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{84A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{19A}为卤素。在实施方案中, X^{19A}为F。

[0411] R^{84A}独立地为氧代、卤素、-CX^{84A}₃、-CHX^{84A}₂、-OCH₂X^{84A}、-OCHX^{84A}₂、-CN、-OH、-NH₂、-

COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{84A}₃、-OCHX^{84A}₂、R^{85A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{85A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{85A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{85A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{85A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{85A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{84A}为卤素。在实施方案中, X^{84A}为F。

[0412] R^{85A}独立地为氧代、卤素、-CX^{85A}₃、-CHX^{85A}₂、-OCH₂X^{85A}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{85A}₃、-OCHX^{85A}₂、R^{86A}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{86A}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{86A}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{86A}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{86A}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{86A}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{85A}为卤素。在实施方案中, X^{85A}为F。

[0413] 在实施方案中, R^{16B}独立地为氢、氧代、卤素、-CX^{16B}₃、-CHX^{16B}₂、-OCH₂X^{16B}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{16B}₃、-OCHX^{16B}₂、R^{75B}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{75B}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{75B}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{75B}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{75B}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{75B}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{16B}为卤素。在实施方案中, X^{16B}为F。

[0414] R^{75B}独立地为氧代、卤素、-CX^{75B}₃、-CHX^{75B}₂、-OCH₂X^{75B}、-OCHX^{75B}₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{75B}₃、-OCHX^{75B}₂、R^{76B}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{76B}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{76B}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{76B}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{76B}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{76B}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{75B}为卤素。在实施方案中, X^{75B}为F。

[0415] R^{76B}独立地为氧代、卤素、-CX^{76B}₃、-CHX^{76B}₂、-OCH₂X^{76B}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{76B}₃、-OCHX^{76B}₂、R^{77B}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{77B}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{77B}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{77B}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{77B}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{77B}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{76B}为卤素。在实施方案中, X^{76B}为F。

[0416] 在实施方案中, R^{17B} 独立地为氢、氧代、卤素、 $-CX^{17B}_3$ 、 $-CHX^{17B}_2$ 、 $-OCH_2X^{17B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{17B}_3$ 、 $-OCHX^{17B}_2$ 、 R^{78B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{78B} -取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、 R^{78B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{78B} -取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、 R^{78B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{78B} -取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。 X^{17B} 为卤素。在实施方案中, X^{17B} 为F。

[0417] R^{78B} 独立地为氧代、卤素、 $-CX^{78B}_3$ 、 $-CHX^{78B}_2$ 、 $-OCH_2X^{78B}$ 、 $-OCHX^{78B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{78B}_3$ 、 $-OCHX^{78B}_2$ 、 R^{79B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{79B} -取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、 R^{79B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{79B} -取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、 R^{79B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{79B} -取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。 X^{78B} 为卤素。在实施方案中, X^{78B} 为F。

[0418] R^{79B} 独立地为氧代、卤素、 $-CX^{79B}_3$ 、 $-CHX^{79B}_2$ 、 $-OCH_2X^{79B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{79B}_3$ 、 $-OCHX^{79B}_2$ 、 R^{80B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{80B} -取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、 R^{80B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{80B} -取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、 R^{80B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{80B} -取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。 X^{79B} 为卤素。在实施方案中, X^{79B} 为F。

[0419] 在实施方案中, R^{18B} 独立地为氢、氧代、卤素、 $-CX^{18B}_3$ 、 $-CHX^{18B}_2$ 、 $-OCH_2X^{18B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{18B}_3$ 、 $-OCHX^{18B}_2$ 、 R^{81B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{81B} -取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、 R^{81B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{81B} -取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、 R^{81B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{81B} -取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。 X^{18B} 为卤素。在实施方案中, X^{18B} 为F。

[0420] R^{81B} 独立地为氧代、卤素、 $-CX^{81B}_3$ 、 $-CHX^{81B}_2$ 、 $-OCH_2X^{81B}$ 、 $-OCHX^{81B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{81B}_3$ 、 $-OCHX^{81B}_2$ 、 R^{82B} -取代的或未取代的烷基 (例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{82B} -取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、 R^{82B} -取代的或未取代的环烷基 (例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{82B} -取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、 R^{82B} -取代的或未取代的芳基 (例如, C_6-C_{10} 、 C_{10} 或苯基) 或 R^{82B} -取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。 X^{81B} 为卤素。在实施方案

中, X^{81B} 为 F。

[0421] R^{82B} 独立地为氧代、卤素、 $-CX^{82B}_3$ 、 $-CHX^{82B}_2$ 、 $-OCH_2X^{82B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{82B}_3$ 、 $-OCHX^{82B}_2$ 、 R^{83B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{83B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{83B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{83B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{83B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{83B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{82B} 为卤素。在实施方案中, X^{82B} 为F。

[0422] 在实施方案中, R^{19B} 独立地为氢、氧代、卤素、 $-CX^{19B}_3$ 、 $-CHX^{19B}_2$ 、 $-OCH_2X^{19B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{19B}_3$ 、 $-OCHX^{19B}_2$ 、 R^{84B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{84B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{84B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{84B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{84B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{84B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{19B} 为卤素。在实施方案中, X^{19B} 为F。

[0423] R^{84B} 独立地为氧代、卤素、 $-CX^{84B}_3$ 、 $-CHX^{84B}_2$ 、 $-OCH_2X^{84B}$ 、 $-OCHX^{84B}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{84B}_3$ 、 $-OCHX^{84B}_2$ 、 R^{85B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{85B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{85B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{85B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{85B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{85B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{84B} 为卤素。在实施方案中, X^{84B} 为F。

[0424] R^{85B} 独立地为氧代、卤素、 $-CX^{85B}_3$ 、 $-CHX^{85B}_2$ 、 $-OCH_2X^{85B}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{85B}_3$ 、 $-OCHX^{85B}_2$ 、 R^{86B} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{86B} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{86B} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{86B} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{86B} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{86B} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{85B} 为卤素。在实施方案中, X^{85B} 为F。

[0425] 在实施方案中, R^{16C} 独立地为氢、氧代、卤素、 $-CX^{16C}_3$ 、 $-CHX^{16C}_2$ 、 $-OCH_2X^{16C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{16C}_3$ 、 $-OCHX^{16C}_2$ 、 R^{75C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{75C} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{75C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{75C} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{75C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)

或 R^{75C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{16C} 为卤素。在实施方案中, X^{16C} 为F。

[0426] R^{75C} 独立地为氧代、卤素、 $-CX^{75C}_3$ 、 $-CHX^{75C}_2$ 、 $-OCH_2X^{75C}$ 、 $-OCHX^{75C}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{75C}_3$ 、 $-OCHX^{75C}_2$ 、 R^{76C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{76C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{76C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{76C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{76C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{76C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{75C} 为卤素。在实施方案中, X^{75C} 为F。

[0427] R^{76C} 独立地为氧代、卤素、 $-CX^{76C}_3$ 、 $-CHX^{76C}_2$ 、 $-OCH_2X^{76C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{76C}_3$ 、 $-OCHX^{76C}_2$ 、 R^{77C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{77C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{77C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{77C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{77C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{77C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{76C} 为卤素。在实施方案中, X^{76C} 为F。

[0428] 在实施方案中, R^{17C} 独立地为氢、氧代、卤素、 $-CX^{17C}_3$ 、 $-CHX^{17C}_2$ 、 $-OCH_2X^{17C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{17C}_3$ 、 $-OCHX^{17C}_2$ 、 R^{78C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{78C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{78C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{78C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{78C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{78C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{17C} 为卤素。在实施方案中, X^{17C} 为F。

[0429] R^{78C} 独立地为氧代、卤素、 $-CX^{78C}_3$ 、 $-CHX^{78C}_2$ 、 $-OCH_2X^{78C}$ 、 $-OCHX^{78C}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{78C}_3$ 、 $-OCHX^{78C}_2$ 、 R^{79C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{79C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{79C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{79C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{79C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{79C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{78C} 为卤素。在实施方案中, X^{78C} 为F。

[0430] R^{79C} 独立地为氧代、卤素、 $-CX^{79C}_3$ 、 $-CHX^{79C}_2$ 、 $-OCH_2X^{79C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{79C}_3$ 、 $-OCHX^{79C}_2$ 、 R^{80C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{80C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{80C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{80C} -取代的或未取代的杂环烷

基(例如,3-8元、3-6元或5-6元)、 R^{80C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{80C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{79C} 为卤素。在实施方案中, X^{79C} 为F。

[0431] 在实施方案中, R^{18C} 独立地为氢、氧代、卤素、 $-CX^{18C}_3$ 、 $-CHX^{18C}_2$ 、 $-OCH_2X^{18C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{18C}_3$ 、 $-OCHX^{18C}_2$ 、 R^{81C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{81C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{81C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{81C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{81C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{81C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{18C} 为卤素。在实施方案中, X^{18C} 为F。

[0432] R^{81C} 独立地为氧代、卤素、 $-CX^{81C}_3$ 、 $-CHX^{81C}_2$ 、 $-OCH_2X^{81C}$ 、 $-OCHX^{81C}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{81C}_3$ 、 $-OCHX^{81C}_2$ 、 R^{82C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{82C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{82C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{82C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{82C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{82C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{81C} 为卤素。在实施方案中, X^{81C} 为F。

[0433] R^{82C} 独立地为氧代、卤素、 $-CX^{82C}_3$ 、 $-CHX^{82C}_2$ 、 $-OCH_2X^{82C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{82C}_3$ 、 $-OCHX^{82C}_2$ 、 R^{83C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{83C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{83C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{83C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{83C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{83C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{82C} 为卤素。在实施方案中, X^{82C} 为F。

[0434] 在实施方案中, R^{19C} 独立地为氢、氧代、卤素、 $-CX^{19C}_3$ 、 $-CHX^{19C}_2$ 、 $-OCH_2X^{19C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{19C}_3$ 、 $-OCHX^{19C}_2$ 、 R^{84C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{84C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{84C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{84C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{84C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{84C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{19C} 为卤素。在实施方案中, X^{19C} 为F。

[0435] R^{84C} 独立地为氧代、卤素、 $-CX^{84C}_3$ 、 $-CHX^{84C}_2$ 、 $-OCH_2X^{84C}$ 、 $-OCHX^{84C}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC=$ (O) $NHNH_2$ 、 $-NHC=$ (O) NH_2 、 $-NHSO_2H$ 、 $-NHC=$ (O) H 、 $-NHC$ (O) $-OH$ 、 $-NHOH$ 、 $-OCX^{84C}_3$ 、 $-OCHX^{84C}_2$ 、 R^{85C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{85C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4

元)、 R^{85C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{85C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{85C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{85C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{84C} 为卤素。在实施方案中, X^{84C} 为F。

[0436] R^{85C} 独立地为氧代、卤素、 $-CX^{85C}_3$ 、 $-CHX^{85C}_2$ 、 $-OCH_2X^{85C}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{85C}_3$ 、 $-OCHX^{85C}_2$ 、 R^{86C} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{86C} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{86C} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{86C} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{86C} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{86C} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{85C} 为卤素。在实施方案中, X^{85C} 为F。

[0437] 在实施方案中, R^{16D} 独立地为氢、氧代、卤素、 $-CX^{16D}_3$ 、 $-CHX^{16D}_2$ 、 $-OCH_2X^{16D}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{16D}_3$ 、 $-OCHX^{16D}_2$ 、 R^{75D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{75D} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{75D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{75D} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{75D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{75D} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{16D} 为卤素。在实施方案中, X^{16D} 为F。

[0438] R^{75D} 独立地为氧代、卤素、 $-CX^{75D}_3$ 、 $-CHX^{75D}_2$ 、 $-OCH_2X^{75D}$ 、 $-OCHX^{75D}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{75D}_3$ 、 $-OCHX^{75D}_2$ 、 R^{76D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{76D} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{76D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{76D} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{76D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{76D} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{75D} 为卤素。在实施方案中, X^{75D} 为F。

[0439] R^{76D} 独立地为氧代、卤素、 $-CX^{76D}_3$ 、 $-CHX^{76D}_2$ 、 $-OCH_2X^{76D}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{76D}_3$ 、 $-OCHX^{76D}_2$ 、 R^{77D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{77D} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{77D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{77D} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{77D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{77D} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{76D} 为卤素。在实施方案中, X^{76D} 为F。

[0440] 在实施方案中, R^{17D} 独立地为氢、氧代、卤素、 $-CX^{17D}_3$ 、 $-CHX^{17D}_2$ 、 $-OCH_2X^{17D}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{17D}_3$ 、 $-OCHX^{17D}_2$ 、 R^{78D} -取代的或未取代

的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{78D} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{78D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{78D} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{78D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{78D} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{17D} 为卤素。在实施方案中, X^{17D} 为F。

[0441] R^{78D} 独立地为氧代、卤素、 $-CX^{78D}_3$ 、 $-CHX^{78D}_2$ 、 $-OCH_2X^{78D}$ 、 $-OCHX^{78D}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{78D}_3$ 、 $-OCHX^{78D}_2$ 、 R^{79D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{79D} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{79D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{79D} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{79D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{79D} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{78D} 为卤素。在实施方案中, X^{78D} 为F。

[0442] R^{79D} 独立地为氧代、卤素、 $-CX^{79D}_3$ 、 $-CHX^{79D}_2$ 、 $-OCH_2X^{79D}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{79D}_3$ 、 $-OCHX^{79D}_2$ 、 R^{80D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{80D} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{80D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{80D} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{80D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{80D} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{79D} 为卤素。在实施方案中, X^{79D} 为F。

[0443] 在实施方案中, R^{18D} 独立地为氢、氧代、卤素、 $-CX^{18D}_3$ 、 $-CHX^{18D}_2$ 、 $-OCH_2X^{18D}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{18D}_3$ 、 $-OCHX^{18D}_2$ 、 R^{81D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{81D} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{81D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{81D} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{81D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{81D} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{18D} 为卤素。在实施方案中, X^{18D} 为F。

[0444] R^{81D} 独立地为氧代、卤素、 $-CX^{81D}_3$ 、 $-CHX^{81D}_2$ 、 $-OCH_2X^{81D}$ 、 $-OCHX^{81D}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O) - OH$ 、 $-NHOH$ 、 $-OCX^{81D}_3$ 、 $-OCHX^{81D}_2$ 、 R^{82D} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{82D} -取代的或未取代的杂烷基(例如, 2-8元、2-6元或2-4元)、 R^{82D} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{82D} -取代的或未取代的杂环烷基(例如, 3-8元、3-6元或5-6元)、 R^{82D} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{82D} -取代的或未取代的杂芳基(例如, 5-10元、5-9元或5-6元)。 X^{81D} 为卤素。在实施方案中, X^{81D} 为F。

[0445] R^{82D} 独立地为氧代、卤素、 $-CX^{82D}_3$ 、 $-CHX^{82D}_2$ 、 $-OCH_2X^{82D}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、

NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{82D}₃、-OCHX^{82D}₂、R^{83D}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{83D}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{83D}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{83D}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{83D}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{83D}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{82D}为卤素。在实施方案中, X^{82D}为F。

[0446] 在实施方案中, R^{19D}独立地为氢、氧代、卤素、-CX^{19D}₃、-CHX^{19D}₂、-OCH₂X^{19D}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{19D}₃、-OCHX^{19D}₂、R^{84D}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{84D}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{84D}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{84D}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{84D}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{84D}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{19D}为卤素。在实施方案中, X^{19D}为F。

[0447] R^{84D}独立地为氧代、卤素、-CX^{84D}₃、-CHX^{84D}₂、-OCH₂X^{84D}、-OCHX^{84D}₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{84D}₃、-OCHX^{84D}₂、R^{85D}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{85D}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{85D}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{85D}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{85D}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{85D}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{84D}为卤素。在实施方案中, X^{84D}为F。

[0448] R^{85D}独立地为氧代、卤素、-CX^{85D}₃、-CHX^{85D}₂、-OCH₂X^{85D}、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX^{85D}₃、-OCHX^{85D}₂、R^{86D}-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R^{86D}-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R^{86D}-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R^{86D}-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R^{86D}-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R^{86D}-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X^{85D}为卤素。在实施方案中, X^{85D}为F。

[0449] 在实施方案中, R²⁰独立地为氢、氧代、卤素、-CX²⁰₃、-CHX²⁰₂、-OCH₂X²⁰、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX²⁰₃、-OCHX²⁰₂、R⁸⁷-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁸⁷-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁸⁷-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁸⁷-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁸⁷-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁸⁷-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X²⁰为卤素。在实施方案中, X²⁰为F。

[0450] R⁸⁷独立地为氧代、卤素、-CX⁸⁷₃、-CHX⁸⁷₂、-OCH₂X⁸⁷、-OCHX⁸⁷₂、-CN、-OH、-NH₂、-COOH、-

CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁸⁷₃、-OCHX⁸⁷₂、R⁸⁸-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁸⁸-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁸⁸-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁸⁸-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁸⁸-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁸⁸-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁸⁷为卤素。在实施方案中, X⁸⁷为F。

[0451] R⁸⁸独立地为氧代、卤素、-CX⁸⁸₃、-CHX⁸⁸₂、-OCH₂X⁸⁸、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁸⁸₃、-OCHX⁸⁸₂、R⁸⁹-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁸⁹-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁸⁹-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁸⁹-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁸⁹-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁸⁹-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁸⁸为卤素。在实施方案中, X⁸⁸为F。

[0452] 在实施方案中, R²¹独立地为氢、氧代、卤素、-CX²¹₃、-CHX²¹₂、-OCH₂X²¹、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX²¹₃、-OCHX²¹₂、R⁹⁰-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁹⁰-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁹⁰-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁹⁰-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁹⁰-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁹⁰-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X²¹为卤素。在实施方案中, X²¹为F。

[0453] R⁹⁰独立地为氧代、卤素、-CX⁹⁰₃、-CHX⁹⁰₂、-OCH₂X⁹⁰、-OCHX⁹⁰₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁹⁰₃、-OCHX⁹⁰₂、R⁹¹-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁹¹-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁹¹-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁹¹-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁹¹-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁹¹-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁹⁰为卤素。在实施方案中, X⁹⁰为F。

[0454] R⁹¹独立地为氧代、卤素、-CX⁹¹₃、-CHX⁹¹₂、-OCH₂X⁹¹、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX⁹¹₃、-OCHX⁹¹₂、R⁹²-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁹²-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4元)、R⁹²-取代的或未取代的环烷基 (例如, C₃-C₈、C₃-C₆或C₅-C₆)、R⁹²-取代的或未取代的杂环烷基 (例如, 3-8元、3-6元或5-6元)、R⁹²-取代的或未取代的芳基 (例如, C₆-C₁₀、C₁₀或苯基) 或R⁹²-取代的或未取代的杂芳基 (例如, 5-10元、5-9元或5-6元)。X⁹¹为卤素。在实施方案中, X⁹¹为F。

[0455] 在实施方案中, R²²独立地为氢、氧代、卤素、-CX²²₃、-CHX²²₂、-OCH₂X²²、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC = (O) NHNH₂、-NHC = (O) NH₂、-NHSO₂H、-NHC = (O) H、-NHC (O) -OH、-NHOH、-OCX²²₃、-OCHX²²₂、R⁹³-取代的或未取代的烷基 (例如, C₁-C₈、C₁-C₆或C₁-C₄)、R⁹³-取代的或未取代的杂烷基 (例如, 2-8元、2-6元或2-4

元)、 R^{93} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{93} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{93} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{93} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{22} 为卤素。在实施方案中, X^{22} 为F。

[0456] R^{93} 独立地为氧代、卤素、 $-CX^{93}_3$ 、 $-CHX^{93}_2$ 、 $-OCH_2X^{93}$ 、 $-OCHX^{93}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{93}_3$ 、 $-OCHX^{93}_2$ 、 R^{94} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{94} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{94} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{94} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{94} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{94} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{93} 为卤素。在实施方案中, X^{93} 为F。

[0457] R^{94} 独立地为氧代、卤素、 $-CX^{94}_3$ 、 $-CHX^{94}_2$ 、 $-OCH_2X^{94}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{94}_3$ 、 $-OCHX^{94}_2$ 、 R^{95} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{95} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{95} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{95} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{95} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{95} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{94} 为卤素。在实施方案中, X^{94} 为F。

[0458] 在实施方案中, R^{23} 独立地为氢、氧代、卤素、 $-CX^{23}_3$ 、 $-CHX^{23}_2$ 、 $-OCH_2X^{23}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{23}_3$ 、 $-OCHX^{23}_2$ 、 R^{96} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{96} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{96} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{96} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{96} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{96} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{23} 为卤素。在实施方案中, X^{23} 为F。

[0459] R^{96} 独立地为氧代、卤素、 $-CX^{96}_3$ 、 $-CHX^{96}_2$ 、 $-OCH_2X^{96}$ 、 $-OCHX^{96}_2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{96}_3$ 、 $-OCHX^{96}_2$ 、 R^{97} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{97} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{97} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{97} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{97} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{97} -取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。 X^{96} 为卤素。在实施方案中, X^{96} 为F。

[0460] R^{97} 独立地为氧代、卤素、 $-CX^{97}_3$ 、 $-CHX^{97}_2$ 、 $-OCH_2X^{97}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC = (O)NHNH_2$ 、 $-NHC = (O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC = (O)H$ 、 $-NHC(O)-OH$ 、 $-NHOH$ 、 $-OCX^{97}_3$ 、 $-OCHX^{97}_2$ 、 R^{98} -取代的或未取代的烷基(例如, C_1-C_8 、 C_1-C_6 或 C_1-C_4)、 R^{98} -取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、 R^{98} -取代的或未取代的环烷基(例如, C_3-C_8 、 C_3-C_6 或 C_5-C_6)、 R^{98} -取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、 R^{98} -取代的或未取代的芳基(例如, C_6-C_{10} 、 C_{10} 或苯基)或 R^{98} -取代的或未取代

的杂芳基(例如,5-10元、5-9元或5-6元)。X⁹⁷为卤素。在实施方案中,X⁹⁷为F。

[0461] 在实施方案中,R²⁴独立地为氢、氧代、卤素、-CX²⁴₃、-CHX²⁴₂、-OCH₂X²⁴、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC=(O)NHNH₂、-NHC=(O)NH₂、-NHSO₂H、-NHC=(O)H、-NHC(O)-OH、-NHOH、-OCX²⁴₃、-OCHX²⁴₂、R⁹⁹-取代的或未取代的烷基(例如,C₁-C₈、C₁-C₆或C₁-C₄)、R⁹⁹-取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、R⁹⁹-取代的或未取代的环烷基(例如,C₃-C₈、C₃-C₆或C₅-C₆)、R⁹⁹-取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、R⁹⁹-取代的或未取代的芳基(例如,C₆-C₁₀、C₁₀或苯基)或R⁹⁹-取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。X²⁴为卤素。在实施方案中,X²⁴为F。

[0462] R⁹⁹独立地为氧代、卤素、-CX⁹⁹₃、-CHX⁹⁹₂、-OCH₂X⁹⁹、-OCHX⁹⁹₂、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC=(O)NHNH₂、-NHC=(O)NH₂、-NHSO₂H、-NHC=(O)H、-NHC(O)-OH、-NHOH、-OCX⁹⁹₃、-OCHX⁹⁹₂、R¹⁰⁰-取代的或未取代的烷基(例如,C₁-C₈、C₁-C₆或C₁-C₄)、R¹⁰⁰-取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、R¹⁰⁰-取代的或未取代的环烷基(例如,C₃-C₈、C₃-C₆或C₅-C₆)、R¹⁰⁰-取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、R¹⁰⁰-取代的或未取代的芳基(例如,C₆-C₁₀、C₁₀或苯基)或R¹⁰⁰-取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。X⁹⁹为卤素。在实施方案中,X⁹⁹为F。

[0463] R¹⁰⁰独立地为氧代、卤素、-CX¹⁰⁰₃、-CHX¹⁰⁰₂、-OCH₂X¹⁰⁰、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC=(O)NHNH₂、-NHC=(O)NH₂、-NHSO₂H、-NHC=(O)H、-NHC(O)-OH、-NHOH、-OCX¹⁰⁰₃、-OCHX¹⁰⁰₂、R¹⁰¹-取代的或未取代的烷基(例如,C₁-C₈、C₁-C₆或C₁-C₄)、R¹⁰¹-取代的或未取代的杂烷基(例如,2-8元、2-6元或2-4元)、R¹⁰¹-取代的或未取代的环烷基(例如,C₃-C₈、C₃-C₆或C₅-C₆)、R¹⁰¹-取代的或未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、R¹⁰¹-取代的或未取代的芳基(例如,C₆-C₁₀、C₁₀或苯基)或R¹⁰¹-取代的或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。X¹⁰⁰为卤素。在实施方案中,X¹⁰⁰为F。

[0464] R³²、R³⁵、R³⁸、R⁴¹、R⁴⁴、R⁴⁷、R⁵⁰、R⁵³、R⁵⁶、R⁵⁹、R^{50A}、R^{53A}、R^{56A}、R^{59A}、R^{50B}、R^{53B}、R^{56B}、R^{59B}、R⁶²、R⁶⁵、R⁶⁸、R⁷¹、R⁷⁴、R⁷⁷、R⁸⁰、R⁸³、R⁸⁶、R^{77A}、R^{80A}、R^{83A}、R^{86A}、R^{77B}、R^{80B}、R^{83B}、R^{86B}、R^{77C}、R^{80C}、R^{83C}、R^{86C}、R^{77D}、R^{80D}、R^{83D}、R^{86D}、R⁸⁹、R⁹²、R⁹⁵、R⁹⁸和R¹⁰¹独立地为氢、氧代、卤素、-CF₃、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC=(O)NHNH₂、-NHC=(O)NH₂、-NHSO₂H、-NHC=(O)H、-NHC(O)-OH、-NHOH、-OCF₃、-OCHF₂、未取代的烷基(例如,C₁-C₈、C₁-C₆或C₁-C₄)、未取代的杂烷基(例如,2-8元、2-6元或2-4元)、未取代的环烷基(例如,C₃-C₈、C₃-C₆或C₅-C₆)、未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、未取代的芳基(例如,C₆-C₁₀、C₁₀或苯基)或未取代的杂芳基(例如,5-10元、5-9元或5-6元)。R³²、R³⁵、R³⁸、R⁴¹、R⁴⁴、R⁴⁷、R⁵⁰、R⁵³、R⁵⁶、R⁵⁹、R^{50A}、R^{53A}、R^{56A}、R^{59A}、R^{50B}、R^{53B}、R^{56B}、R^{59B}、R⁶²、R⁶⁵、R⁶⁸、R⁷¹、R⁷⁴、R⁷⁷、R⁸⁰、R⁸³、R⁸⁶、R^{77A}、R^{80A}、R^{83A}、R^{86A}、R^{77B}、R^{80B}、R^{83B}、R^{86B}、R^{77C}、R^{80C}、R^{83C}、R^{86C}、R^{77D}、R^{80D}、R^{83D}、R^{86D}、R⁸⁹、R⁹²、R⁹⁵、R⁹⁸和R¹⁰¹独立地为氧代、卤素、-CF₃、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC=(O)NHNH₂、-NHC=(O)NH₂、-NHSO₂H、-NHC=(O)H、-NHC(O)-OH、-NHOH、-OCF₃、-OCHF₂、未取代的烷基(例如,C₁-C₈、C₁-C₆或C₁-C₄)、未取代的杂烷基(例如,2-8元、2-6元或2-4元)、未取代的环烷基(例如,C₃-C₈、C₃-C₆或C₅-C₆)、未取代的杂环烷基(例如,3-8元、3-6元或5-6元)、未取代的芳基(例如,C₆-C₁₀、C₁₀或苯基)或未取代的杂芳基(例如,5-

10元、5-9元或5-6元)。

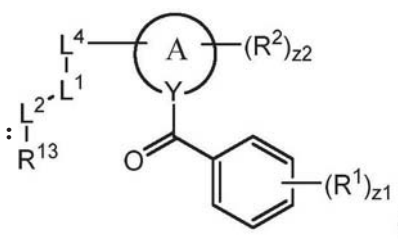
[0465] 在实施方案中,除非另有说明,否则本文描述的化合物是所有立体异构体的外消旋混合物。在实施方案中,除非另有说明,否则本文描述的化合物是所有对映异构体的外消旋混合物。在实施方案中,除非另有说明,否则本文描述的化合物是两种相反立体异构体的外消旋混合物。在实施方案中,除非另有说明,否则本文描述的化合物是两种相对映异构体的外消旋混合物。在实施方案中,除非另有说明,否则本文描述的化合物是单一立体异构体。在实施方案中,除非另有说明,否则本文描述的化合物是单一对映异构体。

[0466] 在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在营养缺乏条件下的增殖。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在营养缺乏条件下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在血清剥夺条件下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在血清剥夺条件下的增殖。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在模拟血清剥夺的条件(例如患者的局部细胞环境)下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在模拟血清剥夺的条件(例如患者的局部细胞环境)下的增殖。

[0467] 在一些实施方案中,化合物是本文(例如,在方面、实施方案、权利要求、图、表或实例中)描述的任一种化合物。

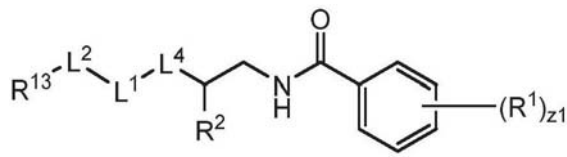
[0468] 在一些实施方案中,如本文所描述的化合物可包括 R^1 、 R^2 、 R^7 、 R^8 、 R^9 、 R^{10} 、 X 、 X^1 、 X^2 、 m_1 、 n_1 、 v_1 、 m_2 、 n_2 、 v_2 和/或其它变量的多种情况。在此类实施方案中,每个变量可任选地不同并且为了更加清楚起见可适当地标记以区分每个基团。例如,每个 R^1 、 R^2 、 R^7 、 R^8 、 R^9 、 R^{10} 、 X 、 X^1 、 X^2 、 m_1 、 n_1 、 v_1 、 m_2 、 n_2 和/或 v_2 不同时,可将其分别称为,例如 $R^{1.1}$ 、 $R^{1.2}$ 、 $R^{1.3}$ 、 $R^{1.4}$ 、 $R^{1.5}$ 、 $R^{1.6}$ 、 $R^{1.7}$ 、 $R^{2.1}$ 、 $R^{2.2}$ 、 $R^{2.3}$ 、 $R^{2.4}$ 、 $R^{2.5}$ 、 $R^{2.6}$ 、 $R^{2.7}$ 、 $R^{2.8}$ 、 $R^{2.9}$ 、 $R^{2.10}$ 、 $R^{7.1}$ 、 $R^{7.2}$ 、 $R^{7.3}$ 、 $R^{7.4}$ 、 $R^{7.5}$ 、 $R^{7.6}$ 、 $R^{7.7}$ 、 $R^{8.1}$ 、 $R^{8.2}$ 、 $R^{8.3}$ 、 $R^{8.4}$ 、 $R^{8.5}$ 、 $R^{8.6}$ 、 $R^{8.7}$ 、 $R^{9.1}$ 、 $R^{9.2}$ 、 $R^{9.3}$ 、 $R^{9.4}$ 、 $R^{9.5}$ 、 $R^{9.6}$ 、 $R^{9.7}$ 、 $R^{10.1}$ 、 $R^{10.2}$ 、 $R^{10.3}$ 、 $R^{10.4}$ 、 $R^{10.5}$ 、 $R^{10.6}$ 、 $R^{10.7}$ 、 X^1 、 X^2 、 X^3 、 X^4 、 X^5 、 X^6 、 X^7 、 $X^{1.1}$ 、 $X^{1.2}$ 、 $X^{1.3}$ 、 $X^{1.4}$ 、 $X^{1.5}$ 、 $X^{1.6}$ 、 $X^{2.1}$ 、 $X^{2.2}$ 、 $X^{2.3}$ 、 $X^{2.4}$ 、 $X^{2.5}$ 、 $X^{2.6}$ 、 $X^{2.7}$ 、 $X^{2.8}$ 、 $X^{2.9}$ 、 $X^{2.10}$ 、 m^1 、 m^2 、 m^3 、 m^4 、 m^5 、 m^6 、 m^7 、 n^1 、 n^2 、 n^3 、 n^4 、 n^5 、 n^6 、 n^7 、 v^1 、 v^2 、 v^3 、 v^4 、 v^5 、 v^6 、 v^7 、 m_1^1 、 m_1^2 、 m_1^3 、 m_1^4 、 m_1^5 、 m_1^6 、 n_1^1 、 n_1^2 、 n_1^3 、 n_1^4 、 n_1^5 、 n_1^6 、 v_1^1 、 v_1^2 、 v_1^3 、 v_1^4 、 v_1^5 、 v_1^6 ,其中由 $R^{1.1}$ 、 $R^{1.2}$ 、 $R^{1.3}$ 、 $R^{1.4}$ 、 $R^{1.5}$ 、 $R^{1.6}$ 、 $R^{1.7}$ 假定 R^1 的定义,由 $R^{2.1}$ 、 $R^{2.2}$ 、 $R^{2.3}$ 、 $R^{2.4}$ 、 $R^{2.5}$ 、 $R^{2.6}$ 、 $R^{2.7}$ 、 $R^{2.8}$ 、 $R^{2.9}$ 、 $R^{2.10}$ 假定 R^2 的定义,由 $R^{7.1}$ 、 $R^{7.2}$ 、 $R^{7.3}$ 、 $R^{7.4}$ 、 $R^{7.5}$ 、 $R^{7.6}$ 、 $R^{7.7}$ 假定 R^7 的定义,由 $R^{8.1}$ 、 $R^{8.2}$ 、 $R^{8.3}$ 、 $R^{8.4}$ 、 $R^{8.5}$ 、 $R^{8.6}$ 、 $R^{8.7}$ 假定 R^8 的定义,由 $R^{9.1}$ 、 $R^{9.2}$ 、 $R^{9.3}$ 、 $R^{9.4}$ 、 $R^{9.5}$ 、 $R^{9.6}$ 、 $R^{9.7}$ 假定 R^9 的定义,由 $R^{10.1}$ 、 $R^{10.2}$ 、 $R^{10.3}$ 、 $R^{10.4}$ 、 $R^{10.5}$ 、 $R^{10.6}$ 、 $R^{10.7}$ 假定 R^{10} 的定义,由 X^1 、 X^2 、 X^3 、 X^4 、 X^5 、 X^6 、 X^7 假定 X 的定义,由 $X^{1.1}$ 、 $X^{1.2}$ 、 $X^{1.3}$ 、 $X^{1.4}$ 、 $X^{1.5}$ 、 $X^{1.6}$ 假定 X^1 的定义,由 $X^{2.1}$ 、 $X^{2.2}$ 、 $X^{2.3}$ 、 $X^{2.4}$ 、 $X^{2.5}$ 、 $X^{2.6}$ 、 $X^{2.7}$ 、 $X^{2.8}$ 、 $X^{2.9}$ 、 $X^{2.10}$ 假定 X^2 的定义,由 m^1 、 m^2 、 m^3 、 m^4 、 m^5 、 m^6 、 m^7 假定 m 的定义,由 n^1 、 n^2 、 n^3 、 n^4 、 n^5 、 n^6 、 n^7 假定 n 的定义,由 v^1 、 v^2 、 v^3 、 v^4 、 v^5 、 v^6 、 v^7 假定 v 的定义,由 m_1^1 、 m_1^2 、 m_1^3 、 m_1^4 、 m_1^5 、 m_1^6 假定 m_1 的定义,由 n_1^1 、 n_1^2 、 n_1^3 、 n_1^4 、 n_1^5 、 n_1^6 假定 n_1 的定义,由 v_1^1 、 v_1^2 、 v_1^3 、 v_1^4 、 v_1^5 、 v_1^6 假定 v_1 的定义,由 m_2^1 、 m_2^2 、 m_2^3 、 m_2^4 、 m_2^5 、 m_2^6 、 m_2^7 、 m_2^8 、 m_2^9 、 m_2^{10} 假定 m_2 的定义,由 n_2^1 、 n_2^2 、 n_2^3 、 n_2^4 、 n_2^5 、 n_2^6 、 n_2^7 、 n_2^8 、 n_2^9 、 n_2^{10} 假定 n_2 的定义,由 v_2^1 、 v_2^2 、 v_2^3 、 v_2^4 、 v_2^5 、 v_2^6 、 v_2^7 、 v_2^8 、 v_2^9 、 v_2^{10} 假定 v_2 的定义。

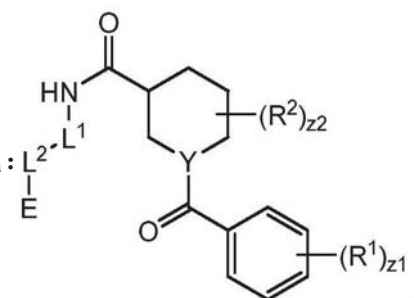
[0469] R^1 、 R^2 、 R^7 、 R^8 、 R^9 、 R^{10} 、 X 、 X^1 、 X^2 、 m_1 、 n_1 、 v_1 、 m_2 、 n_2 、 v_2 和/或其它变量的定义中所用的出现在多种情况下并且不同的变量,为了更加清楚起见可适当地标记以区分每个基团。

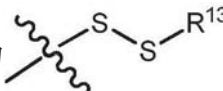
[0470] 一方面,提供了一种具有下式的化合物:  (IJ)。

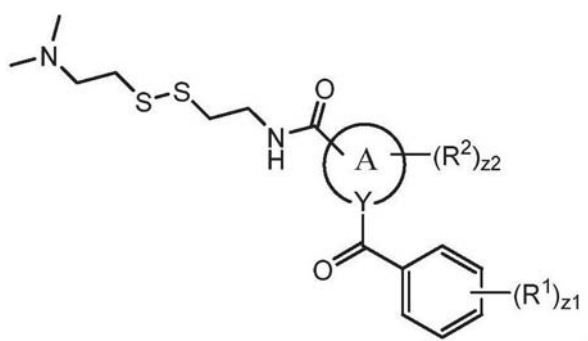
z_1 、 R^2 、 z_2 、 L^1 、 L^2 、 L^4 和 R^{13} 如本文所述。在实施方案中, R^{13} 为氢。在实施方案中, R^{13} 为未取代的甲基。在实施方案中,化合物为LB9。在实施方案中,化合物为DB9。

[0471] 一方面,提供了一种具有下式的化合物:

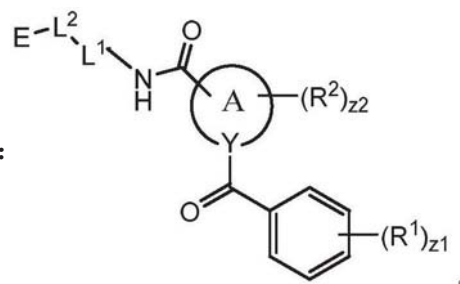
 R^1 、 R^2 、 L^1 、 L^2 、 L^4 、 R^{13} 和 z_1 如本文所述。在实施方案中, R^{13} 为氢。在实施方案中, R^{13} 为未取代的甲基。

[0472] 在实施方案中,化合物不具有下式:  Y 、 R^1 、 z_1 、 R^2 、 L^2 、 E

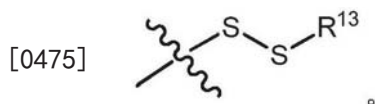
和 z_2 如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中, E 为 。

[0473] 在实施方案中,化合物不具有下式:  环

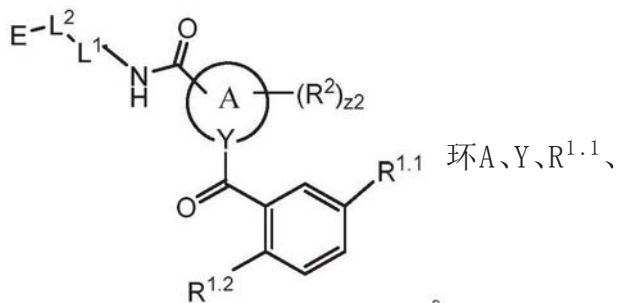
A 、 Y 、 R^1 、 z_1 、 R^2 和 z_2 如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中, R^1 为卤素。

[0474] 在实施方案中,化合物不具有下式:  环 A 、 Y 、 R^1 、

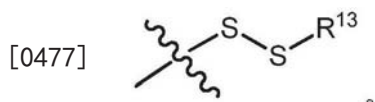
$z1$ 、 R^2 、 $z2$ 、 L^1 、 L^2 和E如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中, R^1 为卤素。在实施方案中,E为



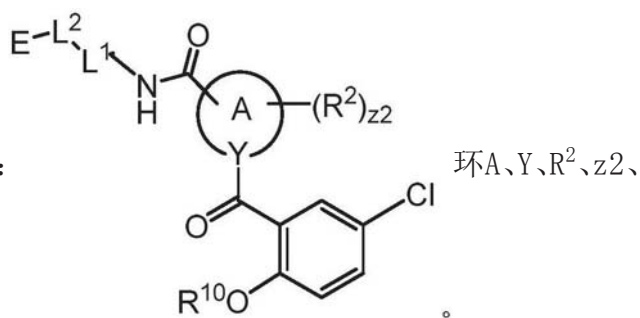
[0476] 在实施方案中,化合物不具有下式:



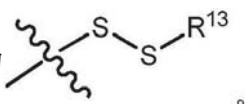
$R^{1.2}$ 、 R^2 、 $z2$ 、 L^1 、 L^2 和E如本文所述。在实施方案中, $R^{1.1}$ 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中, $R^{1.2}$ 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中, $R^{1.1}$ 为卤素。在实施方案中, $R^{1.2}$ 为卤素。在实施方案中,E为



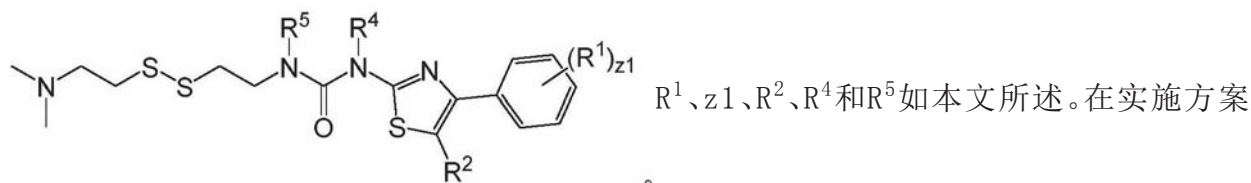
[0478] 在实施方案中,化合物不具有下式:



L^1 、 L^2 、E和 R^{10} 如本文所述。在实施方案中,E为

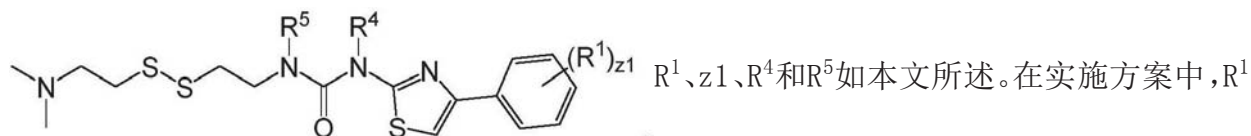


[0479] 在实施方案中,化合物不具有下式:



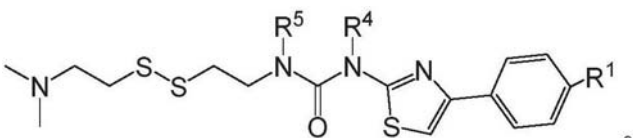
中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。

[0480] 在实施方案中,化合物不具有下式:



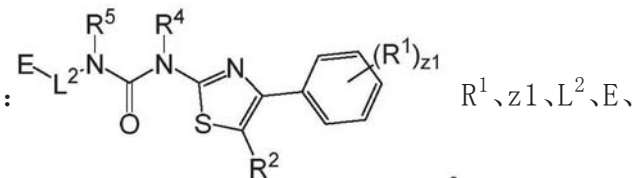
为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。

[0481] 在实施方案中,化合物不具有下式:



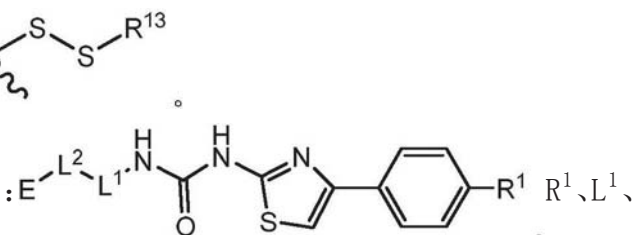
R^1 、 R^4 和 R^5 如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。

[0482] 在实施方案中,化合物不具有下式:



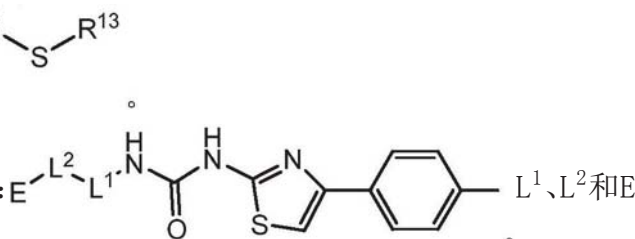
R^2 、 R^4 和 R^5 如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中,E为

[0483] 在实施方案中,化合物不具有下式:



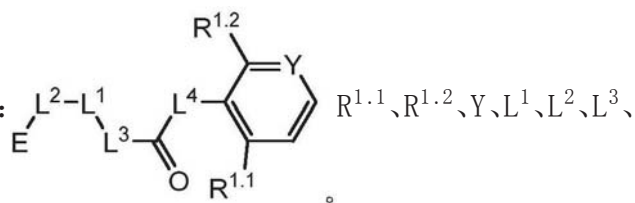
R^1 、 L^1 、 L^2 和E如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中,E为

[0484] 在实施方案中,化合物不具有下式:



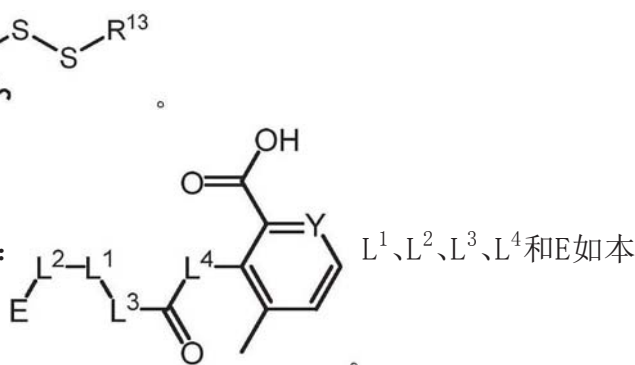
如本文所述。在实施方案中,E为

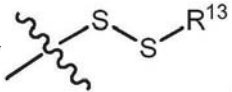
[0485] 在实施方案中,化合物不具有下式:

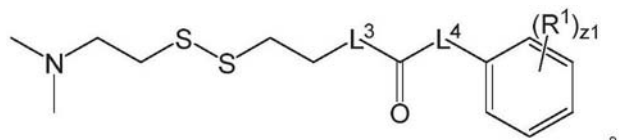


L^4 和E如本文所述。在实施方案中, $R^{1.1}$ 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中, $R^{1.2}$ 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。在实施方案中,E为

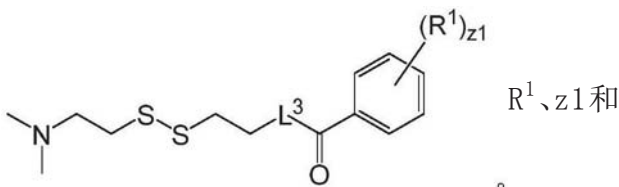
[0486] 在实施方案中,化合物不具有下式:

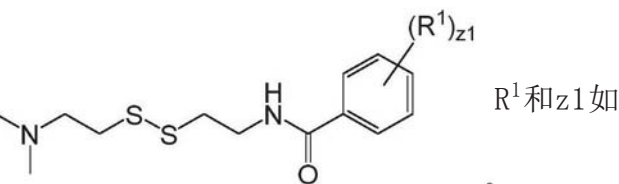


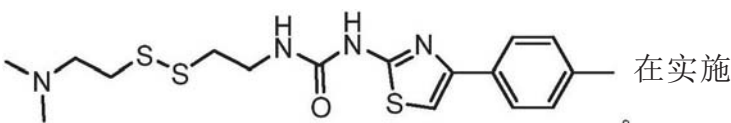
文所述。在实施方案中,E为 。

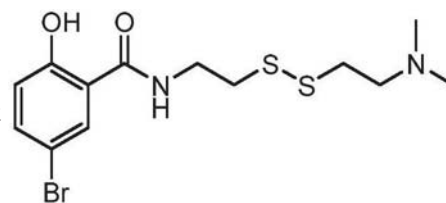
[0487] 在实施方案中,化合物不具有下式: 。

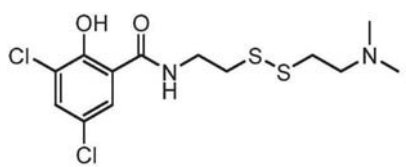
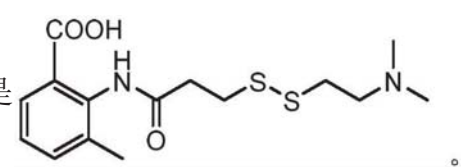
R^1 、 $z1$ 、 L^3 和 L^4 如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。

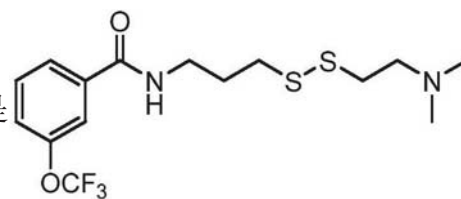
[0488] 在实施方案中,化合物不具有下式: 。 R^1 、 $z1$ 和 L^3 如本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。

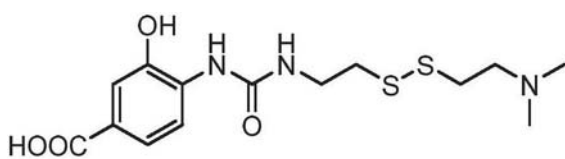
[0489] 在实施方案中,化合物不具有下式: 。 R^1 和 $z1$ 如 本文所述。在实施方案中, R^1 为卤素、-OH、-COOH、-OCF₃、C₁-C₄未取代的烷基或2-4元未取代的杂烷基。

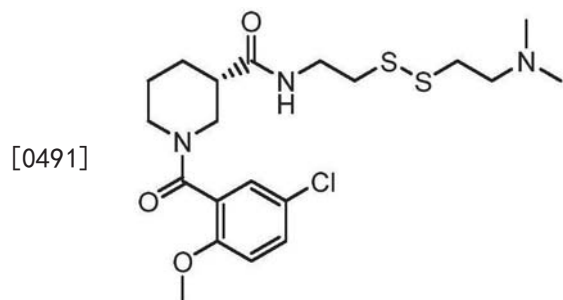
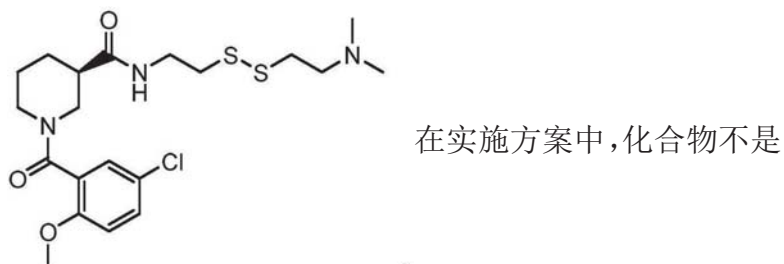
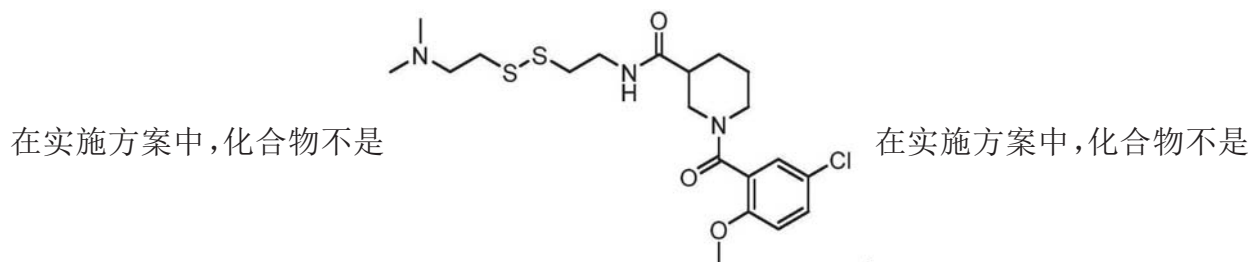
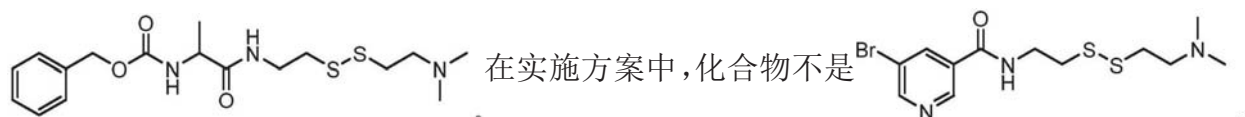
[0490] 在实施方案中,化合物不是 。在实施

方案中,化合物不是 。在实施方案中,化合物不是

。在实施方案中,化合物不是 。

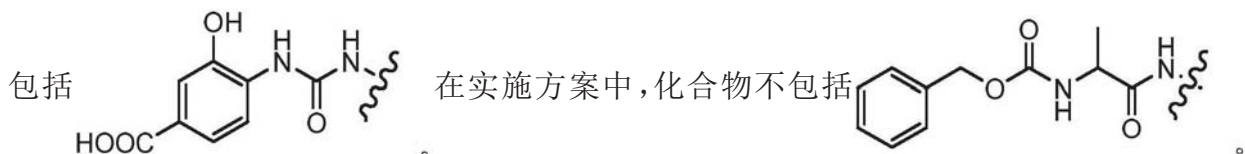
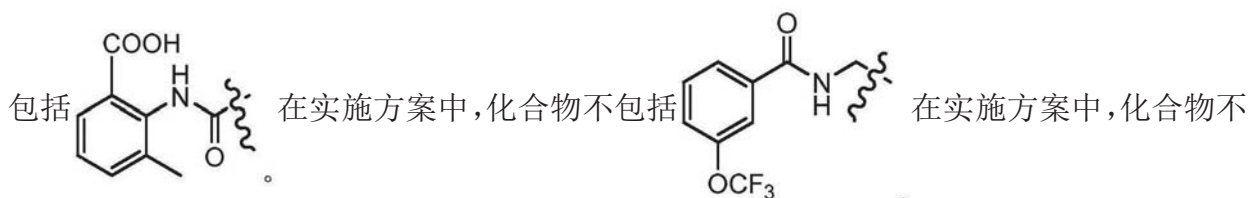
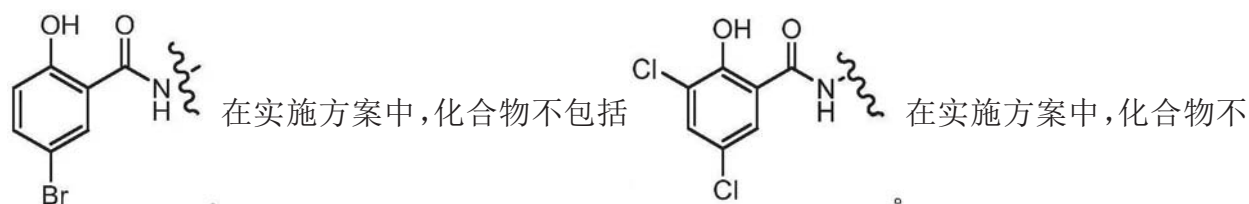
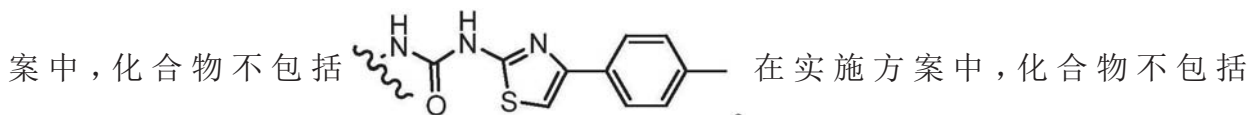
在实施方案中,化合物不是 。在实施方案中,化合物不是

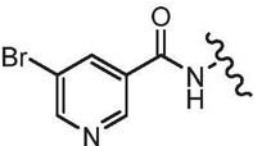
。在实施方案中,化合物不是

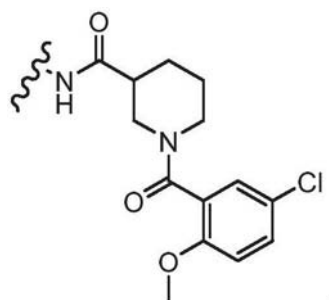


[0491]

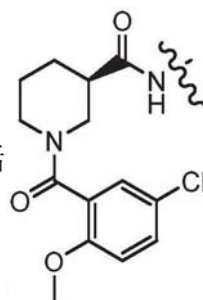
[0492] 在实施方案中,化合物不是本文,包括在实例、图或表中描述的化合物。在实施方案中,化合物不包括



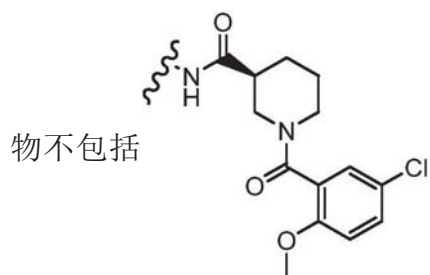
在实施方案中,化合物不包括  在实施方案中,化合物不包括



在实施方案中,化合物不包括

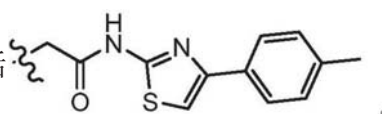


在实施方案中,化合



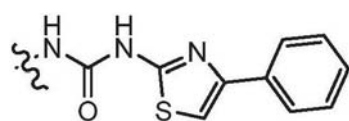
物不包括

在实施方案中,化合物不包括

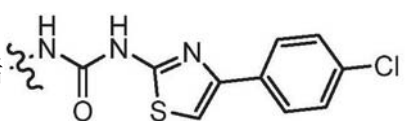


在实施方案中,化合物不包括

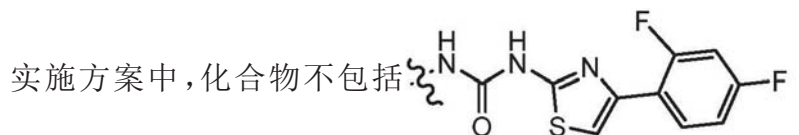
在实施方案中,化合物不包括



在实施方案中,化合物不包括

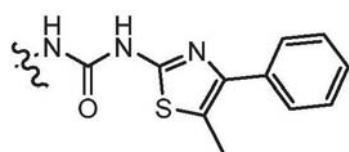


在

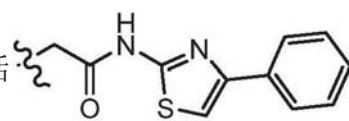


实施方案中,化合物不包括

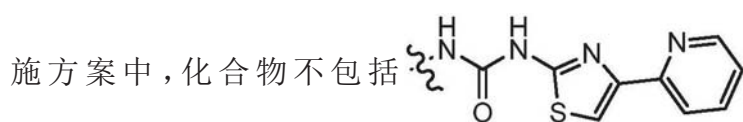
在实施方案中,化合物不包括



在实施方案中,化合物不包括

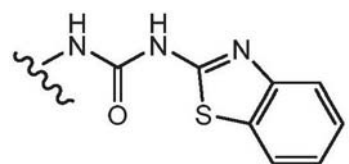


在实



施方案中,化合物不包括

在实施方案中,化合物不包括



[0493] III. 药物组合物

[0494] 一方面,提供了一种包括本文描述的化合物和药学上可接受的赋形剂的药物组合物。

[0495] 在实施方案中,该药物组合物包括有效量的化合物。在实施方案中,该药物组合物包括治疗有效量的化合物。在实施方案中,该药物组合物包括第二药剂(例如,抗癌剂)。在该药物组合物的实施方案中,该药物组合物包括治疗有效量的第二药剂。在实施方案中,抗癌剂为EGFR抑制剂(例如吉非替尼(IressaTM)、厄洛替尼(TarcevaTM)、西妥昔单抗(ErbituxTM)、拉帕替尼(TykerbTM)、帕尼单抗(VectibixTM)、凡德他尼(CaprelsaTM)、阿法替尼/BIBW2992、CI-1033/卡奈替尼、来那替尼/HKI-272、CP-724714、TAK-285、AST-1306、ARRY334543、ARRY-380、AG-1478、达克替尼/PF299804、OSI-420/去甲基厄洛替尼、AZD8931、AEE788、培利替尼/EKB-569、CUDC-101、WZ8040、WZ4002、WZ3146、AG-490、XL647、PD153035或BMS-599626)。在实施方案中,抗癌剂为厄洛替尼。在实施方案中,抗癌剂为吉非替尼。在实施方案中,抗癌剂为拉帕替尼。在实施方案中,抗癌剂为帕尼单抗。在实施方案中,抗癌剂为帕尼单抗。

[0496] 药物组合物可包括本文公开的调节剂的光学异构体、非对映异构体或药学上可接受的盐。药物组合物中包括的化合物可与载体部分共价附连。可选地,药物组合物中包括的化合物不与载体部分共价连接。

[0497] IV. 治疗疾病的方法

[0498] 另一方面,提供了一种治疗需要此类治疗的受试者(患者)的疾病的方法。该方法包括向患者施用治疗有效量的本文(包括实施方案、实例、图、表)描述的化合物。在一些实施方案中,疾病为癌症。在一些实施方案中,癌症为肺癌、结直肠癌、结肠癌、胰腺癌、乳腺癌或白血病。在一些实施方案中,癌症为肺癌。在一些实施方案中,癌症为非小细胞肺癌。在一些实施方案中,癌症为结肠癌。在一些实施方案中,癌症为结直肠癌。在一些实施方案中,癌症为乳腺癌。在一些实施方案中,癌症为白血病。在一些实施方案中,癌症为胰腺癌。在一些实施方案中,癌症是与异常K-Ras相关的癌症。在一些实施方案中,癌症是与突变K-Ras相关的癌症。在一些实施方案中,癌症是与K-Ras G12C相关的癌症。在一些实施方案中,癌症是与K-Ras G12D相关的癌症。在一些实施方案中,癌症是与K-Ras G12V相关的癌症。在一些实施方案中,癌症是与K-Ras G12S相关的癌症。在一些实施方案中,癌症是与K-Ras G13C相关的癌症。在一些实施方案中,癌症是与K-Ras G13D相关的癌症。

[0499] 在一些实施方案中,提供了一种治疗有需要的受试者的病症的方法,其包括a) 确定从受试者分离的恶性或增生性细胞中的Ras蛋白中(例如K-Ras、N-Ras或H-Ras蛋白中)突变的存在或不存在并且b) 如果确定受试者中存在突变,则向受试者施用治疗有效量的本发明的化合物或药学上可接受的盐。在一些实施方案中,病症为癌症。

[0500] 本发明的化合物(即本文,包括在实施方案、实例、图、表中描述的化合物)可以单独施用或者可以联合施用给患者。联合施用意在包括化合物单独地或呈组合(一种以上化合物)同时或依次施用。因此,在需要时,制剂也可与其它活性物质组合(例如以减少代谢降解或抗癌剂)。在实施方案中,抗癌剂为EGFR抑制剂(例如吉非替尼(IressaTM)、厄洛替尼(TarcevaTM)、西妥昔单抗(ErbituxTM)、拉帕替尼(TykerbTM)、帕尼单抗(VectibixTM)、凡德他尼(CaprelsaTM)、阿法替尼/BIBW2992、CI-1033/卡奈替尼、来那替尼/HKI-272、CP-724714、TAK-285、AST-1306、ARRY334543、ARRY-380、AG-1478、达克替尼/PF299804、OSI-420/去甲基厄洛替尼、AZD8931、AEE788、培利替尼/EKB-569、CUDC-101、WZ8040、WZ4002、WZ3146、AG-490、XL647、PD153035或BMS-599626)。在实施方案中,抗癌剂为厄洛替尼。在实施方案中,抗

癌剂为吉非替尼。在实施方案中,抗癌剂为拉帕替尼。在实施方案中,抗癌剂为帕尼单抗。在实施方案中,抗癌剂为帕尼单抗。

[0501] V. 调节活性的方法

[0502] 一方面提供了降低K-Ras蛋白(例如,人K-Ras 4B)的活性水平的方法,该方法包括使K-Ras蛋白与本文(包括在实施方案、实例、图和表中)描述的化合物接触。在一些实施方案中,K-Ras蛋白的活性是其GTP酶活性、核苷酸交换、差异性GDP或GTP结合、效应蛋白结合、效应蛋白活化、鸟嘌呤交换因子(GEF)结合、GEF促进的核苷酸交换、磷酸释放、核苷酸释放、核苷酸结合、K-Ras亚细胞定位、K-Ras翻译后加工、K-Ras翻译后修饰、异戊二烯化或GTP结合的K-Ras信号传导途径。在一些实施方案中,K-Ras蛋白的活性是其GTP酶活性、核苷酸交换、效应蛋白结合、效应蛋白活化、鸟嘌呤交换因子(GEF)结合、GEF促进的核苷酸交换、磷酸释放、核苷酸释放、核苷酸结合或GTP结合的K-Ras信号传导途径的活性。在一些实施方案中,K-Ras蛋白的活性是受GTP结合的K-Ras活化的信号传导途径的活性。在一些实施方案中,调节是增加所述K-Ras蛋白的活性。在一些实施方案中,调节是降低所述K-Ras蛋白的活性。在一些实施方案中,K-Ras蛋白是人K-Ras蛋白。在一些实施方案中,人K-Ras蛋白含有G12C突变。在一些实施方案中,人K-Ras蛋白含有G12V突变。在一些实施方案中,人K-Ras蛋白含有G12S突变。在一些实施方案中,人K-Ras蛋白含有G12D突变。在一些实施方案中,人K-Ras蛋白含有G13C突变。在一些实施方案中,人K-Ras蛋白含有G13D突变。在一些实施方案中,K-Ras蛋白是人K-Ras4A蛋白。在一些实施方案中,K-Ras蛋白是人K-Ras4B蛋白。在一些实施方案中,K-Ras蛋白是突变K-Ras蛋白。在一些实施方案中,K-Ras蛋白是活化K-Ras蛋白。在一些实施方案中,K-Ras蛋白在生物细胞内。在一些实施方案中,生物细胞形成生物体的一部分。在包括使K-Ras蛋白与有效量的本文(包括在实施方案、实例、图和表中)描述的化合物接触的调节K-Ras蛋白活性的方法的一些实施方案中,化合物在调节H-Ras蛋白活性时(例如,与调节K-Ras的水平相比)不太有效。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节H-Ras的活性多至少两倍。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节H-Ras的活性多至少五倍。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节H-Ras的活性多至少十倍。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节H-Ras的活性多至少五十倍。在包括使K-Ras蛋白与有效量的本文(包括在实施方案、实例、图和表中)描述的化合物接触的调节K-Ras蛋白活性的方法的一些实施方案中,化合物在调节N-Ras蛋白活性时不太有效。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节N-Ras的活性多至少两倍。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节N-Ras的活性多至少五倍。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节N-Ras的活性多至少十倍。在所述方法的一些实施方案中,化合物调节K-Ras的活性比其调节N-Ras的活性多至少五十倍。

[0503] 另一方面,提供了一种调节K-Ras蛋白的方法。该方法包括使K-Ras蛋白与有效量的本文(包括在实施方案、实例、图和表中)描述的化合物接触。在一些实施方案中,在K-Ras亚细胞定位、K-Ras翻译后加工、K-Ras翻译后修饰或GTP结合的K-Ras信号传导途径上调节K-Ras蛋白。在一些实施方案中,调节是增加K-Ras蛋白的翻译后加工或修饰。在一些实施方案中,调节是降低K-Ras蛋白的翻译后加工或修饰。在一些实施方案中,K-Ras蛋白是人K-Ras蛋白。在一些实施方案中,人K-Ras蛋白含有G12C突变。在一些实施方案中,人K-Ras蛋白

含有G12V突变。在一些实施方案中,人K-Ras蛋白含有G12S突变。在一些实施方案中,人K-Ras蛋白含有G12D突变。在一些实施方案中,人K-Ras蛋白含有G13C突变。在一些实施方案中,人K-Ras蛋白含有G13D突变。在一些实施方案中,K-Ras蛋白是人K-Ras4A蛋白。在一些实施方案中,K-Ras蛋白是人K-Ras4B蛋白。在一些实施方案中,K-Ras蛋白是突变K-Ras蛋白。在一些实施方案中,K-Ras蛋白是活化K-Ras蛋白。在一些实施方案中,K-Ras蛋白在生物细胞内。在一些实施方案中,生物细胞形成生物体的一部分。在实施方案中,化合物(例如,本文描述的化合物)调节K-Ras蛋白的稳定性。在实施方案中,化合物(例如,本文描述的化合物)相对于该化合物不存在的情况降低K-Ras蛋白的稳定性。在实施方案中,化合物(例如,本文描述的化合物)相对于该化合物不存在的情况增加K-Ras蛋白的降解速率。

[0504] 在实施方案中,化合物(例如,本文描述的化合物)与对应K-Ras(例如,K-Ras 4B)中的His95的氨基酸结合。在实施方案中,化合物(例如,本文描述的化合物)与K-Ras(K-Ras 4B)中的His95反应。在实施方案中,化合物(例如,本文描述的化合物)与对应K-Ras(例如,K-Ras 4B)中的His95的氨基酸共价结合。在实施方案中,化合物(例如,本文描述的化合物)与K-Ras(K-Ras 4B)中的His95共价反应。在实施方案中,化合物(例如,本文描述的化合物)能够与对应K-Ras(例如,K-Ras 4B)中的His95或Cys185的氨基酸结合。在实施方案中,化合物(例如,本文描述的化合物)能够与K-Ras(K-Ras 4B)中的His95或Cys185反应。

[0505] 在实施方案中,当K-Ras(例如,K-Ras 4B)蛋白Cys185(或对应K-Ras 4B的Cys185的氨基酸)经共价修饰(例如,异戊二烯化、法尼基化)时,所述化合物(例如,本文描述的化合物)与对应K-Ras(例如,K-Ras 4B)蛋白中的His95的氨基酸结合。在实施方案中,当K-Ras(例如,K-Ras 4B)蛋白Cys185(或对应K-Ras 4B的Cys185的氨基酸)未经共价修饰(例如,异戊二烯化、法尼基化)时,所述化合物(例如,本文描述的化合物)与对应K-Ras(例如,K-Ras 4B)蛋白中的Cys185的氨基酸结合。在实施方案中,当K-Ras(例如,K-Ras 4B)蛋白Cys185(或对应K-Ras 4B的Cys185的氨基酸)尚未经共价修饰(例如,异戊二烯化、法尼基化)时,在蛋白质合成后所述化合物(例如,本文描述的化合物)与对应K-Ras(例如,K-Ras 4B)蛋白中的Cys185的氨基酸结合。

[0506] 在实施方案中,相对于所述化合物不存在的情况,所述化合物防止K-Ras蛋白生产性折叠(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,所述化合物增加K-Ras蛋白的错折叠(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,所述化合物增加K-Ras蛋白的解折叠(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,所述化合物增加K-Ras蛋白的降解(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,所述化合物减少GTP与K-Ras蛋白的结合(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,所述化合物减少K-Ras蛋白的GTP释放(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在

的情况,所述化合物减少第二蛋白(例如,途径组分、效应子)与K-Ras蛋白的相互作用(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,所述化合物减少K-Ras蛋白的异戊二烯化(例如,法尼基化、香叶酰香叶酰化)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。

[0507] 在实施方案中,相对于所述化合物不存在的情况,在少于约1小时(例如,少于约1、2、3、4、5、6、7、8、9、10、20、30、40或50分钟)内,所述化合物降低细胞中的K-Ras功能水平(例如,至少1、2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、80、90、91、92、93、94、95、96、97、98或99%)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,在少于1小时(例如,少于1、2、3、4、5、6、7、8、9、10、20、30、40或50分钟)内,所述化合物降低细胞中的K-Ras功能水平(例如,至少1、2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、80、90、91、92、93、94、95、96、97、98或99%)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,在少于约1天(例如,少于约1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22或23小时)内,所述化合物降低细胞中的K-Ras功能水平(例如,至少1、2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、80、90、91、92、93、94、95、96、97、98或99%)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,在少于1天(例如,少于1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22或23小时)内,所述化合物降低细胞中的K-Ras功能水平(例如,至少1、2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、80、90、91、92、93、94、95、96、97、98或99%)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,在少于约1个月(例如,少于约1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30天)内,所述化合物降低细胞中的K-Ras功能水平(例如,至少1、2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、80、90、91、92、93、94、95、96、97、98或99%)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,相对于所述化合物不存在的情况,在少于1个月(例如,少于1、2、3、4、5、6、7、8、9、10、11、12、13、14、15、16、17、18、19、20、21、22、23、24、25、26、27、28、29或30天)内,所述化合物降低细胞中的K-Ras功能水平(例如,至少1、2、3、4、5、6、7、8、9、10、20、30、40、50、60、70、80、90、91、92、93、94、95、96、97、98或99%)(例如,通过与K-Ras蛋白结合,通过与对应K-Ras的His95的氨基酸结合,通过与对应K-Ras的Cys185的氨基酸结合)。在实施方案中,化合物结合K-Ras(例如,仅K-Ras 4B,仅K-Ras 4A,或K-Ras 4A和K-Ras 4B两者)。

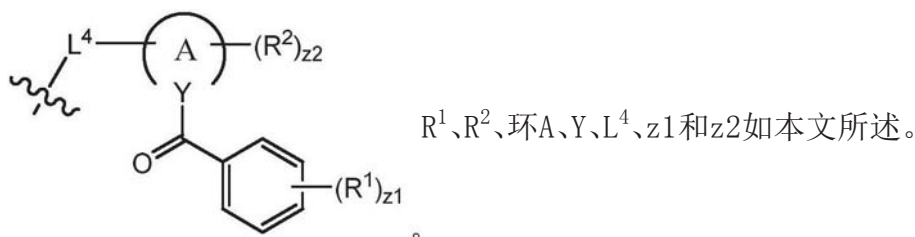
[0508] VI. 组合物

[0509] 另一方面,提供了与化合物,例如本文描述的化合物(包括在实施方案、实例、图和表中描述的调节剂、抑制剂)共价(例如,可逆或不可逆地)键合的K-Ras蛋白。在实施方案中,化合物是本文描述的化合物。在实施方案中,化合物与蛋白质的半胱氨酸残基共价键合。在实施方案中,化合物与蛋白质的半胱氨酸残基不可逆地共价键合。在实施方案中,化

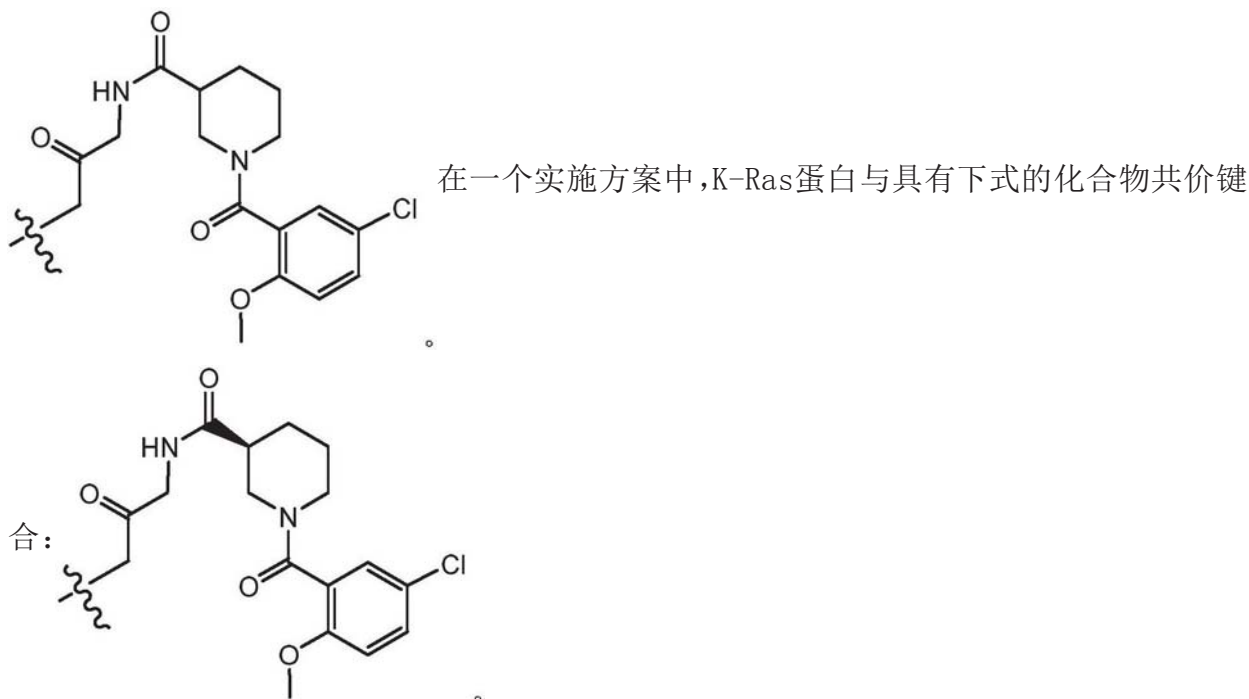
合物与对应人K-Ras 4B的C185的残基共价键合。在实施方案中,化合物与蛋白质的组氨酸残基共价键合。在实施方案中,化合物与蛋白质的组氨酸残基不可逆地共价键合。在实施方案中,化合物与对应人K-Ras 4B的H95的残基共价键合。

[0510] 在实施方案中,经共价修饰的K-Ras蛋白相对于对照具有经调节的活性,其中所述活性选自GTP酶活性、核苷酸交换、效应蛋白结合、效应蛋白活化、鸟嘌呤交换因子(GEF)结合、GEF促进的核苷酸交换、磷酸释放、核苷酸释放、核苷酸结合、K-Ras亚细胞定位、K-Ras翻译后加工和K-Ras翻译后修饰。在一些实施方案中,经共价修饰的K-Ras蛋白在K-Ras亚细胞定位、K-Ras翻译后加工或K-Ras翻译后修饰上受调节。在一些实施方案中,经共价修饰的K-Ras蛋白含有G12C突变。在一些实施方案中,经共价修饰的K-Ras蛋白含有G12V突变。在一些实施方案中,经共价修饰的K-Ras蛋白含有G12S突变。在一些实施方案中,化合物与半胱氨酸残基185共价键合。在一些实施方案中,化合物与组氨酸残基95(对应于K-Ras的H95)共价键合。在一些实施方案中,经共价修饰的K-Ras蛋白含有G13C突变。在一些实施方案中,K-Ras蛋白与K-Ras抑制剂、突变K-Ras抑制剂、K-Ras H95抑制剂或K-Ras C185抑制剂键合。在一些实施方案中,K-Ras蛋白与K-Ras调节剂、突变K-Ras调节剂、K-Ras H95抑制剂或K-Ras C185调节剂键合。

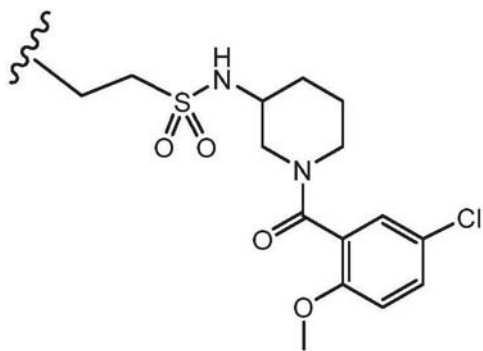
[0511] 一方面,提供了与具有下式的化合物共价键合的K-Ras蛋白:



[0512] 一方面,提供了与具有下式的化合物共价键合的K-Ras蛋白:

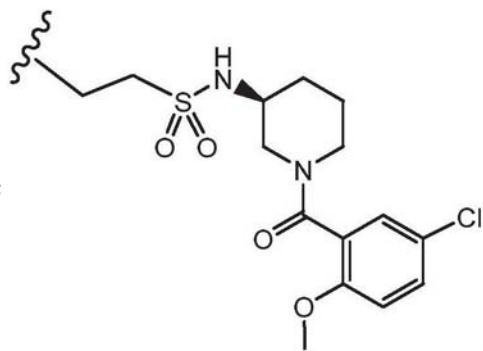


[0513] 一方面,提供了与具有下式的化合物共价键合的K-Ras蛋白:



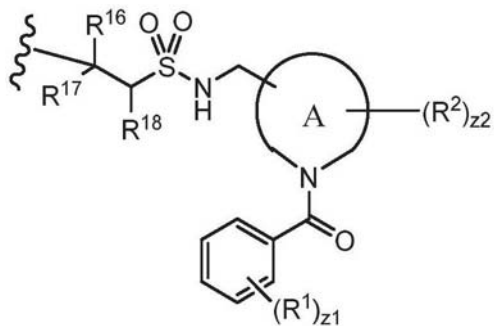
在一个实施方案中,K-Ras蛋白与具有下式的化合物共

价键合:



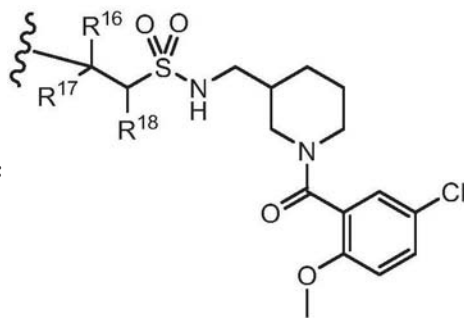
在一个实施方案中,K-Ras蛋白与具有下式的

化合物共价键合:



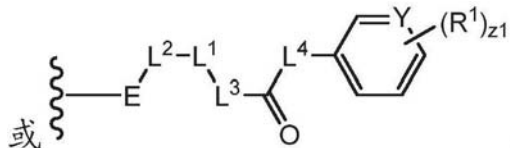
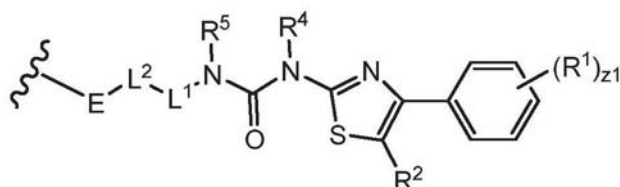
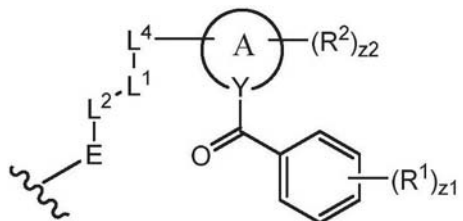
在一个实施方案中,K-Ras蛋白与具

有下式的化合物共价键合:



在一个实施方案中,K-Ras蛋

白与具有下式的化合物共价键合:



或

E、R¹、R²、R³、R⁴、R⁵、环A、Y、L¹、L²、L³、L⁴、z1和z2如本文

所述。

[0514] 在实施方案中,化合物与蛋白质的半胱氨酸残基共价键合。在实施方案中,化合物与蛋白质对应人K-Ras-4B的C185的半胱氨酸残基共价键合。在实施方案中,化合物与蛋白质的半胱氨酸(例如,对应人K-Ras-4B的C185)不可逆地共价键合。在实施方案中,化合物与蛋白质的组氨酸残基共价键合。在实施方案中,化合物与蛋白质对应人K-Ras-4B的H95的组氨酸残基共价键合。在实施方案中,化合物与蛋白质的组氨酸(例如,对应人K-Ras-4B的H95)不可逆地共价键合。

[0515] 另一方面,提供了与化合物,例如本文描述的化合物(包括在实施方案、图和表中描述的调节剂、抑制剂)共价键合的(例如,可逆或不可逆地)Ras蛋白(例如K-Ras、N-Ras、H-Ras或本文描述的另一种Ras蛋白)。在一些实施方案中,化合物为调节剂。在一些实施方案中,化合物为调节剂例如抑制剂。在一些实施方案中,化合物为Ras调节剂。在一些实施方案中,化合物为Ras抑制剂。

[0516] 在实施方案中,化合物在CAAX盒处结合Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)。在实施方案中,化合物使Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与对应人K-Ras 4B的C185的残基结合。在实施方案中,化合物使Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与对应人K-Ras 4B的H95的残基结合。

[0517] 在实施方案中,化合物调节蛋白质的构象。在实施方案中,化合物调节CAAX盒的构象。在实施方案中,化合物调节(例如,减少或抑制)蛋白质在CAAX盒(例如,对应人K-Ras 4B的C185的残基)处的异戊二烯化。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)活性(例如,约0.1、0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9、1.0、2.0、3.0、4.0、5.0、6.0、7.0、8.0、9.0、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、65、70、75、80、85、90、95、100、200、300、400、500、600、700、800、900、1000、2000、3000、4000、5000、6000、7000、8000、9000、10000倍或更多)。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)活性(例如约0.1、0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9、1.0、2.0、3.0、4.0、5.0、6.0、7.0、8.0、9.0、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、65、70、75、80、85、90、95或100%)。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)异戊二烯化(例如约0.1、0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9、1.0、2.0、3.0、4.0、5.0、6.0、7.0、8.0、9.0、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、65、70、75、80、85、90、95或100%)。在实施方案中,相对于所述化合物不存在的情况,所述化合物减少Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)蛋白(例如在细胞中)的量(例如约0.1、

0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9、1.0、2.0、3.0、4.0、5.0、6.0、7.0、8.0、9.0、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、65、70、75、80、85、90、95或100%)。在实施方案中,相对于所述化合物不存在的情况,所述化合物减少Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)蛋白(例如在细胞中)的生成(例如约0.1、0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9、1.0、2.0、3.0、4.0、5.0、6.0、7.0、8.0、9.0、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、65、70、75、80、85、90、95或100%)。在实施方案中,相对于所述化合物不存在的情况,所述化合物增加Ras(例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)蛋白(例如在细胞中)的降解(例如约0.1、0.2、0.3、0.4、0.5、0.6、0.7、0.8、0.9、1.0、2.0、3.0、4.0、5.0、6.0、7.0、8.0、9.0、10、11、12、13、14、15、16、17、18、19、20、25、30、35、40、45、50、55、60、65、70、75、80、85、90、95或100%)。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制蛋白质与膜的缔合。

[0518] 在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在营养缺乏条件下的增殖。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在营养缺乏条件下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在营养缺乏条件下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在血清剥夺条件下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在血清剥夺条件下的增殖。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在模拟血清剥夺的条件(例如患者的局部细胞环境)下的生长。在实施方案中,相对于所述化合物不存在的情况,所述化合物抑制癌细胞在模拟血清剥夺的条件(例如患者的局部细胞环境)下的增殖。

[0519] 在实施方案中,相对于所述化合物不存在的情况,所述化合物增加了CAAX盒的柔性(蛋白质C端的氨基酸序列,其中C是可以异戊二烯化的半胱氨酸,A是脂族氨基酸,且X是根据蛋白质而定具有可变序列的氨基酸(例如,M、S、Q、A或C;L或E))。在实施方案中,相对于所述化合物不存在的情况,所述化合物增加了CAAX盒的混乱。在实施方案中,化合物抑制Ras((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与另一种蛋白的结合。在实施方案中,化合物抑制Ras((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与另一种蛋白的结合,其中所述结合依赖于Ras异戊二烯化。在实施方案中,化合物抑制Ras((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与另一种蛋白的结合,其中所述结合依赖于Ras膜缔合。

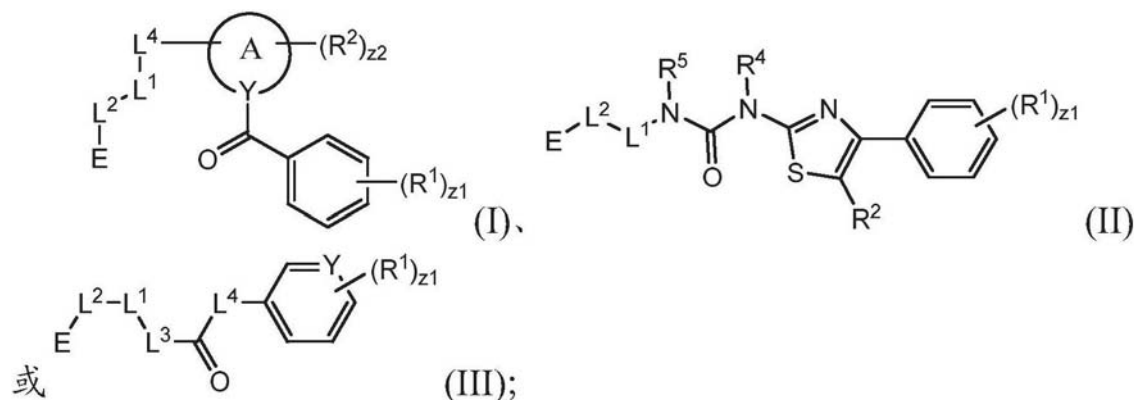
[0520] 在实施方案中,化合物抑制Ras((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与Raf(例如Raf1)的结合。在实施方案中,化合物抑制Ras((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D)与SOS的结合。在实施方案中,化合物抑制Ras((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras

G13C、K-Ras G12D、K-Ras G13D) 与GEF的结合。在实施方案中,化合物抑制Ras ((例如K-Ras、K-Ras 4B、人K-Ras 4B、H-Ras、N-Ras、突变Ras、K-Ras G12C、K-Ras G12V、K-Ras G12S、K-Ras G13C、K-Ras G12D、K-Ras G13D) 与PI3K的结合。

[0521] VII. 选定的实施方案

[0522] 实施方案P1. 一种具有下式的化合物:

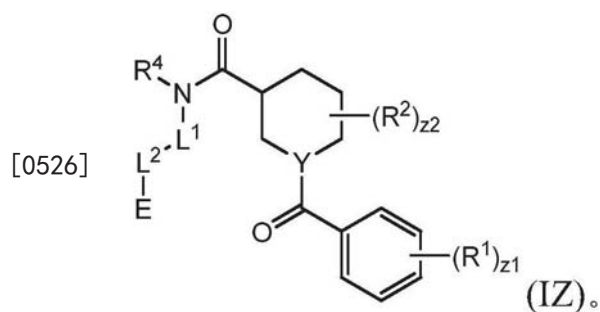
[0523]



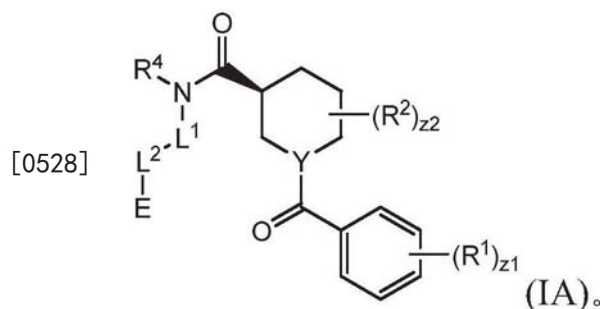
[0524] 其中, Y为N或CH; 环A为C₅-C₇环烷基或5-7元杂环烷基; R¹独立地为卤素、CX¹₃、-CHX¹₂、-CH₂X¹、-CN、-SO₂Cl、-SO_{n1}R¹⁰、-SO_{v1}NR⁷R⁸、-NHN⁷R⁸、-ONR⁷R⁸、-NHC(=O)NHN⁷R⁸、-NHC(=O)NR⁷R⁸、-N(O)_{m1}、-NR⁷R⁸、-C(O)R⁹、-C(O)-OR⁹、-C(O)NR⁷R⁸、-OR¹⁰、-NR⁷SO₂R¹⁰、-NR⁷C(O)R⁹、-NR⁷C(O)OR⁹、-NR⁷OR⁹、-OCX¹₃、-OCHX¹₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; 两个相邻的R¹取代基可任选地连接形成经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基; L¹为键、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基; L²为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7B}-、-NR^{7B}C(O)-、-C(O)NR^{7B}-、-SO₂NR^{7B}-、-NR^{7B}SO₂-、-OC(O)NR^{7B}-、-NR^{7B}C(O)O-、-CR^{9B}=NO-、-ON=CR^{9B}-、-NR^{8B}C(O)NR^{7B}-、-NR^{8B}C(=NR^{10B})NR^{7B}-、-NR^{8B}C(=NR^{10B})-、-C(=NR^{10B})NR^{7B}-、-OC(=NR^{10B})-、-C(=NR^{10B})O-、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基; L³为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR⁵-、-NR⁵C(O)-、-C(O)NR⁵-、-SO₂NR⁵-、-NR⁵SO₂-、-OC(O)NR⁵-、-NR⁵C(O)O-、经取代或未取代的C₁-C₆亚烷基、经取代或未取代的2-6元杂亚烷基; L⁴为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR⁴-、-NR⁴C(O)-、-C(O)NR⁴-、-SO₂NR⁴-、-NR⁴SO₂-、-NR⁴SO₂-、-OC(O)NR⁴-、-NR⁴C(O)O-、经取代或未取代的C₁-C₃亚烷基、经取代或未取代的2-3元杂亚烷基; E为共价半胱氨酸修饰部分; R²独立地为氧代、卤素、CX²₃、-CHX²₂、-CH₂X²、-CN、-SO₂Cl、-SO_{n2}R¹⁴、-SO_{v2}NR¹¹R¹²、-NHN¹¹R¹²、-ONR¹¹R¹²、-NHC(=O)NHN¹¹R¹²、-NHC(=O)NR¹¹R¹²、-N(O)_{m2}、-NR¹¹R¹²、-C(O)R¹⁴、-C(O)-OR¹⁴、-C(O)NR¹¹R¹²、-OR¹⁵、-NR¹¹SO₂R¹⁵、-NR¹¹C(O)R¹⁴、-NR¹¹C(O)OR¹⁴、-NR¹¹OR¹⁴、-OCX²₃、-OCHX²₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; 两个相邻的R²取代基或两个键合至相同原子的R²取代基可任选地连接形成经取代或未取代的环烷基或

经取代或未取代的杂环烷基; R^4 独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; R^5 独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; R^7 、 R^8 、 R^9 、 R^{10} 、 R^{7B} 、 R^{8B} 、 R^{9B} 、 R^{10B} 、 R^{11} 、 R^{12} 、 R^{14} 和 R^{15} 独立地为氢、卤素、 $-CX_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX_3$ 、 $-OCHX_2$ 、 $-CHX_2$ 、 $-CH_2X$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基; 键合至相同氮原子的 R^7 和 R^8 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基; 键合至相同氮原子的 R^{11} 和 R^{12} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基; 每个 X 、 X^1 和 X^2 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$; n_1 、 n_2 、 v_1 和 v_2 独立地为 0 至 4 的整数; m_1 和 m_2 独立地为介于 1 和 2 之间的整数; z_1 独立地为 0 至 5 的整数; 并且 z_2 独立地为 0 至 10 的整数。

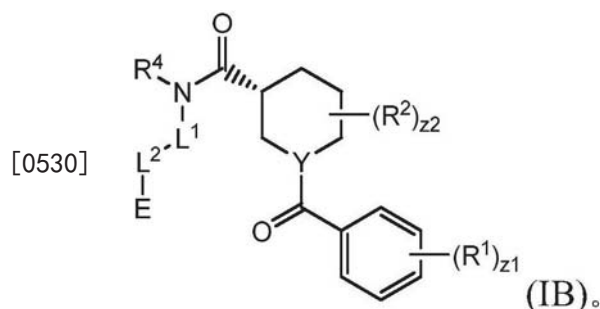
[0525] 实施方案 P2. 根据实施方案 P1 所述的化合物, 其具有下式:



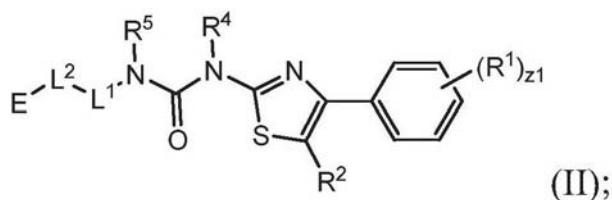
[0527] 实施方案 P3. 根据实施方案 P1 所述的化合物, 其具有下式:



[0529] 实施方案 P4. 根据实施方案 P1 所述的化合物, 其具有下式:

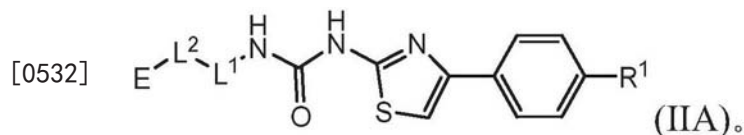


[0531] 实施方案 P5. 根据实施方案 P1 所述的化合物, 其具有下式:

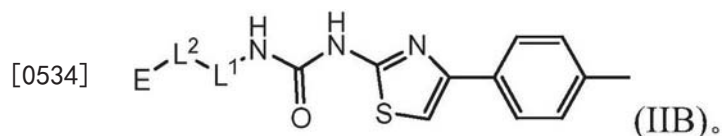


其中 R^2 、 R^4 和 R^5 为氢。实施方案P6. 根据实施方

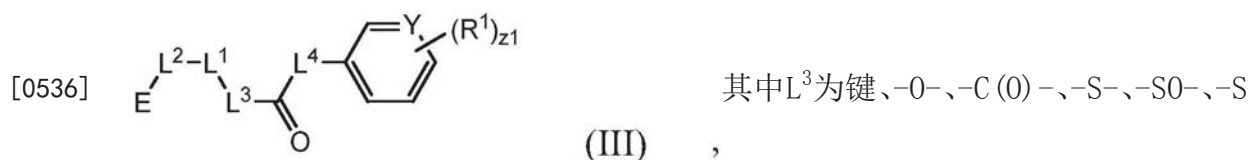
案P5所述的化合物,其具有下式:



[0533] 实施方案P7. 根据实施方案P5所述的化合物,其具有下式:



[0535] 实施方案P8. 根据实施方案P1所述的化合物,其具有下式:



其中 L^3 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NH-$ 、 $-NHC(CH_3)C(O)NH-$,或未取代的 C_1-C_3 亚烷基;并且 L^4 为键、 $-CH_2O-$ 、 $-C(O)-$ 、 $-NH-$ 或 $-O-$ 。

[0537] 实施方案P9. 根据实施方案P1-P8中的一项所述的化合物,其中Y为CH。

[0538] 实施方案P10. 根据实施方案P1-P8中的一项所述的化合物,其中Y为N。

[0539] 实施方案P11. 根据实施方案P1-P10中的一项所述的化合物,其中 R^1 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、经取代或未取代的 C_1-C_6 烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的 C_3-C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的5-6元杂芳基。

[0540] 实施方案P12. 根据实施方案P1-P10中的一项所述的化合物,其中 R^1 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-OH$ 、 $-SH$ 、 $-COOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。

[0541] 实施方案P13. 根据实施方案P1-P12中的一项所述的化合物,其中 z_1 为2。

[0542] 实施方案P14. 根据实施方案P1-P12中的一项所述的化合物,其中 z_1 为3。

[0543] 实施方案P15. 根据实施方案P1-P14中的一项所述的化合物,其中 R^2 独立地为氧代、卤素、 CX^2_3 、 $-CHX^2_2$ 、 $-CH_2X^2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、经取代或未取代的 C_1-C_6 烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的 C_3-C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的5-6元杂芳基。

[0544] 实施方案P16. 根据实施方案P1-P14中的一项所述的化合物,其中 R^2 独立地为氧

代、卤素、 $-CX^2_3$ 、 $-CHX^2_2$ 、 $-CH_2X^2$ 、 $--OH$ 、 $-SH$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。

[0545] 实施方案P17. 根据实施方案P1-P16中的一项所述的化合物, 其中 z_2 为0。

[0546] 实施方案P18. 根据实施方案P1-P17中的所述一项的化合物, 其中 R^4 为氢。

[0547] 实施方案P19. 根据实施方案P1-P18中的一项所述的化合物, 其中 R^5 为氢。

[0548] 实施方案P20. 根据实施方案P1-P19中的一项所述的化合物, 其中 L^1 为键、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。

[0549] 实施方案P21. 根据实施方案P1-P19中的一项所述的化合物, 其中 L^1 为键、未取代的 C_1 - C_4 亚烷基或未取代的2-4元杂亚烷基。

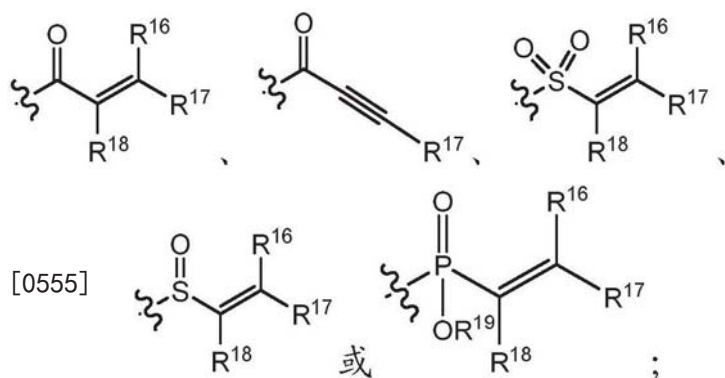
[0550] 实施方案P22. 根据实施方案P1-P19中的一项所述的化合物, 其中 L^1 为键。

[0551] 实施方案P23. 根据实施方案P1-P22中的一项所述的化合物, 其中 L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、 $-SO_2NH-$ 、 $-NHSO_2-$ 、 $-OC(O)NH-$ 、 $-NHC(O)O-$ 、 $-NHC(O)NH-$ 、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。

[0552] 实施方案P24. 根据实施方案P1-P22中的一项所述的化合物, 其中 L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、未取代的 C_1 - C_4 亚烷基或未取代的2-4元杂亚烷基。

[0553] 实施方案P25. 根据实施方案P1-P22中的一项所述的化合物, 其中 L^2 为键。

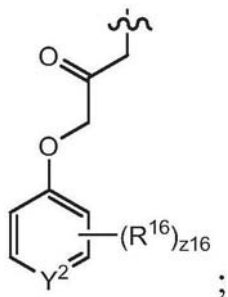
[0554] 实施方案P26. 根据实施方案P1-P25中的一项所述的化合物, 其中E为



[0556] 其中 R^{16} 独立地为氢、卤素、 CX^{16}_3 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n16}R^{16D}$ 、 $-SO_{v16}NR^{16A}R^{16B}$ 、 $-NHN R^{16A}R^{16B}$ 、 $-ONR^{16A}R^{16B}$ 、 $-NHC(=O)NHN R^{16A}R^{16B}$ 、 $-NHC(O)NR^{16A}R^{16B}$ 、 $-N(O)_{m16}$ 、 $-NR^{16A}R^{16B}$ 、 $-C(O)R^{16C}$ 、 $-C(O)OR^{16C}$ 、 $-C(O)NR^{16A}R^{16B}$ 、 $-OR^{16D}$ 、 $-NR^{16A}SO_2R^{16D}$ 、 $-NR^{16A}C(O)R^{16C}$ 、 $-NR^{16A}C(O)OR^{16C}$ 、 $-NR^{16A}OR^{16C}$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; R^{17} 独立地为氢、卤素、 CX^{17}_3 、 $-CHX^{17}_2$ 、 $-CH_2X^{17}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n17}R^{17D}$ 、 $-SO_{v17}NR^{17A}R^{17B}$ 、 $-NHN R^{17A}R^{17B}$ 、 $-ONR^{17A}R^{17B}$ 、 $-NHC(=O)NHN R^{17A}R^{17B}$ 、 $-NHC(O)NR^{17A}R^{17B}$ 、 $-N(O)_{m17}$ 、 $-NR^{17A}R^{17B}$ 、 $-C(O)R^{17C}$ 、 $-C(O)OR^{17C}$ 、 $-C(O)NR^{17A}R^{17B}$ 、 $-OR^{17D}$ 、 $-NR^{17A}SO_2R^{17D}$ 、 $-NR^{17A}C(O)R^{17C}$ 、 $-NR^{17A}C(O)OR^{17C}$ 、 $-NR^{17A}OR^{17C}$ 、 $-OCX^{17}_3$ 、 $-OCHX^{17}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; R^{18} 独立地为氢、卤素、 CX^{18}_3 、 $-CHX^{18}_2$ 、 $-CH_2X^{18}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n18}R^{18D}$ 、 $-SO_{v18}NR^{18A}R^{18B}$ 、 $-NHN R^{18A}R^{18B}$ 、 $-ONR^{18A}R^{18B}$ 、 $-NHC(=O)NHN R^{18A}R^{18B}$ 、 $-NHC(O)NR^{18A}R^{18B}$ 、 $-N(O)_{m18}$ 、 $-NR^{18A}R^{18B}$ 、 $-C(O)R^{18C}$ 、 $-C(O)OR^{18C}$ 、 $-C(O)NR^{18A}R^{18B}$ 、 $-OR^{18D}$ 、 $-NR^{18A}SO_2R^{18D}$ 、 $-NR^{18A}C(O)R^{18C}$ 、 $-NR^{18A}C(O)OR^{18C}$ 、 $-NR^{18A}OR^{18C}$ 、 $-OCX^{18}_3$ 、 $-OCHX^{18}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基。

代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基； R^{19} 独立地为氢、卤素、 CX^{19}_3 、 $-CHX^{19}_2$ 、 $-CH_2X^{19}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-SO_{n19}R^{19D}$ 、 $-SO_{v19}NR^{19A}R^{19B}$ 、 $-NHN R^{19A}R^{19B}$ 、 $-ONR^{19A}R^{19B}$ 、 $-NHC = (O)NHN R^{19A}R^{19B}$ 、 $-NHC(O)NR^{19A}R^{19B}$ 、 $-N(O)_{m19}$ 、 $-NR^{19A}R^{19B}$ 、 $-C(O)R^{19C}$ 、 $-C(O)-OR^{19C}$ 、 $-C(O)NR^{19A}R^{19B}$ 、 $-OR^{19D}$ 、 $-NR^{19A}SO_2R^{19D}$ 、 $-NR^{19A}C(O)R^{19C}$ 、 $-NR^{19A}C(O)OR^{19C}$ 、 $-NR^{19A}OR^{19C}$ 、 $-OCX^{19}_3$ 、 $-OCHX^{19}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基； R^{16A} 、 R^{16B} 、 R^{16C} 、 R^{16D} 、 R^{17A} 、 R^{17B} 、 R^{17C} 、 R^{17D} 、 R^{18A} 、 R^{18B} 、 R^{18C} 、 R^{18D} 、 R^{19A} 、 R^{19B} 、 R^{19C} 、 R^{19D} 独立地为氢、卤素、 $-CX_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NH_2OH$ 、 $-OCX_3$ 、 $-OCHX_2$ 、 $-CHX_2$ 、 $-CH_2X$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{16A} 和 R^{16B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{17A} 和 R^{17B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{18A} 和 R^{18B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{19A} 和 R^{19B} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；每个 X 、 X^{16} 、 X^{17} 、 X^{18} 和 X^{19} 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ ； $n16$ 、 $n17$ 、 $n18$ 、 $n19$ 、 $v16$ 、 $v17$ 、 $v18$ 和 $v19$ 独立地为0至4的整数；并且 $m16$ 、 $m17$ 、 $m18$ 和 $m19$ 独立地为1至2的整数。

[0557] 实施方案P27. 根据实施方案P1-P25中的一项所述的化合物，其中E为



[0558] 其中 R^{16} 独立地为卤素、 CX^{16}_3 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NH_2OH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基； Y^2 为N或CH； $z16$ 为介于0和4之间的整数；并且每个 X^{16} 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ 。

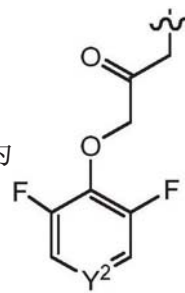
[0559] 实施方案P28. 根据实施方案P27所述的化合物，其中 R^{16} 独立地为卤素。

[0560] 实施方案P29. 根据实施方案P27所述的化合物，其中 R^{16} 独立地为 $-F$ 。

[0561] 实施方案P30. 根据实施方案P27-P29中的一项所述的化合物，其中 $z16$ 为4。

[0562] 实施方案P31. 根据实施方案P27-P29中的一项所述的化合物，其中 $z16$ 为2。

[0563] 实施方案P32.根据实施方案P31所述的化合物,其中E为

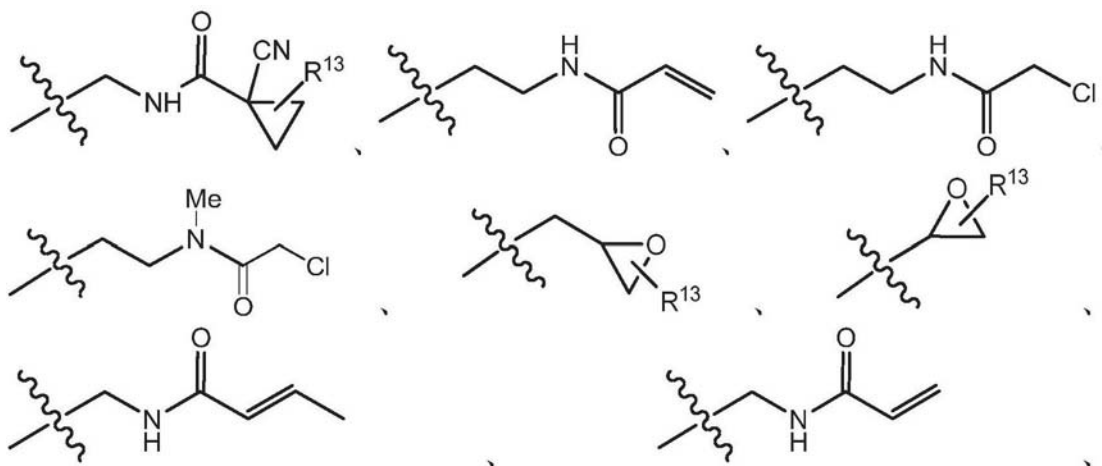


[0564] 实施方案P33.根据实施方案P27-P32中的一项所述的化合物,其中Y²为CH。

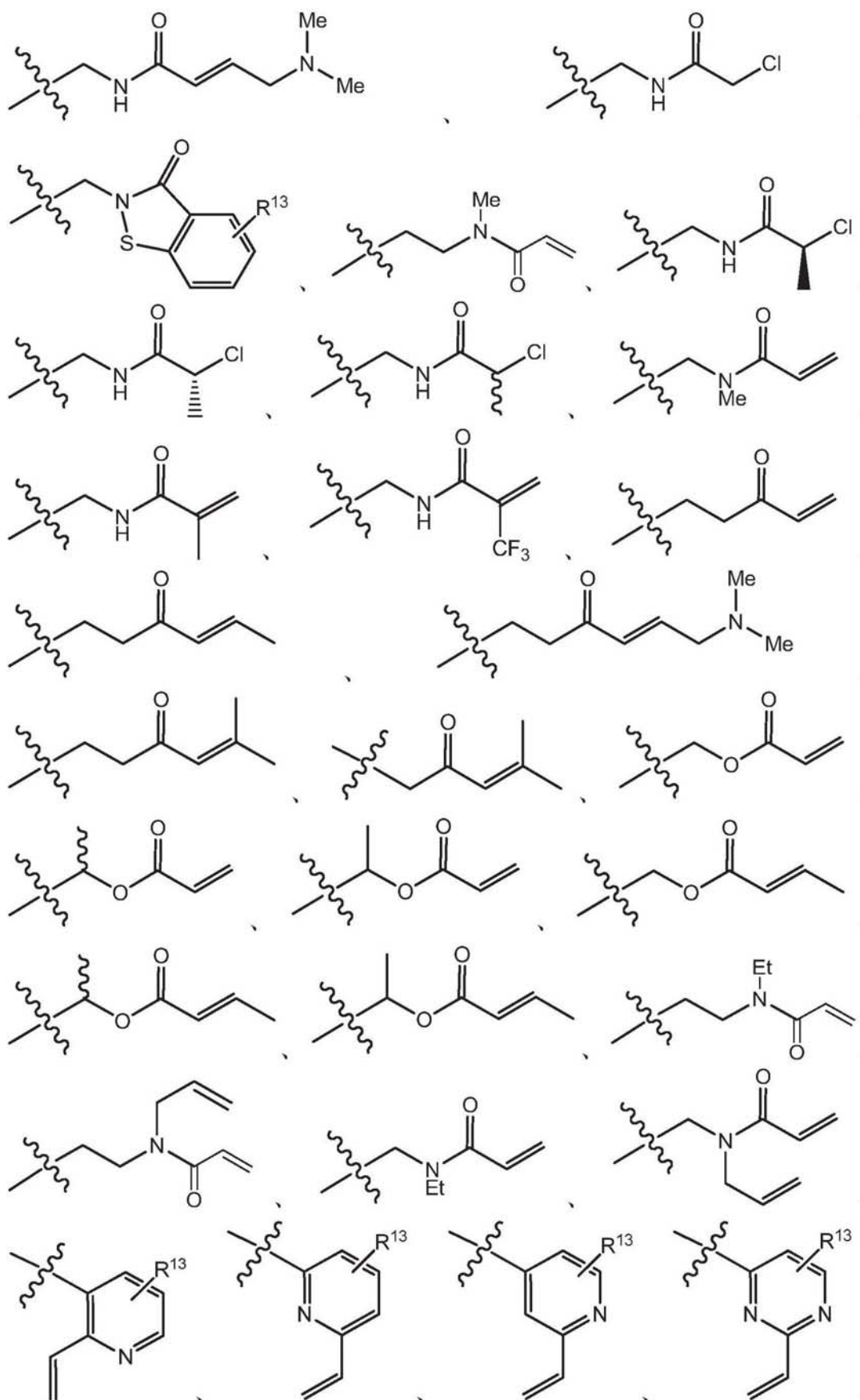
[0565] 实施方案P34.根据实施方案P27-P32中的一项所述的化合物,其中Y²为N。

[0566] 实施方案P35.根据实施方案P1-P25中的一项所述的化合物,其中E包含经取代或未取代的乙烯砜部分、经取代或未取代的乙烯基磺酰胺部分、经取代或未取代的氟(C₁-C₄)烷基酮部分、经取代或未取代的氯(C₁-C₄)烷基酮部分、经取代或未取代的丙烯酰胺部分、经取代或未取代的二硫化物部分、经取代或未取代的硫醇部分、经取代或未取代的膦酸酯部分、经取代或未取代的醛部分、经取代或未取代的烯酮部分、经取代或未取代的重氮甲基酮部分、经取代或未取代的重氮甲酰胺部分、经取代或未取代的氰基环丙基羧酰胺部分、经取代或未取代的环氧化物部分、经取代或未取代的环氧酮部分、经取代或未取代的环氧酰胺部分、经取代或未取代的芳醛部分、经取代或未取代的芳二醛部分、经取代或未取代的二醛部分、经取代或未取代的氮芥部分、经取代或未取代的炔丙基部分、经取代或未取代的炔丙基酰胺部分、

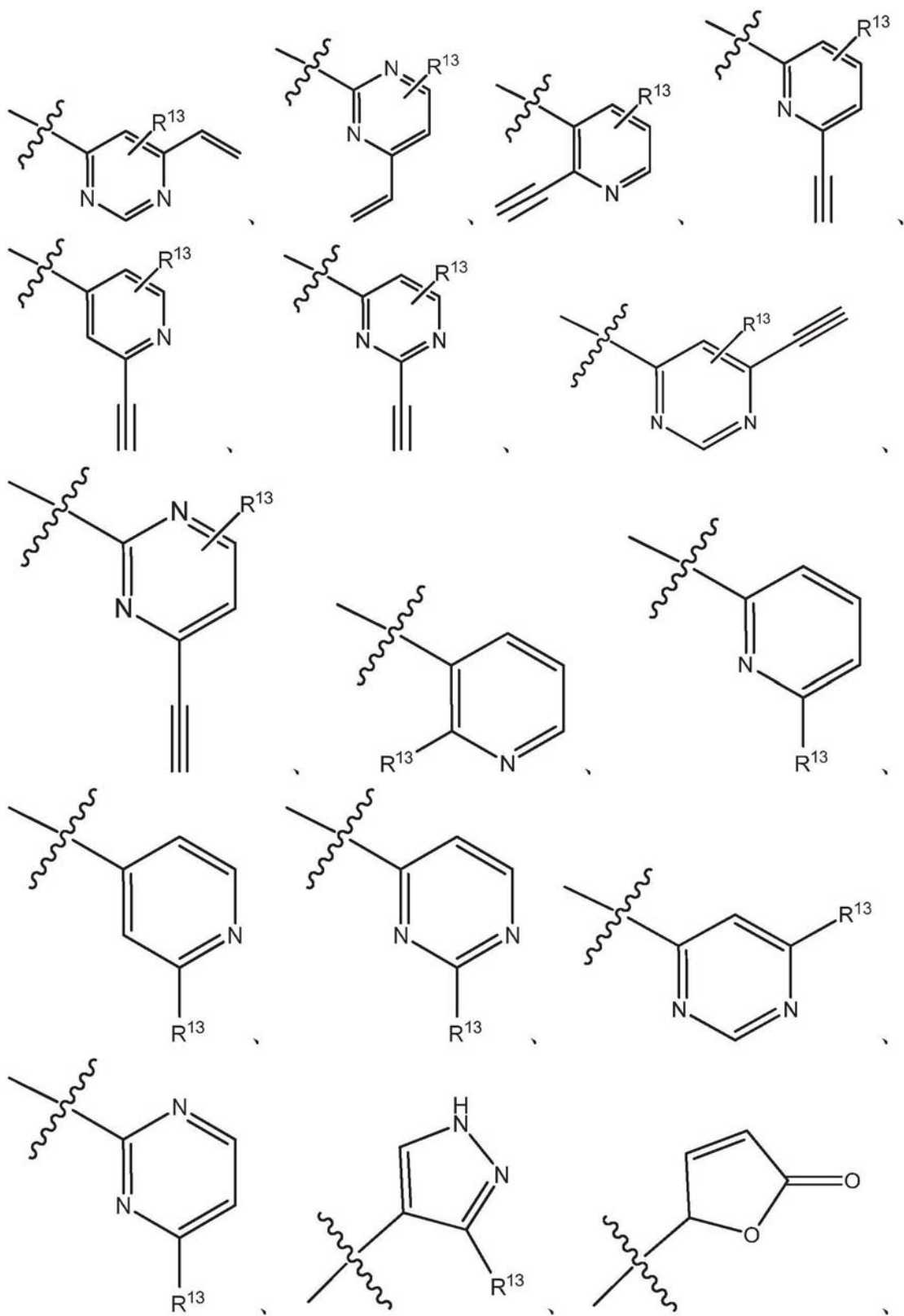
[0567]



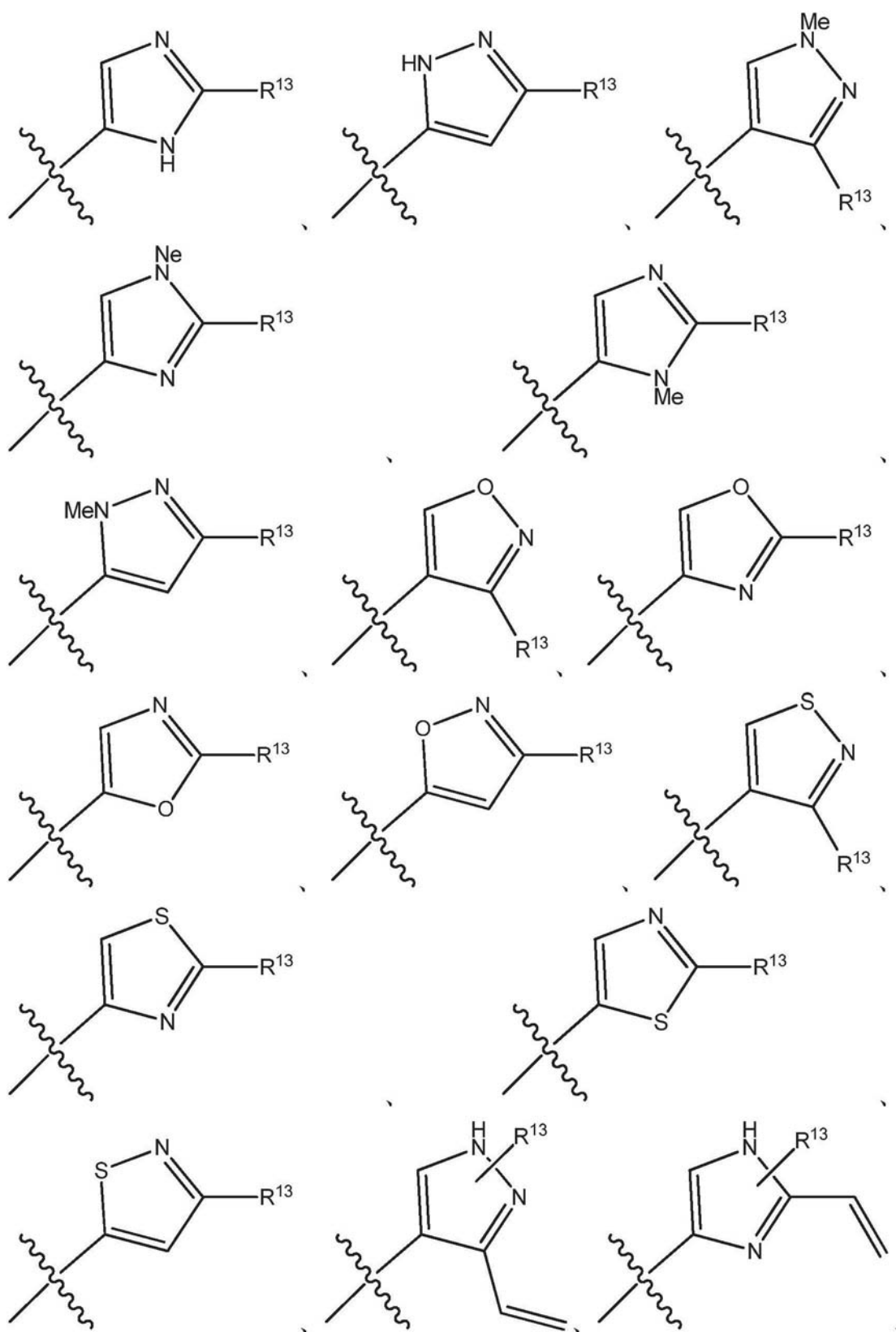
[0568]



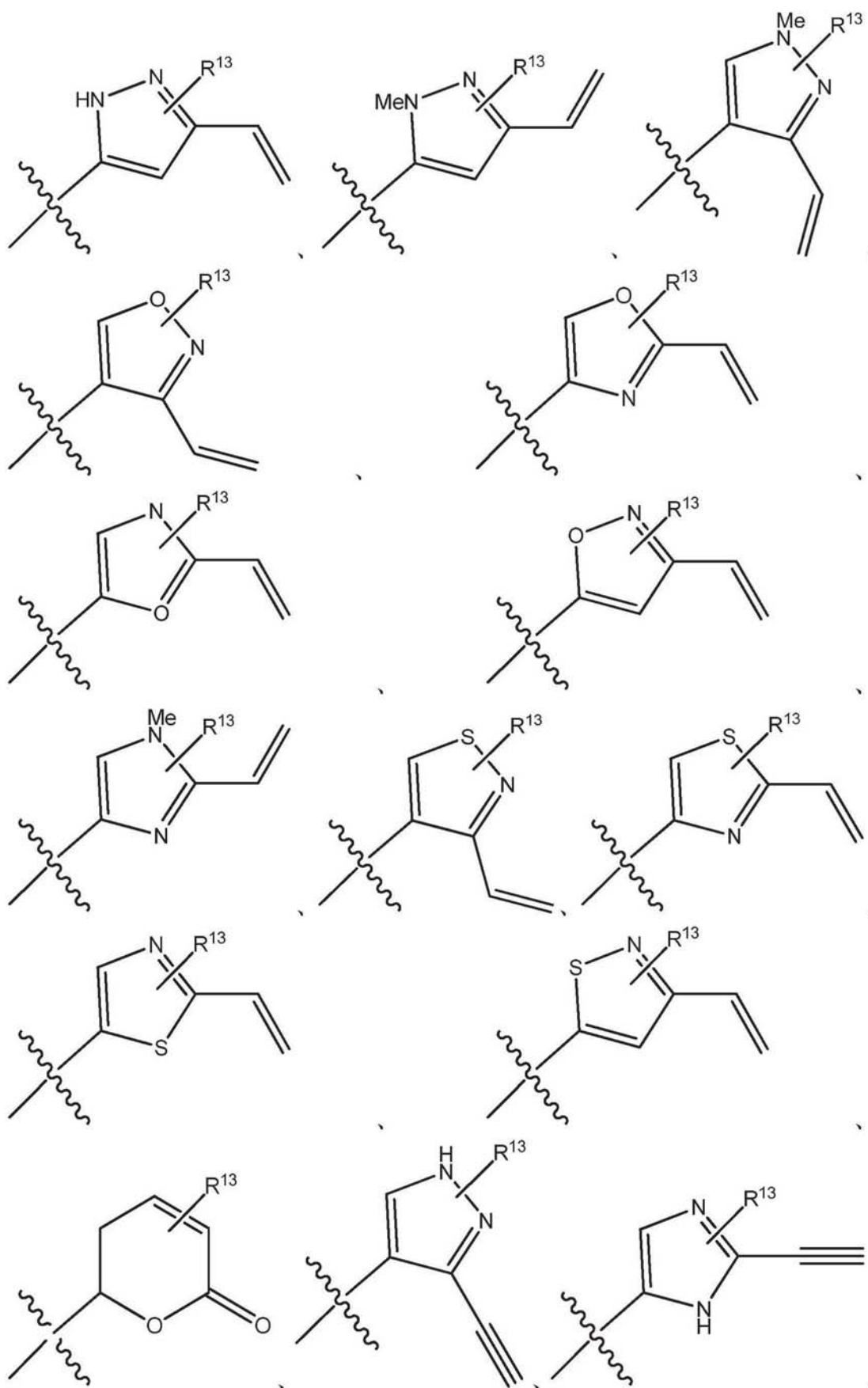
[0569]



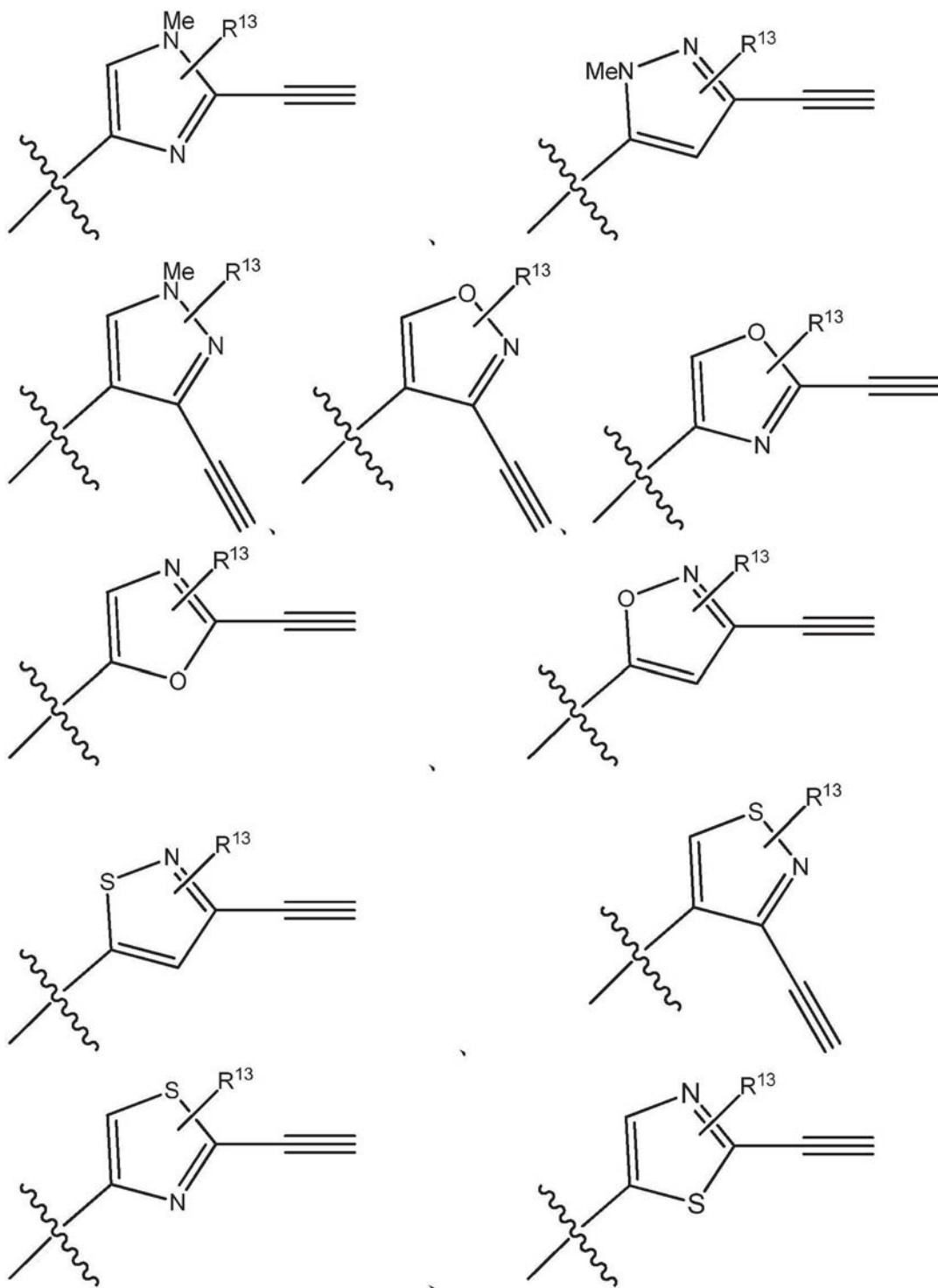
[0570]



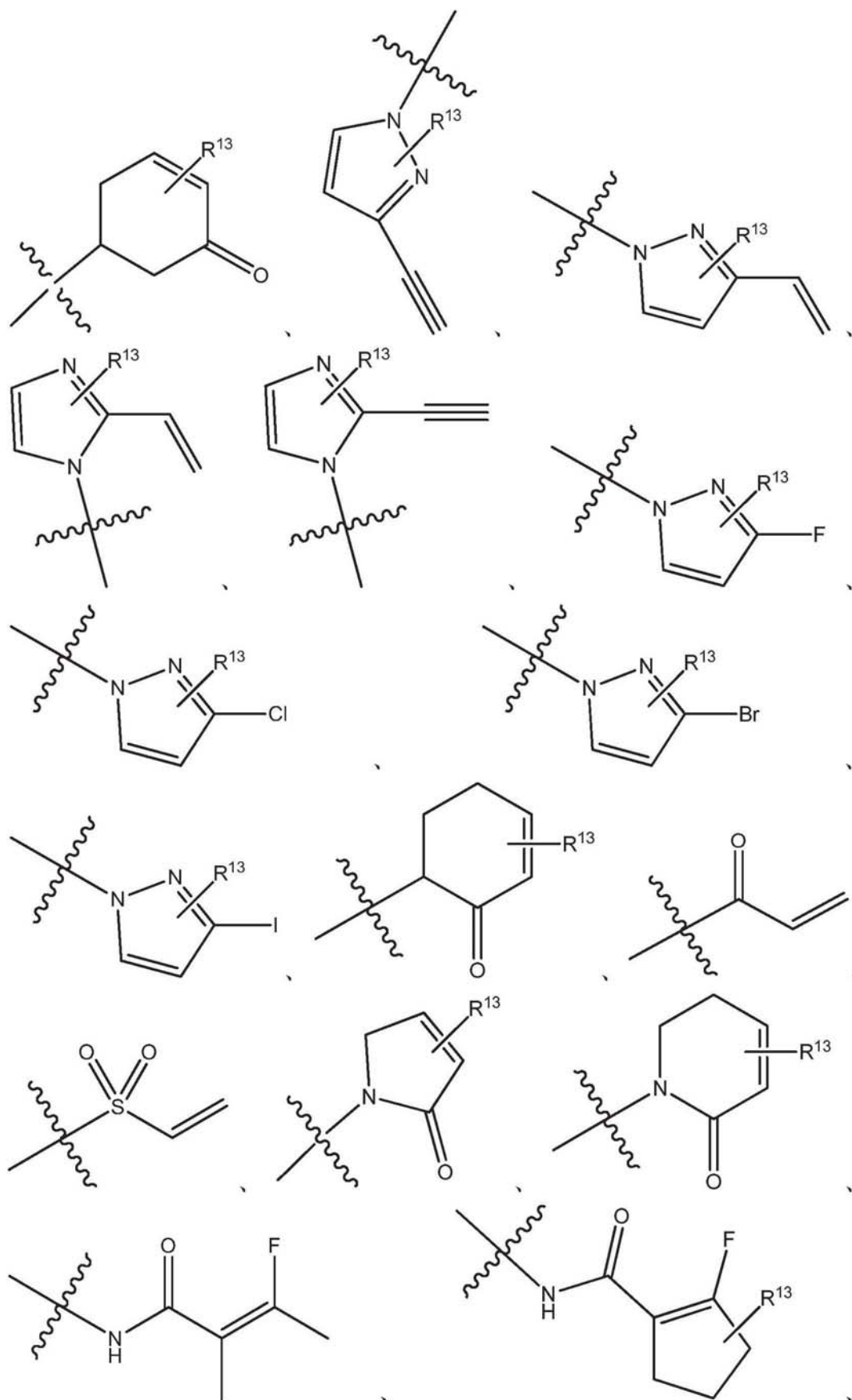
[0571]



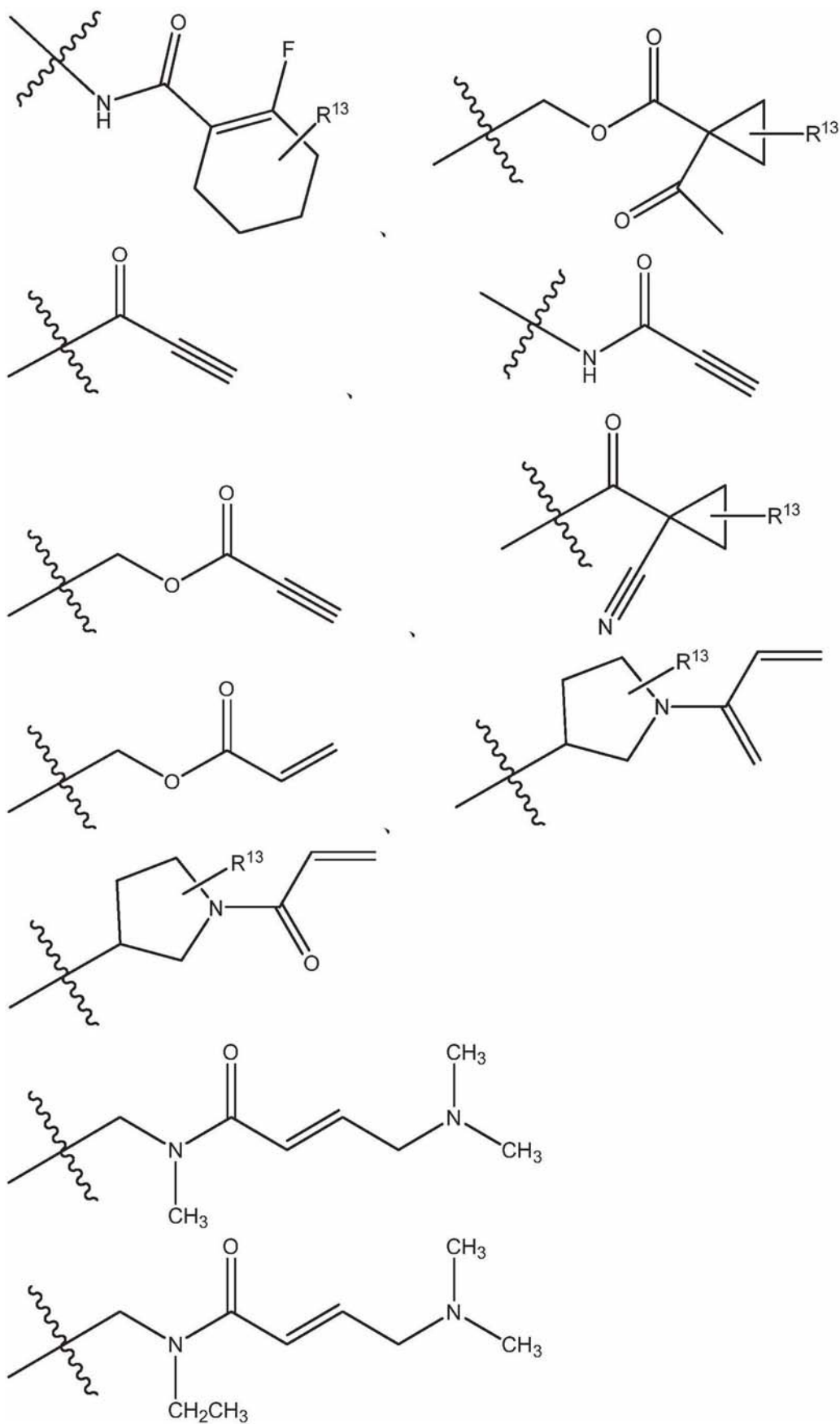
[0572]

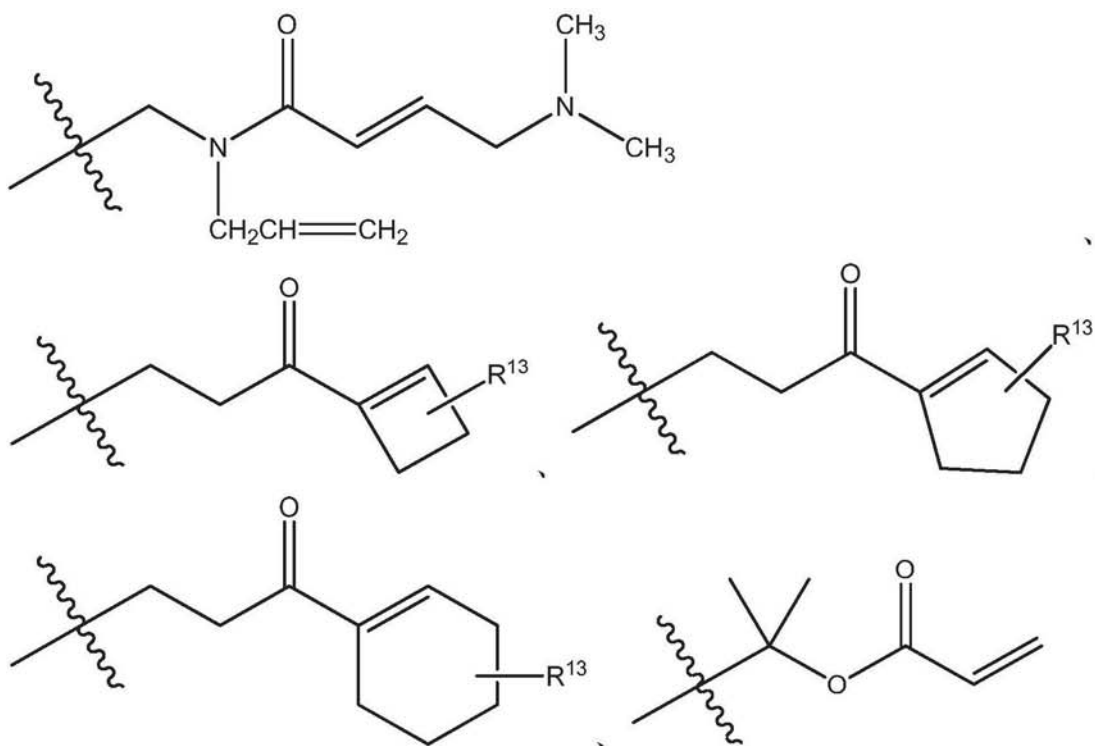


[0573]

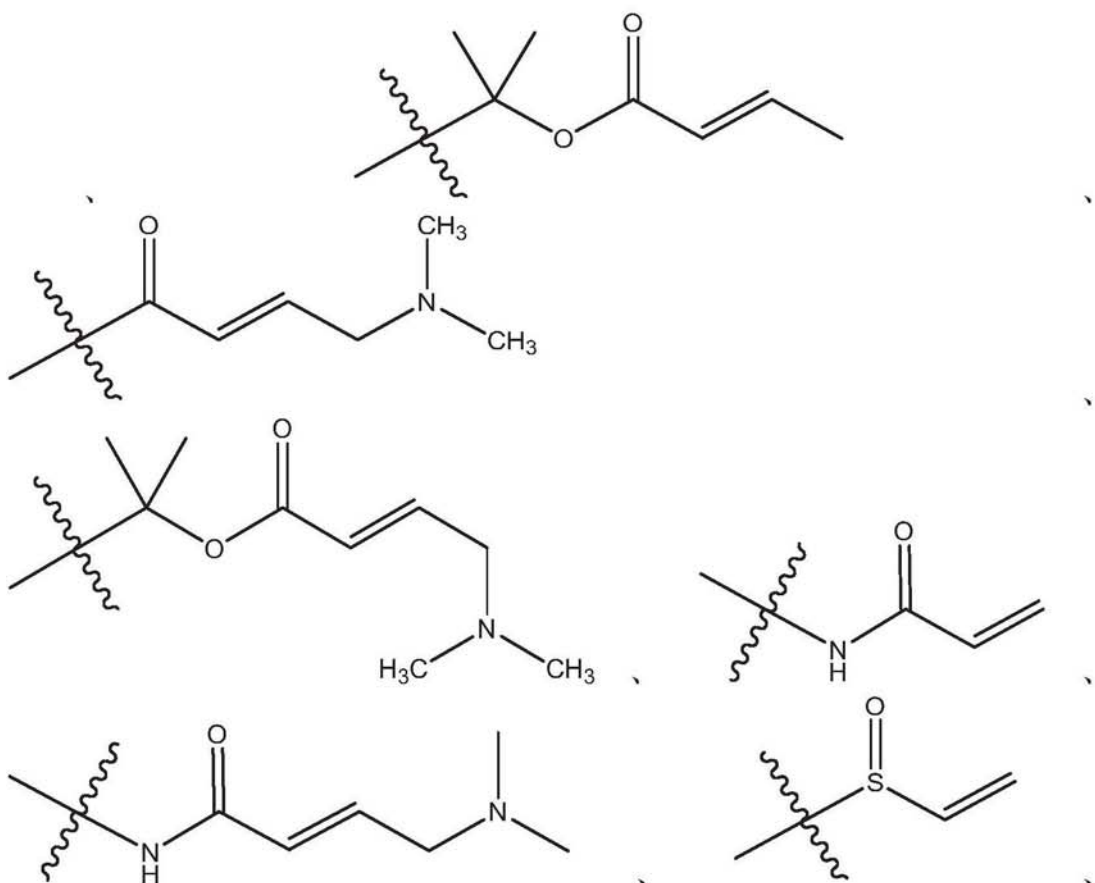


[0574]

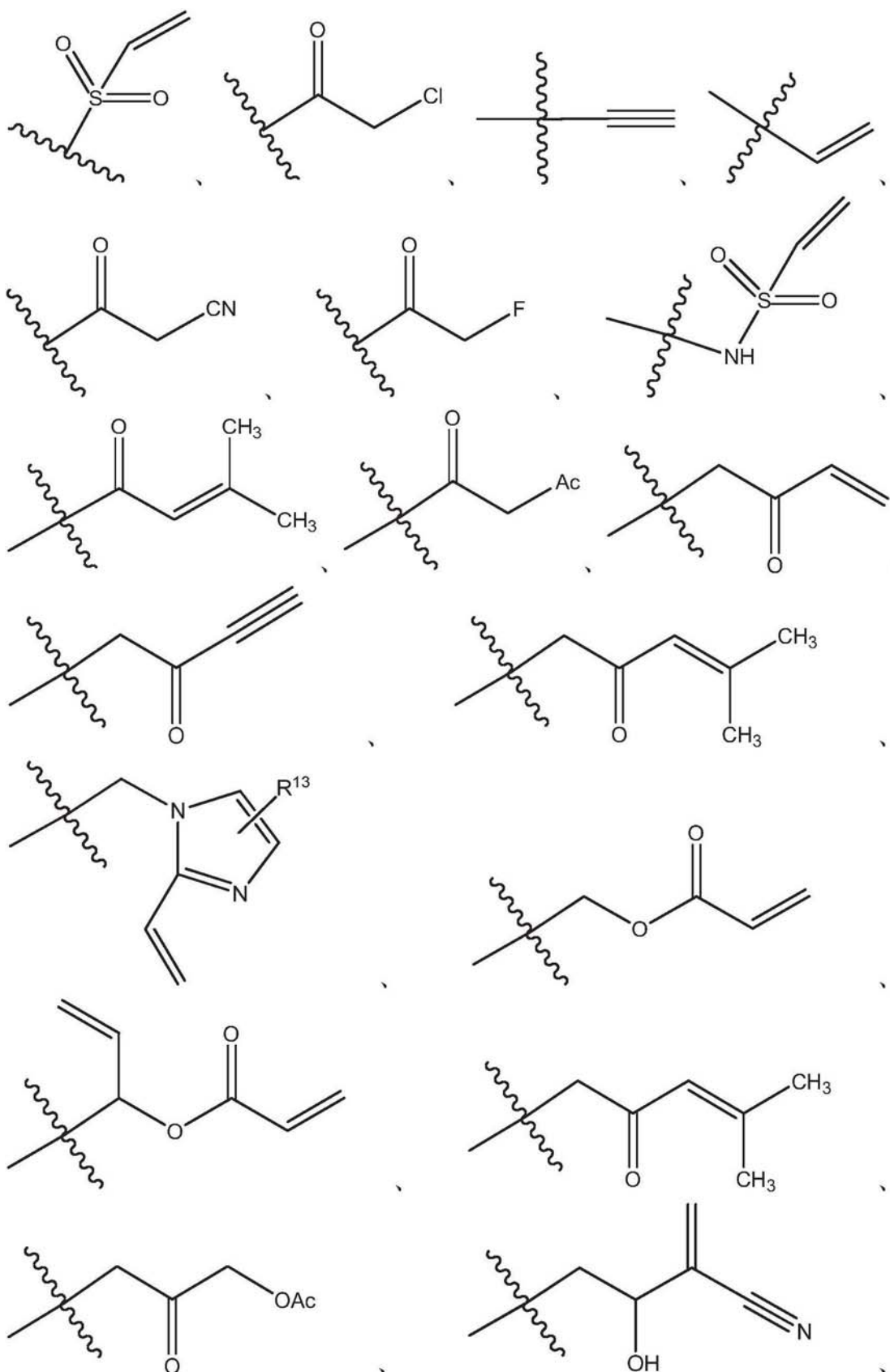




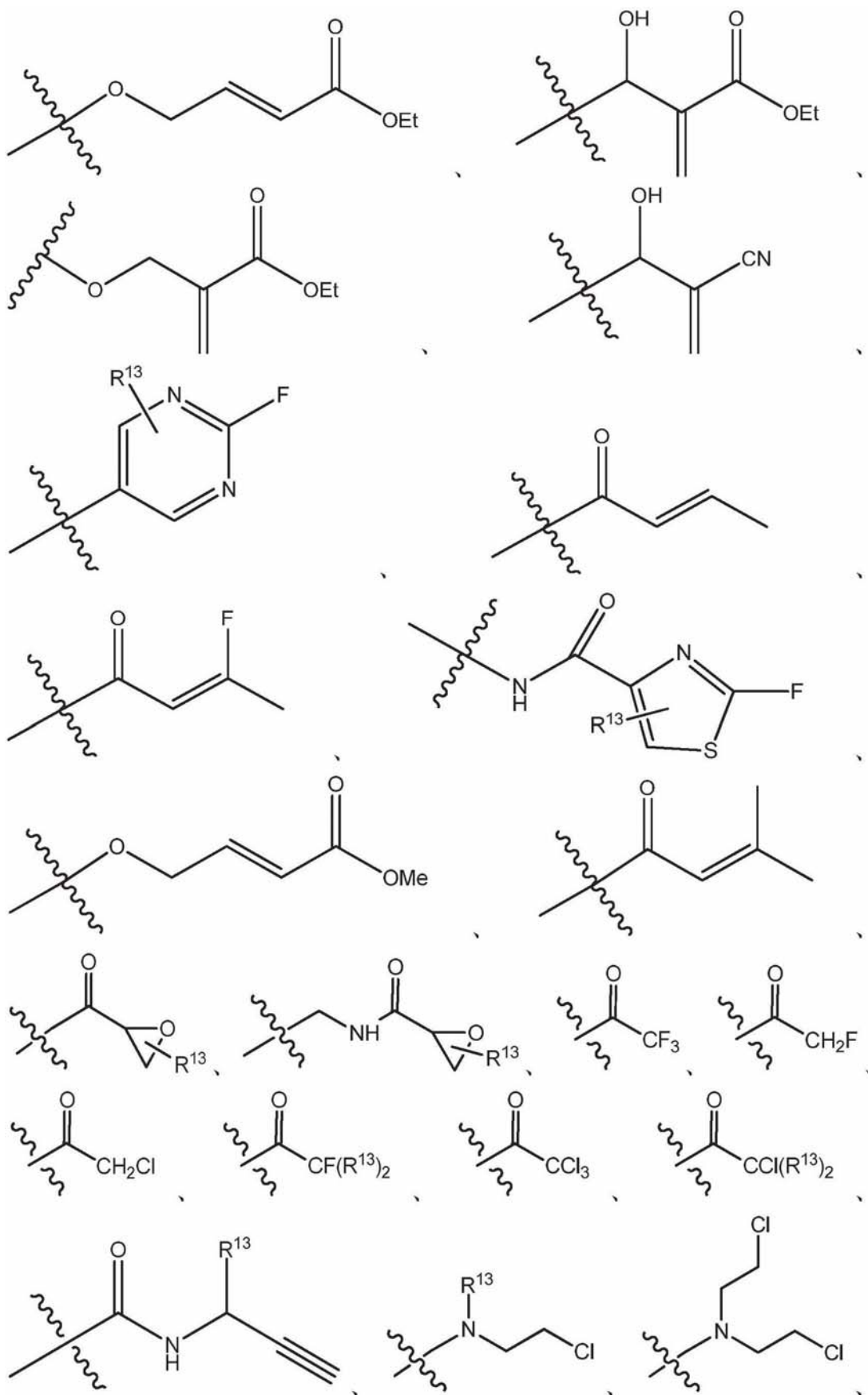
[0575]



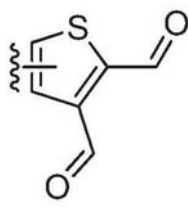
[0576]



[0577]



[0579]

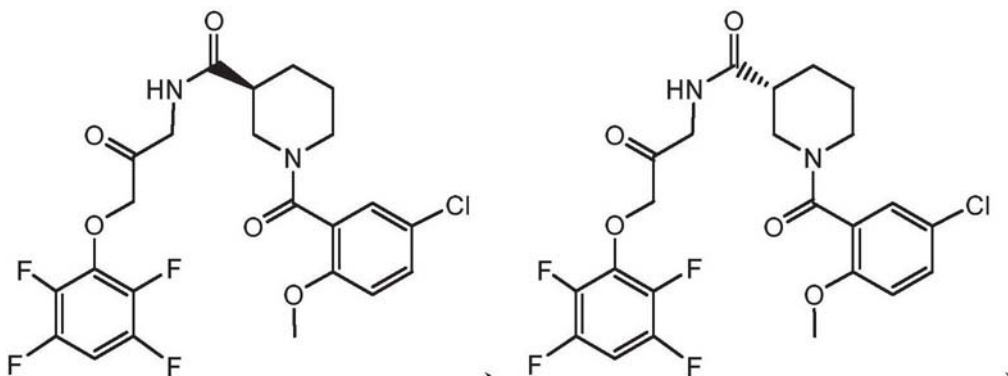

 R^{13} 独立地为氢、氧代、卤素、 CX^{13}_3 、 $-CHX^{13}_2$ 、 $-CH_2X^{13}$ 、 $-CN$ 、 $-SO_2Cl$ 、 $-$

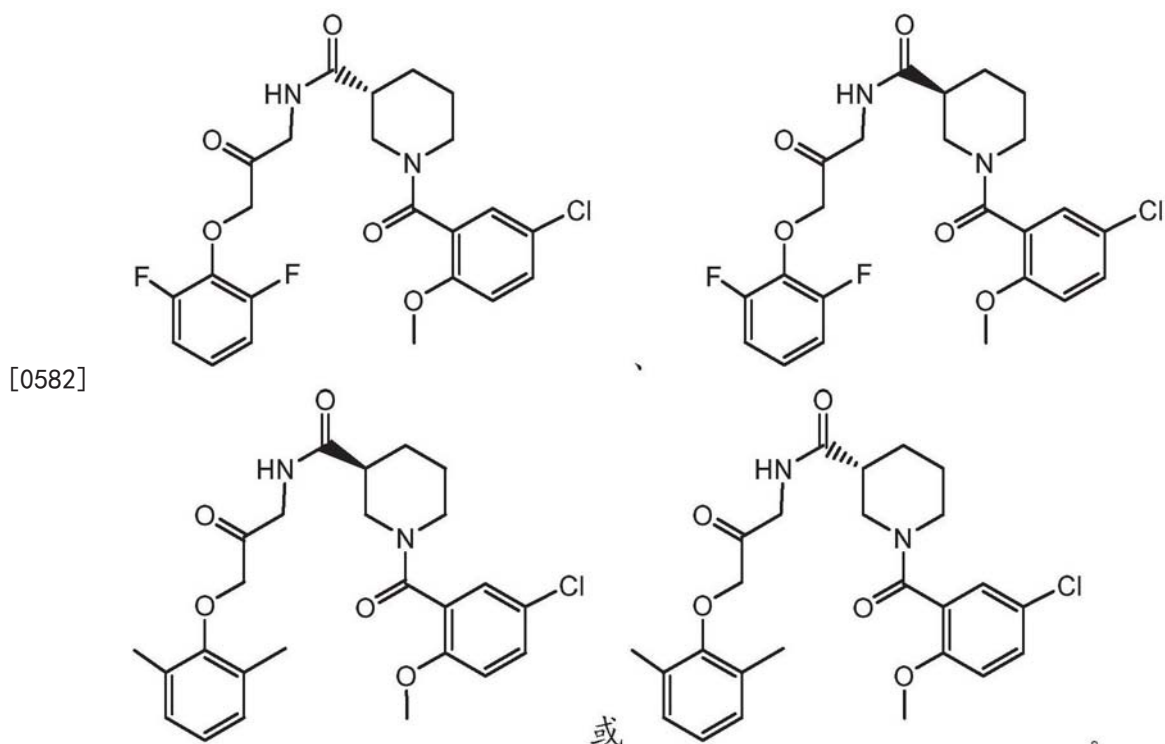
;

$SO_{n13}R^{22}$ 、 $-SO_{v13}NR^{20}R^{21}$ 、 $-NHN R^{20}R^{21}$ 、 $-ONR^{20}R^{21}$ 、 $-NHC(=O)NHN R^{20}R^{21}$ 、 $-NHC(=O)NR^{20}R^{21}$ 、 $-N(O)_{m13}$ 、 $-NR^{20}R^{21}$ 、 $-C(O)R^{22}$ 、 $-C(O)-OR^{22}$ 、 $-C(O)NR^{20}R^{21}$ 、 $-OR^{23}$ 、 $-NR^{20}SO_2R^{23}$ 、 $-NR^{20}C(O)R^{22}$ 、 $-NR^{20}C(O)OR^{22}$ 、 $-NR^{20}OR^{22}$ 、 $-OCX^{13}_3$ 、 $-OCHX^{13}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；两个相邻的 R^2 取代基或两个键合至相同原子的 R^2 取代基可任选地连接形成经取代或未取代的环烷基或经取代或未取代的杂环烷基； R^{20} 、 R^{21} 、 R^{22} 和 R^{23} 独立地为氢、卤素、 $-CX^A_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(=O)NHNH_2$ 、 $-NHC(=O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(=O)H$ 、 $-NHC(=O)OH$ 、 $-NHOH$ 、 $-OCX^A_3$ 、 $-OCHX^A_2$ 、 $-CHX^A_2$ 、 $-CH_2X^A$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{20} 和 R^{21} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；每个 X^A 和 X^{13} 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ ； $n13$ 和 $v13$ 独立地为0至4的整数；并且 $m13$ 独立地为1至2的整数。

[0580] 实施方案P36.一种具有下式的化合物：

[0581]





[0583] 实施方案P37.一种药物组合物,其包含根据实施方案P1-P36中任一项的化合物和药学上可接受的赋形剂。

[0584] 实施方案P38.一种降低K-Ras蛋白的活性水平的方法,所述方法包括使K-Ras蛋白与根据实施方案P1-P36中的一项所述的化合物接触。

[0585] 实施方案P39.一种降低K-Ras-4B蛋白的活性水平的方法,所述方法包括使K-Ras-4B蛋白与根据实施方案P1-P36中的一项所述的化合物接触。

[0586] 实施方案P40.一种治疗癌症的方法,所述方法包括向有需要的受试者施用治疗有效量的根据实施方案P1-P36中的一项所述的化合物。

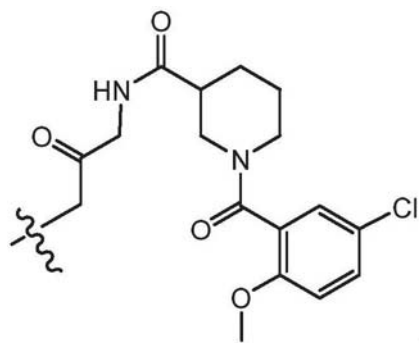
[0587] 实施方案P41.根据实施方案P40所述的方法,其中所述癌症为胰腺癌、肺癌或结直肠癌。

[0588] 实施方案P42.一种K-Ras蛋白,其与根据实施方案P1-P36中的一项所述的化合物共价键合。

[0589] 实施方案P43.根据实施方案P42所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基共价键合。

[0590] 实施方案P44.根据实施方案P42所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基不可逆地共价键合。

[0591] 实施方案P45.一种K-Ras蛋白,其与具有下式的化合物共价键合:

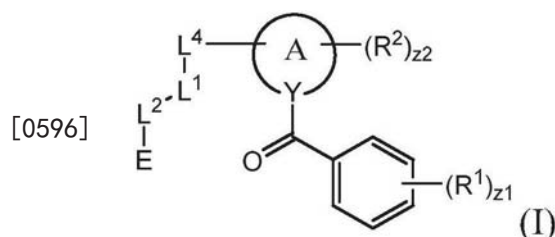


[0592] 实施方案P46.根据实施方案P45所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基共价键合。

[0593] 实施方案P47.根据实施方案P45所述的K-Ras蛋白,其中所述化合物与所述蛋白对应人K-Ras-4B的C185的半胱氨酸残基共价键合。

[0594] VIII.附加实施方案

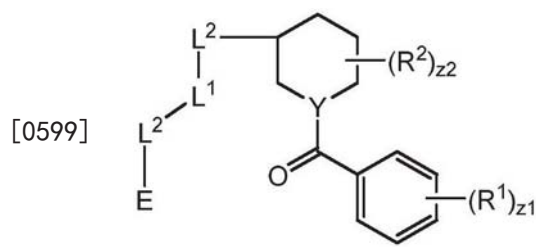
[0595] 实施方案1.一种具有下式的化合物:



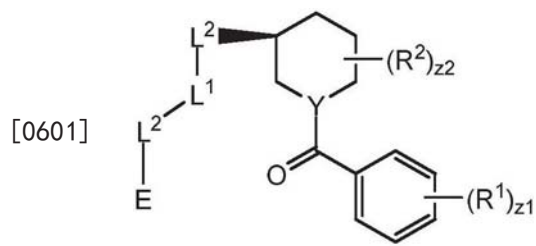
[0597] 其中,Y为N或CH;环A为C₃-C₇环烷基或3-7元杂环烷基;R¹独立地为卤素、CX¹₃、-CHX¹₂、-CH₂X¹、-CN、-SO₂Cl、-SO_{n1}R¹⁰、-SO_{v1}NR⁷R⁸、-NHN⁷R⁸、-ONR⁷R⁸、-NHC(=O)NHN⁷R⁸、-NHC(=O)NR⁷R⁸、-N(O)_{m1}、-NR⁷R⁸、-C(O)R⁹、-C(O)-OR⁹、-C(O)NR⁷R⁸、-OR¹⁰、-NR⁷SO₂R¹⁰、-NR⁷C(O)R⁹、-NR⁷C(O)OR⁹、-NR⁷OR⁹、-OCX¹₃、-OCHX¹₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基;两个相邻的R¹取代基可任选地连接形成经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基;L¹为键、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基;L²为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR^{7B}-、-NR^{7B}C(O)-、-C(O)NR^{7B}-、-SO₂NR^{7B}-、-NR^{7B}SO₂-、-OC(O)NR^{7B}-、-NR^{7B}C(O)O-、-CR^{9B}=NO-、-ON=CR^{9B}-、-NR^{8B}C(O)NR^{7B}-、-NR^{8B}C(=NR^{10B})NR^{7B}-、-NR^{8B}C(=NR^{10B})-、-C(=NR^{10B})NR^{7B}-、-OC(=NR^{10B})-、-C(=NR^{10B})O-、经取代或未取代的亚烷基、经取代或未取代的杂亚烷基、经取代或未取代的亚环烷基、经取代或未取代的杂亚环烷基、经取代或未取代的亚芳基、经取代或未取代的杂亚芳基;L⁴为键、-O-、-C(O)-、-S-、-SO-、-S(O)₂-、-NR⁴-、-NR⁴C(O)-、-C(O)NR⁴-、-SO₂NR⁴-、-NR⁴SO₂-、-NR⁴SO₂-、-OC(O)NR⁴-、-NR⁴C(O)O-、经取代或未取代的C₁-C₃亚烷基、经取代或未取代的2-3元杂亚烷基;E为亲电子部分;R²独立地为氧代、卤素、CX²₃、-CHX²₂、-CH₂X²、-CN、-SO₂Cl、-SO_{n2}R¹⁴、-SO_{v2}NR¹¹R¹²、-NHN¹¹R¹²、-ONR¹¹R¹²、-NHC(=O)NHN¹¹R¹²、-NHC(=O)NR¹¹R¹²、-N(O)_{m2}、-NR¹¹R¹²、-C(O)R¹⁴、-C(O)-OR¹⁴、-C(O)NR¹¹R¹²、-OR¹⁵、-NR¹¹SO₂R¹⁵、-NR¹¹C(O)R¹⁴、-NR¹¹C(O)OR¹⁴、-NR¹¹OR¹⁴、-OCX²₃、-OCHX²₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代

的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；两个相邻的 R^2 取代基或两个键合至相同原子的 R^2 取代基可任选地连接形成经取代或未取代的环烷基或经取代或未取代的杂环烷基； R^4 独立地为氢、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基； R^7 、 R^8 、 R^9 、 R^{10} 、 R^{7B} 、 R^{8B} 、 R^{9B} 、 R^{10B} 、 R^{11} 、 R^{12} 、 R^{14} 和 R^{15} 独立地为氢、卤素、 $-CX_3$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_2Cl$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX_3$ 、 $-OCHX_2$ 、 $-CHX_2$ 、 $-CH_2X$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的 R^7 和 R^8 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的 R^{11} 和 R^{12} 取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；每个 X 、 X^1 和 X^2 独立地为 $-F$ 、 $-Cl$ 、 $-Br$ 或 $-I$ ； n_1 、 n_2 、 v_1 和 v_2 独立地为0至4的整数； m_1 和 m_2 独立地为1至2的整数； z_1 独立地为0至5的整数；并且 z_2 独立地为0至10的整数。

[0598] 实施方案2. 根据实施方案1所述的化合物，其具有下式：



[0600] 实施方案3. 根据实施方案1所述的化合物，其具有下式：



[0602] 实施方案4. 根据实施方案1-3中的一项所述的化合物，其中Y为CH。

[0603] 实施方案5. 根据实施方案1-3中的一项所述的化合物，其中Y为N。

[0604] 实施方案6. 根据实施方案1-5中的一项所述的化合物，其中 R^1 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、经取代或未取代的 C_1 - C_6 烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的5-6元杂芳基。

[0605] 实施方案7. 根据实施方案1-5中的一项所述的化合物，其中 R^1 独立地为卤素、 $-CX^1_3$ 、 $-CHX^1_2$ 、 $-CH_2X^1$ 、 $-OH$ 、 $-SH$ 、 $-COOH$ 、 $-OCX^1_3$ 、 $-OCHX^1_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。

[0606] 实施方案8. 根据实施方案1-5中的一项所述的化合物，其中 R^1 独立地为卤素或 $-OCH_3$ 。

[0607] 实施方案9.根据实施方案1-8中的一项所述的化合物,其中 z_1 为2。

[0608] 实施方案10.根据实施方案1-8中的一项所述的化合物,其中 z_1 为3。

[0609] 实施方案11.根据实施方案1-10中的一项所述的化合物,其中 R^2 独立地为氧代、卤素、 CX^2_3 、 $-CHX^2_2$ 、 $-CH_2X^2$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、经取代或未取代的 C_1 - C_6 烷基、经取代或未取代的2-6元杂烷基、经取代或未取代的 C_3 - C_8 环烷基、经取代或未取代的3-8元杂环烷基、经取代或未取代的 C_6 芳基或经取代或未取代的5-6元杂芳基。

[0610] 实施方案12.根据实施方案1-10中的一项所述的化合物,其中 R^2 独立地为氧代、卤素、 $-CX^2_3$ 、 $-CHX^2_2$ 、 $-CH_2X^2$ 、 $-OH$ 、 $-SH$ 、 $-OCX^2_3$ 、 $-OCHX^2_2$ 、 $-CH_3$ 、 $-CH_2CH_3$ 、 $-OCH_3$ 、 $-OCH_2CH_3$ 、 $-SCH_3$ 或 $-SCH_2CH_3$ 。

[0611] 实施方案13.根据实施方案1-12中的一项所述的化合物,其中 z_2 为0。

[0612] 实施方案14.根据实施方案1-13中的一项所述的化合物,其中 L^1 为键、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。

[0613] 实施方案15.根据实施方案1-13中的一项所述的化合物,其中 L^1 为键、未取代的 C_1 - C_4 亚烷基或未取代的2-4元杂亚烷基。

[0614] 实施方案16.根据实施方案1-13中的一项所述的化合物,其中 L^1 为键。

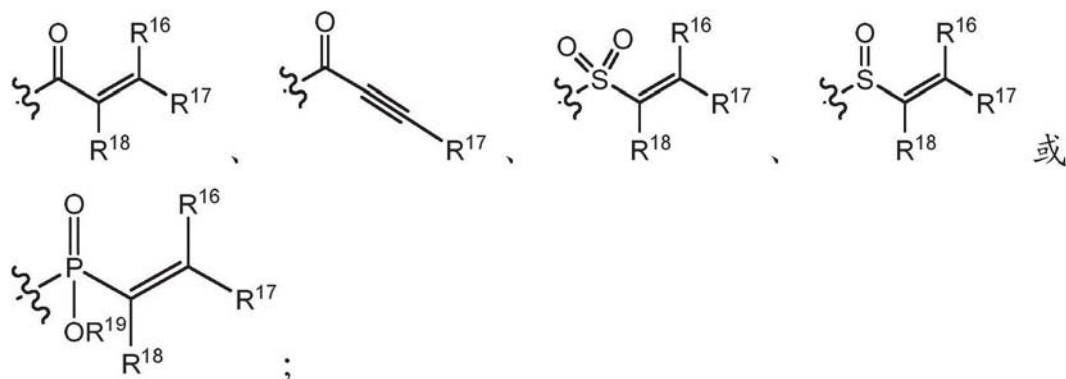
[0615] 实施方案17.根据实施方案1-16中的一项所述的化合物,其中 L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-SO-$ 、 $-S(O)_2-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、 $-SO_2NH-$ 、 $-NHSO_2-$ 、 $-OC(O)NH-$ 、 $-NHC(O)O-$ 、 $-NHC(O)NH-$ 、经取代或未取代的亚烷基或经取代或未取代的杂亚烷基。

[0616] 实施方案18.根据实施方案1-16中的一项所述的化合物,其中 L^2 为键、 $-O-$ 、 $-C(O)-$ 、 $-S-$ 、 $-NH-$ 、 $-NHC(O)-$ 、 $-C(O)NH-$ 、未取代的 C_1 - C_4 亚烷基或未取代的2-4元杂亚烷基。

[0617] 实施方案19.根据实施方案1-16中的一项所述的化合物,其中 L^2 为 $-NH-$ 。

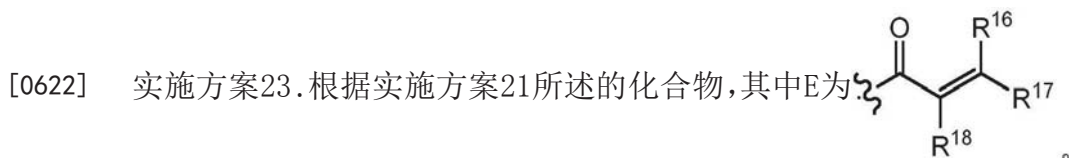
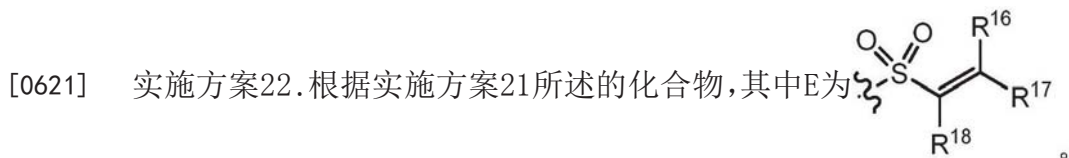
[0618] 实施方案20.根据实施方案1-16中的一项所述的化合物,其中 L^2 为键。

[0619] 实施方案21.根据实施方案1-20中的一项所述的化合物,其中E为



[0620] 其中 R^{16} 独立地为氢、卤素、 CX^{16}_3 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-SO_{n16}R^{16D}$ 、 $-SO_{v16}NR^{16A}R^{16B}$ 、 $-NHN R^{16A}R^{16B}$ 、 $-ONR^{16A}R^{16B}$ 、 $-NHC(=O)NHN R^{16A}R^{16B}$ 、 $-NHC(O)NR^{16A}R^{16B}$ 、 $-N(O)_{m16}$ 、 $-NR^{16A}R^{16B}$ 、 $-C(O)R^{16C}$ 、 $-C(O)OR^{16C}$ 、 $-C(O)NR^{16A}R^{16B}$ 、 $-OR^{16D}$ 、 $-NR^{16A}SO_2R^{16D}$ 、 $-NR^{16A}C(O)R^{16C}$ 、 $-NR^{16A}C(O)OR^{16C}$ 、 $-NR^{16A}OR^{16C}$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基; R^{17} 独立地为氢、卤素、 CX^{17}_3 、 $-CHX^{17}_2$ 、 $-CH_2X^{17}$ 、 $-CN$ 、 $-SO_{n17}R^{17D}$ 、 $-SO_{v17}NR^{17A}R^{17B}$ 、

NHNR^{17A}R^{17B}、-ONR^{17A}R^{17B}、-NHC = (O) NHNR^{17A}R^{17B}、-NHC (O) NR^{17A}R^{17B}、-N (O)_{m17}、-NR^{17A}R^{17B}、-C (O) R^{17C}、-C (O) -OR^{17C}、-C (O) NR^{17A}R^{17B}、-OR^{17D}、-NR^{17A}SO₂R^{17D}、-NR^{17A}C (O) R^{17C}、-NR^{17A}C (O) OR^{17C}、-NR^{17A}OR^{17C}、-OCX¹⁷₃、-OCHX¹⁷₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；R¹⁸独立地为氢、卤素、CX¹⁸₃、-CHX¹⁸₂、-CH₂X¹⁸、-CN、-SO_{n18}R^{18D}、-SO_{v18}NR^{18A}R^{18B}、-NHNR^{18A}R^{18B}、-ONR^{18A}R^{18B}、-NHC = (O) NHNR^{18A}R^{18B}、-NHC (O) NR^{18A}R^{18B}、-N (O)_{m18}、-NR^{18A}R^{18B}、-C (O) R^{18C}、-C (O) -OR^{18C}、-C (O) NR^{18A}R^{18B}、-OR^{18D}、-NR^{18A}SO₂R^{18D}、-NR^{18A}C (O) R^{18C}、-NR^{18A}C (O) OR^{18C}、-NR^{18A}OR^{18C}、-OCX¹⁸₃、-OCHX¹⁸₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；R¹⁹独立地为氢、卤素、CX¹⁹₃、-CHX¹⁹₂、-CH₂X¹⁹、-CN、-SO_{n19}R^{19D}、-SO_{v19}NR^{19A}R^{19B}、-NHNR^{19A}R^{19B}、-ONR^{19A}R^{19B}、-NHC = (O) NHNR^{19A}R^{19B}、-NHC (O) NR^{19A}R^{19B}、-N (O)_{m19}、-NR^{19A}R^{19B}、-C (O) R^{19C}、-C (O) -OR^{19C}、-C (O) NR^{19A}R^{19B}、-OR^{19D}、-NR^{19A}SO₂R^{19D}、-NR^{19A}C (O) R^{19C}、-NR^{19A}C (O) OR^{19C}、-NR^{19A}OR^{19C}、-OCX¹⁹₃、-OCHX¹⁹₂、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基；R^{16A}、R^{16B}、R^{16C}、R^{16D}、R^{17A}、R^{17B}、R^{17C}、R^{17D}、R^{18A}、R^{18B}、R^{18C}、R^{18D}、R^{19A}、R^{19B}、R^{19C}、R^{19D}独立地为氢、卤素、-CX₃、-CN、-OH、-NH₂、-COOH、-CONH₂、-NO₂、-SH、-SO₃H、-SO₄H、-SO₂NH₂、-NHNH₂、-ONH₂、-NHC (O) NHNH₂、-NHC (O) NH₂、-NHSO₂H、-NHC (O) H、-NHC (O) OH、-NHOH、-OCX₃、-OCHX₂、-CHX₂、-CH₂X、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基或经取代或未取代的杂芳基；键合至相同氮原子的R^{16A}和R^{16B}取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的R^{17A}和R^{17B}取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的R^{18A}和R^{18B}取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；键合至相同氮原子的R^{19A}和R^{19B}取代基可任选地连接形成经取代或未取代的杂环烷基或经取代或未取代的杂芳基；每个X、X¹⁶、X¹⁷、X¹⁸和X¹⁹独立地为-F、-Cl、-Br或-I；n₁₆、n₁₇、n₁₈、n₁₉、v₁₆、v₁₇、v₁₈和v₁₉独立地为0至4的整数；并且m₁₆、m₁₇、m₁₈和m₁₉独立地为1至2的整数。



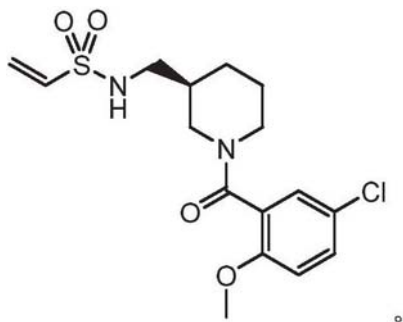
[0623] 实施方案24. 根据实施方案21-23中的一项所述的化合物, 其中

[0624] R¹⁶、R¹⁷和R¹⁸独立地为氢、-CH₂NH₂、-CH₂CH₂NH₂、-CH₂N (CH₃)₂或-CH₂CH₂N (CH₃)₂。

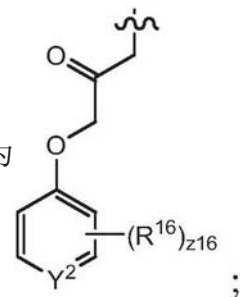
[0625] 实施方案25. 根据实施方案21-24中的一项所述的化合物, 其中L⁴为键或-CH₂-。

[0626] 实施方案26. 根据实施方案21、22、24或25中的一项所述的化合物, 其具有下式:

[0627]



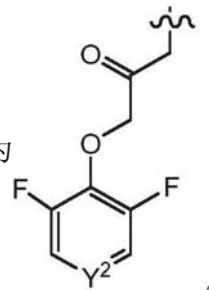
[0628] 实施方案27. 根据实施方案1-20中的一项所述的化合物, 其中E为



其中 R^{16} 独立地为卤素、 CX^{16}_3 、 $-CHX^{16}_2$ 、 $-CH_2X^{16}$ 、 $-CN$ 、 $-OH$ 、 $-NH_2$ 、 $-COOH$ 、 $-CONH_2$ 、 $-NO_2$ 、 $-SH$ 、 $-SO_3H$ 、 $-SO_4H$ 、 $-SO_2NH_2$ 、 $-NHNH_2$ 、 $-ONH_2$ 、 $-NHC(O)NHNH_2$ 、 $-NHC(O)NH_2$ 、 $-NHSO_2H$ 、 $-NHC(O)H$ 、 $-NHC(O)OH$ 、 $-NHOH$ 、 $-OCX^{16}_3$ 、 $-OCHX^{16}_2$ 、经取代或未取代的烷基、经取代或未取代的杂烷基、经取代或未取代的环烷基、经取代或未取代的杂环烷基、经取代或未取代的芳基、经取代或未取代的杂芳基； Y^2 为N或CH； z_{16} 为0至4的整数；并且每个 X^{16} 独立地为-F、-Cl、-Br或-I。

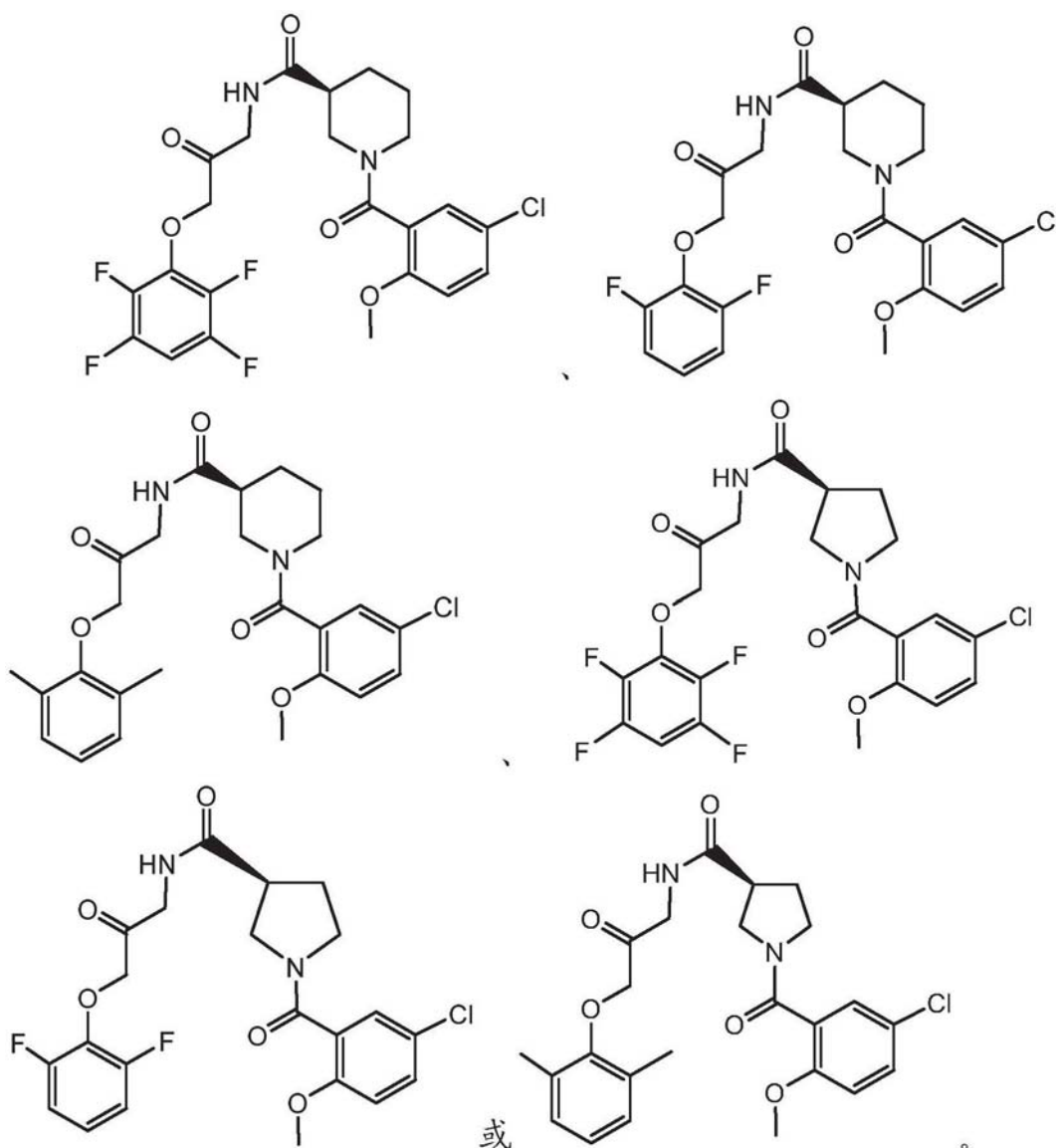
[0629] 实施方案28. 根据实施方案27所述的化合物, 其中 R^{16} 独立地为卤素。[0630] 实施方案29. 根据实施方案27所述的化合物, 其中 R^{16} 独立地为-F。[0631] 实施方案30. 根据实施方案27-29中的一项所述的化合物, 其中 z_{16} 为4。[0632] 实施方案31. 根据实施方案27-29中的一项所述的化合物, 其中 z_{16} 为2。

[0633] 实施方案32. 根据实施方案31所述的化合物, 其中E为

[0634] 实施方案33. 根据实施方案27-32中的一项所述的化合物, 其中 Y^2 为CH。[0635] 实施方案34. 根据实施方案27-32中的一项所述的化合物, 其中 Y^2 为N。[0636] 实施方案35. 根据实施方案27-34中的一项所述的化合物, 其中 L^4 为 $-N(R^4)C(O)-$ 。[0637] 实施方案36. 根据实施方案27-35中的一项所述的化合物, 其中 R^4 为氢。

[0638] 实施方案37. 根据实施方案27-36中的一项所述的化合物, 其具有下式:

[0639]



[0640] 实施方案38.一种药物组合物,其包含根据实施方案1-37中任一项所述的化合物和药学上可接受的赋形剂。

[0641] 实施方案39.一种降低K-Ras蛋白的活性水平的方法,所述方法包括使所述K-Ras蛋白与根据实施方案1-37中的一项所述的化合物接触。

[0642] 实施方案40.一种降低K-Ras-4B蛋白的活性水平的方法,所述方法包括使所述K-Ras-4B蛋白与根据实施方案1-37中的一项所述的化合物接触。

[0643] 实施方案41.一种治疗癌症的方法,所述方法包括向有需要的受试者施用治疗有效量的根据实施方案1-37中的一项所述的化合物。

[0644] 实施方案42.根据实施方案41所述的方法,其中所述癌症为胰腺癌、肺癌或结直肠癌。

[0645] 实施方案43.一种K-Ras蛋白,其与根据实施方案1-37中的一项所述的化合物共价键合。

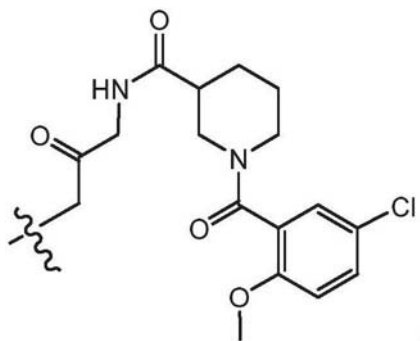
[0646] 实施方案44.根据实施方案43所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基共价键合。

[0647] 实施方案45.根据实施方案43所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基不可逆地共价键合。

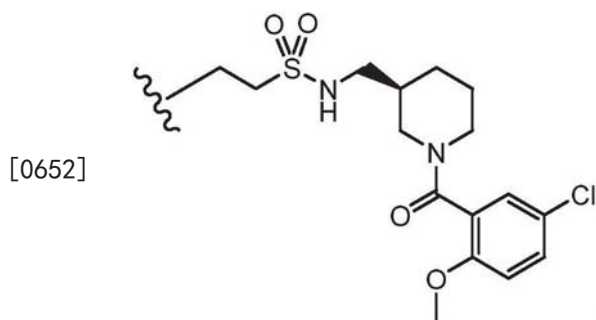
[0648] 实施方案46.根据实施方案43所述的K-Ras蛋白,其中所述化合物与所述蛋白的组氨酸残基共价键合。

[0649] 实施方案47.根据实施方案43所述的K-Ras蛋白,其中所述化合物与所述蛋白的组氨酸残基不可逆地共价键合。

[0650] 实施方案48.一种K-Ras蛋白,其与具有下式的化合物共价键合:



[0651] 实施方案49.一种K-Ras蛋白,其与具有下式的化合物共价键合:



[0653] 实施方案50.根据实施方案48-49中的一项所述的K-Ras蛋白,其中所述化合物与所述蛋白的半胱氨酸残基共价键合。

[0654] 实施方案51.根据实施方案48所述的K-Ras蛋白,其中所述化合物与所述蛋白对应于人K-Ras-4B的C185的半胱氨酸残基共价键合。

[0655] 实施方案52.根据实施方案48-49中的一项所述的K-Ras蛋白,其中所述化合物与所述蛋白的组氨酸残基共价键合。

[0656] 实施方案53.根据实施方案48所述的K-Ras蛋白,其中所述化合物与所述蛋白对应于人K-Ras-4B的H95的组氨酸残基共价键合。

IX. 实施例

[0657] 实施例1.使用系链小分子化合物共价修饰Kras中的H95残基

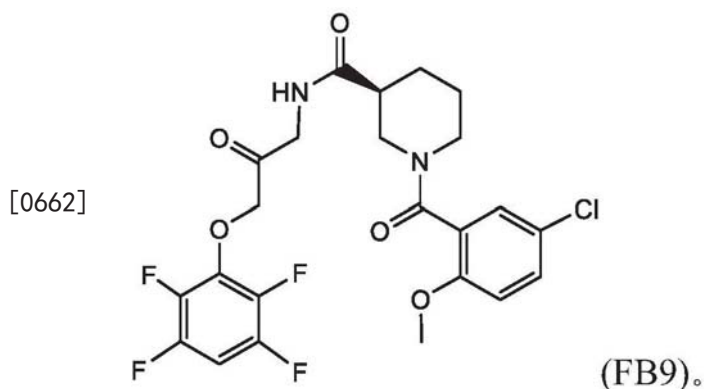
[0658] K-Ras是最常突变的致癌基因,在30%人类癌症中发现激活了这种小GTP酶中的突变。K-Ras中的突变与对化学疗法或辐射的耐受性相关。肿瘤藏有这些突变的患者常常从靶向疗法中排除,并且往往整体生存率不佳。尽管进行了几十年的研究,但对于具有突变K-Ras的癌症仍无有效的治疗。

[0659] 开发直接靶向Ras的小分子抑制剂非常理想,但已经证实是一个重大的挑战。Ras

蛋白的同种型(H-Ras、N-Ras和K-Ras)在正常细胞中起至关重要的作用。因此,理想的Ras靶向药物将特异性靶向蛋白的致癌形式。然而,靶向K-Ras(即不区分野生型和突变蛋白)可能是有效方法,因为所有同种型在正常组织中都冗余,并且预计消除一种是可耐受的。

[0660] 针对抑制Ras翻译后加工已经做出相当大的努力。已经研究了法尼基转移酶(FTI)的抑制剂减少正确质膜定位和后续信号传导所需的Ras的C端脂质修饰的潜力。这种方法具有挑战性,因为发现K-Ras经历替代性异戊二烯化且保持致癌活性。

[0661] 共价修饰K-Ras的CAAX-盒半胱氨酸可阻断该位点处的异戊二烯化并抑制K-Ras蛋白后续转位/附着于对其活性而言所必需的膜上。这可以用设计用于结合K-Ras的CAAX-盒半胱氨酸的小分子抑制剂实现。将绕过在抑制Ras异戊二烯化的替代性方法中固有的替代性异戊二烯化的复杂化。系链化合物由赋予和蛋白质上的潜在口袋的非共价相互作用的片段基团组成。另外,有在还原条件下以可逆性方式通过二硫化物交换与CAAX-盒半胱氨酸共价相互作用的二硫化物部分。从1600种系链化合物的文库筛选重组His标记的K-Ras G12D蛋白,接着进行SAR,导致开发出下面描述的FB9:



[0663] 在实施方案中,本文描述的化合物(例如,FB9)共价标记全长重组K-Ras4B中的C185。然而,如果FB9与重组FME-Kras4B蛋白(法尼基化-羧甲基化)反应,其中C185受法尼基修饰/阻断(如同其在体内于天然、完全翻译后加工的K-Ras 4B中一样),FB9无法置换来自C185的法尼基;相反,其共价修饰K-Ras4B蛋白中的其它残基。

[0664] 在本文中我们证实,在实施方案中重组FME-Kras4B,FB9共价修饰对于Kras而言独一无二的组氨酸95残基(H95)(H-Ras中的Q或N-Ras中的L)。这个残基是亲核性的,使其易受亲电子攻击。不但用重组FME-Kras4B蛋白观察到这种修饰;而且在从用该化合物处理的细胞纯化的Kras4B G12V中也检测到这种修饰。

[0665] 未加工KRAS-4b在His-95处的化学修饰(蛋白G-Hs.KRAS4b(1-188),质量(平均值)21481.59 Da)。

[0666] KRAS4b(图43)在体外用FB9修饰(使用8.8倍摩尔过量的FB9,在37℃下1小时,接着在室温22℃下16小时)。MALDI-TOF MS分析揭示蛋白质的化学修饰接近完成。存在具有1和2和3个修饰基团的分子种类(图44)。

[0667] 为鉴定经修饰的氨基酸残基,用蛋白酶Glu-C消化蛋白制剂。通过MALDI-TOF MS分析消化物揭示存在具有m/z 2324和2674的肽,2324对应未修饰的肽KMSKDGGKKKKKSKTKCVIM(SEQ ID NO:4)(170-189)而2674对应在Cys-186处受FB9修饰的相同肽(图45)(通过片段化确认)。具有m/z 1735的肽对应序列GKKKKKSKTKCVIM(SEQ ID NO:3)(174-189)且m/z 2085对应在Cys-186处受FB9修饰的相同肽(通过片段化确认)。

[0668] 为鉴定受FB9修饰的其它可能残基,用Glu-C消化后获得的肽进一步用胰蛋白酶消化(图46A)。具有 m/z 1320.614的肽的片段化光谱揭示了969的主要片段,其接近于肽DIHHYRE (SEQ ID NO:2)的 m/z (预期 m/z 969.4537,93-99),表明 m/z 1320对应受FB9修饰的肽DIHHYRE (SEQ ID NO:2) (图45)。实际上,比较肽969.485和1320.614的片段化光谱证明了它们的关系。图46B中示出了常见片段。

[0669] 经加工的(法尼基化和羧甲基化KRAS4b)的修饰。用FB9修饰蛋白制剂GG-HsKRAS-4b,RP1151105092454 FmeKRAS4b (图47A),用7.6倍摩尔过量FB9,在37℃下1小时,接着在室温(22℃)下16小时。对蛋白质化学修饰的MALDI-TOF MS分析揭示主要形式表示具有1个增加的修饰基团的种类,较少蛋白具有2个修饰基团,并且很少具有3个修饰基团,一些蛋白保持未经修饰(图47B)。为鉴定经修饰的氨基酸残基,用胰蛋白酶消化蛋白制剂。

[0670] MALDI-TOF MS证明具有 m/z 1203 (SFEDIHHYR, SEQ ID NO:6)、1702 (SFEDIHHYREQIK, SEQ ID NO:8)、1858 (SFEDIHHYREQIKR, SEQ ID NO:7)的K-RAS胰蛋白酶肽也呈经修饰的形式+ (350-351) Da存在。片段化期间,这些经修饰的肽产生大量对应未修饰肽的片段和肽片段(大部分未修饰)。

[0671] 这些肽在His残基上经修饰。为鉴定被修饰的残基(即所用重组KRAS序列中的95或96),在序列编辑器中在这些His残基之一上设置FB9修饰(C17H20C11N2O4,350/351)时,在BioTools中分析片段化光谱。

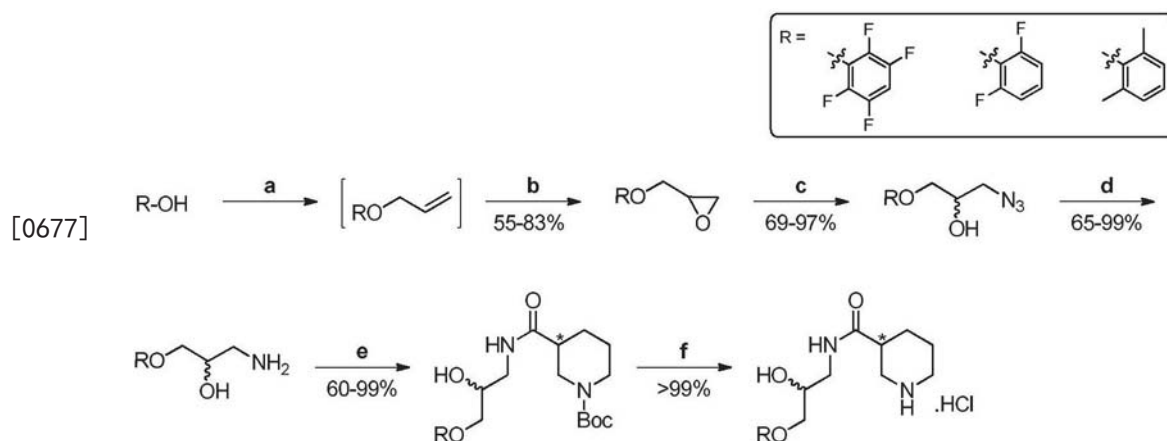
[0672] 对在反射器模式下观察到的 m/z 1203.660和1554.856片段化的分析(在反射器模式下为低强度,但是在线性模式下很好地检测到为1554.7),允许推断在肽SFEDIHHYR (SEQ ID NO:6)中His7(即天然蛋白中的H95)被修饰。在1554的片段化光谱中存在片段825.409,但在1203的光谱中不存在。当FB9修饰在His-7上时,如同经修饰的 y -3那样用BioTools指定该片段。对光谱的手动检查确认了这个推断。

[0673] 细胞中Kras4B G12V中的H95的修饰。

[0674] 在四环素诱导型逆转录病毒表达载体中用HA标记的KRas4BG12V转导小鼠肺II型上皮细胞系E10。开发单独的克隆物。用500ng/ml多西环素(doxycycline)诱导KRas4B转基因表达48小时,然后用20 μ M FB9的相近类似物,即化合物SMDC 993784处理细胞30分钟。通过离心使细胞匀浆澄清,并且使用HA-琼脂糖免疫亲和色谱法从裂解物中纯化Kras4B G12V,通过SDS-PAGE分解并进行对Kras4B G12V修饰的MALDI-TOF分析。图42示出了含有经所述化合物修饰的H95的Kras4b肽的片段。该片段在获自未经受药物处理的细胞的对照样品(图41)中不存在。

[0675] 实施例2. 合成方案

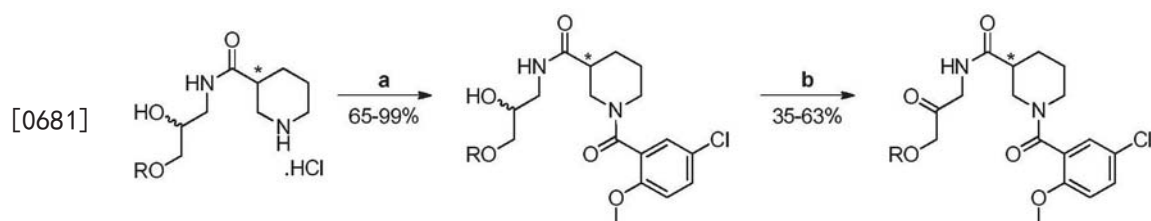
[0676] 方案1. 6B9共价类似物的合成。



[0678] 条件: (a) 烯丙基溴、 K_2CO_3 、DMF, 室温, 24小时; (b) mCPBA、DCM, 室温, 24小时; (c) NaN_3 、 NH_4Cl 、MeOH/ H_2O (8:1), 室温, 72小时; (d) 10% Pd/C、 H_2 、MeOH, 室温, 18小时; (e) (R)-Boc-哌啶甲酸或(S)-Boc-哌啶甲酸、HATU、DIPEA、DMF, 室温, 18小时; (f) 4N二噁烷HCl, 室温, 3小时。

[0679] 从适当的酚类开始, 设计亲电子前体基团的六步对映体选择性合成(方案1)。每个步骤以可接受的产率进行并且非常适合以克规模进行。

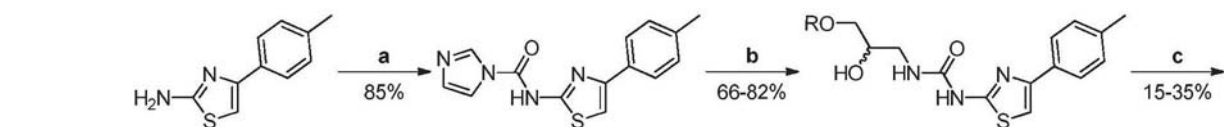
[0680] 方案2. 6B9共价类似物的合成(续)



[0682] 条件: (a) HATU、DIPEA、DMF, 室温, 18小时; (b) 戴斯马丁氧化剂(Dess-Martin periodinane)、DCM, 0°C-室温, 72小时

[0683] 使用肽偶合条件使亲电子前体基团以较高产率与酸性片段附连(方案2a)。在反应方案的最后一步, 使用戴斯马丁氧化剂使醇官能团氧化为酮, 形成反应性共价物类。通过改变该合成途径(方案2a)中的酸性片段, 可能制备用于未来SAR研究的6B9类似物小文库。

[0684] 方案3. 3G4共价类似物的合成



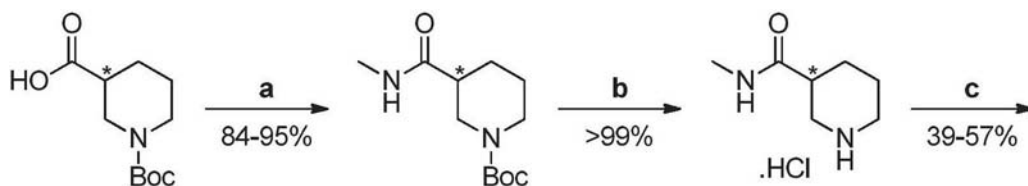
[0685]



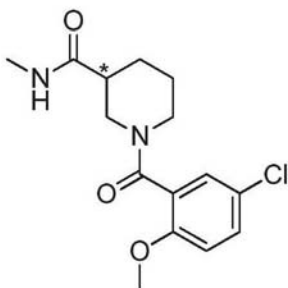
[0686] 条件: (a) CDI、THF, 室温, 18小时; (b) 1、2或3、THF, 室温, 18小时; (c) 戴斯马丁氧化剂、DCM, 0°C-室温, 72小时。

[0687] 按照方案3经三步合成3G4的亲电子衍生物。与高产的前两步大不相同,对于最终反应(方案3c)而言获得适度产率(15-35%),这归因于多种未鉴定的副产物的形成。

[0688] 方案4. 用于SPR研究的6B9非共价类似物的合成



[0689]

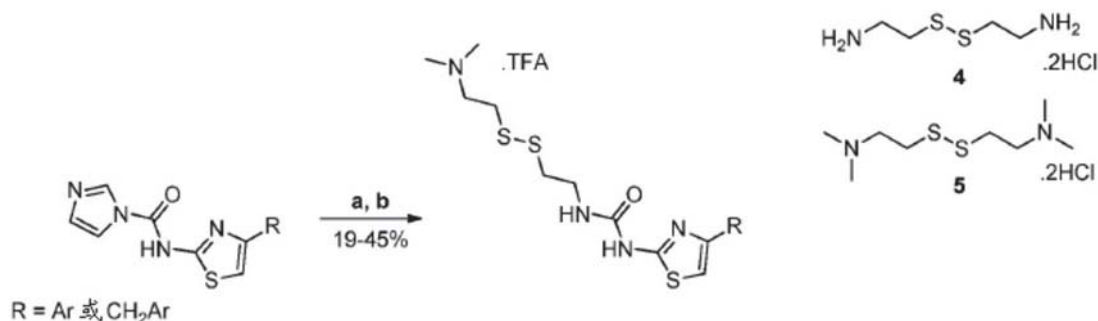


[0690] 条件: (a) $\text{MeNH}_2 \cdot \text{HCl}$ 、 $\text{EDC} \cdot \text{HCl}$ 、 HOBT 、 Et_3N 、 THF/DCM (1:3), 室温, 18小时; (b) 4N二噁烷 HCl , 室温, 3小时; (c) HATU 、 DIPEA 、 DMF , 室温, 18小时

[0691] 按照方案4经三步以满意的产率制备6B9的非系链类似物。选择Boc保护的(R)或(S)-哌啶甲酸作为原料并允许靶分子的对映体选择性合成。这种合成方法很可能会适于未来的非系链衍生物,包括6B9的N-乙酰胺和N-丙酰胺类似物。

[0692] 方案5. 34G脲类似物的合成

[0693]

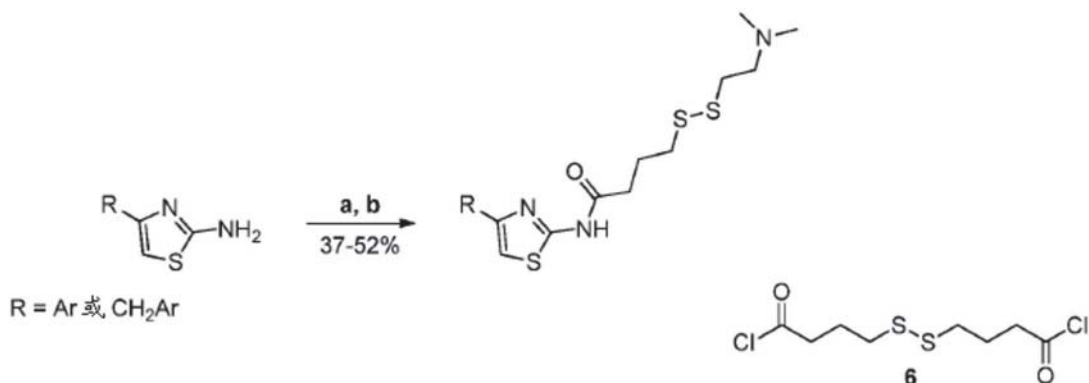


[0694] 条件: (a) 4、 Et_3N 、水/ DMF (1:2); (b) 5、 TCEP (0.1个当量)、 Et_3N 、水/ DMF 。

[0695] 简单的两步一锅法允许由其各自的CDI加成物制备6B9基于脲的类似物的小文库。脲产物的溶解性问题使得纯化成问题,这很可能是适度产率的原因。

[0696] 方案6. 6B9丙酰胺类似物的合成

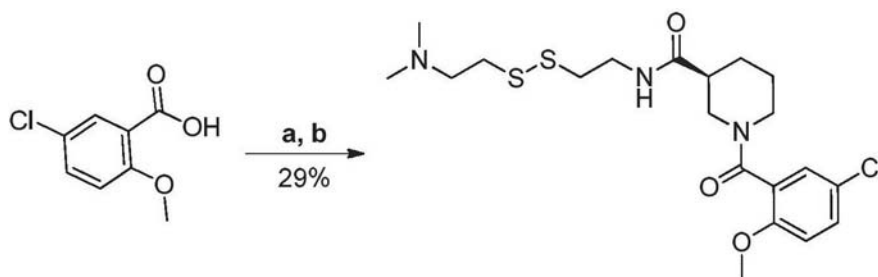
[0697]



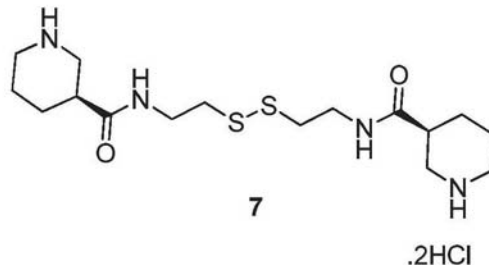
[0698] 条件：(a) **6** (0.5个当量)、DIPEA、DCM, 室温, 3小时；(b) **5**、TCEP (0.1个当量)、Et₃N、水/DMF, 室温, 18小时。

[0699] 经由2-氨基噻唑与酰基氯**6**的反应, 接着在TCEP的存在下通过与二甲基胱胺**5**的二硫化物交换, 制备丙酰胺小文库。

[0700] 方案7. 二硫化物系链剂**6B9**的合成



[0701]



[0702] 条件：(a) **7** (0.5个当量)、EDC·HCl、HOBT、Et₃N、DMF, 室温, 18小时；(b) **5**、TCEP (0.1个当量)、Et₃N、水/DMF, 室温, 18小时

[0703] 使5-氯-2-甲氧基苯甲酸与胺**7**偶合, 接着使用内部开发用于制备二硫化物片段文库的方法在TCEP的存在下进行与胱胺**5**的二硫化物交换。

[0704] QC验证

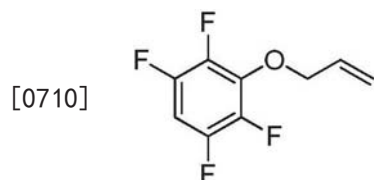
[0705] 对所有中间产物和靶分子进行¹H-NMR和LC-MS分析以允许结构确定。提交用于生物学评价的化合物被视为纯度超过95%并且储存在-80℃下以防分解。

[0706] 设备

[0707] 使用Bruker Avance III 300MHz波谱仪由溶于氘代氯仿 (CDCl₃) 中的样品获得¹H-NMR光谱。化学位移值 (δ) 以百万分率 (ppm) 报告, 裂分模式缩写为:s (单峰)、br.s (宽单峰)、d (双峰)、t (三重峰) 和m (多重峰)。偶合常数 (J) 以Hz给出并且使用软件包ACD Labs™12.0计算。化学位移值 (δ) 以百万分率 (ppm) 报告, 裂分模式缩写为:s (单峰)、br.s (宽单峰)、d (双峰)、t (三重峰) 和m (多重峰)。偶合常数 (J) 以Hz给出并且使用软件包ACD Labs™12.0计算。

[0708] 使用带有通过MassLynx 4.1软件控制的Waters 2795色谱分离模块、Waters 2996光电二极管阵列检测器和Waters 2424蒸发光散射检测器(ELSD)系统的Waters Micromass ZQ质谱仪进行LC-MS分析。使用的HPLC柱为Waters XTerra MS C18 5 μ m 4.6x50mm柱,流动相为水(0.01%甲酸)/MeOH(0.01%甲酸)。

[0709] 1,2,4,5-四氟-3-(丙-2-烯-1-基氧基)苯



[0711] 向2,3,5,6-四氟苯酚(1.0g,6.02mmol)于DMF(15mL)中的溶液添加K2CO3(1.66g,0.12mol),接着滴加烯丙基溴(547 μ L,6.32mmol)。搅拌反应混合物(室温,3小时),之后没有原料留下(通过二氧化硅TLC观察,1:9 EtOAc/己烷)。用水(100mL)稀释反应混合物,然后用DCM(150mL)萃取。去除水层并用水(4x100mL)洗涤剩余有机层,然后干燥(Na2SO4)。通过半真空减小溶剂的体积并且将所得DCM溶液直接用于下一反应中,无需进一步纯化。

[0712] Rf=0.75(1:9 EtOAc/己烷)。

[0713] 2-(2,3,5,6-四氟苯氧基甲基)环氧乙烷



[0715] 向0℃的1,2,4,5-四氟-3-(丙-2-烯-1-基氧基)苯(1.24g,6.02mmol)于DCM(50mL)中的溶液(先前制备的)添加3-氯过氧苯甲酸(2.7g,12.0mmol)。在0℃下搅拌反应物,然后升温至室温再3天。将所得溶液倒入硫代硫酸钠饱和水溶液(50mL)中并允许搅拌30分钟。去除有机层,然后依次用饱和NaHCO3(50mL)、水(50mL)和盐水(50mL)洗涤,干燥(Na2SO4)并在二氧化硅(0-50% EtOAc/己烷)上通过MPLC纯化以产生呈无色油的2-(2,3,5,6-四氟苯氧基甲基)环氧乙烷(735mg,3.31mmol,55%)。

[0716] Rf=0.28(1:9 EtOAc/己烷);¹H NMR(300MHz,CDC13) δ 6.70-6.93(m,1H),4.49(dd,J=2.92,11.59Hz,1H),4.12-4.25(m,1H),3.30-3.50(m,1H),2.89(dd,J=3.70,4.90Hz,1H),2.73(dd,J=2.64,4.90Hz,1H)。

[0717] 1-叠氮基-3-(2,3,5,6-四氟苯氧基)丙-2-醇



[0719] 向2-(2,3,5,6-四氟苯氧基甲基)环氧乙烷(1.89g,8.5mmol)于MeOH(30mL)中的溶液添加叠氮化钠(5.11g,78.6mmol)于水(3.8mL)中的悬浮液。添加氯化铵(915mg,210mmol)并在室温下搅拌反应物24小时。用盐水(100mL)稀释反应混合物,然后用EtOAc(2x50mL)萃取。用盐水(2x100mL)洗涤合并的有机层,干燥(Na2SO4)并在真空中去除溶剂。在二氧化硅(1:9 EtOAc:己烷)上通过MPLC纯化粗产物以产生呈无色油的标题化合物(1.92g,7.3mmol,

85%)。

[0720] $R_f=0.14$ (1:9 EtOAc/己烷); $^1\text{H NMR}$ (300MHz, CDCl_3) δ 6.72–6.93 (m, 1H), 4.22–4.36 (m, 2H), 4.07–4.22 (m, 1H), 3.45–3.65 (m, 2H), 2.56 (br. s., 1H)。

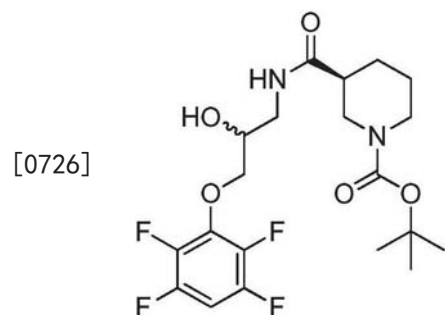
[0721] 1-氨基-3-(2,3,5,6-四氟苯氧基)丙-2-醇



[0723] 向1-叠氮基-3-(2,3,5,6-四氟苯氧基)丙-2-醇 (1.9g, 7.3mmol) 于MeOH (15ml) 中的溶液添加10%钯碳 (386mg, 3.6mmol)。将反应容器置于氢气气氛下并搅拌过夜 (室温, 18小时)。通过硅藻土过滤所得混合物并去除溶剂以产生呈白色固体的1-氨基-3-(2,3,5,6-四氟苯氧基)丙-2-醇 (1.2g, 5.0mmol, 69%)。

[0724] $^1\text{H NMR}$ (300MHz, MeOD) δ 7.01–7.21 (m, 1H), 4.22 (d, $J=5.09\text{Hz}$, 2H), 3.85–3.99 (m, 1H), 2.90 (dd, $J=3.96, 12.81\text{Hz}$, 1H), 2.77 (dd, $J=7.70, 13.00\text{Hz}$, 1H); LRMS (ES+) $m/z=239.9$ [M+H]⁺。

[0725] (3S)-3-{[2-羟基-3-(2,3,5,6-四氟苯氧基)丙基]氨甲酰基}哌啶-1-羧酸叔丁酯

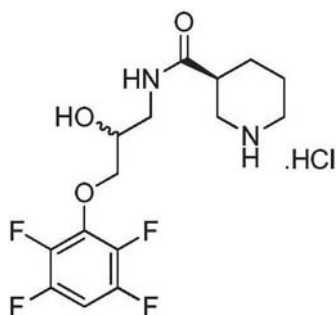


[0727] 向1-氨基-3-(2,3,5,6-四氟苯氧基)丙-2-醇 (1.1g, 4.6mmol) 于DMF (26ml) 中的溶液添加羟基苯并三唑 (HOBt) (59mg, 0.4mmol)、1-乙基-3-(3-二甲基氨基丙基)碳二亚胺盐酸盐 (EDC.HCl) (1.84g, 11.9mmol) 和水 (4.1ml)。添加三乙胺 (608 μ l, 4.4mmol) 并搅拌所得混合物 (室温, 3小时), 引起原料的消耗 (通过TLC观察到)。将反应物添加到饱和盐水溶液 (100mL) 中, 然后用EtOAc (150mL) 萃取。去除有机层, 然后依次用饱和 NaHCO_3 水溶液 (100mL) 和盐水 (100mL) 洗涤, 然后干燥 (MgSO_4) 并在真空中去除溶剂。在二氧化硅 (0–10% MeOH/DCM) 上通过MPLC纯化粗产物以产生呈无色油的标题化合物 (1.94g, 4.3mmol, 99%)。

[0728] $R_f=0.45$ (1:9 MeOH/DCM); $^1\text{H NMR}$ (300MHz, CDCl_3) δ 6.73–6.93 (m, 1H), 4.01–4.30 (m, 3H), 3.55–4.00 (m, 3H), 3.24–3.54 (m, 2H), 3.12 (m, 1H), 2.84–3.01 (m, 1H), 2.29–2.50 (m, 1H), 1.77–2.05 (m, 2H), 1.57–1.77 (m, 1H), 1.47 (s, 9H); LRMS (ES+) $m/z=451.1$ [M+H]⁺。

[0729] (3S)-N-[2-羟基-3-(2,3,5,6-四氟苯氧基)丙基]哌啶-3-羧酰胺盐酸盐

[0730]

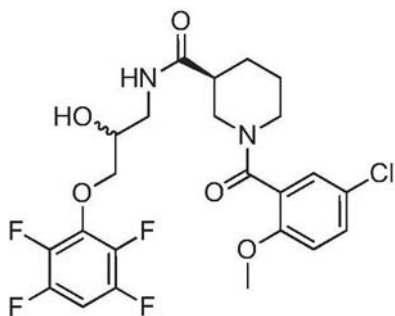


[0731] 向装有 (3S)-3-([2-羟基-3-(2,3,5,6-四氟苯氧基)丙基]氨甲酰基)哌啶-1-羧酸叔丁酯 (50mg, 0.1mmol) 的烧瓶中添加 4N 于二噁烷中的盐酸 (500 μ l, 2.0mmol)。在室温下搅拌所得溶液 30 分钟, 然后在真空中去除溶剂以产生呈无色油的标题化合物 (41mg, 0.1mmol, 96%)。

[0732] ^1H NMR (300MHz, CDCl_3) δ 8.95 (br. s., 2H), 7.75–8.43 (m, 1H), 6.77 (br. s., 1H), 4.02–4.68 (m, 3H), 2.65–3.97 (m, 9H), 1.55–2.32 (m, 3H); LRMS (ES+) m/z = 351.1 $[\text{M}+\text{H}]^+$ 。

[0733] (3S)-1-[(5-氯-2-甲氧基苯基)羰基]-N-[2-羟基-3-(2,3,5,6-四氟苯氧基)丙基]哌啶-3-羧酰胺

[0734]

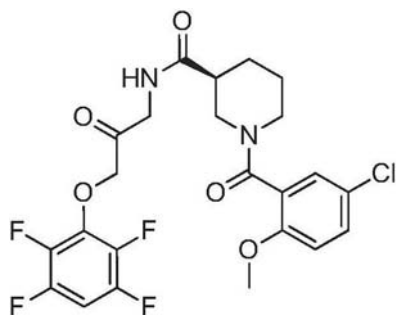


[0735] 向 (3S)-N-[2-羟基-3-(2,3,5,6-四氟苯氧基)丙基]哌啶-3-羧酰胺盐酸盐 (155mg, 0.40mmol)、(1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化六氟磷酸盐) (HATU) (168mg, 0.44mmol) 和 N,N-二异丙基乙胺 (243 μ l, 1.4mmol) 于 DMF (2.3ml) 中的溶液, 添加 5-氯-2-甲氧基苯甲酸 (75mg, 0.40mmol)。搅拌反应混合物过夜 (室温, 18 小时), 然后添加到饱和盐水溶液 (25mL) 中。用 EtOAc (2x25mL) 萃取水性混合物并合并有机层, 用盐水 (25mL) 洗涤, 干燥 (Na_2SO_4) 并在真空中去除溶剂。在二氧化硅 (0–80% 己烷/EtOAc) 上通过 MPLC 纯化粗产物以产生呈无色油的标题产物 (206mg, 0.40mmol)。

[0736] R_f = 0.40 (10% MeOH/DCM); ^1H NMR (300MHz, CDCl_3) δ 7.32 (dd, J = 2.45, 8.85Hz, 1H), 7.13–7.21 (m, 1H), 6.86 (d, J = 8.85Hz, 1H), 6.68–6.79 (m, 1H), 4.16–4.30 (m, 1H), 3.99–4.16 (m, 2H), 3.80–3.87 (s, 3H), 3.66–3.76 (m, 1H), 3.43–3.65 (m, 1H), 3.07–3.43 (m, 3H), 2.67–2.78 (m, 1H), 2.55 (m, 1H), 1.96–2.31 (m, 1H), 1.71–1.95 (m, 1H), 1.41–1.69 (m, 2H); LRMS (ES+) m/z = 519.1 $[\text{M}+\text{H}]^+$ 。

[0737] (3S)-1-[(5-氯-2-甲氧基苯基)羰基]-N-[2-氧代-3-(2,3,5,6-四氟苯氧基)丙基]哌啶-3-羧酰胺 ('FB9')

[0738]



[0739] 向0℃的(3S)-1-[(5-氯-2-甲氧基苯基)羰基]-N-[2-羟基-3-(2,3,5,6-四氟苯氧基)丙基]哌啶-3-羧酰胺(17mg, 3.4×10^{-2} mmol)于DCM(500 μ l, 7.8 mmol)中的溶液,添加戴斯马丁氧化剂(28mg, 6.8×10^{-2} mmol)。在0℃下搅拌反应混合物1小时,然后允许再升温72小时至室温。用DCM(2mL)稀释粗产物,然后添加到硫代硫酸钠于NaHCO₃水溶液(3mL)中的饱和溶液中。快速搅拌所得混合物1小时,此时去除水层。依次用NaHCO₃(3mL)和盐水(3mL)洗涤剩余有机层,然后干燥(Na₂SO₄)并在真空中去除溶剂。在二氧化硅(0-10%MeOH/DCM)上通过MPLC纯化粗产物以产生呈无色油的标题化合物(12mg, 2.3×10^{-2} mmol, 69%)。

[0740] $R_f = 0.43$ (1:9MeOH/DCM); ¹H NMR (300MHz, CDCl₃) δ 7.31 (dd, $J = 2.64, 8.85$ Hz, 1H), 7.16-7.25 (m, 1H), 6.75-6.92 (m, 2H), 4.80-4.97 (m, 2H), 4.17-4.59 (m, 2H), 3.75-3.95 (m, 3H), 3.51-3.74 (m, 1H), 3.11-3.38 (m, 2H), 2.52-2.72 (m, 2H), 2.00-2.22 (m, 1H), 1.89 (d, $J = 11.87$ Hz, 1H), 1.35-1.80 (m, 2H); ¹⁹F NMR (282MHz, CDCl₃) δ -138.0, -156.7; LRMS (ES+) $m/z = 517.1$ [M+H]⁺。

[0741] 应理解本文描述的实施例和实施方案仅仅是为了说明的目的并且据其所做的各种修改或变化将被推荐给本领域的技术人员并且包括在本申请的精神和权限及所附权利要求的范围之内。本文引用的所有出版物、专利和专利申请据此以引用的方式整体并入用于所有目的。

序列表

<110> 加利福尼亚大学董事会

雷多思生物医学研究有限公司

F·麦考密克

A·R·伦斯洛

D·特纳

S·吉森

A·E·玛西雅格

O·切尔托夫

<120> K-RAS调节剂

<130> 48536-569001W0

<160> 12

<170> PatentIn版本3.5

<210> 1

<211> 189

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 1

Gly Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly

1 5 10 15

Lys Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu

20 25 30

Tyr Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp

35 40 45

Gly Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu

50 55 60

Tyr Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu

65 70 75 80

Cys Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His

85 90 95

Tyr Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met

100 105 110

Val Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr

115 120 125

Lys Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu

130 135 140

Thr Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu
145 150 155 160
Val Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys
165 170 175
Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys Val Ile Met
180 185

<210> 2

<211> 7

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 2

Asp Ile His His Tyr Arg Glu

1 5

<210> 3

<211> 15

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 3

Gly Lys Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys Val Ile Met

1 5 10 15

<210> 4

<211> 20

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 4

Lys Met Ser Lys Asp Gly Lys Lys Lys Lys Lys Lys Ser Lys Thr Lys

1 5 10 15

Cys Val Ile Met

20

<210> 5

<211> 186

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 5

Gly Gly Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly
1 5 10 15
Lys Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu
 20 25 30
Tyr Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp
 35 40 45
Gly Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu
 50 55 60
Tyr Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu
65 70 75 80
Cys Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His
 85 90 95
Tyr Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met
 100 105 110
Val Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr
 115 120 125
Lys Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu
 130 135 140
Thr Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu
145 150 155 160
Val Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys
 165 170 175
Lys Lys Lys Lys Lys Ser Lys Thr Lys Cys
 180 185

<210> 6

<211> 9

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 6

Ser Phe Glu Asp Ile His His Tyr Arg
1 5

<210> 7

<211> 14

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 7

Ser Phe Glu Asp Ile His His Tyr Arg Glu Gln Ile Lys Arg

1 5 10

<210> 8

<211> 13

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 8

Ser Phe Glu Asp Ile His His Tyr Arg Glu Gln Ile Lys

1 5 10

<210> 9

<211> 19

<212> PRT

<213> 人工序列

<220>

<223> 合成多肽

<400> 9

Asp Ser Glu Asp Val Pro Met Val Leu Val Gly Asn Lys Cys Asp Leu

1 5 10 15

Pro Ser Arg

<210> 10

<211> 189

<212> PRT

<213> 智人

<400> 10

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys

1 5 10 15

Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr

20 25 30

Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly

35 40 45

Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr

50 55 60

Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys

65	70	75	80
Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His Gln Tyr			
	85	90	95
Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Asp Asp Val Pro Met Val			
	100	105	110
Leu Val Gly Asn Lys Cys Asp Leu Ala Ala Arg Thr Val Glu Ser Arg			
	115	120	125
Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Tyr Ile Glu Thr			
	130	135	140
Ser Ala Lys Thr Arg Gln Gly Val Glu Asp Ala Phe Tyr Thr Leu Val			
145	150	155	160
Arg Glu Ile Arg Gln His Lys Leu Arg Lys Leu Asn Pro Pro Asp Glu			
	165	170	175
Ser Gly Pro Gly Cys Met Ser Cys Lys Cys Val Leu Ser			
	180	185	

<210> 11

<211> 189

<212> PRT

<213> 智人

<220>

<221> MOD_RES

<222> (186) .. (186)

<223> 残基可法尼基化

<400> 11

Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys			
1	5	10	15
Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr			
	20	25	30
Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly			
	35	40	45
Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr			
	50	55	60
Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys			
65	70	75	80
Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr			
	85	90	95
Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val			
	100	105	110
Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys			

115	120	125
Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr		
130	135	140
Ser Ala Lys Thr Arg Gln Arg Val Glu Asp Ala Phe Tyr Thr Leu Val		
145	150	155
Arg Glu Ile Arg Gln Tyr Arg Leu Lys Lys Ile Ser Lys Glu Glu Lys		
165	170	175
Thr Pro Gly Cys Val Lys Ile Lys Lys Cys Ile Ile Met		
180	185	
<210> 12		
<211> 188		
<212> PRT		
<213> 智人		
<220>		
<221> MOD_RES		
<222> (185) .. (185)		
<223> 残基可法尼基化		
<400> 12		
Met Thr Glu Tyr Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys		
1	5	10
Ser Ala Leu Thr Ile Gln Leu Ile Gln Asn His Phe Val Asp Glu Tyr		
20	25	30
Asp Pro Thr Ile Glu Asp Ser Tyr Arg Lys Gln Val Val Ile Asp Gly		
35	40	45
Glu Thr Cys Leu Leu Asp Ile Leu Asp Thr Ala Gly Gln Glu Glu Tyr		
50	55	60
Ser Ala Met Arg Asp Gln Tyr Met Arg Thr Gly Glu Gly Phe Leu Cys		
65	70	75
Val Phe Ala Ile Asn Asn Thr Lys Ser Phe Glu Asp Ile His His Tyr		
85	90	95
Arg Glu Gln Ile Lys Arg Val Lys Asp Ser Glu Asp Val Pro Met Val		
100	105	110
Leu Val Gly Asn Lys Cys Asp Leu Pro Ser Arg Thr Val Asp Thr Lys		
115	120	125
Gln Ala Gln Asp Leu Ala Arg Ser Tyr Gly Ile Pro Phe Ile Glu Thr		
130	135	140
Ser Ala Lys Thr Arg Gln Gly Val Asp Asp Ala Phe Tyr Thr Leu Val		
145	150	155
Arg Glu Ile Arg Lys His Lys Glu Lys Met Ser Lys Asp Gly Lys Lys		

				165					170				175
Lys	Lys	Lys	Lys	Ser	Lys	Thr	Lys	Cys	Val	Ile	Met		
				180					185				

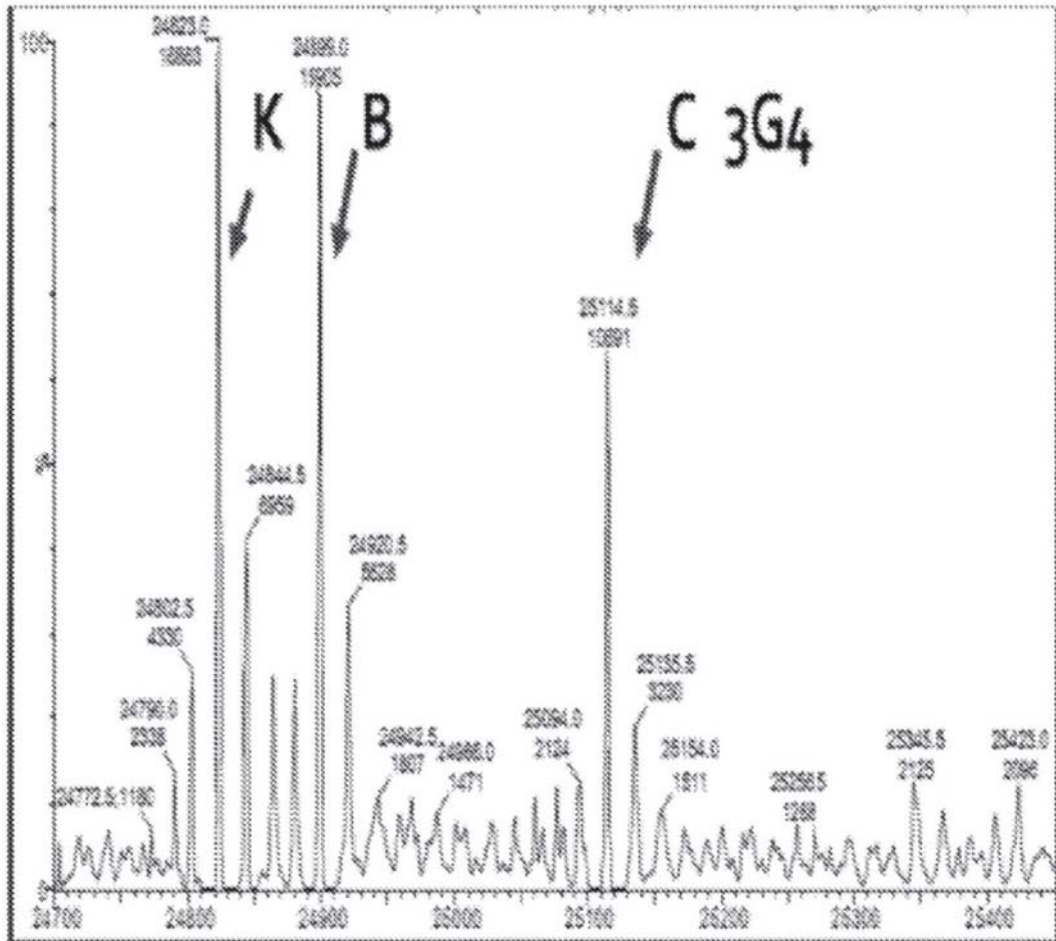


图1A

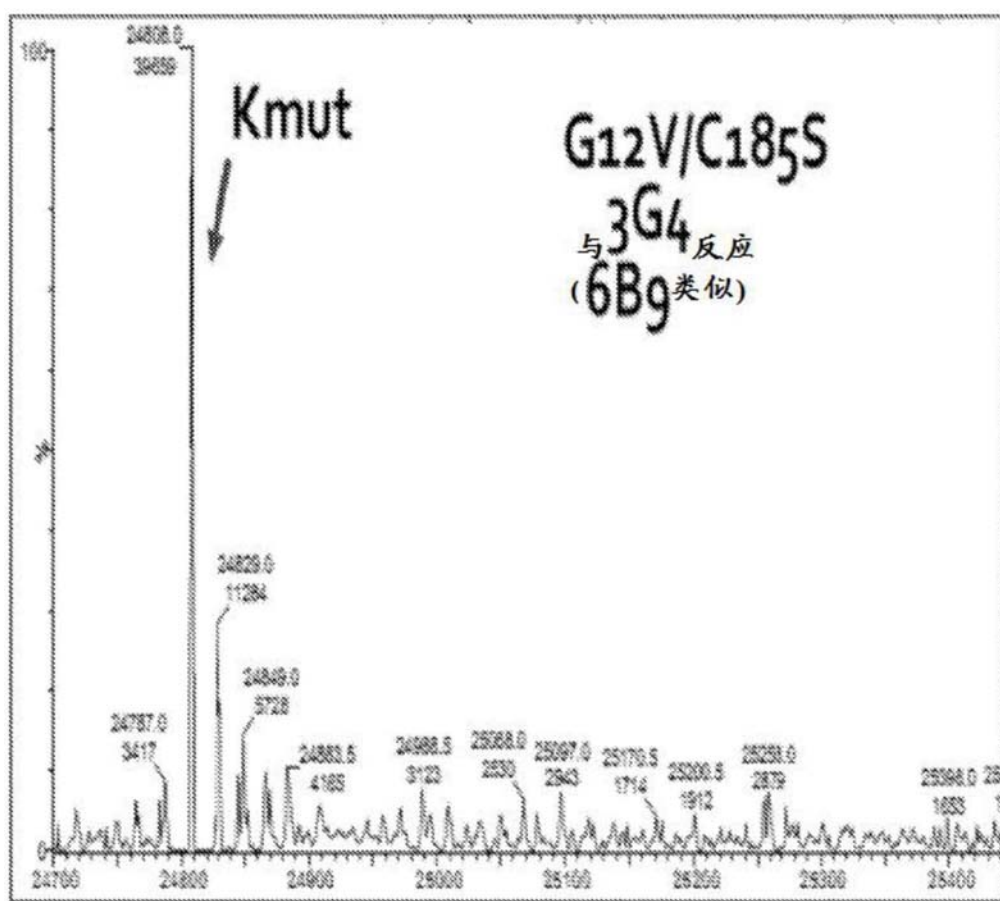


图1C

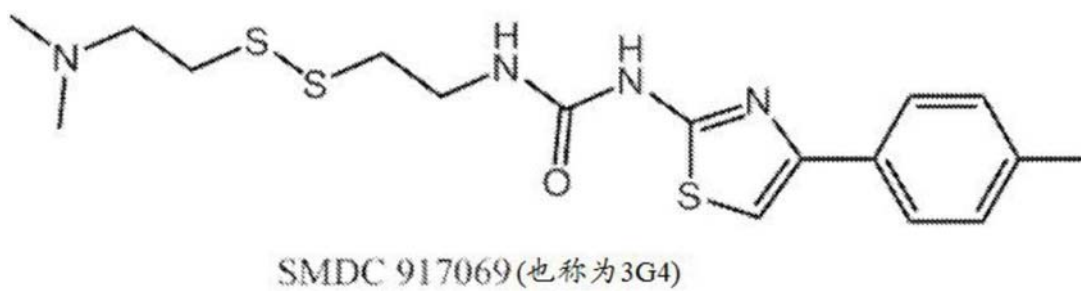
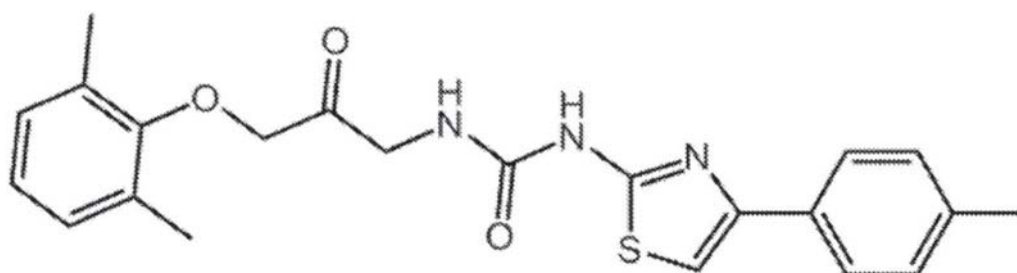
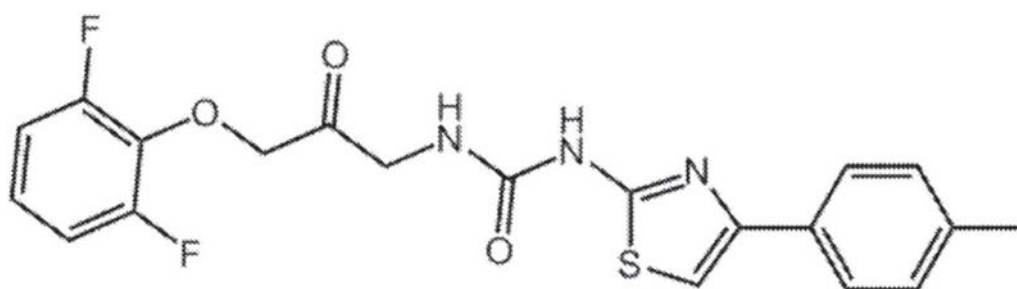


图2A



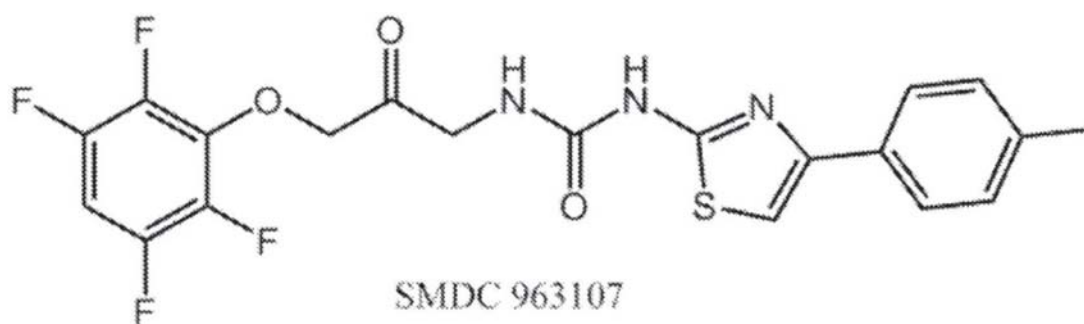
SMDC 963109

图2B



SMDC 963108

图2C



SMDC 963107

图2D

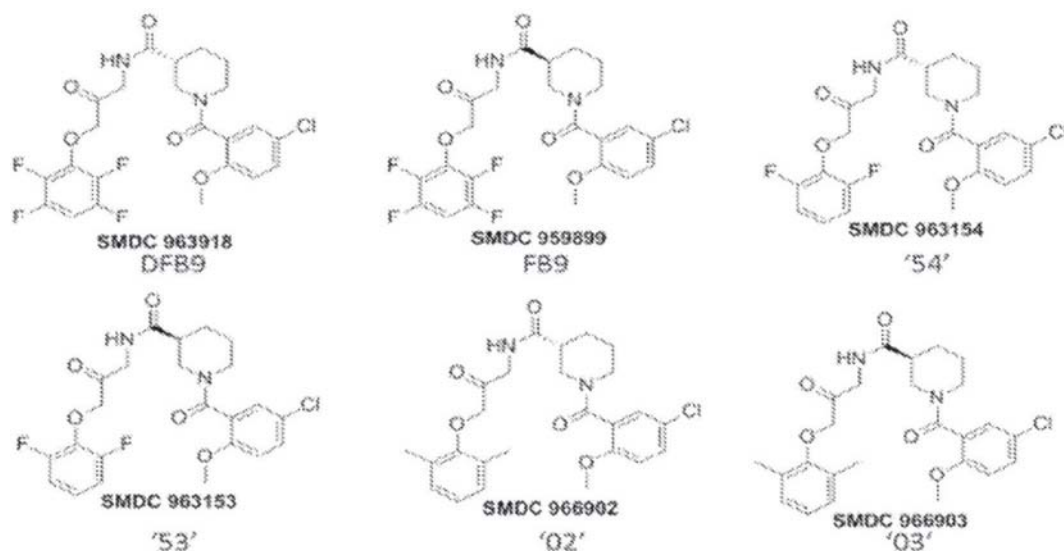


图3A



图3B



图3C

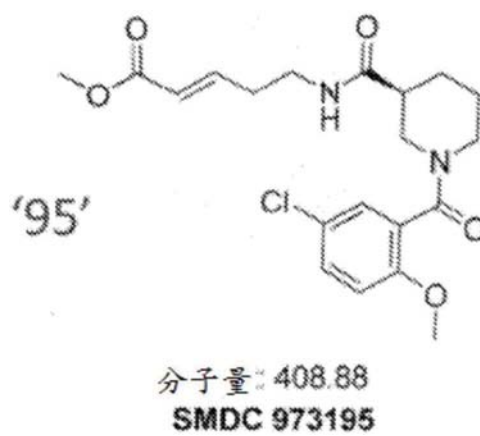


图4A

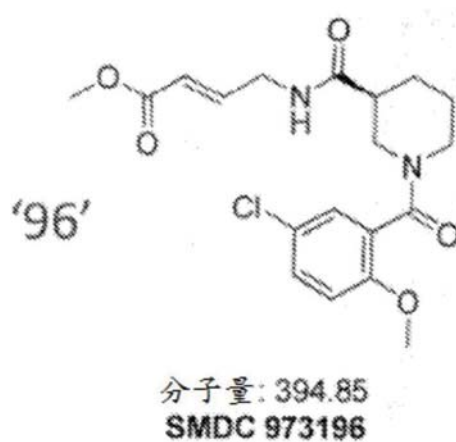


图4B



图4C

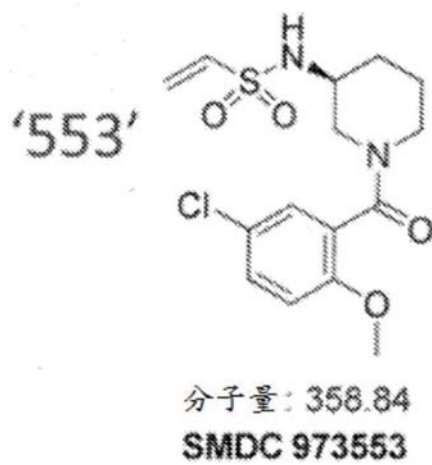


图4D

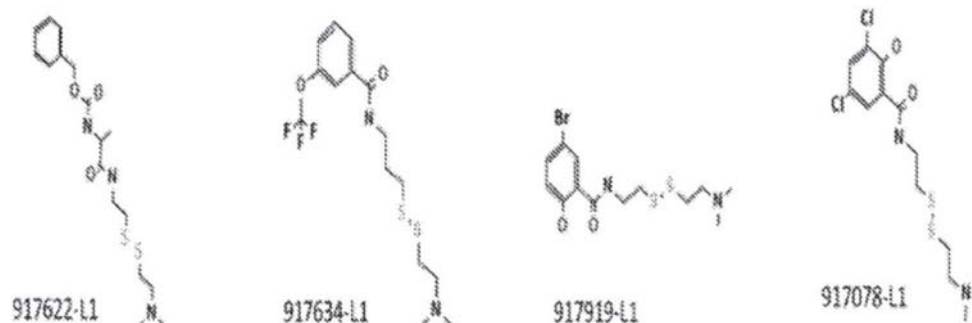


图5A

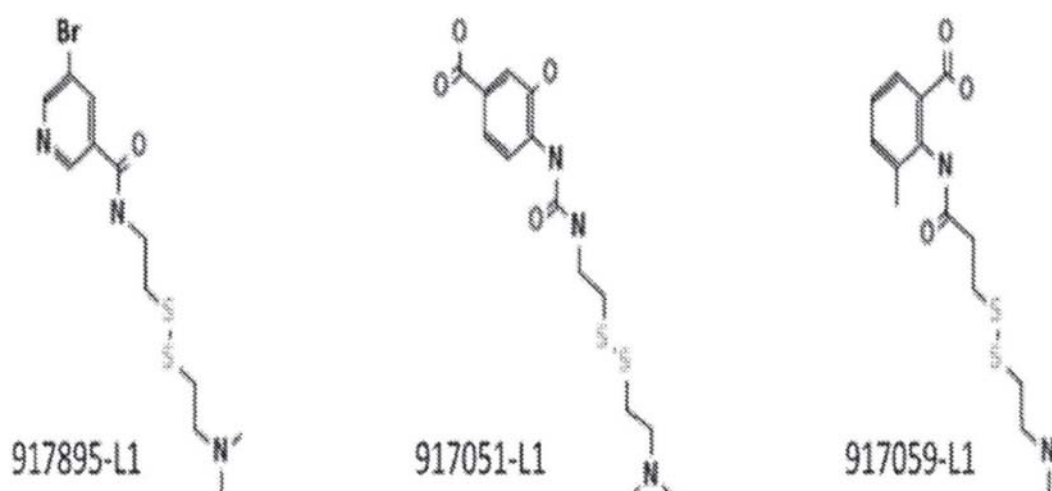


图5B

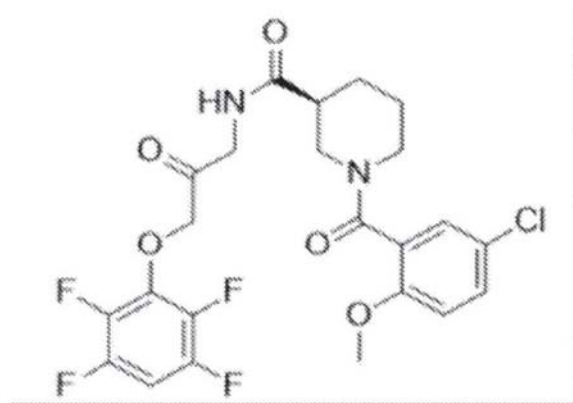


图6A

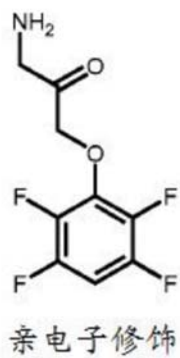
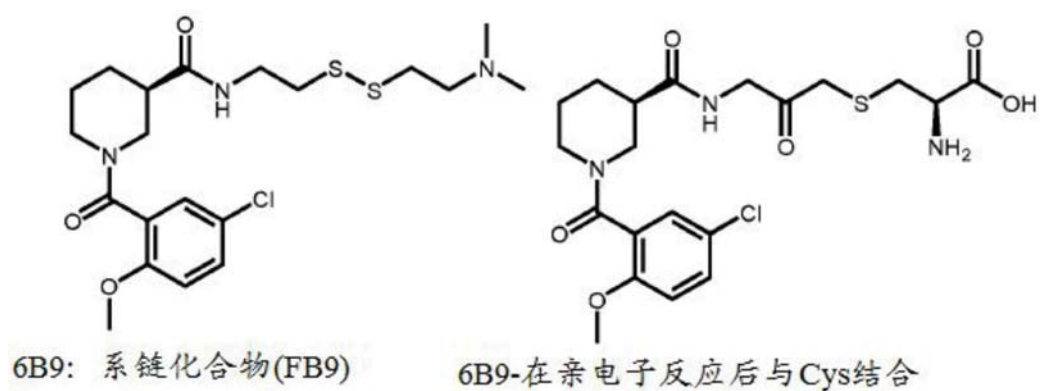


图6B

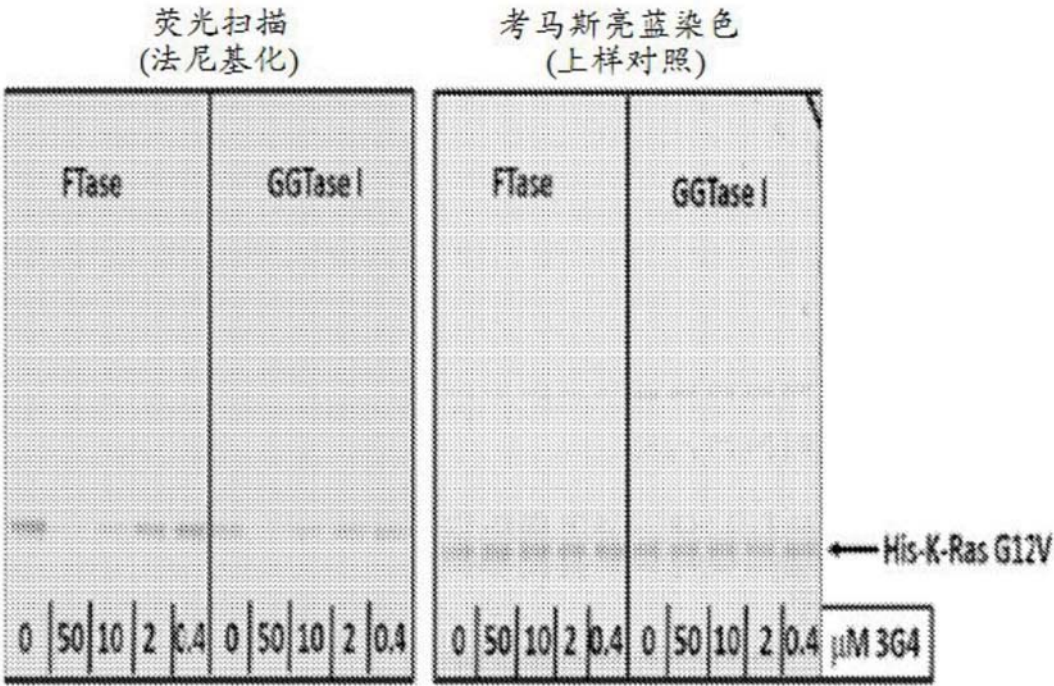


图7A

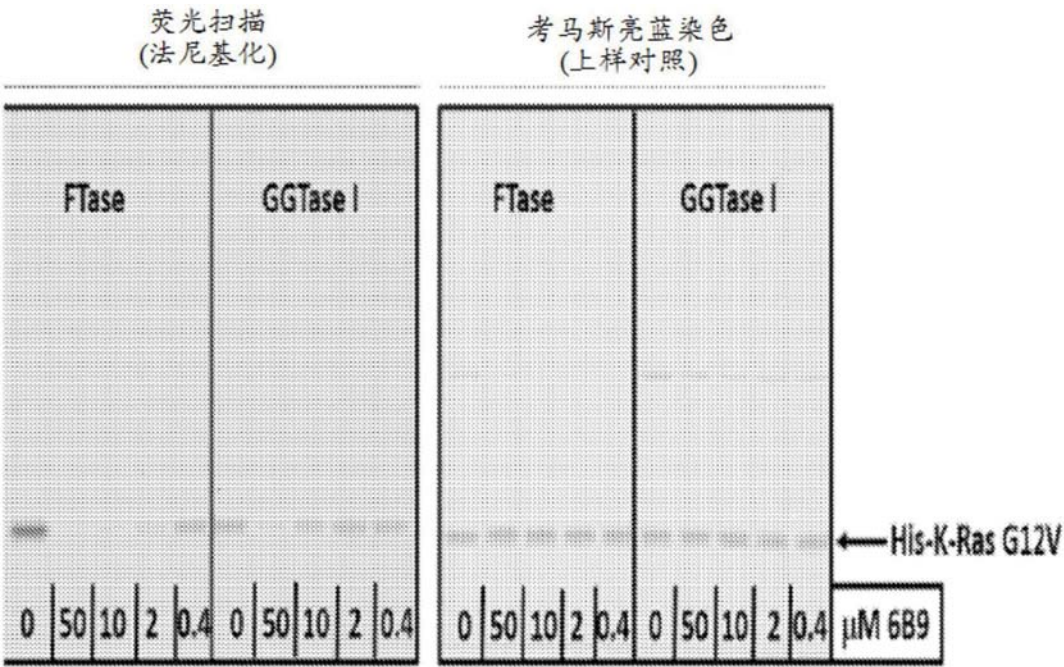


图7B

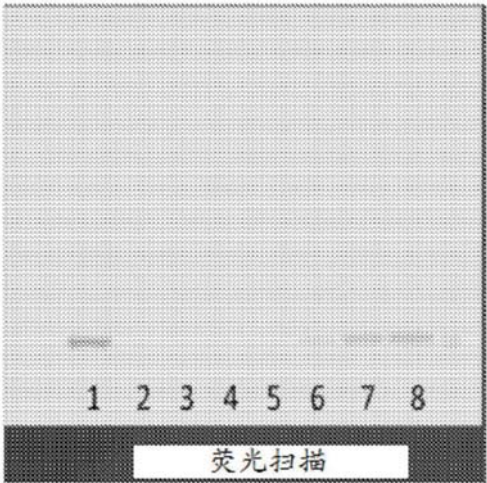


图8A

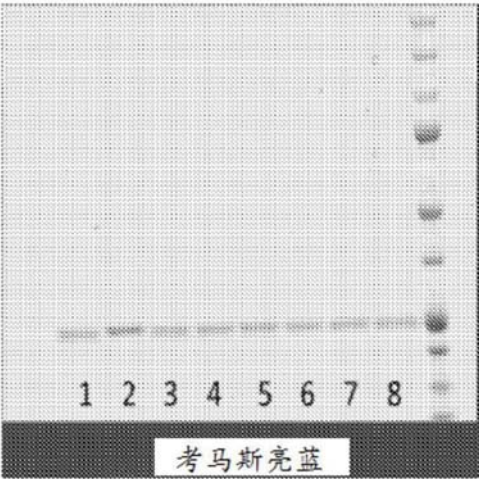


图8B

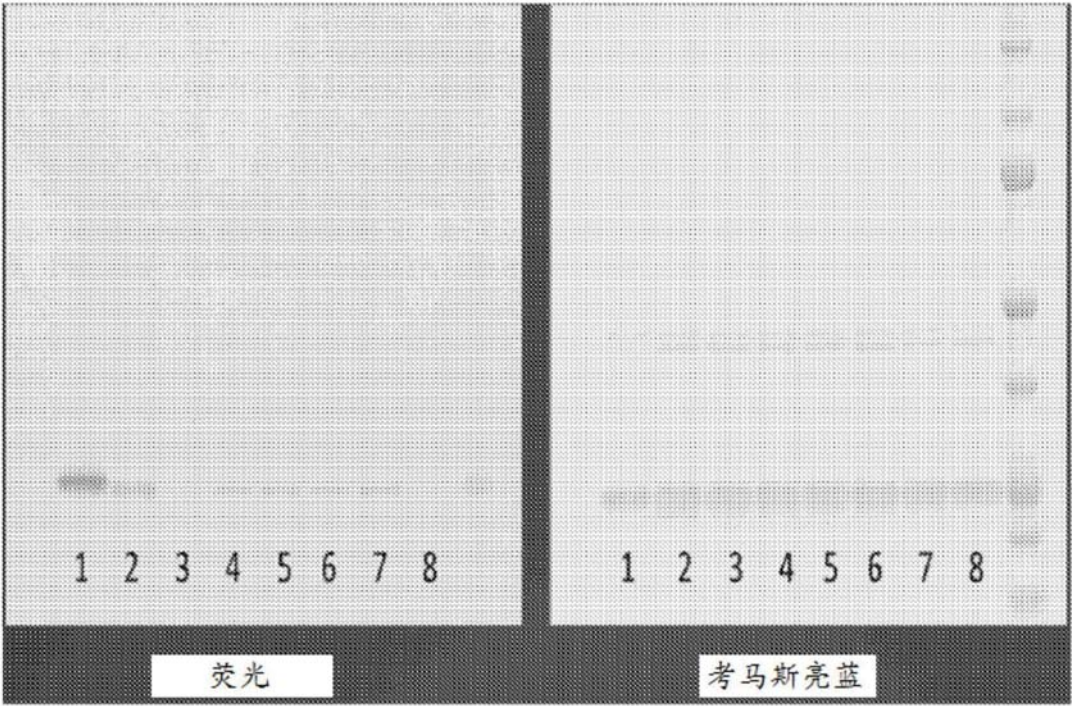


图9

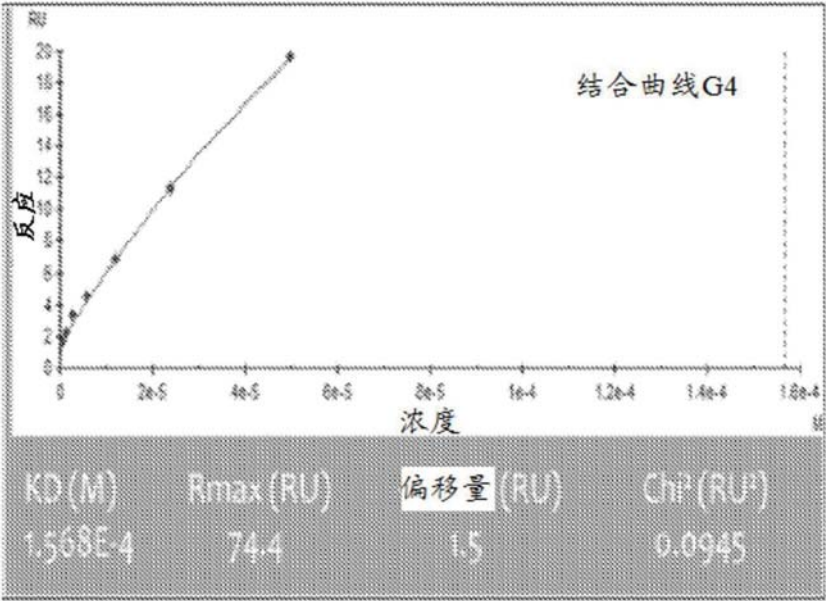


图10

K-Ras4B G12D – GTPγS - LB9

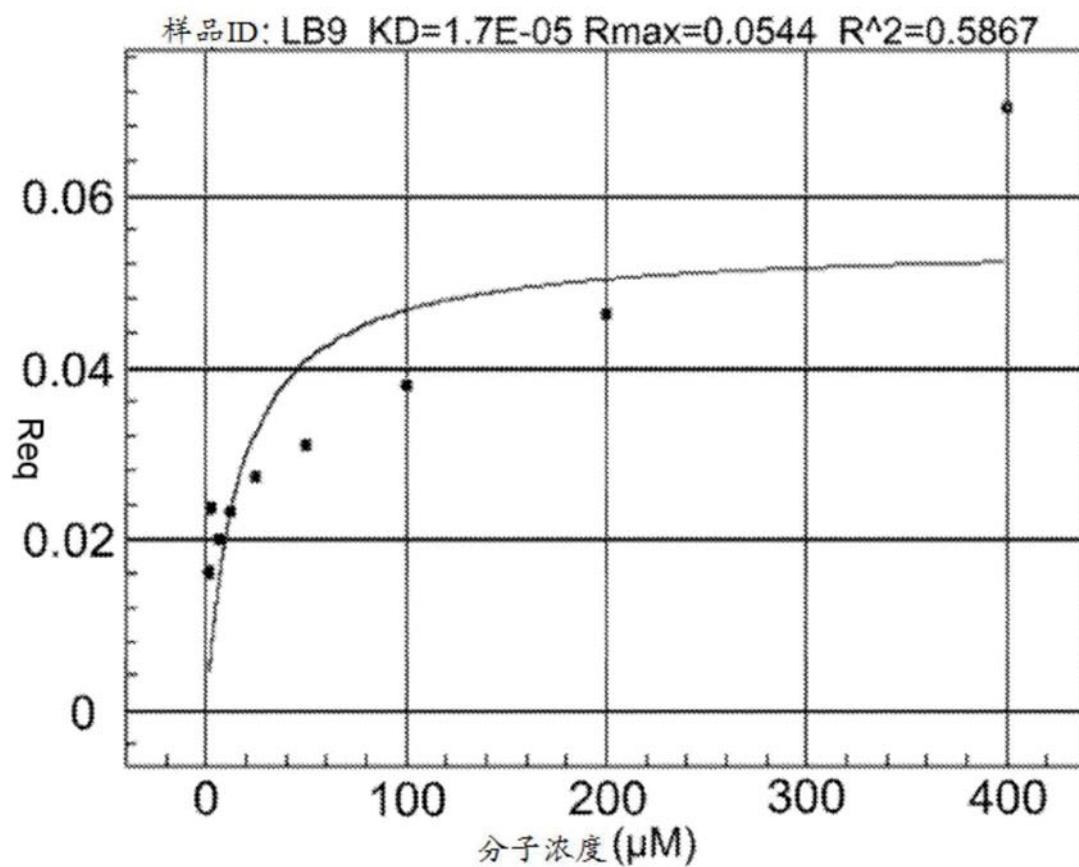


图11A

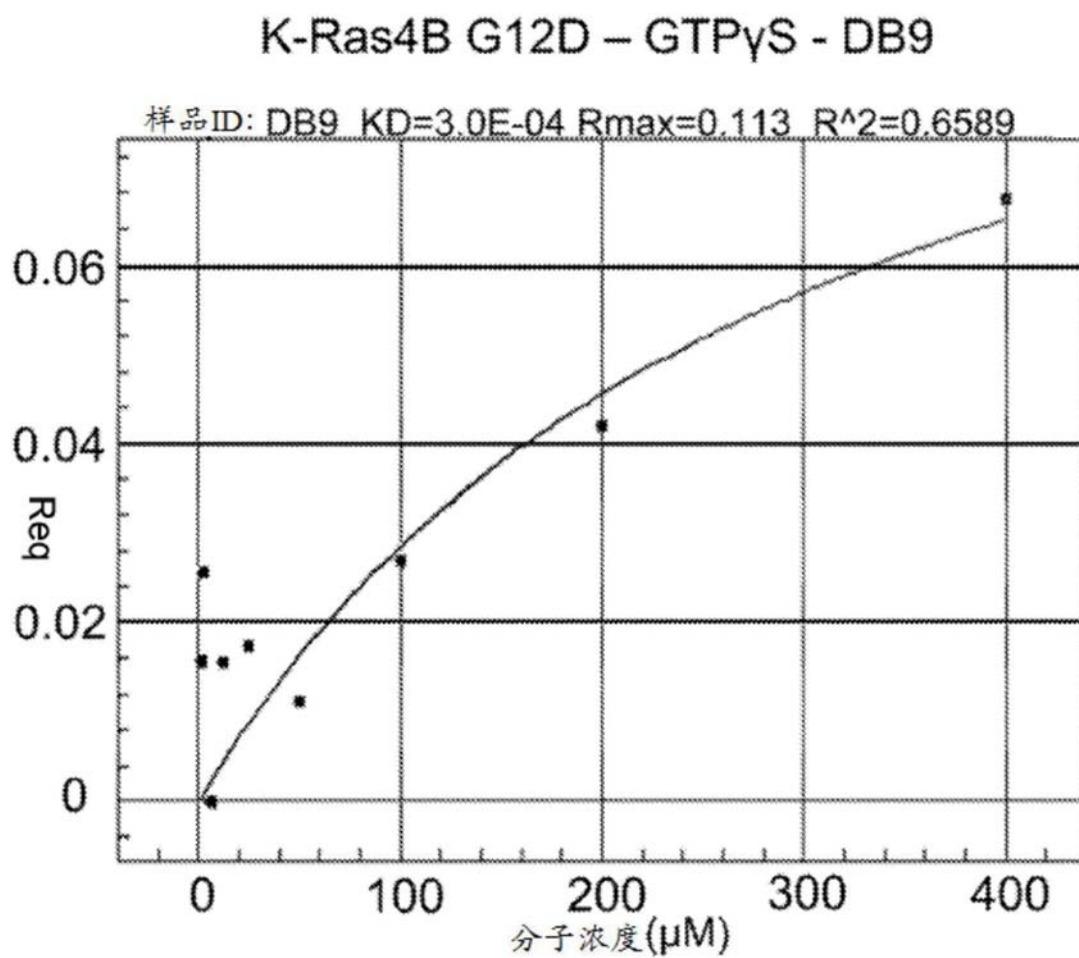


图11B

EDA-GTP-ATTO 390
(K-Ras 4B G12V C185S)

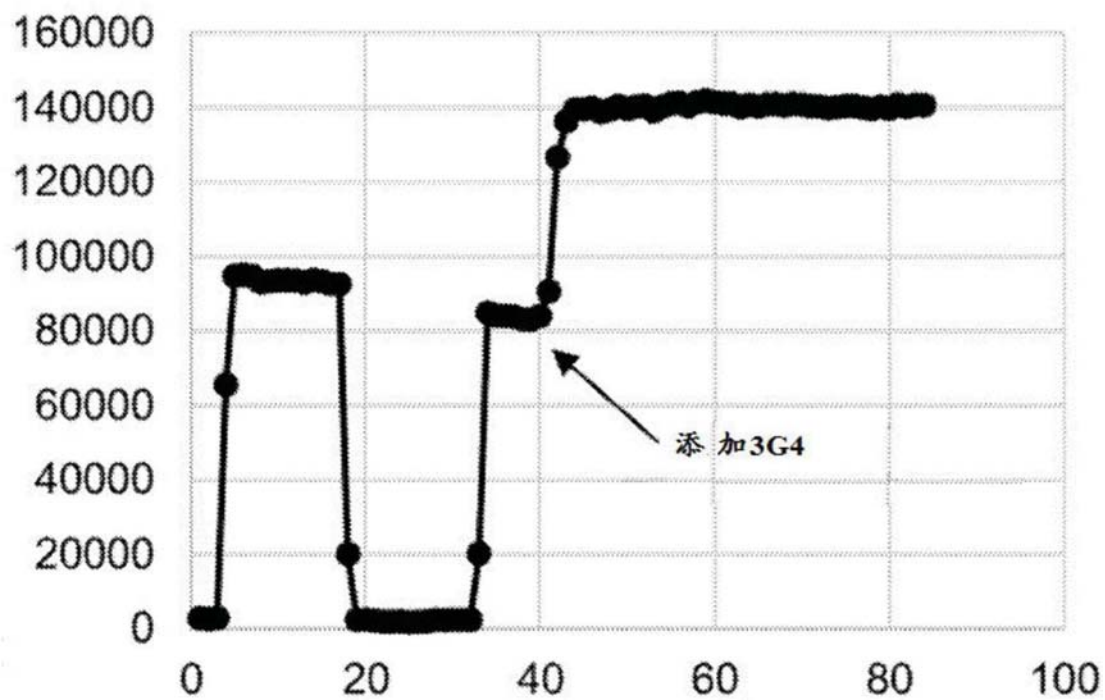


图12A

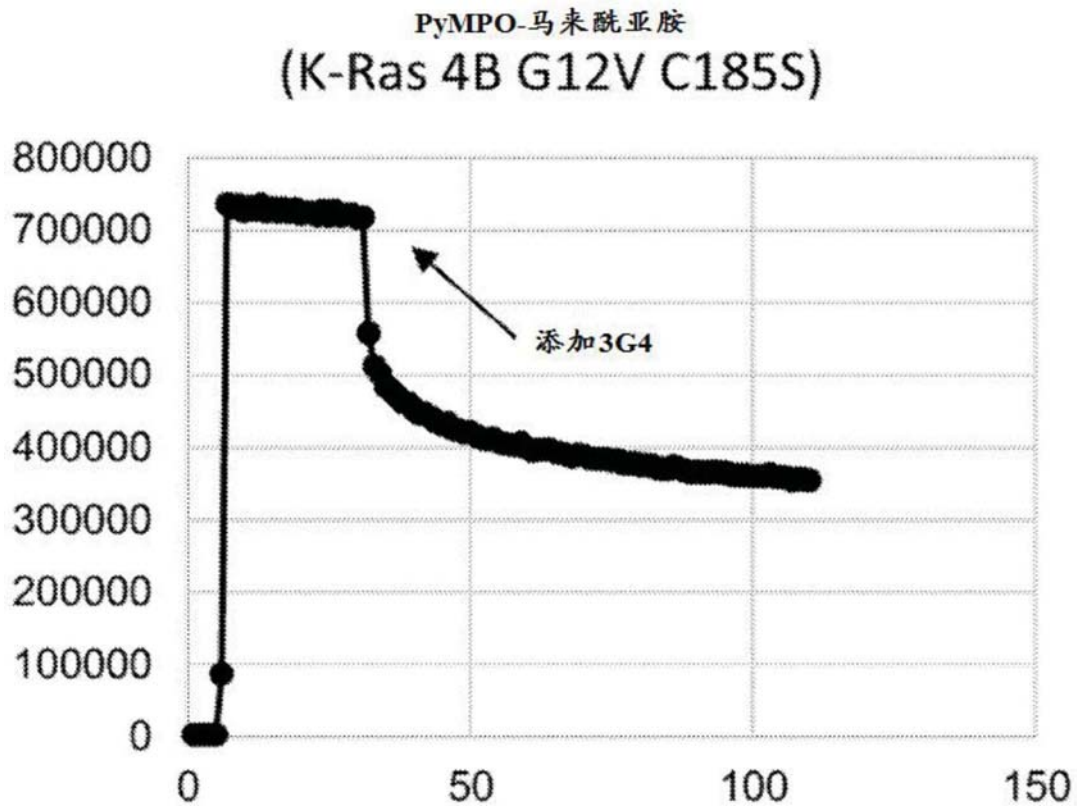


图12B

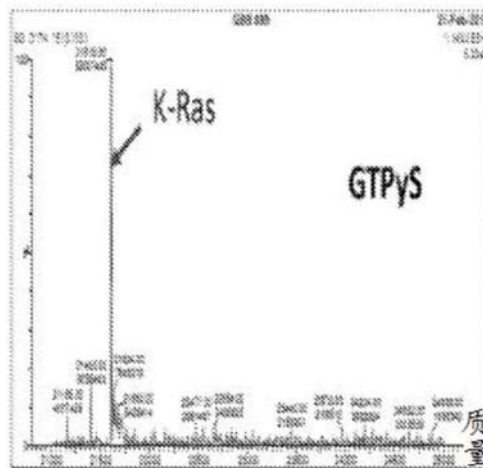


图13A

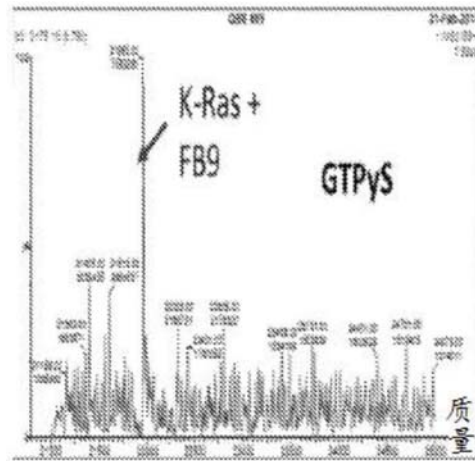


图13B

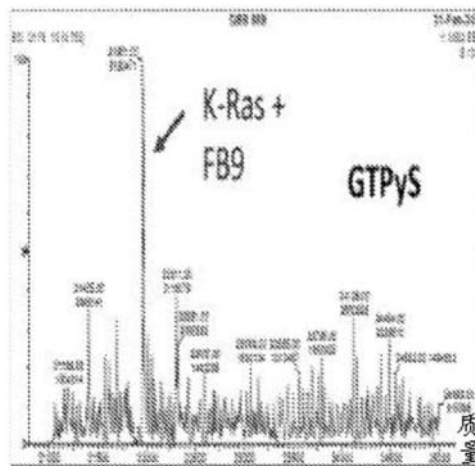


图13C

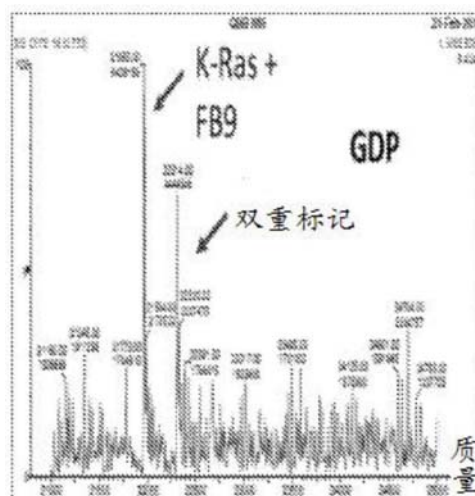


图13D

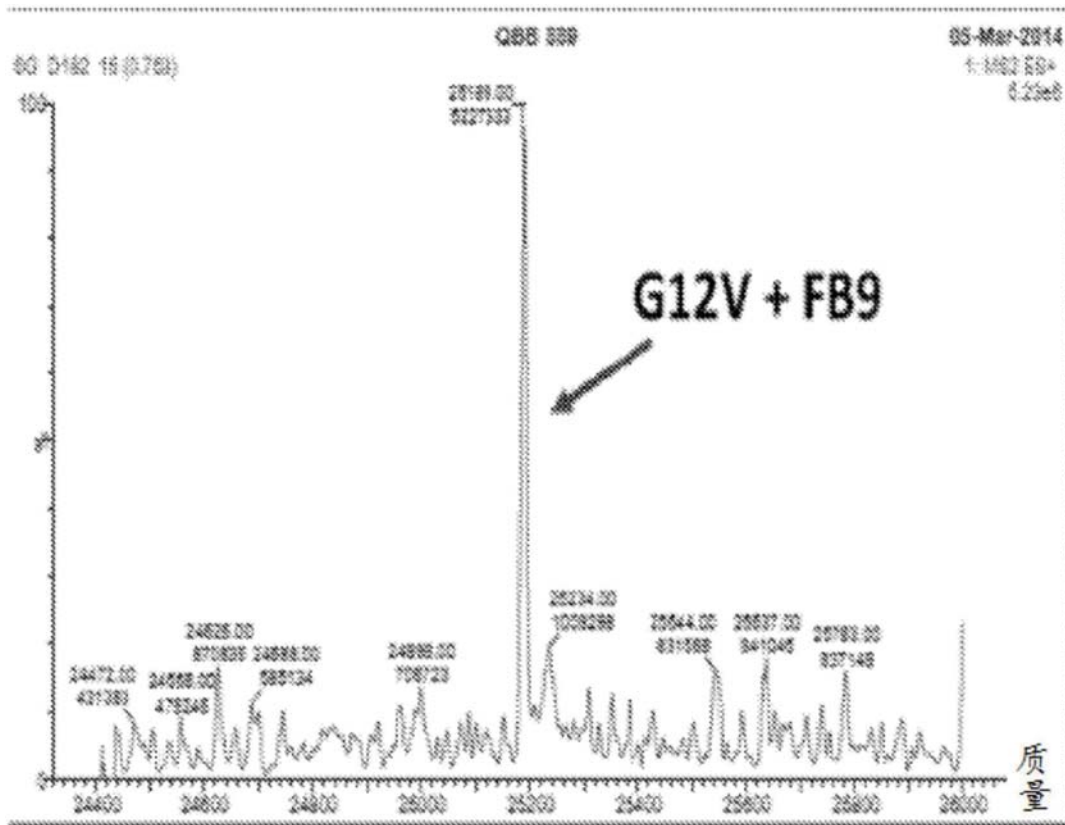


图14B

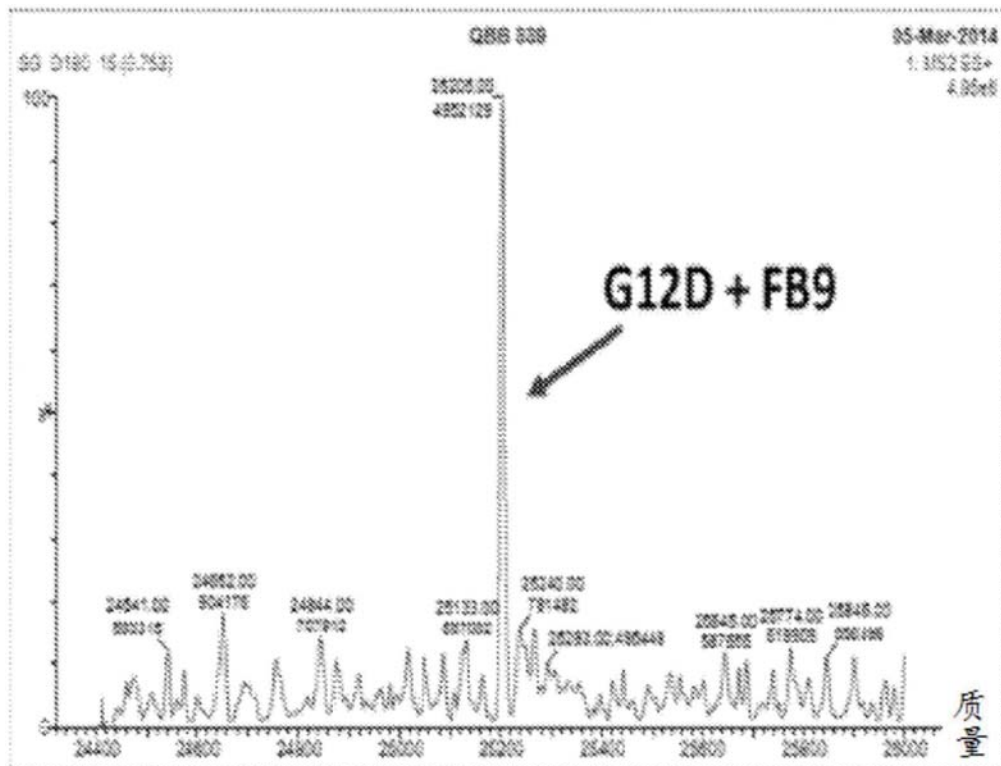


图14C

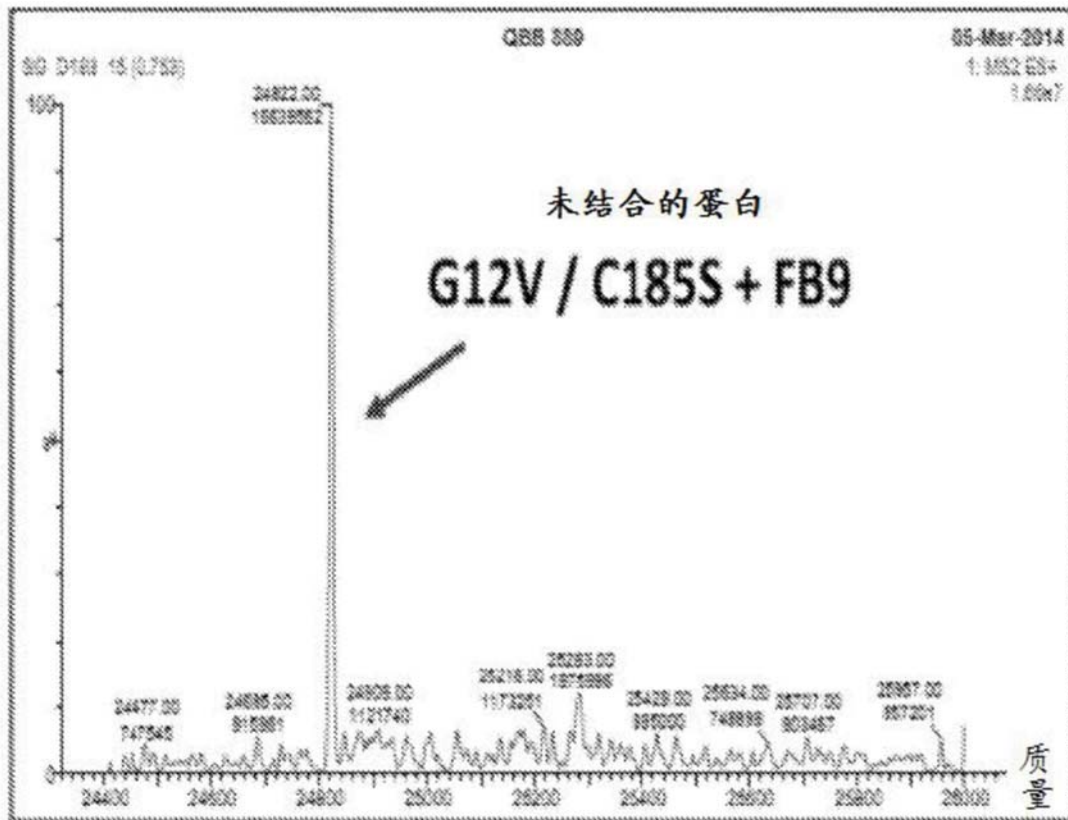


图14D

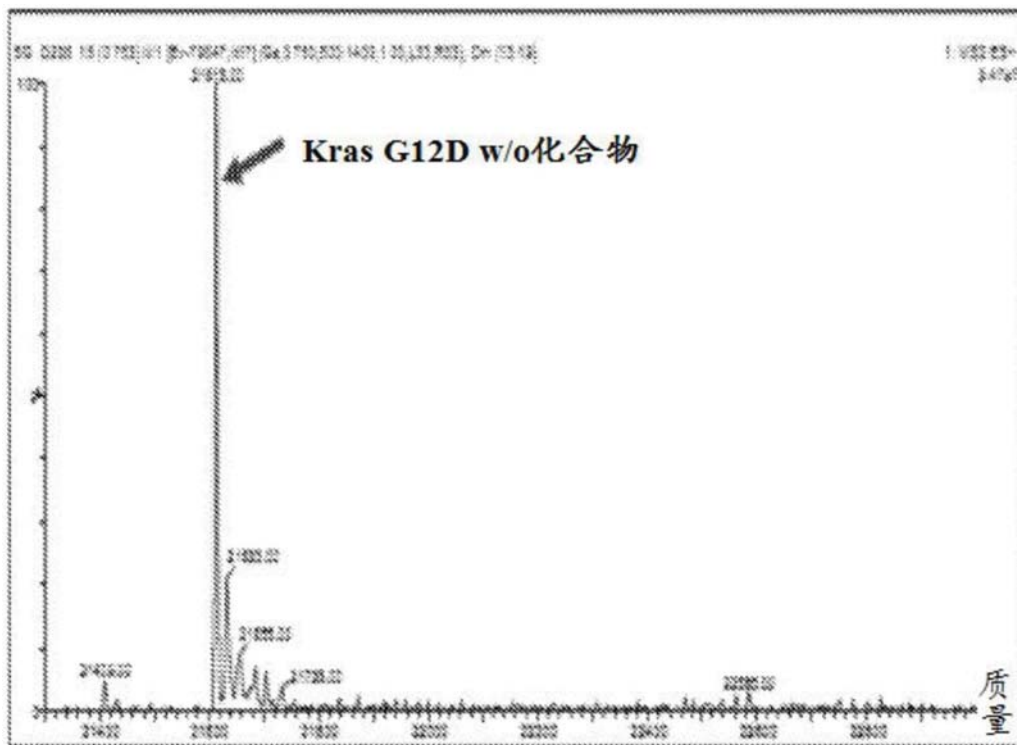


图15A

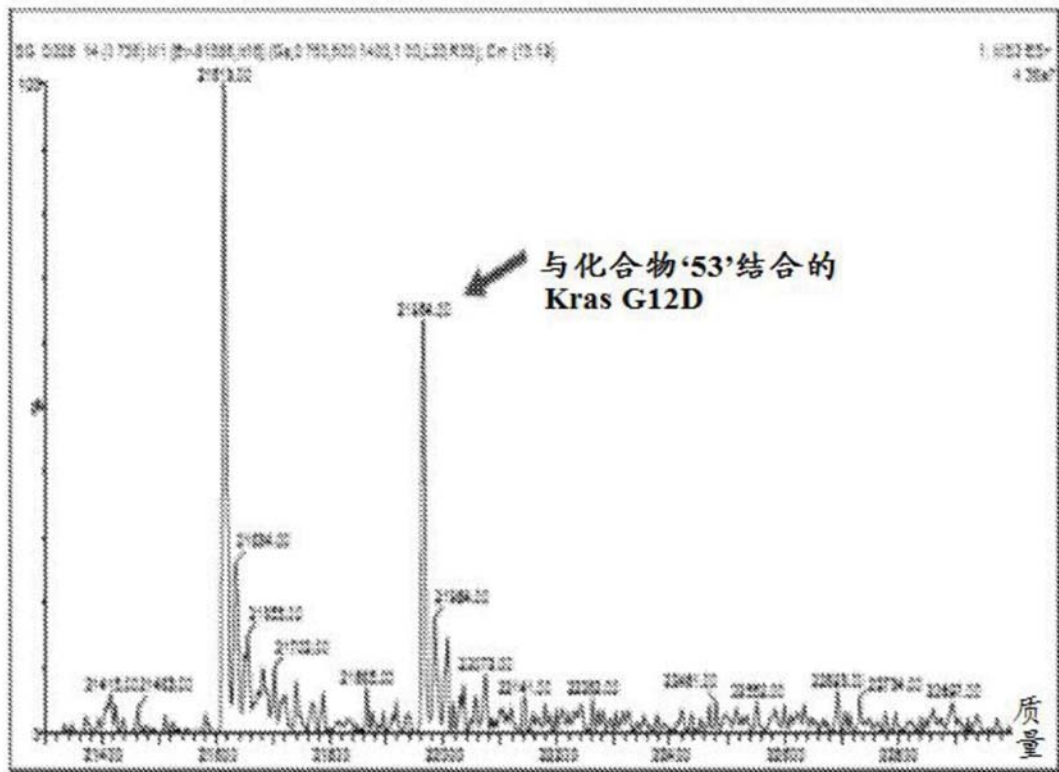


图15B

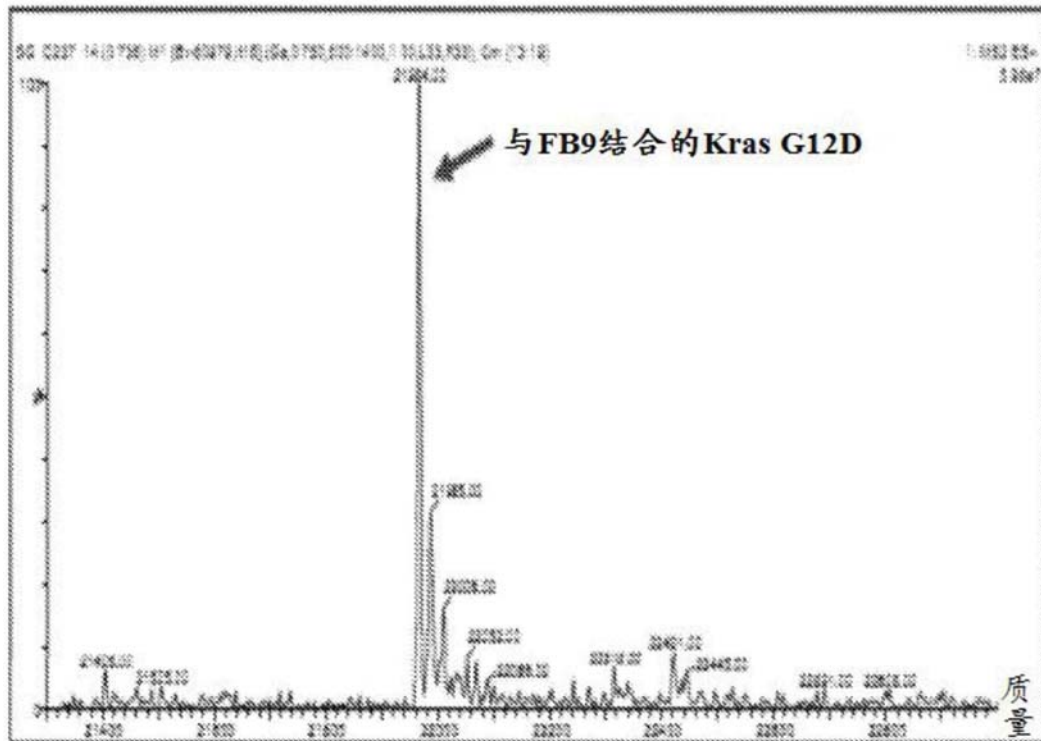


图15C

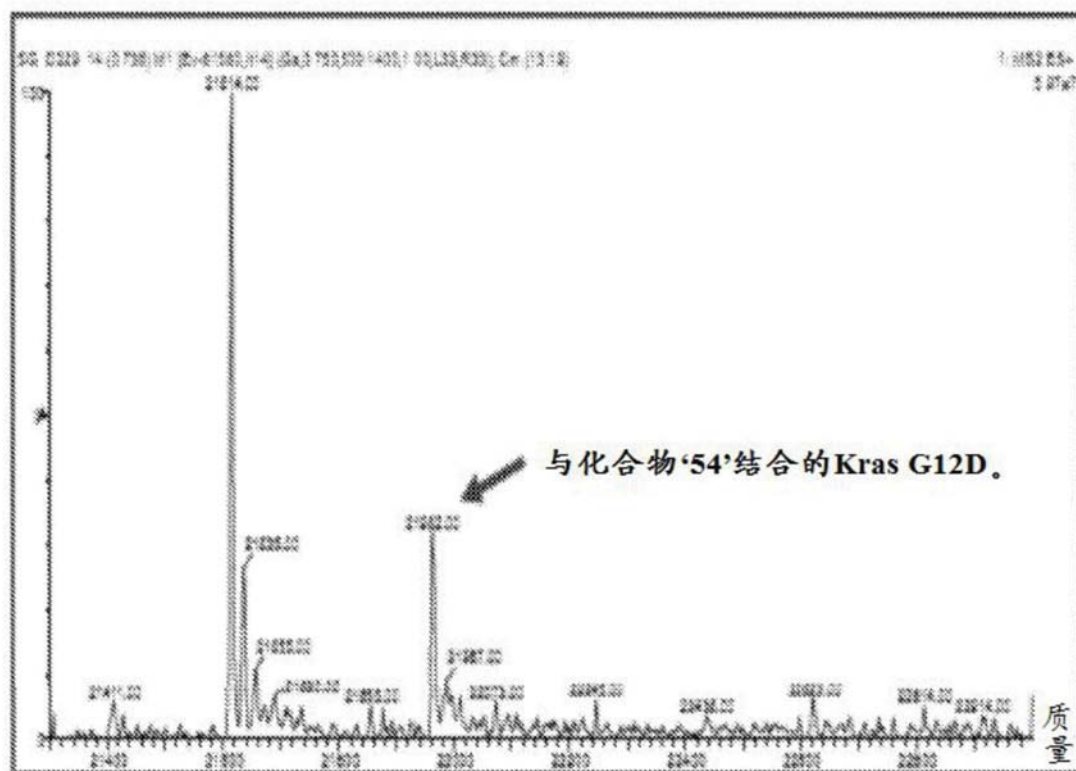


图15D

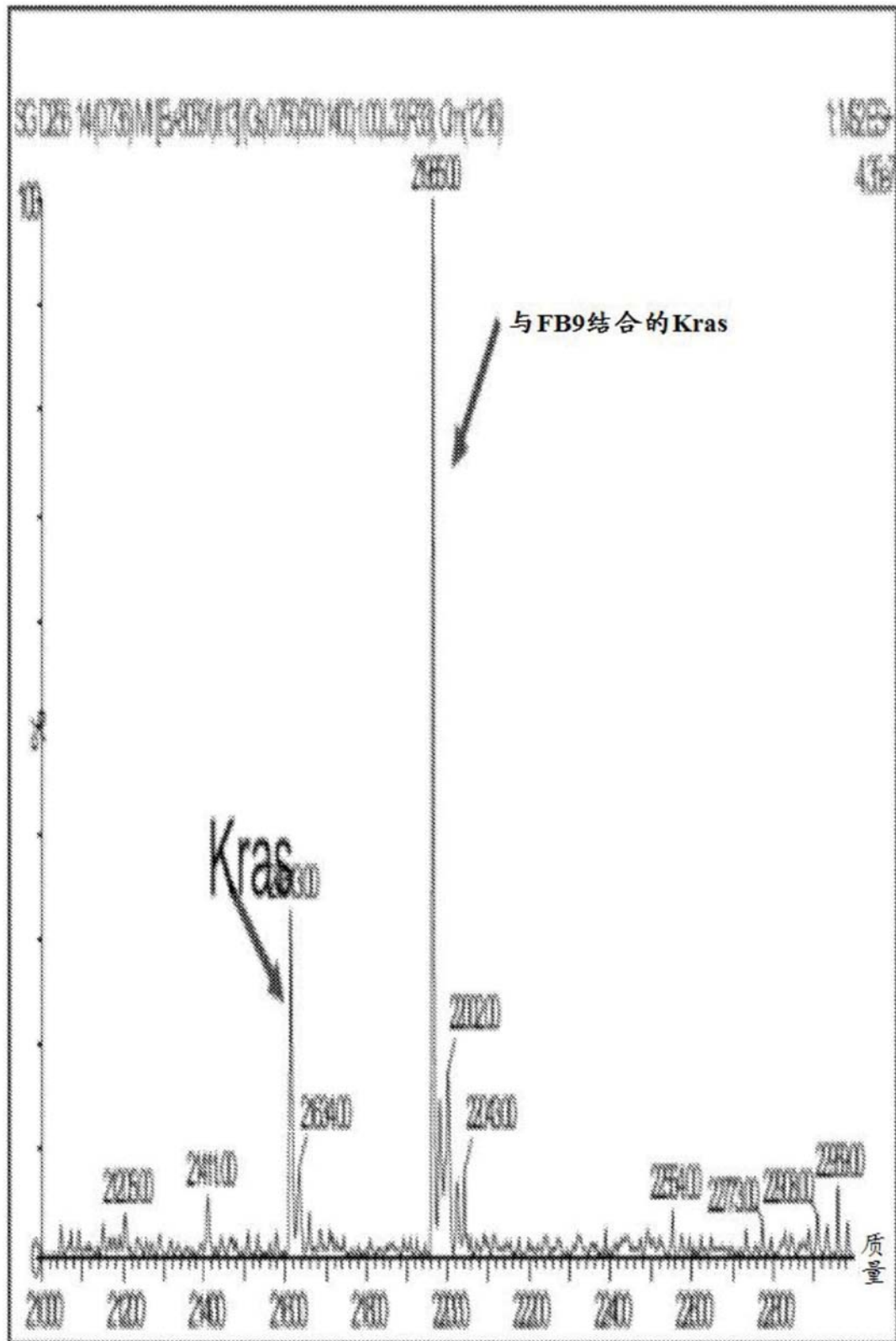


图16A

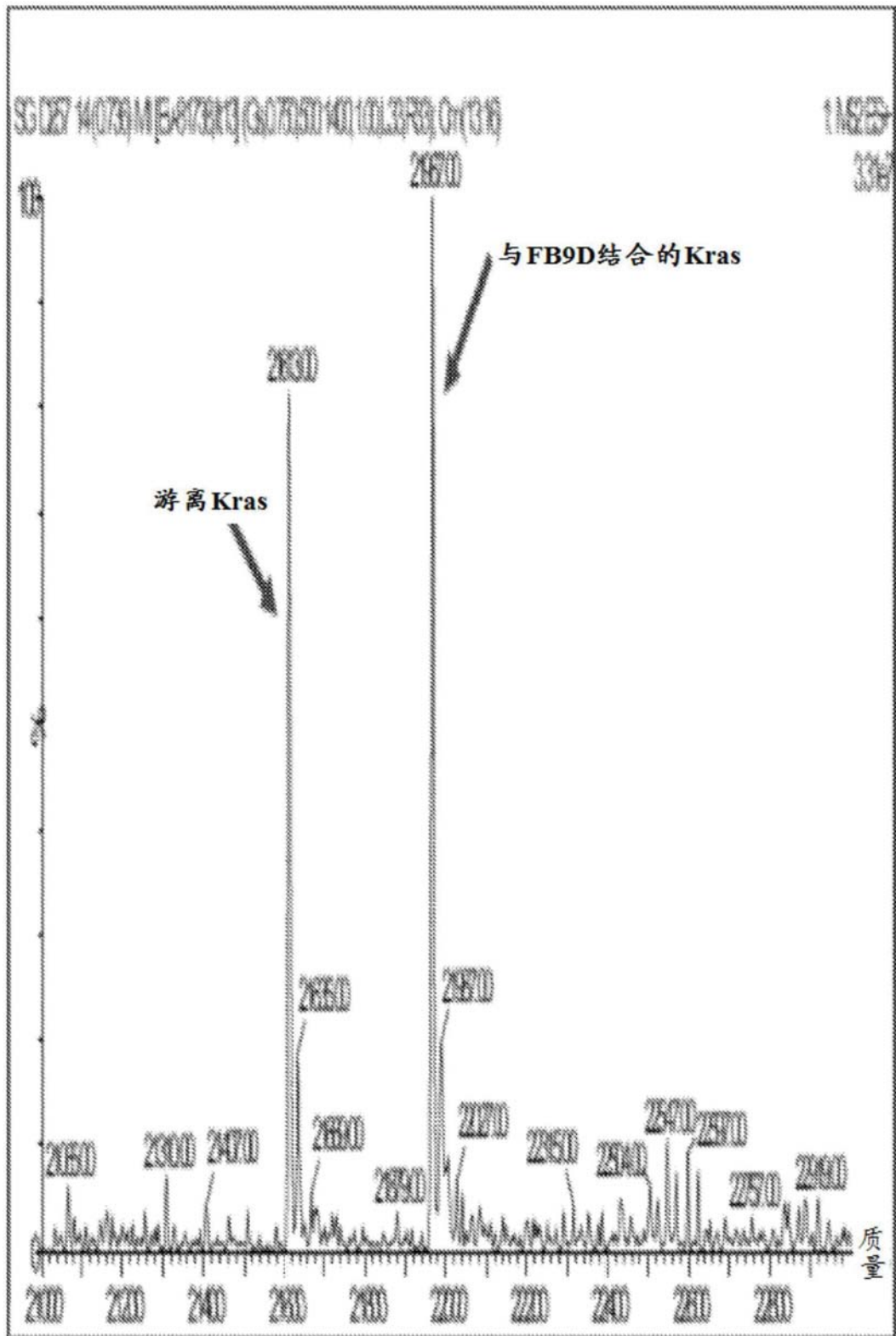


图16B

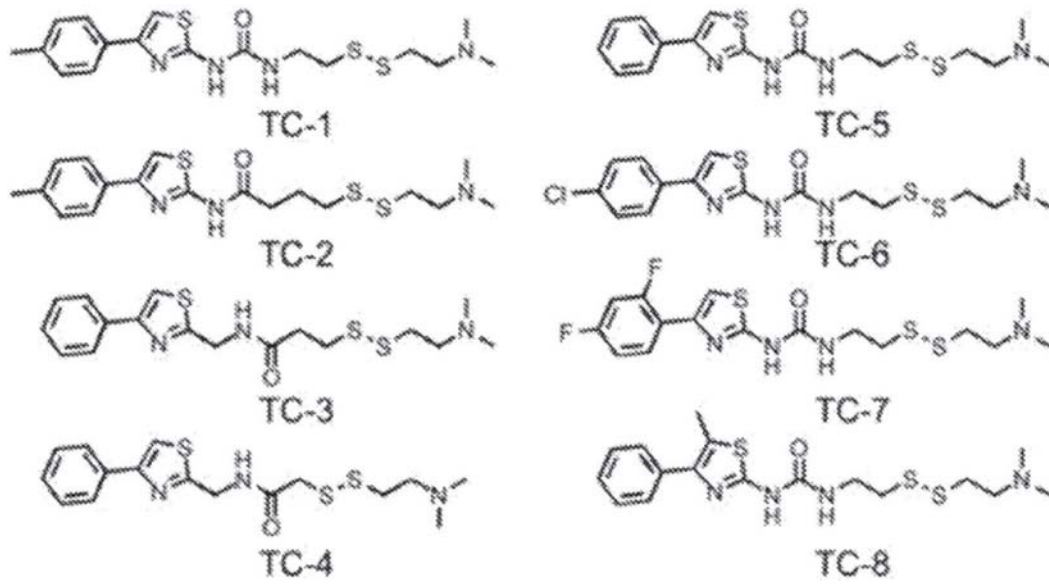


图17A

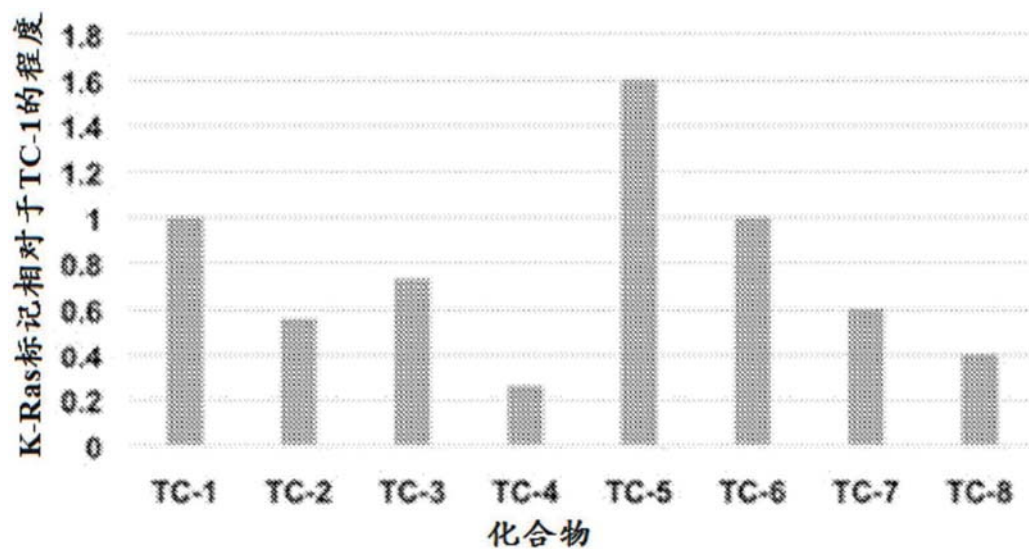


图17B

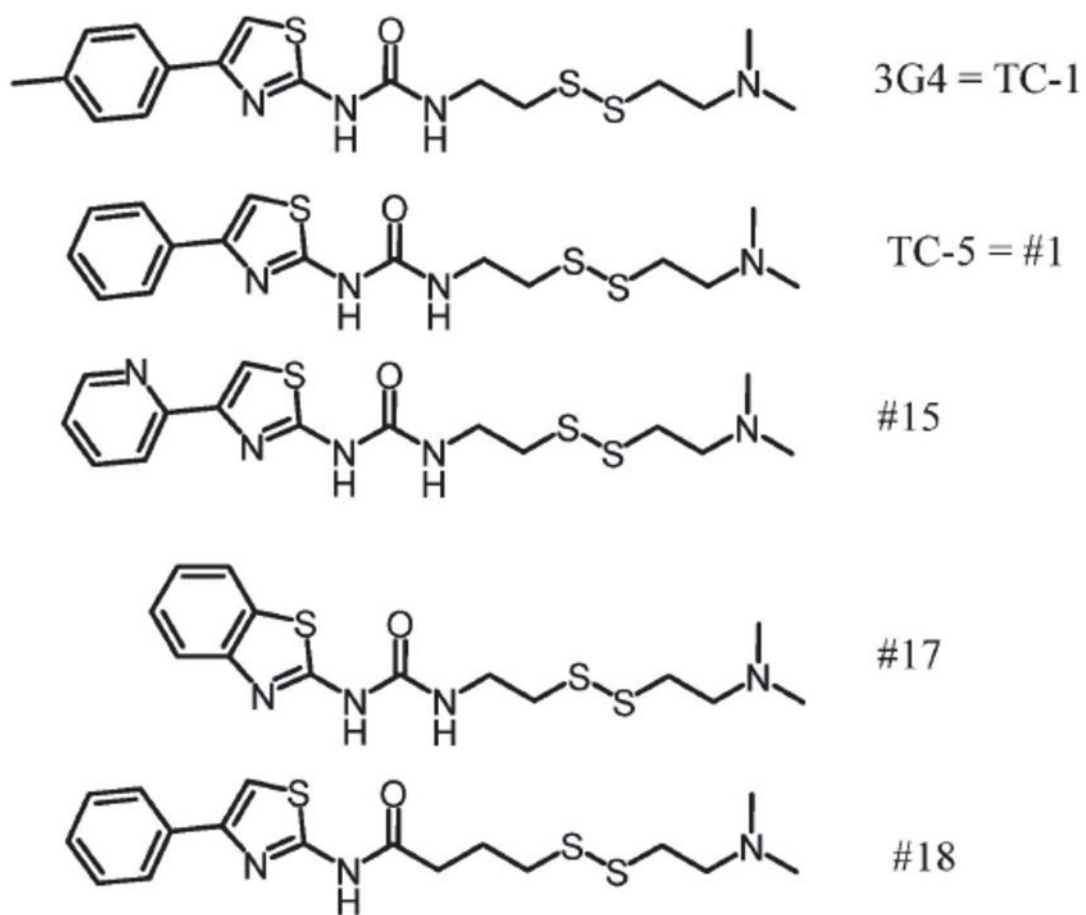


图18A

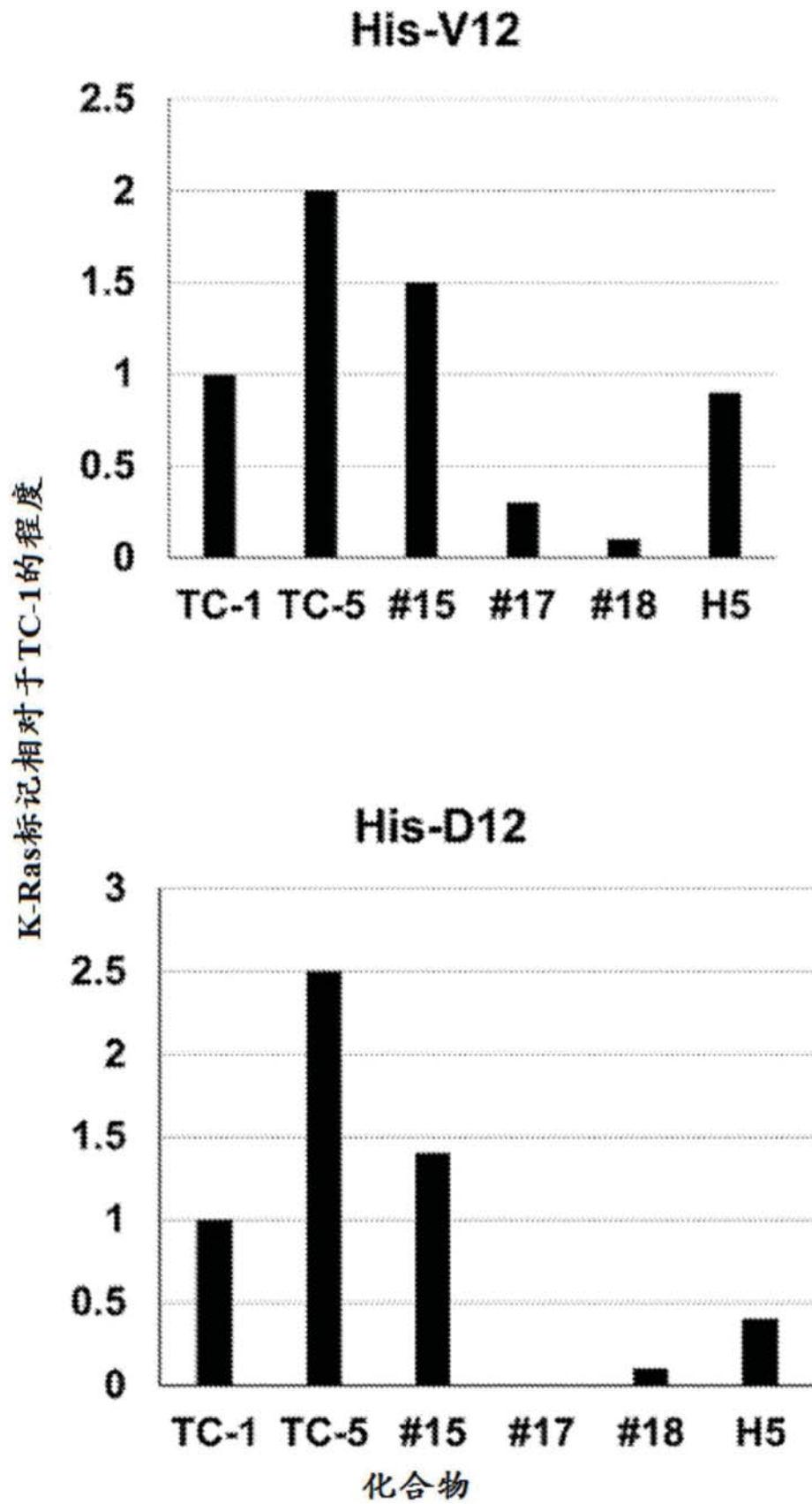


图18B

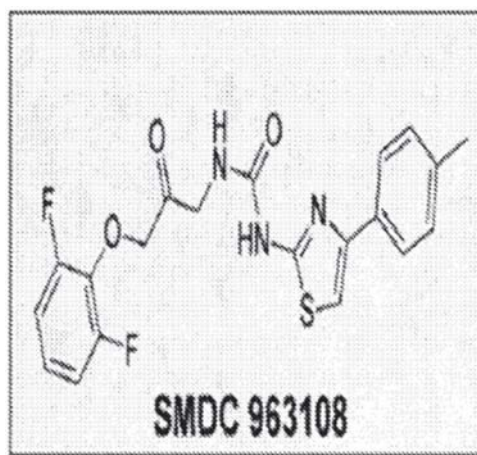


图19A

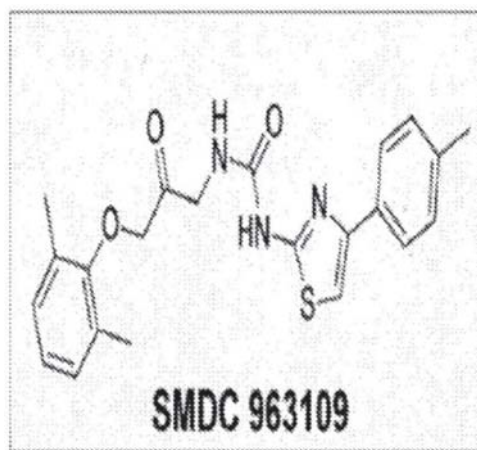


图19B

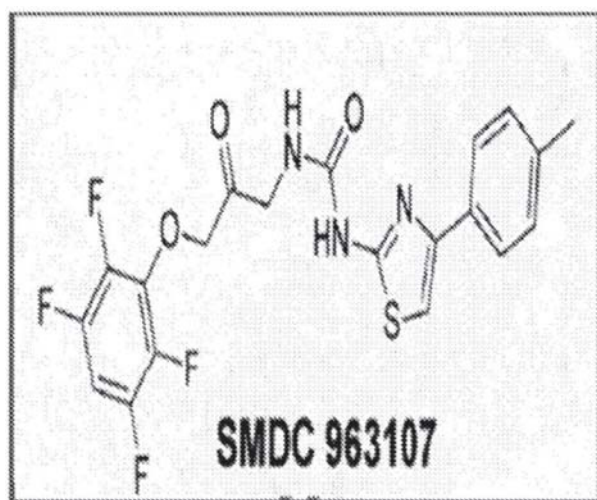


图19C

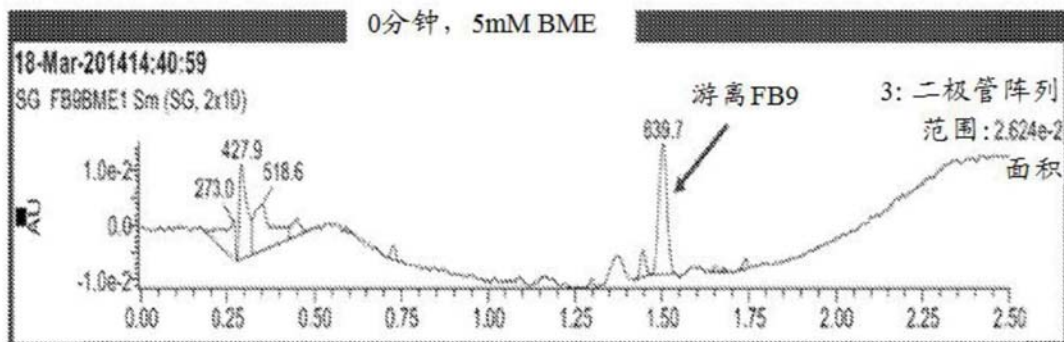


图20A

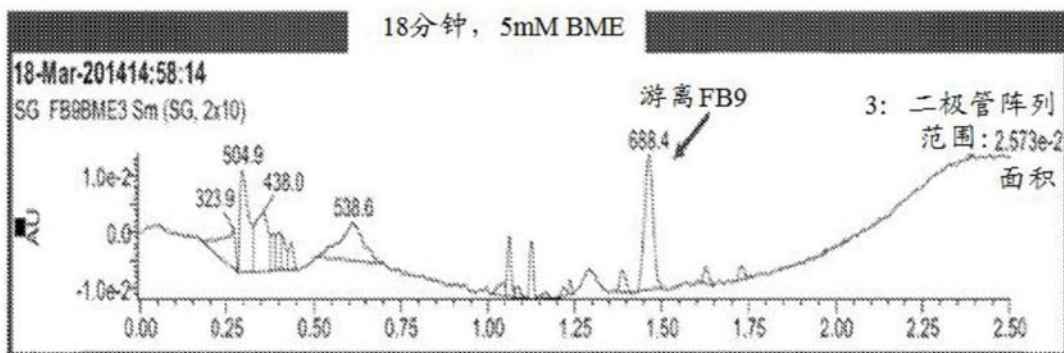


图20B

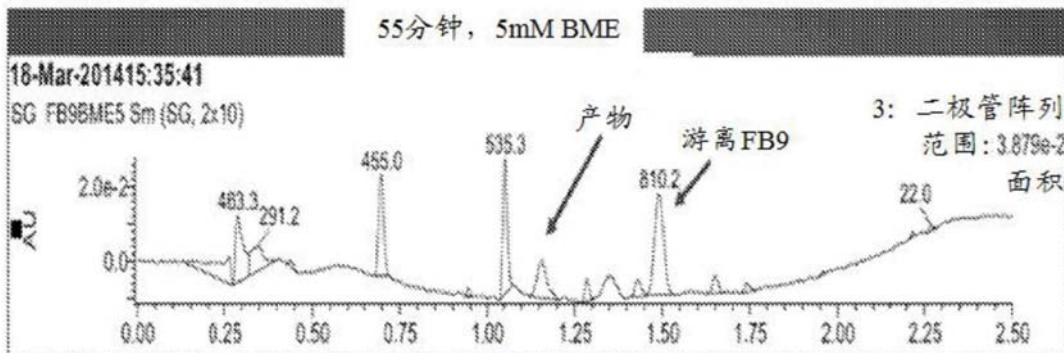


图20C

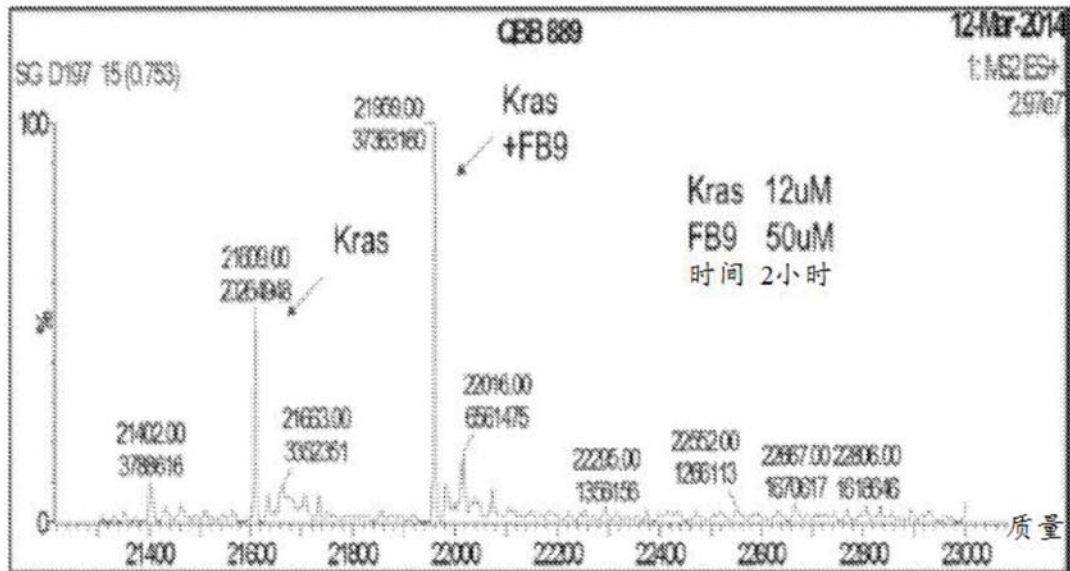


图21A

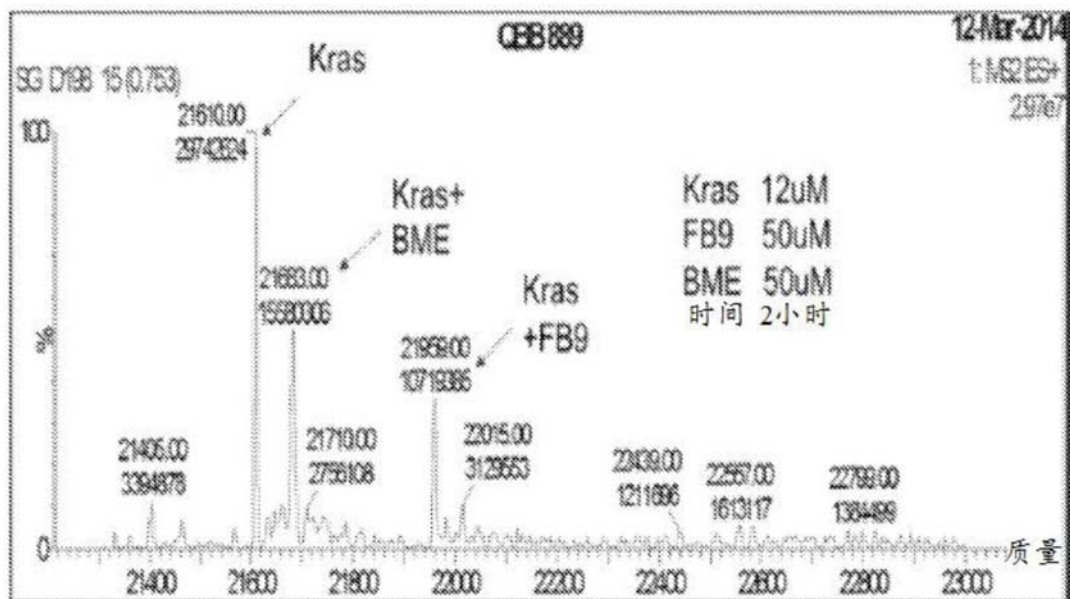


图21B

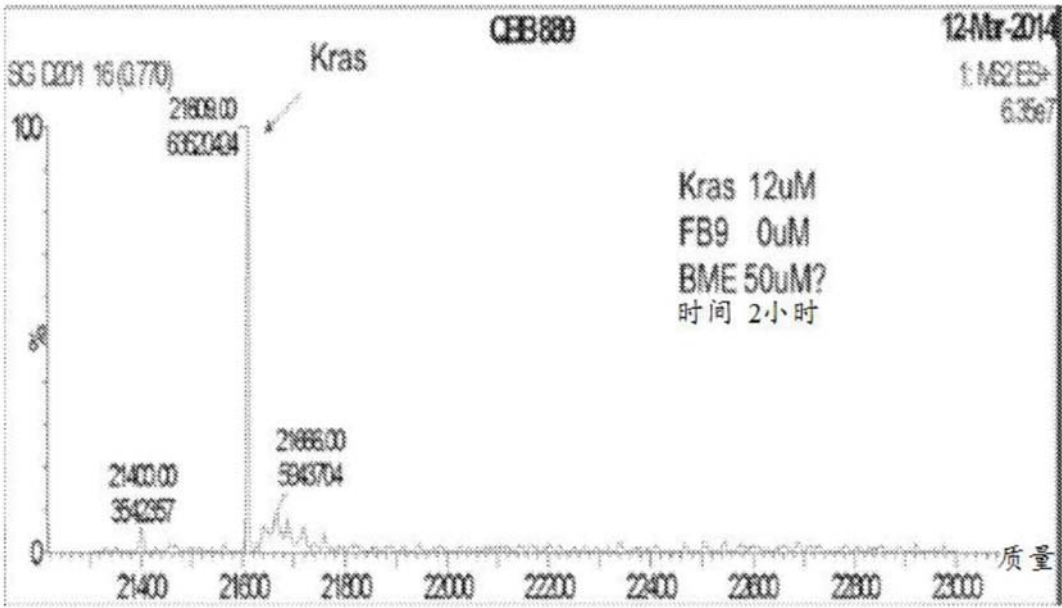


图21C

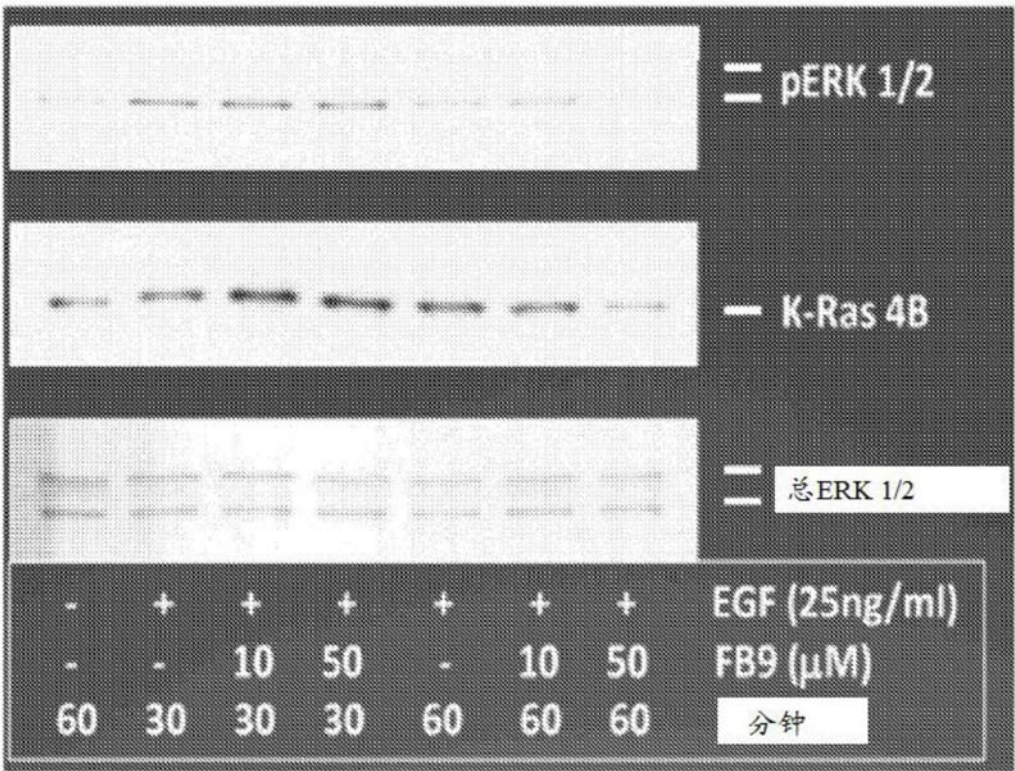


图22

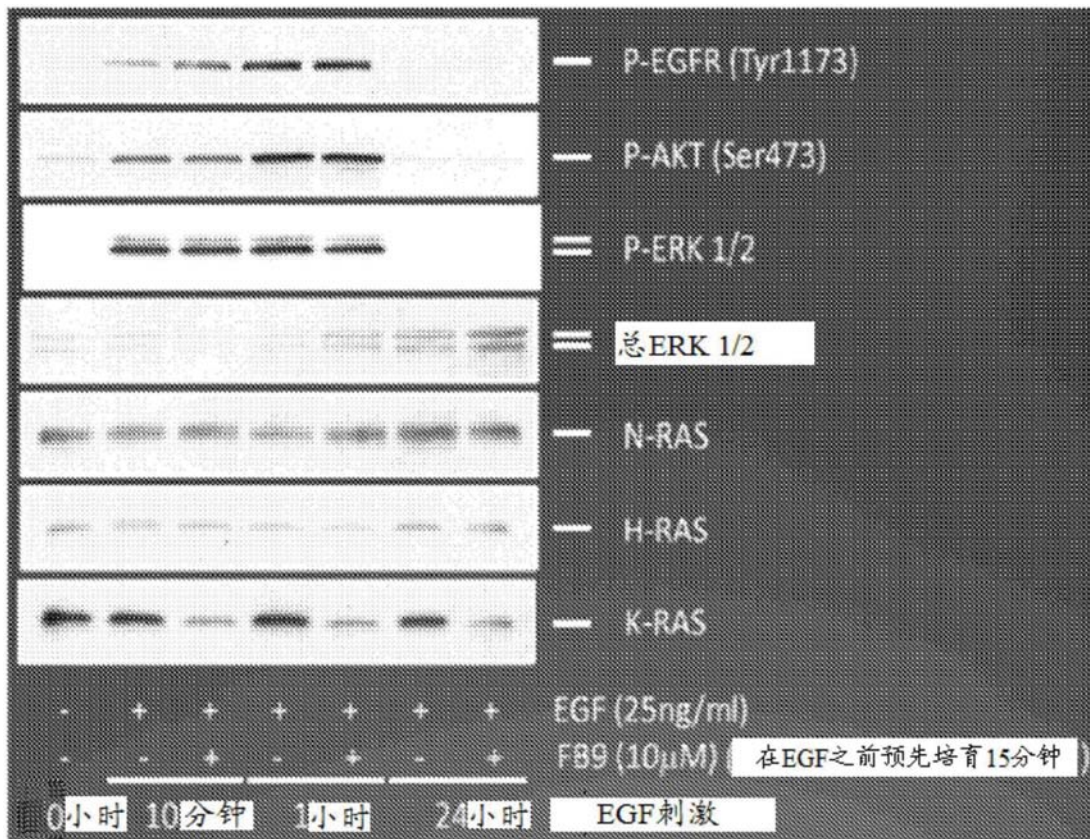


图23

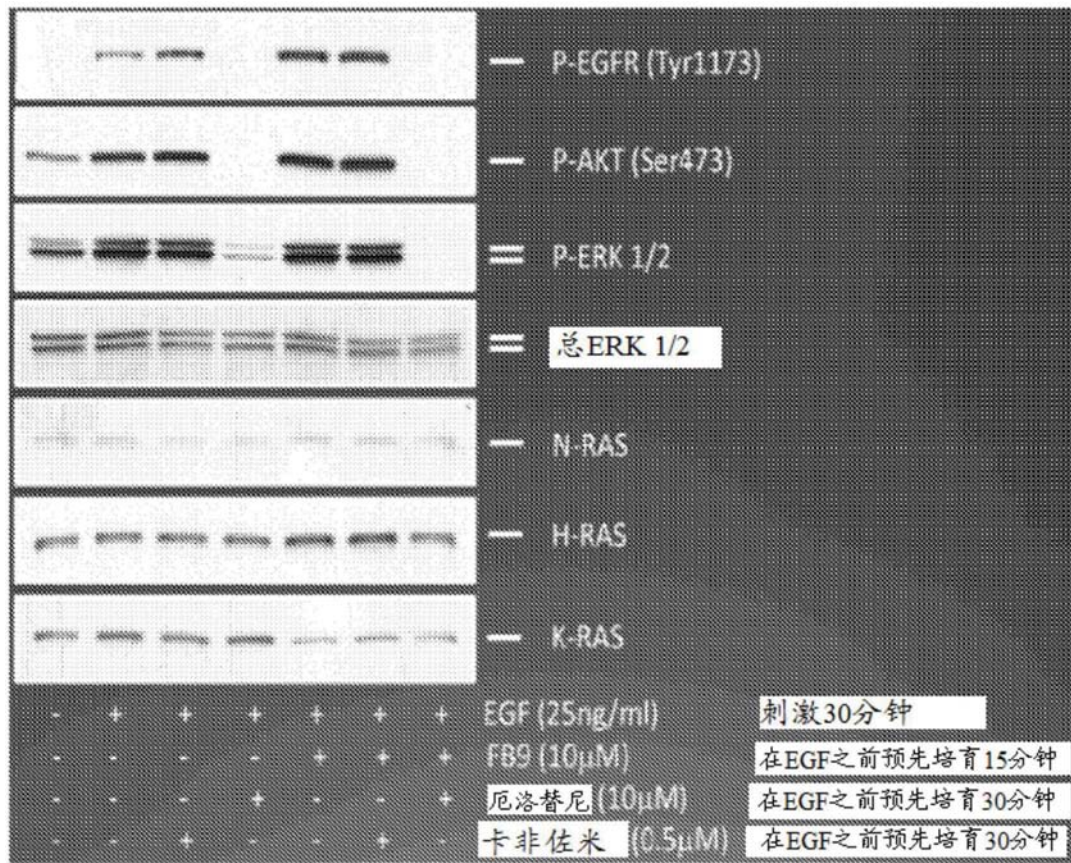


图24

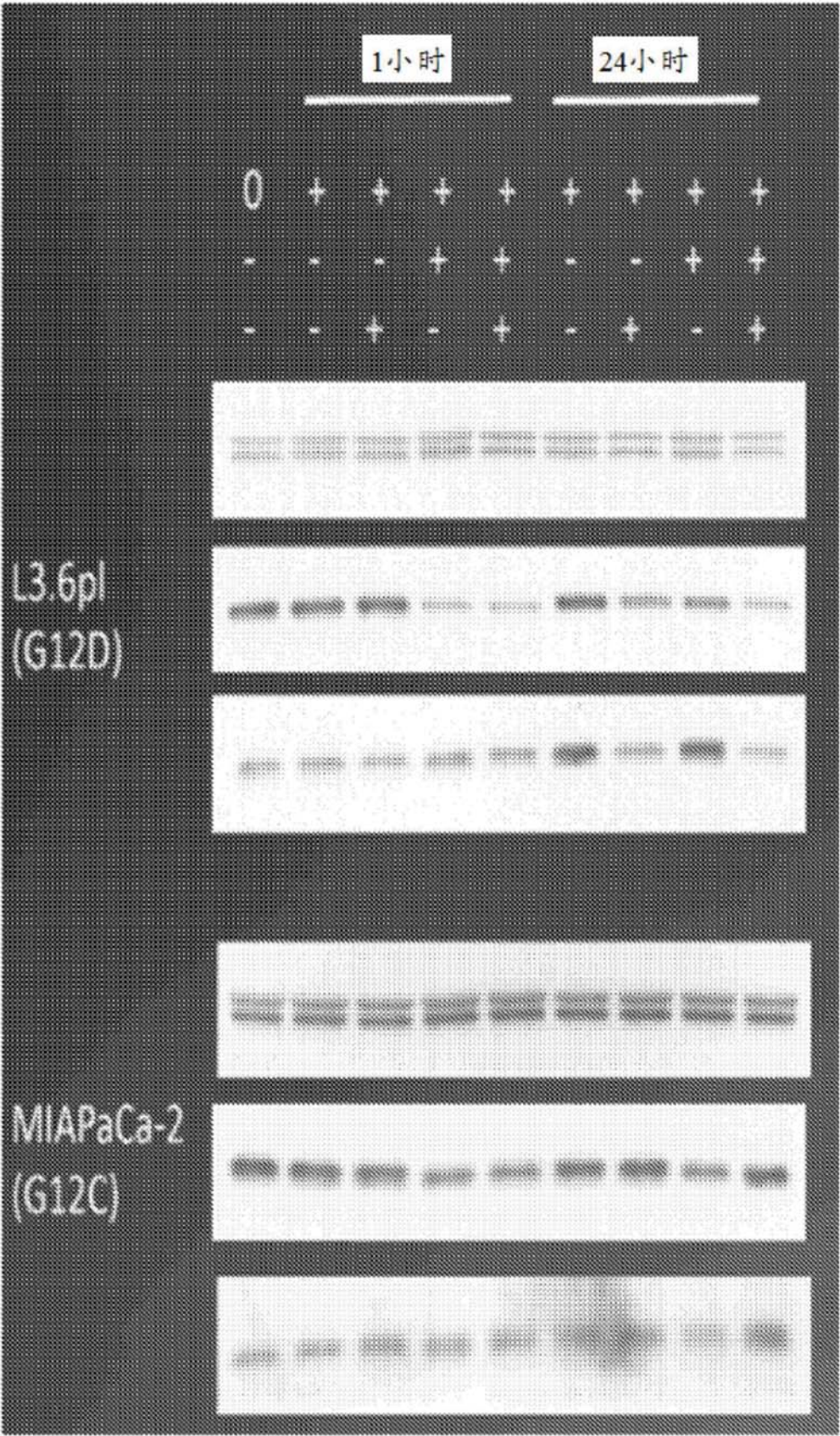


图25A

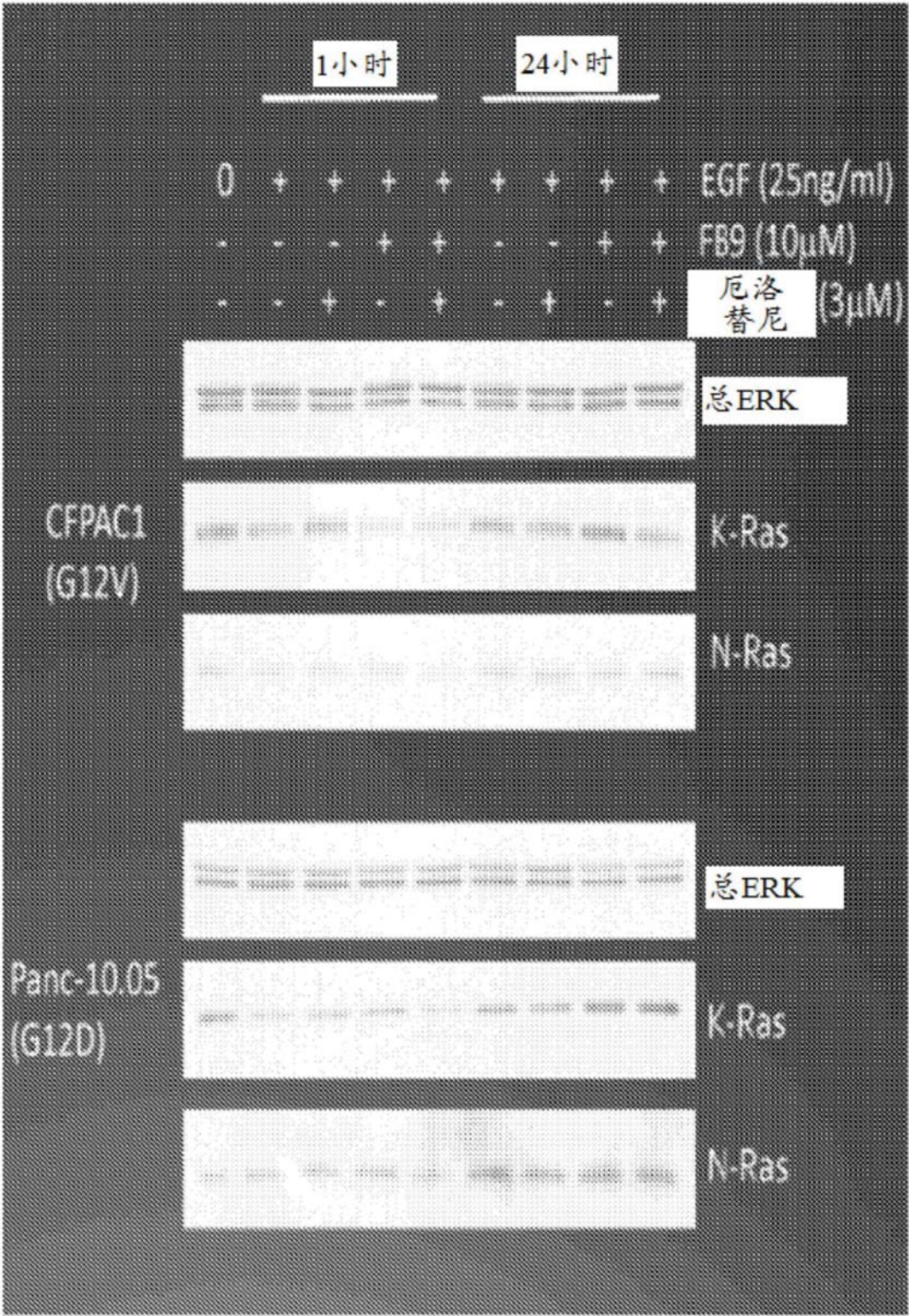


图25B

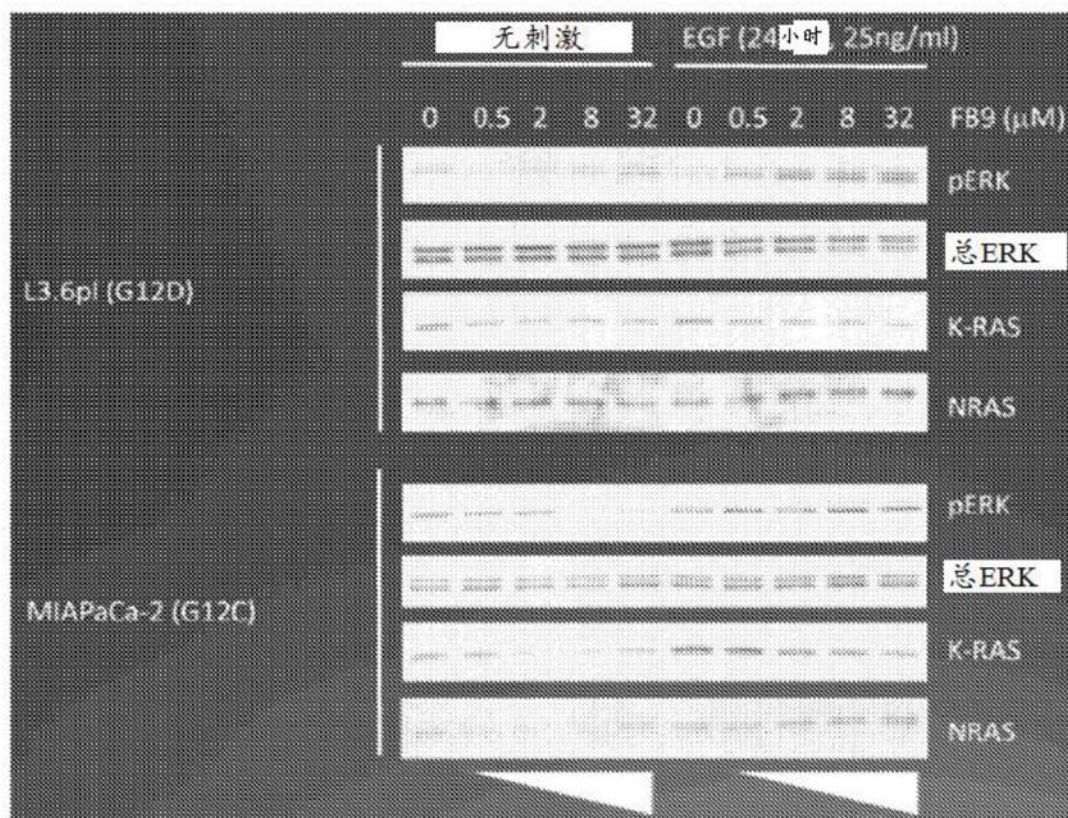


图26

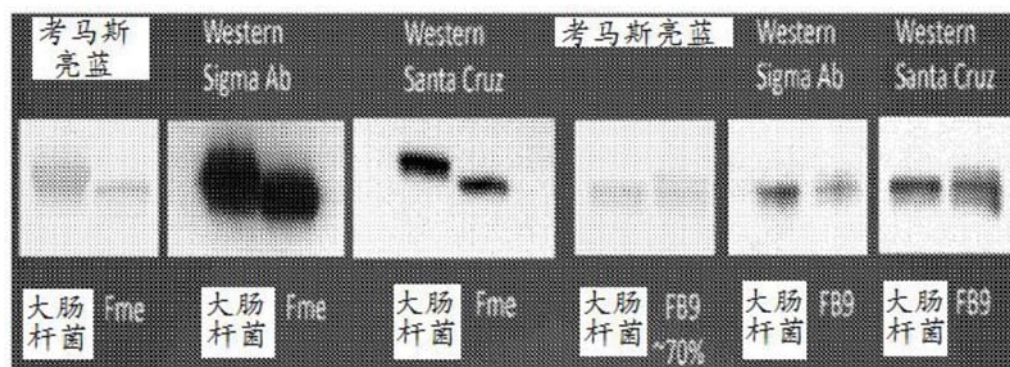


图27

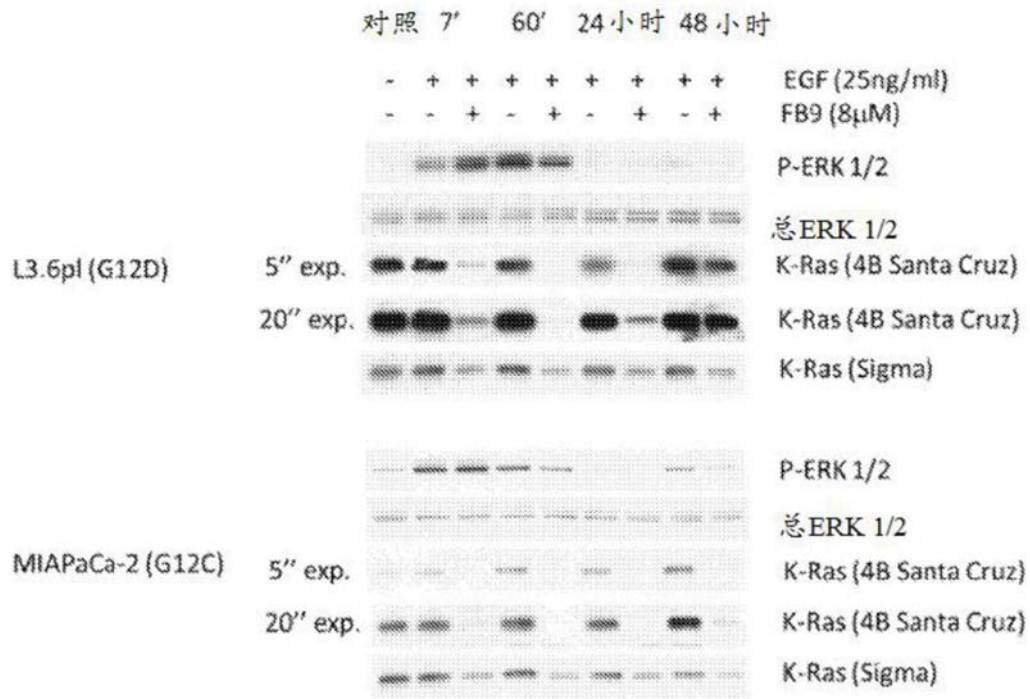


图28

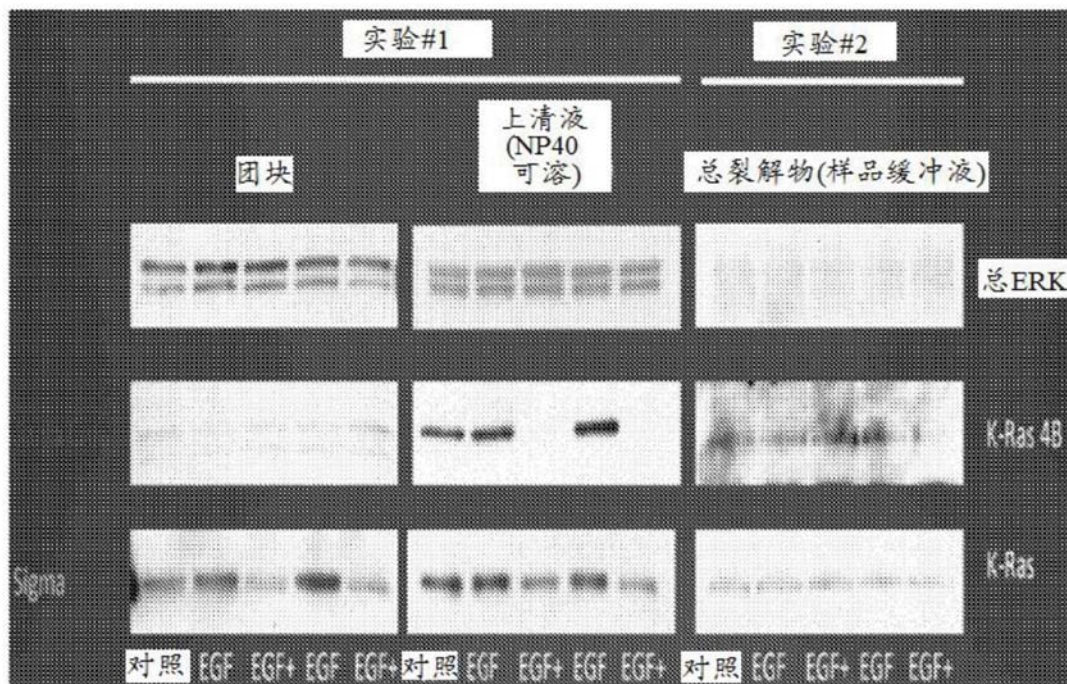


图29

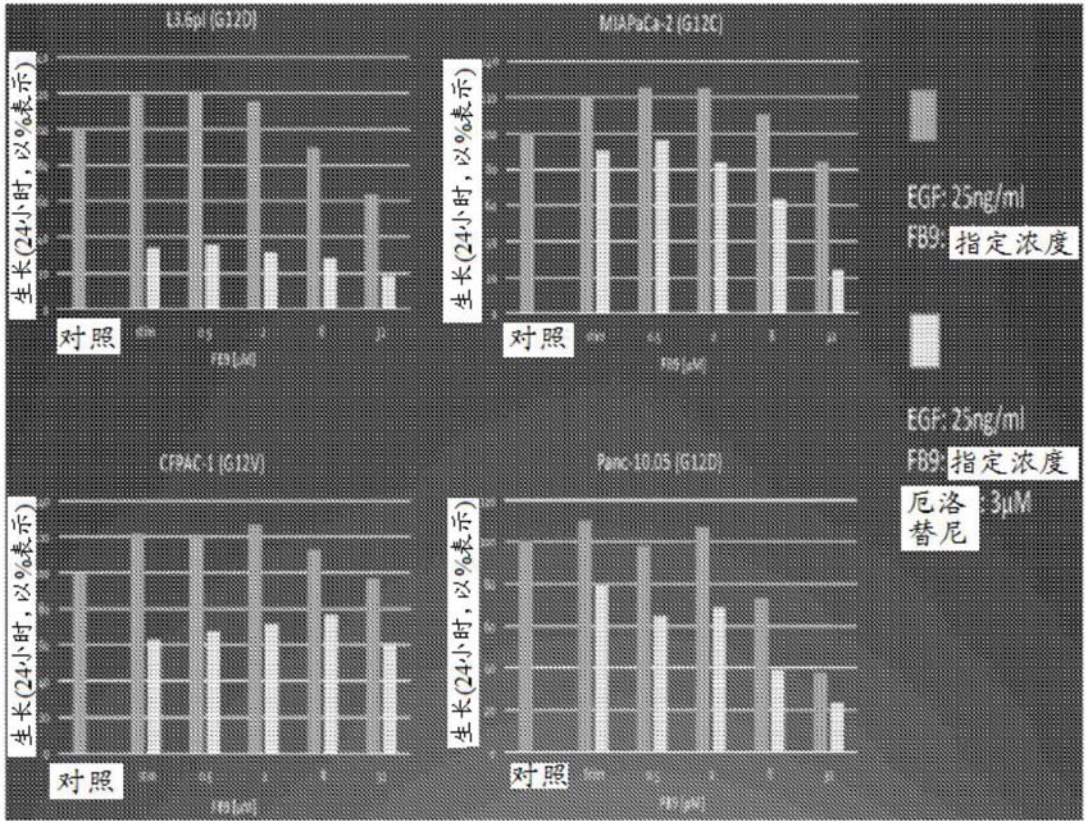


图30

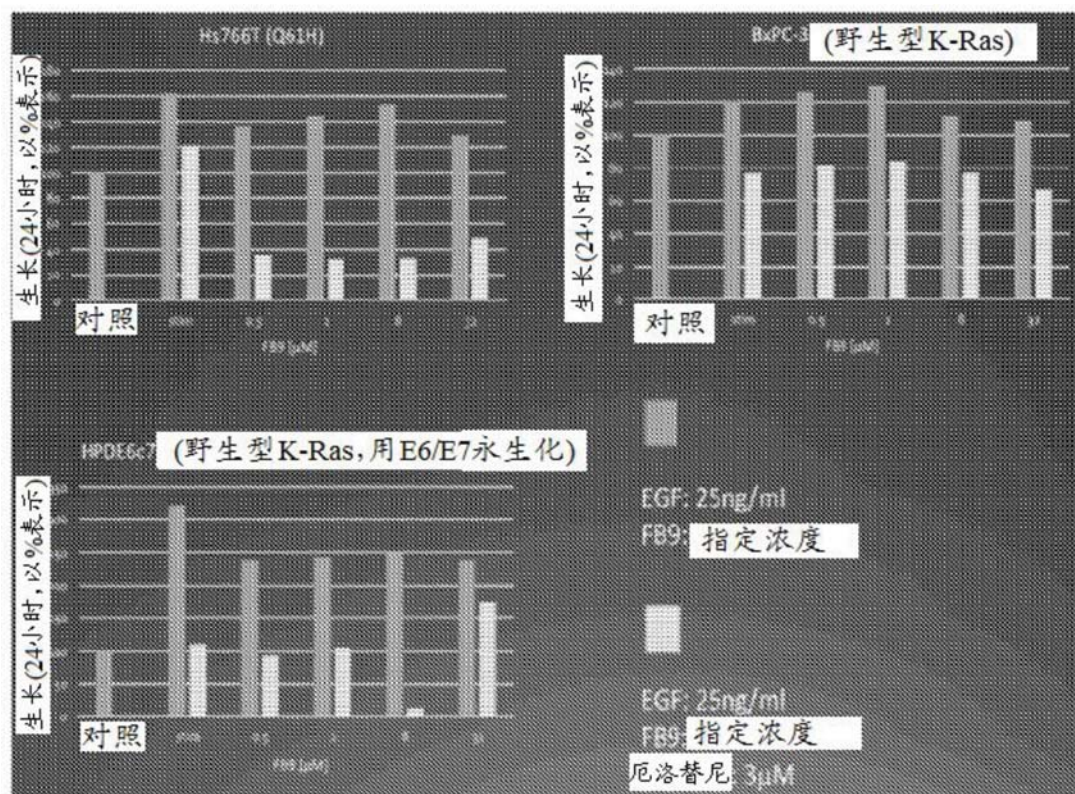


图31

K-Ras 4B野生型C-末端: 化合物3G4

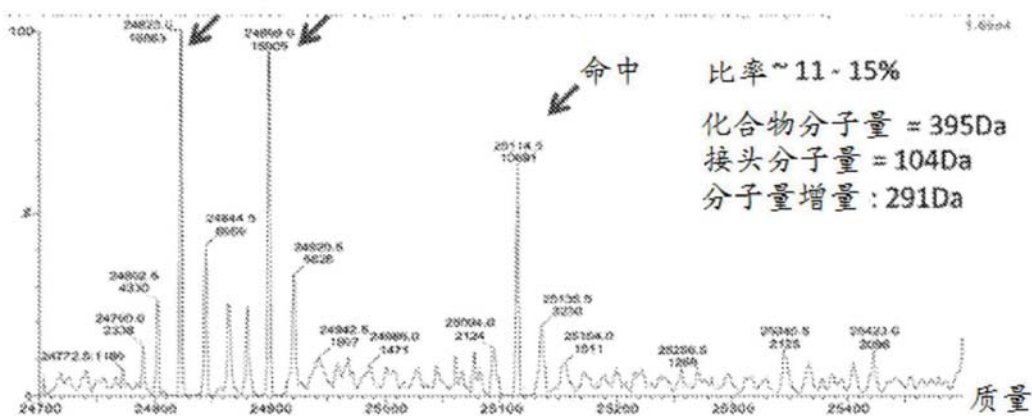
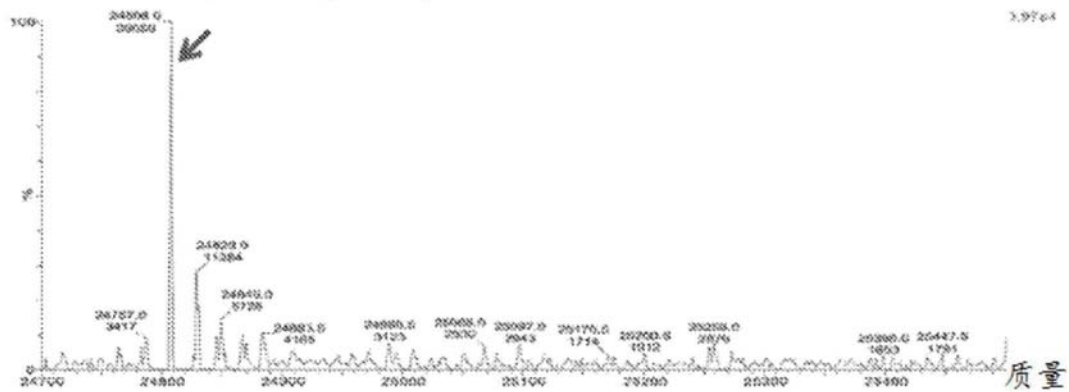


图32A

K-Ras 4B突变体C-末端(C185S): 化合物3G4



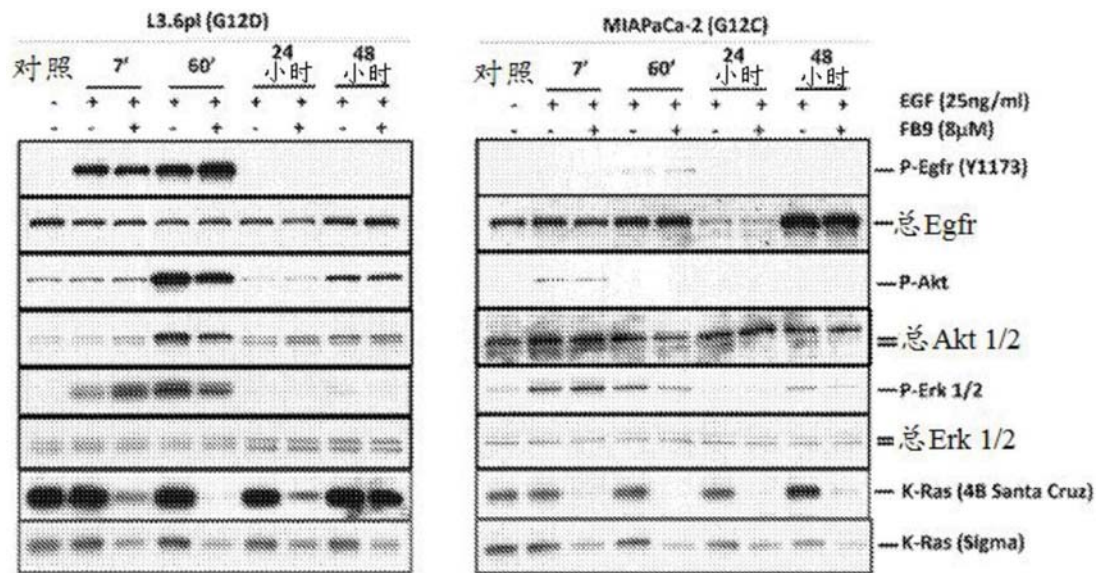


图34

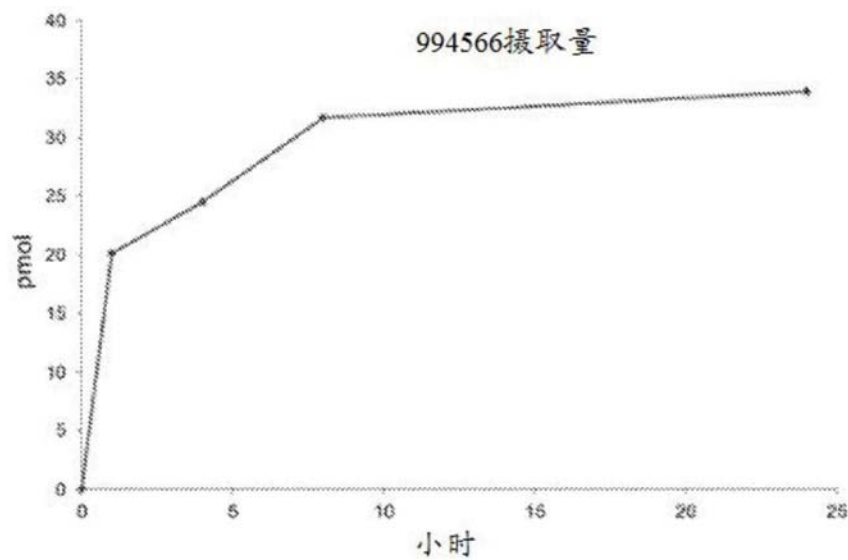


图35

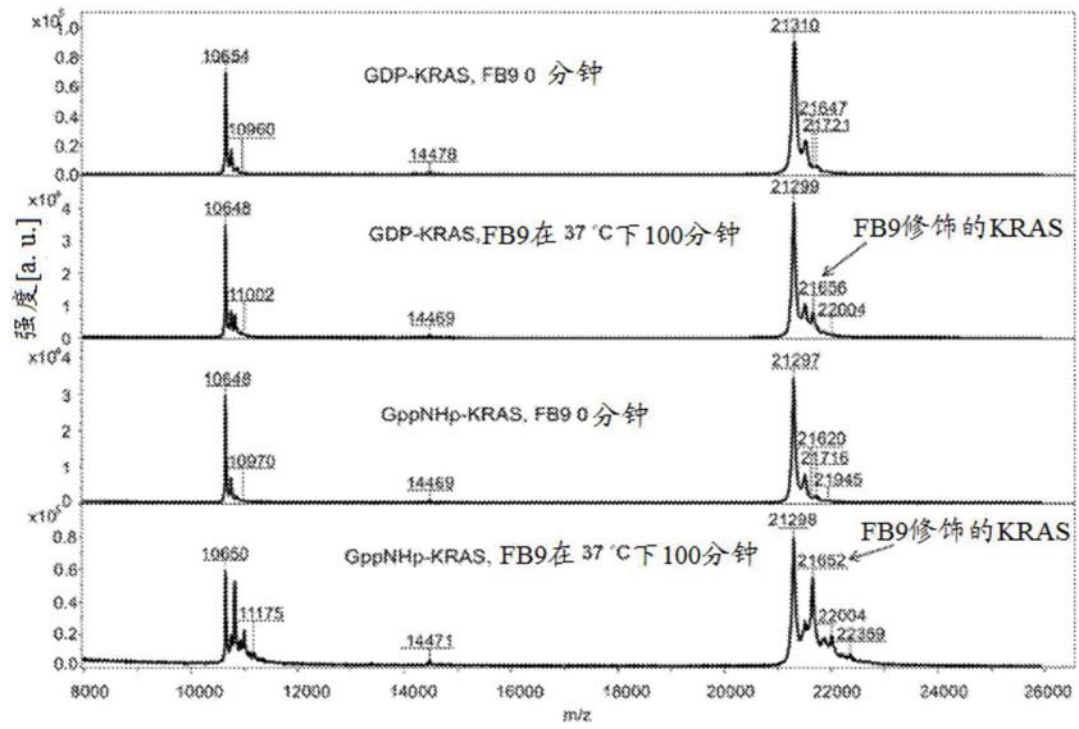


图36

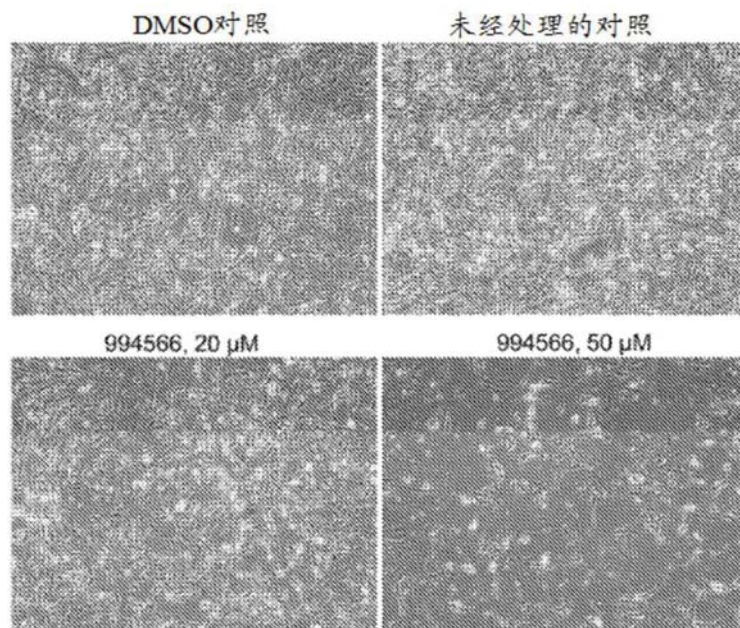


图37

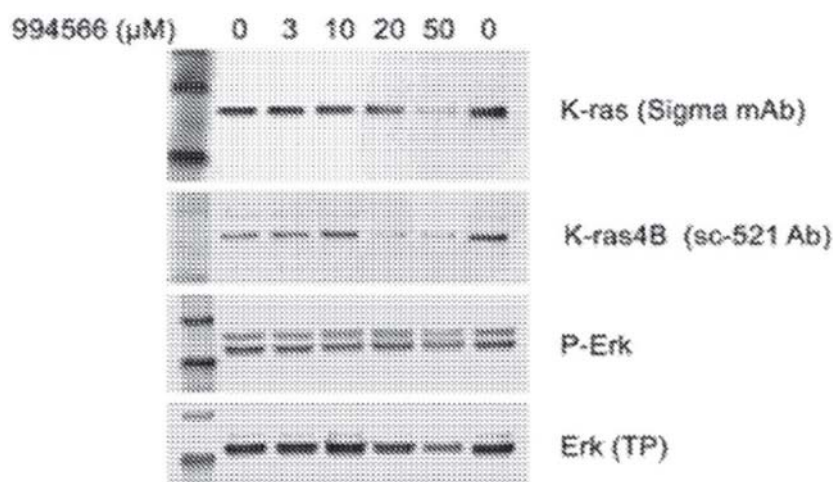


图38A

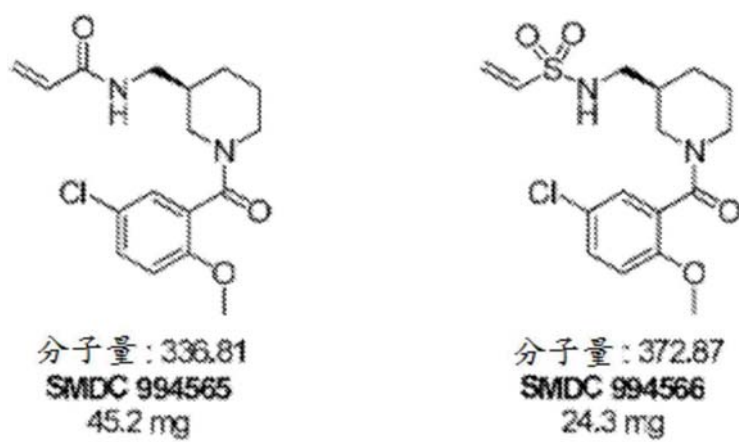


图38B

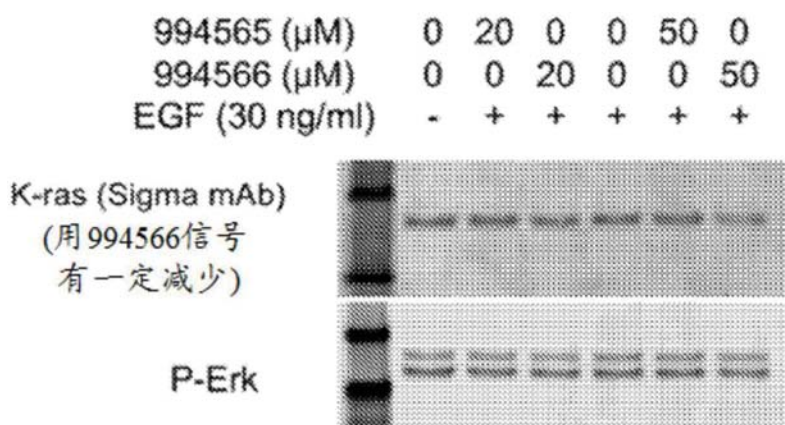


图39

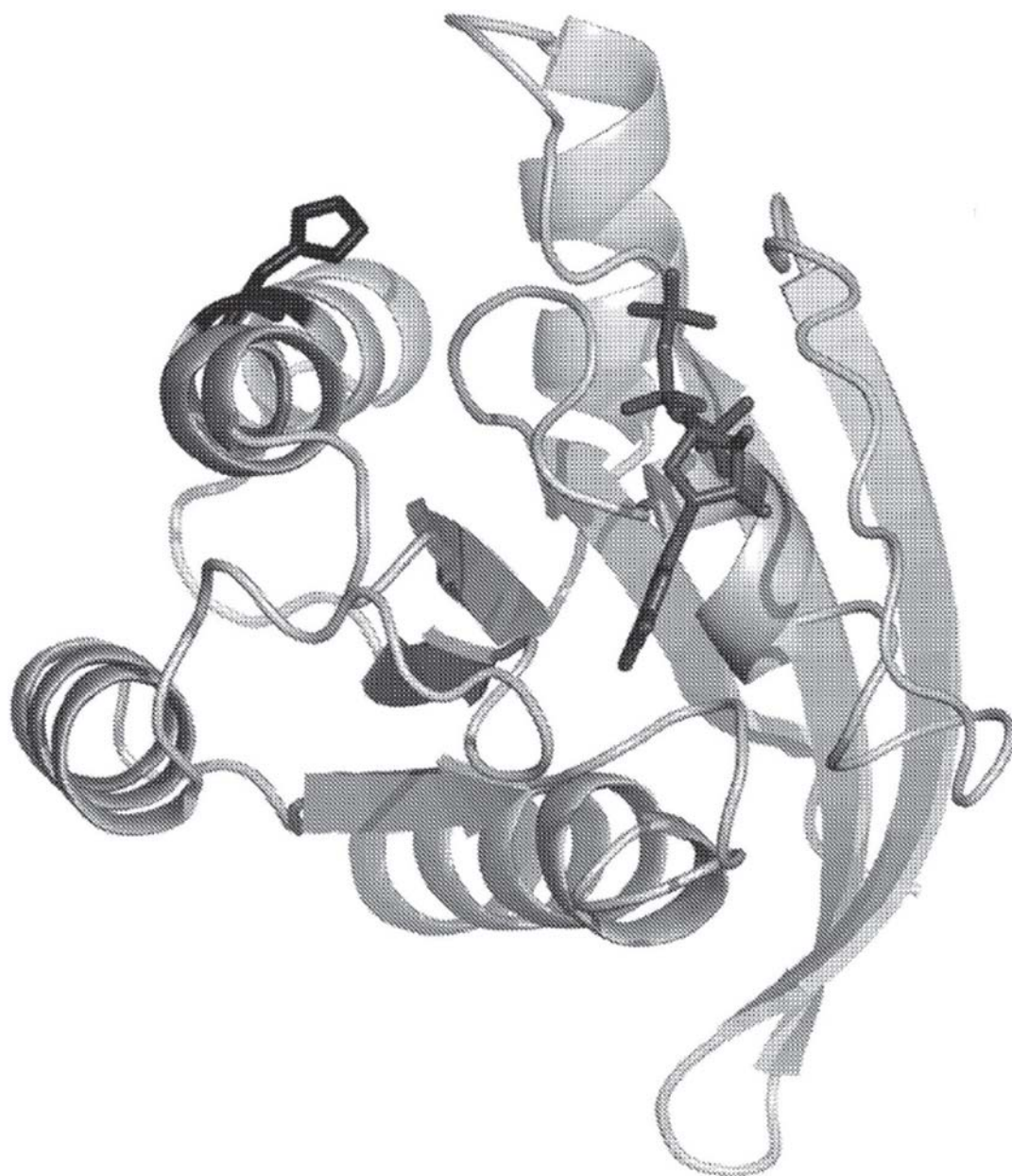


图40

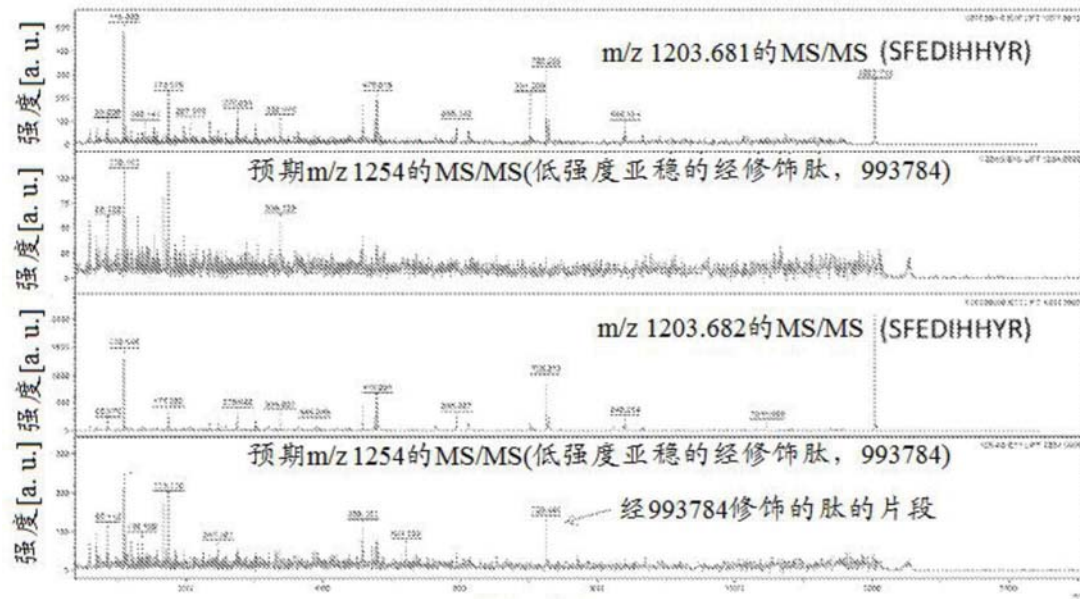


图41

全尺寸KRAS (G-Hs.KRAS4b, 1-188); RPX150917.19; RP1150917140242
平均[M+H]⁺ 21482.5940

GMTEYKLVVVGAGGVGKSALTIQLIQNHFVDEYDPTIEDSYRKQVVIDGETCLLDILDTAGQEEYS
AMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIKRVKDESDVPMVLVGNKCDLPSRTVDTK
QAQDLARSYGIPFIETSAKTRQGVDDAFYTLVREIRKHKEKMSKDGKSKKSKTKCVIM

```

      10      20      30      40      50      60
GMTEYKLVVY GAGGVGKSAE TQLIQNHFV DEYDPTIED SYRKQVVIDE TLLDILDTA
      70      80      90     100     110     120
AGQEEYSAMD QVHRTGEGFL CVFAINNTK SFEDIHHYR EQIKRVKDESD VPMVLVGNK
     130     140     150     160     170     180
CDLPSRTVDT QAQDLARSYG IPFIETSAK TRQGVDDAF YTLVREIRK HKEKMSKDG
KSKSKTKCVIM

```

图42

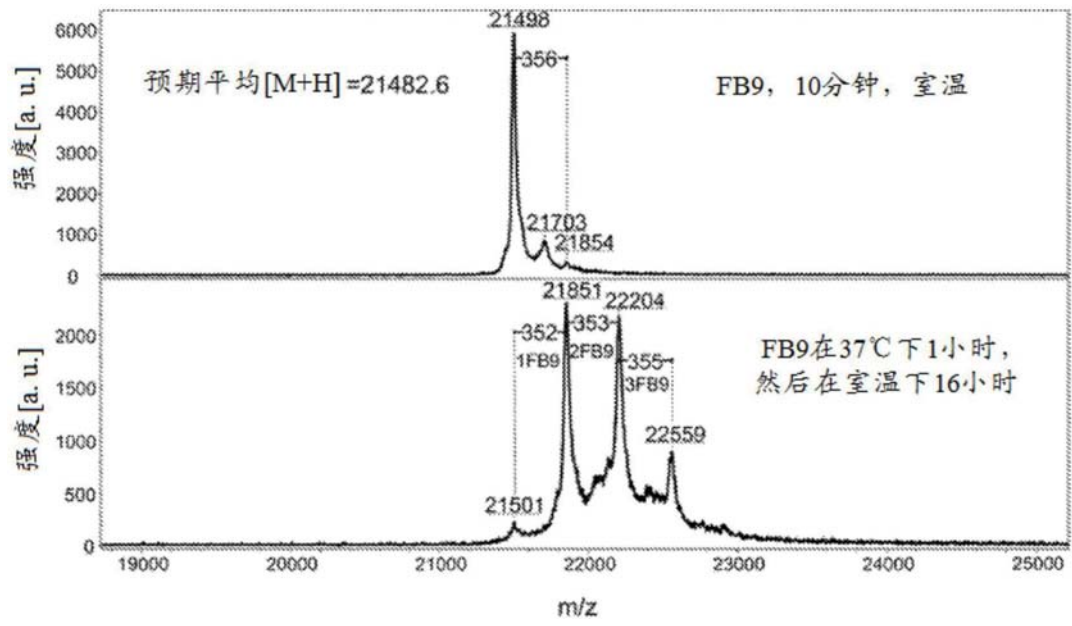


图43

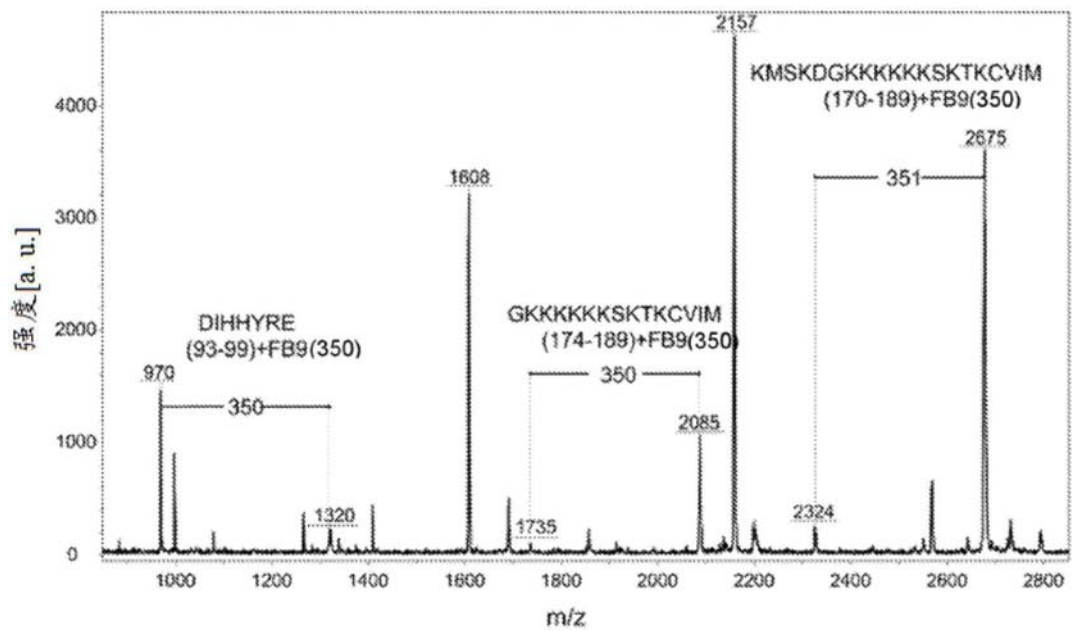


图44

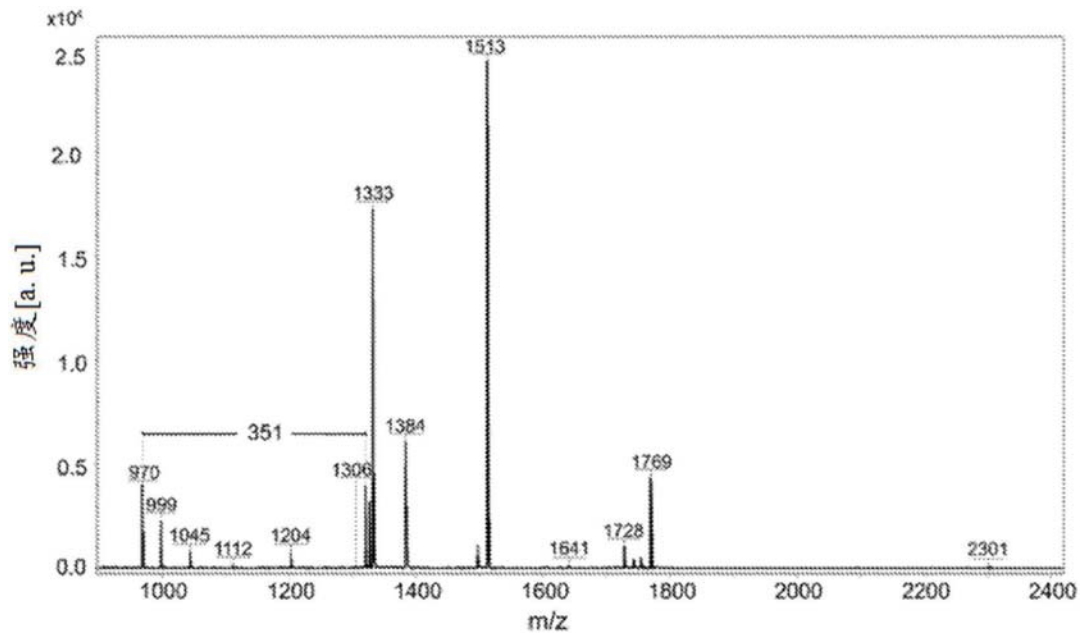


图45A

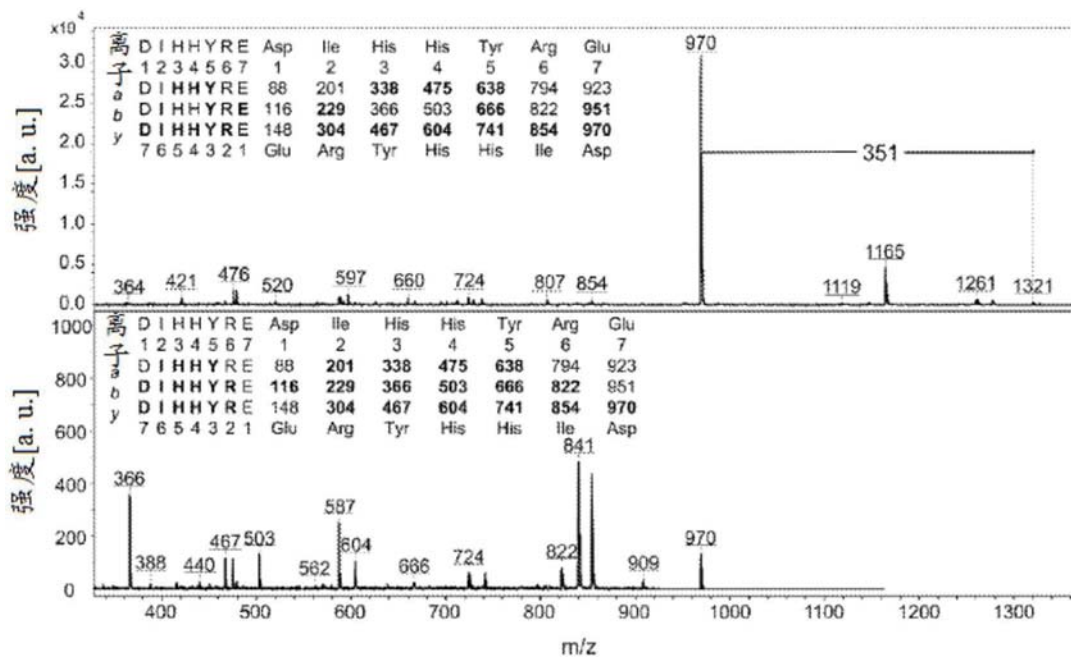


图45B

法尼基化羧甲基化KRAS4b GG-HsKRAS-4b,
RP1151105092454平均[M+H]⁺ 21283.35
GGTEYKLVVVGAGGVGKSALTIQLIQNHFVDEYDPTIEDSYRKQVVIDGET
CLLDILDTAGQEEYSAMRDQYMRTGEGFLCVFAINNTKSFEDIHHYREQIK
RVKDSQEDVPMVLVGNKCDLPSRTVDTKQAQDLARSYGIPFIETSAKTRQG
VDDAFYTLVREIRKHKEKMSKDGKKKKKKSKTKC-farnMe

图46A

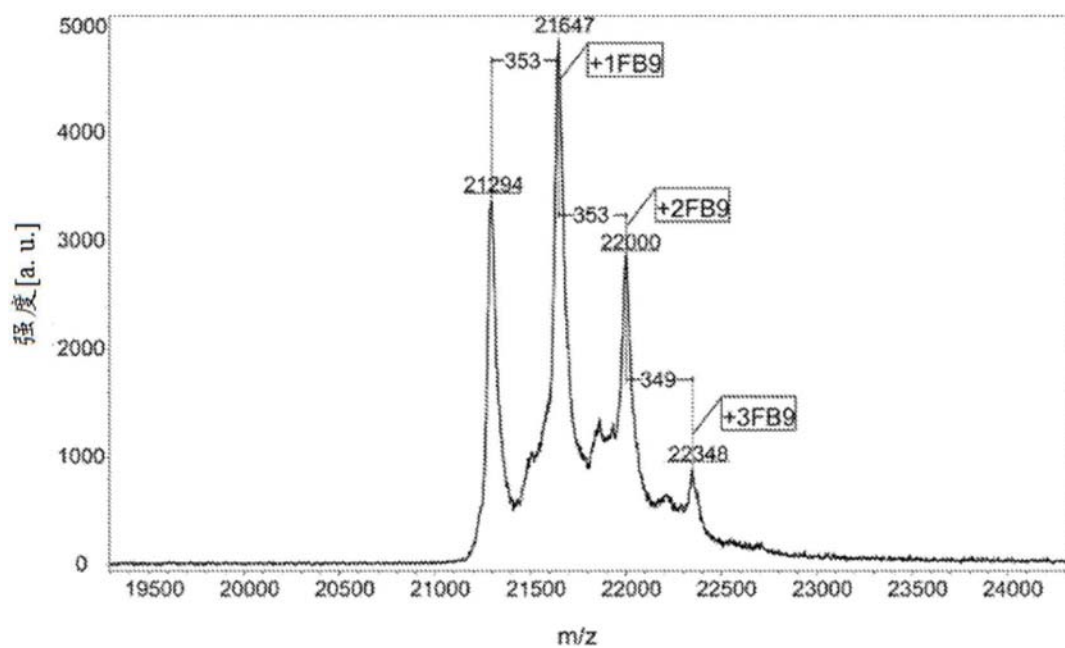


图46B

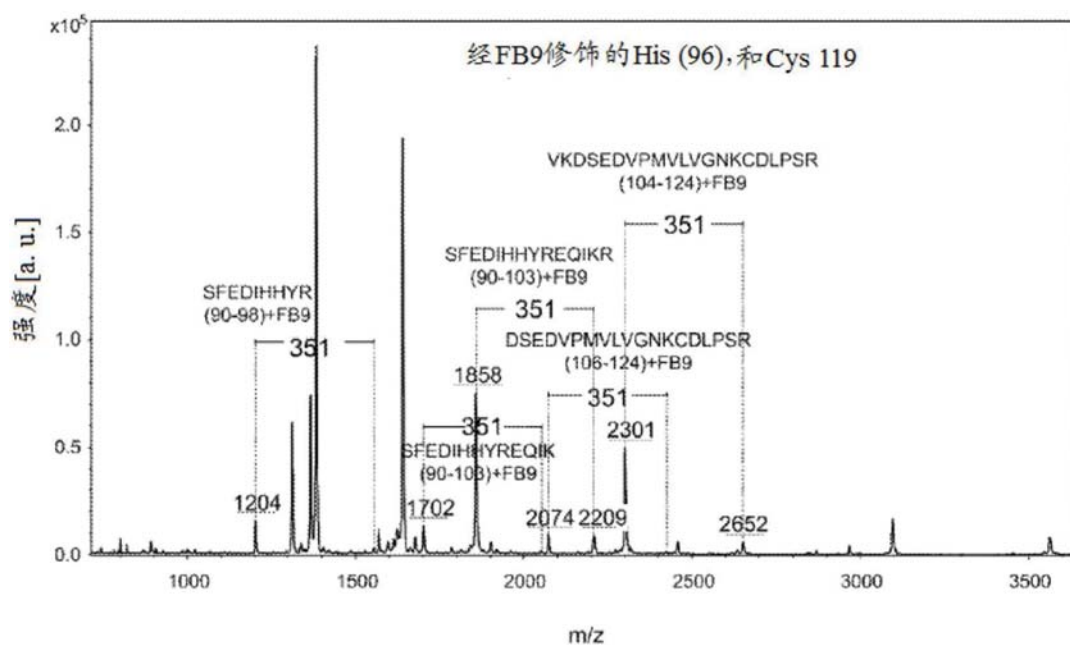


图47