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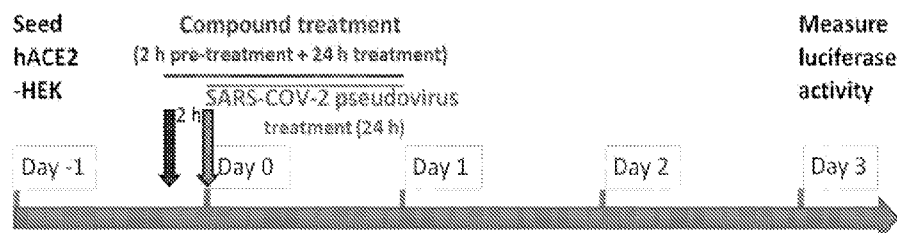
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FIG. 1A



(57) Abstract: Disclosed herein, inter alia, are peptidomimetic or peptide analog compounds for inhibiting SARS-CoV-2, compounds utilized in a method of treating COVID-19, the method comprising administering to a subject in need thereof an effective amount of such a compound, and further disclosed are compounds utilized in a method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), the method comprising contacting the SARS-CoV-2 spike protein with such a compound.



INHIBITORS OF SARS-COV-2

[0001] This application claims the benefit of priority to U.S. Provisional Application Serial number 63/247,501 filed September 23, 2021. The disclosure of this application is incorporated herein by reference in its entirety and for all purposes.

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

[0002] This invention was made with government support under grant no. R01 AG056305, RF1 AG061794, and R56 AG061171, awarded by the National Institutes of Aging of the National Institutes of Health. The government has certain rights in the invention.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY

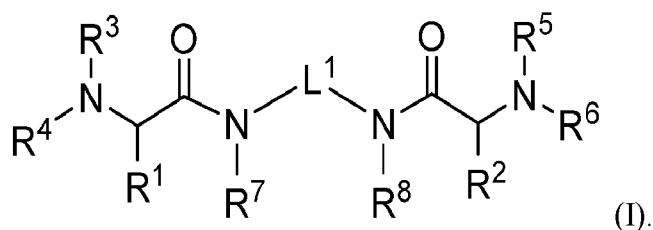
[0003] The material in the accompanying Sequence Listing is hereby incorporated by reference in its entirety. The accompanying file, named "048440-780001WO_SL_ST26.xml" was created on September 9, 2022 and is 11,191 bytes. The file can be accessed using Microsoft Word on a computer that uses Windows OS.

BACKGROUND

[0004] The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapid and widespread outbreak of SARS-CoV-2 poses a serious threat to global public health. However, there are no approved therapeutics or prophylactics for the treatment or prevention of SARS-CoV-2 infection in the clinics. Disclosed herein, inter alia, are solutions to these and other problems known in the art.

BRIEF SUMMARY OF THE INVENTION

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



[0006] L¹ is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted

heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0007] R^1 is independently hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NR^{1C}NR^{1A}R^{1B}$, $-ONR^{1A}R^{1B}$, $-NHC(O)NR^{1C}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0008] R^2 is independently hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2D}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NR^{2C}NR^{2A}R^{2B}$, $-ONR^{2A}R^{2B}$, $-NHC(O)NR^{2C}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-C(O)R^{2C}$, $-C(O)-OR^{2C}$, $-C(O)NR^{2A}R^{2B}$, $-OR^{2D}$, $-NR^{2A}SO_2R^{2D}$, $-NR^{2A}C(O)R^{2C}$, $-NR^{2A}C(O)OR^{2C}$, $-NR^{2A}OR^{2C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0009] R^3 is independently hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NR^{3C}NR^{3A}R^{3B}$, $-ONR^{3A}R^{3B}$, $-NHC(O)NR^{3C}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0010] R^4 is independently hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NR^{4C}NR^{4A}R^{4B}$, $-ONR^{4A}R^{4B}$, $-NHC(O)NR^{4C}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0011] R^5 is independently hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5D}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NR^{5C}NR^{5A}R^{5B}$, $-ONR^{5A}R^{5B}$, $-NHC(O)NR^{5C}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-C(O)R^{5C}$, $-C(O)-OR^{5C}$, $-C(O)NR^{5A}R^{5B}$, $-OR^{5D}$, $-NR^{5A}SO_2R^{5D}$, $-NR^{5A}C(O)R^{5C}$, $-NR^{5A}C(O)OR^{5C}$, $-NR^{5A}OR^{5C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0012] R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0013] R^7 and R^8 are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0014] R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0015] X, X¹, X², X³, X⁴, X⁵, and X⁶ are independently -F, -Cl, -Br, or -I.

[0016] n1, n2, n3, n4, n5, and n6 are independently an integer from 0 to 4.

[0017] m1, m2, m3, m4, m5, m6, v1, v2, v3, v4, v5, and v6, are independently 1 or 2.

[0018] In an aspect is provided a pharmaceutical composition including a compound as described herein and a pharmaceutically acceptable excipient.

[0019] In an aspect is provided a method of treating a coronavirus infection in a subject in need thereof, the method including administering to the subject in need thereof an effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0020] In an aspect is provided a method of treating COVID-19, the method including administering to a subject in need thereof an effective amount of a compound as described herein, including embodiments.

[0021] In an aspect is provided a method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), the method including: contacting the SARS-CoV-2 spike protein with a compound as described herein, including embodiments.

[0022] In an aspect is provided a method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), the method including: contacting human angiotensin-converting enzyme 2 (ACE-2) with a compound as described herein, including embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] FIGS. 1A-1D. Identification of compound Q34 as an inhibitor of SARS-CoV-2 cellular entry. FIG. 1A: Schematics for secondary screen of candidate inhibitors against pseudotyped SARS-CoV-2 entry into hACE2-HEK cells, including cell seeding and treatment with compounds and SARS-CoV-2 pseudovirus. FIG. 1B: Compound Q34 inhibits pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. $n=4$ experimental replicates. FIG. 1C: Validation of compound Q34 in inhibition of cellular entry of pseudotyped SARS-CoV-2. $n=4$ experimental replicates (for 24 h time point), $n=8$ experimental replicates (for 2 h time point). $*p < 0.05$, and $***p < 0.001$ by Student's t test. FIG. 1D: Toxicity test of compound Q34 in HEK293T-luc (HEK-luc) cells. $n=4$ experimental replicates. Error bars are SE of the mean for panels FIG. 1B, FIG. 1C and FIG. 1D.

[0024] FIGS. 2A-2D. Compound Q34 specifically affects infection of SARS-CoV-2 pseudovirus. FIG. 2A: Dose response of compound Q34 in inhibition of pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. $n=8$ experimental replicates. $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$ by one-way ANOVA test. FIG. 2B: Compound Q34 does not inhibit pseudotyped VSV-G cellular entry. $n=4$ experimental replicates. ns means $p > 0.05$ by one-way ANOVA test. FIG. 2C: Toxicity test of compound Q34 treatment (2 h pre-treatment plus 2 h treatment) of HEK-luc cells. $n=4$ experimental replicates. FIG. 2D: Toxicity test of compound Q34 treatment (2 h pre-treatment plus 24 h treatment) of HEK-luc cells. $n=4$ experimental replicates. Error bars are SE of the mean for panels FIGS. 2A-2D.

[0025] FIG. 3. IC₅₀ test of compound Q34 inhibition of SARS-CoV-2 pseudovirus infection. Dose response of compound Q34 in inhibition of pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. $n=4$ experimental replicates. Left panel: 2 h pre-treatment plus 2 h treatment; right panel: 2 h pre-treatment plus 24 h treatment. Error bars are SE of the mean.

[0026] FIGS. 4A-4E. Compound Q34 inhibits SARS-CoV-2 infection. FIG. 4A: Immunostaining for SARS-CoV-2 in hACE2-HEK cells treated with compound Q34 at concentrations from 0 to 100 μ M along with SARS-CoV-2 virus. Scale bar: 50 μ m. FIG. 4B: Phase contrast images for hACE2-HEK cells treated with compound Q34 at concentrations from 0 to 100 μ M along with SARS-CoV-2 virus. Scale bar: 50 μ m. FIG. 4C: The percentage of SARS-CoV-2 infected cells in hACE2-HEK cells treated with compound Q34 at concentrations

from 0 to 100 μ M along with SARS-CoV-2 virus. n=10 image fields. ***p < 0.001 by one-way ANOVA. FIG. 4D: Number of DAPI positive cells per fields in hACE2-HEK cells treated with compound Q34 at concentrations from 0 to 100 μ M along with SARS-CoV-2 virus. n=10 image fields. ns means p > 0.05 by one-way ANOVA test. FIG. 4E: The viral RNA level of SARS-CoV-2 in hACE2-HEK cells treated with 100 μ M compound Q34 along with SARS-CoV-2. n=3 experimental replicates. ***p < 0.001 by Student's t test. Error bars are SE of the mean for panels FIG. 4C, FIG. 4D and FIG. 4E.

[0027] FIGS. 5A-5H. Compound Q34 inhibits authentic SAR-CoV-2 infection of neurons and astrocytes. (FIG. 5A, FIG. 5E) Immunostaining for SARS-CoV-2 in neurons (FIG. 5A) or astrocytes (FIG. 5E) treated with compound Q34 along with SARS-CoV-2 virus. Scale bar: 50 μ m. (FIG. 5B, FIG. 5F) The percentage of SARS-CoV-2 infected cells in neurons (FIG. 5B) or astrocytes (FIG. 5F) treated with compound Q34 along with SARS-CoV-2 virus. n=5 image fields. *p < 0.05, ***p < 0.001 by Student's t test. (FIG. 5C, FIG. 5G) Number of DAPI positive cells per fields in neurons (FIG. 5C) or astrocytes (FIG. 5G) treated with compound Q34 along with SARS-CoV-2 virus. n=5 image fields. ns means p > 0.05 by Student's t test. (FIG. 5D, FIG. 5H) The viral RNA level of SARS-CoV-2 in neurons (FIG. 5D) or astrocytes (FIG. 5H) treated with compound Q34 along with SARS-CoV-2 virus. n=3. ***p < 0.001 by Student's t test. Error bars are SE of the mean for panels FIGS. 5B-5D, and FIGS. 5F-5H.

[0028] FIGS. 6A-6B. ACE2 expression in hACE2-HEK cells. FIG. 6A: Immunostaining for ACE2 in HEK and hACE2-HEK cells. Scale bar: 50 μ m. FIG. 6B: Western blot analysis for ACE2 in HEK and hACE2-HEK cells.

[0029] FIGS. 7A-7E. Compound Q34 analogs inhibit cellular entry mediated by the SARS-CoV-2 spike protein. (FIG. 7A, FIG. 7B) Analog compounds (C2 to C7) of compound Q34 in inhibition of cellular entry of pseudotyped SARS-CoV-2 into hACE2-HEK cells at 10 μ M (A) or 100 μ M (B). n=4 experimental replicates. **p < 0.01, and ***p < 0.001 by one-way ANOVA test. ns means p > 0.05 by one-way ANOVA test. (FIG. 7C, FIG. 7D) Toxicity test of analog compounds (C2 to C7) of compound Q34 in HEK293T-luc (HEK-luc) cells. n=4 experimental replicates. Error bars are SE of the mean for this figure. (FIG. 7E) The structure of analog compounds C2 to C7.

[0030] FIG. 8. The structure of analog compounds C11 to C16.

[0031] FIGS. 9A-9D. Screening of compound C1 analogs as inhibitors of SARS-CoV-2 cellular entry. (FIG. 9A) Compound C1 and its analogs (10 μ M) screen for inhibition of pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. n=4 experimental replicates. (FIG. 9B) Toxicity test of compound C1 and its analogs (10 μ M) in HEK293T-luc (HEK-luc) cells. n=4 experimental replicates. (FIG. 9C) Compound C1 and its analogs (100 μ M) screen for inhibition of pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. n=4 experimental replicates. (FIG. 9D) Toxicity test of compound C1 and its analogs (100 μ M) in HEK293T-luc (HEK-luc) cells. n=4 experimental replicates. Error bars are SE of the mean for this figure. **p < 0.01 and ***p < 0.001 by one-way ANOVA test.

[0032] FIGS. 10A-10H. Compound C12 specifically affects infection of SARS-CoV-2 pseudovirus. (FIG. 10A) IC50 test of compound C12 in inhibition of pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. n=4 experimental replicates. (FIG. 10B) Toxicity test of compound C12 and Remdesivir (RDV) in HEK293T-luc (HEK-luc) cells. n=4 experimental replicates. (FIGS. 10C, 10F) Dose response of compound C12 in inhibition of pseudotyped SARS-CoV-2 entry into hACE2-HEK cells. n=4 experimental replicates. FIG. 10C: 2 h pre-treatment plus 24 h treatment; FIG. 10F: 2 h pre-treatment plus 2 h treatment. (FIGS. 10D, 10G) Compound C12 does not inhibit pseudotyped VSV-G cellular entry. n=4 experimental replicates. FIG. 10D: 2 h pre-treatment plus 24 h treatment; FIG. 10G: 2 h pre-treatment plus 2 h treatment. (FIGS. 10E, 10H) Toxicity test of compound C12 in HEK293T-luc (HEK-luc) cells. n=4 experimental replicates. FIG. 10E: 2 h pre-treatment plus 24 h treatment; FIG. 10H: 2 h pre-treatment plus 2 h treatment. Error bars are SE of the mean for this figure. *p < 0.05, **p < 0.01, and ***p < 0.001 by one-way ANOVA test.

[0033] FIGS. 11A-11B. Compounds C1 and C12 inhibit SARS-CoV-2 Delta pseudovirus infection. Treatment of HEK-ACE2 cells with compound C1 or C12 suppresses SARS-CoV-2 spike pseudotyped virus (FIG. 11A) and SARS-CoV-2 delta strain spike pseudotyped virus (FIG. 11B) infection with virus levels in cells quantified by luciferase reporter activity. For FIG. 11A and FIG. 11B, n=4 experimental replicates. ***p < 0.001 by One-way ANOVA test. Error bars are SE of the mean.

[0034] FIGS. 12A-12E. Compound C12 inhibits the infection of human astrocytes by both the delta variant and the parental form of SARS-CoV-2. (FIG. 12A) Immunostaining for the

spike protein of parental SARS-CoV-2 and the delta variant of SARS-CoV-2 in human iPSC-derived astrocytes pre-treated with or without compound C12. Scale bar: 50 μ m. The percentage of parental SARS-CoV-2 (FIG. 12B) or the delta variant of SARS-CoV-2-infected cells (FIG. 12C) in astrocytes pre-treated with vehicle control (-C12) or compound C12 (+C12). n=5 image fields. **p < 0.01 by Student's t test. The viral RNA level of parental SARS-CoV-2 (FIG. 12D) or the delta variant of SARS-CoV-2 (FIG. 12E) in astrocytes pre-treated with vehicle control or compound C12 followed by corresponding SARS-CoV-2 infection. n=3 experimental replicates. ***p < 0.001 by Student's t test. Error bars are SE of the mean for FIGS. 12B-12E.

[0035] FIGS. 13A-13D. Compounds C1 and C12 inhibit the infection of human kidney and lung cells by both the delta variant and the parental form of SARS-CoV-2. The viral RNA level of parental SARS-CoV-2 (FIGS. 13A and 13B) or the delta variant of SARS-CoV-2 (FIGS. 13C and 13D) in HEK-ACE2 cells (FIGS. 13A and 13C) and Calu-3 cells (FIGS. 13B and 13D) pre-treated with vehicle control or compound C1 or C12 followed by corresponding SARS-CoV-2 infection. n=3 experimental replicates. **p < 0.01 and ***p < 0.001 by One-way ANOVA test. Error bars are SE of the mean for FIGS. 13A-13D.

[0036] FIGS. 14A-14C. Compound C12 inhibits the infection of hACE2-HEK293T cells by both the delta variant and the parental form of SARS-CoV-2. (FIG. 14A) Immunostaining for the spike protein of parental SARS-CoV-2 and the delta variant of SARS-CoV-2 in hACE2-HEK293T cells pre-treated with or without compound C12. Scale bar: 50 μ m. (FIG. 14B) The percentage of parental SARS-CoV-2 or the delta variant of SARS-CoV-2-infected cells in hACE2-HEK293T pre-treated with vehicle control (-C12) or compound C12 (+C12). n=5 image fields. ***p < 0.001 by Student's t test. (FIG. 14C) The viral RNA level of parental SARS-CoV-2 or the delta variant of SARS-CoV-2 in hACE2-HEK293T cells pre-treated with vehicle control or compound C12 followed by corresponding SARS-CoV-2 infection. n=3 experimental replicates. **p < 0.01 and ***p < 0.001 by Student's t test. Error bars are SE of the mean for FIGS. 14B-14C.

[0037] FIGS. 15A-15D. Compound C12 inhibits the infection of Calu3 cells by the SARS-CoV-2. (FIG. 15A) Immunostaining for the spike protein of SARS-CoV-2 in Calu3 cells pre-treated with or without compound C12. Scale bar: 50 μ m. (FIG. 15B) The percentage of SARS-CoV-2-infected cells in Calu3 cells pre-treated with vehicle control (-C12) or compound

C12 (+C12). n=5 image fields. ***p < 0.001 by Student's t test. (FIG. 15C) The viral RNA level of SARS-CoV-2 in Calu3 cells pre-treated with vehicle control or compound C12 followed by SARS-CoV-2 infection. n=3 experimental replicates. ***p < 0.001 by Student's t test. (FIG. 15D) The RBD level of SARS-CoV-2 in supernatant of Calu3 cells pre-treated with vehicle control or compound C12 followed by SARS-CoV-2 infection. n = 3 experimental replicates. ***p < 0.001 by Student's t test. Error bars are SE of the mean for FIGS. 15B-15D.

DETAILED DESCRIPTION

I. Definitions

[0038] 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.

[0039] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH₂O- is equivalent to -OCH₂-.

[0040] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched carbon chain (or carbon), or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include mono-, di- and multivalent radicals. The alkyl may include a designated number of carbons (e.g., C₁-C₁₀ means one to ten carbons). In embodiments, the alkyl is fully saturated. In embodiments, the alkyl is monounsaturated. In embodiments, the alkyl is polyunsaturated. Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, methyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. An alkoxy is an alkyl attached to the remainder of the molecule via an oxygen linker (-O-). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an

alkynyl moiety. An alkenyl includes one or more double bonds. An alkynyl includes one or more triple bonds.

[0041] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, -CH₂CH₂CH₂CH₂-. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene. In embodiments, the alkylene is fully saturated. In embodiments, the alkylene is monounsaturated. In embodiments, the alkylene is polyunsaturated. An alkenylene includes one or more double bonds. An alkynylene includes one or more triple bonds.

[0042] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom (e.g., O, N, P, Si, and S), and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) (e.g., O, N, S, Si, or P) may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Heteroalkyl is an uncyclized chain. Examples include, but are not limited to: -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-S-CH₂, -S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH=CH-N(CH₃)-CH₃, -O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. A heteroalkyl moiety may include one heteroatom (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include two optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include three optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include four optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include five optionally different heteroatoms (e.g., O, N, S, Si, or P). A heteroalkyl moiety may include up to 8 optionally different heteroatoms (e.g., O, N, S, Si, or P). The term “heteroalkenyl,” by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one double bond. A heteroalkenyl may optionally include more than one double bond and/or one

or more triple bonds in addition to the one or more double bonds. The term “heteroalkynyl,” by itself or in combination with another term, means, unless otherwise stated, a heteroalkyl including at least one triple bond. A heteroalkynyl may optionally include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds. In embodiments, the heteroalkyl is fully saturated. In embodiments, the heteroalkyl is monounsaturated. In embodiments, the heteroalkyl is polyunsaturated.

[0043] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'$ represents both $-\text{C}(\text{O})_2\text{R}'$ and $-\text{R}'\text{C}(\text{O})_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as $-\text{C}(\text{O})\text{R}'$, $-\text{C}(\text{O})\text{NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}'$, and/or $-\text{SO}_2\text{R}'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}''$ are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as $-\text{NR}'\text{R}''$ or the like. The term “heteroalkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from a heteroalkene. The term “heteroalkynylene” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from a heteroalkyne. In embodiments, the heteroalkylene is fully saturated. In embodiments, the heteroalkylene is monounsaturated. In embodiments, the heteroalkylene is polyunsaturated. A heteroalkenylene includes one or more double bonds. A heteroalkynylene includes one or more triple bonds.

[0044] The terms “cycloalkyl” and “heterocycloalkyl,” by themselves or in combination with other terms, mean, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl,” respectively. Cycloalkyl and heterocycloalkyl are not aromatic. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to

the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. A “cycloalkylene” and a “heterocycloalkylene,” alone or as part of another substituent, means a divalent radical derived from a cycloalkyl and heterocycloalkyl, respectively. In embodiments, the cycloalkyl is fully saturated. In embodiments, the cycloalkyl is monounsaturated. In embodiments, the cycloalkyl is polyunsaturated. In embodiments, the heterocycloalkyl is fully saturated. In embodiments, the heterocycloalkyl is monounsaturated. In embodiments, the heterocycloalkyl is polyunsaturated.

[0045] In embodiments, the term “cycloalkyl” means a monocyclic, bicyclic, or a multicyclic cycloalkyl ring system. In embodiments, monocyclic ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups can be saturated or unsaturated, but not aromatic. In embodiments, cycloalkyl groups are fully saturated. A bicyclic or multicyclic cycloalkyl ring system refers to multiple rings fused together wherein at least one of the fused rings is a cycloalkyl ring and wherein the multiple rings are attached to the parent molecular moiety through any carbon atom contained within a cycloalkyl ring of the multiple rings.

[0046] In embodiments, a cycloalkyl is a cycloalkenyl. The term “cycloalkenyl” is used in accordance with its plain ordinary meaning. In embodiments, a cycloalkenyl is a monocyclic, bicyclic, or a multicyclic cycloalkenyl ring system. A bicyclic or multicyclic cycloalkenyl ring system refers to multiple rings fused together wherein at least one of the fused rings is a cycloalkenyl ring and wherein the multiple rings are attached to the parent molecular moiety through any carbon atom contained within a cycloalkenyl ring of the multiple rings.

[0047] In embodiments, the term “heterocycloalkyl” means a monocyclic, bicyclic, or a multicyclic heterocycloalkyl ring system. In embodiments, heterocycloalkyl groups are fully saturated. A bicyclic or multicyclic heterocycloalkyl ring system refers to multiple rings fused together wherein at least one of the fused rings is a heterocycloalkyl ring and wherein the

multiple rings are attached to the parent molecular moiety through any atom contained within a heterocycloalkyl ring of the multiple rings.

[0048] 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.

[0049] 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.

[0050] 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 and wherein the multiple rings are attached to the parent molecular moiety through any carbon atom contained within an aryl ring of the multiple rings. 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 and wherein the multiple rings are attached to the parent molecular moiety through any atom contained within a heteroaromatic ring of the multiple rings). 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.

[0051] A fused ring heterocycloalkyl-aryl is an aryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-heteroaryl is a heteroaryl fused to a heterocycloalkyl. A fused ring heterocycloalkyl-cycloalkyl is a heterocycloalkyl fused to a cycloalkyl. A fused ring heterocycloalkyl-heterocycloalkyl is a heterocycloalkyl fused to another heterocycloalkyl. Fused ring heterocycloalkyl-aryl, fused ring heterocycloalkyl-heteroaryl, fused ring heterocycloalkyl-cycloalkyl, or fused ring heterocycloalkyl-heterocycloalkyl may each independently be unsubstituted or substituted with one or more of the substituents described herein.

[0052] 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

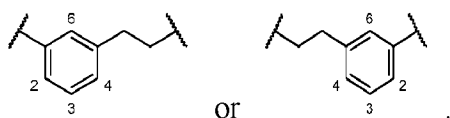
heterocycloalkylene). When referring to a spirocyclic ring system, heterocyclic spirocyclic rings means a spirocyclic rings wherein at least one ring is a heterocyclic ring and wherein each ring may be a different ring. When referring to a spirocyclic ring system, substituted spirocyclic rings means that at least one ring is substituted and each substituent may optionally be different.

[0053] The symbol “~” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0054] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0055] The term “alkylsulfonyl,” as used herein, means a moiety having the formula $-S(O_2)-R'$, where R' is a substituted or unsubstituted alkyl group as defined above. R' may have a specified number of carbons (e.g., “ C_1-C_4 alkylsulfonyl”).

[0056] The term “alkylarylene” as an arylen moiety covalently bonded to an alkylene moiety (also referred to herein as an alkylene linker). In embodiments, the alkylarylene group has the formula:



[0057] An alkylarylene moiety may be substituted (e.g. with a substituent group) on the alkylene moiety or the arylen linker (e.g. at carbons 2, 3, 4, or 6) with halogen, oxo, $-N_3$, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-CN$, $-CHO$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_2CH_3$, $-SO_3H$, $-OSO_3H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, substituted or unsubstituted C_1-C_5 alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0058] Each of the above terms (e.g., “alkyl,” “heteroalkyl,” “cycloalkyl,” “heterocycloalkyl,” “aryl,” and “heteroaryl”) includes both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0059] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of

groups selected from, but not limited to, $-OR'$, $=O$, $=NR'$, $=N-OR'$, $-NR'R''$, $-SR'$, $-halogen$, $-SiR'R''R'''$, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, $-NR''C(O)R'$, $-NR'-C(O)NR''R'''$, $-NR''C(O)_2R'$, $-NR-C(NR'R''R''')=NR'''$, $-NR-C(NR'R'')=NR'''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, $-NR'NR''R'''$, $-ONR'R''$, $-NR'C(O)NR''NR'''R''''$, $-CN$, $-NO_2$, $-NR'SO_2R''$, $-NR'C(O)R''$, $-NR'C(O)-OR''$, $-NR'OR''$, in a number ranging from zero to $(2m'+1)$, where m' is the total number of carbon atoms in such radical. R , R' , R'' , R''' , and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R' , R'' , R''' , and R'''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, $-NR'R''$ includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0060] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: $-OR'$, $-NR'R''$, $-SR'$, $-halogen$, $-SiR'R''R'''$, $-OC(O)R'$, $-C(O)R'$, $-CO_2R'$, $-CONR'R''$, $-OC(O)NR'R''$, $-NR''C(O)R'$, $-NR'-C(O)NR''R'''$, $-NR''C(O)_2R'$, $-NR-C(NR'R''R''')=NR'''$, $-NR-C(NR'R'')=NR'''$, $-S(O)R'$, $-S(O)_2R'$, $-S(O)_2NR'R''$, $-NRSO_2R'$, $-NR'NR''R'''$, $-ONR'R''$, $-NR'C(O)NR''NR'''R''''$, $-CN$, $-NO_2$, $-R'$, $-N_3$, $-CH(Ph)_2$, fluoro(C_1 - C_4)alkoxy, and fluoro(C_1 - C_4)alkyl, $-NR'SO_2R''$, $-NR'C(O)R''$, $-NR'C(O)-OR''$, $-NR'OR''$, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R' , R'' , R''' , and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R' , R'' , R''' , and R'''' groups when more than one of these groups is present.

[0061] Substituents for rings (e.g. cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylene, heterocycloalkylene, arylene, or heteroarylene) may be depicted as substituents on the ring rather than on a specific atom of a ring (commonly referred to as a floating substituent). In such a case, the substituent may be attached to any of the ring atoms (obeying the rules of chemical valency) and in the case of fused rings or spirocyclic rings, a substituent depicted as associated with one member of the fused rings or spirocyclic rings (a floating substituent on a single ring), may be a substituent on any of the fused rings or spirocyclic rings (a floating substituent on multiple rings). When a substituent is attached to a ring, but not a specific atom (a floating substituent), and a subscript for the substituent is an integer greater than one, the multiple substituents may be on the same atom, same ring, different atoms, different fused rings, different spirocyclic rings, and each substituent may optionally be different. Where a point of attachment of a ring to the remainder of a molecule is not limited to a single atom (a floating substituent), the attachment point may be any atom of the ring and in the case of a fused ring or spirocyclic ring, any atom of any of the fused rings or spirocyclic rings while obeying the rules of chemical valency. Where a ring, fused rings, or spirocyclic rings contain one or more ring heteroatoms and the ring, fused rings, or spirocyclic rings are shown with one more floating substituents (including, but not limited to, points of attachment to the remainder of the molecule), the floating substituents may be bonded to the heteroatoms. Where the ring heteroatoms are shown bound to one or more hydrogens (e.g. a ring nitrogen with two bonds to ring atoms and a third bond to a hydrogen) in the structure or formula with the floating substituent, when the heteroatom is bonded to the floating substituent, the substituent will be understood to replace the hydrogen, while obeying the rules of chemical valency.

[0062] Two or more substituents may optionally be joined to form aryl, heteroaryl, cycloalkyl, or heterocycloalkyl groups. Such so-called ring-forming substituents are typically, though not necessarily, found attached to a cyclic base structure. In one embodiment, the ring-forming substituents are attached to adjacent members of the base structure. For example, two ring-forming substituents attached to adjacent members of a cyclic base structure create a fused ring structure. In another embodiment, the ring-forming substituents are attached to a single member of the base structure. For example, two ring-forming substituents attached to a single member of a cyclic base structure create a spirocyclic structure. In yet another embodiment, the ring-forming substituents are attached to non-adjacent members of the base structure.

[0063] 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.

[0064] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0065] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -N₃, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

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

(i) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -N₃, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

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

(a) oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃,

-OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -N₃, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

(b) alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), substituted with at least one substituent selected from: oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -N₃, unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0066] 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.

[0067] 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 phenyl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 6 membered heteroaryl.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] In embodiments, a substituted or unsubstituted moiety (e.g., substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or

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

[0072] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, wherein if the substituted moiety is substituted with a plurality of substituent groups, each substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of substituent groups, each substituent group is different.

[0073] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one size-limited substituent group, wherein if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of size-limited substituent groups, each size-limited substituent group is different.

[0074] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one lower substituent group, wherein if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of lower substituent groups, each lower substituent group is different.

[0075] In embodiments, a substituted moiety (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, if the substituted moiety is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group is different.

[0076] In a recited claim or chemical formula description herein, each R substituent or L linker that is described as being “substituted” without reference as to the identity of any chemical moiety that composes the “substituted” group (also referred to herein as an “open substitution” on an R substituent or L linker or an “openly substituted” R substituent or L linker), the recited R substituent or L linker may, in embodiments, be substituted with one or more first substituent groups as defined below.

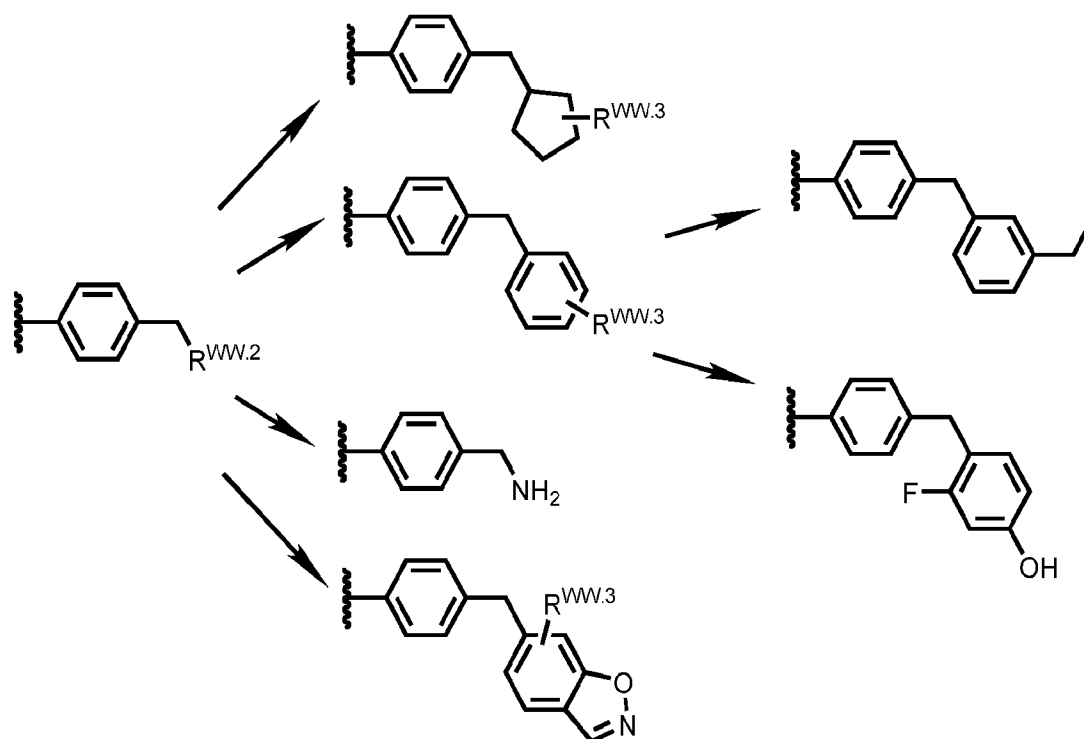
[0077] The first substituent group is denoted with a corresponding first decimal point numbering system such that, for example, R^1 may be substituted with one or more first substituent groups denoted by $R^{1.1}$, R^2 may be substituted with one or more first substituent groups denoted by $R^{2.1}$, R^3 may be substituted with one or more first substituent groups denoted by $R^{3.1}$, R^4 may be substituted with one or more first substituent groups denoted by $R^{4.1}$, R^5 may

be substituted with one or more first substituent groups denoted by $R^{5.1}$, and the like up to or exceeding an R^{100} that may be substituted with one or more first substituent groups denoted by $R^{100.1}$. As a further example, R^{1A} may be substituted with one or more first substituent groups denoted by $R^{1A.1}$, R^{2A} may be substituted with one or more first substituent groups denoted by $R^{2A.1}$, R^{3A} may be substituted with one or more first substituent groups denoted by $R^{3A.1}$, R^{4A} may be substituted with one or more first substituent groups denoted by $R^{4A.1}$, R^{5A} may be substituted with one or more first substituent groups denoted by $R^{5A.1}$ and the like up to or exceeding an R^{100A} may be substituted with one or more first substituent groups denoted by $R^{100A.1}$. As a further example, L^1 may be substituted with one or more first substituent groups denoted by $R^{L1.1}$, L^2 may be substituted with one or more first substituent groups denoted by $R^{L2.1}$, L^3 may be substituted with one or more first substituent groups denoted by $R^{L3.1}$, L^4 may be substituted with one or more first substituent groups denoted by $R^{L4.1}$, L^5 may be substituted with one or more first substituent groups denoted by $R^{L5.1}$ and the like up to or exceeding an L^{100} which may be substituted with one or more first substituent groups denoted by $R^{L100.1}$. Thus, each numbered R group or L group (alternatively referred to herein as R^{WW} or L^{WW} wherein “WW” represents the stated superscript number of the subject R group or L group) described herein may be substituted with one or more first substituent groups referred to herein generally as $R^{WW.1}$ or $R^{LWW.1}$, respectively. In turn, each first substituent group (e.g., $R^{1.1}$, $R^{2.1}$, $R^{3.1}$, $R^{4.1}$, $R^{5.1}$... $R^{100.1}$, $R^{1A.1}$, $R^{2A.1}$, $R^{3A.1}$, $R^{4A.1}$, $R^{5A.1}$... $R^{100A.1}$, $R^{L1.1}$, $R^{L2.1}$, $R^{L3.1}$, $R^{L4.1}$, $R^{L5.1}$... $R^{L100.1}$) may be further substituted with one or more second substituent groups (e.g., $R^{1.2}$, $R^{2.2}$, $R^{3.2}$, $R^{4.2}$, $R^{5.2}$... $R^{100.2}$, $R^{1A.2}$, $R^{2A.2}$, $R^{3A.2}$, $R^{4A.2}$, $R^{5A.2}$... $R^{100A.2}$, $R^{L1.2}$, $R^{L2.2}$, $R^{L3.2}$, $R^{L4.2}$, $R^{L5.2}$... $R^{L100.2}$, respectively). Thus, each first substituent group, which may alternatively be represented herein as $R^{WW.1}$ as described above, may be further substituted with one or more second substituent groups, which may alternatively be represented herein as $R^{WW.2}$.

[0078] Finally, each second substituent group (e.g., $R^{1.2}$, $R^{2.2}$, $R^{3.2}$, $R^{4.2}$, $R^{5.2}$... $R^{100.2}$, $R^{1A.2}$, $R^{2A.2}$, $R^{3A.2}$, $R^{4A.2}$, $R^{5A.2}$... $R^{100A.2}$, $R^{L1.2}$, $R^{L2.2}$, $R^{L3.2}$, $R^{L4.2}$, $R^{L5.2}$... $R^{L100.2}$) may be further substituted with one or more third substituent groups (e.g., $R^{1.3}$, $R^{2.3}$, $R^{3.3}$, $R^{4.3}$, $R^{5.3}$... $R^{100.3}$, $R^{1A.3}$, $R^{2A.3}$, $R^{3A.3}$, $R^{4A.3}$, $R^{5A.3}$... $R^{100A.3}$, $R^{L1.3}$, $R^{L2.3}$, $R^{L3.3}$, $R^{L4.3}$, $R^{L5.3}$... $R^{L100.3}$, respectively). Thus, each second substituent group, which may alternatively be represented herein as $R^{WW.2}$ as described above, may be further substituted with one or more third substituent groups, which may alternatively be represented herein as $R^{WW.3}$. Each of the first substituent groups may be

optionally different. Each of the second substituent groups may be optionally different. Each of the third substituent groups may be optionally different.

[0079] Thus, as used herein, R^{WW} represents a substituent recited in a claim or chemical formula description herein which is openly substituted. “WW” represents the stated superscript number of the subject R group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). Likewise, L^{WW} is a linker recited in a claim or chemical formula description herein which is openly substituted. Again, “WW” represents the stated superscript number of the subject L group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). As stated above, in embodiments, each R^{WW} may be unsubstituted or independently substituted with one or more first substituent groups, referred to herein as $R^{WW.1}$; each first substituent group, $R^{WW.1}$, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as $R^{WW.2}$; and each second substituent group may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as $R^{WW.3}$. Similarly, each L^{WW} linker may be unsubstituted or independently substituted with one or more first substituent groups, referred to herein as $R^{LWW.1}$; each first substituent group, $R^{LWW.1}$, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as $R^{LWW.2}$; and each second substituent group may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as $R^{LWW.3}$. Each first substituent group is optionally different. Each second substituent group is optionally different. Each third substituent group is optionally different. For example, if R^{WW} is phenyl, the said phenyl group is optionally substituted by one or more $R^{WW.1}$ groups as defined herein below, e.g., when $R^{WW.1}$ is $R^{WW.2}$ -substituted or unsubstituted alkyl, examples of groups so formed include but are not limited to itself optionally substituted by 1 or more $R^{WW.2}$, which $R^{WW.2}$ is optionally substituted by one or more $R^{WW.3}$. By way of example when the R^{WW} group is phenyl substituted by $R^{WW.1}$, which is methyl, the methyl group may be further substituted to form groups including but not limited to:



[0080] $\text{R}^{\text{WW}.1}$ is independently oxo, halogen, $-\text{CX}^{\text{WW}.1}_3$, $-\text{CHX}^{\text{WW}.1}_2$, $-\text{CH}_2\text{X}^{\text{WW}.1}$, $-\text{OCX}^{\text{WW}.1}_3$, $-\text{OCH}_2\text{X}^{\text{WW}.1}$, $-\text{OCHX}^{\text{WW}.1}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}=\text{(O)NHNH}_2$,

$-\text{NHC}=\text{(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}=\text{(O)H}$, $-\text{NHC}(\text{O})-\text{OH}$, $-\text{NHOH}$, $-\text{N}_3$, $\text{R}^{\text{WW}.2}$ -substituted or unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), $\text{R}^{\text{WW}.2}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $\text{R}^{\text{WW}.2}$ -substituted or unsubstituted cycloalkyl (e.g., $\text{C}_3\text{-C}_8$, $\text{C}_3\text{-C}_6$, $\text{C}_4\text{-C}_6$, or $\text{C}_5\text{-C}_6$), $\text{R}^{\text{WW}.2}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $\text{R}^{\text{WW}.2}$ -substituted or unsubstituted aryl (e.g., $\text{C}_6\text{-C}_{12}$, $\text{C}_6\text{-C}_{10}$, or phenyl), or $\text{R}^{\text{WW}.2}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

In embodiments, $\text{R}^{\text{WW}.1}$ is independently oxo,

halogen, $-\text{CX}^{\text{WW}.1}_3$, $-\text{CHX}^{\text{WW}.1}_2$, $-\text{CH}_2\text{X}^{\text{WW}.1}$, $-\text{OCX}^{\text{WW}.1}_3$, $-\text{OCH}_2\text{X}^{\text{WW}.1}$, $-\text{OCHX}^{\text{WW}.1}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC}=\text{(O)NHNH}_2$, $-\text{NHC}=\text{(O)NH}_2$, $-\text{NHSO}_2\text{H}$, $-\text{NHC}=\text{(O)H}$, $-\text{NHC}(\text{O})-\text{OH}$, $-\text{NHOH}$, $-\text{N}_3$, unsubstituted alkyl (e.g., $\text{C}_1\text{-C}_8$, $\text{C}_1\text{-C}_6$, $\text{C}_1\text{-C}_4$, or $\text{C}_1\text{-C}_2$), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered),

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

[0081] R^{WW.2} is independently oxo, halogen, -CX^{WW.2}, -CHX^{WW.2}, -CH₂X^{WW.2}, -OCX^{WW.2}, -OCH₂X^{WW.2}, -OCHX^{WW.2}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, R^{WW.3}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{WW.3}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{WW.3}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{WW.3}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{WW.3}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{WW.3}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{WW.2} is independently oxo, halogen, -CX^{WW.2}, -CHX^{WW.2}, -CH₂X^{WW.2}, -OCX^{WW.2}, -OCH₂X^{WW.2}, -OCHX^{WW.2}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW.2} is independently -F, -Cl, -Br, or -I.

[0082] R^{WW.3} is independently oxo, halogen, -CX^{WW.3}, -CHX^{WW.3}, -CH₂X^{WW.3}, -OCX^{WW.3}, -OCH₂X^{WW.3}, -OCHX^{WW.3}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g.,

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

[0083] Where two different R^{WW} substituents are joined together to form an openly substituted ring (e.g. substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl or substituted heteroaryl), in embodiments the openly substituted ring may be independently substituted with one or more first substituent groups, referred to herein as R^{WW.1}; each first substituent group, R^{WW.1}, may be unsubstituted or independently substituted with one or more second substituent groups, referred to herein as R^{WW.2}; and each second substituent group, R^{WW.2}, may be unsubstituted or independently substituted with one or more third substituent groups, referred to herein as R^{WW.3}; and each third substituent group, R^{WW.3}, is unsubstituted. Each first substituent group is optionally different. Each second substituent group is optionally different. Each third substituent group is optionally different. In the context of two different R^{WW} substituents joined together to form an openly substituted ring, the “WW” symbol in the R^{WW.1}, R^{WW.2} and R^{WW.3} refers to the designated number of one of the two different R^{WW} substituents. For example, in embodiments where R^{100A} and R^{100B} are optionally joined together to form an openly substituted ring, R^{WW.1} is R^{100A.1}, R^{WW.2} is R^{100A.2}, and R^{WW.3} is R^{100A.3}. Alternatively, in embodiments where R^{100A} and R^{100B} are optionally joined together to form an openly substituted ring, R^{WW.1} is R^{100B.1}, R^{WW.2} is R^{100B.2}, and R^{WW.3} is R^{100B.3}. R^{WW.1}, R^{WW.2} and R^{WW.3} in this paragraph are as defined in the preceding paragraphs.

[0084] R^{LWW.1} is independently oxo, halogen, -CX^{LWW.1.3}, -CHX^{LWW.1.2}, -CH₂X^{LWW.1}, -OCX^{LWW.1.3}, -OCH₂X^{LWW.1}, -OCHX^{LWW.1.2}, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, R^{LWW.2}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{LWW.2}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{LWW.2}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{LWW.2}-substituted or

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

[0085] $R^{LWW.2}$ is independently oxo, halogen, $-CX^{LWW.2}_3$, $-CHX^{LWW.2}_2$, $-CH_2X^{LWW.2}$, $-OCX^{LWW.2}_3$, $-OCH_2X^{LWW.2}$, $-OCHX^{LWW.2}_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$, $R^{LWW.3}$ -substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), $R^{LWW.3}$ -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{WW.3}$ -substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), $R^{LWW.3}$ -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{LWW.3}$ -substituted or unsubstituted aryl (e.g., C_6-C_{12} , C_6-C_{10} , or phenyl), or $R^{LWW.3}$ -substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, $R^{LWW.2}$ is independently oxo, halogen, $-CX^{LWW.2}_3$, $-CHX^{LWW.2}_2$, $-CH_2X^{LWW.2}$, $-OCX^{LWW.2}_3$, $-OCH_2X^{LWW.2}$, $-OCHX^{LWW.2}_2$, $-CN$,
 $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)-OH$, $-NHOH$, $-N_3$,

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

[0086] R^{LWW.3} is independently oxo, halogen, -CX^{LWW.3}₃, -CHX^{LWW.3}₂, -CH₂X^{LWW.3}, -OCX^{LWW.3}₃, -OCH₂X^{LWW.3}, -OCHX^{LWW.3}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{LWW.3} is independently -F, -Cl, -Br, or -I.

[0087] In the event that any R group recited in a claim or chemical formula description set forth herein (R^{WW} substituent) is not specifically defined in this disclosure, then that R group (R^{WW} group) is hereby defined as independently oxo, halogen, -CX^{WW}₃, -CHX^{WW}₂, -CH₂X^{WW}, -OCX^{WW}₃, -OCH₂X^{WW}, -OCHX^{WW}₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(=O)NHNH₂, -NHC(=O)NH₂, -NHSO₂H, -NHC(=O)H, -NHC(O)-OH, -NHOH, -N₃, R^{WW.1}-substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), R^{WW.1}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), R^{WW.1}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), R^{WW.1}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), R^{WW.1}-substituted or unsubstituted aryl (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or R^{WW.1}-substituted or unsubstituted heteroaryl (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). X^{WW} is independently -F, -Cl, -Br, or -I. Again, "WW"

represents the stated superscript number of the subject R group (e.g., 1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ are as defined above.

[0088] In the event that any L linker group recited in a claim or chemical formula description set forth herein (i.e., an L^{WW} substituent) is not explicitly defined, then that L group (L^{WW} group) is herein defined as independently a bond, -O-, -NH-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -S-, -SO₂-, -SO₂NH-, $R^{LWW.1}$ -substituted or unsubstituted alkylene (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), $R^{LWW.1}$ -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), $R^{LWW.1}$ -substituted or unsubstituted cycloalkylene (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), $R^{LWW.1}$ -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), $R^{LWW.1}$ -substituted or unsubstituted arylene (e.g., C₆-C₁₂, C₆-C₁₀, or phenyl), or $R^{LWW.1}$ -substituted or unsubstituted heteroarylene (e.g., 5 to 12 membered, 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). Again, “WW” represents the stated superscript number of the subject L group (1, 2, 3, 1A, 2A, 3A, 1B, 2B, 3B, etc.). $R^{LWW.1}$, as well as $R^{LWW.2}$ and $R^{LWW.3}$ are as defined above.

[0089] Certain compounds of the present disclosure possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those that are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0090] 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.

[0091] 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.

[0092] It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure.

[0093] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

[0094] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure.

[0095] The compounds of the present disclosure may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I), or carbon-14 (^{14}C). All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure.

[0096] 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.

[0097] As used herein, the terms “bioconjugate” and “bioconjugate linker” refers to the resulting association between atoms or molecules of “bioconjugate reactive groups” or “bioconjugate reactive moieties”. The association can be direct or indirect. For example, a conjugate between a first bioconjugate reactive group (e.g., $-\text{NH}_2$, $-\text{C}(\text{O})\text{OH}$, $-\text{N}-$

hydroxysuccinimide, or –maleimide) and a second bioconjugate reactive group (e.g., sulfhydryl, sulfur-containing amino acid, amine, amine sidechain containing amino acid, or carboxylate) provided herein can be direct, e.g., by covalent bond or linker (e.g. a first linker of second linker), or indirect, e.g., by non-covalent bond (e.g. electrostatic interactions (e.g. ionic bond, hydrogen bond, halogen bond), van der Waals interactions (e.g. dipole-dipole, dipole-induced dipole, London dispersion), ring stacking (pi effects), hydrophobic interactions and the like). In embodiments, bioconjugates or bioconjugate linkers are formed using bioconjugate chemistry (i.e. the association of two bioconjugate reactive groups) including, but are not limited to nucleophilic substitutions (e.g., reactions of amines and alcohols with acyl halides, active esters), electrophilic substitutions (e.g., enamine reactions) and additions to carbon-carbon and carbon-heteroatom multiple bonds (e.g., Michael reaction, Diels-Alder addition). These and other useful reactions are discussed in, for example, March, ADVANCED ORGANIC CHEMISTRY, 3rd Ed., John Wiley & Sons, New York, 1985; Hermanson, BIOCONJUGATE TECHNIQUES, Academic Press, San Diego, 1996; and Feeney et al., MODIFICATION OF PROTEINS; Advances in Chemistry Series, Vol. 198, American Chemical Society, Washington, D.C., 1982. In embodiments, the first bioconjugate reactive group (e.g., maleimide moiety) is covalently attached to the second bioconjugate reactive group (e.g. a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., haloacetyl moiety) is covalently attached to the second bioconjugate reactive group (e.g. a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., pyridyl moiety) is covalently attached to the second bioconjugate reactive group (e.g. a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., –N-hydroxysuccinimide moiety) is covalently attached to the second bioconjugate reactive group (e.g. an amine). In embodiments, the first bioconjugate reactive group (e.g., maleimide moiety) is covalently attached to the second bioconjugate reactive group (e.g. a sulfhydryl). In embodiments, the first bioconjugate reactive group (e.g., –sulfo–N-hydroxysuccinimide moiety) is covalently attached to the second bioconjugate reactive group (e.g. an amine).

[0098] Useful bioconjugate reactive moieties used for bioconjugate chemistries herein include, for example:

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

- (b) hydroxyl groups which can be converted to esters, ethers, aldehydes, etc.
- (c) haloalkyl groups wherein the halide can be later displaced with a nucleophilic group such as, for example, an amine, a carboxylate anion, thiol anion, carbanion, or an alkoxide ion, thereby resulting in the covalent attachment of a new group at the site of the halogen atom;
- (d) dienophile groups which are capable of participating in Diels-Alder reactions such as, for example, maleimido or maleimide groups;
- (e) aldehyde or ketone groups such that subsequent derivatization is possible via formation of carbonyl derivatives such as, for example, imines, hydrazones, semicarbazones or oximes, or via such mechanisms as Grignard addition or alkyllithium addition;
- (f) sulfonyl halide groups for subsequent reaction with amines, for example, to form sulfonamides;
- (g) thiol groups, which can be converted to disulfides, reacted with acyl halides, or bonded to metals such as gold, or react with maleimides;
- (h) amine or sulfhydryl groups (e.g., present in cysteine), which can be, for example, acylated, alkylated or oxidized;
- (i) alkenes, which can undergo, for example, cycloadditions, acylation, Michael addition, etc;
- (j) epoxides, which can react with, for example, amines and hydroxyl compounds;
- (k) phosphoramidites and other standard functional groups useful in nucleic acid synthesis;
- (l) metal silicon oxide bonding; and
- (m) metal bonding to reactive phosphorus groups (e.g. phosphines) to form, for example, phosphate diester bonds.
- (n) azides coupled to alkynes using copper catalyzed cycloaddition click chemistry.

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

[0099] The bioconjugate reactive groups can be chosen such that they do not participate in, or interfere with, the chemical stability of the conjugate described herein. Alternatively, a reactive functional group can be protected from participating in the crosslinking reaction by the presence of a protecting group. In embodiments, the bioconjugate comprises a molecular entity derived from the reaction of an unsaturated bond, such as a maleimide, and a sulfhydryl group.

[0100] “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.

[0101] The terms “a” or “an,” as used in herein means one or more. In addition, the phrase “substituted with a[n],” as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is “substituted with an unsubstituted C₁-C₂₀ alkyl, or unsubstituted 2 to 20 membered heteroalkyl,” the group may contain one or more unsubstituted C₁-C₂₀ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0102] Moreover, where a moiety is substituted with an R substituent, the group may be referred to as “R-substituted.” Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different. Where a particular R group is present in the description of a chemical genus (such as Formula (I)), a Roman alphabetic symbol may be used to distinguish each appearance of that particular R group. For example, where multiple R¹³ substituents are present, each R¹³ substituent may be distinguished as R^{13.A}, R^{13.B}, R^{13.C}, R^{13.D}, etc., wherein each of R^{13.A}, R^{13.B}, R^{13.C}, R^{13.D}, etc. is defined within the scope of the definition of R¹³ and optionally differently.

[0103] A “detectable agent” or “detectable moiety” is a composition, substance, element, or compound; or moiety thereof; detectable by appropriate means such as spectroscopic, photochemical, biochemical, immunochemical, chemical, magnetic resonance imaging, or other physical means. For example, useful detectable agents include ^{18}F , ^{32}P , ^{33}P , ^{45}Ti , ^{47}Sc , ^{52}Fe , ^{59}Fe , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , ^{77}As , ^{86}Y , ^{90}Y , ^{89}Sr , ^{89}Zr , ^{94}Tc , ^{94}Tc , $^{99\text{m}}\text{Tc}$, ^{99}Mo , ^{105}Pd , ^{105}Rh , ^{111}Ag , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{142}Pr , ^{143}Pr , ^{149}Pm , ^{153}Sm , $^{154-1581}\text{Gd}$, ^{161}Tb , ^{166}Dy , ^{166}Ho , ^{169}Er , ^{175}Lu , ^{177}Lu , ^{186}Re , ^{188}Re , ^{189}Re , ^{194}Ir , ^{198}Au , ^{199}Au , ^{211}At , ^{211}Pb , ^{212}Bi , ^{212}Pb , ^{213}Bi , ^{223}Ra , ^{225}Ac , Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, ^{32}P , fluorophore (e.g. fluorescent dyes), electron-dense reagents, enzymes (e.g., as commonly used in an ELISA), biotin, digoxigenin, paramagnetic molecules, paramagnetic nanoparticles, ultrasmall superparamagnetic iron oxide (“USPIO”) nanoparticles, USPIO nanoparticle aggregates, superparamagnetic iron oxide (“SPIO”) nanoparticles, SPIO nanoparticle aggregates, monocrystalline iron oxide nanoparticles, monocrystalline iron oxide, nanoparticle contrast agents, liposomes or other delivery vehicles containing Gadolinium chelate (“Gd-chelate”) molecules, Gadolinium, radioisotopes, radionuclides (e.g. carbon-11, nitrogen-13, oxygen-15, fluorine-18, rubidium-82), fluorodeoxyglucose (e.g. fluorine-18 labeled), any gamma ray emitting radionuclides, positron-emitting radionuclide, radiolabeled glucose, radiolabeled water, radiolabeled ammonia, biocolloids, microbubbles (e.g. including microbubble shells including albumin, galactose, lipid, and/or polymers; microbubble gas core including air, heavy gas(es), perfluorocarbon, nitrogen, octafluoropropane, perflhexane lipid microsphere, perflutren, etc.), iodinated contrast agents (e.g. iohexol, iodixanol, ioversol, iopamidol, ioxilan, iopromide, diatrizoate, metrizoate, ioxaglate), barium sulfate, thorium dioxide, gold, gold nanoparticles, gold nanoparticle aggregates, fluorophores, two-photon fluorophores, or haptens and proteins or other entities which can be made detectable, e.g., by incorporating a radiolabel into a peptide or antibody specifically reactive with a target peptide. A detectable moiety is a monovalent detectable agent or a detectable agent capable of forming a bond with another composition.

[0104] Radioactive substances (e.g., radioisotopes) that may be used as imaging and/or labeling agents in accordance with the embodiments of the disclosure include, but are not limited to, ^{18}F , ^{32}P , ^{33}P , ^{45}Ti , ^{47}Sc , ^{52}Fe , ^{59}Fe , ^{62}Cu , ^{64}Cu , ^{67}Cu , ^{67}Ga , ^{68}Ga , ^{77}As , ^{86}Y , ^{90}Y , ^{89}Sr , ^{89}Zr , ^{94}Tc , ^{94}Tc , $^{99\text{m}}\text{Tc}$, ^{99}Mo , ^{105}Pd , ^{105}Rh , ^{111}Ag , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{142}Pr , ^{143}Pr , ^{149}Pm , ^{153}Sm , $^{154-1581}\text{Gd}$, ^{161}Tb , ^{166}Dy , ^{166}Ho , ^{169}Er , ^{175}Lu , ^{177}Lu , ^{186}Re , ^{188}Re , ^{189}Re , ^{194}Ir , ^{198}Au , ^{199}Au , ^{211}At ,

^{211}Pb , ^{212}Bi , ^{212}Pb , ^{213}Bi , ^{223}Ra and ^{225}Ac . Paramagnetic ions that may be used as additional imaging agents in accordance with the embodiments of the disclosure include, but are not limited to, ions of transition and lanthanide metals (e.g. metals having atomic numbers of 21-29, 42, 43, 44, or 57-71). These metals include ions of Cr, V, Mn, Fe, Co, Ni, Cu, La, Ce, Pr, Nd, Pm, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb and Lu.

[0105] Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0106] A person of ordinary skill in the art will understand when a variable (e.g., moiety or linker) of a compound or of a compound genus (e.g., a genus described herein) is described by a name or formula of a standalone compound with all valencies filled, the unfilled valence(s) of the variable will be dictated by the context in which the variable is used. For example, when a variable of a compound as described herein is connected (e.g., bonded) to the remainder of the compound through a single bond, that variable is understood to represent a monovalent form (i.e., capable of forming a single bond due to an unfilled valence) of a standalone compound (e.g., if the variable is named “methane” in an embodiment but the variable is known to be attached by a single bond to the remainder of the compound, a person of ordinary skill in the art would understand that the variable is actually a monovalent form of methane, i.e., methyl or —CH_3). Likewise, for a linker variable (e.g., L^1 , L^2 , or L^3 as described herein), a person of ordinary skill in the art will understand that the variable is the divalent form of a standalone compound (e.g., if the variable is assigned to “PEG” or “polyethylene glycol” in an embodiment but the variable is connected by two separate bonds to the remainder of the compound, a person of ordinary skill in the art would understand that the variable is a divalent (i.e., capable of forming two bonds through two unfilled valences) form of PEG instead of the standalone compound PEG).

[0107] The term “exogenous” refers to a molecule or substance (*e.g.*, a compound, nucleic acid or protein) that originates from outside a given cell or organism. For example, an “exogenous promoter” as referred to herein is a promoter that does not originate from the plant it is expressed by. Conversely, the term “endogenous” or “endogenous promoter” refers to a molecule or substance that is native to, or originates within, a given cell or organism.

[0108] The term “lipid moiety” is used in accordance with its ordinary meaning in chemistry and refers to a hydrophobic molecule which is typically characterized by an aliphatic hydrocarbon chain. In embodiments, the lipid moiety includes a carbon chain of 3 to 100 carbons. In embodiments, the lipid moiety includes a carbon chain of 5 to 50 carbons. In embodiments, the lipid moiety includes a carbon chain of 5 to 25 carbons. In embodiments, the lipid moiety includes a carbon chain of 8 to 525 carbons. Lipid moieties may include saturated or unsaturated carbon chains, and may be optionally substituted. In embodiments, the lipid moiety is optionally substituted with a charged moiety at the terminal end. In embodiments, the lipid moiety is an alkyl or heteroalkyl optionally substituted with a carboxylic acid moiety at the terminal end.

[0109] A charged moiety refers to a functional group possessing an abundance of electron density (*i.e.* electronegative) or is deficient in electron density (*i.e.* electropositive). Non-limiting examples of a charged moiety includes carboxylic acid, alcohol, phosphate, aldehyde, and sulfonamide. In embodiments, a charged moiety is capable of forming hydrogen bonds.

[0110] The term “solution” is used in accor and refers to a liquid mixture in which the minor component (*e.g.*, a solute or compound) is uniformly distributed within the major component (*e.g.*, a solvent).

[0111] The term “organic solvent” as used herein is used in accordance with its ordinary meaning in chemistry and refers to a solvent which includes carbon. Non-limiting examples of organic solvents include acetic acid, acetone, acetonitrile, benzene, 1-butanol, 2-butanol, 2-butanone, t-butyl alcohol, carbon tetrachloride, chlorobenzene, chloroform, cyclohexane, 1,2-dichloroethane, diethylene glycol, diethyl ether, diglyme (diethylene glycol , dimethyl ether), 1,2-dimethoxyethane (glyme, DME), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,4-dioxane, ethanol, ethyl acetate, ethylene glycol, glycerin, heptane, hexamethylphosphoramide (HMPA), hexamethylphosphorous, triamide (HMPT), hexane,

methanol, methyl t-butyl ether (MTBE), methylene chloride, N-methyl-2-pyrrolidinone (NMP), nitromethane, pentane, petroleum ether (ligroine), 1-propanol, 2-propanol, pyridine, tetrahydrofuran (THF), toluene, triethyl amine, o-xylene, m-xylene, or p-xylene. In embodiments, the organic solvent is or includes chloroform, dichloromethane, methanol, ethanol, tetrahydrofuran, or dioxane.

[0112] As used herein, the term “salt” refers to acid or base salts of the compounds used in the methods of the present invention. Illustrative examples of acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, quaternary ammonium (methyl iodide, ethyl iodide, and the like) salts.

[0113] The terms “bind” and “bound” as used herein is used in accordance with its plain and ordinary meaning and refers to the association between atoms or molecules. The association can be direct or indirect. For example, bound atoms or molecules may be bound, e.g., by covalent bond, linker (e.g. a first linker or second linker), or non-covalent bond (e.g. electrostatic interactions (e.g. ionic bond, hydrogen bond, halogen bond), van der Waals interactions (e.g. dipole-dipole, dipole-induced dipole, London dispersion), ring stacking (pi effects), hydrophobic interactions and the like).

[0114] The term “capable of binding” as used herein refers to a moiety (e.g. a compound as described herein) that is able to measurably bind to a target. In embodiments, where a moiety is capable of binding a target, the moiety is capable of binding with a K_d of less than about 10 μM , 5 μM , 1 μM , 500 nM, 250 nM, 100 nM, 75 nM, 50 nM, 25 nM, 15 nM, 10 nM, 5 nM, 1 nM, or about 0.1 nM.

[0115] As used herein, the term “conjugated” when referring to two moieties means the two moieties are bonded, wherein the bond or bonds connecting the two moieties may be covalent or non-covalent. In embodiments, the two moieties are covalently bonded to each other (e.g. directly or through a covalently bonded intermediary). In embodiments, the two moieties are non-covalently bonded (e.g. through ionic bond(s), van der waal’s bond(s)/interactions, hydrogen bond(s), polar bond(s), or combinations or mixtures thereof).

[0116] The term “non-nucleophilic base” as used herein refers to any sterically hindered base that is a poor nucleophile.

[0117] The term “nucleophile” as used herein refers to a chemical species that donates an electron pair to an electrophile to form a chemical bond in relation to a reaction. All molecules or ions with a free pair of electrons or at least one pi bond can act as nucleophiles.

[0118] The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, “Pharmaceutical Salts”, *Journal of Pharmaceutical Science*, **1977**, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0119] Thus, the compounds of the present disclosure may exist as salts, such as with pharmaceutically acceptable acids. The present disclosure includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, propionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl

iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0120] 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.

[0121] In addition to salt forms, the present disclosure provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present disclosure. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0122] Certain compounds of the present disclosure can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present disclosure. Certain compounds of the present disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present disclosure and are intended to be within the scope of the present disclosure.

[0123] “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 disclosure 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 disclosure. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present disclosure.

[0124] 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.

[0125] As used herein, the term "about" means a range of values including the specified value, which a person of ordinary skill in the art would consider reasonably similar to the specified value. In embodiments, about means within a standard deviation using measurements generally acceptable in the art. In embodiments, about means a range extending to +/- 10% of the specified value. In embodiments, about includes the specified value.

[0126] A "synergistic amount" as used herein refers to the sum of a first amount (e.g., an amount of a compound provided herein) and a second amount (e.g., a therapeutic agent) that results in a synergistic effect (i.e. an effect greater than an additive effect). Therefore, the terms "synergy", "synergism", "synergistic", "combined synergistic amount", and "synergistic therapeutic effect" which are used herein interchangeably, refer to a measured effect of the compound administered in combination where the measured effect is greater than the sum of the individual effects of each of the compounds provided herein administered alone as a single agent.

[0127] In embodiments, a synergistic amount may be about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% of the amount of the compound provided herein when used separately from the therapeutic agent. In embodiments, a

synergistic amount may be about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% of the amount of the therapeutic agent when used separately from the compound provided herein.

[0128] The term “vaccine” refers to a composition that can provide active acquired immunity to and/or therapeutic effect (e.g. treatment) of a particular disease or a pathogen. A vaccine typically contains one or more agents that can induce an immune response in a subject against a pathogen or disease, i.e. a target pathogen or disease. The immunogenic agent stimulates the body’s immune system to recognize the agent as a threat or indication of the presence of the target pathogen or disease, thereby inducing immunological memory so that the immune system can more easily recognize and destroy any of the pathogen on subsequent exposure. Vaccines can be prophylactic (e.g. preventing or ameliorating the effects of a future infection by any natural or pathogen, or of an anticipated occurrence of cancer in a predisposed subject) or therapeutic (e.g., treating cancer in a subject who has been diagnosed with the cancer). The administration of vaccines is referred to vaccination. In some examples, a vaccine composition can provide nucleic acid, e.g. mRNA that encodes antigenic molecules (e.g. peptides) to a subject. The nucleic acid that is delivered via the vaccine composition in the subject can be expressed into antigenic molecules and allow the subject to acquire immunity against the antigenic molecules. In the context of the vaccination against infectious disease, the vaccine composition can provide mRNA encoding antigenic molecules that are associated with a certain pathogen, e.g. one or more peptides that are known to be expressed in the pathogen (e.g. pathogenic bacterium or virus). In the context of cancer vaccine, the vaccine composition can provide mRNA encoding certain peptides that are associated with cancer, e.g. peptides that are substantially exclusively or highly expressed in cancer cells as compared to normal cells. The

subject, after vaccination with the cancer vaccine composition, can have immunity against the peptides that are associated with cancer and kill the cancer cells with specificity.

[0129] The term “immune response” used herein encompasses, but is not limited to, an “adaptive immune response”, also known as an “acquired immune response” in which adaptive immunity elicits immunological memory after an initial response to a specific pathogen or a specific type of cells that is targeted by the immune response, and leads to an enhanced response to that target on subsequent encounters. The induction of immunological memory can provide the basis of vaccination.

[0130] The term “EC50” or “half maximal effective concentration” as used herein refers to the concentration of a molecule (e.g., antibody, chimeric antigen receptor or bispecific antibody) capable of inducing a response which is halfway between the baseline response and the maximum response after a specified exposure time. In embodiments, the EC50 is the concentration of a molecule (e.g., antibody, chimeric antigen receptor or bispecific antibody) that produces 50% of the maximal possible effect of that molecule.

[0131] An “inhibitor” refers to a compound (e.g. compounds described herein) that reduces activity when compared to a control, such as absence of the compound or a compound with known inactivity.

[0132] “Contacting” is used in accordance with its plain ordinary meaning and refers to the process of allowing at least two distinct species (e.g. chemical compounds including biomolecules or cells) to become sufficiently proximal to react, interact or physically touch. It should be appreciated; however, the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents that can be produced in the reaction mixture.

[0133] The term “contacting” may include allowing two species to react, interact, or physically touch, wherein the two species may be a compound as described herein and a protein or enzyme. In some embodiments contacting includes allowing a compound described herein to interact with a protein or enzyme that is involved in a signaling pathway.

[0134] As defined herein, the term “activation”, “activate”, “activating”, “activator” and the like in reference to a protein-inhibitor interaction means positively affecting (e.g. increasing) the

activity or function of the protein relative to the activity or function of the protein in the absence of the activator. In embodiments activation means positively affecting (e.g. increasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the activator. The terms may reference activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease. Thus, activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein associated with a disease (e.g., a protein which is decreased in a disease relative to a non-diseased control). Activation may include, at least in part, partially or totally increasing stimulation, increasing or enabling activation, or activating, sensitizing, or up-regulating signal transduction or enzymatic activity or the amount of a protein

[0135] The terms “agonist,” “activator,” “upregulator,” etc. refer to a substance capable of detectably increasing the expression or activity of a given gene or protein. The agonist can increase expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the agonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or higher than the expression or activity in the absence of the agonist.

[0136] 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 relative to the activity or function of the protein in the absence of the inhibitor. In embodiments inhibition means negatively affecting (e.g. decreasing) the concentration or levels of the protein relative to the concentration or level of the protein in the absence of the inhibitor. In embodiments inhibition refers to reduction of a disease or symptoms of disease. In embodiments, inhibition refers to a reduction in the activity of a particular protein target. Thus, inhibition includes, at least in part, partially or totally blocking stimulation, decreasing, preventing, or delaying activation, or inactivating, desensitizing, or down-regulating signal transduction or enzymatic activity or the amount of a protein. In embodiments, inhibition refers to a reduction of activity of a target protein resulting from a direct interaction (e.g. an inhibitor binds to the target protein). In embodiments, inhibition refers to a reduction of activity of a target protein from an indirect interaction (e.g. an inhibitor binds to a protein that activates the target protein, thereby preventing target protein activation).

[0137] The terms “inhibitor,” “repressor” or “antagonist” or “downregulator” interchangeably refer to a substance capable of detectably decreasing the expression or activity of a given gene or protein. The antagonist can decrease expression or activity 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or more in comparison to a control in the absence of the antagonist. In certain instances, expression or activity is 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 10-fold or lower than the expression or activity in the absence of the antagonist.

[0138] The term “expression” includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and secretion. Expression can be detected using conventional techniques for detecting protein (*e.g.*, ELISA, Western blotting, flow cytometry, immunofluorescence, immunohistochemistry, *etc.*).

[0139] The term “modulator” refers to a composition that increases or decreases the level of a target molecule or the function of a target molecule or the physical state of the target of the molecule relative to the absence of the modulator.

[0140] 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.

[0141] 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 (*e.g.*, cancer, inflammatory disease, autoimmune disease, or infectious disease)) means that the disease (*e.g.* cancer, inflammatory disease, autoimmune disease, or infectious disease) 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. 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.

[0142] The term “aberrant” as used herein refers to different from normal. When used to describe enzymatic activity or protein function, aberrant refers to activity or function that is greater or less than a normal control or the average of normal non-diseased control samples. Aberrant activity may refer to an amount of activity that results in a disease, wherein returning

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

[0143] 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.

[0144] In this disclosure, “comprises,” “comprising,” “containing” and “having” and the like can have the meaning ascribed to them in U.S. Patent law and can mean “includes,” “including,” and the like. “Consisting essentially of or “consists essentially” likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

[0145] The terms “disease” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be an inflammatory disease. The disease may be an infectious disease. The disease may be a viral disease.

[0146] “Treating” or “treatment” as used herein (and as well-understood in the art) also broadly includes any approach for obtaining beneficial or desired results in a subject’s condition, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of the extent of a disease, stabilizing (*i.e.*, not worsening) the state of disease, prevention of a disease’s transmission or spread, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease, and remission, whether partial or total and whether detectable or undetectable. In other words, “treatment” as used herein includes any cure, amelioration, or prevention of a disease. Treatment may prevent the disease from occurring; inhibit the disease’s spread; relieve the disease’s symptoms, fully or partially remove the disease’s underlying cause, shorten a disease’s duration, or do a combination of these things.

[0147] “Treating” and “treatment” as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of an active agent. The administering step may consist of a single administration or may include a series of administrations. The length of the treatment period depends on a variety of factors, such as the severity of the condition, the age of the patient, the concentration of active agent, the activity of the compositions used in the treatment, or a combination thereof. It will also be appreciated that the effective dosage of an agent used for the treatment or prophylaxis may increase or decrease over the course of a particular treatment or prophylaxis regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration may be required. For example, the compositions are administered to the subject in an amount and for a duration sufficient to treat the patient. In embodiments, the treating or treatment is no prophylactic treatment.

[0148] The term “prevent” refers to a decrease in the occurrence of disease symptoms in a patient. As indicated above, the prevention may be complete (no detectable symptoms) or partial, such that fewer symptoms are observed than would likely occur absent treatment.

[0149] “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.

[0150] 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 a signaling pathway, or reduce one or more symptoms of a disease or condition). An example of an “effective amount” is an amount sufficient to contribute to the treatment, prevention, or reduction of a symptom or symptoms of a disease, which could also be referred to as a “therapeutically effective amount.” A “reduction” of a symptom or symptoms (and grammatical equivalents of this phrase) means decreasing of the severity or frequency of the symptom(s), or elimination of the symptom(s). A “prophylactically effective amount” of a drug is an amount of a drug that, when administered to a subject, will have the intended prophylactic effect, e.g.,

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

[0151] For any compound described herein, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of achieving the methods described herein, as measured using the methods described herein or known in the art.

[0152] As is well known in the art, therapeutically effective amounts for use in humans can also be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring compounds effectiveness and adjusting the dosage upwards or downwards, as described above. Adjusting the dose to achieve maximal efficacy in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0153] The term “therapeutically effective amount,” as used herein, refers to that amount of the therapeutic agent sufficient to ameliorate the disorder, as described above. For example, for the given parameter, a therapeutically effective amount will show an increase or decrease of at least 5%, 10%, 15%, 20%, 25%, 40%, 50%, 60%, 75%, 80%, 90%, or at least 100%.

Therapeutic efficacy can also be expressed as “-fold” increase or decrease. For example, a

therapeutically effective amount can have at least a 1.2-fold, 1.5-fold, 2-fold, 5-fold, or more effect over a control.

[0154] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present disclosure, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

[0155] As used herein, the term “administering” means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including 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.* In embodiments, the administering does not include administration of any active agent other than the recited active agent.

[0156] “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 provided herein 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 disclosure 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.

[0157] 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.

[0158] “Control” or “control experiment” is used in accordance with its plain ordinary meaning and refers to an experiment in which the subjects or reagents of the experiment are treated as in a parallel experiment except for omission of a procedure, reagent, or variable of the experiment. In some instances, the control is used as a standard of comparison in evaluating experimental effects. In some embodiments, a control is the measurement of the activity of a protein in the absence of a compound as described herein (including embodiments and examples).

[0159] “Selective” or “selectivity” or the like of a compound refers to the compound’s ability to discriminate between molecular targets.

[0160] “Specific”, “specifically”, “specificity”, or the like of a compound refers to the compound’s ability to cause a particular action, such as inhibition, to a particular molecular target with minimal or no action to other proteins in the cell.

[0161] The term “infection” or “infectious disease” refers to a disease or condition that can be caused by organisms such as a bacterium, virus, fungi or any other pathogenic microbial agents. In embodiments, the infectious disease is caused by a virus. In embodiments, the virus is a coronavirus. In embodiments, the virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In embodiments, the virus is severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1). In embodiments, the virus is MERS-coronavirus (MERS-CoV). In embodiments, the infectious disease is COVID-19.

[0162] The terms “immune response” and the like refer, in the usual and customary sense, to a response by an organism that protects against disease. The response can be mounted by the innate immune system or by the adaptive immune system, as well known in the art.

[0163] The terms “modulating immune response” and the like refer to a change in the immune response of a subject as a consequence of administration of an agent, e.g., a compound as disclosed herein, including embodiments thereof. Accordingly, an immune response can be activated or deactivated as a consequence of administration of an agent, e.g., a compound as disclosed herein, including embodiments thereof.

[0164] The terms “virus” or “virus particle” are used according to its plain ordinary meaning within Virology and refers to a virion including the viral genome (e.g. DNA, RNA, single strand, double strand), viral capsid and associated proteins, and in the case of enveloped viruses (e.g. herpesvirus), an envelope including lipids and optionally components of host cell membranes, and/or viral proteins.

[0165] The term “viral infection” or “viral disease” refers to a disease or condition that is caused by a virus. Non-limiting examples of viral infections include hepatic viral diseases (e.g., hepatitis A, B, C, D, E), herpes virus infection (e.g., HSV-1, HSV-2, herpes zoster), flavivirus infection, Zika virus infection, cytomegalovirus infection, a respiratory viral infection (e.g., adenovirus infection, influenza, severe acute respiratory syndrome, coronavirus infection (e.g., SARS-CoV-1, SARS-CoV-2, MERS-CoV, COVID-19, MERS)), a gastrointestinal viral infection (e.g., norovirus infection, rotavirus infection, astrovirus infection), an exanthematous viral infection (e.g., measles, shingles, smallpox, rubella), viral hemorrhagic disease (e.g., Ebola, Lassa fever, dengue fever, yellow fever), a neurologic viral infection (e.g., West Nile viral infection, polio, viral meningitis, viral encephalitis, Japanese encephalitis, rabies), and human papilloma viral infection.

[0166] The term “plaque forming units” is used according to its plain ordinary meaning in Virology and refers to a unit of measurement based on the number of plaques per unit volume of a sample. In some embodiments the units are based on the number of plaques that could form when infecting a monolayer of susceptible cells. Plaque forming unit equivalents are units of measure of inactivated virus. In some embodiments, plaque forming unit equivalents are derived

from plaque forming units for a sample prior to inactivation. In embodiments, plaque forming units are abbreviated “Pfu”.

[0167] The terms “multiplicity of infection” or “MOI” are used according to its plain ordinary meaning in Virology and refers to the ratio of components (e.g., poxvirus) to the target (e.g., cell) in a given area. In embodiments, the area is assumed to be homogenous.

[0168] The term “replicate” is used in accordance with its plain ordinary meaning and refers to the ability of a cell or virus to produce progeny. A person of ordinary skill in the art will immediately understand that the term replicate when used in connection with DNA, refers to the biological process of producing two identical replicas of DNA from one original DNA molecule. In the context of a virus, the term “replicate” includes the ability of a virus to replicate (duplicate the viral genome and packaging said genome into viral particles) in a host cell and subsequently release progeny viruses from the host cell, which results in the lysis of the host cell. A “replication-competent” virus as provided herein refers to a virus (chimeric poxvirus) that is capable of replicating in a cell (e.g., a cancer cell). Similarly, an “oncolytic virus” as referred to herein, is a virus that is capable of infecting and killing cancer cells. As the infected cancer cells are destroyed by oncolysis, they release new infectious virus particles or virions to help destroy the remaining tumor. In embodiments, the chimeric poxvirus is able to replicate in a cancer cell. In embodiments, the chimeric poxvirus does not detectably replicate in a healthy cell relative to a standard control. In embodiments, the chimeric poxvirus provided herein has an increased oncolytic activity compared to its parental virus. In embodiments, the oncolytic activity (ability to induce cell death in an infected cell) is more than 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 100, 10000, 10000 times increased compared to the oncolytic activity of a parental virus (one of the viruses used to form the chimeric virus provided herein).

[0169] The terms “numbered with reference to” or “corresponding to,” when used in the context of the numbering of a given amino acid or polynucleotide sequence, refers to the numbering of the residues of a specified reference sequence when the given amino acid or polynucleotide sequence is compared to the reference sequence or 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.

[0170] The term “isolated”, when applied to a nucleic acid or protein, denotes that the nucleic acid or protein is essentially free of other cellular components with which it is associated in the natural state. It can be, for example, in a homogeneous state and may be in either a dry or aqueous solution. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified.

[0171] The term “amino acid” refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. The terms “non-naturally occurring amino acid” and “unnatural amino acid” refer to amino acid analogs, synthetic amino acids, and amino acid mimetics which are not found in nature.

[0172] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0173] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may in embodiments be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid

polymers and non-naturally occurring amino acid polymers. A "fusion protein" refers to a chimeric protein encoding two or more separate protein sequences that are recombinantly expressed as a single moiety.

[0174] As may be used herein, the terms “nucleic acid,” “nucleic acid molecule,” “nucleic acid oligomer,” “oligonucleotide,” “nucleic acid sequence,” “nucleic acid fragment” and “polynucleotide” are used interchangeably and are intended to include, but are not limited to, a polymeric form of nucleotides covalently linked together that may have various lengths, either deoxyribonucleotides or ribonucleotides, or analogs, derivatives or modifications thereof. Different polynucleotides may have different three-dimensional structures, and may perform various functions, known or unknown. Non-limiting examples of polynucleotides include a gene, a gene fragment, an exon, an intron, intergenic DNA (including, without limitation, heterochromatic DNA), messenger RNA (mRNA), transfer RNA, ribosomal RNA, a ribozyme, cDNA, a recombinant polynucleotide, a branched polynucleotide, a plasmid, a vector, isolated DNA of a sequence, isolated RNA of a sequence, a nucleic acid probe, and a primer. Polynucleotides useful in the methods of the disclosure may comprise natural nucleic acid sequences and variants thereof, artificial nucleic acid sequences, or a combination of such sequences.

[0175] A polynucleotide is typically composed of a specific sequence of four nucleotide bases: adenine (A); cytosine (C); guanine (G); and thymine (T) (uracil (U) for thymine (T) when the polynucleotide is RNA). Thus, the term “polynucleotide sequence” is the alphabetical representation of a polynucleotide molecule; alternatively, the term may be applied to the polynucleotide molecule itself. This alphabetical representation can be input into databases in a computer having a central processing unit and used for bioinformatics applications such as functional genomics and homology searching. Polynucleotides may optionally include one or more non-standard nucleotide(s), nucleotide analog(s) and/or modified nucleotides.

[0176] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a “conservatively modified variant” where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing

functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the disclosure.

[0177] The following eight groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Glycine (G);
- 2) Aspartic acid (D), Glutamic acid (E);
- 3) Asparagine (N), Glutamine (Q);
- 4) Arginine (R), Lysine (K);
- 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V);
- 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W);
- 7) Serine (S), Threonine (T); and
- 8) Cysteine (C), Methionine (M)

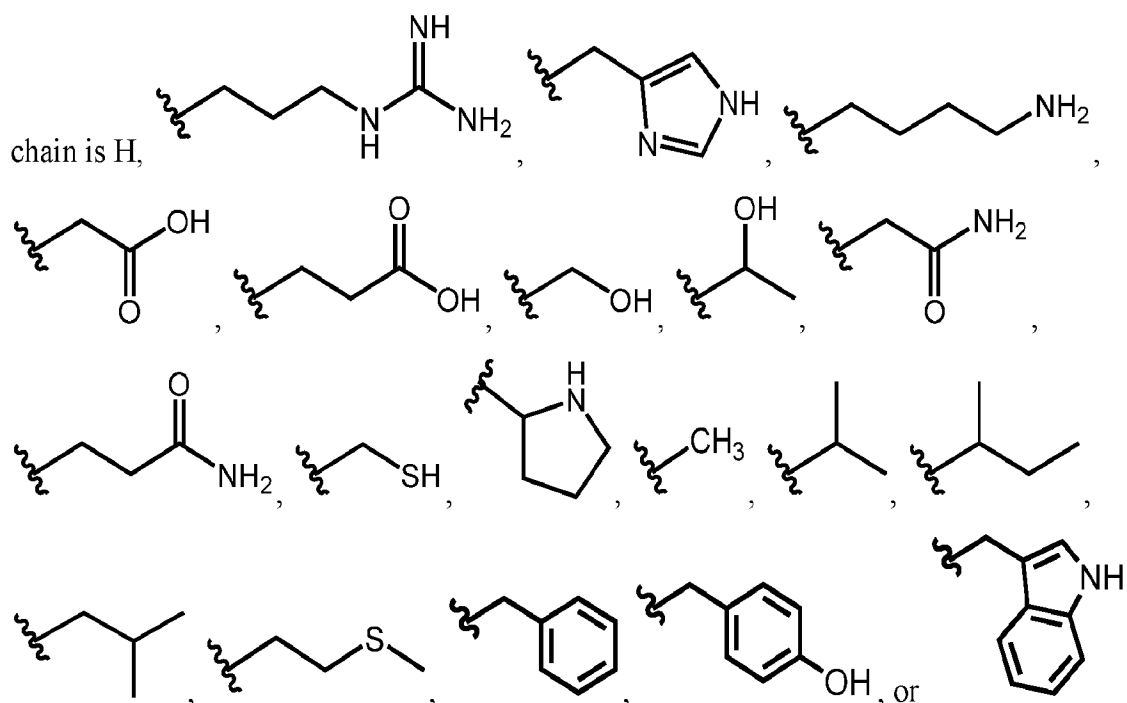
(see, e.g., Creighton, *Proteins* (1984)).

[0178] “Percentage of sequence identity” is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0179] The terms “identical” or percent “identity,” in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (*i.e.*, about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site <http://www.ncbi.nlm.nih.gov/BLAST/> or the like). Such sequences are then said to be “substantially identical.” This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0180] The term “amino acid side chain” refers to the functional substituent contained on amino acids. For example, an amino acid side chain may be the side chain of a naturally occurring amino acid. Naturally occurring amino acids are those encoded by the genetic code (e.g., alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine), as well as those amino acids that are later modified, e.g., hydroxyproline, γ -carboxyglutamate, and O-phosphoserine. In embodiments, the amino acid side chain may be a non-natural amino acid side chain. In embodiments, the amino acid side



[0181] The term “non-natural amino acid side chain” refers to the functional substituent of compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium, allylalanine, 2-aminoisobutyric acid. Non-natural amino acids are non-proteinogenic amino acids that either occur naturally or are chemically synthesized. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Non-limiting examples include *exo-cis*-3-Aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid hydrochloride, *cis*-2-Aminocycloheptanecarboxylic acid hydrochloride, *cis*-6-Amino-3-cyclohexene-1-carboxylic acid hydrochloride, *cis*-2-Amino-2-methylcyclohexanecarboxylic acid hydrochloride, *cis*-2-Amino-2-methylcyclopentanecarboxylic acid hydrochloride, 2-(Boc-aminomethyl)benzoic acid, 2-(Boc-amino)octanedioic acid, Boc-4,5-dehydro-Leu-OH (dicyclohexylammonium), Boc-4-(Fmoc-amino)-L-phenylalanine, Boc- β -Homopyr-OH, Boc-(2-indanyl)-Gly-OH, 4-Boc-3-morpholineacetic acid, 4-Boc-3-morpholineacetic acid, Boc-pentafluoro-D-phenylalanine, Boc-pentafluoro-L-phenylalanine, Boc-Phe(2-Br)-OH, Boc-Phe(4-Br)-OH, Boc-D-Phe(4-Br)-OH, Boc-D-Phe(3-Cl)-OH, Boc-Phe(4-NH₂)-OH, Boc-Phe(3-NO₂)-OH, Boc-Phe(3,5-F₂)-OH, 2-(4-Boc-piperazino)-2-(3,4-dimethoxyphenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(2-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(3-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(4-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(4-methoxyphenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-phenylacetic acid purum, 2-(4-Boc-piperazino)-2-(3-pyridyl)acetic acid purum, 2-(4-Boc-piperazino)-2-[4-(trifluoromethyl)phenyl]acetic acid purum, Boc- β -(2-quinolyl)-Ala-OH, N-Boc-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid, Boc- β -(4-thiazolyl)-Ala-OH, Boc- β -(2-thienyl)-D-Ala-OH, Fmoc-N-(4-Boc-aminobutyl)-Gly-OH, Fmoc-N-(2-Boc-aminoethyl)-Gly-OH, Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH, Fmoc-(2-indanyl)-Gly-OH, Fmoc-pentafluoro-L-phenylalanine, Fmoc-Pen(Trt)-OH, Fmoc-Phe(2-Br)-OH, Fmoc-Phe(4-Br)-OH, Fmoc-Phe(3,5-F₂)-OH, Fmoc- β -(4-thiazolyl)-Ala-OH, Fmoc- β -(2-thienyl)-Ala-OH, 4-(Hydroxymethyl)-D-phenylalanine.

[0182] “Percentage of sequence identity” is determined by comparing two optimally aligned sequences over a comparison window, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) as

compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid base or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison and multiplying the result by 100 to yield the percentage of sequence identity.

[0183] The terms “identical” or percent “identity,” in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60% identity, preferably 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region) as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site <http://www.ncbi.nlm.nih.gov/BLAST/> or the like). Such sequences are then said to be “substantially identical.” This definition also refers to, or may be applied to, the complement of a test sequence. The definition also includes sequences that have deletions and/or additions, as well as those that have substitutions. As described below, the preferred algorithms can account for gaps and the like. Preferably, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or more preferably over a region that is 50-100 amino acids or nucleotides in length.

[0184] The term “coronavirus” refers to a group of RNA viruses that cause diseases in mammals and birds. In embodiments, the coronavirus can cause disease in humans. Non-limiting examples of coronaviruses include human coronavirus OC43 (HCoV-OC43), human coronavirus HKU1 (HCoV-HKU1), human coronavirus 229E (HCoV-229E), human coronavirus NL63 (HCoV-NL63), Middle East respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

[0185] The term “SARS-CoV-2” refers to severe acute respiratory syndrome coronavirus 2, which is the strain of coronavirus that cause COVID-19. Like other coronaviruses, SARS-CoV-

2 has four structural proteins, known as the S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins. The N protein holds the RNA genome, and the S, E, and M proteins together create the viral envelope.

[0186] The term “SARS-CoV-2 spike protein” refers to the protein that is responsible for allowing the virus to attach to and fuse with the membrane of a host cell; specifically, the S1 subunit of the spike protein catalyzes attachment, and the S2 subunit of the spike protein catalyzes fusion.

[0187] The terms “ACE2”, “ACE-2”, “ACE2 receptor” and “ACE-2 receptor” refer to angiotensin-converting enzyme 2, which is an enzyme attached to the cell membranes of cell sin the lungs, arteries, heart, kidney, and intestines. ACE2 serves as the entry point into cells for some coronaviruses, including HCoV-NL63, SARS-CoV, and SARS-CoV-2. The human version of the enzyme is often referred to as hACE2. The term includes any recombinant or naturally-occurring form of ACE2 variants thereof that maintain ACE2 function or activity (e.g., within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% function or activity compared to wildtype ACE2). In embodiments, ACE2 is encoded by the ACE2 gene. In embodiments, ACE2 has the amino acid sequence set forth in or corresponding to Entrez 59272, UniProt Q9BYF1, or RefSeq (protein) NP_068576 or NP_001358344. In embodiments, ACE2 has the sequence:

MSSSSWLLLSLVAVTAAQSTIEEQAKTFLDKFNHEAEDLFYQSSLASWNYNTNITEENVQNMNN
AGDKWSAFLKEQSTLAQMYPLQEIQNLTVKLQLQALQQNGSSVLSEDKSKRLNTILNTMSTIYST
GKVCNPDNPQECLLLEPGLNEIMANSLDYNERLWAWESWRSEVGKQLRPLYEEYVVLKNEMA
RANHIEDYGDYWRGDYEVNGVDGYDYSRGLIEDVEHTFEEIKPLYEHLHAYVRAKLMNAYP
SYISPIGCLPAHLLGDMWGRFWTNLYSLTVPFGQKPNIDVTDAMVDQAWDAQRIFKEAEKFFVS
VGLPNMTQGFWENSMLTDPGNVQKAVCHPTAWDLGKGDFRILMCTKVTMDDFLTAHHEMGHI
QYDMAYAAQPFLLRNGANEGFHEAVGEIMSLSAATPKHLKSIGLLSPDFQEDNETEINFLLKQAL
TIVGTLPFTYMLEKWRWMVFKGEIPKDQWMKKWWEMKREIVGVVEPVPHDETYCDPASLFHV
SNDYSFIRYYTRTLYQFQFQEALCQAAKHEGPLHKCDISNSTEAGQKLFNMLRLGKSEPWTAL
ENVVGAKNMNVRPLLNYFEPLFTWLKDQNKNSFVGWSTDWSPYADQSIKVRISLKSALGDKAY
EWNDNEMYLFRSSVAYAMRQYFLKVKNQMILFGEEDVRVANLKPRISFNFFVTAPKNVSDIIPR
TEVEKAIRMSRSRINDAFRLNDNSLEFLGIQPTLGPPNQPPVSIWLIVFGVVMGVIVVGIVILIFTGI
RDRKKKNKARSGENPYASIDISKGENNPGFQNTDDVQTSF (SEQ ID NO. 1).

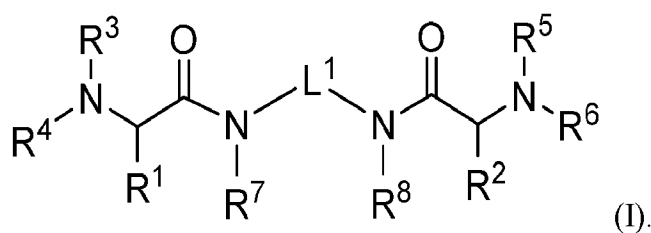
In embodiments, ACE2 has the sequence:

MSSSSWLLLSLVAVTAAQSTIEEQAKTFLDKFNHEAEDLFYQSSLASWNYNTNITEENV
QMNNAGDKWSAFLKEQSTLAQMYPLQEIQNLTVKLQLQALQQNGSSVLSEDKSKRLNT
ILNTMSTIYSTGKVCNPDNPQECLLLEPGLNEIMANSLDYNERLWAWESWRSEVGKQLR
PLYEEYVVLKNEMARANHYEDYGDYWRGDYEVNGVDGYDYSRGQLIEDVEHTFEEK
PLYEHLHAYVRAKLMNAYPSYISPIGCLPAHLLGDMWGRFWTNLYSLTVPFGQKPNID
VTDAMVDQAWDAQRIFKEAEKFFVSVGLPNMTQGFWENSMLTDPGNVQKAVCHPTA
WDLGKGDFRILMCTKVTMDDFLTAAHEMGGHIQYDMAYAAQPFLLRNGANEGFHEAV
GEIMSLSAATPKHLKSIGLLSPDFQEDNETEINFLKQALTIVGTLPTFTYMLEKWRWMVF
KGEIPKDQWMKKWWEMKREIVGVVEPVPHDETYCDPASLFHVSNDYSFIRYYTRTLYQ
FQFQEALCQAAKHEGPLHKCDISNSTEAGQKLFNMLRLGKSEPWTALENVVGAKNMN
VRPLLNYFEPLFTWLKDQNKNSFVGWSTDWSPYADQSIKVRISLKSALGDKAYEWDN
EMYLFRSSVAYAMRQYFLKVKNQMILFGEEDVRVANLKPRI SFNFFVTAPKNVSDIIPRT
EVEKAIRMSRSRINDAFRLNDNSLEFLGIQPTLGPPNQPPVSIWLIVFGVVMGVIVVGIVIL
IFTGIRDRKKKKNKARSGENPYASIDISKGENNPGFQNTDDVQTSF (SEQ ID NO. 2).

[0188] The terms “COVID-19”, “2019-nCoV”, “2019 novel coronavirus”, “hCoV-19”, “hCoV-19”, or “human coronavirus 2019” refer to coronavirus disease 2019, which is the respiratory illness responsible for the COVID-19 pandemic.

II. Compounds

[0189] In an aspect is provided a compound having the formula:



[0190] L^1 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0191] R^1 is independently hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NR^{1C}NR^{1A}R^{1B}$, $-ONR^{1A}R^{1B}$, $-NHC(O)NR^{1C}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0192] R^2 is independently hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2D}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NR^{2C}NR^{2A}R^{2B}$, $-ONR^{2A}R^{2B}$, $-NHC(O)NR^{2C}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-C(O)R^{2C}$, $-C(O)-OR^{2C}$, $-C(O)NR^{2A}R^{2B}$, $-OR^{2D}$, $-NR^{2A}SO_2R^{2D}$, $-NR^{2A}C(O)R^{2C}$, $-NR^{2A}C(O)OR^{2C}$, $-NR^{2A}OR^{2C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0193] R^3 is independently hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{n3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NR^{3C}NR^{3A}R^{3B}$, $-ONR^{3A}R^{3B}$, $-NHC(O)NR^{3C}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0194] R^4 is independently hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NR^{4C}NR^{4A}R^{4B}$, $-ONR^{4A}R^{4B}$, $-NHC(O)NR^{4C}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0195] R^5 is independently hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{n5}R^{5D}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NR^{5C}NR^{5A}R^{5B}$, $-ONR^{5A}R^{5B}$, $-NHC(O)NR^{5C}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-C(O)R^{5C}$, $-C(O)-OR^{5C}$, $-C(O)NR^{5A}R^{5B}$, $-OR^{5D}$, $-NR^{5A}SO_2R^{5D}$, $-NR^{5A}C(O)R^{5C}$, $-NR^{5A}C(O)OR^{5C}$, $-NR^{5A}OR^{5C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0196] R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl.

[0197] R^7 and R^8 are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0198] R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted

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

[0199] X, X^1 , X^2 , X^3 , X^4 , X^5 , and X^6 are independently -F, -Cl, -Br, or -I.

[0200] n_1 , n_2 , n_3 , n_4 , n_5 , and n_6 are independently an integer from 0 to 4.

[0201] m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 , are independently 1 or 2.

[0202] In embodiments, n_1 is 0. In embodiments, n_1 is 1. In embodiments, n_1 is 2. In embodiments, n_1 is 3. In embodiments, n_1 is 4. In embodiments, n_2 is 0. In embodiments, n_2 is 1. In embodiments, n_2 is 2. In embodiments, n_2 is 3. In embodiments, n_2 is 4. In embodiments, n_3 is 0. In embodiments, n_3 is 1. In embodiments, n_3 is 2. In embodiments, n_3 is 3. In embodiments, n_3 is 4. In embodiments, n_4 is 0. In embodiments, n_4 is 1. In embodiments, n_4 is 2. In embodiments, n_4 is 3. In embodiments, n_4 is 4. In embodiments, n_5 is 0. In embodiments, n_5 is 1. In embodiments, n_5 is 2. In embodiments, n_5 is 3. In embodiments, n_5 is 4. In embodiments, n_6 is 0. In embodiments, n_6 is 1. In embodiments, n_6 is 2. In embodiments, n_6 is 3. In embodiments, n_6 is 4.

[0203] In embodiments, m_1 is 1. In embodiments, m_1 is 2. In embodiments, v_1 is 1. In embodiments, v_1 is 2. In embodiments, m_2 is 1. In embodiments, m_2 is 2. In embodiments, v_2 is 1. In embodiments, v_2 is 2. In embodiments, m_3 is 1. In embodiments, m_3 is 2. In embodiments, v_3 is 1. In embodiments, v_3 is 2. In embodiments, m_4 is 1. In embodiments, m_4 is 2. In embodiments, v_4 is 1. In embodiments, v_4 is 2. In embodiments, m_5 is 1. In embodiments, m_5 is 2. In embodiments, v_5 is 1. In embodiments, v_5 is 2. In embodiments, m_6 is 1. In embodiments, m_6 is 2. In embodiments, v_6 is 1. In embodiments, v_6 is 2.

[0204] In embodiments, L^1 is independently substituted or unsubstituted C_2 - C_{10} alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C_3 - C_{10}

cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

[0205] In embodiments, L^1 is independently R^{10} -substituted or unsubstituted C_2 - C_{10} alkylene, R^{10} -substituted or unsubstituted 2 to 8 membered heteroalkylene, R^{10} -substituted or unsubstituted C_3 - C_{10} cycloalkylene, R^{10} -substituted or unsubstituted 3 to 8 membered heterocycloalkylene, R^{10} -substituted or unsubstituted phenylene, or R^{10} -substituted or unsubstituted 5 to 6 membered heteroarylene.

[0206] R^{10} is independently halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10D}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NR^{10C}NR^{10A}R^{10B}$, $-ONR^{10A}R^{10B}$, $-NHC(O)NR^{10C}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-C(O)R^{10C}$, $-C(O)-OR^{10C}$, $-C(O)NR^{10A}R^{10B}$, $-OR^{10D}$, $-NR^{10A}SO_2R^{10D}$, $-NR^{10A}C(O)R^{10C}$, $-NR^{10A}C(O)OR^{10C}$, $-NR^{10A}OR^{10C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0207] R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0208] X and X^{10} are independently $-F$, $-Cl$, $-Br$, or $-I$.

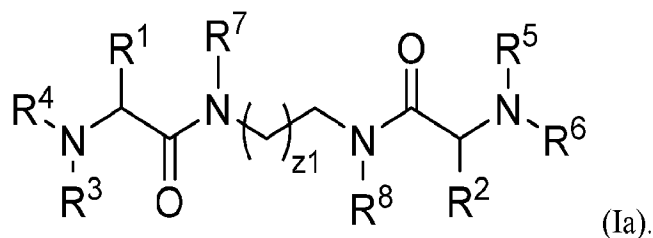
[0209] n_{10} is independently an integer from 0 to 4. In embodiments, n_{10} is 0. In embodiments, n_{10} is 1. In embodiments, n_{10} is 2. In embodiments, n_{10} is 3. In embodiments, n_{10} is 4.

[0210] m_{10} and v_{10} are independently 1 or 2. In embodiments, m_{10} is 1. In embodiments, m_{10} is 2. In embodiments, v_{10} is 1. In embodiments, v_{10} is 2.

[0211] In embodiments, L^1 is independently substituted or unsubstituted C_2 - C_6 alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene, substituted or unsubstituted C_3 - C_6

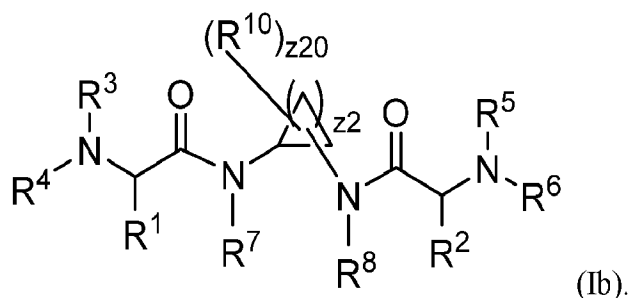
cycloalkylene, substituted or unsubstituted 3 to 6 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

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



[0213] z_1 is an integer from 1 to 9. In embodiments, z_1 is an integer from 1 to 6. In embodiments, z_1 is 1. In embodiments, z_1 is 2. In embodiments, z_1 is 3. In embodiments, z_1 is 4. In embodiments, z_1 is 5. In embodiments, z_1 is 6. In embodiments, z_1 is 7. In embodiments, z_1 is 8. In embodiments, z_1 is 9.

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

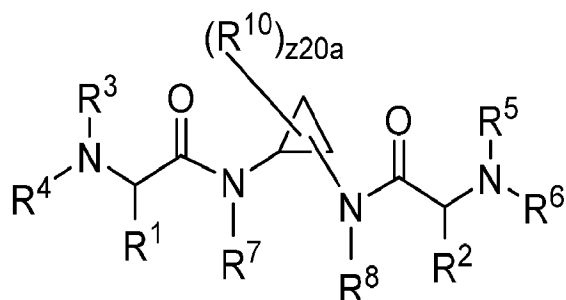


[0215] z_2 is an integer from 1 to 8. In embodiments, z_2 is an integer from 1 to 6. In embodiments, z_2 is an integer from 1 to 4. In embodiments, z_2 is 1. In embodiments, z_2 is 2. In embodiments, z_2 is 3. In embodiments, z_2 is 4. In embodiments, z_2 is 5. In embodiments, z_2 is 6. In embodiments, z_2 is 7. In embodiments, z_2 is 8.

[0216] z_{20} is an integer from 0 to 18. In embodiments, z_{20} is an integer from 0 to 6. In embodiments, z_{20} is an integer from 0 to 4. In embodiments, z_{20} is 0. In embodiments, z_{20} is 1. In embodiments, z_{20} is 2. In embodiments, z_{20} is 3. In embodiments, z_{20} is 4. In embodiments, z_{20} is 5. In embodiments, z_{20} is 6. In embodiments, z_{20} is 7. In embodiments, z_{20} is 8. In embodiments, z_{20} is 9. In embodiments, z_{20} is 10. In embodiments, z_{20} is 11. In embodiments, z_{20} is 12. In embodiments, z_{20} is 13. In embodiments, z_{20} is 14. In

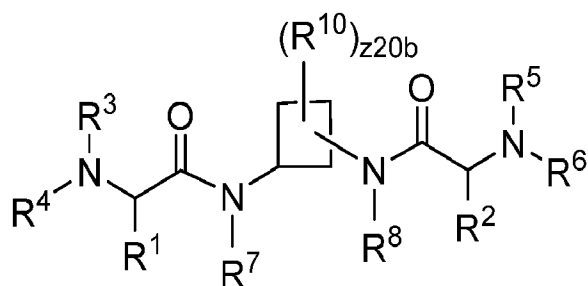
embodiments, z20 is 15. In embodiments, z20 is 16. In embodiments, z20 is 17. In embodiments, z20 is 18.

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



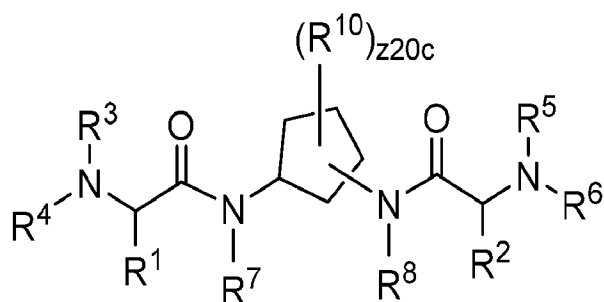
[0218] z20a is an integer from 0 to 4. In embodiments, z20a is 0. In embodiments, z20a is 1. In embodiments, z20a is 2. In embodiments, z20a is 3. In embodiments, z20a is 4.

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



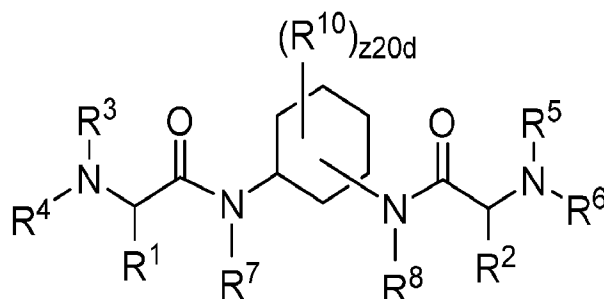
[0220] z20b is an integer from 0 to 6. In embodiments, z20b is an integer from 0 to 4. In embodiments, z20b is 0. In embodiments, z20b is 1. In embodiments, z20b is 2. In embodiments, z20b is 3. In embodiments, z20b is 4. In embodiments, z20b is 5. In embodiments, z20b is 6.

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



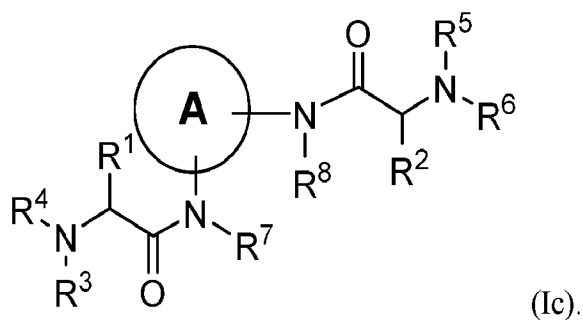
[0222] z20c is an integer from 0 to 8. In embodiments, z20c is an integer from 0 to 6. In embodiments, z20c is an integer from 0 to 4. In embodiments, z20c is 0. In embodiments, z20c is 1. In embodiments, z20c is 2. In embodiments, z20c is 3. In embodiments, z20c is 4. In embodiments, z20c is 5. In embodiments, z20c is 6. In embodiments, z20c is 7. In embodiments, z20c is 8.

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



[0224] z20d is an integer from 0 to 10. In embodiments, z20d is an integer from 0 to 8. In embodiments, z20d is an integer from 0 to 6. In embodiments, z20d is an integer from 0 to 4. In embodiments, z20d is 0. In embodiments, z20d is 1. In embodiments, z20d is 2. In embodiments, z20d is 3. In embodiments, z20d is 4. In embodiments, z20d is 5. In embodiments, z20d is 6. In embodiments, z20d is 7. In embodiments, z20d is 8. In embodiments, z20d is 9. In embodiments, z20d is 10.

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



[0226] Ring A is substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene. In embodiments, Ring A is substituted or unsubstituted arylene. In embodiments, Ring A is substituted or unsubstituted heteroarylene.

[0227] In embodiments, Ring A is R¹⁰-substituted or unsubstituted arylene or R¹⁰-substituted or unsubstituted heteroarylene. In embodiments, Ring A is R¹⁰-substituted or unsubstituted arylene. In embodiments, Ring A is R¹⁰-substituted or unsubstituted heteroarylene.

[0228] In embodiments, Ring A is R¹⁰-substituted or unsubstituted phenylene or R¹⁰-substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, Ring A is R¹⁰-substituted or unsubstituted phenylene. In embodiments, Ring A is R¹⁰-substituted or unsubstituted 5 to 6 membered heteroaryl.

[0229] In embodiments, Ring A is substituted or unsubstituted phenylene, substituted or unsubstituted pyridylene, substituted or unsubstituted pyridazinylene, substituted or unsubstituted triazinylene, substituted or unsubstituted pyrimidinylene, substituted or unsubstituted pyrazinylene, substituted or unsubstituted pyrrolylene, substituted or unsubstituted pyrazolylene, substituted or unsubstituted naphthylene, substituted or unsubstituted imidazolylene, substituted or unsubstituted purinylene, substituted or unsubstituted oxazolylene, substituted or unsubstituted isoxazolylene, substituted or unsubstituted thiazolylene, substituted or unsubstituted furylene, substituted or unsubstituted thienylene, substituted or unsubstituted benzothiazolylene, substituted or unsubstituted benzoxazoylene, substituted or unsubstituted benzimidazolylene, substituted or unsubstituted benzofuranylene, substituted or unsubstituted isobenzofuranylene, substituted or unsubstituted indolylene, substituted or unsubstituted isoindolene, substituted or unsubstituted benzothiophenylene, substituted or unsubstituted isoquinolylene, substituted or unsubstituted quinoxalinylene, or substituted or unsubstituted quinolylene. In embodiments, Ring A is substituted or unsubstituted phenylene. In embodiments, Ring A is substituted or unsubstituted pyridylene. In embodiments, Ring A is substituted or unsubstituted pyridazinylene. In embodiments, Ring A is substituted or unsubstituted triazinylene. In embodiments, Ring A is substituted or unsubstituted pyrimidinylene. In embodiments, Ring A is substituted or unsubstituted pyrazinylene. In embodiments, Ring A is substituted or unsubstituted pyrrolylene. In embodiments, Ring A is substituted or unsubstituted pyrazolylene. In embodiments, Ring A is substituted or unsubstituted naphthylene. In embodiments, Ring A is substituted or unsubstituted imidazolylene. In embodiments, Ring A is substituted or unsubstituted purinylene. In embodiments, Ring A is substituted or unsubstituted oxazolylene. In embodiments, Ring A is substituted or unsubstituted isoxazolylene. In embodiments, Ring A is substituted or

unsubstituted thiazolylene. In embodiments, Ring A is substituted or unsubstituted furylene. In embodiments, Ring A is substituted or unsubstituted thienylene. In embodiments, Ring A is substituted or unsubstituted benzothiazolylene. In embodiments, Ring A is substituted or unsubstituted benzoxazolylene. In embodiments, Ring A is substituted or unsubstituted benzimidazolylene. In embodiments, Ring A is substituted or unsubstituted benzofuranylene. In embodiments, Ring A is substituted or unsubstituted isobenzofuranylene. In embodiments, Ring A is substituted or unsubstituted indolylene. In embodiments, Ring A is substituted or unsubstituted isoindolene. In embodiments, Ring A is substituted or unsubstituted benzothiophenylene. In embodiments, Ring A is substituted or unsubstituted isoquinolylene. In embodiments, Ring A is substituted or unsubstituted quinoxalinyne. In embodiments, Ring A is substituted or unsubstituted quinolylene.

[0230] In embodiments, Ring A is unsubstituted phenylene, unsubstituted pyridylene, unsubstituted pyridazinyne, unsubstituted triazinyne, unsubstituted pyrimidinyne, unsubstituted pyrazinyne, unsubstituted pyrrolyne, unsubstituted pyrazolylene, unsubstituted naphthylene, unsubstituted imidazolylene, unsubstituted purinyne, unsubstituted oxazolylene, unsubstituted isoxazolylene, unsubstituted thiazolylene, unsubstituted furylene, unsubstituted thienylene, unsubstituted benzothiazolylene, unsubstituted benzoxazolylene, unsubstituted benzimidazolylene, unsubstituted benzofuranylene, unsubstituted isobenzofuranylene, unsubstituted indolylene, unsubstituted isoindolene, unsubstituted benzothiophenylene, unsubstituted isoquinolylene, unsubstituted quinoxalinyne, or unsubstituted quinolylene. In embodiments, Ring A is unsubstituted phenylene. In embodiments, Ring A is unsubstituted pyridylene. In embodiments, Ring A is unsubstituted pyridazinyne. In embodiments, Ring A is unsubstituted triazinyne. In embodiments, Ring A is unsubstituted pyrimidinyne. In embodiments, Ring A is unsubstituted pyrazinyne. In embodiments, Ring A is unsubstituted pyrrolyne. In embodiments, Ring A is unsubstituted pyrazolylene. In embodiments, Ring A is unsubstituted naphthylene. In embodiments, Ring A is unsubstituted imidazolylene. In embodiments, Ring A is unsubstituted purinyne. In embodiments, Ring A is unsubstituted oxazolylene. In embodiments, Ring A is unsubstituted isoxazolylene. In embodiments, Ring A is unsubstituted thiazolylene. In embodiments, Ring A is unsubstituted furylene. In embodiments, Ring A is unsubstituted thienylene. In embodiments, Ring A is unsubstituted benzothiazolylene. In embodiments, Ring A is unsubstituted benzoxazolylene. In embodiments,

Ring A is unsubstituted benzimidazolylene. In embodiments, Ring A is unsubstituted benzofuranylene. In embodiments, Ring A is unsubstituted isobenzofuranylene. In embodiments, Ring A is unsubstituted indolylene. In embodiments, Ring A is unsubstituted isoindolylene. In embodiments, Ring A is unsubstituted benzothiophenylene. In embodiments, Ring A is unsubstituted isoquinolylene. In embodiments, Ring A is unsubstituted quinoxalinylene. In embodiments, Ring A is unsubstituted quinolylene.

[0231] It will be understood that when Ring A is substituted, Ring A is bonded to one or more non-hydrogen substituents in addition to being bonded to the two nitrogen atoms that are in turn bonded to R⁷ and R⁸. It will be understood that when Ring A is unsubstituted, Ring A is not bonded to non-hydrogen substituents in addition to being bonded to the two nitrogen atoms that are in turn bonded to R⁷ and R⁸.

[0232] In embodiments, Ring A is substituted or unsubstituted phenylene, substituted or unsubstituted pyridazinylene, substituted or unsubstituted triazinylene, substituted or unsubstituted pyrimidinylene, substituted or unsubstituted pyrazinylene, substituted or unsubstituted pyrrolylene, substituted or unsubstituted pyrazolylene, substituted or unsubstituted 1-naphthylene, substituted or unsubstituted 2-naphthylene, substituted or unsubstituted 1-pyrrolylene, substituted or unsubstituted 2-pyrrolylene, substituted or unsubstituted 3-pyrrolylene, substituted or unsubstituted 3-pyrazolylene, substituted or unsubstituted 2-imidazolylene, substituted or unsubstituted 4-imidazolylene, substituted or unsubstituted pyrazinylene, substituted or unsubstituted 2-oxazolylene, substituted or unsubstituted 4-oxazolylene, substituted or unsubstituted 5-oxazolylene, substituted or unsubstituted 3-isoxazolylene, substituted or unsubstituted 4-isoxazolylene, substituted or unsubstituted 5-isoxazolylene, substituted or unsubstituted 2-thiazolylene, substituted or unsubstituted 4-thiazolylene, substituted or unsubstituted 5-thiazolylene, substituted or unsubstituted 2-furylene, substituted or unsubstituted 3-furylene, substituted or unsubstituted 2-thienylene, substituted or unsubstituted 3-thienylene, substituted or unsubstituted 2-pyridylene, substituted or unsubstituted 3-pyridylene, substituted or unsubstituted 4-pyridylene, substituted or unsubstituted 2-pyrimidylene, substituted or unsubstituted 4-pyrimidylene, substituted or unsubstituted 5-benzothiazolylene, substituted or unsubstituted purinylene, substituted or unsubstituted 2-benzimidazolylene, substituted or unsubstituted 5-indolylene, substituted or unsubstituted 1-isoquinolylene, substituted or unsubstituted 5-isoquinolylene, substituted or unsubstituted 2-

quinoxalinylenes, substituted or unsubstituted 5-quinoxalinylenes, substituted or unsubstituted 3-quinolylenes, or substituted or unsubstituted 6-quinolylenes. In embodiments, Ring A is substituted or unsubstituted phenylene. In embodiments, Ring A is substituted or unsubstituted pyridazinylenes. In embodiments, Ring A is substituted or unsubstituted triazinylene. In embodiments, Ring A is substituted or unsubstituted pyrimidinylene. In embodiments, Ring A is substituted or unsubstituted pyrazinylenes. In embodiments, Ring A is substituted or unsubstituted pyrrolylenes. In embodiments, Ring A is substituted or unsubstituted pyrazolylenes. In embodiments, Ring A is substituted or unsubstituted 1-naphthylene. In embodiments, Ring A is substituted or unsubstituted 2-naphthylene. In embodiments, Ring A is substituted or unsubstituted 1-pyrrolylene. In embodiments, Ring A is substituted or unsubstituted 2-pyrrolylene. In embodiments, Ring A is substituted or unsubstituted 3-pyrrolylene. In embodiments, Ring A is substituted or unsubstituted 3-pyrazolylene. In embodiments, Ring A is substituted or unsubstituted 2-imidazolylenes. In embodiments, Ring A is substituted or unsubstituted 4-imidazolylenes. In embodiments, Ring A is substituted or unsubstituted pyrazinylenes. In embodiments, Ring A is substituted or unsubstituted 2-oxazolylenes. In embodiments, Ring A is substituted or unsubstituted 4-oxazolylenes. In embodiments, Ring A is substituted or unsubstituted 5-oxazolylenes. In embodiments, Ring A is substituted or unsubstituted 3-isoxazolylenes. In embodiments, Ring A is substituted or unsubstituted 4-isoxazolylenes. In embodiments, Ring A is substituted or unsubstituted 5-isoxazolylenes. In embodiments, Ring A is substituted or unsubstituted 2-thiazolylenes. In embodiments, Ring A is substituted or unsubstituted 4-thiazolylenes. In embodiments, Ring A is substituted or unsubstituted 5-thiazolylenes. In embodiments, Ring A is substituted or unsubstituted 2-furylenes. In embodiments, Ring A is substituted or unsubstituted 3-furylenes. In embodiments, Ring A is substituted or unsubstituted 2-thienylenes. In embodiments, Ring A is substituted or unsubstituted 3-thienylenes. In embodiments, Ring A is substituted or unsubstituted 2-pyridylenes. In embodiments, Ring A is substituted or unsubstituted 3-pyridylenes. In embodiments, Ring A is substituted or unsubstituted 4-pyridylenes. In embodiments, Ring A is substituted or unsubstituted 2-pyrimidylenes. In embodiments, Ring A is substituted or unsubstituted 4-pyrimidylenes. In embodiments, Ring A is substituted or unsubstituted 5-benzothiazolylenes. In embodiments, Ring A is substituted or unsubstituted purinylenes. In embodiments, Ring A is substituted or unsubstituted 2-benzimidazolylenes. In embodiments, Ring A is substituted or

unsubstituted 5-indolylene. In embodiments, Ring A is 1 substituted or unsubstituted -isoquinolylene. In embodiments, Ring A is substituted or unsubstituted 5-isoquinolylene. In embodiments, Ring A is substituted or unsubstituted 2-quinoxalinylenes. In embodiments, Ring A is substituted or unsubstituted 5-quinoxalinylenes. In embodiments, Ring A is substituted or unsubstituted 3-quinolylene. In embodiments, Ring A is substituted or unsubstituted 6-quinolylene.

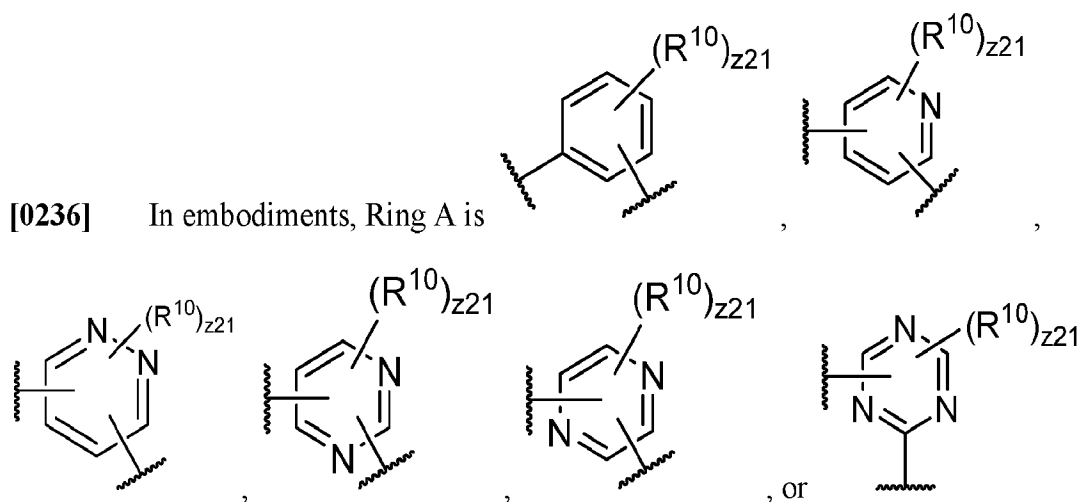
[0233] In embodiments, Ring A is unsubstituted phenylene, unsubstituted pyridazinylenes, unsubstituted triazinylene, unsubstituted pyrimidinylene, unsubstituted pyrazinylene, unsubstituted pyrrolylene, unsubstituted pyrazolylene, unsubstituted 1-naphthylene, unsubstituted 2-naphthylene, unsubstituted 1-pyrrolylene, unsubstituted 2-pyrrolylene, unsubstituted 3-pyrrolylene, unsubstituted 3-pyrazolylene, unsubstituted 2-imidazolylene, unsubstituted 4-imidazolylene, unsubstituted pyrazinylene, unsubstituted 2-oxazolylene, unsubstituted 4-oxazolylene, unsubstituted 5-oxazolylene, unsubstituted 3-isoxazolylene, unsubstituted 4-isoxazolylene, unsubstituted 5-isoxazolylene, unsubstituted 2-thiazolylene, unsubstituted 4-thiazolylene, unsubstituted 5-thiazolylene, unsubstituted 2-furylene, unsubstituted 3-furylene, unsubstituted 2-thienylene, unsubstituted 3-thienylene, unsubstituted 2-pyridylene, unsubstituted 3-pyridylene, unsubstituted 4-pyridylene, unsubstituted 2-pyrimidylene, unsubstituted 4-pyrimidylene, unsubstituted 5-benzothiazolylene, unsubstituted purinylene, unsubstituted 2-benzimidazolylene, unsubstituted 5-indolylene, unsubstituted 1-isoquinolylene, unsubstituted 5-isoquinolylene, unsubstituted 2-quinoxalinylenes, unsubstituted 5-quinoxalinylenes, unsubstituted 3-quinolylene, or unsubstituted 6-quinolylene. In embodiments, Ring A is unsubstituted phenylene. In embodiments, Ring A is unsubstituted pyridazinylenes. In embodiments, Ring A is unsubstituted triazinylene. In embodiments, Ring A is unsubstituted pyrimidinylene. In embodiments, Ring A is unsubstituted pyrazinylene. In embodiments, Ring A is unsubstituted pyrrolylene. In embodiments, Ring A is unsubstituted pyrazolylene. In embodiments, Ring A is unsubstituted 1-naphthylene. In embodiments, Ring A is unsubstituted 2-naphthylene. In embodiments, Ring A is unsubstituted 1-pyrrolylene. In embodiments, Ring A is unsubstituted 2-pyrrolylene. In embodiments, Ring A is unsubstituted 3-pyrrolylene. In embodiments, Ring A is unsubstituted 3-pyrazolylene. In embodiments, Ring A is unsubstituted 2-imidazolylene. In embodiments, Ring A is unsubstituted 4-imidazolylene. In embodiments, Ring A is unsubstituted pyrazinylene. In embodiments, Ring A is unsubstituted 2-oxazolylene.

In embodiments, Ring A is unsubstituted 4-oxazolylene. In embodiments, Ring A is unsubstituted 5-oxazolylene. In embodiments, Ring A is unsubstituted 3-isoxazolylene. In embodiments, Ring A is unsubstituted 4-isoxazolylene. In embodiments, Ring A is unsubstituted 5-isoxazolylene. In embodiments, Ring A is unsubstituted 2-thiazolylene. In embodiments, Ring A is unsubstituted 4-thiazolylene. In embodiments, Ring A is unsubstituted 5-thiazolylene. In embodiments, Ring A is unsubstituted 2-furylene. In embodiments, Ring A is unsubstituted 3-furylene. In embodiments, Ring A is unsubstituted 2-thienylene. In embodiments, Ring A is unsubstituted 3-thienylene. In embodiments, Ring A is unsubstituted 2-pyridylene. In embodiments, Ring A is unsubstituted 3-pyridylene. In embodiments, Ring A is unsubstituted 4-pyridylene. In embodiments, Ring A is unsubstituted 2-pyrimidylene. In embodiments, Ring A is unsubstituted 4-pyrimidylene. In embodiments, Ring A is unsubstituted 5-benzothiazolylene. In embodiments, Ring A is unsubstituted purinylene. In embodiments, Ring A is unsubstituted 2-benzimidazolylene. In embodiments, Ring A is unsubstituted 5-indolylene. In embodiments, Ring A is unsubstituted 1-isoquinolylene. In embodiments, Ring A is unsubstituted 5-isoquinolylene. In embodiments, Ring A is unsubstituted 2-quinoxalinylen. In embodiments, Ring A is unsubstituted 5-quinoxalinylen. In embodiments, Ring A is unsubstituted 3-quinolylene. In embodiments, Ring A is unsubstituted 6-quinolylene.

[0234] In embodiments, Ring A is substituted or unsubstituted phenylene, substituted or unsubstituted pyridylene, substituted or unsubstituted pyridazinylen, substituted or unsubstituted triazinylene, substituted or unsubstituted pyrimidinylene, substituted or unsubstituted pyrazinylen, substituted or unsubstituted pyrrolylen, or substituted or unsubstituted pyrazolylene. In embodiments, Ring A is substituted or unsubstituted phenylene, substituted or unsubstituted pyridylene, substituted or unsubstituted pyridazinylen, substituted or unsubstituted triazinylene, substituted or unsubstituted pyrimidinylene, or substituted or unsubstituted pyrazinylen. In embodiments, Ring A is substituted or unsubstituted phenylene. In embodiments, Ring A is substituted or unsubstituted pyridylene. In embodiments, Ring A is substituted or unsubstituted pyridazinylen. In embodiments, Ring A is substituted or unsubstituted triazinylene. In embodiments, Ring A is substituted or unsubstituted pyrimidinylene. In embodiments, Ring A is substituted or unsubstituted pyrazinylen. In embodiments, Ring A is substituted or unsubstituted pyrrolylen. In embodiments, Ring A is substituted or unsubstituted pyrazolylene.

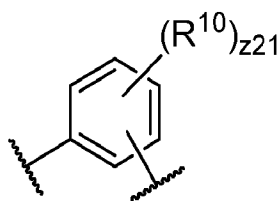
[0235] In embodiments, Ring A is unsubstituted phenylene, pyridylene, unsubstituted pyridazinylene, unsubstituted triazinylene, unsubstituted pyrimidinylene, unsubstituted pyrazinylene, unsubstituted pyrrolylene, or unsubstituted pyrazolylene. In embodiments, Ring A is unsubstituted phenylene, unsubstituted pyridylene, unsubstituted pyridazinylene, unsubstituted triazinylene, unsubstituted pyrimidinylene, or unsubstituted pyrazinylene. In embodiments, Ring A is unsubstituted phenylene. In embodiments, Ring A is unsubstituted pyridylene. In embodiments, Ring A is unsubstituted pyridazinylene. In embodiments, Ring A is unsubstituted triazinylene. In embodiments, Ring A is unsubstituted pyrimidinylene. In embodiments, Ring A is unsubstituted pyrazinylene. In embodiments, Ring A is unsubstituted pyrrolylene. In embodiments, Ring A is unsubstituted pyrazolylene.

[0236] In embodiments, Ring A is

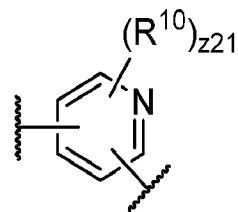


[0237] z_{21} is independently an integer from 0 to 4. In embodiments, z_{21} is 0. In embodiments, z_{21} is 1. In embodiments, z_{21} is 2. In embodiments, z_{21} is 3. In embodiments, z_{21} is 4.

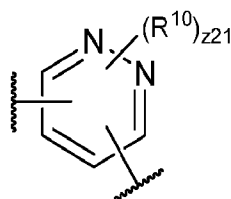
In embodiments, Ring A is



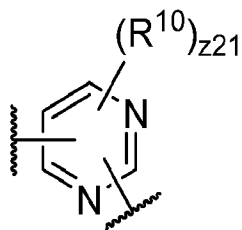
. In embodiments, Ring A is



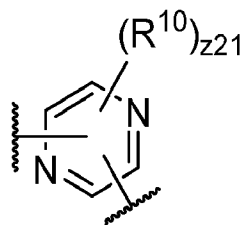
. In embodiments, Ring A is



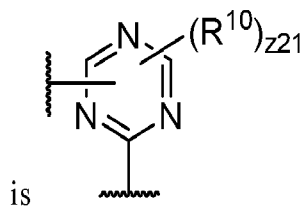
. In embodiments, Ring A is



. In embodiments, Ring A is

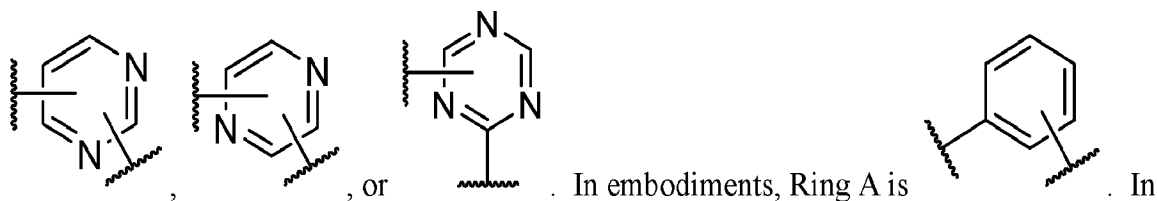
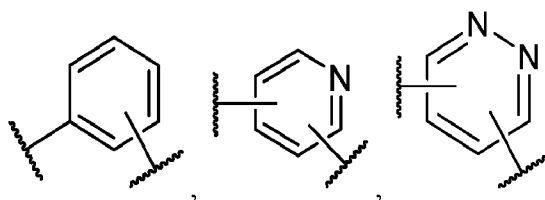


. In embodiments, Ring A

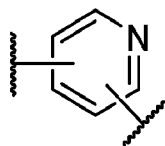


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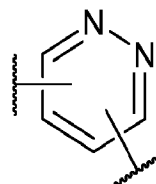
[0238] In embodiments, Ring A is



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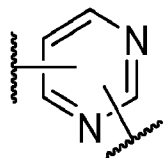


. In embodiments, Ring A is

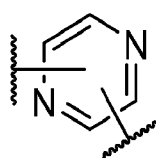


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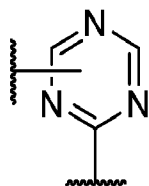


. In embodiments, Ring A is



. In

embodiments, Ring A is



[0239] In embodiments, R^1 is independently hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NR^{1C}NR^{1A}R^{1B}$, $-ONR^{1A}R^{1B}$, $-NHC(O)NR^{1C}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$,

$-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, R^{11} -substituted or unsubstituted alkyl, R^{11} -substituted or unsubstituted heteroalkyl, R^{11} -substituted or unsubstituted cycloalkyl, R^{11} -substituted or unsubstituted heterocycloalkyl, R^{11} -substituted or unsubstituted aryl, or R^{11} -substituted or unsubstituted heteroaryl.

[0240] In embodiments, R^2 is independently hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_nR^{2D}$, $-SO_vR^{2A}R^{2B}$, $-NR^{2C}NR^{2A}R^{2B}$, $-ONR^{2A}R^{2B}$, $-NHC(O)NR^{2C}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-C(O)R^{2C}$, $-C(O)-OR^{2C}$, $-C(O)NR^{2A}R^{2B}$, $-OR^{2D}$, $-NR^{2A}SO_2R^{2D}$, $-NR^{2A}C(O)R^{2C}$, $-NR^{2A}C(O)OR^{2C}$, $-NR^{2A}OR^{2C}$, $-N_3$, R^{12} -substituted or unsubstituted alkyl, R^{12} -substituted or unsubstituted heteroalkyl, R^{12} -substituted or unsubstituted cycloalkyl, R^{12} -substituted or unsubstituted heterocycloalkyl, R^{12} -substituted or unsubstituted aryl, or R^{12} -substituted or unsubstituted heteroaryl.

[0241] In embodiments, R^1 is independently hydrogen, 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 6 membered heterocycloalkyl, substituted or unsubstituted C_6 - C_{12} aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0242] In embodiments, R^2 is independently hydrogen, 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 6 membered heterocycloalkyl, substituted or unsubstituted C_6 - C_{12} aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0243] In embodiments, R^1 is independently an amino acid side chain. In embodiments, the amino acid side chain is a side chain of a natural amino acid (e.g., alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine (e.g., $-H$), histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, or valine). In embodiments, the amino acid side chain is a side chain of a non-natural amino acid side-chain. In embodiments, R^1 is independently an amino acid side chain of an L-amino acid. In embodiments, R^1 is independently an amino acid side chain of a D-amino acid.

[0244] In embodiments, R^2 is independently an amino acid side chain. In embodiments, the amino acid side chain is a side chain of a natural amino acid (e.g., alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine (e.g., $-H$), histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, or valine). In

embodiments, the amino acid side chain is a side chain of a non-natural amino acid side-chain. In embodiments, R^2 is independently an amino acid side chain of an L-amino acid. In embodiments, R^2 is independently an amino acid side chain of an D-amino acid.

[0245] In embodiments, R^1 is independently hydrogen, substituted or unsubstituted arginine side chain, substituted or unsubstituted histidine side chain, substituted or unsubstituted lysine side chain, substituted or unsubstituted aspartic acid side chain, substituted or unsubstituted glutamic acid side chain, substituted or unsubstituted serine side chain, substituted or unsubstituted threonine side chain, substituted or unsubstituted asparagine side chain, substituted or unsubstituted glutamine side chain, substituted or unsubstituted cysteine side chain, substituted or unsubstituted glycine side chain, substituted or unsubstituted proline side chain, substituted or unsubstituted alanine side chain, substituted or unsubstituted valine side chain, substituted or unsubstituted isoleucine side chain, substituted or unsubstituted leucine side chain, substituted or unsubstituted methionine side chain, substituted or unsubstituted phenylalanine side chain, substituted or unsubstituted tyrosine side chain, or substituted or unsubstituted tryptophan side chain.

[0246] In embodiments, R^2 is independently hydrogen, substituted or unsubstituted arginine side chain, substituted or unsubstituted histidine side chain, substituted or unsubstituted lysine side chain, substituted or unsubstituted aspartic acid side chain, substituted or unsubstituted glutamic acid side chain, substituted or unsubstituted serine side chain, substituted or unsubstituted threonine side chain, substituted or unsubstituted asparagine side chain, substituted or unsubstituted glutamine side chain, substituted or unsubstituted cysteine side chain, substituted or unsubstituted glycine side chain, substituted or unsubstituted proline side chain, substituted or unsubstituted alanine side chain, substituted or unsubstituted valine side chain, substituted or unsubstituted isoleucine side chain, substituted or unsubstituted leucine side chain, substituted or unsubstituted methionine side chain, substituted or unsubstituted phenylalanine side chain, substituted or unsubstituted tyrosine side chain, or substituted or unsubstituted tryptophan side chain.

[0247] In embodiments, R^1 is independently hydrogen, R^{11} -substituted or unsubstituted arginine side chain, R^{11} -substituted or unsubstituted histidine side chain, R^{11} -substituted or unsubstituted lysine side chain, R^{11} -substituted or unsubstituted aspartic acid side chain, R^{11} -

substituted or unsubstituted glutamic acid side chain, R^{11} -substituted or unsubstituted serine side chain, R^{11} -substituted or unsubstituted threonine side chain, R^{11} -substituted or unsubstituted asparagine side chain, R^{11} -substituted or unsubstituted glutamine side chain, R^{11} -substituted or unsubstituted cysteine side chain, R^{11} -substituted or unsubstituted glycine side chain, R^{11} -substituted or unsubstituted proline side chain, R^{11} -substituted or unsubstituted alanine side chain, R^{11} -substituted or unsubstituted valine side chain, R^{11} -substituted or unsubstituted isoleucine side chain, R^{11} -substituted or unsubstituted leucine side chain, R^{11} -substituted or unsubstituted methionine side chain, R^{11} -substituted or unsubstituted phenylalanine side chain, R^{11} -substituted or unsubstituted tyrosine side chain, or R^{11} -substituted or unsubstituted tryptophan side chain.

[0248] In embodiments, R^2 is independently hydrogen, R^{12} -substituted or unsubstituted arginine side chain, R^{12} -substituted or unsubstituted histidine side chain, R^{12} -substituted or unsubstituted lysine side chain, R^{12} -substituted or unsubstituted aspartic acid side chain, R^{12} -substituted or unsubstituted glutamic acid side chain, R^{12} -substituted or unsubstituted serine side chain, R^{12} -substituted or unsubstituted threonine side chain, R^{12} -substituted or unsubstituted asparagine side chain, R^{12} -substituted or unsubstituted glutamine side chain, R^{12} -substituted or unsubstituted cysteine side chain, R^{12} -substituted or unsubstituted glycine side chain, R^{12} -substituted or unsubstituted proline side chain, R^{12} -substituted or unsubstituted alanine side chain, R^{12} -substituted or unsubstituted valine side chain, R^{12} -substituted or unsubstituted isoleucine side chain, R^{12} -substituted or unsubstituted leucine side chain, R^{12} -substituted or unsubstituted methionine side chain, R^{12} -substituted or unsubstituted phenylalanine side chain, R^{12} -substituted or unsubstituted tyrosine side chain, or R^{12} -substituted or unsubstituted tryptophan side chain.

[0249] Each R^{11} is independently halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11D}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NR^{11C}NR^{11A}R^{11B}$, $-ONR^{11A}R^{11B}$, $-NHC(O)NR^{11C}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-C(O)R^{11C}$, $-C(O)-OR^{11C}$, $-C(O)NR^{11A}R^{11B}$, $-OR^{11D}$, $-NR^{11A}SO_2R^{11D}$, $-NR^{11A}C(O)R^{11C}$, $-NR^{11A}C(O)OR^{11C}$, $-NR^{11A}OR^{11C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0250] R^{11A} , R^{11B} , R^{11C} , R^{11D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0251] X and X^{11} are independently $-F$, $-Cl$, $-Br$, or $-I$.

[0252] n_{11} is independently an integer from 0 to 4. In embodiments, n_{11} is 0. In embodiments, n_{11} is 1. In embodiments, n_{11} is 2. In embodiments, n_{11} is 3. In embodiments, n_{11} is 4.

[0253] m_{11} and v_{11} are independently 1 or 2. In embodiments, m_{11} is 1. In embodiments, m_{11} is 2. In embodiments, v_{11} is 1. In embodiments, v_{11} is 2.

[0254] Each R^{12} is independently halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, $-CN$, $-SO_{n_{12}}R^{12D}$, $-SO_{v_{12}}NR^{12A}R^{12B}$, $-NR^{12C}NR^{12A}R^{12B}$, $-ONR^{12A}R^{12B}$, $-NHC(O)NR^{12C}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m_{12}}$, $-NR^{12A}R^{12B}$, $-C(O)R^{12C}$, $-C(O)-OR^{12C}$, $-C(O)NR^{12A}R^{12B}$, $-OR^{12D}$, $-NR^{12A}SO_2R^{12D}$, $-NR^{12A}C(O)R^{12C}$, $-NR^{12A}C(O)OR^{12C}$, $-NR^{12A}OR^{12C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0255] R^{12A} , R^{12B} , R^{12C} , R^{12D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0256] X and X^{12} are independently $-F$, $-Cl$, $-Br$, or $-I$.

[0257] n_{12} is independently an integer from 0 to 4. In embodiments, n_{12} is 0. In embodiments, n_{12} is 1. In embodiments, n_{12} is 2. In embodiments, n_{12} is 3. In embodiments, n_{12} is 4.

[0258] m_{12} and v_{12} are independently 1 or 2. In embodiments, m_{12} is 1. In embodiments, m_{12} is 2. In embodiments, v_{12} is 1. In embodiments, v_{12} is 2.

[0259] In embodiments, R^{1A} is independently hydrogen. In embodiments, R^{1B} is independently hydrogen. In embodiments, R^{1C} is independently hydrogen. In embodiments, R^{1D} is independently hydrogen.

[0260] In embodiments, R^{2A} is independently hydrogen. In embodiments, R^{2B} is independently hydrogen. In embodiments, R^{2C} is independently hydrogen. In embodiments, R^{2D} is independently hydrogen.

[0261] In embodiments, R^{3A} is independently hydrogen. In embodiments, R^{3B} is independently hydrogen. In embodiments, R^{3C} is independently hydrogen. In embodiments, R^{3D} is independently hydrogen.

[0262] In embodiments, R^{4A} is independently hydrogen. In embodiments, R^{4B} is independently hydrogen. In embodiments, R^{4C} is independently hydrogen. In embodiments, R^{4D} is independently hydrogen.

[0263] In embodiments, R^{5A} is independently hydrogen. In embodiments, R^{5B} is independently hydrogen. In embodiments, R^{5C} is independently hydrogen. In embodiments, R^{5D} is independently hydrogen.

[0264] In embodiments, R^{6A} is independently hydrogen. In embodiments, R^{6B} is independently hydrogen. In embodiments, R^{6C} is independently hydrogen. In embodiments, R^{6D} is independently hydrogen.

[0265] In embodiments, R^{10A} is independently hydrogen. In embodiments, R^{10B} is independently hydrogen. In embodiments, R^{10C} is independently hydrogen. In embodiments, R^{10D} is independently hydrogen.

[0266] In embodiments, R^{11A} is independently hydrogen. In embodiments, R^{11B} is independently hydrogen. In embodiments, R^{11C} is independently hydrogen. In embodiments, R^{11D} is independently hydrogen.

[0267] In embodiments, R^{12A} is independently hydrogen. In embodiments, R^{12B} is independently hydrogen. In embodiments, R^{12C} is independently hydrogen. In embodiments, R^{12D} is independently hydrogen.

[0268] In embodiments, X is independently –F. In embodiments, X is independently –Cl. In embodiments, X is independently –Br. In embodiments, X is independently –I.

[0269] In embodiments, X^1 is independently –F. In embodiments, X^1 is independently –Cl. In embodiments, X^1 is independently –Br. In embodiments, X^1 is independently –I.

[0270] In embodiments, X^2 is independently –F. In embodiments, X^2 is independently –Cl. In embodiments, X^2 is independently –Br. In embodiments, X^2 is independently –I.

[0271] In embodiments, X^3 is independently –F. In embodiments, X^3 is independently –Cl. In embodiments, X^3 is independently –Br. In embodiments, X^3 is independently –I.

[0272] In embodiments, X^4 is independently –F. In embodiments, X^4 is independently –Cl. In embodiments, X^4 is independently –Br. In embodiments, X^4 is independently –I.

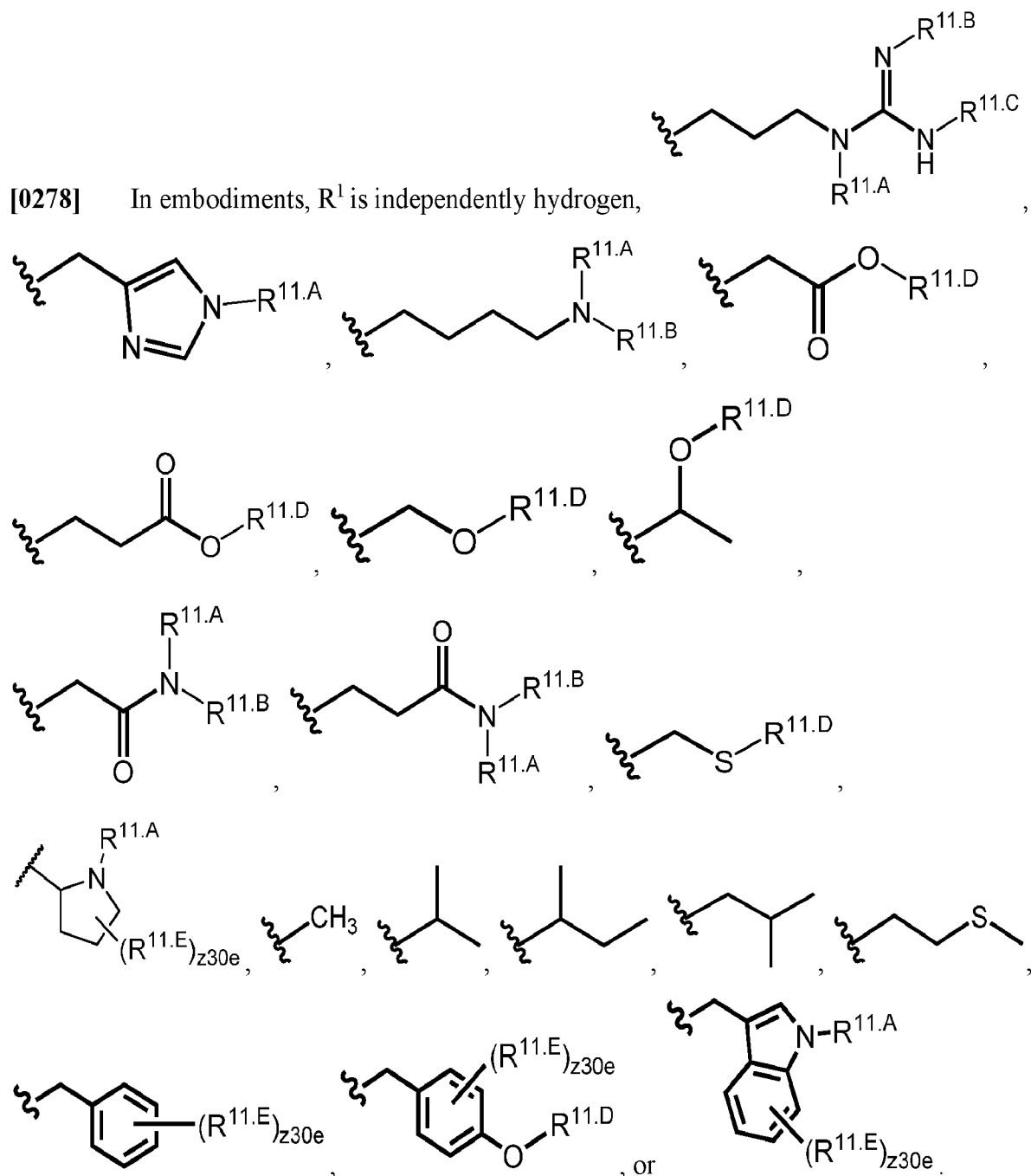
[0273] In embodiments, X^5 is independently –F. In embodiments, X^5 is independently –Cl. In embodiments, X^5 is independently –Br. In embodiments, X^5 is independently –I.

[0274] In embodiments, X^6 is independently –F. In embodiments, X^6 is independently –Cl. In embodiments, X^6 is independently –Br. In embodiments, X^6 is independently –I.

[0275] In embodiments, X^{10} is independently –F. In embodiments, X^{10} is independently –Cl. In embodiments, X^{10} is independently –Br. In embodiments, X^{10} is independently –I.

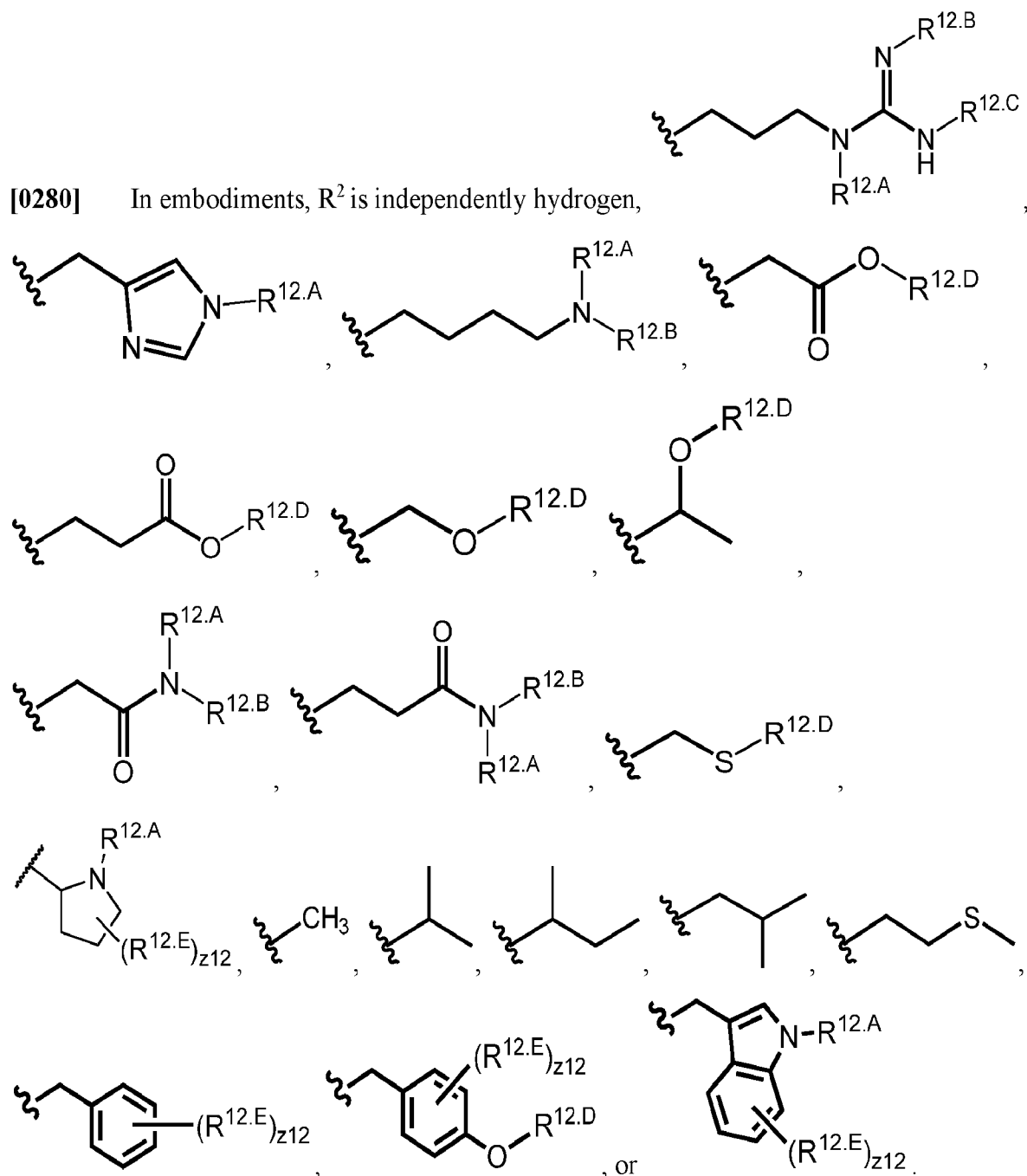
[0276] In embodiments, X^{11} is independently –F. In embodiments, X^{11} is independently –Cl. In embodiments, X^{11} is independently –Br. In embodiments, X^{11} is independently –I.

[0277] In embodiments, X^{12} is independently –F. In embodiments, X^{12} is independently –Cl. In embodiments, X^{12} is independently –Br. In embodiments, X^{12} is independently –I.



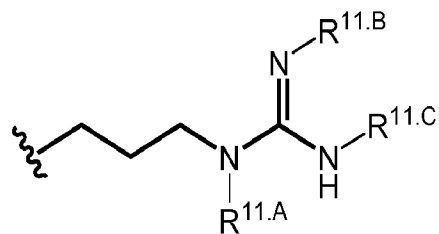
[0279] z30e is an integer from 0 to 7. In embodiments, z30e is an integer from 0 to 5. In embodiments, z30e is an integer from 0 to 4. In embodiments, z30e is 0. In embodiments, z30e is 1. In embodiments, z30e is 2. In embodiments, z30e is 3. In embodiments, z30e is 4. In embodiments, z30e is an integer from 5. In embodiments, z30e is 6. In embodiments, z30e is 7.

[0280] In embodiments, R^2 is independently hydrogen,

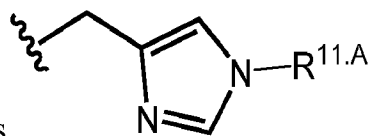


[0281] $z12$ is an integer from 0 to 7. In embodiments, $z12$ is an integer from 0 to 5. In embodiments, $z12$ is an integer from 0 to 4. In embodiments, $z12$ is 0. In embodiments, $z12$ is 1. In embodiments, $z12$ is 2. In embodiments, $z12$ is 3. In embodiments, $z12$ is 4. In embodiments, $z12$ is an integer from 5. In embodiments, $z12$ is 6. In embodiments, $z12$ is 7.

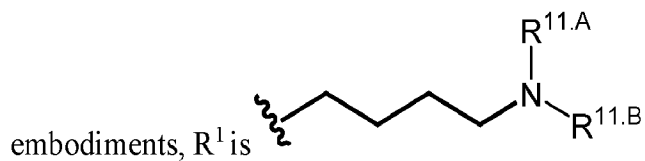
[0282] In embodiments, R^1 is hydrogen. In embodiments, R^1 is



. In embodiments, R^1 is

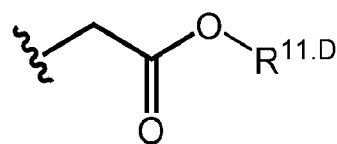


. In

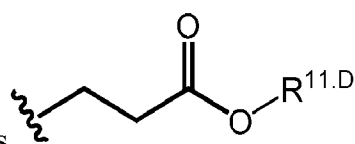


embodiments, R^1 is

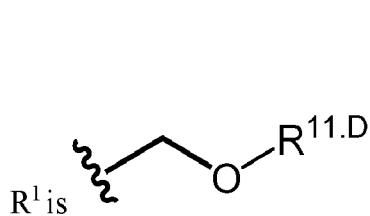
. In embodiments, R^1 is



. In embodiments, R^1 is

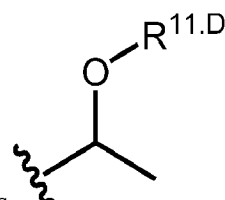


. In embodiments,

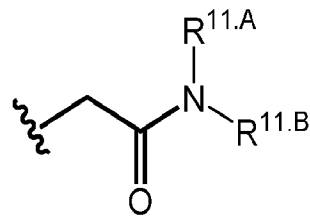


R^1 is

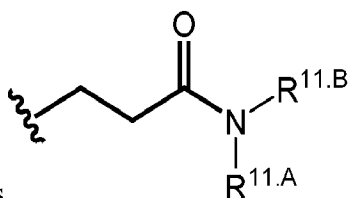
. In embodiments, R^1 is



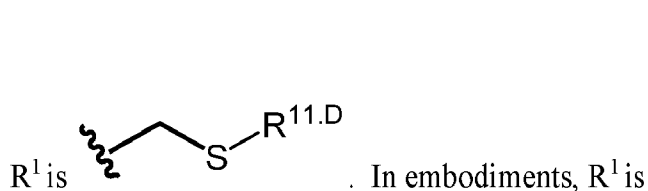
. In embodiments, R^1 is



. In embodiments, R^1 is

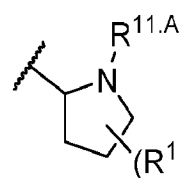


. In embodiments,

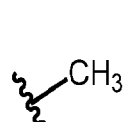


R^1 is

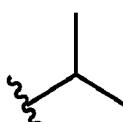
. In embodiments, R^1 is



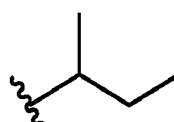
. In embodiments, R^1 is



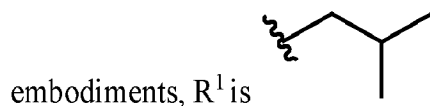
. In embodiments, R^1 is



. In embodiments, R^1 is

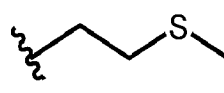


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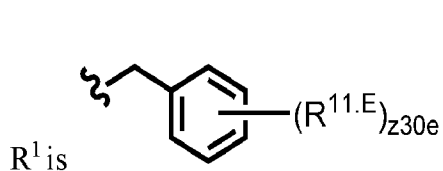


embodiments, R^1 is

. In embodiments, R^1 is

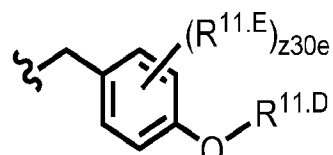


. In embodiments,

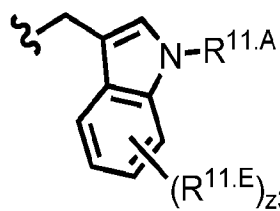


R^1 is

. In embodiments, R^1 is

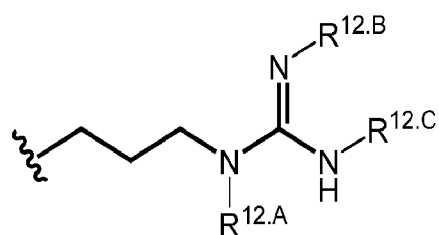


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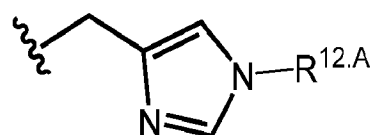


embodiments, R^1 is

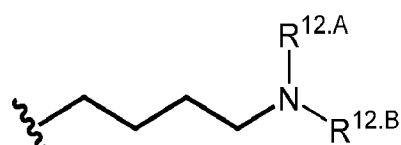
. In embodiments, R^2 is independently hydrogen,



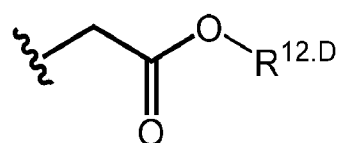
. In embodiments, R^2 is independently



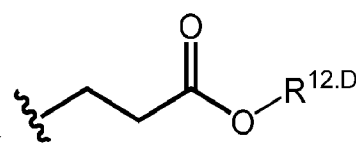
. In embodiments, R^2 is independently



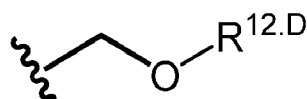
. In embodiments, R^2 is independently



. In embodiments, R^2 is independently

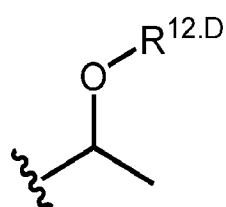


In embodiments, R^2 is independently

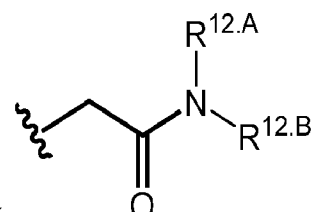


. In embodiments, R^2 is

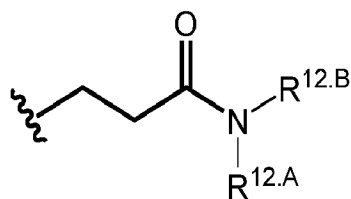
independently



. In embodiments, R^2 is independently

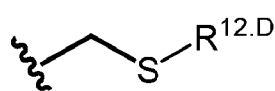


In embodiments, R^2 is independently

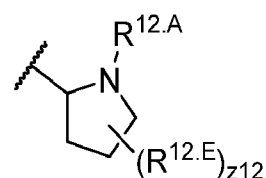


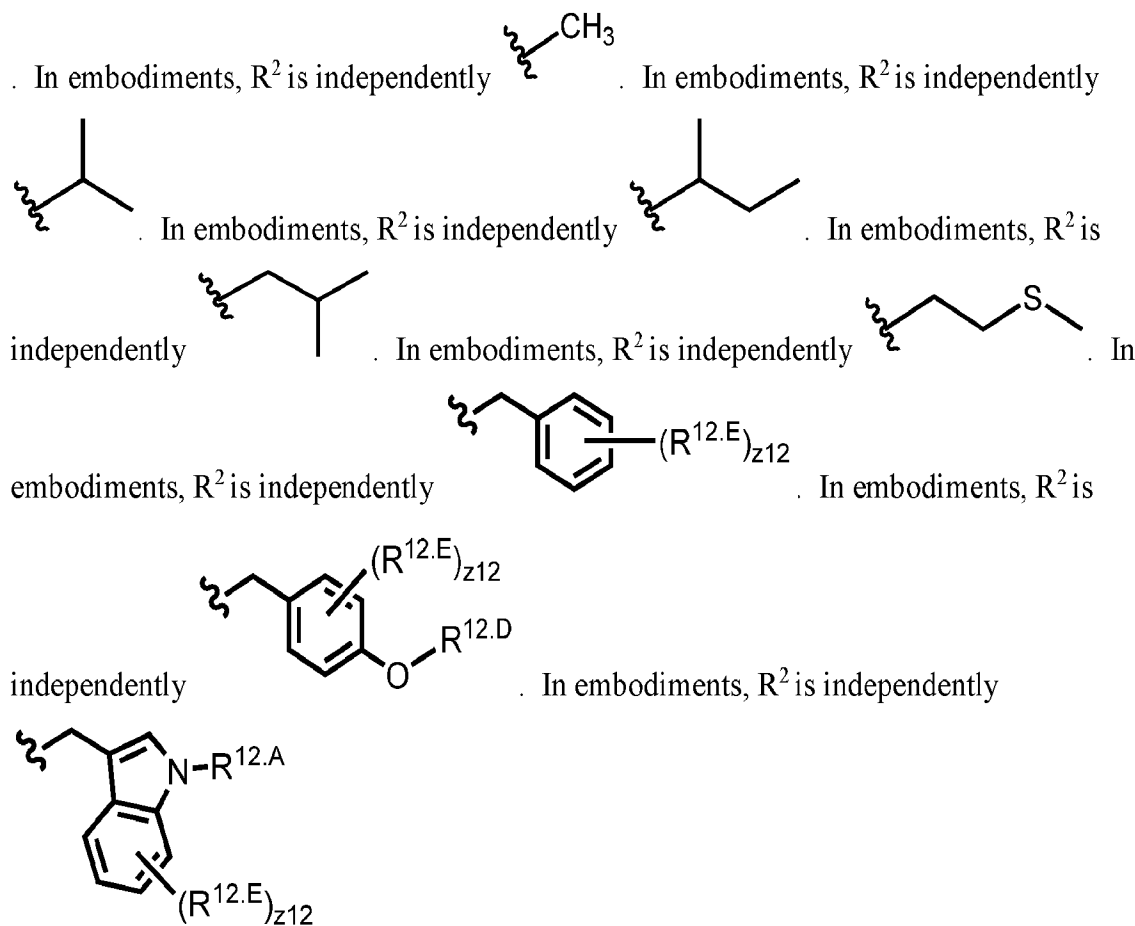
. In embodiments, R^2 is

independently



. In embodiments, R^2 is independently





[0283] $R^{11.A}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0284] $R^{11.B}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0285] $R^{11.C}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0286] $R^{11.D}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0287] $R^{11.E}$ is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-CN$, $-SH$, $-SCH_3$, $-SCF_3$, $-SCHF_2$, $-SCH_2F$, $-SCCl_3$, $-SCHCl_2$, $-SCH_2Cl$, $-SCBr_3$, $-SCHBr_2$, $-SCH_2Br$, $-SCI_3$, $-SCHI_2$, $-SCH_2I$, $-SOCH_3$, $-SO_2CH_3$, $-NH_2$, $-NHCH_3$, $-OH$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0288] In embodiments, $R^{11.A}$, $R^{11.B}$, $R^{11.C}$, and $R^{11.D}$ may independently be any value of R^{11} or hydrogen. In embodiments, $R^{11.E}$ may independently be any value of R^{11} .

[0289] $R^{12.A}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0290] $R^{12.B}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

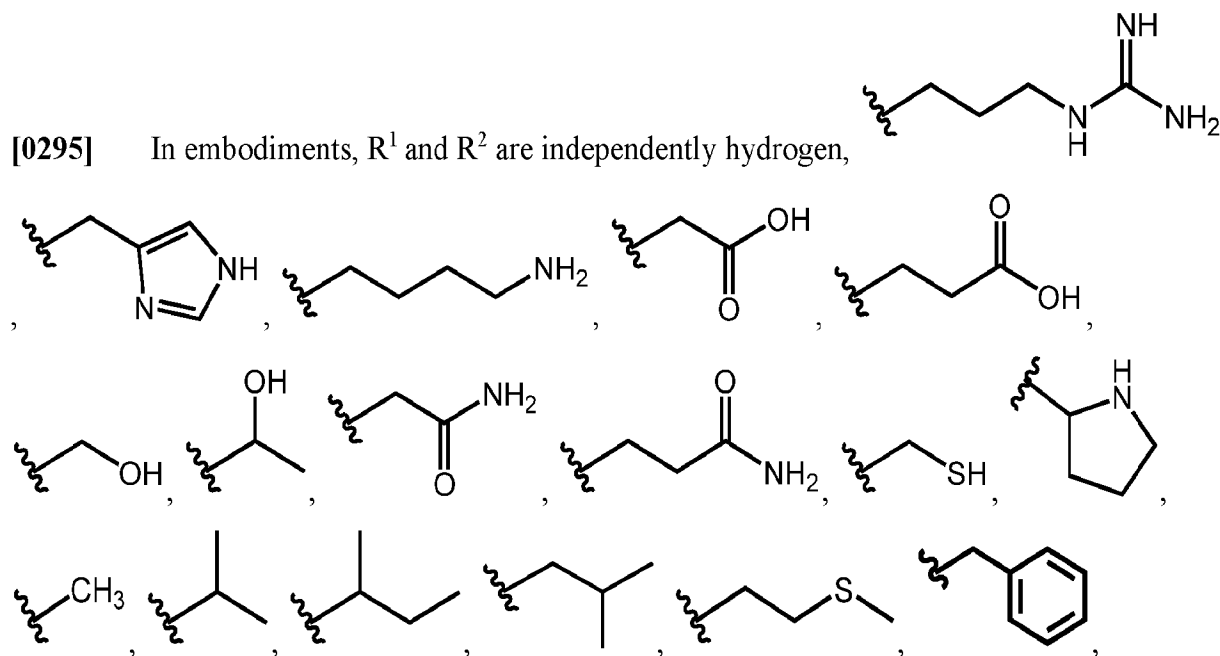
[0291] $R^{12.C}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl,

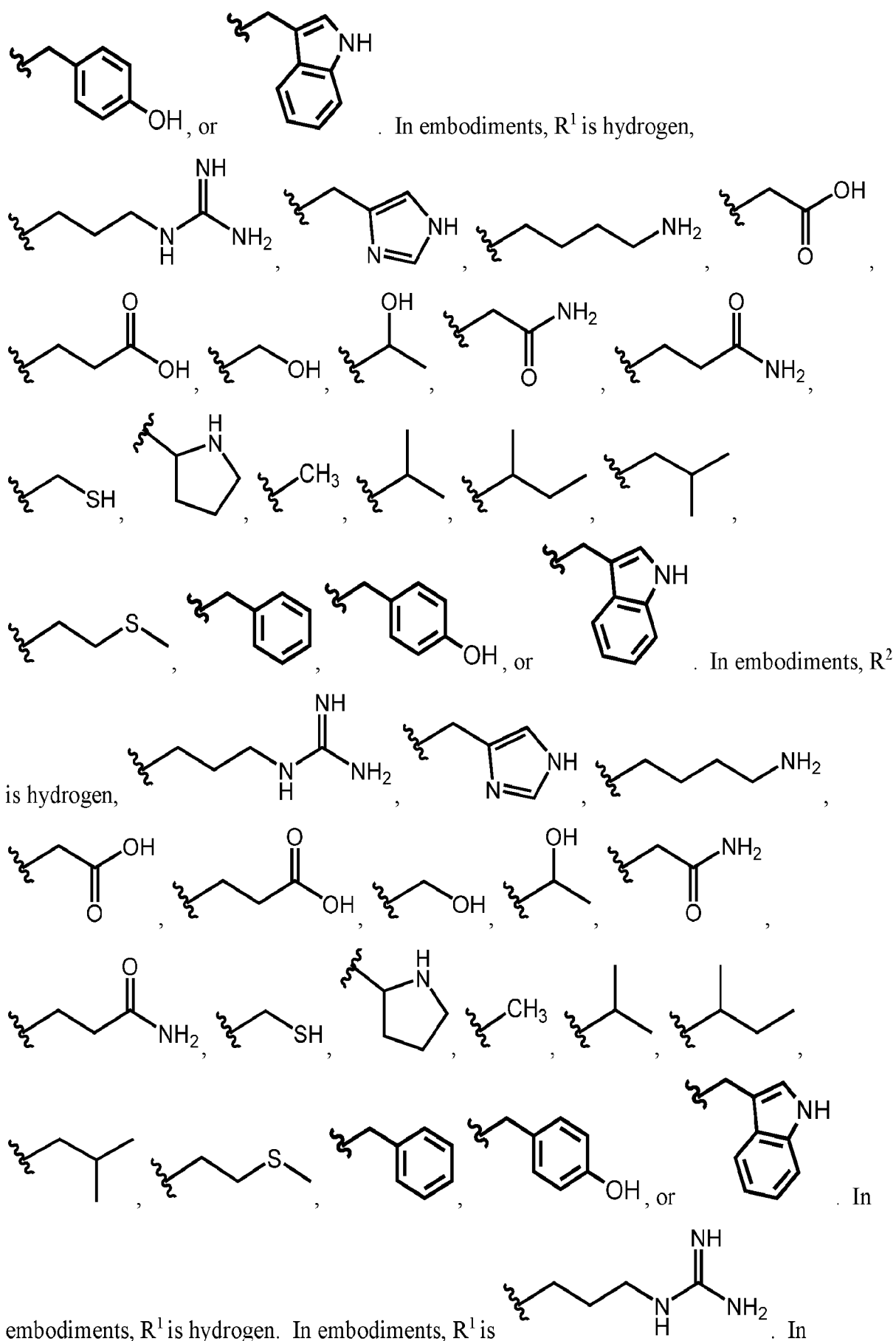
substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

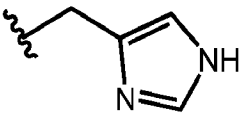
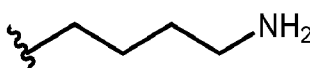
[0292] $R^{12.D}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

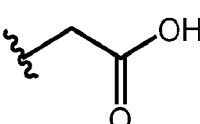
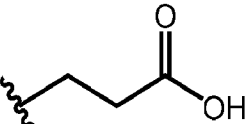
[0293] $R^{12.E}$ is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-CN$, $-SH$, $-SCH_3$, $-SCF_3$, $-SCHF_2$, $-SCH_2F$, $-SCCl_3$, $-SCHCl_2$, $-SCH_2Cl$, $-SCBr_3$, $-SCHBr_2$, $-SCH_2Br$, $-SCI_3$, $-SCHI_2$, $-SCH_2I$, $-SOCH_3$, $-SO_2CH_3$, $-NH_2$, $-NHCH_3$, $-OH$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

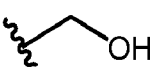
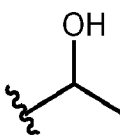
[0294] In embodiments, $R^{12.A}$, $R^{12.B}$, $R^{12.C}$, and $R^{12.D}$ may independently be any value of R^{12} or hydrogen. In embodiments, $R^{12.E}$ may independently be any value of R^{12} .

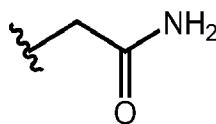
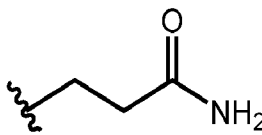


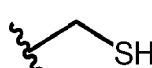
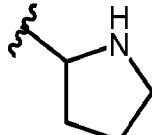
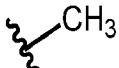


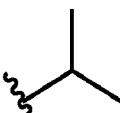
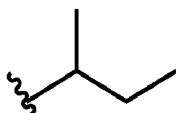
embodiments, R^1 is  . In embodiments, R^1 is  . In

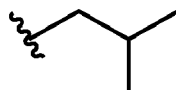
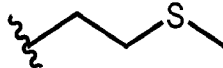
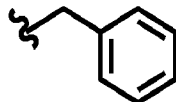
embodiments, R^1 is  . In embodiments, R^1 is  . In

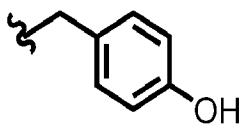
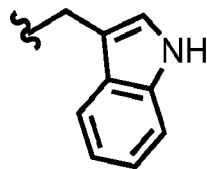
embodiments, R^1 is  . In embodiments, R^1 is  . In embodiments, R^1 is

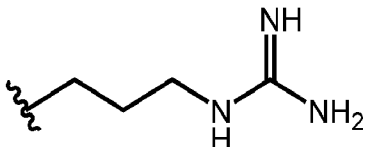
 . In embodiments, R^1 is  . In embodiments, R^1 is

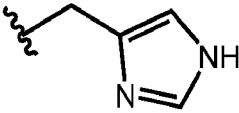
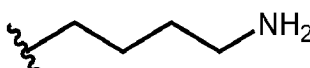
 . In embodiments, R^1 is  . In embodiments, R^1 is  . In

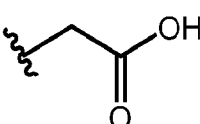
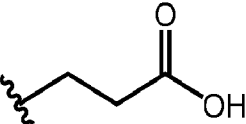
embodiments, R^1 is  . In embodiments, R^1 is  . In embodiments, R^1 is

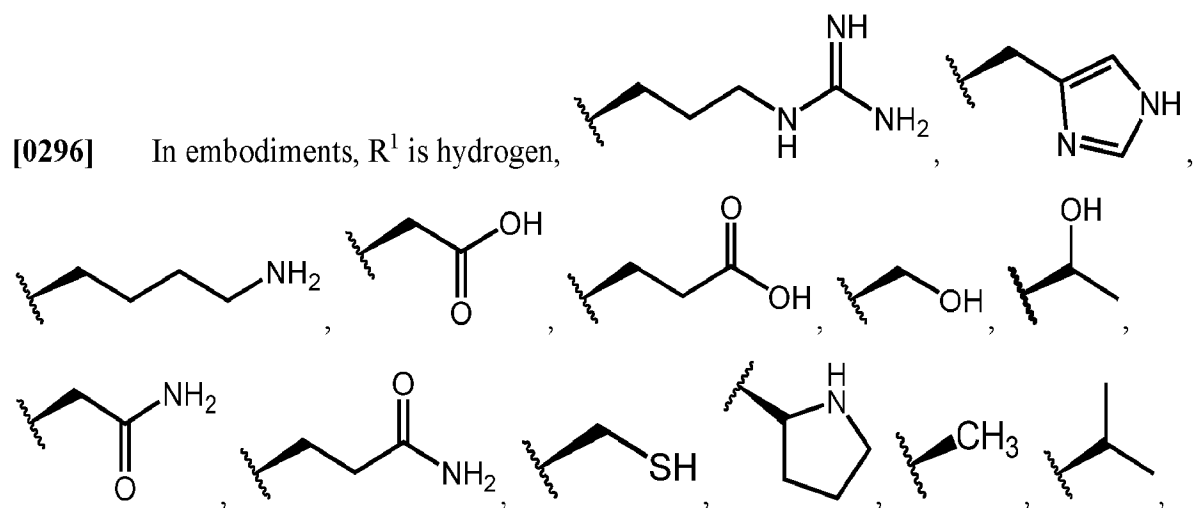
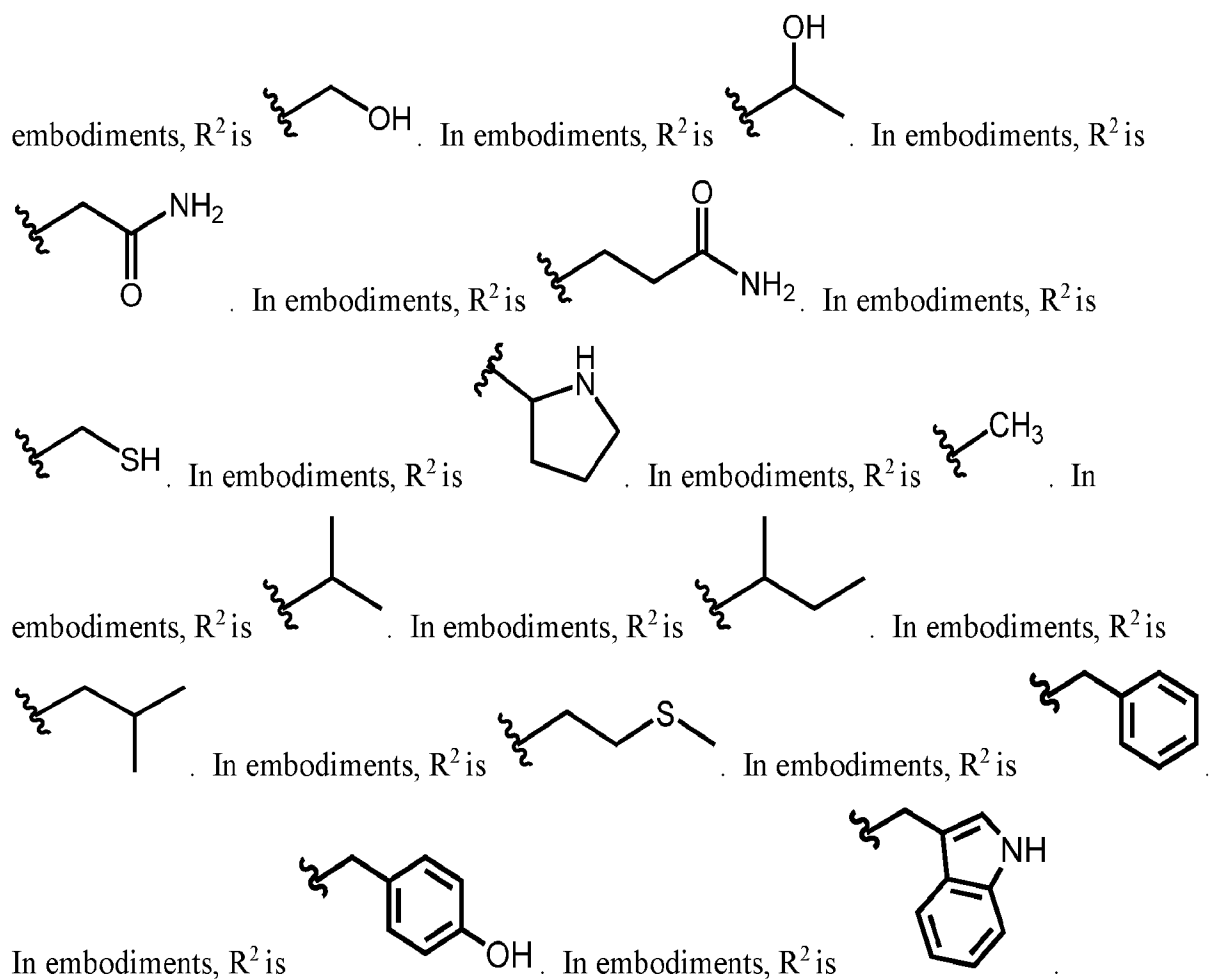
 . In embodiments, R^1 is  . In embodiments, R^1 is  .

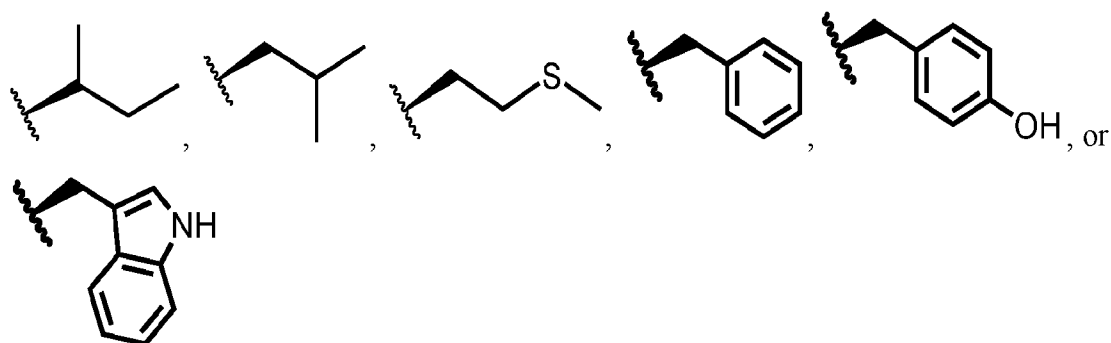
In embodiments, R^1 is  . In embodiments, R^1 is  . In

embodiments, R^2 is hydrogen. In embodiments, R^2 is  . In

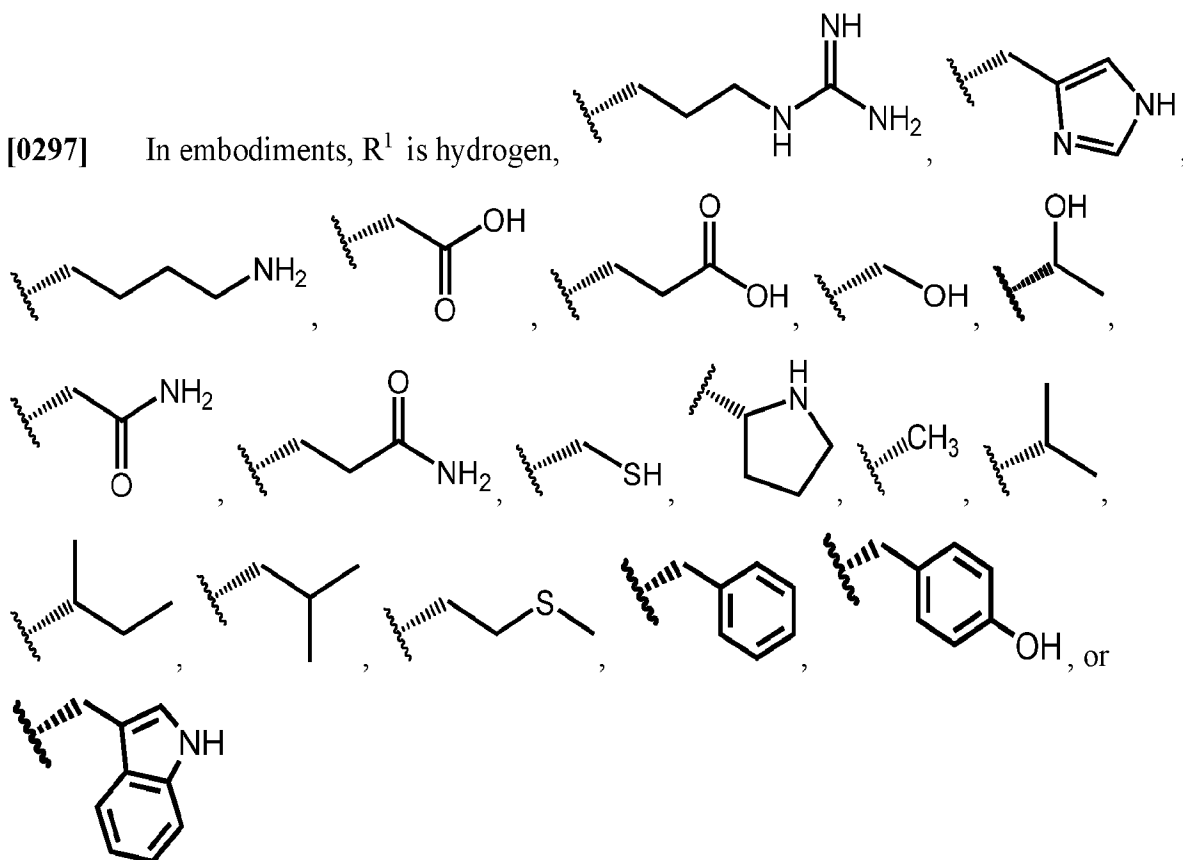
embodiments, R^2 is  . In embodiments, R^2 is  . In

embodiments, R^2 is  . In embodiments, R^2 is  . In

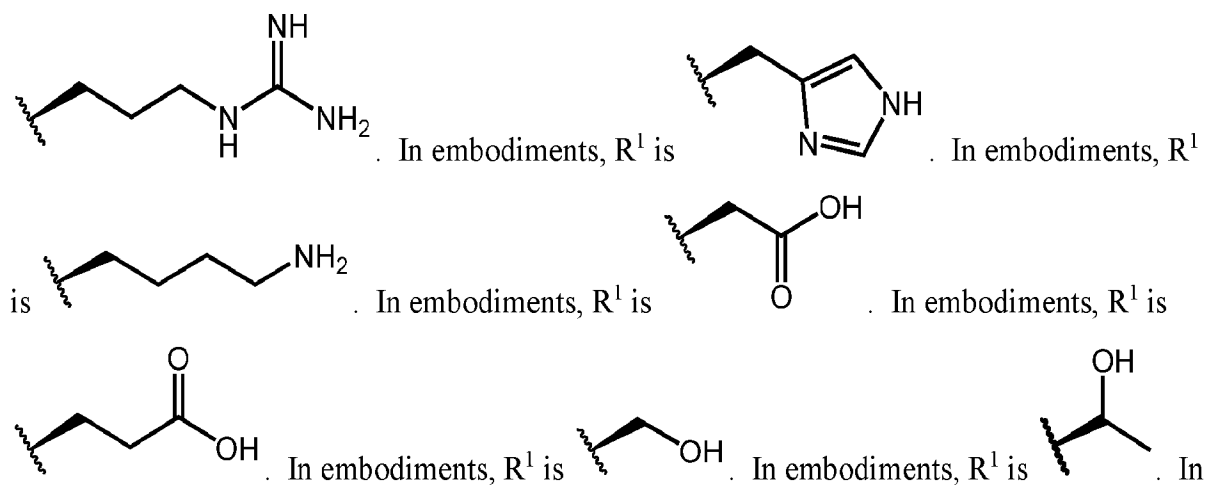


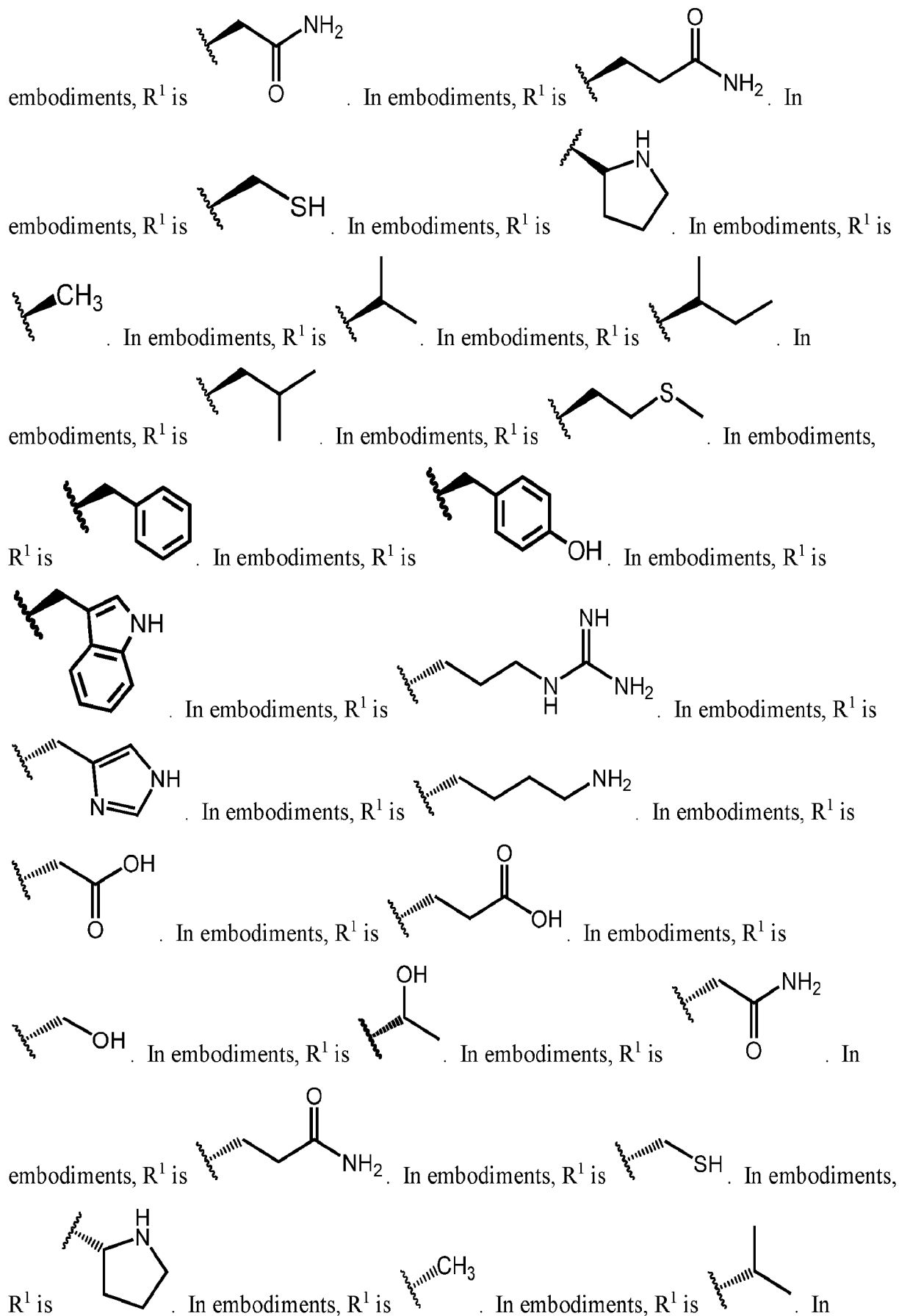


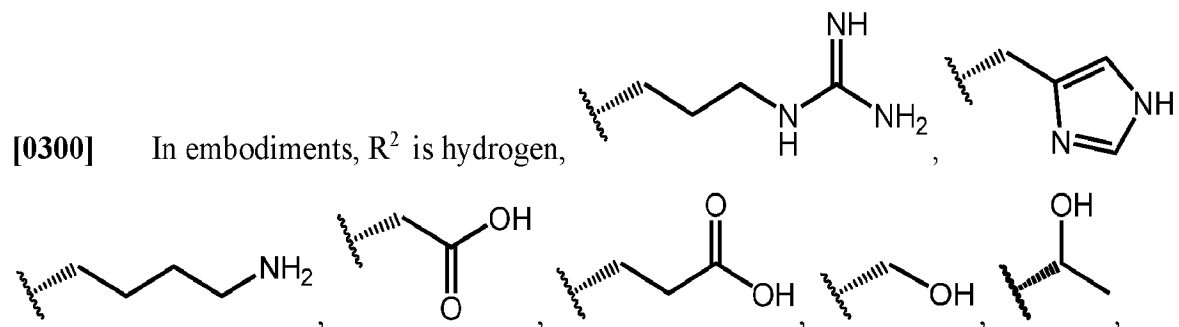
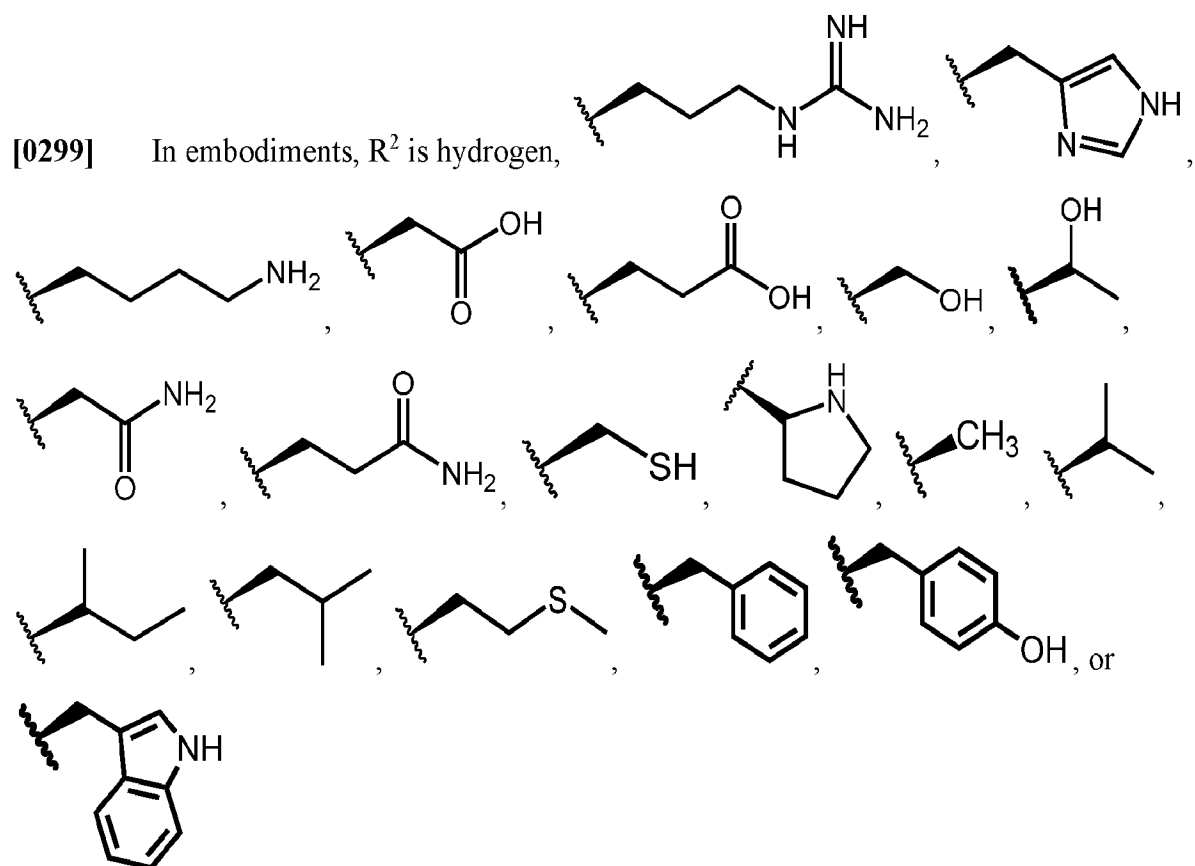
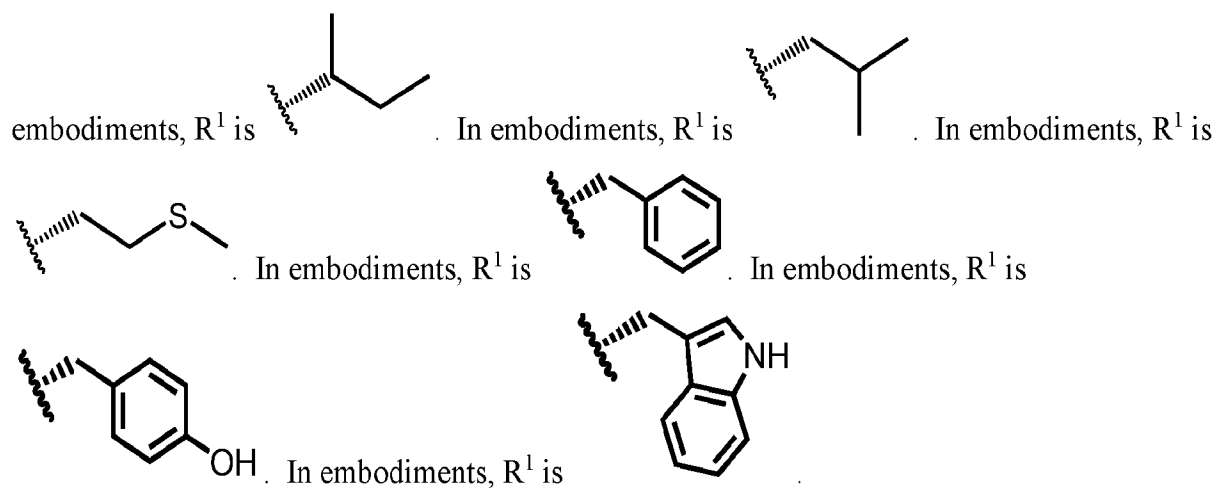
[0297] In embodiments, R¹ is hydrogen,

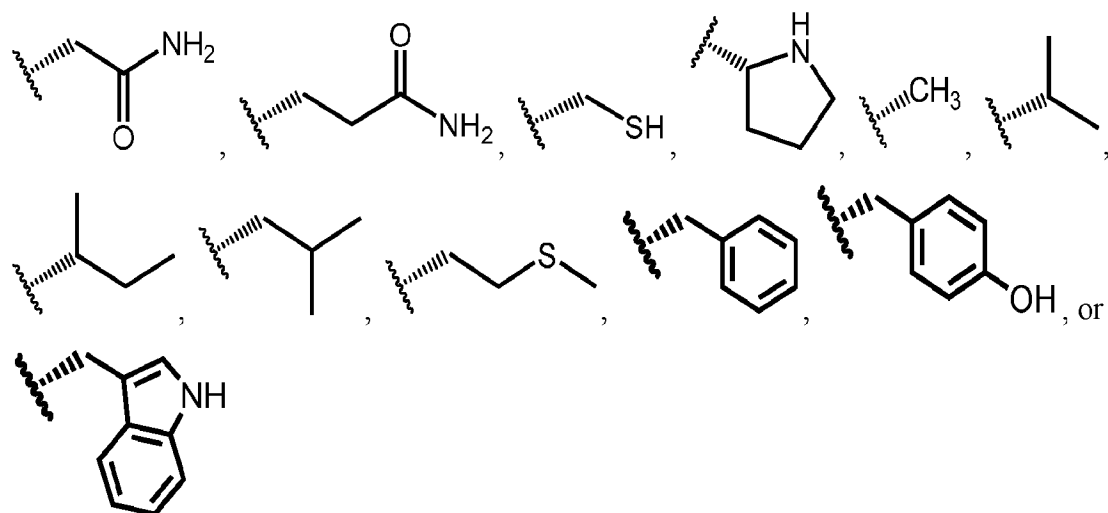


[0298] In embodiments, R¹ is hydrogen. In embodiments, R¹ is

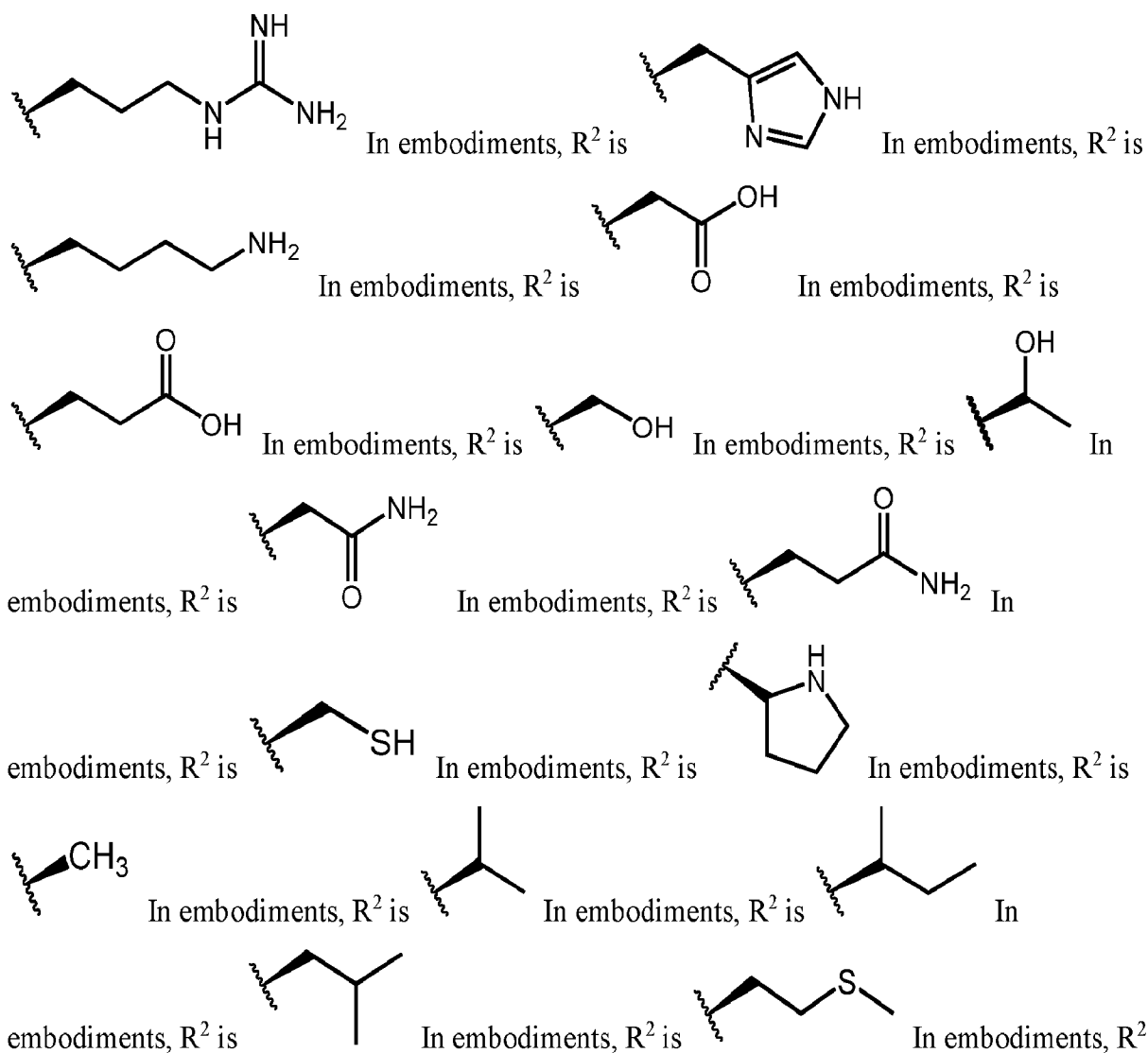


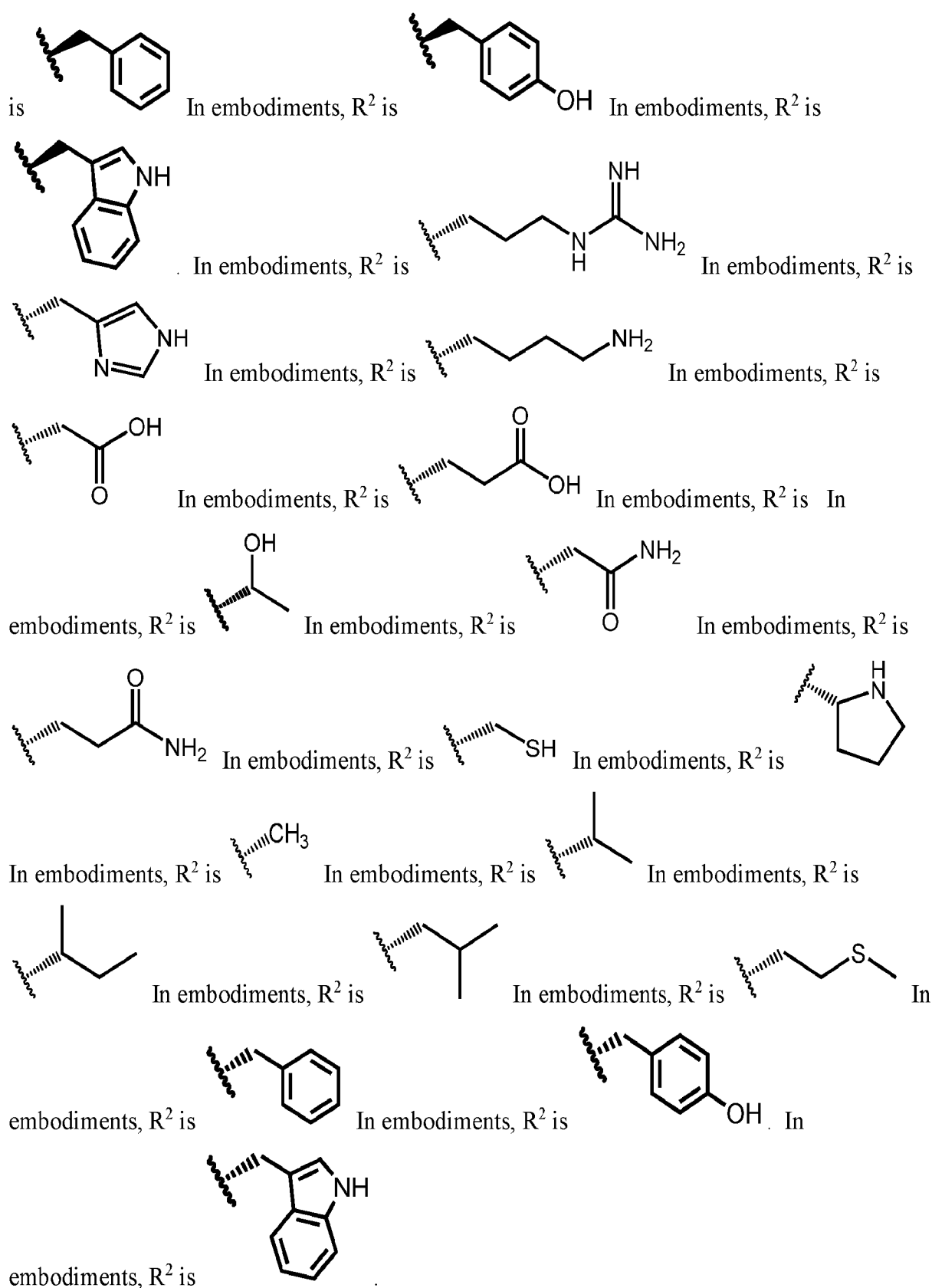






[0301] In embodiments, R^2 is hydrogen. In embodiments, R^2 is





[0302] In embodiments, R¹ is independently a non-natural amino acid side-chain or a natural amino acid side-chain.

[0303] In embodiments, R^2 is independently a non-natural amino acid side-chain or a natural amino acid side-chain.

[0304] In embodiments, R^1 is the side-chain of: exo-cis-3-Aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid hydrochloride, cis-2-Aminocycloheptanecarboxylic acid hydrochloride, cis-6-Amino-3-cyclohexene-1-carboxylic acid hydrochloride, cis-2-Amino-2-methylcyclohexanecarboxylic acid hydrochloride, cis-2-Amino-2-methylcyclopentanecarboxylic acid hydrochloride, 2-(Boc-aminomethyl)benzoic acid, 2-(Boc-amino)octanedioic acid, Boc-4,5-dehydro-Leu-OH (dicyclohexylammonium), Boc-4-(Fmoc-amino)-L-phenylalanine, Boc- β -Homopyr-OH, Boc-(2-indanyl)-Gly-OH, 4-Boc-3-morpholineacetic acid, 4-Boc-3-morpholineacetic acid, Boc-pentafluoro-D-phenylalanine, Boc-pentafluoro-L-phenylalanine, Boc-Phe(2-Br)-OH, Boc-Phe(4-Br)-OH, Boc-D-Phe(4-Br)-OH, Boc-D-Phe(3-Cl)-OH, Boc-Phe(4-NH₂)-OH, Boc-Phe(3-NO₂)-OH, Boc-Phe(3,5-F₂)-OH, 2-(4-Boc-piperazino)-2-(3,4-dimethoxyphenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(2-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(3-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(4-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(4-methoxyphenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-phenylacetic acid purum, 2-(4-Boc-piperazino)-2-(3-pyridyl)acetic acid purum, 2-(4-Boc-piperazino)-2-[4-(trifluoromethyl)phenyl]acetic acid purum, Boc- β -(2-quinolyl)-Ala-OH, N-Boc-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid, Boc- β -(4-thiazolyl)-Ala-OH, Boc- β -(2-thienyl)-D-Ala-OH, Fmoc-N-(4-Boc-aminobutyl)-Gly-OH, Fmoc-N-(2-Boc-aminoethyl)-Gly-OH, Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH, Fmoc-(2-indanyl)-Gly-OH, Fmoc-pentafluoro-L-phenylalanine, Fmoc-Pen(Trt)-OH, Fmoc-Phe(2-Br)-OH, Fmoc-Phe(4-Br)-OH, Fmoc-Phe(3,5-F₂)-OH, Fmoc- β -(4-thiazolyl)-Ala-OH, or Fmoc- β -(2-thienyl)-Ala-OH, 4-(Hydroxymethyl)-D-phenylalanine.

[0305] In embodiments, R^2 is the side-chain of: exo-cis-3-Aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acid hydrochloride, cis-2-Aminocycloheptanecarboxylic acid hydrochloride, cis-6-Amino-3-cyclohexene-1-carboxylic acid hydrochloride, cis-2-Amino-2-methylcyclohexanecarboxylic acid hydrochloride, cis-2-Amino-2-methylcyclopentanecarboxylic acid hydrochloride, 2-(Boc-aminomethyl)benzoic acid, 2-(Boc-amino)octanedioic acid, Boc-4,5-dehydro-Leu-OH (dicyclohexylammonium), Boc-4-(Fmoc-amino)-L-phenylalanine, Boc- β -Homopyr-OH, Boc-(2-indanyl)-Gly-OH, 4-Boc-3-morpholineacetic acid, 4-Boc-3-morpholineacetic acid, Boc-pentafluoro-D-phenylalanine, Boc-pentafluoro-L-phenylalanine,

Boc-Phe(2-Br)-OH, Boc-Phe(4-Br)-OH, Boc-D-Phe(4-Br)-OH, Boc-D-Phe(3-Cl)-OH, Boc-Phe(4-NH₂)-OH, Boc-Phe(3-NO₂)-OH, Boc-Phe(3,5-F₂)-OH, 2-(4-Boc-piperazino)-2-(3,4-dimethoxyphenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(2-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(3-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(4-fluorophenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-(4-methoxyphenyl)acetic acid purum, 2-(4-Boc-piperazino)-2-phenylacetic acid purum, 2-(4-Boc-piperazino)-2-(3-pyridyl)acetic acid purum, 2-(4-Boc-piperazino)-2-[4-(trifluoromethyl)phenyl]acetic acid purum, Boc-β-(2-quinolyl)-Ala-OH, N-Boc-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid, Boc-β-(4-thiazolyl)-Ala-OH, Boc-β-(2-thienyl)-D-Ala-OH, Fmoc-N-(4-Boc-aminobutyl)-Gly-OH, Fmoc-N-(2-Boc-aminoethyl)-Gly-OH, Fmoc-N-(2,4-dimethoxybenzyl)-Gly-OH, Fmoc-(2-indanyl)-Gly-OH, Fmoc-pentafluoro-L-phenylalanine, Fmoc-Pen(Trt)-OH, Fmoc-Phe(2-Br)-OH, Fmoc-Phe(4-Br)-OH, Fmoc-Phe(3,5-F₂)-OH, Fmoc-β-(4-thiazolyl)-Ala-OH, or Fmoc-β-(2-thienyl)-Ala-OH, 4-(Hydroxymethyl)-D-phenylalanine.

[0306] In embodiments, R¹ is a side chain of alanine and R² is a side chain of alanine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of isoleucine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of leucine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of methionine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of valine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of phenylalanine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of tryptophan. In embodiments, R¹ is a side chain of alanine and R² is a side chain of tyrosine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of asparagine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of cysteine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of glutamine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of serine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of threonine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of aspartic acid. In embodiments, R¹ is a side chain of alanine and R² is a side chain of glutamic acid. In embodiments, R¹ is a side chain of alanine and R² is a side chain of arginine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of histidine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of lysine. In embodiments, R¹ is a side chain of alanine and R² is a side chain of glycine (e.g., H). In embodiments, R¹ is a side chain of isoleucine and R² is a side chain of alanine. In embodiments, R¹ is a side chain of isoleucine and

R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of isoleucine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of histidine. In embodiments, R^1 is a side

chain of leucine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of leucine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of methionine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of valine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of aspartic acid. In

embodiments, R^1 is a side chain of valine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of valine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of phenylalanine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of

asparagine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of tryptophan and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of tyrosine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of

phenylalanine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of asparagine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of cysteine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of glutamine

and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of glutamine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of serine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of serine and R^2 is a side chain of glycine (e.g., H). In

embodiments, R^1 is a side chain of threonine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of threonine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side

chain of aspartic acid and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of aspartic acid and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of glutamic acid and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of asparagine. In

embodiments, R^1 is a side chain of arginine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of arginine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of histidine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of lysine and

R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of lysine and R^2 is a side chain of glycine (e.g., H). In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of alanine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of isoleucine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of leucine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of methionine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of valine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of phenylalanine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of tryptophan. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of tyrosine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of asparagine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of cysteine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of glutamine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of serine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of threonine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of aspartic acid. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of glutamic acid. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of arginine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of histidine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of lysine. In embodiments, R^1 is a side chain of glycine (e.g., H) and R^2 is a side chain of glycine (e.g., H).

[0307] In embodiments, R^3 is independently hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

[0308] In embodiments, R^4 is independently hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

[0309] In embodiments, R^5 is independently hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

[0310] In embodiments, R^6 is independently hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

[0311] In embodiments, R^3 is independently hydrogen or substituted or unsubstituted C_1 - C_6 alkyl.

[0312] In embodiments, R^4 is independently hydrogen or substituted or unsubstituted C_1 - C_6 alkyl.

[0313] In embodiments, R^5 is independently hydrogen or substituted or unsubstituted C_1 - C_6 alkyl.

[0314] In embodiments, R^6 is independently hydrogen or substituted or unsubstituted C_1 - C_6 alkyl.

[0315] In embodiments, R^3 is independently hydrogen, substituted methyl, substituted ethyl, or substituted propyl.

[0316] In embodiments, R^4 is independently hydrogen, substituted methyl, substituted ethyl, or substituted propyl.

[0317] In embodiments, R^5 is independently hydrogen, substituted methyl, substituted ethyl, or substituted propyl.

[0318] In embodiments, R^6 is independently hydrogen, substituted methyl, substituted ethyl, or substituted propyl.

[0319] In embodiments, R^3 is independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

[0320] In embodiments, R^4 is independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

[0321] In embodiments, R^5 is independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

[0322] In embodiments, R^6 is independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

[0323] In embodiments, R^1 and R^2 are independently substituted or unsubstituted C_1 - C_6 alkyl or substituted or unsubstituted 2 to 6 membered heteroalkyl; z_1 is an integer from 1 to 5; and R^3 , R^4 , R^5 , and R^6 are independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

[0324] In embodiments, R^1 and R^2 are independently substituted or unsubstituted C_1 - C_4 alkyl; z_1 is an integer from 1 to 5; and R^3 , R^4 , R^5 , and R^6 are independently hydrogen.

[0325] In embodiments, R^1 is independently

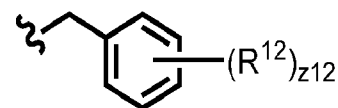


[0326] In embodiments, R^2 is independently

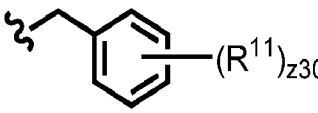
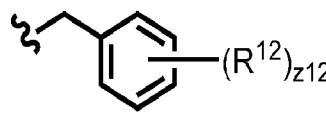


[0327] In embodiments, z_{12} is an integer from 0 to 5. In embodiments, z_{12} is 0. In embodiments, z_{12} is 1. In embodiments, z_{12} is 2. In embodiments, z_{12} is 3. In embodiments, z_{12} is 4. In embodiments, z_{12} is 5.

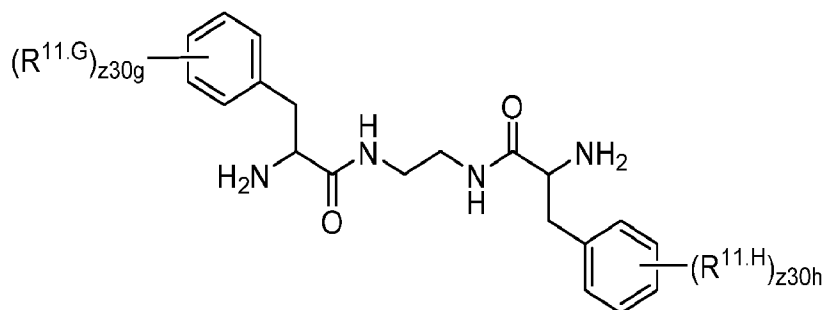
[0328] In embodiments, R^1 is independently



; R^2 is independently hydrogen. z_1 is an integer from 1 to 5; and R^3 , R^4 , R^5 , and R^6 are independently hydrogen.

[0329] In embodiments, R^1 is independently ; R^2 is independently ; z_1 is an integer from 1 to 5; z_{30} and z_{12} are independently 0; and R^3 , R^4 , R^5 , and R^6 are independently hydrogen.

[0330] In embodiments, the compound has the formula



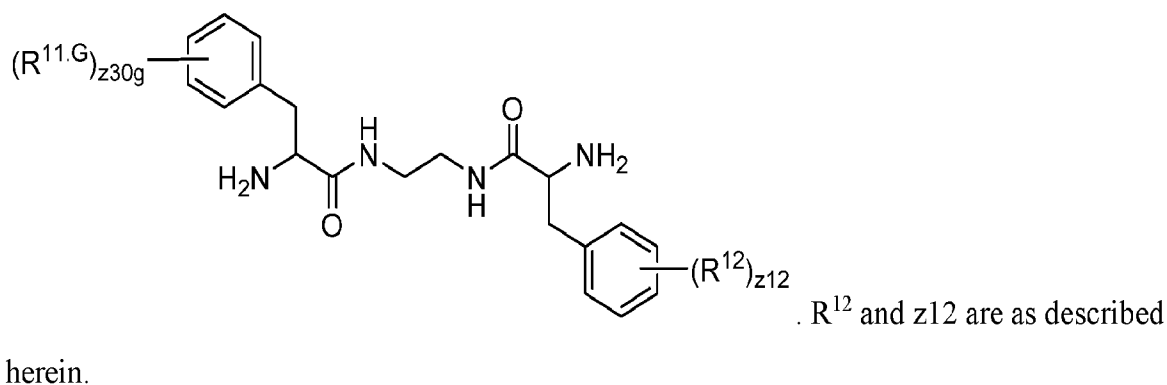
[0331] $R^{11.G}$ and $R^{11.H}$ are independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-CN$, $-SH$, $-SCH_3$, $-SCF_3$, $-SCHF_2$, $-SCH_2F$, $-SCCl_3$, $-SCHCl_2$, $-SCH_2Cl$, $-SCBr_3$, $-SCHBr_2$, $-SCH_2Br$, $-SCl_3$, $-SCHI_2$, $-SCH_2I$, $-SOCH_3$, $-SO_2CH_3$, $-NH_2$, $-NHCH_3$, $-OH$, $-N_3$, substituted or unsubstituted C_1 - C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

[0332] z_{30g} is an integer from 0 to 2. In embodiments, z_{30g} is 0. In embodiments, z_{30g} is 1. In embodiments, z_{30g} is 2.

[0333] z_{30h} is an integer from 0 to 2. In embodiments, z_{30h} is 0. In embodiments, z_{30h} is 1. In embodiments, z_{30h} is 2.

[0334] In embodiments, $R^{11.G}$ and $R^{11.H}$ may independently be any value of R^{11} .

[0335] In embodiments, the compound has the formula



[0336] R^{11.G} is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -SH, -SCH₃, -SCF₃, -SCHF₂, -SCH₂F, -SCCl₃, -SCHCl₂, -SCH₂Cl, -SCBr₃, -SCHBr₂, -SCH₂Br, -SCI₃, -SCHI₂, -SCH₂I, -SOCH₃, -SO₂CH₃, -NH₂, -NHCH₃, -OH, -N₃, substituted or unsubstituted C₁-C₆ alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

[0337] z_{30g} is an integer from 0 to 2. In embodiments, z_{30g} is 0. In embodiments, z_{30g} is 1. In embodiments, z_{30g} is 2.

[0338] In embodiments, R¹² is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -SH, -SCH₃, -SCF₃, -SCHF₂, -SCH₂F, -SCCl₃, -SCHCl₂, -SCH₂Cl, -SCBr₃, -SCHBr₂, -SCH₂Br, -SCI₃, -SCHI₂, -SCH₂I, -SOCH₃, -SO₂CH₃, -NH₂, -NHCH₃, -OH, -N₃, substituted or unsubstituted C₁-C₆ alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl.

[0339] In embodiments, z₁₂ is an integer from 0 to 2. In embodiments, z₁₂ is 0. In embodiments, z₁₂ is 1. In embodiments, z₁₂ is 2.

[0340] In embodiments, R^{11.G} may independently be any value of R¹¹.

[0341] In embodiments, R¹ is independently -L¹⁴-R¹⁵.

[0342] L^{14} is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{14} is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, unsubstituted alkylene, or unsubstituted heteroalkylene. In embodiments, L^{14} is independently substituted or unsubstituted alkylene. In embodiments, L^{14} is independently substituted or unsubstituted methylene. In embodiments, L^{14} is substituted or unsubstituted methylene.

[0343] In embodiments, L^{14} is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, R^{14} -substituted or unsubstituted alkylene, or R^{14} -substituted or unsubstituted heteroalkylene. In embodiments, L^{14} is R^{14} -substituted or unsubstituted alkylene. In embodiments, L^{14} is R^{14} -substituted or unsubstituted heteroalkylene. In embodiments, L^{14} is R^{14} -substituted alkylene. In embodiments, L^{14} is unsubstituted alkylene. In embodiments, L^{14} is R^{14} -substituted methylene. In embodiments, L^{14} is unsubstituted methylene. In embodiments, L^{14} is R^{14} -substituted or unsubstituted methylene.

[0344] R^{14} is independently oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{14} is substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{14} is 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). In embodiments, R^{14} is unsubstituted phenyl. In embodiments, R^{14} is unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{14} is substituted phenyl. In embodiments, R^{14} is substituted 5 to 6 membered

heteroaryl. In embodiments, R^{14} is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R^{14} is independently substituted or unsubstituted phenyl.

[0345] R^{15} is independently hydrogen, oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{15} is independently substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{15} is independently substituted or unsubstituted C_6 - C_{10} aryl. In embodiments, R^{15} is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{15} is independently substituted or unsubstituted phenyl. In embodiments, R^{15} is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{15} is independently substituted C_6 - C_{10} aryl. In embodiments, R^{15} is independently substituted 5 to 10 membered heteroaryl. In embodiments, R^{15} is independently substituted phenyl. In embodiments, R^{15} is independently substituted 5 to 6 membered heteroaryl. In embodiments, R^{15} is independently unsubstituted C_6 - C_{10} aryl. In embodiments, R^{15} is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R^{15} is independently unsubstituted phenyl. In embodiments, R^{15} is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, R^{15} is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R^{15} is independently substituted or unsubstituted phenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted triazinyl,

substituted or unsubstituted naphthyl, substituted or unsubstituted quinoliny, substituted or unsubstituted isoquinoliny, substituted or unsubstituted quinoxaliny, substituted or unsubstituted phthalaziny, substituted or unsubstituted quinazoliny, substituted or unsubstituted cinnoliny, substituted or unsubstituted 1, 8-naphthyridiny, substituted or unsubstituted pyrido[3,2-d]pyrimidiny, substituted or unsubstituted pyrido[4,3-d]pyrimidiny, substituted or unsubstituted pyrido[3,4-b]pyraziny, substituted or unsubstituted pyrido[2,3-b]pyraziny, or substituted or unsubstituted pteridiny. In embodiments, R^{15} is independently unsubstituted phenyl, unsubstituted pyridyl, unsubstituted pyridaziny, unsubstituted pyrimidiny, unsubstituted pyraziny, unsubstituted triaziny, unsubstituted naphthyl, unsubstituted quinoliny, unsubstituted isoquinoliny, unsubstituted quinoxaliny, unsubstituted phthalaziny, unsubstituted quinazoliny, unsubstituted cinnoliny, unsubstituted 1, 8-naphthyridiny, unsubstituted pyrido[3,2-d]pyrimidiny, unsubstituted pyrido[4,3-d]pyrimidiny, unsubstituted pyrido[3,4-b]pyraziny, unsubstituted pyrido[2,3-b]pyraziny, or unsubstituted pteridiny.

[0346] In embodiments, R^2 is independently $-L^{16}-R^{17}$.

[0347] L^{16} is a bond, $-NH-$, $-O-$, $-S-$, $-SO_2-$, $-C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, $-C(O)O-$, $-OC(O)-$, $-SO_2NH-$, $-NHSO_2-$, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene. In embodiments, L^{16} is a bond, $-NH-$, $-O-$, $-S-$, $-SO_2-$, $-C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, $-C(O)O-$, $-OC(O)-$, $-SO_2NH-$, $-NHSO_2-$, unsubstituted alkylene, or unsubstituted heteroalkylene. In embodiments, L^{16} is independently substituted or unsubstituted alkylene. In embodiments, L^{16} is independently substituted or unsubstituted methylene. In embodiments, L^{16} is substituted or unsubstituted methylene.

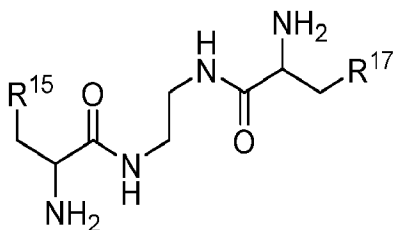
[0348] In embodiments, L^{16} is a bond, $-NH-$, $-O-$, $-S-$, $-SO_2-$, $-C(O)-$, $-C(O)NH-$, $-NHC(O)-$, $-NHC(O)NH-$, $-C(O)O-$, $-OC(O)-$, $-SO_2NH-$, $-NHSO_2-$, R^{16} -substituted or unsubstituted alkylene, or R^{16} -substituted or unsubstituted heteroalkylene. In embodiments, L^{16} is R^{16} -substituted or unsubstituted alkylene. In embodiments, L^{16} is R^{16} -substituted or unsubstituted heteroalkylene. In embodiments, L^{16} is R^{16} -substituted alkylene. In embodiments, L^{16} is unsubstituted alkylene. In embodiments, L^{16} is R^{16} -substituted methylene. In embodiments, L^{16} is unsubstituted methylene. In embodiments, L^{16} is R^{16} -substituted or unsubstituted methylene.

[0349] R^{16} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, -

SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁶ is substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁶ is 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). In embodiments, R¹⁶ is unsubstituted phenyl. In embodiments, R¹⁶ is unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is substituted phenyl. In embodiments, R¹⁶ is substituted 5 to 6 membered heteroaryl. In embodiments, R¹⁶ is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R¹⁶ is independently substituted or unsubstituted phenyl.

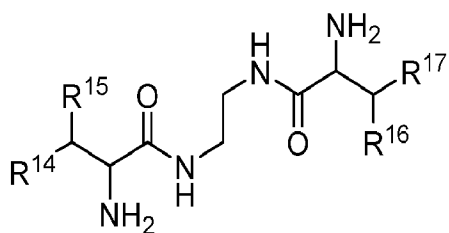
[0350] R¹⁷ is independently hydrogen, oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁷ is independently substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

membered). In embodiments, R¹⁷ is independently substituted or unsubstituted C₆-C₁₀ aryl. In embodiments, R¹⁷ is independently substituted or unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹⁷ is independently substituted or unsubstituted phenyl. In embodiments, R¹⁷ is independently substituted or unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁷ is independently substituted C₆-C₁₀ aryl. In embodiments, R¹⁷ is independently substituted 5 to 10 membered heteroaryl. In embodiments, R¹⁷ is independently substituted phenyl. In embodiments, R¹⁷ is independently substituted 5 to 6 membered heteroaryl. In embodiments, R¹⁷ is independently unsubstituted C₆-C₁₀ aryl. In embodiments, R¹⁷ is independently unsubstituted 5 to 10 membered heteroaryl. In embodiments, R¹⁷ is independently unsubstituted phenyl. In embodiments, R¹⁷ is independently unsubstituted 5 to 6 membered heteroaryl. In embodiments, R¹⁷ is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R¹⁷ is independently substituted or unsubstituted phenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted naphthyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted phthalazinyl, substituted or unsubstituted quinazolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted 1, 8-naphthyridinyl, substituted or unsubstituted pyrido[3,2-d]pyrimidinyl, substituted or unsubstituted pyrido[4,3-d]pyrimidinyl, substituted or unsubstituted pyrido[3,4-b]pyrazinyl, substituted or unsubstituted pyrido[2,3-b]pyrazinyl, or substituted or unsubstituted pteridinyl. In embodiments, R¹⁷ is independently unsubstituted phenyl, unsubstituted pyridyl, unsubstituted pyridazinyl, unsubstituted pyrimidinyl, unsubstituted pyrazinyl, unsubstituted triazinyl, unsubstituted naphthyl, unsubstituted quinolinyl, unsubstituted isoquinolinyl, unsubstituted quinoxalinyl, unsubstituted phthalazinyl, unsubstituted quinazolinyl, unsubstituted cinnolinyl, unsubstituted 1, 8-naphthyridinyl, unsubstituted pyrido[3,2-d]pyrimidinyl, unsubstituted pyrido[4,3-d]pyrimidinyl, unsubstituted pyrido[3,4-b]pyrazinyl, unsubstituted pyrido[2,3-b]pyrazinyl, or unsubstituted pteridinyl.

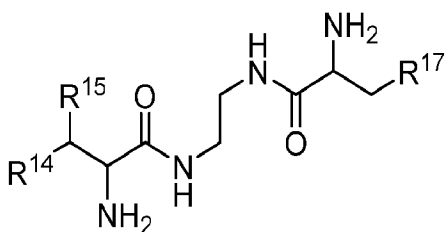


[0351] In embodiments, the compound is

or

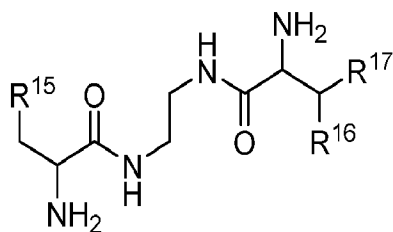


. R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are as described herein.

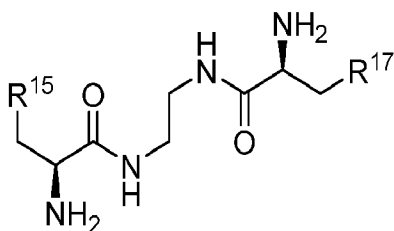


[0352] In embodiments, the compound is

or

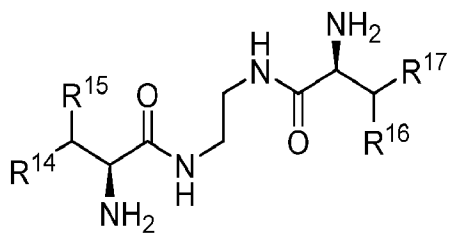


. R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are as described herein.

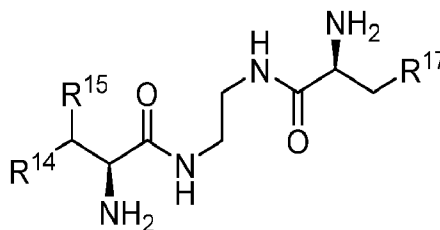


[0353] In embodiments, the compound is

or

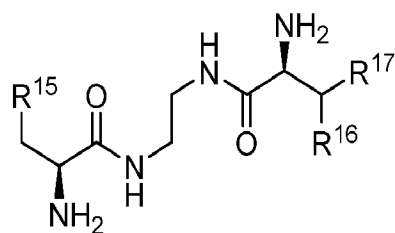


. R¹⁴, R¹⁵, R¹⁶, and R¹⁷ are as described herein.

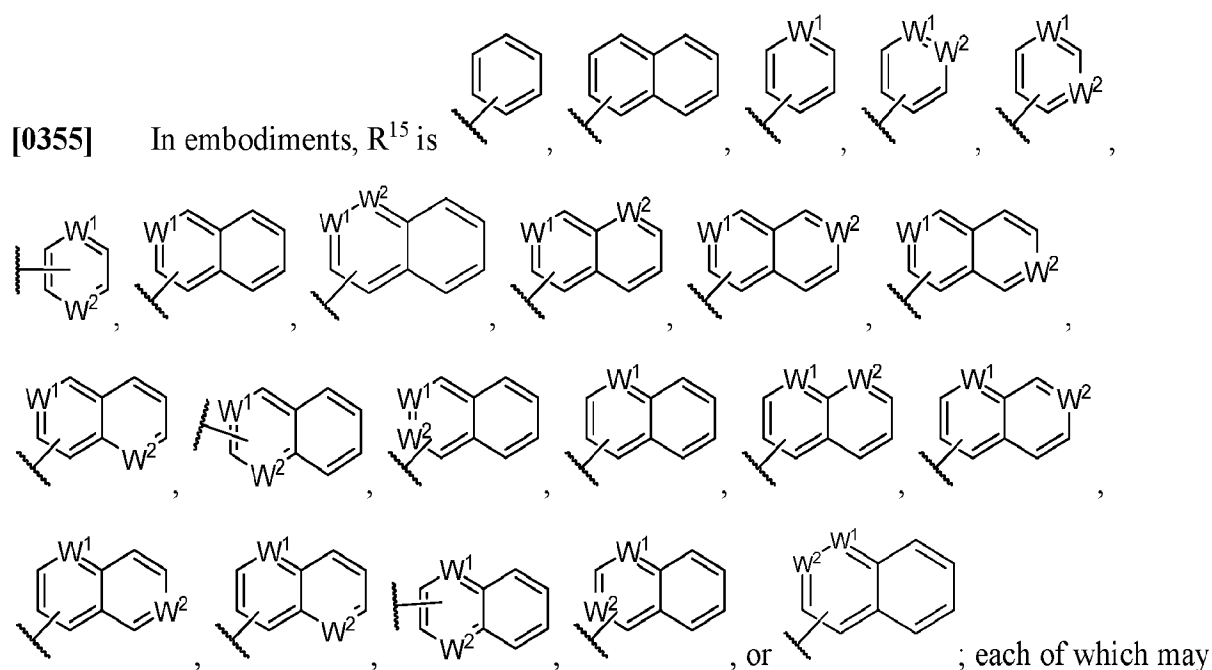


[0354] In embodiments, the compound is

or



. R^{14} , R^{15} , R^{16} , and R^{17} are as described herein.



be optionally substituted with at least one substituent independently selected from the group consisting of

halogen, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CF}_3$, $-\text{Cl}_3$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{I}$, $-\text{CHCl}_2$, $-\text{CHBr}_2$, $-\text{CHF}_2$, $-\text{CHI}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{COOH}$, $-\text{CONH}_2$, $-\text{NO}_2$, $-\text{SH}$, $-\text{SO}_3\text{H}$, $-\text{SO}_4\text{H}$, $-\text{SO}_2\text{NH}_2$, $-\text{NHNH}_2$, $-\text{ONH}_2$, $-\text{NHC(O)NHNH}_2$, $-\text{NHC(O)NH}_2$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC(O)H}$, $-\text{NHC(O)OH}$, $-\text{NHOH}$, $-\text{OCCl}_3$, $-\text{OCF}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{OCH}_2\text{F}$, $-\text{N}_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or

unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁵ is monosubstituted. In embodiments, R¹⁵ is disubstituted.

[0356] In embodiments, a substituted R¹⁵ is substituted with at least one substituent independently selected from the group consisting of halogen, optionally substituted -OH, optionally substituted -NH₂, optionally substituted -COOH, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0357] W¹ and W² are independently -CH=; -N=; or -C= directly bonded to halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

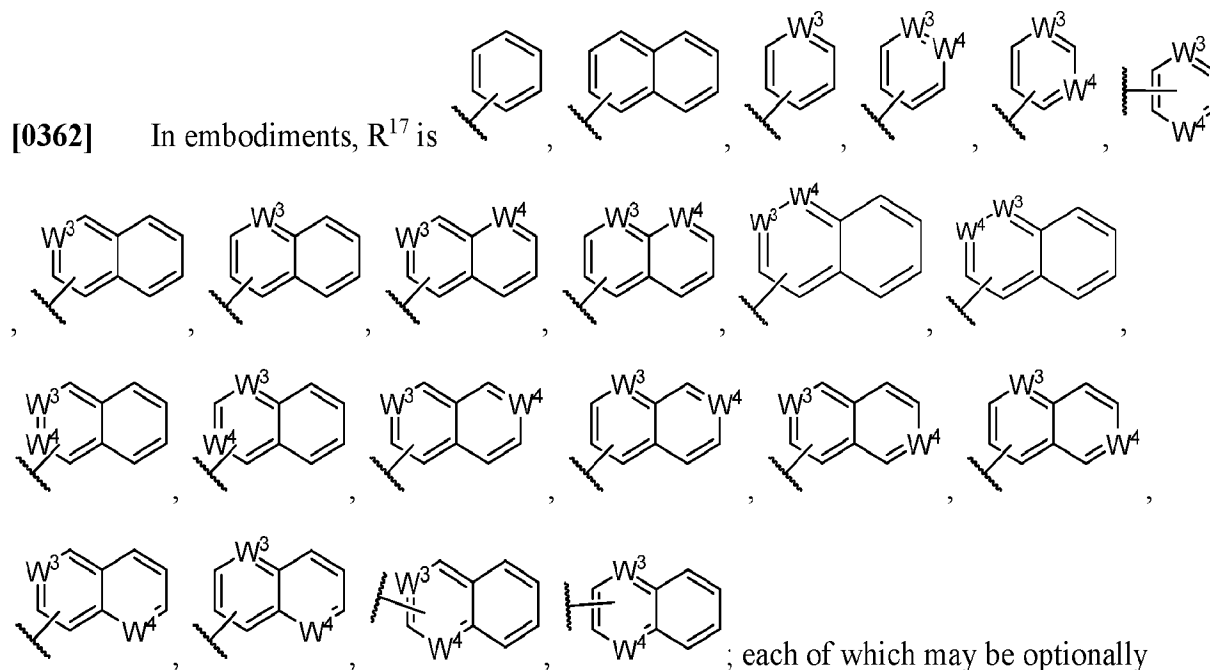
[0358] In embodiments, R¹⁴ is substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0359] In embodiments, R¹⁴ is 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).

[0360] In embodiments, R¹⁴ is substituted with at least one substituent independently selected from the group consisting of halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I,

-CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁴ is monosubstituted. In embodiments, R¹⁴ is disubstituted.

[0361] In embodiments, a substituted R¹⁴ is substituted with at least one substituent independently selected from the group consisting of: halogen, optionally substituted -OH, optionally substituted -NH₂, optionally substituted -COOH, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).



substituted with at least one substituent independently selected from the group consisting of halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CH

I₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R¹⁷ is monosubstituted. In embodiments, R¹⁷ is disubstituted.

[0363] In embodiments, a substituted R¹⁷ is substituted with at least one substituent independently selected from the group consisting of halogen, optionally substituted -OH, optionally substituted -NH₂, optionally substituted -COOH, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0364] W³ and W⁴ are independently -CH=; -N=; or -C= directly bonded to halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, or C₁-C₄), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀, C₁₀, or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0365] In embodiments, R^{16} is substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

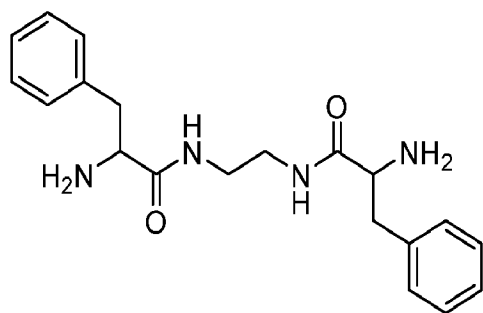
[0366] In embodiments, R^{14} is unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0367] In embodiments, R^{16} is substituted with at least one substituent independently selected from the group consisting of

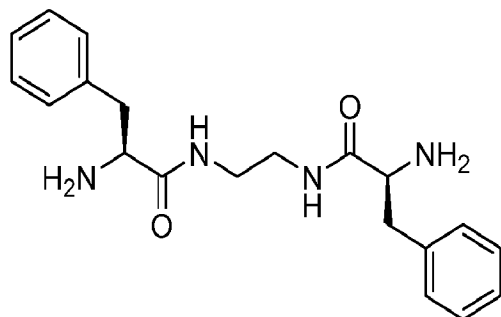
halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered). In embodiments, R^{16} is monosubstituted. In embodiments, R^{16} is disubstituted.

[0368] In embodiments, a substituted R^{16} is substituted with at least one substituent independently selected from the group consisting of halogen, optionally substituted $-OH$, optionally substituted $-NH_2$, optionally substituted $-COOH$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , or C_1 - C_4), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, or 2 to 4 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} , C_{10} , or phenyl), and substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

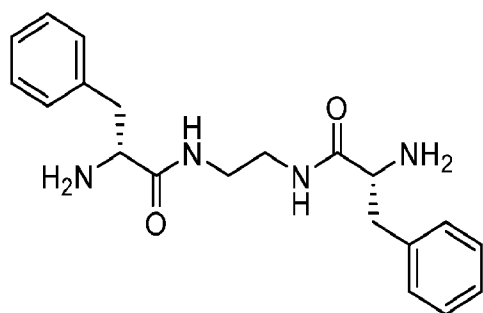
[0369] In embodiments, the compound has the formula



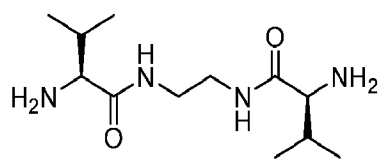
. In embodiments, the compound has the formula



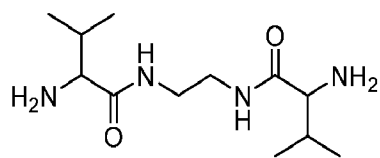
(Q34). In embodiments, the compound has the formula



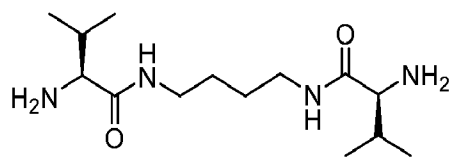
. In embodiments, the compound has the formula



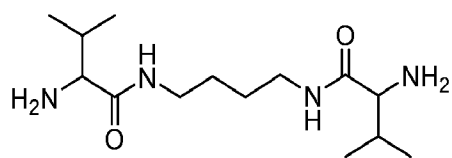
(C2). In embodiments, the compound has the formula



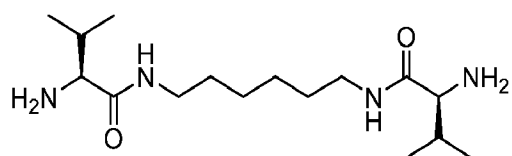
. In embodiments, the compound has the formula



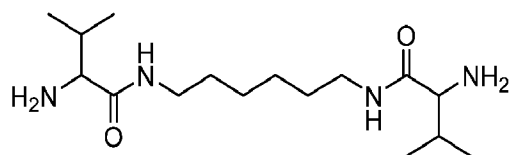
(C3). In embodiments, the compound has the formula



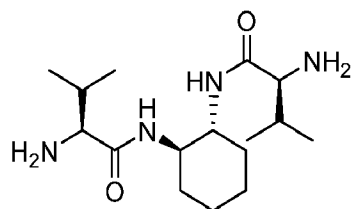
. In embodiments, the compound has the formula



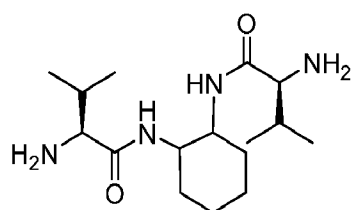
(C4). In embodiments, the compound has the formula



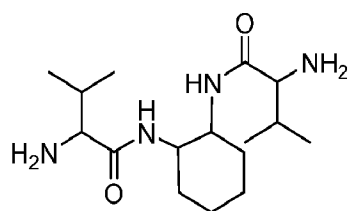
. In embodiments, the compound has the formula



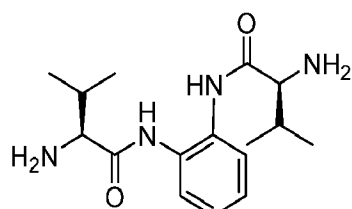
(C5). In embodiments, the compound has the formula



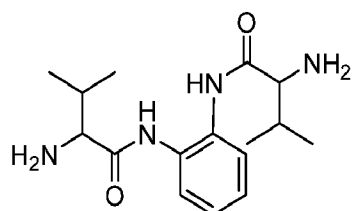
. In embodiments, the compound has the formula



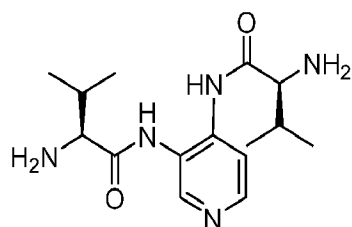
. In embodiments, the compound has the formula



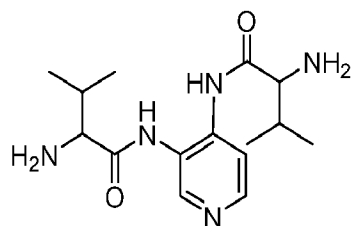
(C6). In embodiments, the compound has the formula



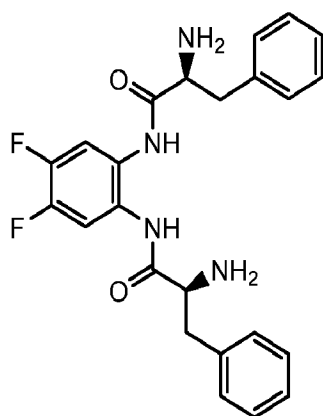
. In embodiments, the compound has the formula



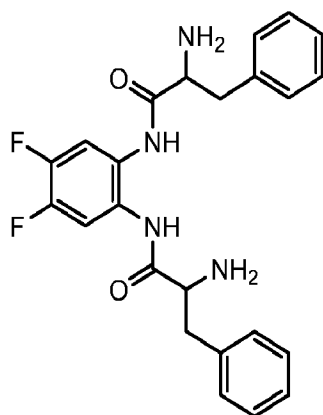
(C7). In embodiments, the compound has the formula



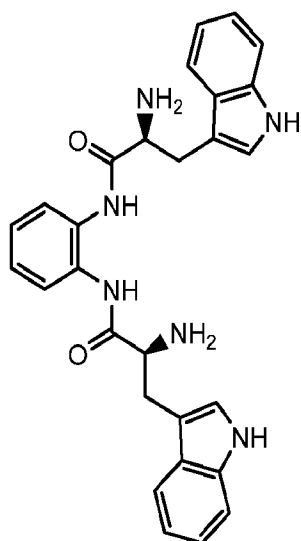
. In embodiments, the compound has the formula



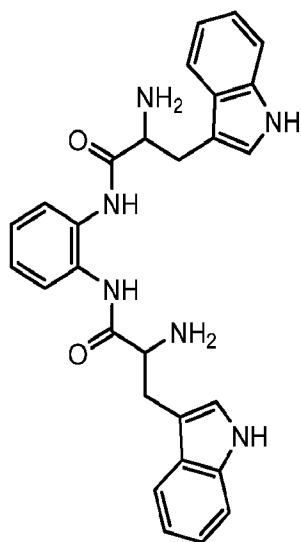
(C11). In embodiments, the compound has the formula



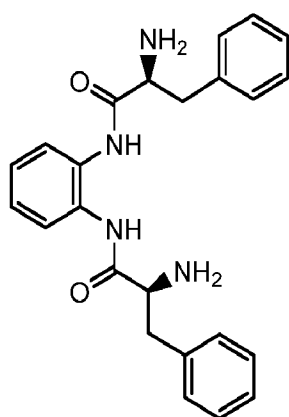
. In embodiments, the compound has the formula



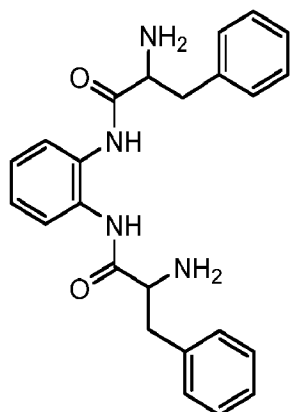
(C12). In embodiments, the compound has the formula



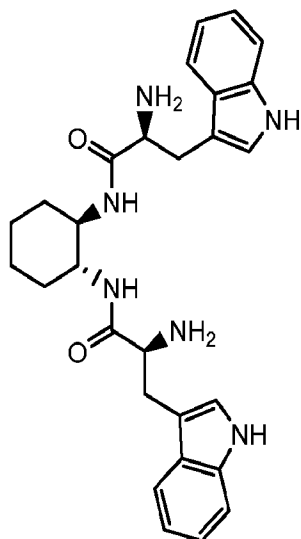
. In embodiments, the compound has the formula



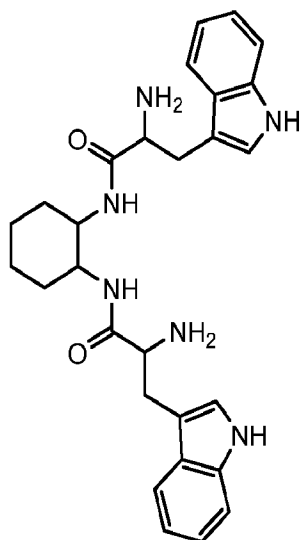
(C13). In embodiments, the compound has the formula



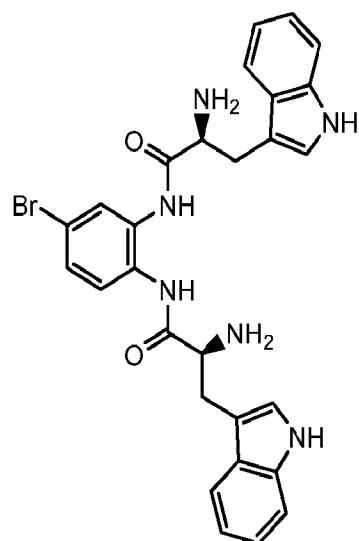
. In embodiments, the compound has the formula



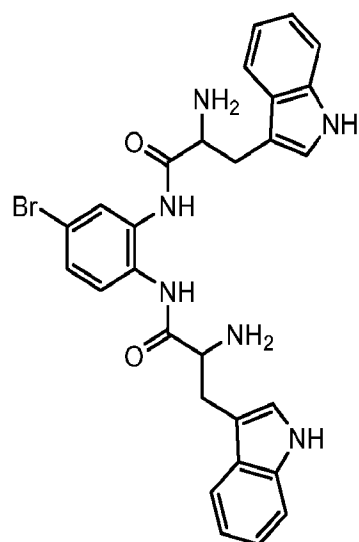
(C14). In embodiments, the compound has the formula



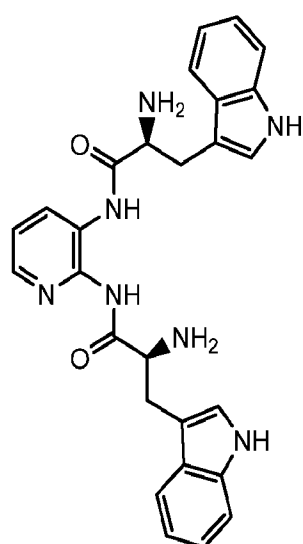
. In embodiments, the compound has the formula



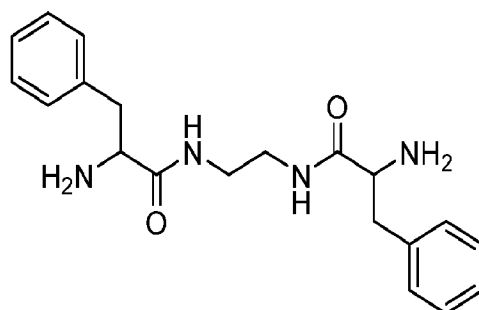
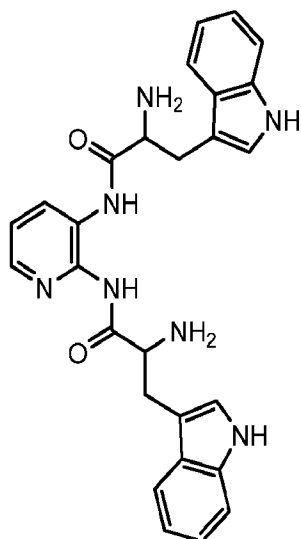
(C15). In embodiments, the compound has the formula



. In embodiments, the compound has the formula

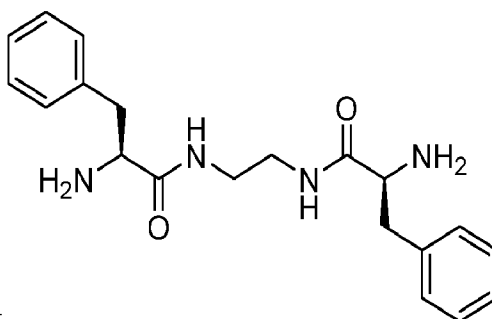


(C16). In embodiments, the compound has the formula



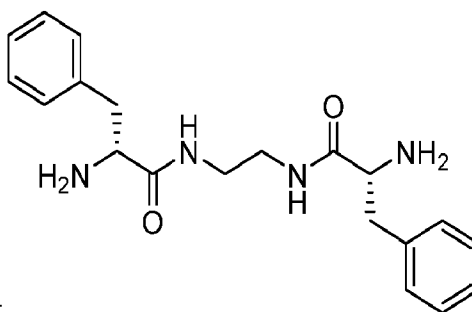
[0370] In embodiments, the compound is not

. In



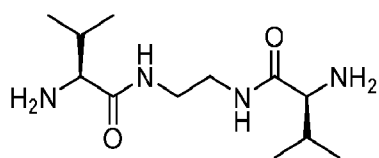
embodiments, the compound is not

(Q34). In



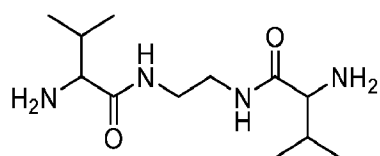
embodiments, the compound is not

. In embodiments, the

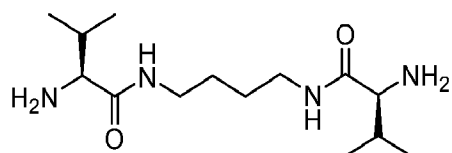


compound is not

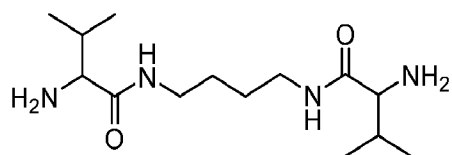
(C2). In embodiments, the compound is not



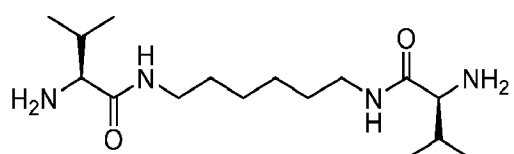
. In embodiments, the compound is not



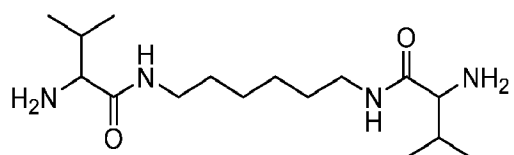
(C3). In embodiments, the compound is not



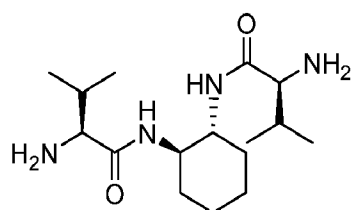
. In embodiments, the compound is not



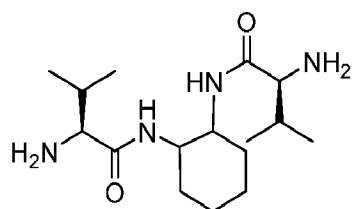
(C4). In embodiments, the compound is not



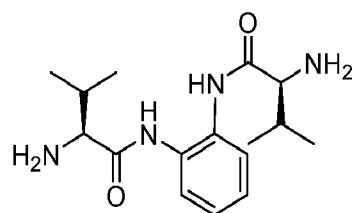
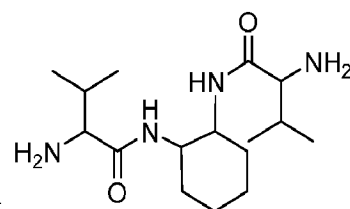
. In embodiments, the compound is not



(C5). In embodiments, the compound is not

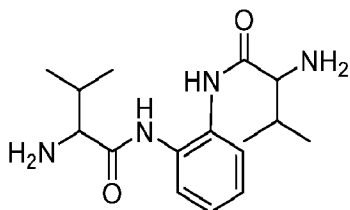


. In embodiments, the compound is not



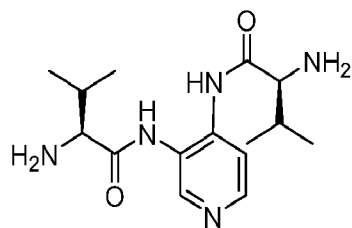
In embodiments, the compound is not

(C6). In embodiments, the

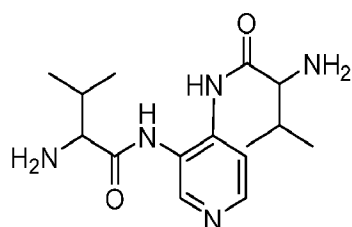


compound is not

. In embodiments, the compound is not

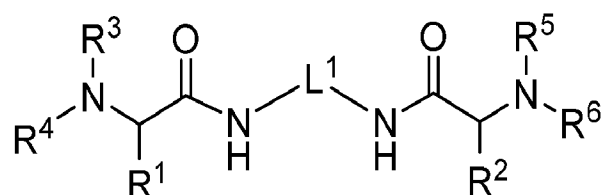


(C7). In embodiments, the compound is not



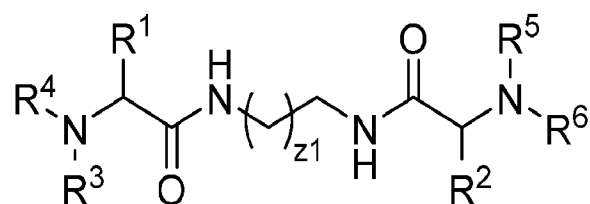
[0371] In embodiments, the compound is not any of the compounds set forth in WO 2006073456. In embodiments, the compound is not a compound set forth in WO 2006073456.

[0372] In embodiments, the compound has the formula:



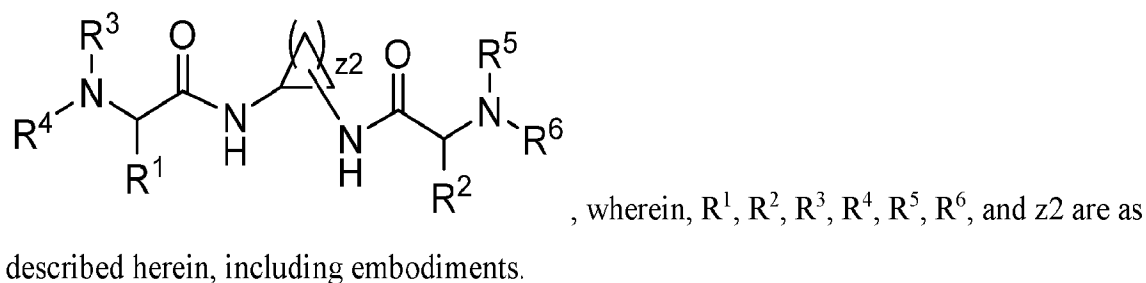
, wherein, L^1 , R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as described herein, including embodiments.

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

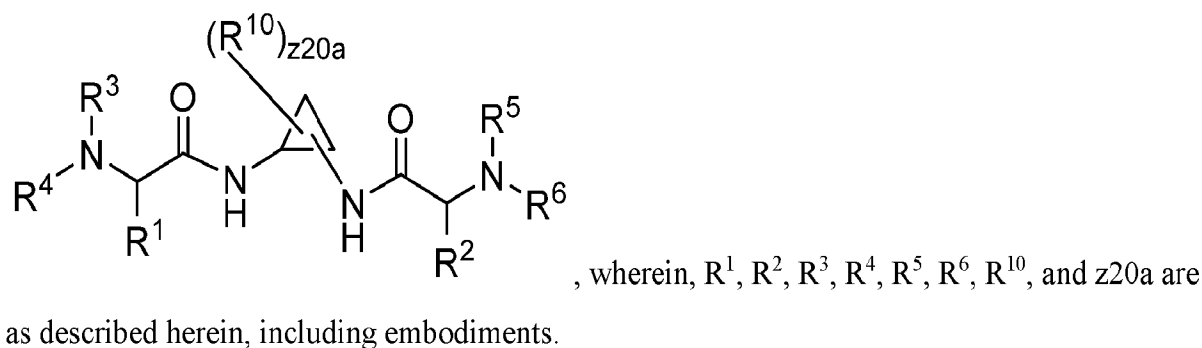


, wherein, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and $z1$ are as described herein, including embodiments.

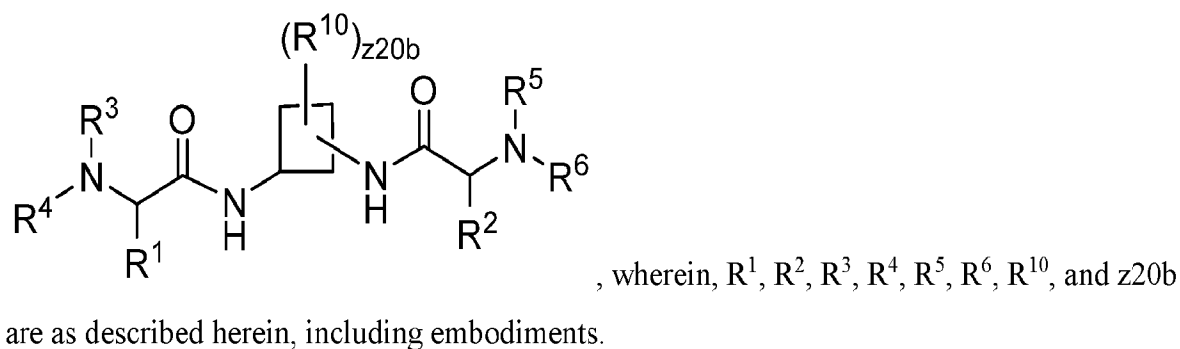
[0374] In embodiments, the compound has the formula:



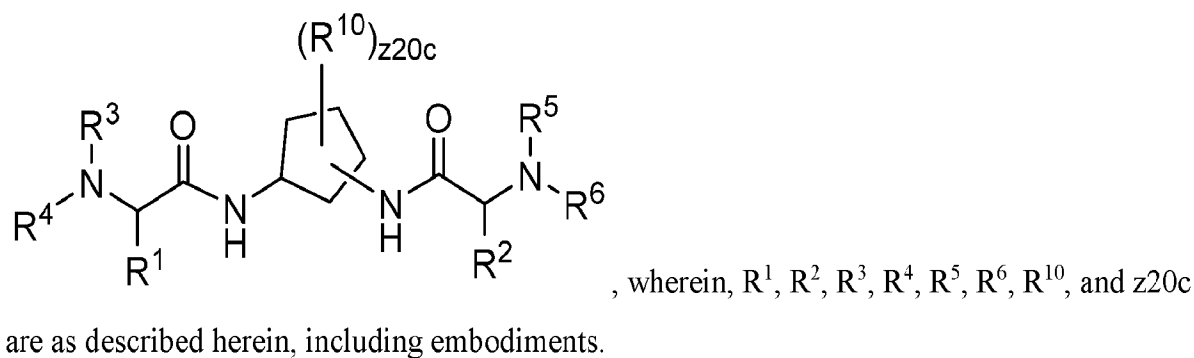
[0375] In embodiments, the compound has the formula:



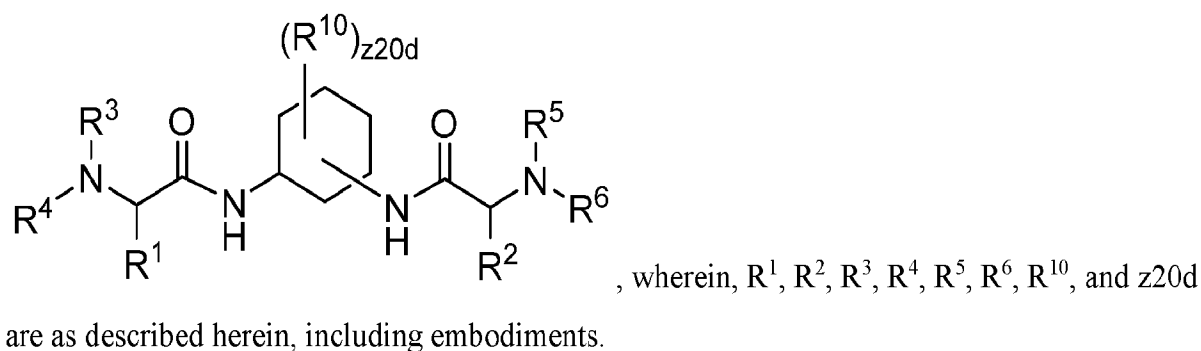
[0376] In embodiments, the compound has the formula:



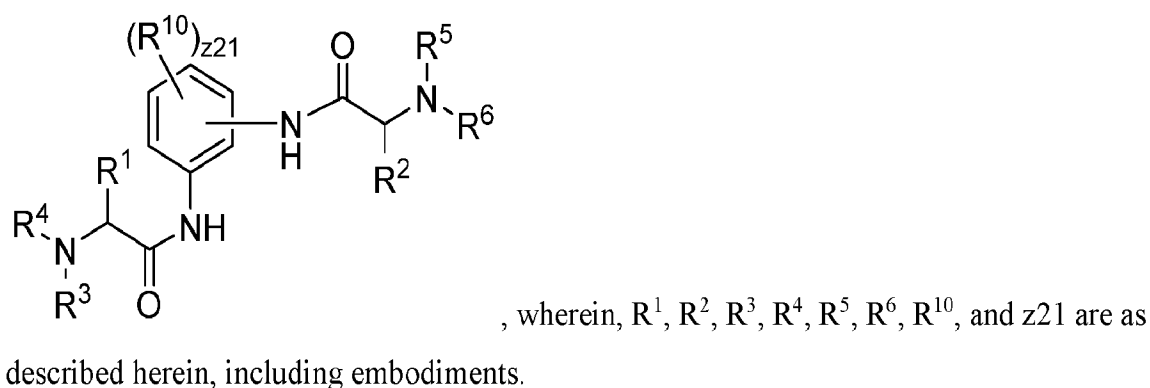
[0377] In embodiments, the compound has the formula:



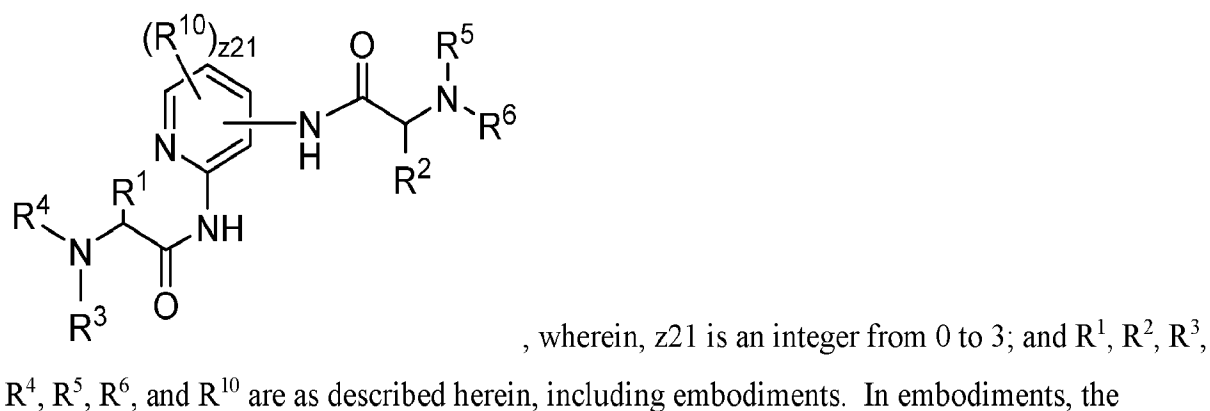
[0378] In embodiments, the compound has the formula:



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



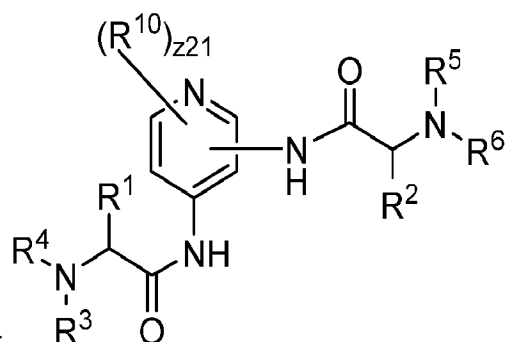
[0380] In embodiments, the compound has the formula:



compound has the formula:

, wherein, z_{21} is an integer

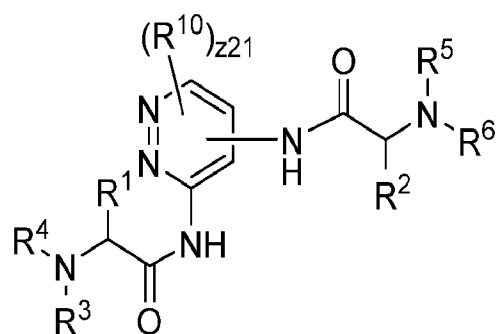
from 0 to 3; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.



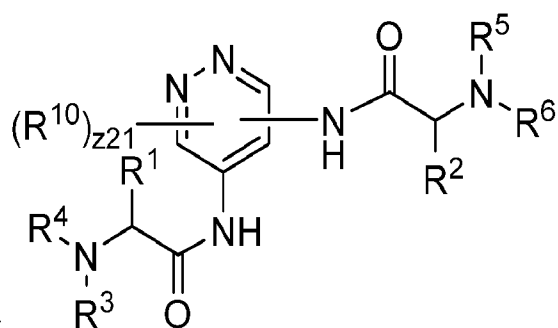
In embodiments, the compound has the formula:

wherein, z_{21} is an integer from 0 to 3; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.

[0381] In embodiments, the compound has the formula:

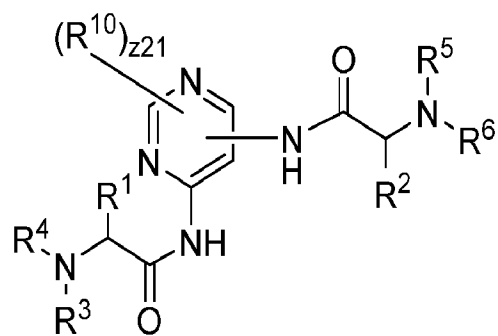


, wherein, z_{21} is an integer from 0 to 2; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments. In embodiments, the

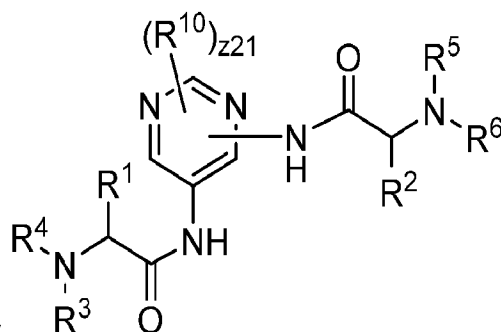


compound has the formula: , wherein, z_{21} is an integer from 0 to 2; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.

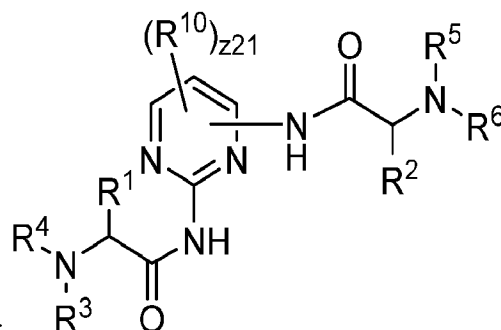
[0382] In embodiments, the compound has the formula:



, wherein, z_{21} is an integer from 0 to 2; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments. In embodiments, the

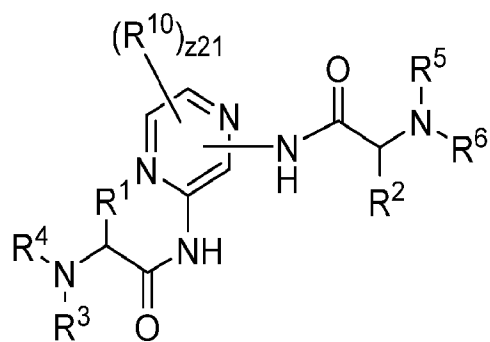


compound has the formula: , wherein, z_{21} is an integer from 0 to 2; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.



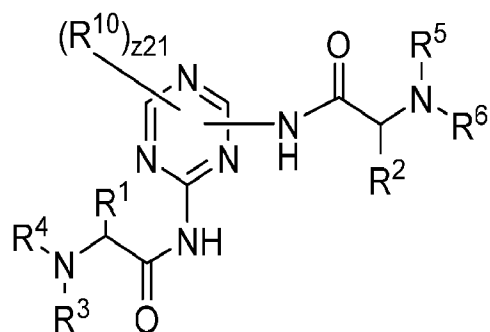
In embodiments, the compound has the formula: , wherein, z_{21} is an integer from 0 to 2; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.

[0383] In embodiments, the compound has the formula:



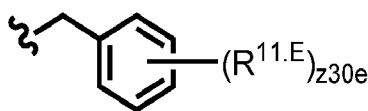
, wherein, z_{21} is an integer from 0 to 2; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.

[0384] In embodiments, the compound has the formula:



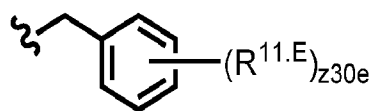
, wherein, z_{21} is 0 or 1; and R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^{10} are as described herein, including embodiments.

[0385] In embodiments, R^1 is

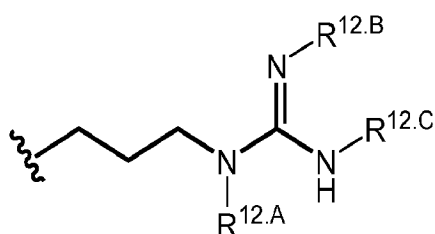


and R^2 is hydrogen. In

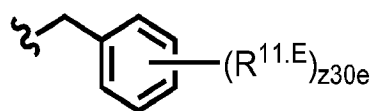
embodiments, R^1 is



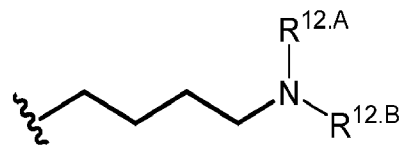
and R^2 is



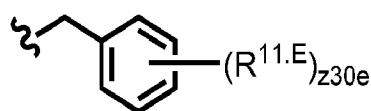
In embodiments, R^1 is



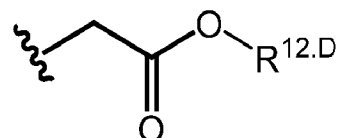
and R^2 is



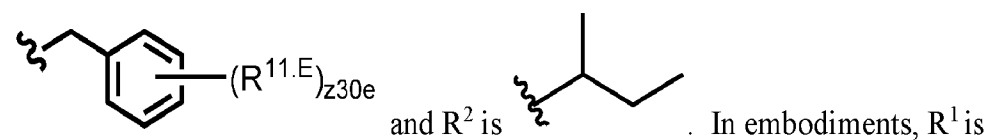
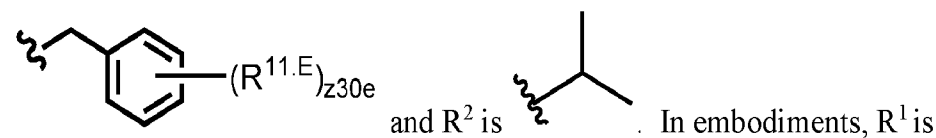
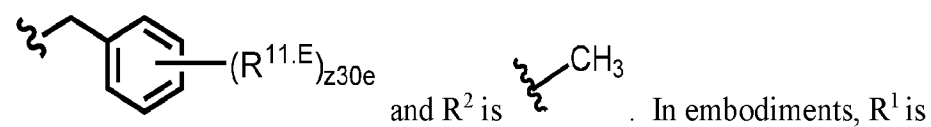
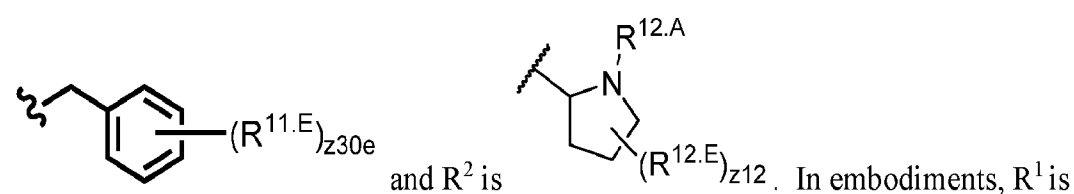
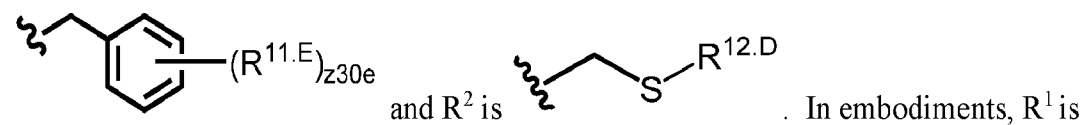
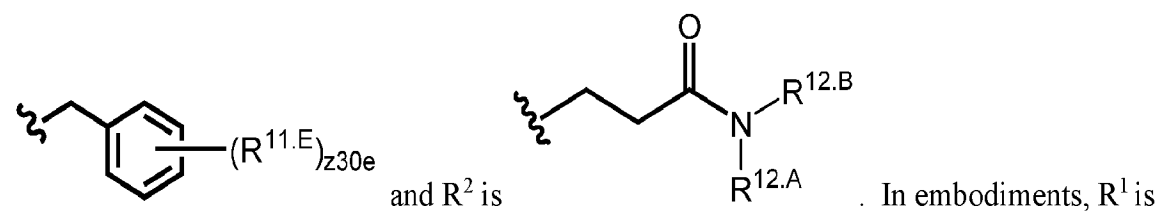
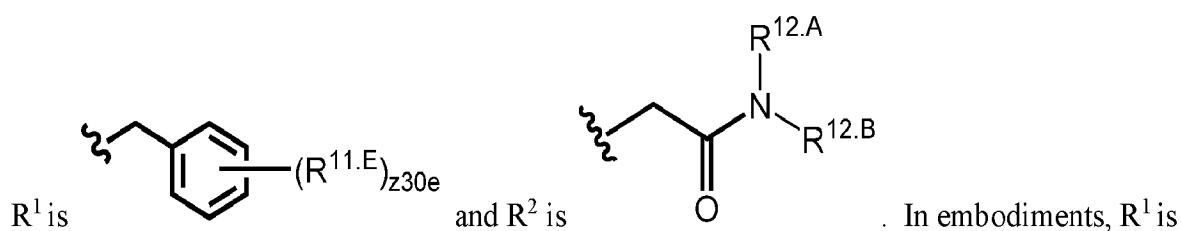
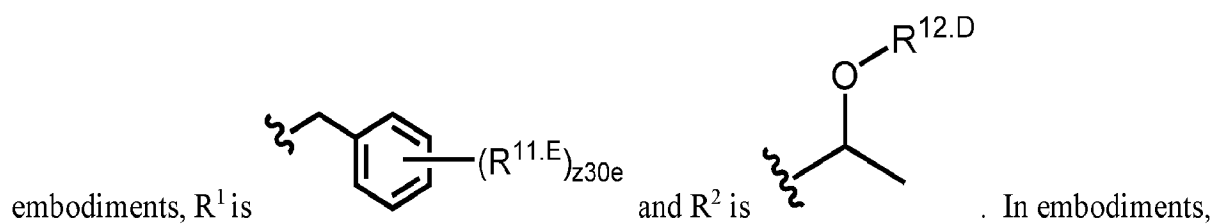
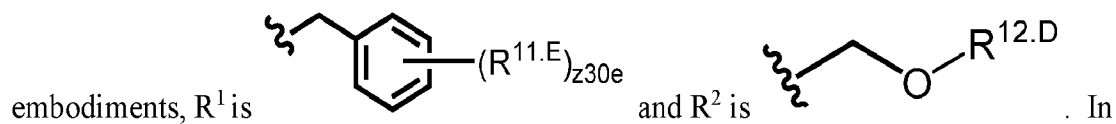
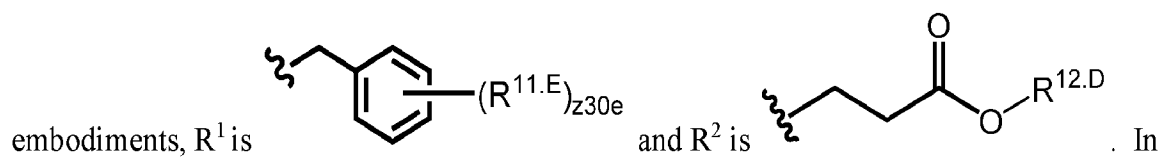
In embodiments, R^1 is

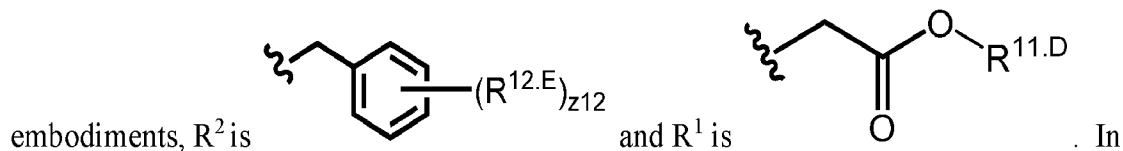
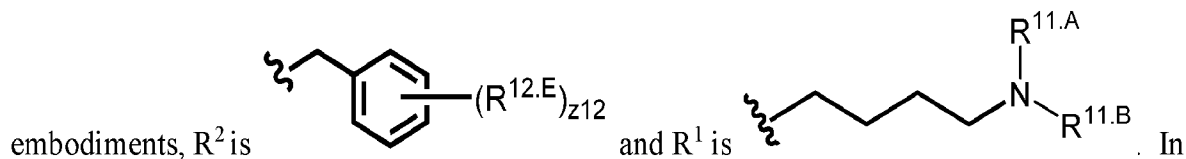
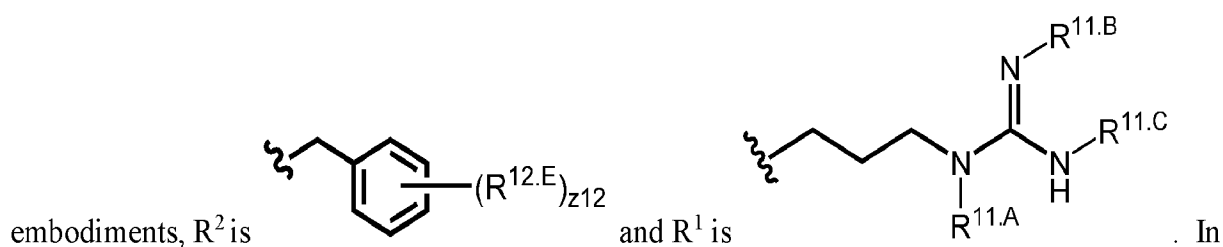
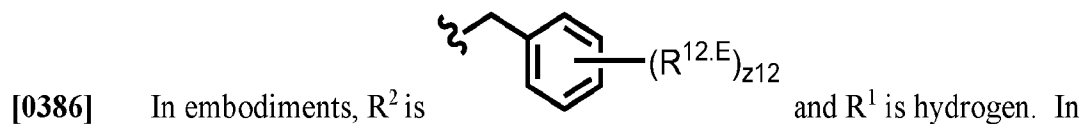
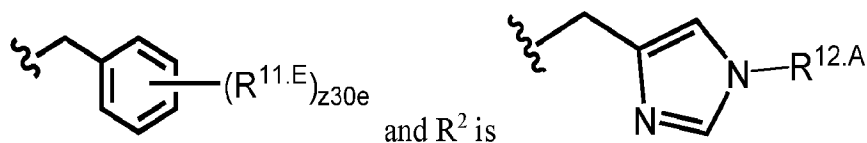
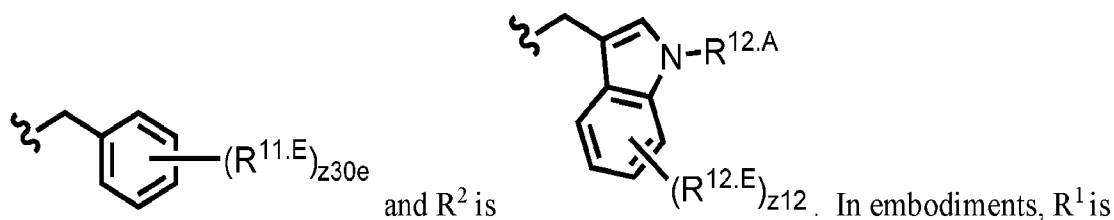
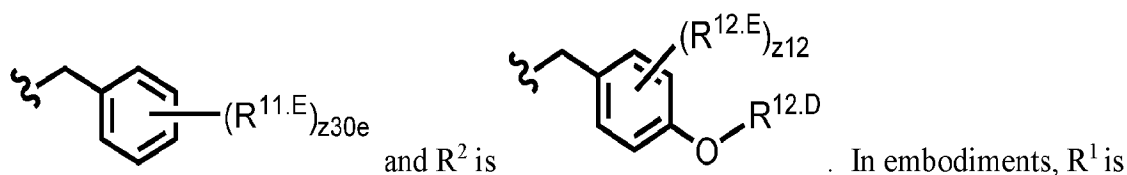
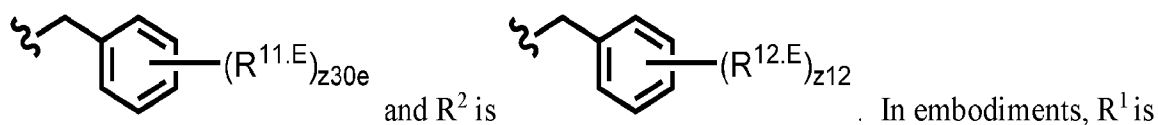
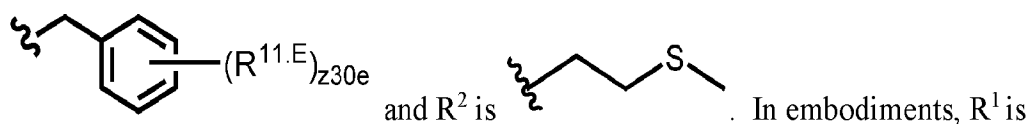
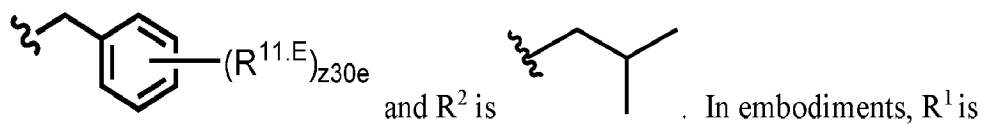


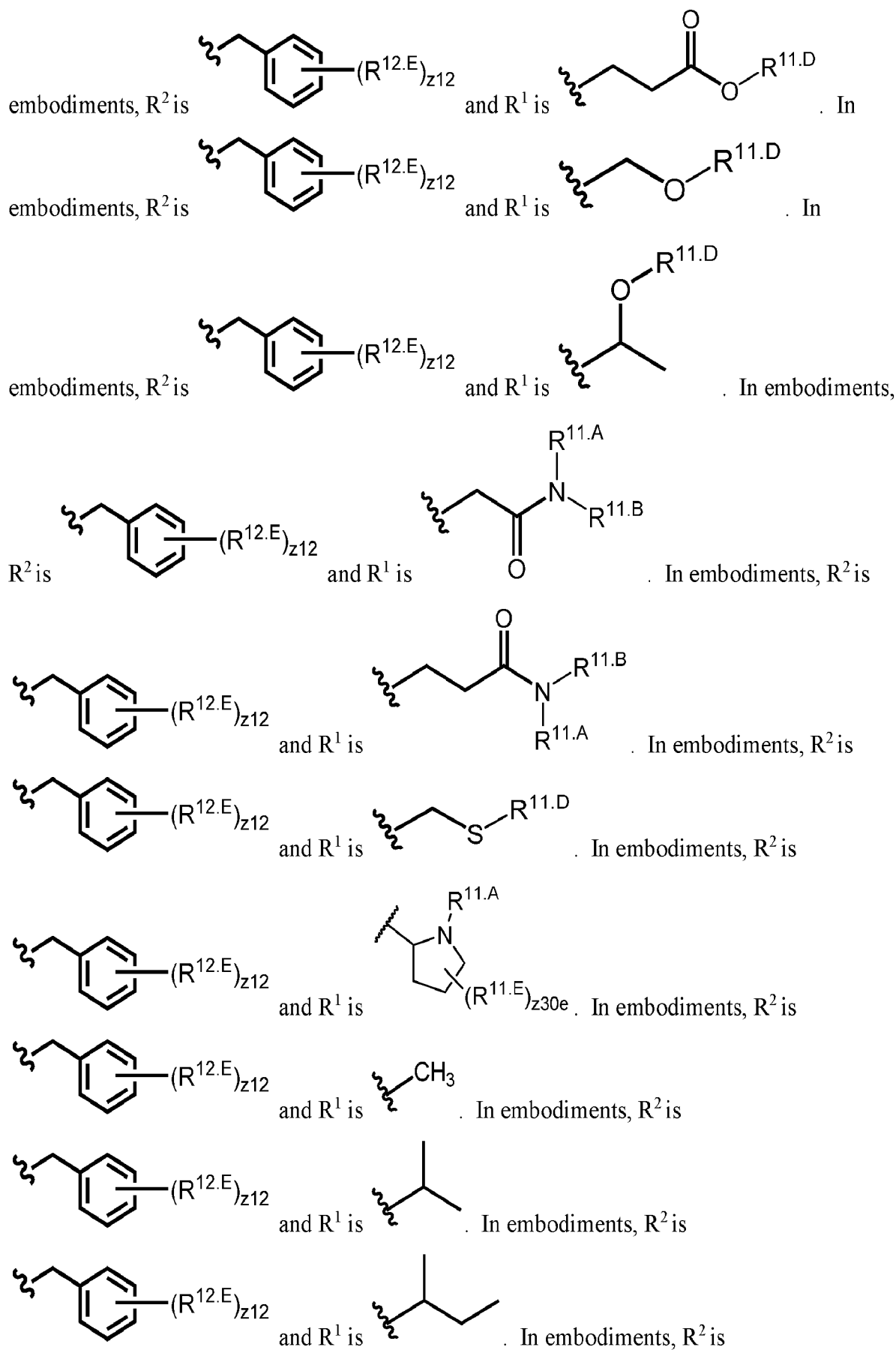
and R^2 is

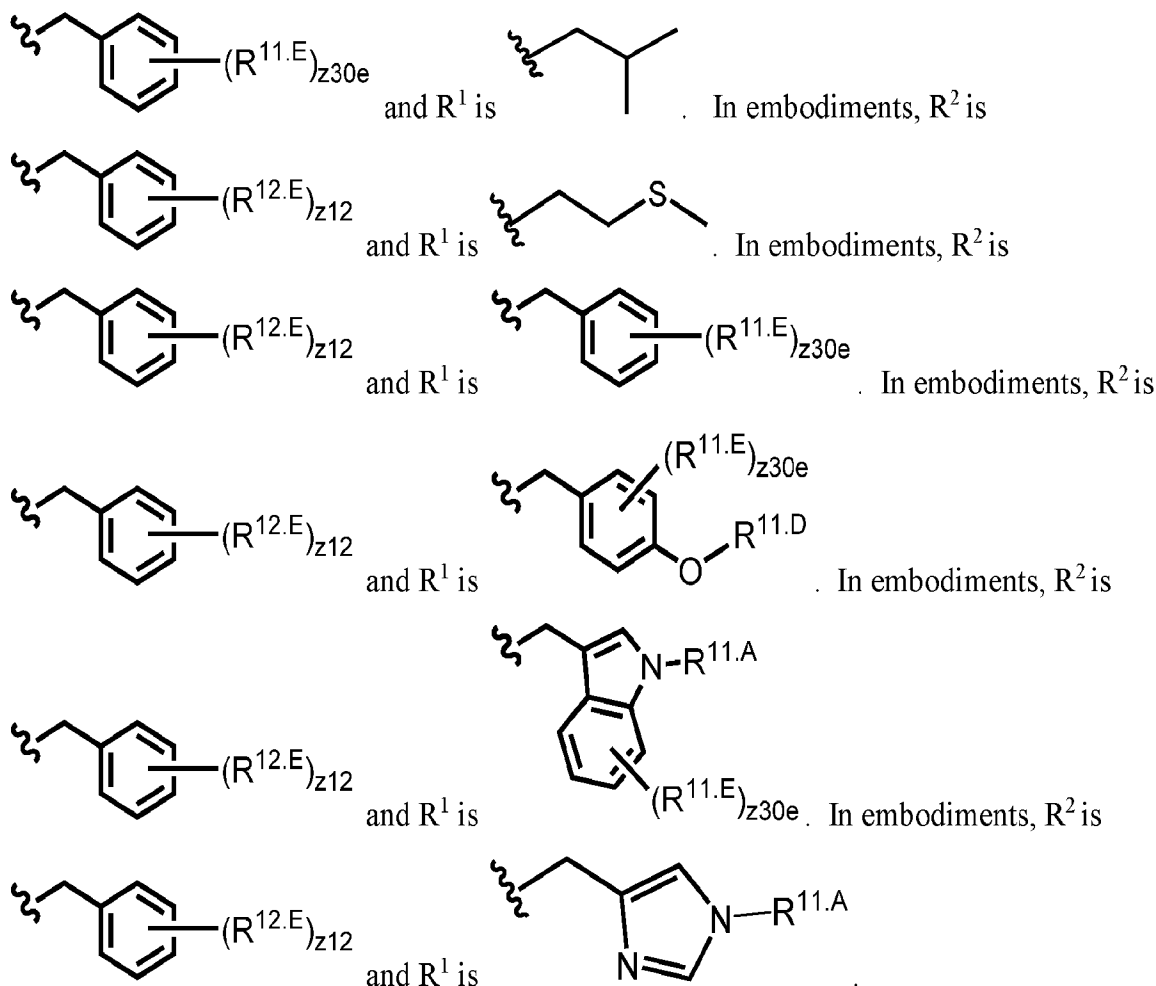


. In









[0387] In embodiments, L¹ is independently substituted or unsubstituted alkylene (e.g., C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₄, C₁-C₂, C₂-C₁₀, C₂-C₈, C₂-C₆, or C₂-C₄), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkylene (e.g., C₃-C₁₀, C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted arylene (e.g., C₆-C₁₀ or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0388] In embodiments, a substituted L¹ (e.g., substituted alkylene, substituted heteroalkylene, substituted cycloalkylene, substituted heterocycloalkylene, substituted arylene, and/or substituted heteroarylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted L¹ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower

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

[0389] In embodiments, R^1 is independently hydrogen, halogen, $-CX^1_3$, $-CHX^1_2$, $-CH_2X^1$, $-OCX^1_3$, $-OCH_2X^1$, $-OCHX^1_2$, $-CN$, $-SO_{n1}R^{1D}$, $-SO_{v1}NR^{1A}R^{1B}$, $-NR^{1C}NR^{1A}R^{1B}$, $-ONR^{1A}R^{1B}$, $-NHC(O)NR^{1C}NR^{1A}R^{1B}$, $-NHC(O)NR^{1A}R^{1B}$, $-N(O)_{m1}$, $-NR^{1A}R^{1B}$, $-C(O)R^{1C}$, $-C(O)-OR^{1C}$, $-C(O)NR^{1A}R^{1B}$, $-OR^{1D}$, $-NR^{1A}SO_2R^{1D}$, $-NR^{1A}C(O)R^{1C}$, $-NR^{1A}C(O)OR^{1C}$, $-NR^{1A}OR^{1C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0390] In embodiments, a substituted R^1 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^1 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^1 is substituted, it is substituted with at least one substituent group. In embodiments, when R^1 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^1 is substituted, it is substituted with at least one lower substituent group.

[0391] In embodiments, R^2 is independently hydrogen, halogen, $-CX^2_3$, $-CHX^2_2$, $-CH_2X^2$, $-OCX^2_3$, $-OCH_2X^2$, $-OCHX^2_2$, $-CN$, $-SO_{n2}R^{2D}$, $-SO_{v2}NR^{2A}R^{2B}$, $-NR^{2C}NR^{2A}R^{2B}$, $-ONR^{2A}R^{2B}$, $-NHC(O)NR^{2C}NR^{2A}R^{2B}$, $-NHC(O)NR^{2A}R^{2B}$, $-N(O)_{m2}$, $-NR^{2A}R^{2B}$, $-C(O)R^{2C}$, $-C(O)-OR^{2C}$, $-C(O)NR^{2A}R^{2B}$, $-OR^{2D}$, $-NR^{2A}SO_2R^{2D}$, $-NR^{2A}C(O)R^{2C}$, $-NR^{2A}C(O)OR^{2C}$, $-NR^{2A}OR^{2C}$

2C , $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0392] In embodiments, a substituted R^2 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^2 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^2 is substituted, it is substituted with at least one substituent group. In embodiments, when R^2 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^2 is substituted, it is substituted with at least one lower substituent group.

[0393] In embodiments, R^3 is independently hydrogen, halogen, $-CX^3_3$, $-CHX^3_2$, $-CH_2X^3$, $-OCX^3_3$, $-OCH_2X^3$, $-OCHX^3_2$, $-CN$, $-SO_{m3}R^{3D}$, $-SO_{v3}NR^{3A}R^{3B}$, $-NR^{3C}NR^{3A}R^{3B}$, $-ONR^{3A}R^{3B}$, $-NHC(O)NR^{3C}NR^{3A}R^{3B}$, $-NHC(O)NR^{3A}R^{3B}$, $-N(O)_{m3}$, $-NR^{3A}R^{3B}$, $-C(O)R^{3C}$, $-C(O)-OR^{3C}$, $-C(O)NR^{3A}R^{3B}$, $-OR^{3D}$, $-NR^{3A}SO_2R^{3D}$, $-NR^{3A}C(O)R^{3C}$, $-NR^{3A}C(O)OR^{3C}$, $-NR^{3A}OR^{3C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0394] In embodiments, a substituted R^3 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^3 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^3 is substituted, it is substituted with at least one substituent group. In embodiments, when R^3 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^3 is substituted, it is substituted with at least one lower substituent group.

[0395] In embodiments, R^4 is independently hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NR^{4C}NR^{4A}R^{4B}$, $-ONR^{4A}R^{4B}$, $-NHC(O)NR^{4C}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0396] In embodiments, a substituted R^4 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^4 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^4 is substituted, it is substituted with at least one

substituent group. In embodiments, when R^4 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^4 is substituted, it is substituted with at least one lower substituent group.

[0397] In embodiments, a substituted ring formed when R^3 and R^4 substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^3 and R^4 substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^3 and R^4 substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^3 and R^4 substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^3 and R^4 substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0398] In embodiments, R^5 is independently hydrogen, halogen, $-CX^5_3$, $-CHX^5_2$, $-CH_2X^5$, $-OCX^5_3$, $-OCH_2X^5$, $-OCHX^5_2$, $-CN$, $-SO_{m5}R^{5D}$, $-SO_{v5}NR^{5A}R^{5B}$, $-NR^{5C}NR^{5A}R^{5B}$, $-ONR^{5A}R^{5B}$, $-NHC(O)NR^{5C}NR^{5A}R^{5B}$, $-NHC(O)NR^{5A}R^{5B}$, $-N(O)_{m5}$, $-NR^{5A}R^{5B}$, $-C(O)R^{5C}$, $-C(O)-OR^{5C}$, $-C(O)NR^{5A}R^{5B}$, $-OR^{5D}$, $-NR^{5A}SO_2R^{5D}$, $-NR^{5A}C(O)R^{5C}$, $-NR^{5A}C(O)OR^{5C}$, $-NR^{5A}OR^{5C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0399] In embodiments, a substituted R^5 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^5 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^5 is substituted, it is substituted with at least one substituent group. In embodiments, when R^5 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^5 is substituted, it is substituted with at least one lower substituent group.

[0400] In embodiments, R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{m6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0401] In embodiments, a substituted R^6 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^6 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups;

each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^6 is substituted, it is substituted with at least one substituent group. In embodiments, when R^6 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^6 is substituted, it is substituted with at least one lower substituent group.

[0402] In embodiments, a substituted ring formed when R^5 and R^6 substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^5 and R^6 substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^5 and R^6 substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^5 and R^6 substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^5 and R^6 substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0403] In embodiments, R^7 and R^8 are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0404] In embodiments, a substituted R^7 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted R^7 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^7 is substituted, it is substituted with at least one substituent group. In embodiments, when R^7 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^7 is substituted, it is substituted with at least one lower substituent group.

[0405] In embodiments, a substituted R^8 (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^8 is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^8 is substituted, it is substituted with at least one substituent group. In embodiments, when R^8 is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^8 is substituted, it is substituted with at least one lower substituent group.

[0406] In embodiments, R^{1A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0407] In embodiments, a substituted R^{1A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups;

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

[0408] In embodiments, R^{1B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0409] In embodiments, a substituted R^{1B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1B} is substituted, it is substituted with at least one lower substituent group.

[0410] In embodiments, a substituted ring formed when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted ring formed when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0411] In embodiments, R^{1C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0412] In embodiments, a substituted R^{1C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1C} is substituted, it is substituted with at least one lower substituent group.

[0413] In embodiments, R^{1D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0414] In embodiments, a substituted R^{1D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{1D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{1D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{1D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{1D} is substituted, it is substituted with at least one lower substituent group.

[0415] In embodiments, R^{2A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0416] In embodiments, a substituted R^{2A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2A} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2A} is substituted, it is substituted with at least one lower substituent group.

[0417] In embodiments, R^{2B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0418] In embodiments, a substituted R^{2B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2B} is substituted, it is substituted with at least one lower substituent group.

[0419] In embodiments, a substituted ring formed when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0420] In embodiments, R^{2C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0421] In embodiments, a substituted R^{2C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2C} is substituted, it is substituted with at least one lower substituent group.

[0422] In embodiments, R^{2D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0423] In embodiments, a substituted R^{2D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{2D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{2D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{2D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{2D} is substituted, it is substituted with at least one lower substituent group.

[0424] In embodiments, R^{3A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0425] In embodiments, a substituted R^{3A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3A} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{3A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3A} is substituted, it is substituted with at least one lower substituent group.

[0426] In embodiments, R^{3B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0427] In embodiments, a substituted R^{3B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{3B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3B} is substituted, it is substituted with at least one lower substituent group.

[0428] In embodiments, a substituted ring formed when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0429] In embodiments, R^{3C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0430] In embodiments, a substituted R^{3C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{3C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3C} is substituted, it is substituted with at least one lower substituent group.

[0431] In embodiments, R^{3D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0432] In embodiments, a substituted R^{3D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{3D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{3D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{3D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{3D} is substituted, it is substituted with at least one lower substituent group.

[0433] In embodiments, R^{4A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0434] In embodiments, a substituted R^{4A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4A} is substituted with a plurality of groups

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

[0435] In embodiments, R^{4B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0436] In embodiments, a substituted R^{4B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{4B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4B} is substituted, it is substituted with at least one lower substituent group.

[0437] In embodiments, a substituted ring formed when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0438] In embodiments, R^{4C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0439] In embodiments, a substituted R^{4C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{4C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4C} is substituted, it is substituted with at least one lower substituent group.

[0440] In embodiments, R^{4D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0441] In embodiments, a substituted R^{4D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{4D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{4D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{4D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{4D} is substituted, it is substituted with at least one lower substituent group.

[0442] In embodiments, R^{5A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0443] In embodiments, a substituted R^{5A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5A} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{5A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5A} is substituted, it is substituted with at least one lower substituent group.

[0444] In embodiments, R^{5B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0445] In embodiments, a substituted R^{5B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{5B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5B} is substituted, it is substituted with at least one lower substituent group.

[0446] In embodiments, a substituted ring formed when R^{5A} and R^{5B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted

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

[0447] In embodiments, R^{5C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0448] In embodiments, a substituted R^{5C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{5C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5C} is substituted, it is substituted with at least one lower substituent group.

[0449] In embodiments, R^{5D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0450] In embodiments, a substituted R^{5D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{5D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{5D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{5D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{5D} is substituted, it is substituted with at least one lower substituent group.

[0451] In embodiments, R^{6A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0452] In embodiments, a substituted R^{6A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6A} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{6A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6A} is substituted, it is substituted with at least one lower substituent group.

[0453] In embodiments, R^{6B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered) or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0454] In embodiments, a substituted R^{6B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{6B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6B} is substituted, it is substituted with at least one lower substituent group.

[0455] In embodiments, a substituted ring formed when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0456] In embodiments, R^{6C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0457] **[0001]** In embodiments, a substituted R^{6C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{6C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6C} is substituted, it is substituted with at least one lower substituent group.

[0458] In embodiments, R^{6D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0459] In embodiments, a substituted R^{6D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{6D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{6D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{6D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{6D} is substituted, it is substituted with at least one lower substituent group.

[0460] In embodiments, R^{10} is independently halogen, $-CX^{10}_3$, $-CHX^{10}_2$, $-CH_2X^{10}$, $-OCX^{10}_3$, $-OCH_2X^{10}$, $-OCHX^{10}_2$, $-CN$, $-SO_{n10}R^{10D}$, $-SO_{v10}NR^{10A}R^{10B}$, $-NR^{10C}NR^{10A}R^{10B}$, $-ONR^{10A}R^{10B}$, $-NHC(O)NR^{10C}NR^{10A}R^{10B}$, $-NHC(O)NR^{10A}R^{10B}$, $-N(O)_{m10}$, $-NR^{10A}R^{10B}$, $-C(O)R^{10C}$, $-C(O)-OR^{10C}$, $-C(O)NR^{10A}R^{10B}$, $-OR^{10D}$, $-NR^{10A}SO_2R^{10D}$, $-NR^{10A}C(O)R^{10C}$, $-NR^{10A}C(O)OR^{10C}$, $-NR^{10A}OR^{10C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0461] In embodiments, a substituted R^{10} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10} is substituted, it is substituted with at least one lower substituent group.

[0462] In embodiments, R^{10A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, s substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0463] In embodiments, a substituted R^{10A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10A} is substituted, it is substituted with at least one lower substituent group.

[0464] In embodiments, R^{10B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, s substituted or unsubstituted alkyl (e.g., C_1 - C_8 ,

C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0465] In embodiments, a substituted R^{10B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10B} is substituted, it is substituted with at least one lower substituent group.

[0466] In embodiments, a substituted ring formed when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed

when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0467] In embodiments, R^{10C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, s substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0468] In embodiments, a substituted R^{10C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10C} is substituted, it is substituted with at least one lower substituent group.

[0469] In embodiments, R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, s substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0470] In embodiments, a substituted R^{10D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{10D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{10D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{10D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{10D} is substituted, it is substituted with at least one lower substituent group.

[0471] In embodiments, each R^{11} is independently halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11D}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NR^{11C}NR^{11A}R^{11B}$, $-ONR^{11A}R^{11B}$, $-NHC(O)NR^{11C}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-C(O)R^{11C}$, $-C(O)-OR^{11C}$, $-C(O)NR^{11A}R^{11B}$, $-OR^{11D}$, $-NR^{11A}SO_2R^{11D}$, $-NR^{11A}C(O)R^{11C}$, $-NR^{11A}C(O)OR^{11C}$, $-NR^{11A}OR^{11C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0472] In embodiments, a substituted R^{11} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11} is substituted, it is substituted with at least one lower substituent group.

[0473] In embodiments, R^{11A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0474] In embodiments, a substituted R^{11A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11A} is substituted, it is substituted with at least one lower substituent group.

[0475] In embodiments, R^{11B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

[0476] In embodiments, a substituted R^{11B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11B} is substituted, it is substituted with at least one lower substituent group.

[0477] In embodiments, a substituted ring formed when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0478] In embodiments, R^{11C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0479] In embodiments, a substituted R^{11C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11C} is substituted, it is substituted with at least one lower substituent group.

[0480] In embodiments, R^{11D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0481] In embodiments, a substituted R^{11D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11D} is substituted, it is substituted with at least one lower substituent group.

[0482] In embodiments, R^{11A} is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or

unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0483] In embodiments, a substituted R^{11.A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11.A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11.A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11.A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11.A} is substituted, it is substituted with at least one lower substituent group.

[0484] In embodiments, R^{11.B} is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0485] In embodiments, a substituted R^{11.B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11.B} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when $R^{11.B}$ is substituted, it is substituted with at least one substituent group. In embodiments, when $R^{11.B}$ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when $R^{11.B}$ is substituted, it is substituted with at least one lower substituent group.

[0486] In embodiments, $R^{11.C}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0487] In embodiments, a substituted $R^{11.C}$ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted $R^{11.C}$ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when $R^{11.C}$ is substituted, it is substituted with at least one substituent group. In embodiments, when $R^{11.C}$ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when $R^{11.C}$ is substituted, it is substituted with at least one lower substituent group.

[0488] In embodiments, $R^{11.D}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6),

substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0489] In embodiments, a substituted R^{11.D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{11.D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{11.D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{11.D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{11.D} is substituted, it is substituted with at least one lower substituent group.

[0490] In embodiments, R^{11.E} is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCI₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -SH, -SCH₃, -SCF₃, -SCHF₂, -SCH₂F, -SCCl₃, -SCHCl₂, -SCH₂Cl, -SCBr₃, -SCHBr₂, -SCH₂Br, -SCI₃, -SCHI₂, -SCH₂I, -SOCH₃, -SO₂CH₃, -NH₂, -NHCH₃, -OH, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0491] In embodiments, a substituted R^{11.E} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or

lower substituent group; wherein if the substituted $R^{11.E}$ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when $R^{11.E}$ is substituted, it is substituted with at least one substituent group. In embodiments, when $R^{11.E}$ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when $R^{11.E}$ is substituted, it is substituted with at least one lower substituent group.

[0492] In embodiments, each R^{12} is independently halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, $-CN$, $-SO_{n12}R^{12D}$, $-SO_{v12}NR^{12A}R^{1B}$, $-NR^{12C}NR^{12A}R^{12B}$, $-ONR^{1A}R^{1B}$, $-NHC(O)NR^{12C}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-C(O)R^{12C}$, $-C(O)-OR^{12C}$, $-C(O)NR^{12A}R^{12B}$, $-OR^{12D}$, $-NR^{12A}SO_2R^{12D}$, $-NR^{12A}C(O)R^{12C}$, $-NR^{12A}C(O)OR^{12C}$, $-NR^{12A}OR^{12C}$, $-N_3$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0493] In embodiments, a substituted R^{12} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12} is substituted, it is substituted with at least one lower substituent group.

[0494] In embodiments, R^{12A} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0495] In embodiments, a substituted R^{12A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12A} is substituted, it is substituted with at least one lower substituent group.

[0496] In embodiments, R^{12B} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered); R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

[0497] In embodiments, a substituted R^{12B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12B} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12B} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12B} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12B} is substituted, it is substituted with at least one lower substituent group.

[0498] In embodiments, a substituted ring formed when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are joined (e.g., substituted heterocycloalkyl and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted ring formed when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are joined is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when the substituted ring formed when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one substituent group. In embodiments, when the substituted ring formed when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when the substituted ring formed when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are joined is substituted, it is substituted with at least one lower substituent group.

[0499] In embodiments, R^{12C} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0500] In embodiments, a substituted R^{12C} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12C} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12C} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12C} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12C} is substituted, it is substituted with at least one lower substituent group.

[0501] In embodiments, R^{12D} is independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl (e.g., C_1 - C_8 , C_1 - C_6 , C_1 - C_4 , or C_1 - C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 , C_3 - C_6 , C_4 - C_6 , or C_5 - C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6 - C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0502] In embodiments, a substituted R^{12D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12D} is substituted, it is substituted with at least one lower substituent group.

[0503] **[0002]** In embodiments, R^{12A} is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, -

CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0504] In embodiments, a substituted R^{12.A} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12.A} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12.A} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12.A} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12.A} is substituted, it is substituted with at least one lower substituent group.

[0505] In embodiments, R^{12.B} is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0506] In embodiments, a substituted R^{12.B} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12.B} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when $R^{12.B}$ is substituted, it is substituted with at least one substituent group. In embodiments, when $R^{12.B}$ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when $R^{12.B}$ is substituted, it is substituted with at least one lower substituent group.

[0507] In embodiments, $R^{12.C}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C_6-C_{10} or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0508] In embodiments, a substituted $R^{12.C}$ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted $R^{12.C}$ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when $R^{12.C}$ is substituted, it is substituted with at least one substituent group. In embodiments, when $R^{12.C}$ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when $R^{12.C}$ is substituted, it is substituted with at least one lower substituent group.

[0509] In embodiments, $R^{12.D}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl (e.g., C_1-C_8 , C_1-C_6 , C_1-C_4 , or C_1-C_2), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C_3-C_8 , C_3-C_6 , C_4-C_6 , or C_5-C_6),

substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0510] In embodiments, a substituted R^{12.D} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12.D} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{12.D} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{12.D} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{12.D} is substituted, it is substituted with at least one lower substituent group.

[0511] In embodiments, R^{12.E} is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCI₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -SH, -SCH₃, -SCF₃, -SCHF₂, -SCH₂F, -SCCl₃, -SCHCl₂, -SCH₂Cl, -SCBr₃, -SCHBr₂, -SCH₂Br, -SCI₃, -SCHI₂, -SCH₂I, -SOCH₃, -SO₂CH₃, -NH₂, -NHCH₃, -OH, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0512] In embodiments, a substituted R^{12.E} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{12.E} is substituted with a plurality of groups

selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when $R^{12.E}$ is substituted, it is substituted with at least one substituent group. In embodiments, when $R^{12.E}$ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when $R^{12.E}$ is substituted, it is substituted with at least one lower substituent group.

[0513] In embodiments, L^{14} is independently a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene (e.g., C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₄, C₁-C₂, C₂-C₁₀, C₂-C₈, C₂-C₆, or C₂-C₄), or substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered).

[0514] In embodiments, a substituted L^{14} (e.g., substituted alkylene or substituted heteroalkylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted L^{14} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when L^{14} is substituted, it is substituted with at least one substituent group. In embodiments, when L^{14} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when L^{14} is substituted, it is substituted with at least one lower substituent group.

[0515] In embodiments, R^{14} is independently oxo, halogen, -CCl₃, -CBr₃, -CF₃, -CI₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -N₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCI₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or

unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0516] In embodiments, a substituted R¹⁴ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R¹⁴ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R¹⁴ is substituted, it is substituted with at least one substituent group. In embodiments, when R¹⁴ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R¹⁴ is substituted, it is substituted with at least one lower substituent group.

[0517] In embodiments, R¹⁵ is independently hydrogen, oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NH₂SO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0518] In embodiments, a substituted R¹⁵ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted

heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{15} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{15} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{15} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{15} is substituted, it is substituted with at least one lower substituent group.

[0519] In embodiments, L^{16} is independently a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene (e.g., C₁-C₁₀, C₁-C₈, C₁-C₆, C₁-C₄, C₁-C₂, C₂-C₁₀, C₂-C₈, C₂-C₆, or C₂-C₄,) or substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered).

[0520] In embodiments, a substituted L^{16} (e.g., substituted alkylene or substituted heteroalkylene) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted L^{16} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when L^{16} is substituted, it is substituted with at least one substituent group. In embodiments, when L^{16} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when L^{16} is substituted, it is substituted with at least one lower substituent group.

[0521] In embodiments, R^{16} is independently oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-

C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0522] In embodiments, a substituted R¹⁶ (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R¹⁶ is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R¹⁶ is substituted, it is substituted with at least one substituent group. In embodiments, when R¹⁶ is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R¹⁶ is substituted, it is substituted with at least one lower substituent group.

[0523] In embodiments, R¹⁷ is independently hydrogen, oxo, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₃H, -SO₄H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -N₃, substituted or unsubstituted alkyl (e.g., C₁-C₈, C₁-C₆, C₁-C₄, or C₁-C₂), substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered, 2 to 6 membered, 4 to 6 membered, 2 to 3 membered, or 4 to 5 membered), substituted or unsubstituted cycloalkyl (e.g., C₃-C₈, C₃-C₆, C₄-C₆, or C₅-C₆), substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered, 3 to 6 membered, 4 to 6 membered, 4 to 5 membered, or 5 to 6 membered), substituted or unsubstituted aryl (e.g., C₆-C₁₀ or phenyl), or substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered, 5 to 9 membered, or 5 to 6 membered).

[0524] In embodiments, a substituted R^{17} (e.g., substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, and/or substituted heteroaryl) is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted R^{17} is substituted with a plurality of groups selected from substituent groups, size-limited substituent groups, and lower substituent groups; each substituent group, size-limited substituent group, and/or lower substituent group may optionally be different. In embodiments, when R^{17} is substituted, it is substituted with at least one substituent group. In embodiments, when R^{17} is substituted, it is substituted with at least one size-limited substituent group. In embodiments, when R^{17} is substituted, it is substituted with at least one lower substituent group.

[0525] In embodiments, when R^1 is substituted, R^1 is substituted with one or more first substituent groups denoted by $R^{1.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.1}$ substituent group is substituted, the $R^{1.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1.2}$ substituent group is substituted, the $R^{1.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^1 , $R^{1.1}$, $R^{1.2}$, and $R^{1.3}$, respectively.

[0526] In embodiments, when R^2 is substituted, R^2 is substituted with one or more first substituent groups denoted by $R^{2.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2.1}$ substituent group is substituted, the $R^{2.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2.2}$ substituent group is substituted, the $R^{2.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^2 , $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$,

$R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^2 , $R^{2.1}$, $R^{2.2}$, and $R^{2.3}$, respectively.

[0527] In embodiments, when R^3 is substituted, R^3 is substituted with one or more first substituent groups denoted by $R^{3.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3.1}$ substituent group is substituted, the $R^{3.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3.2}$ substituent group is substituted, the $R^{3.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^3 , $R^{3.1}$, $R^{3.2}$, and $R^{3.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^3 , $R^{3.1}$, $R^{3.2}$, and $R^{3.3}$, respectively.

[0528] In embodiments, when R^4 is substituted, R^4 is substituted with one or more first substituent groups denoted by $R^{4.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.1}$ substituent group is substituted, the $R^{4.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.2}$ substituent group is substituted, the $R^{4.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^4 , $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^4 , $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$, respectively.

[0529] In embodiments, when R^3 and R^4 substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups

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

[0530] In embodiments, when R^3 and R^4 substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{4.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.1}$ substituent group is substituted, the $R^{4.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4.2}$ substituent group is substituted, the $R^{4.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{4.1}$, $R^{4.2}$, and $R^{4.3}$, respectively.

[0531] In embodiments, when R^5 is substituted, R^5 is substituted with one or more first substituent groups denoted by $R^{5.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5.1}$ substituent group is substituted, the $R^{5.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5.2}$ substituent group is substituted, the $R^{5.2}$ substituent group is

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

[0532] In embodiments, when R^6 is substituted, R^6 is substituted with one or more first substituent groups denoted by $R^{6.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6.1}$ substituent group is substituted, the $R^{6.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6.2}$ substituent group is substituted, the $R^{6.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^6 , $R^{6.1}$, $R^{6.2}$, and $R^{6.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^6 , $R^{6.1}$, $R^{6.2}$, and $R^{6.3}$, respectively.

[0533] In embodiments, when R^5 and R^6 substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{5.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5.1}$ substituent group is substituted, the $R^{5.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5.2}$ substituent group is substituted, the $R^{5.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{5.1}$, $R^{5.2}$, and $R^{5.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first

substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{5.1}$, $R^{5.2}$, and $R^{5.3}$, respectively.

[0534] In embodiments, when R^5 and R^6 substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{6.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6.1}$ substituent group is substituted, the $R^{6.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6.2}$ substituent group is substituted, the $R^{6.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{6.1}$, $R^{6.2}$, and $R^{6.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{6.1}$, $R^{6.2}$, and $R^{6.3}$, respectively.

[0535] In embodiments, when R^7 is substituted, R^7 is substituted with one or more first substituent groups denoted by $R^{7.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{7.1}$ substituent group is substituted, the $R^{7.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{7.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{7.2}$ substituent group is substituted, the $R^{7.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{7.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^7 , $R^{7.1}$, $R^{7.2}$, and $R^{7.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^7 , $R^{7.1}$, $R^{7.2}$, and $R^{7.3}$, respectively.

[0536] In embodiments, when R^8 is substituted, R^8 is substituted with one or more first substituent groups denoted by $R^{8.1}$ as explained in the definitions section above in the description

of “first substituent group(s)”. In embodiments, when an $R^{8.1}$ substituent group is substituted, the $R^{8.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{8.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{8.2}$ substituent group is substituted, the $R^{8.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{8.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^8 , $R^{8.1}$, $R^{8.2}$, and $R^{8.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^8 , $R^{8.1}$, $R^{8.2}$, and $R^{8.3}$, respectively.

[0537] In embodiments, when R^{10} is substituted, R^{10} is substituted with one or more first substituent groups denoted by $R^{10.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10.1}$ substituent group is substituted, the $R^{10.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10.2}$ substituent group is substituted, the $R^{10.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{10} , $R^{10.1}$, $R^{10.2}$, and $R^{10.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{10} , $R^{10.1}$, $R^{10.2}$, and $R^{10.3}$, respectively.

[0538] In embodiments, when R^{11} is substituted, R^{11} is substituted with one or more first substituent groups denoted by $R^{11.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.1}$ substituent group is substituted, the $R^{11.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.2}$ substituent group is substituted, the $R^{11.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{11} , $R^{11.1}$, $R^{11.2}$, and $R^{11.3}$ have values corresponding to the values of R^{WW} ,

$R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{11} , $R^{11.1}$, $R^{11.2}$, and $R^{11.3}$, respectively.

[0539] In embodiments, when R^{12} is substituted, R^{12} is substituted with one or more first substituent groups denoted by $R^{12.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.1}$ substituent group is substituted, the $R^{12.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.2}$ substituent group is substituted, the $R^{12.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{12} , $R^{12.1}$, $R^{12.2}$, and $R^{12.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{12} , $R^{12.1}$, $R^{12.2}$, and $R^{12.3}$, respectively.

[0540] In embodiments, when R^{1A} is substituted, R^{1A} is substituted with one or more first substituent groups denoted by $R^{1A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.1}$ substituent group is substituted, the $R^{1A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.2}$ substituent group is substituted, the $R^{1A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1A} , $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$, respectively.

[0541] In embodiments, when R^{1B} is substituted, R^{1B} is substituted with one or more first substituent groups denoted by $R^{1B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.1}$ substituent group is

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

[0542] In embodiments, when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.1}$ substituent group is substituted, the $R^{1A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1A.2}$ substituent group is substituted, the $R^{1A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{1A.1}$, $R^{1A.2}$, and $R^{1A.3}$, respectively.

[0543] In embodiments, when R^{1A} and R^{1B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{1B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.1}$ substituent group is substituted, the $R^{1B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1B.2}$ substituent group is substituted, the $R^{1B.2}$ substituent group is

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

[0544] In embodiments, when R^{1C} is substituted, R^{1C} is substituted with one or more first substituent groups denoted by $R^{1C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.1}$ substituent group is substituted, the $R^{1C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1C.2}$ substituent group is substituted, the $R^{1C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1C} , $R^{1C.1}$, $R^{1C.2}$, and $R^{1C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1C} , $R^{1C.1}$, $R^{1C.2}$, and $R^{1C.3}$, respectively.

[0545] In embodiments, when R^{1D} is substituted, R^{1D} is substituted with one or more first substituent groups denoted by $R^{1D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1D.1}$ substituent group is substituted, the $R^{1D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{1D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{1D.2}$ substituent group is substituted, the $R^{1D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{1D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{1D} , $R^{1D.1}$, $R^{1D.2}$, and $R^{1D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{1D} , $R^{1D.1}$, $R^{1D.2}$, and $R^{1D.3}$, respectively.

[0546] In embodiments, when R^{2A} is substituted, R^{2A} is substituted with one or more first substituent groups denoted by $R^{2A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2A.1}$ substituent group is substituted, the $R^{2A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2A.2}$ substituent group is substituted, the $R^{2A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2A} , $R^{2A.1}$, $R^{2A.2}$, and $R^{2A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2A} , $R^{2A.1}$, $R^{2A.2}$, and $R^{2A.3}$, respectively.

[0547] In embodiments, when R^{2B} is substituted, R^{2B} is substituted with one or more first substituent groups denoted by $R^{2B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.1}$ substituent group is substituted, the $R^{2B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.2}$ substituent group is substituted, the $R^{2B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2B} , $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2B} , $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$, respectively.

[0548] In embodiments, when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{2A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2A.1}$ substituent group is substituted, the $R^{2A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In

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

[0549] In embodiments, when R^{2A} and R^{2B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{2B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.1}$ substituent group is substituted, the $R^{2B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2B.2}$ substituent group is substituted, the $R^{2B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{2B.1}$, $R^{2B.2}$, and $R^{2B.3}$, respectively.

[0550] In embodiments, when R^{2C} is substituted, R^{2C} is substituted with one or more first substituent groups denoted by $R^{2C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2C.1}$ substituent group is substituted, the $R^{2C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2C.2}$ substituent group is substituted, the $R^{2C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2C} , $R^{2C.1}$, $R^{2C.2}$, and $R^{2C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the

description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2C} , $R^{2C.1}$, $R^{2C.2}$, and $R^{2C.3}$, respectively.

[0551] In embodiments, when R^{2D} is substituted, R^{2D} is substituted with one or more first substituent groups denoted by $R^{2D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2D.1}$ substituent group is substituted, the $R^{2D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{2D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{2D.2}$ substituent group is substituted, the $R^{2D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{2D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{2D} , $R^{2D.1}$, $R^{2D.2}$, and $R^{2D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{2D} , $R^{2D.1}$, $R^{2D.2}$, and $R^{2D.3}$, respectively.

[0552] In embodiments, when R^{3A} is substituted, R^{3A} is substituted with one or more first substituent groups denoted by $R^{3A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3A.1}$ substituent group is substituted, the $R^{3A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3A.2}$ substituent group is substituted, the $R^{3A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3A} , $R^{3A.1}$, $R^{3A.2}$, and $R^{3A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3A} , $R^{3A.1}$, $R^{3A.2}$, and $R^{3A.3}$, respectively.

[0553] In embodiments, when R^{3B} is substituted, R^{3B} is substituted with one or more first substituent groups denoted by $R^{3B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.1}$ substituent group is substituted, the $R^{3B.1}$ substituent group is substituted with one or more second substituent groups

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

[0554] In embodiments, when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{3A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3A.1}$ substituent group is substituted, the $R^{3A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3A.2}$ substituent group is substituted, the $R^{3A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{3A.1}$, $R^{3A.2}$, and $R^{3A.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{3A.1}$, $R^{3A.2}$, and $R^{3A.3}$, respectively.

[0555] In embodiments, when R^{3A} and R^{3B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{3B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.1}$ substituent group is substituted, the $R^{3B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3B.2}$ substituent group is substituted, the $R^{3B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3B.3}$ as explained in the

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

[0556] In embodiments, when R^{3C} is substituted, R^{3C} is substituted with one or more first substituent groups denoted by $R^{3C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3C.1}$ substituent group is substituted, the $R^{3C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3C.2}$ substituent group is substituted, the $R^{3C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3C} , $R^{3C.1}$, $R^{3C.2}$, and $R^{3C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3C} , $R^{3C.1}$, $R^{3C.2}$, and $R^{3C.3}$, respectively.

[0557] In embodiments, when R^{3D} is substituted, R^{3D} is substituted with one or more first substituent groups denoted by $R^{3D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3D.1}$ substituent group is substituted, the $R^{3D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{3D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{3D.2}$ substituent group is substituted, the $R^{3D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{3D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{3D} , $R^{3D.1}$, $R^{3D.2}$, and $R^{3D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{3D} , $R^{3D.1}$, $R^{3D.2}$, and $R^{3D.3}$, respectively.

[0558] In embodiments, when R^{4A} is substituted, R^{4A} is substituted with one or more first substituent groups denoted by $R^{4A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4A.1}$ substituent group is substituted, the $R^{4A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4A.2}$ substituent group is substituted, the $R^{4A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4A} , $R^{4A.1}$, $R^{4A.2}$, and $R^{4A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4A} , $R^{4A.1}$, $R^{4A.2}$, and $R^{4A.3}$, respectively.

[0559] In embodiments, when R^{4B} is substituted, R^{4B} is substituted with one or more first substituent groups denoted by $R^{4B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.1}$ substituent group is substituted, the $R^{4B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.2}$ substituent group is substituted, the $R^{4B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4B} , $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4B} , $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$, respectively.

[0560] In embodiments, when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{4A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4A.1}$ substituent group is substituted, the $R^{4A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In

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

[0561] In embodiments, when R^{4A} and R^{4B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{4B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.1}$ substituent group is substituted, the $R^{4B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4B.2}$ substituent group is substituted, the $R^{4B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{4B.1}$, $R^{4B.2}$, and $R^{4B.3}$, respectively.

[0562] In embodiments, when R^{4C} is substituted, R^{4C} is substituted with one or more first substituent groups denoted by $R^{4C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4C.1}$ substituent group is substituted, the $R^{4C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4C.2}$ substituent group is substituted, the $R^{4C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4C} , $R^{4C.1}$, $R^{4C.2}$, and $R^{4C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the

description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4C} , $R^{4C.1}$, $R^{4C.2}$, and $R^{4C.3}$, respectively.

[0563] In embodiments, when R^{4D} is substituted, R^{4D} is substituted with one or more first substituent groups denoted by $R^{4D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4D.1}$ substituent group is substituted, the $R^{4D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{4D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{4D.2}$ substituent group is substituted, the $R^{4D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{4D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{4D} , $R^{4D.1}$, $R^{4D.2}$, and $R^{4D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{4D} , $R^{4D.1}$, $R^{4D.2}$, and $R^{4D.3}$, respectively.

[0564] In embodiments, when R^{5A} is substituted, R^{5A} is substituted with one or more first substituent groups denoted by $R^{5A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5A.1}$ substituent group is substituted, the $R^{5A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5A.2}$ substituent group is substituted, the $R^{5A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5A} , $R^{5A.1}$, $R^{5A.2}$, and $R^{5A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5A} , $R^{5A.1}$, $R^{5A.2}$, and $R^{5A.3}$, respectively.

[0565] In embodiments, when R^{5B} is substituted, R^{5B} is substituted with one or more first substituent groups denoted by $R^{5B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.1}$ substituent group is substituted, the $R^{5B.1}$ substituent group is substituted with one or more second substituent groups

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

[0566] In embodiments, when R^{5A} and R^{5B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{5A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5A.1}$ substituent group is substituted, the $R^{5A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5A.2}$ substituent group is substituted, the $R^{5A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{5A.1}$, $R^{5A.2}$, and $R^{5A.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{5A.1}$, $R^{5A.2}$, and $R^{5A.3}$, respectively.

[0567] In embodiments, when R^{5A} and R^{5B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{5B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.1}$ substituent group is substituted, the $R^{5B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5B.2}$ substituent group is substituted, the $R^{5B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5B.3}$ as explained in the

definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{5B.1}$, $R^{5B.2}$, and $R^{5B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{5B.1}$, $R^{5B.2}$, and $R^{5B.3}$, respectively.

[0568] In embodiments, when R^{5C} is substituted, R^{5C} is substituted with one or more first substituent groups denoted by $R^{5C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5C.1}$ substituent group is substituted, the $R^{5C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5C.2}$ substituent group is substituted, the $R^{5C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5C} , $R^{5C.1}$, $R^{5C.2}$, and $R^{5C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5C} , $R^{5C.1}$, $R^{5C.2}$, and $R^{5C.3}$, respectively.

[0569] In embodiments, when R^{5D} is substituted, R^{5D} is substituted with one or more first substituent groups denoted by $R^{5D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5D.1}$ substituent group is substituted, the $R^{5D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{5D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{5D.2}$ substituent group is substituted, the $R^{5D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{5D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{5D} , $R^{5D.1}$, $R^{5D.2}$, and $R^{5D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{5D} , $R^{5D.1}$, $R^{5D.2}$, and $R^{5D.3}$, respectively.

[0570] In embodiments, when R^{6A} is substituted, R^{6A} is substituted with one or more first substituent groups denoted by $R^{6A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6A.1}$ substituent group is substituted, the $R^{6A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6A.2}$ substituent group is substituted, the $R^{6A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6A} , $R^{6A.1}$, $R^{6A.2}$, and $R^{6A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6A} , $R^{6A.1}$, $R^{6A.2}$, and $R^{6A.3}$, respectively.

[0571] In embodiments, when R^{6B} is substituted, R^{6B} is substituted with one or more first substituent groups denoted by $R^{6B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6B.1}$ substituent group is substituted, the $R^{6B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6B.2}$ substituent group is substituted, the $R^{6B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6B} , $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6B} , $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$, respectively.

[0572] In embodiments, when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{6A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6A.1}$ substituent group is substituted, the $R^{6A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In

embodiments, when an $R^{6A.2}$ substituent group is substituted, the $R^{6A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{6A.1}$, $R^{6A.2}$, and $R^{6A.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{6A.1}$, $R^{6A.2}$, and $R^{6A.3}$, respectively.

[0573] In embodiments, when R^{6A} and R^{6B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{6B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6B.1}$ substituent group is substituted, the $R^{6B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6B.2}$ substituent group is substituted, the $R^{6B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{6B.1}$, $R^{6B.2}$, and $R^{6B.3}$, respectively.

[0574] In embodiments, when R^{6C} is substituted, R^{6C} is substituted with one or more first substituent groups denoted by $R^{6C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6C.1}$ substituent group is substituted, the $R^{6C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6C.2}$ substituent group is substituted, the $R^{6C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6C} , $R^{6C.1}$, $R^{6C.2}$, and $R^{6C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the

description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6C} , $R^{6C.1}$, $R^{6C.2}$, and $R^{6C.3}$, respectively.

[0575] In embodiments, when R^{6D} is substituted, R^{6D} is substituted with one or more first substituent groups denoted by $R^{6D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6D.1}$ substituent group is substituted, the $R^{6D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{6D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{6D.2}$ substituent group is substituted, the $R^{6D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{6D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{6D} , $R^{6D.1}$, $R^{6D.2}$, and $R^{6D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{6D} , $R^{6D.1}$, $R^{6D.2}$, and $R^{6D.3}$, respectively.

[0576] In embodiments, when R^{10A} is substituted, R^{10A} is substituted with one or more first substituent groups denoted by $R^{10A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10A.1}$ substituent group is substituted, the $R^{10A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10A.2}$ substituent group is substituted, the $R^{10A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{10A} , $R^{10A.1}$, $R^{10A.2}$, and $R^{10A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{10A} , $R^{10A.1}$, $R^{10A.2}$, and $R^{10A.3}$, respectively.

[0577] In embodiments, when R^{10B} is substituted, R^{10B} is substituted with one or more first substituent groups denoted by $R^{10B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10B.1}$ substituent group is substituted, the $R^{10B.1}$ substituent group is substituted with one or more second substituent groups

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

[0578] In embodiments, when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{10A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10A.1}$ substituent group is substituted, the $R^{10A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10A.2}$ substituent group is substituted, the $R^{10A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{10A.1}$, $R^{10A.2}$, and $R^{10A.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{10A.1}$, $R^{10A.2}$, and $R^{10A.3}$, respectively.

[0579] In embodiments, when R^{10A} and R^{10B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{10B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10B.1}$ substituent group is substituted, the $R^{10B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10B.2}$ substituent group is substituted, the $R^{10B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10B.3}$ as explained in the

definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{10B.1}$, $R^{10B.2}$, and $R^{10B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{10B.1}$, $R^{10B.2}$, and $R^{10B.3}$, respectively.

[0580] In embodiments, when R^{10C} is substituted, R^{10C} is substituted with one or more first substituent groups denoted by $R^{10C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10C.1}$ substituent group is substituted, the $R^{10C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10C.2}$ substituent group is substituted, the $R^{10C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{10C} , $R^{10C.1}$, $R^{10C.2}$, and $R^{10C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{10C} , $R^{10C.1}$, $R^{10C.2}$, and $R^{10C.3}$, respectively.

[0581] In embodiments, when R^{10D} is substituted, R^{10D} is substituted with one or more first substituent groups denoted by $R^{10D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10D.1}$ substituent group is substituted, the $R^{10D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{10D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{10D.2}$ substituent group is substituted, the $R^{10D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{10D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{10D} , $R^{10D.1}$, $R^{10D.2}$, and $R^{10D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{10D} , $R^{10D.1}$, $R^{10D.2}$, and $R^{10D.3}$, respectively.

[0582] In embodiments, when R^{11A} is substituted, R^{11A} is substituted with one or more first substituent groups denoted by $R^{11A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11A.1}$ substituent group is substituted, the $R^{11A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11A.2}$ substituent group is substituted, the $R^{11A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{11A} , $R^{11A.1}$, $R^{11A.2}$, and $R^{11A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{11A} , $R^{11A.1}$, $R^{11A.2}$, and $R^{11A.3}$, respectively.

[0583] In embodiments, when R^{11B} is substituted, R^{11B} is substituted with one or more first substituent groups denoted by $R^{11B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11B.1}$ substituent group is substituted, the $R^{11B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11B.2}$ substituent group is substituted, the $R^{11B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{11B} , $R^{11B.1}$, $R^{11B.2}$, and $R^{11B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{11B} , $R^{11B.1}$, $R^{11B.2}$, and $R^{11B.3}$, respectively.

[0584] In embodiments, when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{11A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11A.1}$ substituent group is substituted, the $R^{11A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11A.2}$ as explained in the definitions section above in the description of “first substituent

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

[0585] In embodiments, when R^{11A} and R^{11B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{11B.1}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{11B.1}$ substituent group is substituted, the $R^{11B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11B.2}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{11B.2}$ substituent group is substituted, the $R^{11B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11B.3}$ as explained in the definitions section above in the description of "first substituent group(s)". In the above embodiments, $R^{11B.1}$, $R^{11B.2}$, and $R^{11B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of "first substituent group(s)", wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11B.1}$, $R^{11B.2}$, and $R^{11B.3}$, respectively.

[0586] In embodiments, when R^{11C} is substituted, R^{11C} is substituted with one or more first substituent groups denoted by $R^{11C.1}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{11C.1}$ substituent group is substituted, the $R^{11C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11C.2}$ as explained in the definitions section above in the description of "first substituent group(s)". In embodiments, when an $R^{11C.2}$ substituent group is substituted, the $R^{11C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11C.3}$ as explained in the definitions section above in the description of "first substituent group(s)". In the above embodiments, R^{11C} , $R^{11C.1}$, $R^{11C.2}$, and $R^{11C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the

description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{11C} , $R^{11C.1}$, $R^{11C.2}$, and $R^{11C.3}$, respectively.

[0587] In embodiments, when R^{11D} is substituted, R^{11D} is substituted with one or more first substituent groups denoted by $R^{11D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11D.1}$ substituent group is substituted, the $R^{11D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11D.2}$ substituent group is substituted, the $R^{11D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{11D} , $R^{11D.1}$, $R^{11D.2}$, and $R^{11D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{11D} , $R^{11D.1}$, $R^{11D.2}$, and $R^{11D.3}$, respectively.

[0588] In embodiments, when R^{12A} is substituted, R^{12A} is substituted with one or more first substituent groups denoted by $R^{12A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12A.1}$ substituent group is substituted, the $R^{12A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12A.2}$ substituent group is substituted, the $R^{12A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{12A} , $R^{12A.1}$, $R^{12A.2}$, and $R^{12A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{12A} , $R^{12A.1}$, $R^{12A.2}$, and $R^{12A.3}$, respectively.

[0589] In embodiments, when R^{12B} is substituted, R^{12B} is substituted with one or more first substituent groups denoted by $R^{12B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12B.1}$ substituent group is substituted, the $R^{12B.1}$ substituent group is substituted with one or more second substituent groups

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

[0590] In embodiments, when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{12A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12A.1}$ substituent group is substituted, the $R^{12A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12A.2}$ substituent group is substituted, the $R^{12A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12A.1}$, $R^{12A.2}$, and $R^{12A.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12A.1}$, $R^{12A.2}$, and $R^{12A.3}$, respectively.

[0591] In embodiments, when R^{12A} and R^{12B} substituents bonded to the same nitrogen atom are optionally joined to form a moiety that is substituted (e.g., a substituted heterocycloalkyl or substituted heteroaryl), the moiety is substituted with one or more first substituent groups denoted by $R^{12B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12B.1}$ substituent group is substituted, the $R^{12B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12B.2}$ substituent group is substituted, the $R^{12B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12B.3}$ as explained in the

definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12B.1}$, $R^{12B.2}$, and $R^{12B.3}$ have values corresponding to the values of $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12B.1}$, $R^{12B.2}$, and $R^{12B.3}$, respectively.

[0592] In embodiments, when R^{12C} is substituted, R^{12C} is substituted with one or more first substituent groups denoted by $R^{12C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12C.1}$ substituent group is substituted, the $R^{12C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12C.2}$ substituent group is substituted, the $R^{12C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{12C} , $R^{12C.1}$, $R^{12C.2}$, and $R^{12C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{12C} , $R^{12C.1}$, $R^{12C.2}$, and $R^{12C.3}$, respectively.

[0593] In embodiments, when R^{12D} is substituted, R^{12D} is substituted with one or more first substituent groups denoted by $R^{12D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12D.1}$ substituent group is substituted, the $R^{12D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12D.2}$ substituent group is substituted, the $R^{12D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{12D} , $R^{12D.1}$, $R^{12D.2}$, and $R^{12D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{12D} , $R^{12D.1}$, $R^{12D.2}$, and $R^{12D.3}$, respectively.

[0594] In embodiments, when L^1 is substituted, L^1 is substituted with one or more first substituent groups denoted by $R^{L1.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L1.1}$ substituent group is substituted, the $R^{L1.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{L1.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L1.2}$ substituent group is substituted, the $R^{L1.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{L1.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, L^1 , $R^{L1.1}$, $R^{L1.2}$, and $R^{L1.3}$ have values corresponding to the values of L^{WW} , $R^{LWW.1}$, $R^{LWW.2}$, and $R^{LWW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein L^{WW} , $R^{LWW.1}$, $R^{LWW.2}$, and $R^{LWW.3}$ are L^1 , $R^{L1.1}$, $R^{L1.2}$, and $R^{L1.3}$, respectively.

[0595] In embodiments, when $R^{11.A}$ is substituted, $R^{11.A}$ is substituted with one or more first substituent groups denoted by $R^{11.A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.A.1}$ substituent group is substituted, the $R^{11.A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.A.2}$ substituent group is substituted, the $R^{11.A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.A}$, $R^{11.A.1}$, $R^{11.A.2}$, and $R^{11.A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.A}$, $R^{11.A.1}$, $R^{11.A.2}$, and $R^{11.A.3}$, respectively.

[0596] In embodiments, when $R^{11.B}$ is substituted, $R^{11.B}$ is substituted with one or more first substituent groups denoted by $R^{11.B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.B.1}$ substituent group is substituted, the $R^{11.B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.B.2}$ substituent group is substituted, the $R^{11.B.2}$ substituent group is substituted with one or more third substituent groups denoted by

$R^{11.B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.B}$, $R^{11.B.1}$, $R^{11.B.2}$, and $R^{11.B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.B}$, $R^{11.B.1}$, $R^{11.B.2}$, and $R^{11.B.3}$, respectively.

[0597] In embodiments, when $R^{11.C}$ is substituted, $R^{11.C}$ is substituted with one or more first substituent groups denoted by $R^{11.C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.C.1}$ substituent group is substituted, the $R^{11.C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.C.2}$ substituent group is substituted, the $R^{11.C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.C}$, $R^{11.C.1}$, $R^{11.C.2}$, and $R^{11.C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.C}$, $R^{11.C.1}$, $R^{11.C.2}$, and $R^{11.C.3}$, respectively.

[0598] In embodiments, when $R^{11.D}$ is substituted, $R^{11.D}$ is substituted with one or more first substituent groups denoted by $R^{11.D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.D.1}$ substituent group is substituted, the $R^{11.D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.D.2}$ substituent group is substituted, the $R^{11.D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.D}$, $R^{11.D.1}$, $R^{11.D.2}$, and $R^{11.D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.D}$, $R^{11.D.1}$, $R^{11.D.2}$, and $R^{11.D.3}$, respectively.

[0599] In embodiments, when $R^{11.E}$ is substituted, $R^{11.E}$ is substituted with one or more first substituent groups denoted by $R^{11.E.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.E.1}$ substituent group is substituted, the $R^{11.E.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.E.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.E.2}$ substituent group is substituted, the $R^{11.E.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.E.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.E}$, $R^{11.E.1}$, $R^{11.E.2}$, and $R^{11.E.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.E}$, $R^{11.E.1}$, $R^{11.E.2}$, and $R^{11.E.3}$, respectively.

[0600] In embodiments, when $R^{11.G}$ is substituted, $R^{11.G}$ is substituted with one or more first substituent groups denoted by $R^{11.G.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.G.1}$ substituent group is substituted, the $R^{11.G.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.G.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.G.2}$ substituent group is substituted, the $R^{11.G.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{11.G.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.G}$, $R^{11.G.1}$, $R^{11.G.2}$, and $R^{11.G.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.G}$, $R^{11.G.1}$, $R^{11.G.2}$, and $R^{11.G.3}$, respectively.

[0601] In embodiments, when $R^{11.H}$ is substituted, $R^{11.G}$ is substituted with one or more first substituent groups denoted by $R^{11.H.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.H.1}$ substituent group is substituted, the $R^{11.H.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{11.H.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{11.H.2}$ substituent group is substituted, the $R^{11.H.2}$ substituent group is substituted with one or more third substituent groups denoted by

$R^{11.H.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{11.H}$, $R^{11.H.1}$, $R^{11.H.2}$, and $R^{11.H.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{11.H}$, $R^{11.H.1}$, $R^{11.H.2}$, and $R^{11.H.3}$, respectively.

[0602] In embodiments, when $R^{12.A}$ is substituted, $R^{12.A}$ is substituted with one or more first substituent groups denoted by $R^{12.A.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.A.1}$ substituent group is substituted, the $R^{12.A.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.A.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.A.2}$ substituent group is substituted, the $R^{12.A.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12.A.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12.A}$, $R^{12.A.1}$, $R^{12.A.2}$, and $R^{12.A.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12.A}$, $R^{12.A.1}$, $R^{12.A.2}$, and $R^{12.A.3}$, respectively.

[0603] In embodiments, when $R^{12.B}$ is substituted, $R^{12.B}$ is substituted with one or more first substituent groups denoted by $R^{12.B.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.B.1}$ substituent group is substituted, the $R^{12.B.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.B.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.B.2}$ substituent group is substituted, the $R^{12.B.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12.B.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12.B}$, $R^{12.B.1}$, $R^{12.B.2}$, and $R^{12.B.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12.B}$, $R^{12.B.1}$, $R^{12.B.2}$, and $R^{12.B.3}$, respectively.

[0604] In embodiments, when $R^{12.C}$ is substituted, $R^{12.C}$ is substituted with one or more first substituent groups denoted by $R^{12.C.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.C.1}$ substituent group is substituted, the $R^{12.C.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.C.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.C.2}$ substituent group is substituted, the $R^{12.C.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12.C.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12.C}$, $R^{12.C.1}$, $R^{12.C.2}$, and $R^{12.C.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12.C}$, $R^{12.C.1}$, $R^{12.C.2}$, and $R^{12.C.3}$, respectively.

[0605] In embodiments, when $R^{12.D}$ is substituted, $R^{12.D}$ is substituted with one or more first substituent groups denoted by $R^{12.D.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.D.1}$ substituent group is substituted, the $R^{12.D.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.D.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.D.2}$ substituent group is substituted, the $R^{12.D.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{12.D.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12.D}$, $R^{12.D.1}$, $R^{12.D.2}$, and $R^{12.D.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12.D}$, $R^{12.D.1}$, $R^{12.D.2}$, and $R^{12.D.3}$, respectively.

[0606] In embodiments, when $R^{12.E}$ is substituted, $R^{12.E}$ is substituted with one or more first substituent groups denoted by $R^{12.E.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.E.1}$ substituent group is substituted, the $R^{12.E.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{12.E.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{12.E.2}$ substituent group is substituted, the $R^{12.E.2}$ substituent group is substituted with one or more third substituent groups denoted by

$R^{12.E.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, $R^{12.E}$, $R^{12.E.1}$, $R^{12.E.2}$, and $R^{12.E.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to $R^{12.E}$, $R^{12.E.1}$, $R^{12.E.2}$, and $R^{12.E.3}$, respectively.

[0607] In embodiments, when R^{14} is substituted, R^{14} is substituted with one or more first substituent groups denoted by $R^{14.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{14.1}$ substituent group is substituted, the $R^{14.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{14.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{14.2}$ substituent group is substituted, the $R^{14.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{14.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{14} , $R^{14.1}$, $R^{14.2}$, and $R^{14.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{14} , $R^{14.1}$, $R^{14.2}$, and $R^{14.3}$, respectively.

[0608] In embodiments, when R^{15} is substituted, R^{15} is substituted with one or more first substituent groups denoted by $R^{15.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{15.1}$ substituent group is substituted, the $R^{15.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{15.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{15.2}$ substituent group is substituted, the $R^{15.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{15.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{15} , $R^{15.1}$, $R^{15.2}$, and $R^{15.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{15} , $R^{15.1}$, $R^{15.2}$, and $R^{15.3}$, respectively.

[0609] In embodiments, when L^{14} is substituted, L^{14} is substituted with one or more first substituent groups denoted by $R^{L^{14}.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L^{14}.1}$ substituent group is substituted, the $R^{L^{14}.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{L^{14}.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L^{14}.2}$ substituent group is substituted, the $R^{L^{14}.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{L^{14}.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, L^{14} , $R^{L^{14}.1}$, $R^{L^{14}.2}$, and $R^{L^{14}.3}$ have values corresponding to the values of L^{WW} , $R^{L^{WW}.1}$, $R^{L^{WW}.2}$, and $R^{L^{WW}.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein L^{WW} , $R^{L^{WW}.1}$, $R^{L^{WW}.2}$, and $R^{L^{WW}.3}$ are L^{14} , $R^{L^{14}.1}$, $R^{L^{14}.2}$, and $R^{L^{14}.3}$, respectively.

[0610] In embodiments, when R^{16} is substituted, R^{16} is substituted with one or more first substituent groups denoted by $R^{16.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16.1}$ substituent group is substituted, the $R^{16.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{16.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{16.2}$ substituent group is substituted, the $R^{16.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{16.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{16} , $R^{16.1}$, $R^{16.2}$, and $R^{16.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{16} , $R^{16.1}$, $R^{16.2}$, and $R^{16.3}$, respectively.

[0611] In embodiments, when R^{17} is substituted, R^{17} is substituted with one or more first substituent groups denoted by $R^{17.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17.1}$ substituent group is substituted, the $R^{17.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{17.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{17.2}$ substituent group is substituted, the $R^{17.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{17.3}$ as

explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, R^{17} , $R^{17.1}$, $R^{17.2}$, and $R^{17.3}$ have values corresponding to the values of R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein R^{WW} , $R^{WW.1}$, $R^{WW.2}$, and $R^{WW.3}$ correspond to R^{17} , $R^{17.1}$, $R^{17.2}$, and $R^{17.3}$, respectively.

[0612] In embodiments, when L^{16} is substituted, L^{16} is substituted with one or more first substituent groups denoted by $R^{L16.1}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L16.1}$ substituent group is substituted, the $R^{L16.1}$ substituent group is substituted with one or more second substituent groups denoted by $R^{L16.2}$ as explained in the definitions section above in the description of “first substituent group(s)”. In embodiments, when an $R^{L16.2}$ substituent group is substituted, the $R^{L16.2}$ substituent group is substituted with one or more third substituent groups denoted by $R^{L16.3}$ as explained in the definitions section above in the description of “first substituent group(s)”. In the above embodiments, L^{16} , $R^{L16.1}$, $R^{L16.2}$, and $R^{L16.3}$ have values corresponding to the values of L^{WW} , $R^{LWW.1}$, $R^{LWW.2}$, and $R^{LWW.3}$, respectively, as explained in the definitions section above in the description of “first substituent group(s)”, wherein L^{WW} , $R^{LWW.1}$, $R^{LWW.2}$, and $R^{LWW.3}$ are L^{16} , $R^{L16.1}$, $R^{L16.2}$, and $R^{L16.3}$, respectively.

[0613] In embodiments, the compound described herein is useful as a test compound. In embodiments, the compound described herein is useful in assays. In embodiments, the compound described herein is useful as a test compound in an assay, for example in an assay described herein (e.g., a cell entry assay, protein-protein interaction assay, virus binding to cell assay, cell assay, in vitro assay).

III. Compositions

[0614] In an aspect is provided a pharmaceutical composition including a compound as described herein and a pharmaceutically acceptable excipient.

[0615] 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.

[0616] In embodiments, the pharmaceutical composition includes a second agent. In embodiments, the second agent is an anti-inflammatory agent. In embodiments, the second agent is an agent capable of treating COVID-19. In embodiments, the pharmaceutical composition includes an effective amount of a second agent, wherein the second agent is an anti-inflammatory agent. In embodiments, the second agent treats COVID-19. In embodiments, the second agent treats an inflammatory disease. In embodiments, the pharmaceutical composition includes the second agent in a therapeutically effective amount.

IV. Methods

[0617] In an aspect is provided a method of treating a coronavirus infection in a subject in need thereof, the method including administering to the subject in need thereof an effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof.

[0618] In embodiments, the coronavirus infection is a SARS-CoV-1 infection. In embodiments, the coronavirus infection is Severe Acute Respiratory Disease (SARS). In embodiments, the coronavirus infection is a SARS-CoV-2 infection. In embodiments, the coronavirus infection is coronavirus disease 2019 (COVID-19). In embodiments, the subject in need thereof has or is suspected of having COVID-19.

[0619] In an aspect is provided a method of treating COVID-19, the method including administering to a subject in need thereof an effective amount of a compound as described herein, including embodiments.

[0620] In embodiments, the method includes administering to the subject a therapeutically effective amount of a compound described herein.

[0621] In embodiments, the method of treating COVID-19 includes treating one or more symptoms of COVID-19. In embodiments, the symptom is cough, shortness of breath or difficulty breathing, fever, chills, repeated shaking with chills, muscle pain, headache, sore throat, or new loss of taste or smell. In embodiments, the method includes treating respiratory symptoms. In embodiments, the method includes treating shortness of breath or difficulty breathing. In embodiments, the method includes treating fever. In embodiments, the method includes treating cough. In embodiments, the method includes treating fatigue. In embodiments,

the method includes treating body aches. In embodiments, the method includes treating headache.

[0622] In embodiments, the subject in need thereof is not hospitalized. In embodiments, the subject in need thereof is hospitalized. In embodiments, the subject in need thereof is in an intensive care unit.

[0623] In an aspect is provided a method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), the method including: contacting the SARS-CoV-2 spike protein with a compound as described herein, including embodiments.

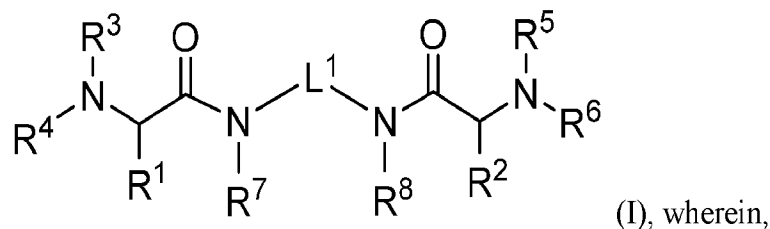
[0624] In an aspect is provided a method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), the method including: contacting human angiotensin-converting enzyme 2 (ACE-2) with a compound as described herein, including embodiments.

[0625] Q34 and C1 structures are identical. Therefore, they are used interchangeably.

[0626] 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.

NUMBERED EMBODIMENTS

[0627] Embodiment 1. A method of treating COVID-19, said method comprising administering to a subject in need thereof an effective amount of a compound having the formula:



L^1 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

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

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

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

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

or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl;

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

R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl;

R^7 and R^8 are independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

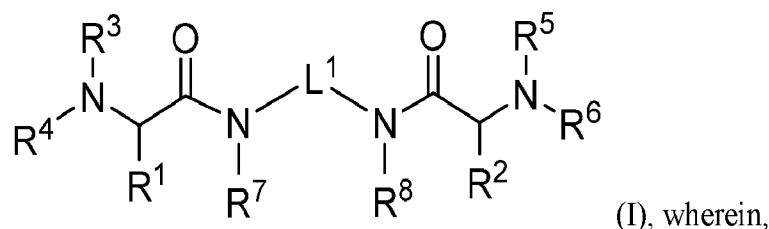
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

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

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

m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 , are independently 1 or 2.

[0628] Embodiment 2. A method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), said method comprising contacting the SARS-CoV-2 spike protein with a compound having the formula:



L^1 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 is independently hydrogen, halogen, $-CX^{1_3}$, $-CHX^{1_2}$, $-CH_2X^1$, $-OCX^{1_3}$, $-OCH_2X^1$, $-OCHX^{1_2}$, $-CN$, $-SO_{n_1}R^{1D}$, $-SO_{v_1}NR^{1A}R^{1B}$, $-NR^{1C}NR^{1A}R^{1B}$, $-ONR^{1A}R^{1B}$,

$-\text{NHC(O)NR}^{1\text{C}}\text{NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{NHC(O)NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{N(O)}_{\text{m1}}$, $-\text{NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{C(O)R}^{1\text{C}}$, $-\text{C(O)-OR}^{1\text{C}}$, $-\text{C(O)NR}^{1\text{A}}\text{R}^{1\text{B}}$, $-\text{OR}^{1\text{D}}$, $-\text{NR}^{1\text{A}}\text{SO}_2\text{R}^{1\text{D}}$, $-\text{NR}^{1\text{A}}\text{C(O)R}^{1\text{C}}$, $-\text{NR}^{1\text{A}}\text{C(O)OR}^{1\text{C}}$, $-\text{NR}^{1\text{A}}\text{OR}^{1\text{C}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

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

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

R^4 is independently hydrogen, halogen, $-\text{CX}^4_3$, $-\text{CHX}^4_2$, $-\text{CH}_2\text{X}^4$, $-\text{OCX}^4_3$, $-\text{OCH}_2\text{X}^4$, $-\text{OCHX}^4_2$, $-\text{CN}$, $-\text{SO}_{\text{n4}}\text{R}^{4\text{D}}$, $-\text{SO}_{\text{v4}}\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NR}^{4\text{C}}\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{ONR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NHC(O)NR}^{4\text{C}}\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{NHC(O)NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{N(O)}_{\text{m4}}$, $-\text{NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{C(O)R}^{4\text{C}}$, $-\text{C(O)-OR}^{4\text{C}}$, $-\text{C(O)NR}^{4\text{A}}\text{R}^{4\text{B}}$, $-\text{OR}^{4\text{D}}$, $-\text{NR}^{4\text{A}}\text{SO}_2\text{R}^{4\text{D}}$, $-\text{NR}^{4\text{A}}\text{C(O)R}^{4\text{C}}$, $-\text{NR}^{4\text{A}}\text{C(O)OR}^{4\text{C}}$, $-\text{NR}^{4\text{A}}\text{OR}^{4\text{C}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

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

R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^7 and R^8 are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted

heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

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

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

m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 , are independently 1 or 2.

[0629] Embodiment 3. The method of embodiment 1 or 2, wherein

L^1 is independently substituted or unsubstituted C_2 - C_{10} alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C_3 - C_{10} cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

[0630] Embodiment 4. The method of embodiment 1 or 2, wherein

L^1 is independently R^{10} -substituted or unsubstituted C_2 - C_{10} alkylene, R^{10} -substituted or unsubstituted 2 to 8 membered heteroalkylene, R^{10} -substituted or unsubstituted C_3 - C_{10} cycloalkylene, R^{10} -substituted or unsubstituted 3 to 8 membered heterocycloalkylene, R^{10} -substituted or unsubstituted phenylene, or R^{10} -substituted or unsubstituted 5 to 6 membered heteroarylene; and

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

R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X and X^{10} are independently $-F$, $-Cl$, $-Br$, or $-I$;

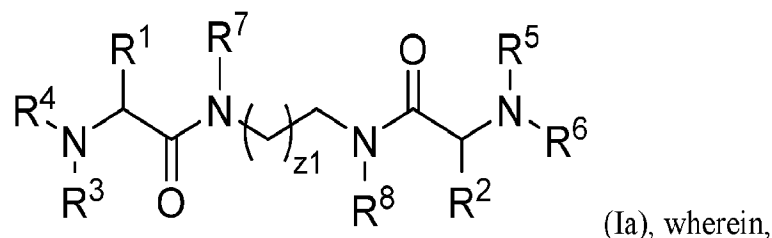
n_{10} , is independently an integer from 0 to 4; and

m_{10} and v_{10} are independently 1 or 2.

[0631] Embodiment 5. The method of embodiment 1 or 2, wherein

L^1 is independently substituted or unsubstituted C_2 - C_6 alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene, substituted or unsubstituted C_3 - C_6 cycloalkylene, substituted or unsubstituted 3 to 6 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

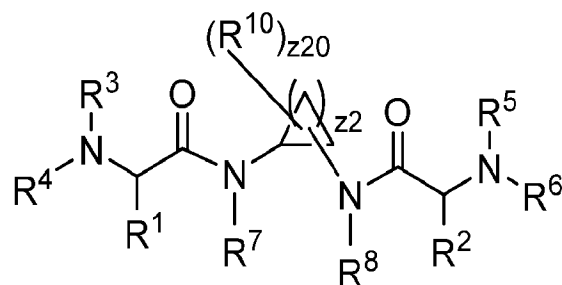
[0632] Embodiment 6. The method of embodiment 1 or 2, wherein the compound has the formula:



z_1 is an integer from 1 to 9.

[0633] Embodiment 7. The method of embodiment 6, wherein z_1 is an integer from 1 to 6.

[0634] Embodiment 8. The method of embodiment 1 or 2, wherein the compound has the formula:



(Ib), wherein,

z2 is an integer from 1 to 8;

z20 is an integer from 0 to 18;

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

R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

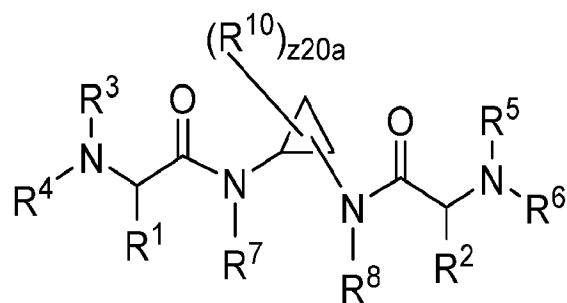
X and X^{10} are independently $-F$, $-Cl$, $-Br$, or $-I$;

n10 is independently an integer from 0 to 4; and

m10 and v10 are independently 1 or 2.

[0635] Embodiment 9. The method of embodiment 8, wherein z2 is an integer from 1 to 4.

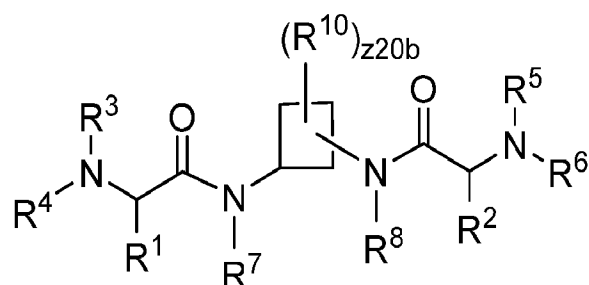
[0636] Embodiment 10. The method of embodiment 8, wherein the compound has the formula:



, wherein $z20a$ is an integer from 0

to 4.

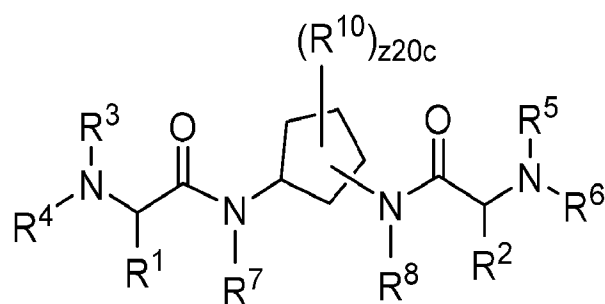
[0637] Embodiment 11. The method of embodiment 8 wherein the compound has the formula:



, wherein $z20b$ is an integer from 0

to 6.

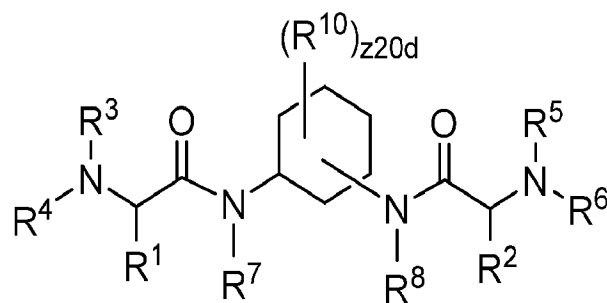
[0638] Embodiment 12. The method of embodiment 8 wherein the compound has the formula:



, wherein $z20c$ is an integer from

0 to 8.

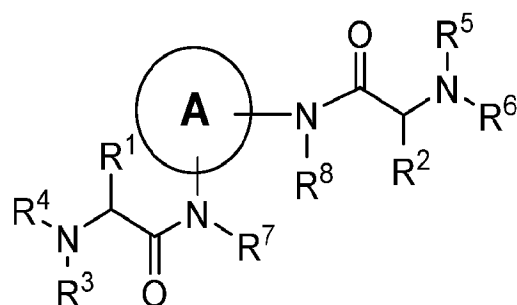
[0639] Embodiment 13. The method of embodiment 8 wherein the compound has the formula:



, wherein z_{20d} is an integer from

0 to 10.

[0640] Embodiment 14. The method of embodiment 1 or 2, wherein the compound has the formula:



(Ic), wherein,

Ring A is substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene.

[0641] Embodiment 15. The method of embodiment **Error! Reference source not found.**, wherein Ring A is R^{10} -substituted or unsubstituted phenylene or R^{10} -substituted or unsubstituted 5 to 6 membered heteroaryl;

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

R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

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

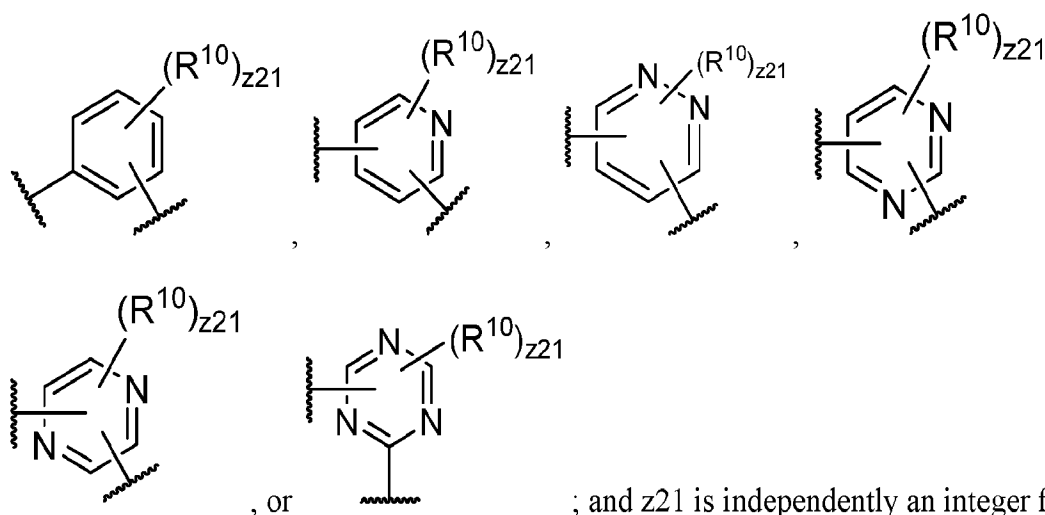
X and X^{10} are independently -F, -Cl, -Br, or -I;

n_{10} is independently an integer from 0 to 4; and

m_{10} and v_{10} are independently 1 or 2.

[0642] Embodiment 16. The method of embodiment 14, wherein Ring A is substituted or unsubstituted phenylene, substituted or unsubstituted pyridylene, substituted or unsubstituted pyridazinylene, substituted or unsubstituted triazinylene, substituted or unsubstituted pyrimidinylene, substituted or unsubstituted pyrazinylene, substituted or unsubstituted pyrrolylene, or substituted or unsubstituted pyrazolylene.

[0643] Embodiment 17. The method of embodiment 16, wherein Ring A is



; and z_{21} is independently an integer from 0 to 4.

[0644] Embodiment 18. The method of any one of embodiments 1 to 17, wherein:

R^1 and R^2 are independently hydrogen, 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 6 membered heterocycloalkyl, substituted or unsubstituted C_6 - C_{12} aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

[0645] Embodiment 19. The method of any one of embodiments 1 to 18, wherein:

R^1 is independently hydrogen, R^{11} -substituted or unsubstituted arginine side chain, R^{11} -substituted or unsubstituted histidine side chain, R^{11} -substituted or unsubstituted lysine side chain, R^{11} -substituted or unsubstituted aspartic acid side chain, R^{11} -substituted or unsubstituted glutamic acid side chain, R^{11} -substituted or unsubstituted serine side chain, R^{11} -substituted or unsubstituted threonine side chain, R^{11} -substituted or unsubstituted asparagine side chain, R^{11} -substituted or unsubstituted glutamine side chain, R^{11} -substituted or unsubstituted cysteine side chain, R^{11} -substituted or unsubstituted glycine side chain, R^{11} -substituted or unsubstituted proline side chain, R^{11} -substituted or unsubstituted alanine side chain, R^{11} -substituted or unsubstituted valine side chain, R^{11} -substituted or unsubstituted isoleucine side chain, R^{11} -substituted or unsubstituted leucine side chain, R^{11} -substituted or unsubstituted methionine side chain, R^{11} -substituted or unsubstituted phenylalanine side chain, R^{11} -substituted or unsubstituted tyrosine side chain, or R^{11} -substituted or unsubstituted tryptophan side chain;

each R^{11} is independently halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11D}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NR^{11C}NR^{11A}R^{11B}$, $-ONR^{11A}R^{11B}$, $-NHC(O)NR^{11C}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-C(O)R^{11C}$, $-C(O)-OR^{11C}$, $-C(O)NR^{11A}R^{11B}$, $-OR^{11D}$, $-NR^{11A}SO_2R^{11D}$, $-NR^{11A}C(O)R^{11C}$, $-NR^{11A}C(O)OR^{11C}$, $-NR^{11A}OR^{11C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{11A} , R^{11B} , R^{11C} , and R^{11D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^2 is independently hydrogen, R^{12} -substituted or unsubstituted arginine side chain, R^{12} -substituted or unsubstituted histidine side chain, R^{12} -substituted or unsubstituted lysine side chain, R^{12} -substituted or unsubstituted aspartic acid side chain, R^{12} -substituted or unsubstituted glutamic acid side chain, R^{12} -substituted or unsubstituted serine side chain, R^{12} -substituted or unsubstituted threonine side chain, R^{12} -substituted or unsubstituted asparagine side

chain, R¹²-substituted or unsubstituted glutamine side chain, R¹²-substituted or unsubstituted cysteine side chain, R¹²-substituted or unsubstituted glycine side chain, R¹²-substituted or unsubstituted proline side chain, R¹²-substituted or unsubstituted alanine side chain, R¹²-substituted or unsubstituted valine side chain, R¹²-substituted or unsubstituted isoleucine side chain, R¹²-substituted or unsubstituted leucine side chain, R¹²-substituted or unsubstituted methionine side chain, R¹²-substituted or unsubstituted phenylalanine side chain, R¹²-substituted or unsubstituted tyrosine side chain, or R¹²-substituted or unsubstituted tryptophan side chain;

each R¹² is independently halogen, -CX¹²₃, -CHX¹²₂, -CH₂X¹², -OCX¹²₃, -OCH₂X¹², -OCHX¹²₂, -CN, -SO_{n12}R^{12D}, -SO_{v12}NR^{12A}R^{1B}, -NR^{12C}NR^{12A}R^{12B}, -ONR^{12A}R^{12B}, -NHC(O)NR^{12C}NR^{12A}R^{12B}, -NHC(O)NR^{12A}R^{12B}, -N(O)_{m12}, -NR^{12A}R^{12B}, -C(O)R^{12C}, -C(O)-OR^{12C}, -C(O)NR^{12A}R^{12B}, -OR^{12D}, -NR^{12A}SO₂R^{12D}, -NR^{12A}C(O)R^{12C}, -NR^{12A}C(O)OR^{12C}, -NR^{12A}OR^{12C}, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

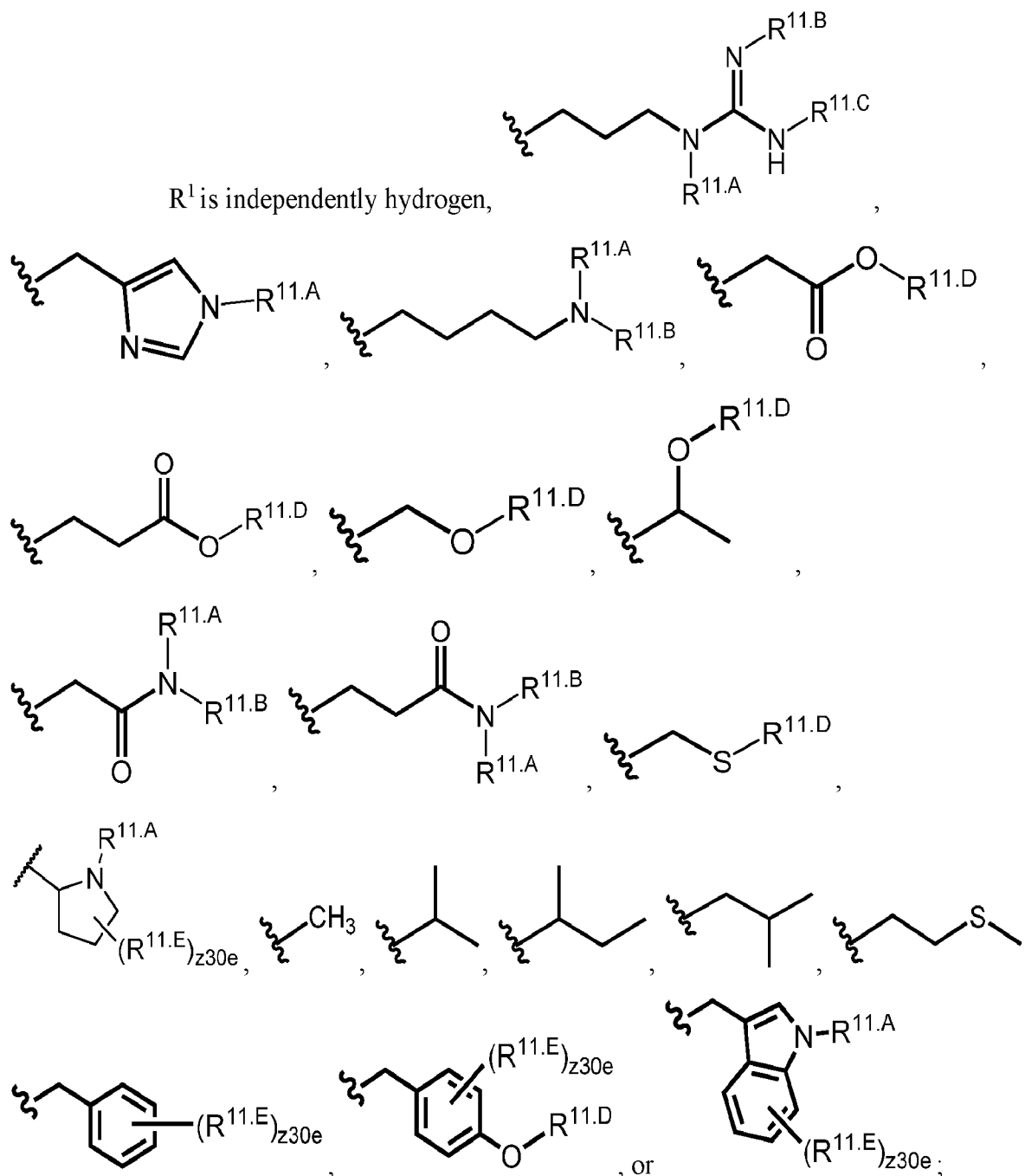
R^{12A}, R^{12B}, R^{12C}, R^{12D}, are each independently hydrogen, -CX₃, -CHX₂, -CH₂X, -CN, -OH, -OCX₃, -OCHX₂, -OCH₂X, -COOH, -CONH₂, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X, X¹¹, and X¹² are independently -F, -Cl, -Br, or -I;

n11 and n12 are independently an integer from 0 to 4; and

m11, m12, v11, and v12 are independently 1 or 2.

[0646] Embodiment 20. The method of any one of embodiments 1 to 17, wherein



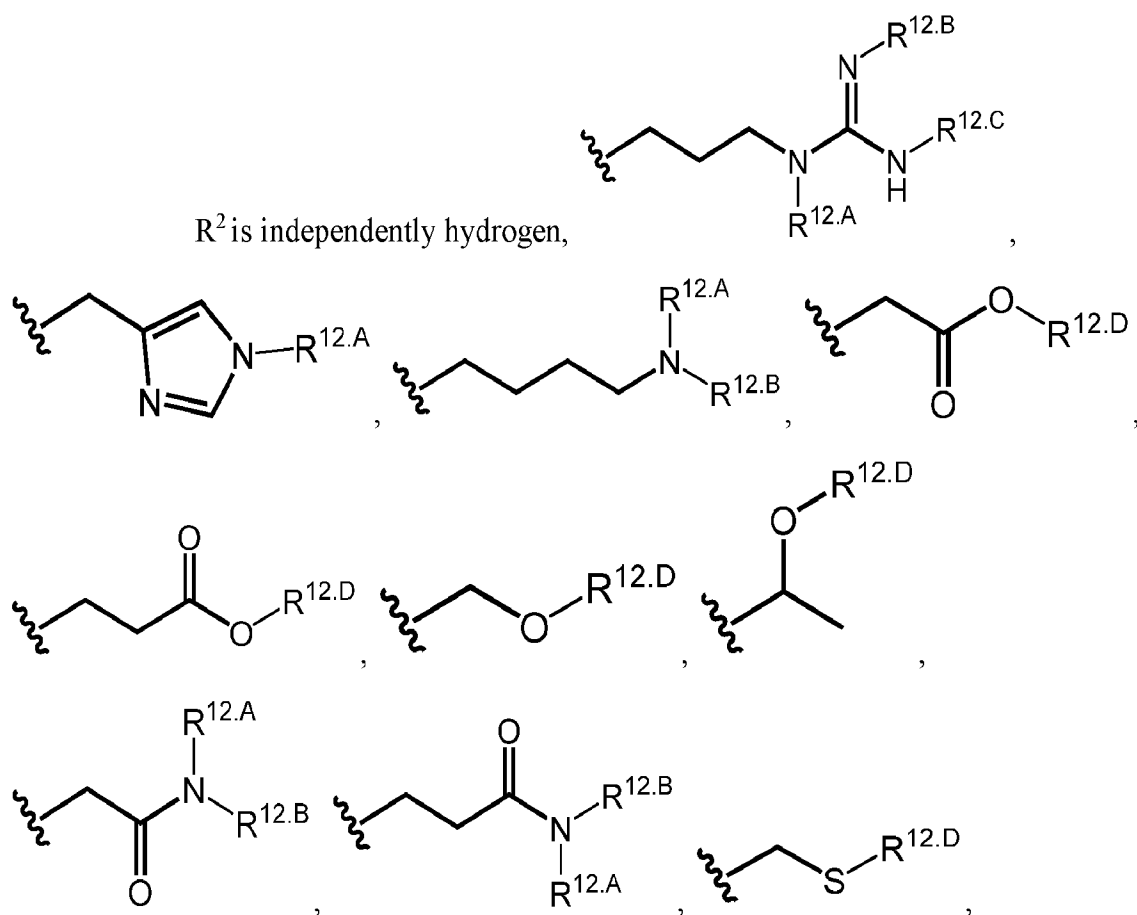
$R^{11.A}$, $R^{11.B}$, and $R^{11.C}$ are each independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

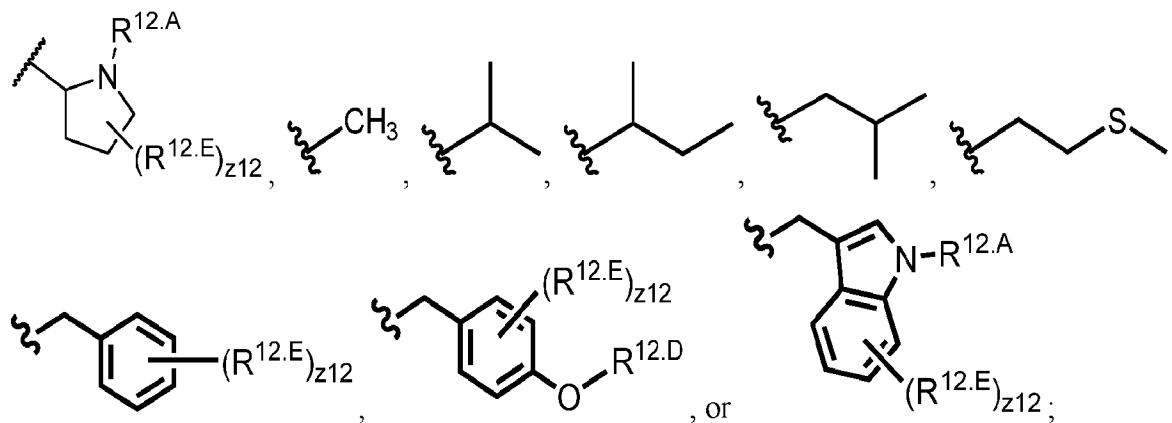
$R^{11.D}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or

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

$R^{11.E}$ is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-CN$, $-SH$, $-SCH_3$, $-SCF_3$, $-SCHF_2$, $-SCH_2F$, $-SCCl_3$, $-SCHCl_2$, $-SCH_2Cl$, $-SCBr_3$, $-SCHBr_2$, $-SCH_2Br$, $-SCI_3$, $-SCHI_2$, $-SCH_2I$, $-SOCH_3$, $-SO_2CH_3$, $-NH_2$, $-NHCH_3$, $-OH$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z_{30e} is an integer from 0 to 7;





$R^{12.A}$, $R^{12.B}$, and $R^{12.C}$ are each independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted 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^{12,D} is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, substituted 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^{12E} is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCl₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -SH, -SCH₃, -SCF₃, -SCHF₂, -SCH₂F, -SCCl₃, -SCHCl₂, -SCH₂Cl, -SCBr₃, -SCHBr₂, -SCH₂Br, -SCI₃, -SCHI₂, -SCH₂I, -SOCH₃, -SO₂CH₃, -NH₂, -NHCH₃, -OH, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

z12 is an integer from 0 to 7.

[0647] Embodiment 21. The method of any one of embodiments 1 to 17, wherein

R^1 is independently $-L^{14}-R^{15}$.

L^{14} is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R^{15} is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

R^2 is independently - L^{16} - R^{17} ;

L^{16} is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

R^{17} is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0648] Embodiment 22. The method of embodiment 21, wherein L^{14} and L^{16} are independently substituted or unsubstituted alkylene.

[0649] Embodiment 23. The method of embodiment 22, wherein L^{14} and L^{16} are independently substituted or unsubstituted methylene.

[0650] Embodiment 24. The method of any one of embodiments 21 to 23, wherein

L^{14} is R^{14} -substituted or unsubstituted methylene;

R^{14} is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

L^{16} is R^{16} -substituted or unsubstituted methylene; and

R^{16} is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

[0651] Embodiment 25. The method of any one of embodiments 21 to 23, wherein

L^{14} is R^{14} -substituted or unsubstituted methylene;

R^{14} is independently substituted or unsubstituted phenyl;

L^{16} is R^{16} -substituted or unsubstituted methylene; and

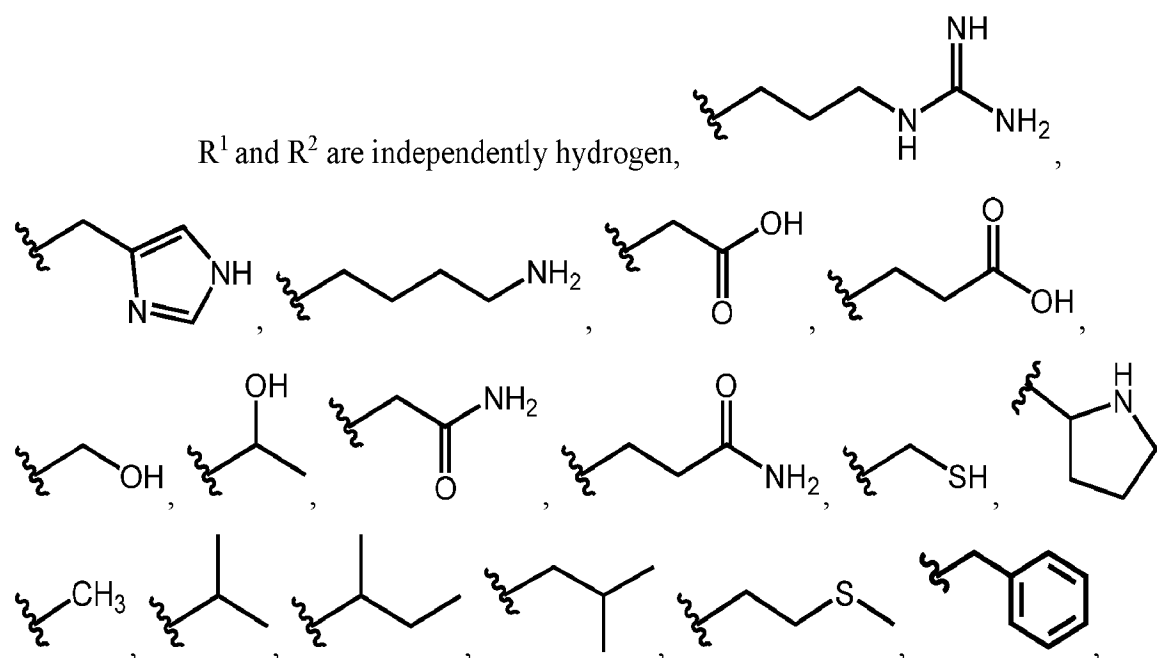
R^{16} is independently substituted or unsubstituted phenyl.

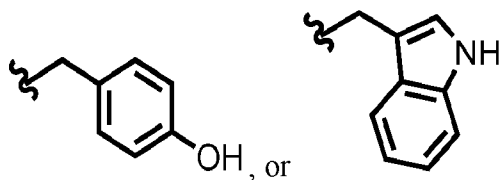
[0652] Embodiment 26. The method of any one of embodiments 21 to 25, wherein R^{15} and R^{17} are independently substituted or unsubstituted phenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or

unsubstituted pyrazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted naphthyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted phthalazinyl, substituted or unsubstituted quinazolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted 1, 8-naphthyridinyl, substituted or unsubstituted pyrido[3,2-d]pyrimidinyl, substituted or unsubstituted pyrido[4,3-d]pyrimidinyl, substituted or unsubstituted pyrido[3,4-b]pyrazinyl, substituted or unsubstituted pyrido[2,3-b]pyrazinyl, or substituted or unsubstituted pteridinyl.

[0653] Embodiment 27. The method of any one of embodiments 21 to 25, wherein R^{15} and R^{17} are independently unsubstituted phenyl, unsubstituted pyridyl, unsubstituted pyridazinyl, unsubstituted pyrimidinyl, unsubstituted pyrazinyl, unsubstituted triazinyl, unsubstituted naphthyl, unsubstituted quinolinyl, unsubstituted isoquinolinyl, unsubstituted quinoxalinyl, unsubstituted phthalazinyl, unsubstituted quinazolinyl, unsubstituted cinnolinyl, unsubstituted 1, 8-naphthyridinyl, unsubstituted pyrido[3,2-d]pyrimidinyl, unsubstituted pyrido[4,3-d]pyrimidinyl, unsubstituted pyrido[3,4-b]pyrazinyl, unsubstituted pyrido[2,3-b]pyrazinyl, or unsubstituted pteridinyl.

[0654] Embodiment 28. The method of any one of embodiments 1 to 18, wherein:





[0655] Embodiment 29. The method of any one of embodiments 1 to 28, wherein:

R^3 , R^4 , R^5 , and R^6 are independently hydrogen, substituted or unsubstituted C_1 - C_6 alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

[0656] Embodiment 30. The method of any one of embodiments 1 to 29, wherein:

R^3 , R^4 , R^5 , and R^6 are independently hydrogen or substituted or unsubstituted C_1 - C_6 alkyl.

[0657] Embodiment 31. The method of any one of embodiments 1 to 30, wherein

R^3 , R^4 , R^5 , and R^6 are independently hydrogen, unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl.

[0658] Embodiment 32. The method of any one of embodiments 1 to 30, wherein:

R^3 , R^4 , R^5 , and R^6 are independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

[0659] Embodiment 33. The method of embodiment 6, wherein:

R^1 and R^2 are independently substituted or unsubstituted C_1 - C_6 alkyl or substituted or unsubstituted 2 to 6 membered heteroalkyl;

$z1$ is an integer from 1 to 5; and

R^3 , R^4 , R^5 , and R^6 are independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

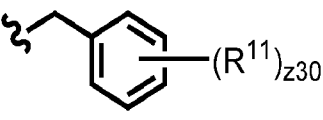
[0660] Embodiment 34. The method of embodiment 6, wherein:

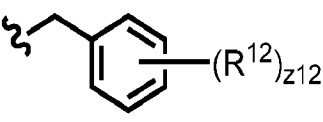
R^1 and R^2 are independently substituted or unsubstituted C_1 - C_4 alkyl;

z_1 is an integer from 1 to 5; and

R^3 , R^4 , R^5 , and R^6 are independently hydrogen.

[0661] Embodiment 35. The method of embodiment 6, wherein

R^1 is independently  ;

R^2 is independently  ;

z_1 is an integer from 1 to 5;

R^3 , R^4 , R^5 , and R^6 are independently hydrogen;

z_{30} is an integer from 0 to 5;

z_{12} is an integer from 0 to 5;

each R^{11} is independently halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11D}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NR^{11C}NR^{11A}R^{11B}$, $-ONR^{11A}R^{11B}$, $-NHC(O)NR^{11C}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-C(O)R^{11C}$, $-C(O)-OR^{11C}$, $-C(O)NR^{11A}R^{11B}$, $-OR^{11D}$, $-NR^{11A}SO_2R^{11D}$, $-NR^{11A}C(O)R^{11C}$, $-NR^{11A}C(O)OR^{11C}$, $-NR^{11A}OR^{11C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{11A} , R^{11B} , R^{11C} , and R^{11D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^{12} is independently halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, $-CN$, $-SO_{n12}R^{12D}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NR^{12C}NR^{12A}R^{12B}$, $-ONR^{12A}R^{12B}$,

$-\text{NHC(O)NR}^{12\text{C}}\text{NR}^{12\text{A}}\text{R}^{12\text{B}}$, $-\text{NHC(O)NR}^{12\text{A}}\text{R}^{12\text{B}}$, $-\text{N(O)}_{\text{m}12}$, $-\text{NR}^{12\text{A}}\text{R}^{12\text{B}}$, $-\text{C(O)R}^{12\text{C}}$, $-\text{C(O)-OR}^{12\text{C}}$, $-\text{C(O)NR}^{12\text{A}}\text{R}^{12\text{B}}$, $-\text{OR}^{12\text{D}}$, $-\text{NR}^{12\text{A}}\text{SO}_2\text{R}^{12\text{D}}$, $-\text{NR}^{12\text{A}}\text{C(O)R}^{12\text{C}}$, $-\text{NR}^{12\text{A}}\text{C(O)OR}^{12\text{C}}$, $-\text{NR}^{12\text{A}}\text{OR}^{12\text{C}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

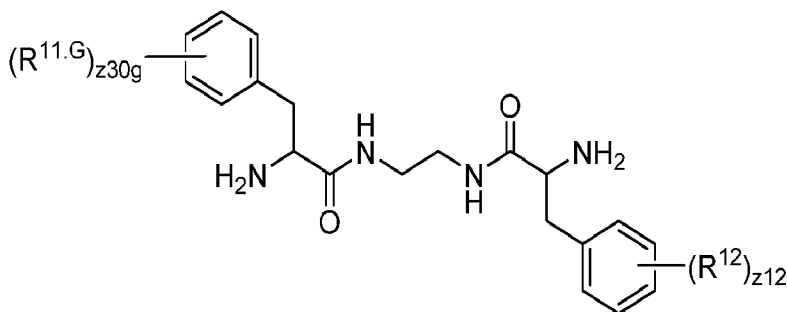
$\text{R}^{12\text{A}}$, $\text{R}^{12\text{B}}$, $\text{R}^{12\text{C}}$, $\text{R}^{12\text{D}}$, are each independently hydrogen, $-\text{CX}_3$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, $-\text{CN}$, $-\text{OH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{OCH}_2\text{X}$, $-\text{COOH}$, $-\text{CONH}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $\text{R}^{12\text{A}}$ and $\text{R}^{12\text{B}}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X , X^{11} , and X^{12} are independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$;

$\text{n}11$ and $\text{n}12$ are independently an integer from 0 to 4; and

$\text{m}11$, $\text{m}12$, $\text{v}11$, and $\text{v}12$ are independently 1 or 2.

[0662] Embodiment 36. The method of embodiment 6, wherein the compound has the



formula

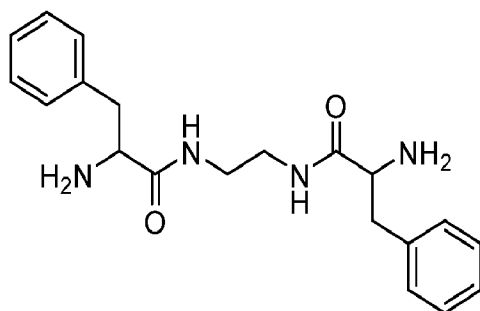
; wherein $\text{R}^{11\text{G}}$ and R^{12}

are independently halogen, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CF}_3$, $-\text{Cl}_3$, CHCl_2 , $-\text{CHBr}_2$, $-\text{CHF}_2$, $-\text{CHI}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{I}$, $-\text{OCCl}_3$, $-\text{OCF}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{OCH}_2\text{F}$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCF}_3$, $-\text{SCHF}_2$, $-\text{SCH}_2\text{F}$, $-\text{SCCl}_3$, $-\text{SCHCl}_2$, $-\text{SCH}_2\text{Cl}$, $-\text{SCBr}_3$, $-\text{SCHBr}_2$, $-\text{SCH}_2\text{Br}$, $-\text{SCl}_3$, $-\text{SCHI}_2$, $-\text{SCH}_2\text{I}$, $-\text{SOCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{OH}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

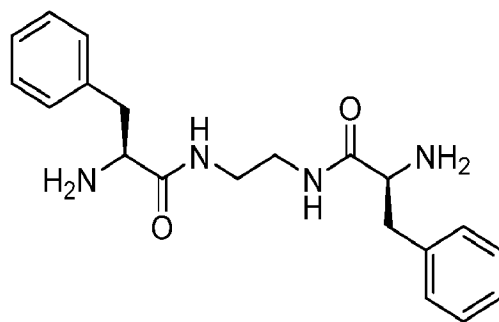
$\text{z}30\text{g}$ is an integer from 0 to 2; and

$\text{z}12$ is an integer from 0 to 2.

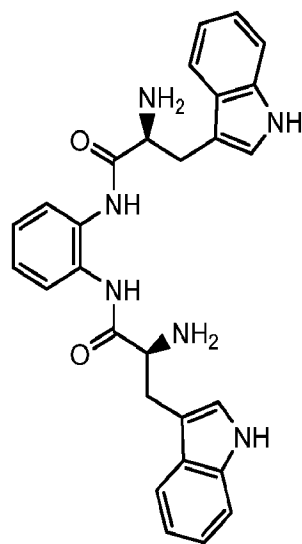
[0663] Embodiment 37. The method of embodiment 6, wherein the compound has the formula:



[0664] Embodiment 38. The method of embodiment 6, wherein the compound has the formula:

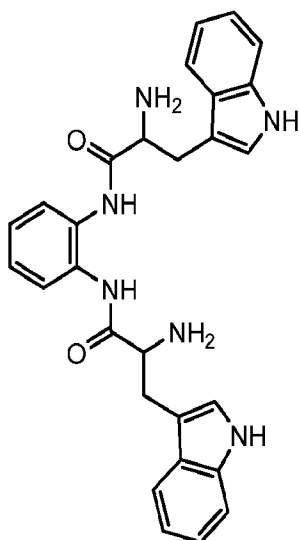


[0665] Embodiment 39. The method of embodiment 14, wherein the compound has the formula:



5

[0666] Embodiment 40. The method of embodiment 14, wherein the compound has the formula:



EXAMPLES

Example 1: Introduction

[0667] The COVID-19 outbreak poses a serious threat to global public health. However, no approved therapeutics or prophylactics for this disease are available yet. With increased death toll every day, effective countermeasures are desperately needed. In this study, we screened a small molecule library containing the NCI-DTP compounds in order to identify molecules that can prevent SARS-CoV-2 cellular entry by targeting the interaction between the viral spike protein and the human ACE2 receptor. Coupling a virtual screen with a luciferase assay-based screening using a pseudotyped SARS-CoV-2 virus-mediated cell entry assay, we identified a small molecule compound Q34 that can efficiently block cellular entry of the pseudotyped SARS-CoV-2 and inhibit the infection of the authentic SARS-CoV-2 virus in human ACE2-expressing HEK293T cells and human iPSC-derived neurons and astrocytes. Importantly, the safety profile of the compound is favorable. There is no obvious cytotoxicity observed in cells treated with this newly identified compound. The compound identified in this study hold great potential to be used as both prophylactics and therapeutics for COVID-19 and future pandemics by blocking the entry of SARS-CoV-2 and related viruses into human cells.

[0668] The coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronaviridae Study Group of the International Committee on Taxonomy of, 2020; Wu et al., 2020b; Zhu et al., 2020). The rapid and widespread outbreak of SARS-CoV-2 poses a serious threat to global public health. However, there are no approved therapeutics or prophylactics for the treatment or prevention of SARS-CoV-2 infection in the clinics. Although a number of nonspecific antiviral drugs including remdesivir and chloroquine have been used in clinics to treat SARS-CoV-2 infection (Riva et al., 2020; Wang et al., 2020a), the in vivo efficacy and safety of these drugs remain to be confirmed. Therefore, there is an urgent need for the prompt development of effective therapeutics and prophylactics for the treatment and prevention of COVID-19.

[0669] A coronavirus has four structural components, including the spike, envelope, membrane, and nucleocapsid proteins (Du et al., 2016; Zhou et al., 2018; Wang et al., 2020b). Among these components, the spike protein plays the most critical roles in viral attachment and entry into host cells (Du et al., 2009). The entry of coronaviruses into host cells relies on the binding of the spike protein to a cellular receptor and subsequent priming of the spike protein by cellular proteases.

[0670] The interaction of the cellular receptor with the virus is an essential aspect that determines the infectivity and host range of coronavirus (Perlman and Netland, 2009; Li, 2016). Angiotensin-converting enzyme-related carboxypeptidase (ACE2) is a protein that is expressed on the surface of the cell membrane. It has been shown that SARS-CoV-2 uses ACE2 as its cellular
5 receptor (Hoffmann et al., 2020; Letko et al., 2020; Shang et al., 2020a; Walls et al., 2020; Zhou et al., 2020). ACE2 is required for host cell entry and subsequent replication of SARS-CoV-2. The spike protein of SARS-CoV-2 binds to ACE2 on the surface of host cells to initiate events that release the viral genome into host cells.

[0671] Because the binding of SARS-CoV-2 spike protein and ACE2 is essential for the
10 attachment and entry of SARS-CoV-2 to host cells, we propose to identify small molecules that target the protein-protein interaction (PPI) interface of human ACE2 with the spike protein of SARS-CoV-2 in order to prevent SARS-CoV-2 infection, which could lead to the development of effective prophylactics and therapeutics for COVID-19 and future related pandemics.

Example 2: Results

[0672] Virtual screen of a compound library to target the interaction of human ACE2 with the
15 SARS-CoV-2 spike protein

[0673] To identify potential inhibitors for SARS-CoV-2 infection, we performed virtual
screening of a small molecule compound library containing the NCI-DTP (developmental
therapeutics program) compounds to identify molecules that can interfere with the interaction
20 between the SARS-CoV-2 spike protein and the human ACE2 protein. The protein-protein interface (PPI) for the interaction of the SARS-CoV-2 spike protein and the human ACE2 protein includes 6 hydrogen bonds (Q24-N487, Q42-G446, Q42-Q498, K353-G502), a network of π -cation interactions (Y41-Q498, Y41-N501, Q42-Y449, Y83-N487, Q493-H34), one π -stacking interaction (Y83-F486), and one hydrophobic interaction pair (M82-F486). The PPI of the human ACE2
25 protein, rather than the spike protein, was selected as the drug target because there is a dynamic tunnel around the PPI of the human ACE2 protein that can be used as the anchor to design inhibitors to penetrate the PPI region, whereas there is no good binding pocket on the PPI of the SARS-CoV-2 spike protein. More importantly, targeting the PPI of the human ACE2 protein may lead to pan-viral inhibitors against existing or future viruses that use ACE2 as a host receptor.

[0674] Ligand Virtual Screen (LiVS) pipeline was used to perform the virtual screening. The LiVS pipeline is a full-coverage (screen every compound in the library), multiple-stage (use three precisions HTVS/SP/XP of Glide docking software to speed-up calculation) (Friesner et al., 2004), multiple-CPU (use about 40 computer CPUs to accelerate computation), and automatic pipeline for virtual ligand screening. It has been proven to be a robust platform with high “hit” rate (up to 37.5%). Several successful inhibitors have been identified using this platform (Liu et al., 2016; Tian et al., 2018; Singh et al., 2020; Su et al., 2020). Among the more than 260,000 NCI-DTP compounds screened, we identified 209 compounds that target the PPI of human ACE2 with the SARS-CoV-2 spike protein.

[0675] Identification of compound Q34 as a potent inhibitor of SARS-CoV-2 cellular entry.

[0676] Among the 209 compounds identified from the virtual screening, 118 compounds are available. To validate the available “hits”, we established a secondary screening using a SARS-CoV-2 pseudovirus system because it has been shown that pseudovirus that contains the coronavirus spike proteins could faithfully recapitulate key features of coronavirus entry into host cells (Hoffmann et al., 2020). We used the HIV packaging system (Li et al., 2018), including plasmids encoding MDL, REV, and the pHIV7-eGFP-ffLuc vector, together with a SARS-CoV-2 spike protein-encoding vector (Shang et al., 2020b) to make the SARS-CoV-2 pseudovirus. The transfer plasmid pHIV7-eGFP-ffLuc contains a luciferase reporter that is used to monitor the cellular entry by the SARS-CoV-2 pseudovirus. Because human ACE2 (hACE2) has been identified as the host receptor for the SARS-CoV-2 spike protein in human cells (Hoffmann et al., 2020; Letko et al., 2020; Walls et al., 2020; Zhou et al., 2020), we transfected hACE2 into human kidney HEK293T cells to make hACE2-HEK293T (hACE2-HEK) and used these cells as the host cells for the pseudovirus. The expression of ACE2 protein was confirmed by immunostaining and Western blot analyses (FIGS. 6A-6B).

[0677] For compound screening, hACE2-HEK cells were pre-treated with the vehicle control (DMSO) or 10 μ M candidate compounds identified from the virtual screening for 2 h, followed by infection with the SARS-CoV-2 pseudovirus along with the compound treatment for 24 h (FIG. 1A). While hACE2-HEK cells alone had no detectable luciferase activity, hACE2-HEK cells infected with the SARS-CoV-2 pseudovirus carrying a luciferase reporter and pre-treated with DMSO exhibited potent luciferase activity (FIG. 1B). When hACE2-HEK cells were pre-treated with the candidate compounds followed by infection with the SARS-CoV-2 pseudovirus, the NCI-DTP

compound Q34 efficiently reduced the luciferase reporter activity in the SARS-CoV-2 pseudovirus-treated cells, among the compounds tested, compared to the DMSO control (FIG. 1B). These data suggest that compound Q34 could inhibit the entry of SARS-CoV-2 pseudovirus into host cells.

[0678] To validate the screening result, we repeated the experiment by pre-treating the hACE2-HEK cells with 10 μ M compound Q34 for 2 h followed by infection with the SARS-CoV-2 pseudovirus along with the compound treatment for 24 hr. Q34 reduced luciferase activity from SARS-CoV-2 pseudovirus substantially, compared to the DMSO control (FIG. 1C, left panel). To find out if the reduced luciferase activity could be resulted from general cytotoxicity of compound treatment, we performed a control experiment by infection of HEK293T cells with a luciferase reporter-encoding lentivirus to get HEK-luc cells and treated these cells with 10 μ M Q34 for 2 h followed for 24 h (2 h + 24 h), mimicking the treatment paradigm in the efficacy test. Treatment with Q34 did not affect the luciferase activity from HEK-luc cells, compared to the DMSO control (FIG. 1D, left panel), suggesting that Q34 is not toxic to the cells treated.

[0679] In addition to treating cells with Q34 for 2 h pre-infection and 24 h along infection (2 h + 24 h), we tested a shorter treatment paradigm of 2 h pre-infection and 2 h along infection (2 h + 2 h). hACE2-HEK cells were pre-treated with 10 μ M Q34 for 2 h, followed by treatment with the SARS-CoV-2 pseudovirus along with the compound for 2 h. Then the pseudovirus and the compound were both removed. DMSO was included as the vehicle control for Q34. Compound Q34 efficiently inhibited the entry of SARS-CoV-2 pseudovirus, compared to the DMSO control, as revealed by substantially reduced luciferase activity from SARS-CoV-2 pseudovirus in Q34-treated cells (FIG. 1C, right panel). In contrast, treatment of the control HEK-luc cells with Q34 with the same concentration and for the same treatment period (2 h + 2 h) did not lead to reduced luciferase activity (FIG. 1D, right panel), suggesting that the inhibitory effect was not likely resulted from general cytotoxicity of compound treatment. Taken together, these results indicate that compound Q34 is a potent inhibitor of SARS-CoV-2 entry into host cells without general cytotoxicity.

[0680] Compound Q34 inhibits cellular entry mediated by the SARS-CoV-2 spike protein specifically.

[0681] To test whether compound Q34 specifically affects cellular entry mediated by the SARS-CoV-2 spike protein, we prepared pseudovirus bearing either the SARS-CoV-2 spike protein or the glycoprotein of the vesicular stomatitis virus (VSV-G). The VSV-G pseudovirus was prepared by transfecting a VSV-G expression vector, instead of the SARS-COV-2 spike protein expression

vector, along with MDL, REV, and pHIV7-eGFP-Luc into HEK293T cells for viral packaging. To test the compound effects, hACE2-HEK cells were pre-treated with Q34 at a concentration range of 0 to 100 μ M for 2 h, followed by infection with the SARS-CoV-2 pseudovirus or the VSV-G pseudovirus along with the compound treatment for 2 h. Compound Q34 specifically reduced luciferase activity from the SARS-CoV-2 pseudovirus-treated cells in a dose-dependent manner (FIG. 2A), with the strongest inhibitory effect by 100 μ M Q34. However, Q34 had no inhibition on luciferase activity in VSV-G pseudovirus-treated cells in all doses tested (FIG. 2B). These results indicate that compound Q34 inhibits cellular entry of virus mediated by the SARS-CoV-2 spike protein specifically, but not by the VSV-G glycoprotein.

[0682] In contrast, treatment of the control HEK-luc cells with Q34 with the same concentrations and for the same treatment period (2 h + 2 h) did not lead to reduced luciferase activity (FIG. 2C), suggesting that the inhibitory effect of Q34 on SARS-CoV-2 pseudovirus was not likely resulted from general cytotoxicity of compound treatment. The lack of toxicity was revealed by the sustained luciferase activity in HEK-luc cells even after 2 h + 24 h compound treatment (FIG. 2D). Taken together, these results indicate that compound Q34 inhibits viral entry mediated by the SARS-CoV-2 spike protein without general cytotoxicity.

[0683] Compound Q34 inhibits cellular entry mediated by the SARS-CoV-2 spike protein in a dose dependent manner.

[0684] To test the IC₅₀ dose of compound Q34 in inhibiting cellular entry mediated by the SARS-CoV-2 spike protein, a range of Q34 compounds (0 to 100 μ M) was tested. hACE2-HEK cells were pre-treated with Q34 at a concentration range of 0 to 100 μ M for 2 h, followed by infection with the SARS-CoV-2 pseudovirus along with the compound treatment for 2 h or 24 h. Compound Q34 inhibits the infection of SARS-CoV-2 pseudovirus in a dose dependent manner for both treatment periods with IC₅₀ 15.58 μ M for 2 h + 2 h treatment period and IC₅₀ 14.40 μ M for 2 h + 24 h period (FIG. 3).

[0685] Compound Q34 inhibits authentic SAR-CoV-2 infection.

[0686] Encouraged by the potent inhibitory effect of compound Q34 on cellular entry by the pseudotyped SARS-CoV-2, we next tested whether Q34 could inhibit the infection of authentic SARS-CoV-2 virus. hACE2-HEK cells were pre-treated with compound Q34 for 2 hr at a concentration range of 0 to 100 μ M and then challenged with the SARS-CoV-2 virus in a BSL3

facility. The cells were incubated with the SARS-CoV-2 virus along with the compound for 24 h. The treated cells were tested for viral infection rate by immunostaining for SARS-CoV-2. Consistent with the suppressive effect on cellular entry by the pseudotyped SARS-CoV-2, compound Q34 dramatically inhibited the infection of SARS-CoV-2 virus in hACE2-HEK cells at both 10 μ M and 100 μ M concentration, compared to the DMSO treatment control (0 μ M Q34) (FIGS. 4A-4C). Moreover, Q34 treatment dramatically reduced viral RNA levels in cells that were pre-treated with the compound followed by SARS-CoV-2 infection, compared to that in cells pre-treated with DMSO followed by SARS-CoV-2 infection (FIG. 4E). Remarkably, while Q34 led to nearly complete blockade of SARS-CoV-2 infection at 100 μ M, there was no obvious cytotoxicity, revealed by no obvious change in cellular number and morphology compared to the DMSO treatment control (FIGS. 4B-4D). These data together demonstrate that compound Q34 efficiently inhibits SARS-CoV-2 infection of human cells without obvious cytotoxicity.

[0687] Compound Q34 inhibits authentic SAR-CoV-2 infection of human iPSC-derived neurons and astrocytes.

[0688] To test whether compound Q34 could inhibit the infection of authentic SARS-CoV-2 virus in physiologically relevant human cells without overexpression of hACE2, we developed human iPSC-derived neurons and astrocytes for compound treatment and SARS-CoV-2 challenge. Human iPSC-derived neurons or astrocytes were pre-treated with compound Q34 for 2 h and then challenged with the SARS-CoV-2 virus in a BSL3 facility. The treated cells were tested for viral infection rate by immunostaining for the SARS-CoV-2 spike protein. Consistent with the suppressive effect on infection of hACE2-HEK cells by SARS-CoV-2, compound Q34 dramatically inhibited the infection of SARS-CoV-2 in both neurons (FIG. 5A, FIG. 5B) and astrocytes (FIG. 5E, FIG. 5F), compared to the DMSO control. Moreover, Q34 treatment dramatically reduced the viral RNA levels in neurons and astrocytes, compared to the DMSO control (FIG. 5D, FIG. 5H). Importantly, Q34 treatment resulted in no obvious cytotoxicity, as revealed by no obvious change in cell number compared to the DMSO control (FIG. 5C, FIG. 5G). These data together demonstrate that compound Q34 efficiently inhibits SARS-CoV-2 infection of physiologically relevant human cells without obvious cytotoxicity.

Example 3: Discussion

[0689] The COVID-19 outbreak spreads rapidly around the world without a foreseeable stop. However, no approved drug or vaccine for SARS-CoV-2 has yet been approved to treat this

pandemic. In this study, we screened a compound library containing the NCI-DTP compounds using a virtual screen and validated the available “hits” by a secondary screen using a luciferase-based pseudotyped SARS-CoV-2 virus-mediated cell entry assay. These screens allowed us to identify a small molecule compound Q34 that can inhibit the cellular entry by the pseudotyped SARS-CoV-2 and cellular infection by the authentic SARS-CoV-2 virus potently. Moreover, there is no obvious cytotoxicity in cells treated with this compound in the same dose range that exhibited potent inhibitory effect on SARS-CoV-2 infection.

[0690] After the initial virtual screening, we used a pseudovirus-based assay for the secondary screening. Pseudovirus is much safer and easier to handle than the actual SARS-CoV-2 virus because the pseudotyped virus no longer contains the virulent viral components and involves only a single round of replication (Zhao et al., 2013; Nie et al., 2020). Moreover, the luciferase reporter in the pseudoviral system provides a quantitative readout, making it a sensitive and robust screening platform. Because pseudovirus can only undergo one round of infection without the ability to replicate in the target cells (Zhao et al., 2013), suppression of pseudovirus infection can be used as a readout for inhibition of cellular entry by the virus (Tai et al., 2020). Therefore, the luciferase-based pseudovirus assay provides a safe and suitable alternative to authentic SARS-CoV-2 viral assay with BSL3 restrictions to screen viral entry inhibitors.

[0691] Vast efforts have been made to develop specific interventions for SARS-CoV-2, in addition to testing general antiviral drugs and therapies for immune regulation to alleviate the symptoms of COVID-19. Various viral components have been used as targets against SARS-CoV-2. Computer-aided virtual screen has used multiple viral components as targets, including the spike protein (Wu et al., 2020a), the spike protein RBD (Benitez-Cardoza and Vique-Sanchez, 2020), RNA polymerase (Mirza and Froeyen, 2020; Naik et al., 2020; Wu et al., 2020a), helicase (Mirza and Froeyen, 2020; Naik et al., 2020), endoribonuclease (Naik et al., 2020), exoribonuclease (Naik et al., 2020), methyltransferase (Naik et al., 2020), and proteases, such as the main protease (Arun et al., 2020; Das et al., 2020; Gahlawat et al., 2020; Gentile et al., 2020; Gurung et al., 2020; Jin et al., 2020; Mirza and Froeyen, 2020; Mohammad et al., 2020; Narkhede et al., 2020; Peele et al., 2020; Ton et al., 2020; Tsuji, 2020), 3-chymotrypsin-like protease (3CL-pro) (Chen et al., 2020; Naik et al., 2020; Rathnayake et al., 2020; Wu et al., 2020a), and papain-like protease (PLpro) (Wu et al., 2020a).

[0692] In addition to viral components, host proteins are also explored as targets for intervening SARS-CoV-2 infection. A map for SARS-CoV-2 and human protein interaction has been used to identify 66 SARS-CoV-2 interacting host factors targeted by 69 compounds (Gordon et al., 2020). Inhibitors for host transmembrane protease serine 2 (TMPRSS2) (Rahman et al., 2020), an enzyme that facilitates viral particle entry into host cells (Hoffmann et al., 2020), various indirect modulators for ACE2 and cellular molecules regulating ACE2 expression (Ragia and Manolopoulos, 2020), and inhibitors for host cell surface GRP78 (Palmeira et al., 2020), a molecule that is predicted to bind the SARS-CoV-2 spike protein by molecule docking (Ibrahim et al., 2020) have also been identified.

[0693] Because human ACE2 (hACE2) has been identified as the host receptor for the SARS-CoV-2 spike protein in human cells (Hoffmann et al., 2020; Letko et al., 2020; Walls et al., 2020; Zhou et al., 2020) and receptor recognition is the first step of viral infection, it becomes a candidate target. However, although ACE2 is hijacked by SARS-CoV-2 as the receptor, the primary function of ACE2 is to act as an enzyme for maturation of angiotensin in its physiological role (Donoghue et al., 2000). ACE2 is expressed in multiple types of cells, including the lung, the heart, and the kidney (Donoghue et al., 2000; Zhao et al., 2020). Decreased expression of ACE2 has been associated with cardiovascular disorders (Crackower et al., 2002; Zisman et al., 2003; Raizada and Ferreira, 2007). Therefore, although ACE2 is a potential target for preventing SARS-CoV-2 infection, direct targeting ACE2 by inhibition of its expression or enzymatic activity could lead to serious side effects. Similar concerns may also be applied to other candidate host factors that have important cellular functions.

[0694] Our approach of targeting the interaction between the SARS-CoV-2 spike protein and the human ACE2 receptor has high probability to be nontoxic because the drugs are not expected to target any host factors but to target the interface of hACE2 interaction with the viral spike protein. Moreover, the “hit” compound has a high chance to remain effective even if the virus keeps evolving by mutating the viral genome as long as the virus will continue to use the ACE2 receptor for their entry into host cells. In summary, we have identified a novel small molecule compound that can inhibit SARS-CoV-2 infection potently but have no detectable cytotoxicity. This compound and its analogs have great potential to be developed into effective prophylactics and therapeutics for COVID-19 and future related pandemic.

Example 4: Methods

Cell Culture

[0695] **[0003]** hACE2-HEK293T (hACE2-HEK) cells were obtained by transducing hACE2 expressing lentivirus (hACE2-encoding plasmid from Addgene #1786 was used for clone hACE2 into lentiviral vector) into HEK293T cells. HEK293T-luc (HEK-luc) cells were obtained by transducing HEK293T cells with a luciferase reporter-encoding lentivirus pHIV7-eGFP-ffluc. Both hACE2-HEK and HEK-luc cells were cultured in DMEM medium (Corning, Catalog # 15-013-CV) supplemented with 10% Fetal Bovine Serum (FBS) (Sigma, Catalog # F4135), 2 mM L-glutamine (Gibco, Catalog # 25030-081) and 1 X Antibiotic-Antimycotic (Gibco, Catalog # 15240-062). All cultures were confirmed for lack of mycoplasma contamination using MycoAlert PLUS Mycoplasma Detection Kit (Lonza, Catalog # LT07-318).

10 Viral Preparation

[0696] The SARS-CoV-2 pseudovirus was prepared by transfecting the plasmids pMDL, pREV, pcDNA3.1-SARS2-Spike (Addgene #145032), and pHIV7-eGFP-ffLuc into HEK293T cells by calcium phosphate precipitation. Virus containing medium was collected 3 days after transfection. The VSV-G pseudovirus was prepared by transfecting the plasmids pMDL, pREV, pVSV-G, and pHIV7-eGFP-ffLuc into HEK293T cells by calcium phosphate precipitation. Virus containing medium was collected 3 days after transfection.

Library screen by reporter assay

[0697] hACE2-HEK cells were seeded in 48-well plates at 10,000 cells per well one day before compound treatment. Cells were pre-treated with the vehicle control DMSO or 10 μ M or 100 μ M compounds for 2 hour (h) followed by addition of the SARS-CoV-2 pseudovirus. Cells were incubated with the SARS-CoV-2 pseudovirus along with DMSO or individual compounds for 24 h, then subjected to medium change. Luciferase activity was measured 3 days after virus treatment using the ONE-Glo Luciferase Assay System (Promega, Catalog # E6120).

Compound validation by reporter assay

[0698] hACE2-HEK cells were seeded in 48-well plates at 10,000 cells per well one day before compound treatment. Cells were pre-treated with DMSO or specific compounds at the indicated dose for 2 h, followed by addition of the SARS-CoV-2 pseudovirus or the VSV-G pseudovirus for 2 h or 24 h, then subjected to medium change. Luciferase activity was measured 3 days after virus treatment using the ONE-Glo Luciferase Assay System (Promega, Catalog # E6120).

30 Compound toxicity test

[0699] HEK-luc cells were seeded in 48-well plates at 10,000 cells one day before compound treatment. Cells were treated with DMSO or specific compounds at the indicated doses for 4 h (2h + 2h) or 26 h (2h + 24 h) followed by medium change. Luciferase activity was measured 3 days after compound treatment using the ONE-Glo Luciferase Assay System (Promega, Catalog # E6120).

5 Inhibition of SARS-CoV-2 infection by the test compound

[0700] hACE2-HEK cells, human iPSC-derived neurons or astrocytes were seeded in 96-well plates at 20,000 cells per well one day before compound treatment. Cells were pre-treated with DMSO or specific compounds for 2 h followed by addition of the SARS-CoV-2 virus at MOI of 0.1(hACE2-HEK) or MOI of 1 (neuron and astrocyte). Cells will be incubated with the SARS-
10 CoV-2 virus along with DMSO or specific compound for 24 h (hACE2-HEK and astrocyte) or 72 h (neuron), then subjected to medium change. At the end of the treatment, cells were harvested in Trizol for RNA extraction or fixed with 4% PFA, followed by immunostaining using antibody specific for the SARS-CoV-2 spike protein (1:200, GeneTex, Catalog # GTX632604).

RT-PCR

15 [0701] Total RNA was isolated using Trizol reagent (Ambion) and subjected to reverse transcription performed using the Tetro cDNA synthesis Kit (BioLINE). RT-PCR reactions were performed using SYBR Green Master Mix (Thermo Scientific) on the Step One Plus Real-Time PCR instrument (Applied Biosystems). The following primers were used for RT-PCR: nCoV-N1-F 5'-GAC CCC AAA ATC AGC GAA AT-3' (SEQ ID NO. 3); nCoV-N1-R 5'-TCT GGT TAC TGC
20 CAG TTG AAT CTG-3' (SEQ ID NO. 4); ACTIN F, 5'-CCG CAA AGA CCT GTA CGC CAA C-3' (SEQ ID NO. 5); and ACTIN R, 5'-CCA GGG CAG TGA TCT CCT TCT G-3' (SEQ ID NO. 6). ACTIN was used as the reference gene for normalization. The $\Delta\Delta C_t$ method was used for quantification analysis.

Antibody

25 [0702] Antibody specific for ACE2 protein was used for immunostaining (1:200, R&D SYSTEMS, Catalog # AF933) and Western blot ((1:1000, R&D SYSTEMS, Catalog # AF933). Antibody specific for MAP2 was used for immunostaining (1:1000, Abcam, Catalog # Ab5392). Mouse anti-GAPDH antibody (1:1000; Santa Cruz Biotechnology; Catalog # sc-47724) was used for Western blot.

30 Example 5: Analog Generation

[0703] We will carry out the structure-based optimization of Q34 compound by using our in-house developed SAG (Side-chain Auto-Growth) program to generate about 20 analogs for synthesis and validation. We will first select two or three “growing points” on Q34 to add various side chains based on our docking model and synthetic experience. For each growing point, SAG can add up to 1,400 side chains that should be easy for synthesis by using Schrödinger Combi-glide software. Thus, for two growing points, SAG can generate up to about 2 million (1,400x1,400) analogs. SAG can automatically produce the analogs and dock them to the binding site. We will use SAG to generate 50,000 analogs *in silico* with different side chains from lead Q34. The top analogs with highest docking scores will be manually analyzed to select 20 analogs that are easy to synthesis, have less protein reactivity, have larger predicted water solubility, and more of other drug propensities. The efficacy and specificity of the 20 analogs will be validated in wet lab.

Example 6: Inhibition of Cellular Entry

[0704] Compound Q34 analogs inhibit cellular entry mediated by the SARS-CoV-2 spike protein.

[0705] In addition to compound Q34, several structure analog compounds (C2 to C7) of Q34 have been synthesized for structure-based optimization. To test the efficacy of these analog compounds in inhibiting SARS-CoV-2 entry, hACE2-HEK cells were pre-treated with the vehicle control (DMSO) or analog compounds (C2 to C7) at 10 μ M or 100 μ M each for 2 h, followed by infection with the SARS-CoV-2 pseudovirus along with the compound treatment for 24 h. In addition to compound Q34, analog compound C5 can effectively reduce the luciferase activity from SARS-CoV-2 pseudovirus at 10 μ M (FIG. 7A). For the higher dose at 100 μ M treatment, analog compound C5 and C6 dramatically inhibit the luciferase activity from SARS-CoV-2 pseudovirus and compound C2, C4, and C7 showed mild but significant reduction of luciferase activity from SARS-CoV-2 pseudovirus (FIG. 7B). Moreover, treatment of the control HEK-luc cells with these analog compounds with the same concentrations and for the same treatment period (2 h + 24 h) did not lead to reduced luciferase activity (FIG. 7C, FIG. D). Taken together, these results indicate that structure analogs of compound Q34 can inhibit viral entry mediated by the SARS-CoV-2 spike protein without general cytotoxicity.

[0706] Incorporated herein by reference in its entirety is: J. Am. Chem. Soc. 125, 6677-6686; describing in part, useful synthetic methods.

Example 7. CoMPOUNDS C1 AND C12 INHIBIT THE DELTA VARIANT OF SARS-COV-2 PSEUDOVIRUS infection in HEK-ACE2 cells

[0707] The delta variant of SARS-CoV-2 is becoming the dominant strain for spreading SARS-CoV-2. To determine the effect of compounds C1 and C12 on inhibiting the infection of the delta variant of SARS-CoV-2, we established a pseudovirus system using the delta strain spike protein. HEK-ACE2 cells were pre-treated with C1 or C12 and challenged with SARS-CoV-2 delta spike pseudotyped virus, including the parental SARS-CoV-2 spike pseudotyped virus as a control. The viral infection was dramatically inhibited by C1 or C12 treatment, compared to vehicle DMSO treatment, for both SARS-CoV-2 delta pseudotyped virus and parental SARS-CoV-2 pseudotyped virus (FIGS. 11A and 11B). These data suggest that compounds C1 and C12 can inhibit the infection of SARS-CoV-2 delta variant in addition to the parental SARS-CoV-2.

Example 8. Compound C12 inhibits the parental and the delta variant of SARS-CoV-2 infection in astrocytes

[0708] To find out if compound C12 can inhibit the infection of the delta variant of SARS-CoV-2, iPSC-derived astrocytes were pre-treated with compound C12 and challenged with the delta variant of authentic SARS-CoV-2 virus or the parental SARS-CoV-2. Compound C12 efficiently inhibited the infection of both the delta variant and the parental version of authentic SARS-CoV-2 (FIGS. 12A-12C) in astrocytes as revealed by substantially reduced Spike positive cells in astrocytes that were pre-treated with C12, compared to that in cells pre-treated with the DMSO vehicle. Consistently, the viral RNA levels in astrocytes pre-treated with C12 were reduced dramatically compared to that in DMSO pre-treated cells (FIGS. 12D and 12E). Taken together, these data demonstrate that compound C12 efficiently suppresses the infection of human cells by both the delta variant and the parental form of authentic SARS-CoV-2.

Example 9. Compounds C1 and C12 inhibit the parental and the delta variant of SARS-CoV-2 infection in HEK-ACE2 cells and Calu-3 cells

[0709] We further tested the effectiveness of compounds C1 and C12 in inhibiting the infection of the delta variant and the parental form of authentic SARS-CoV-2 in human kidney cells (HEK-ACE2 cells) and human lung cells (Calu-3 cells). Consistently, the viral RNA levels in HEK-ACE2 cells and Calu-3 cells pre-treated with compound C1 or C12 were reduced dramatically compared to that in DMSO pre-treated cells (FIGS. 13A-13D). These data support the findings that compounds

C1 and C12 are efficient in inhibiting the infection of the delta variant and the parental form of authentic SARS-CoV-2 in human cells.

Example 10. Compound C12 inhibits both the parental and the delta variant of SARS-CoV-2 infection in hACE2-HEK cells

[0710] To find out if compound C12 can inhibit the infection of the parental SARS-CoV-2 and the delta variant of SARS-CoV-2, we pre-treated hACE2-HEK cells with compound C12 and challenged the pre-treated cells with the delta variant of authentic SARS-CoV-2 virus or the parental SARS-CoV-2. Compound C12 efficiently inhibited the infection of both the delta variant and the parental version of authentic SARS-CoV-2 (FIGS. 14A–14B) in hACE2-HEK cells as revealed by reduced Spike positive cells in hACE2-HEK that were pre-treated with C12, compared to that in cells pre-treated with the DMSO vehicle. Consistently, the viral RNA levels in hACE2-HEK cells pre-treated with C12 were reduced dramatically compared to that in DMSO pre-treated cells (FIG. 14C). Taken together, these data demonstrate that compound C12 efficiently suppresses the infection of human cells by both the delta variant and the parental form of authentic SARS-CoV-2.

Example 11. Compound C12 inhibit the parental SARS-CoV-2 infection in Calu-3 cells

[0711] We further tested human lung cells (Calu-3 cells) to see if compound C12 is effective in inhibiting the infection of authentic SARS-CoV-2. Consistently, the Spike positive cells in Calu3 were reduced in cells that were pre-treated with C12, compared to that in cells pre-treated with the DMSO vehicle (FIGS. 15A-15B). In addition, the viral RNA levels (FIG. 15C) and the spike protein level in the viral supernatant (FIG. 15D) were reduced in Calu-3 cells pre-treated with compound C12 compared to that in DMSO pre-treated cells. These data further support that compound C12 is efficient in inhibiting the infection of authentic SARS-CoV-2 in human cells.

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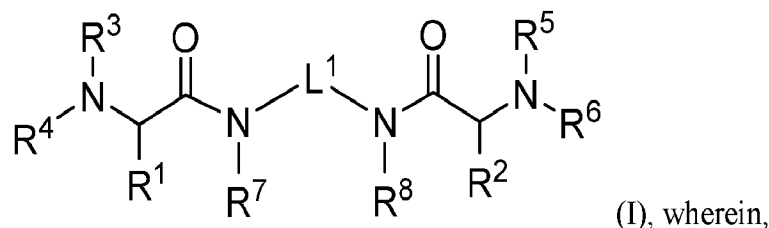
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WHAT IS CLAIMED IS:

1. A method of treating COVID-19, said method comprising administering to a subject in need thereof an effective amount of a compound having the formula:



L^1 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

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

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

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

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

R^4 is independently hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NR^{4C}NR^{4A}R^{4B}$, $-ONR^{4A}R^{4B}$, $-NHC(O)NR^{4C}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl;

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

R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl, or substituted or unsubstituted heteroaryl;

R^7 and R^8 are independently

hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

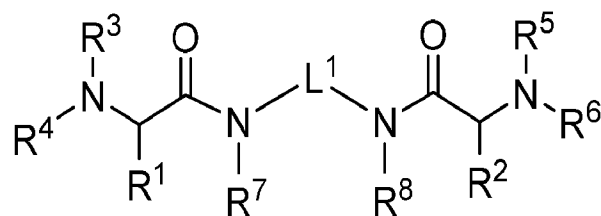
R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

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

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

m_1 , m_2 , m_3 , m_4 , m_5 , m_6 , v_1 , v_2 , v_3 , v_4 , v_5 , and v_6 , are independently 1 or 2.

2. A method of inhibiting the binding of SARS-CoV-2 spike protein to the human angiotensin-converting enzyme 2 (ACE-2), said method comprising contacting the SARS-CoV-2 spike protein with a compound having the formula:



(I), wherein,

L^1 is independently substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

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

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

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

R^4 is independently hydrogen, halogen, $-CX^4_3$, $-CHX^4_2$, $-CH_2X^4$, $-OCX^4_3$, $-OCH_2X^4$, $-OCHX^4_2$, $-CN$, $-SO_{n4}R^{4D}$, $-SO_{v4}NR^{4A}R^{4B}$, $-NR^{4C}NR^{4A}R^{4B}$, $-ONR^{4A}R^{4B}$, $-NHC(O)NR^{4C}NR^{4A}R^{4B}$, $-NHC(O)NR^{4A}R^{4B}$, $-N(O)_{m4}$, $-NR^{4A}R^{4B}$, $-C(O)R^{4C}$, $-C(O)-OR^{4C}$, $-C(O)NR^{4A}R^{4B}$, $-OR^{4D}$, $-NR^{4A}SO_2R^{4D}$, $-NR^{4A}C(O)R^{4C}$, $-NR^{4A}C(O)OR^{4C}$, $-NR^{4A}OR^{4C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 and R^4 substituents bonded to the same nitrogen may optionally be joined to form substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

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

R^6 is independently hydrogen, halogen, $-CX^6_3$, $-CHX^6_2$, $-CH_2X^6$, $-OCX^6_3$, $-OCH_2X^6$, $-OCHX^6_2$, $-CN$, $-SO_{n6}R^{6D}$, $-SO_{v6}NR^{6A}R^{6B}$, $-NR^{6C}NR^{6A}R^{6B}$, $-ONR^{6A}R^{6B}$, $-NHC(O)NR^{6C}NR^{6A}R^{6B}$, $-NHC(O)NR^{6A}R^{6B}$, $-N(O)_{m6}$, $-NR^{6A}R^{6B}$, $-C(O)R^{6C}$, $-C(O)-OR^{6C}$, $-C(O)NR^{6A}R^{6B}$, $-OR^{6D}$, $-NR^{6A}SO_2R^{6D}$, $-NR^{6A}C(O)R^{6C}$, $-NR^{6A}C(O)OR^{6C}$, $-NR^{6A}OR^{6C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^5 and R^6 substituents bonded to the same nitrogen may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^7 and R^8 are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} , R^{3D} , R^{4A} , R^{4B} , R^{4C} , R^{4D} , R^{5A} , R^{5B} , R^{5C} , R^{5D} , R^{6A} , R^{6B} , R^{6C} , and R^{6D} are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{1A} and R^{1B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{2A} and R^{2B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{3A} and R^{3B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{4A} and R^{4B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; R^{5A} and R^{5B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and R^{6A} and R^{6B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

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

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

$m1$, $m2$, $m3$, $m4$, $m5$, $m6$, $v1$, $v2$, $v3$, $v4$, $v5$, and $v6$, are independently 1 or 2.

3. The method of claim 1 or 2, wherein

L^1 is independently substituted or unsubstituted C_2 - C_{10} alkylene, substituted or unsubstituted 2 to 8 membered heteroalkylene, substituted or unsubstituted C_3 - C_{10} cycloalkylene, substituted or unsubstituted 3 to 8 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

4. The method of claim 1 or 2, wherein

L^1 is independently R^{10} -substituted or unsubstituted C_2 - C_{10} alkylene, R^{10} -substituted or unsubstituted 2 to 8 membered heteroalkylene, R^{10} -substituted or unsubstituted C_3 - C_{10} cycloalkylene, R^{10} -substituted or unsubstituted 3 to 8 membered heterocycloalkylene, R^{10} -

substituted or unsubstituted phenylene, or R^{10} -substituted or unsubstituted 5 to 6 membered heteroarylene; and

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

R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X and X^{10} are independently $-F$, $-Cl$, $-Br$, or $-I$;

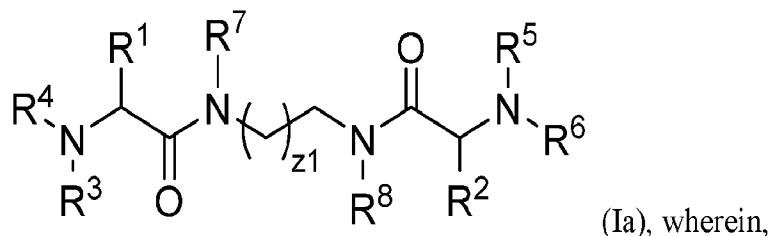
n_{10} , is independently an integer from 0 to 4; and

m_{10} and v_{10} are independently 1 or 2.

5. The method of claim 1 or 2, wherein

L^1 is independently substituted or unsubstituted C_2 - C_6 alkylene, substituted or unsubstituted 2 to 6 membered heteroalkylene, substituted or unsubstituted C_3 - C_6 cycloalkylene, substituted or unsubstituted 3 to 6 membered heterocycloalkylene, substituted or unsubstituted phenylene, or substituted or unsubstituted 5 to 6 membered heteroarylene.

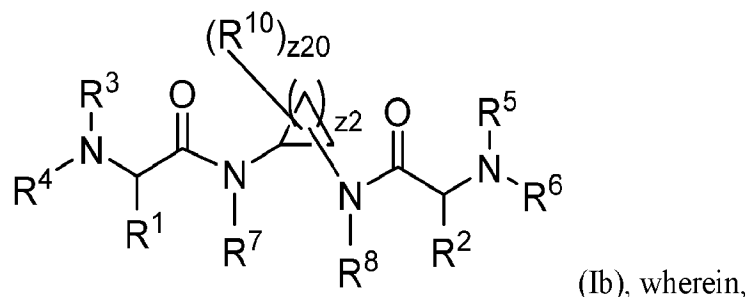
6. The method of claim 1 or 2, wherein the compound has the formula:



z1 is an integer from 1 to 9.

7. The method of claim 6, wherein z1 is an integer from 1 to 6.

8. The method of claim 1 or 2, wherein the compound has the formula:



z2 is an integer from 1 to 8;

z20 is an integer from 0 to 18;

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

R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

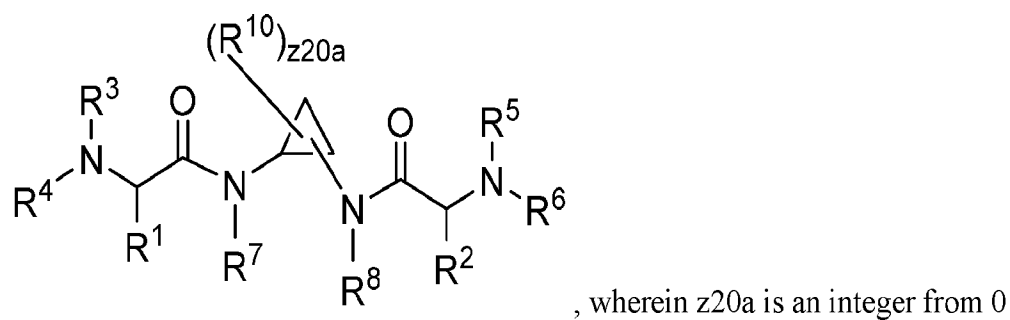
X and X^{10} are independently $-F$, $-Cl$, $-Br$, or $-I$;

n10 is independently an integer from 0 to 4; and

m10 and v10 are independently 1 or 2.

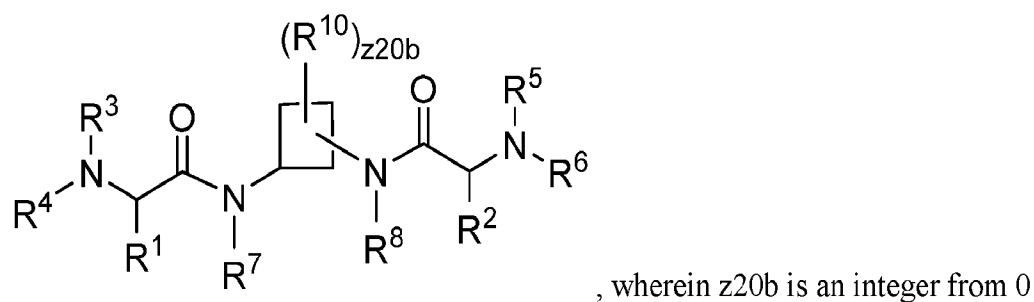
9. The method of claim 8, wherein z2 is an integer from 1 to 4.

10. The method of claim 8 wherein the compound has the formula:



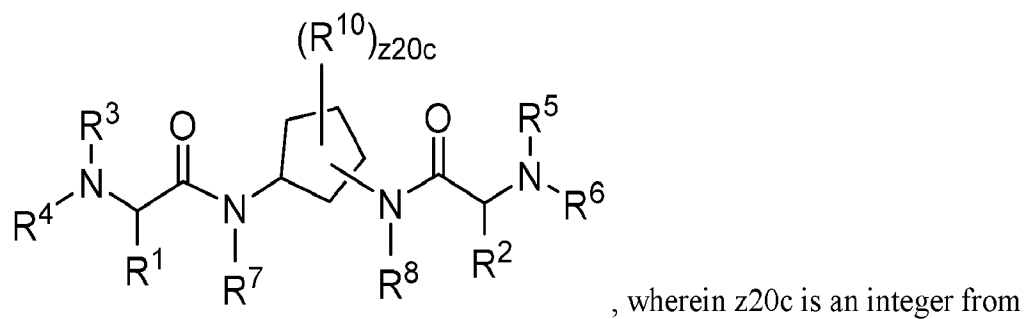
to 4.

11. The method of claim 8 wherein the compound has the formula:



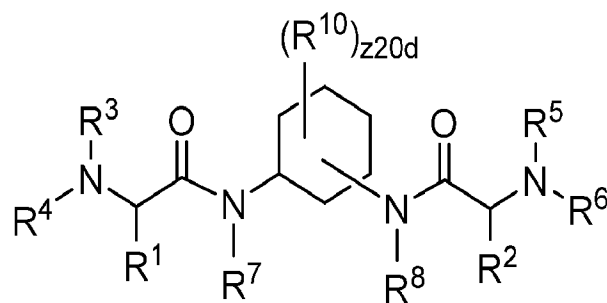
to 6.

12. The method of claim 8 wherein the compound has the formula:



0 to 8.

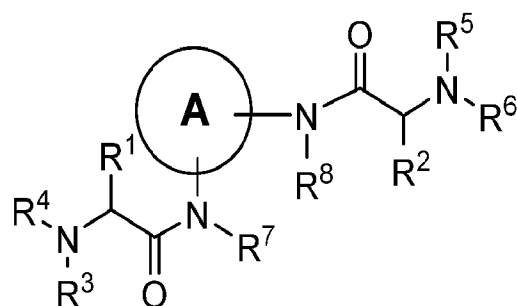
13. The method of claim 8 wherein the compound has the formula:



, wherein z_{20d} is an integer from

0 to 10.

14. The method of claims 1 or 2, wherein the compound has the formula:



(Ic), wherein,

Ring A is substituted or unsubstituted arylene or substituted or unsubstituted heteroarylene.

15. The method of claim 14, wherein Ring A is R^{10} -substituted or unsubstituted phenylene or R^{10} -substituted or unsubstituted 5 to 6 membered heteroaryl;

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

R^{10A} , R^{10B} , R^{10C} , and R^{10D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{10A} and R^{10B} substituents bonded

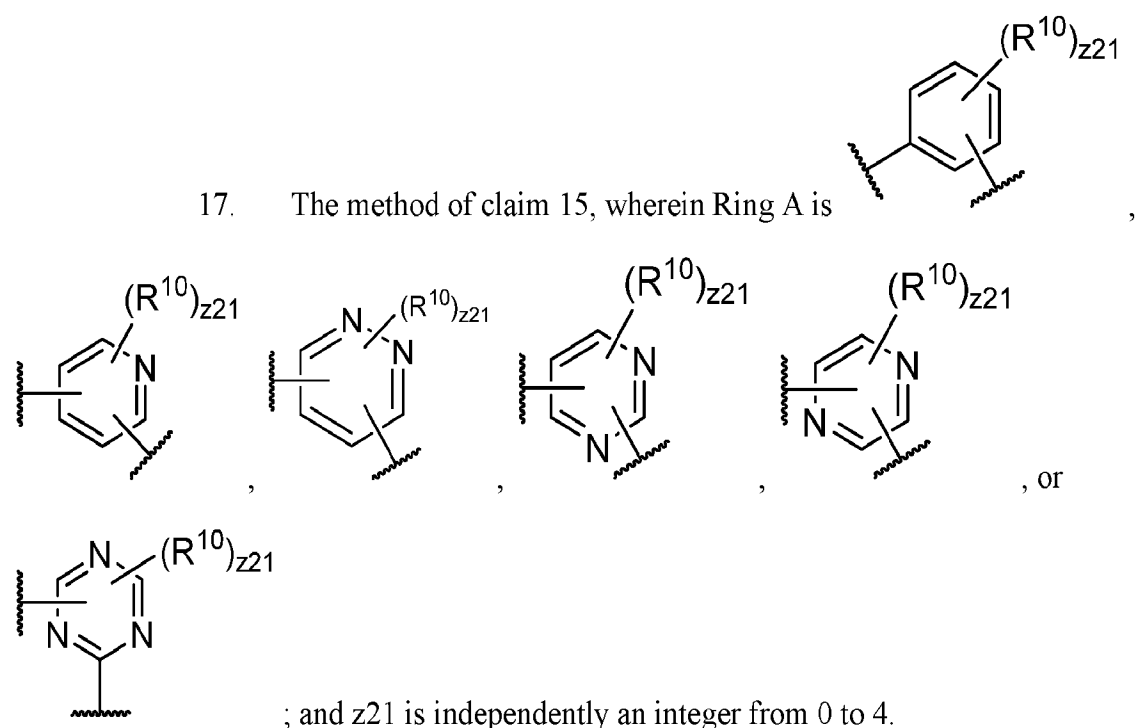
to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X and X¹⁰ are independently -F, -Cl, -Br, or -I;

n₁₀ is independently an integer from 0 to 4; and

m₁₀ and v₁₀ are independently 1 or 2.

16. The method of claim 14, wherein Ring A is substituted or unsubstituted phenylene, substituted or unsubstituted pyridylene, substituted or unsubstituted pyridazinylene, substituted or unsubstituted triazinylene, substituted or unsubstituted pyrimidinylene, substituted or unsubstituted pyrazinylene, substituted or unsubstituted pyrrolylene, or substituted or unsubstituted pyrazolylene.



18. The method of any one of claims 1 to 17, wherein:

R¹ and R² are independently hydrogen, 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 6 membered heterocycloalkyl, substituted or unsubstituted C₆-C₁₂ aryl, or substituted or unsubstituted 5 to 12 membered heteroaryl.

19. The method of any one of claims 1 to 17, wherein:

R^{11} is independently hydrogen, R^{11} -substituted or unsubstituted arginine side chain, R^{11} -substituted or unsubstituted histidine side chain, R^{11} -substituted or unsubstituted lysine side chain, R^{11} -substituted or unsubstituted aspartic acid side chain, R^{11} -substituted or unsubstituted glutamic acid side chain, R^{11} -substituted or unsubstituted serine side chain, R^{11} -substituted or unsubstituted threonine side chain, R^{11} -substituted or unsubstituted asparagine side chain, R^{11} -substituted or unsubstituted glutamine side chain, R^{11} -substituted or unsubstituted cysteine side chain, R^{11} -substituted or unsubstituted glycine side chain, R^{11} -substituted or unsubstituted proline side chain, R^{11} -substituted or unsubstituted alanine side chain, R^{11} -substituted or unsubstituted valine side chain, R^{11} -substituted or unsubstituted isoleucine side chain, R^{11} -substituted or unsubstituted leucine side chain, R^{11} -substituted or unsubstituted methionine side chain, R^{11} -substituted or unsubstituted phenylalanine side chain, R^{11} -substituted or unsubstituted tyrosine side chain, or R^{11} -substituted or unsubstituted tryptophan side chain;

each R^{11} is independently halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$, $-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11D}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NR^{11C}NR^{11A}R^{11B}$, $-ONR^{11A}R^{11B}$, $-NHC(O)NR^{11C}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-C(O)R^{11C}$, $-C(O)-OR^{11C}$, $-C(O)NR^{11A}R^{11B}$, $-OR^{11D}$, $-NR^{11A}SO_2R^{11D}$, $-NR^{11A}C(O)R^{11C}$, $-NR^{11A}C(O)OR^{11C}$, $-NR^{11A}OR^{11C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^{11A} , R^{11B} , R^{11C} , and R^{11D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^2 is independently hydrogen, R^{12} -substituted or unsubstituted arginine side chain, R^{12} -substituted or unsubstituted histidine side chain, R^{12} -substituted or unsubstituted lysine side chain, R^{12} -substituted or unsubstituted aspartic acid side chain, R^{12} -substituted or

unsubstituted glutamic acid side chain, R^{12} -substituted or unsubstituted serine side chain, R^{12} -substituted or unsubstituted threonine side chain, R^{12} -substituted or unsubstituted asparagine side chain, R^{12} -substituted or unsubstituted glutamine side chain, R^{12} -substituted or unsubstituted cysteine side chain, R^{12} -substituted or unsubstituted glycine side chain, R^{12} -substituted or unsubstituted proline side chain, R^{12} -substituted or unsubstituted alanine side chain, R^{12} -substituted or unsubstituted valine side chain, R^{12} -substituted or unsubstituted isoleucine side chain, R^{12} -substituted or unsubstituted leucine side chain, R^{12} -substituted or unsubstituted methionine side chain, R^{12} -substituted or unsubstituted phenylalanine side chain, R^{12} -substituted or unsubstituted tyrosine side chain, or R^{12} -substituted or unsubstituted tryptophan side chain;

each R^{12} is independently halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$, $-OCHX^{12}_2$, $-CN$, $-SO_{n12}R^{12D}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NR^{12C}NR^{12A}R^{12B}$, $-ONR^{12A}R^{12B}$, $-NHC(O)NR^{12C}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-C(O)R^{12C}$, $-C(O)-OR^{12C}$, $-C(O)NR^{12A}R^{12B}$, $-OR^{12D}$, $-NR^{12A}SO_2R^{12D}$, $-NR^{12A}C(O)R^{12C}$, $-NR^{12A}C(O)OR^{12C}$, $-NR^{12A}OR^{12C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

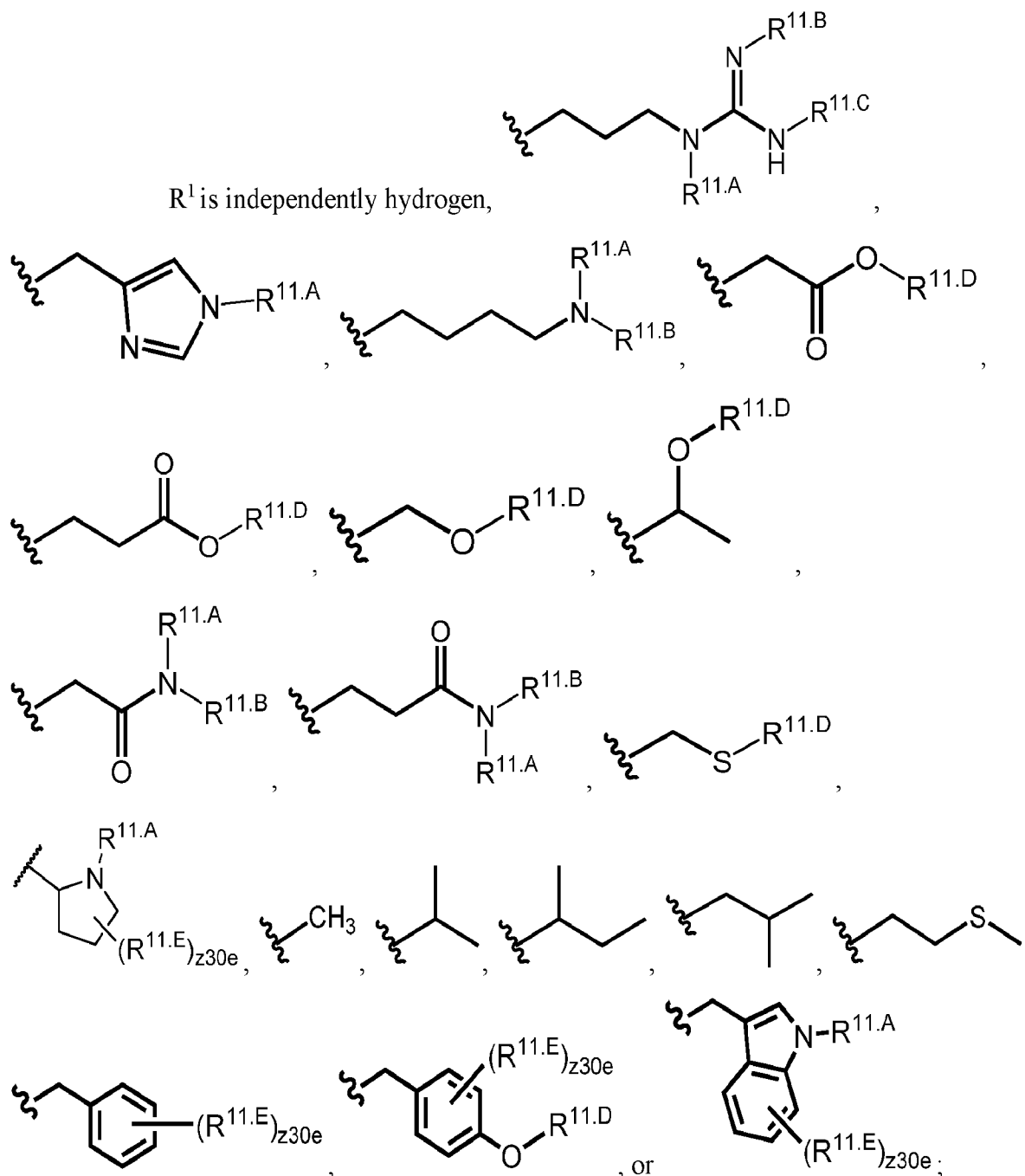
R^{12A} , R^{12B} , R^{12C} , R^{12D} , are each independently hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{12A} and R^{12B} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X , X^{11} , and X^{12} are independently $-F$, $-Cl$, $-Br$, or $-I$;

$n11$ and $n12$ are independently an integer from 0 to 4; and

$m11$, $m12$, $v11$, and $v12$ are independently 1 or 2.

20. The method of any one of claims 1 to 17, wherein



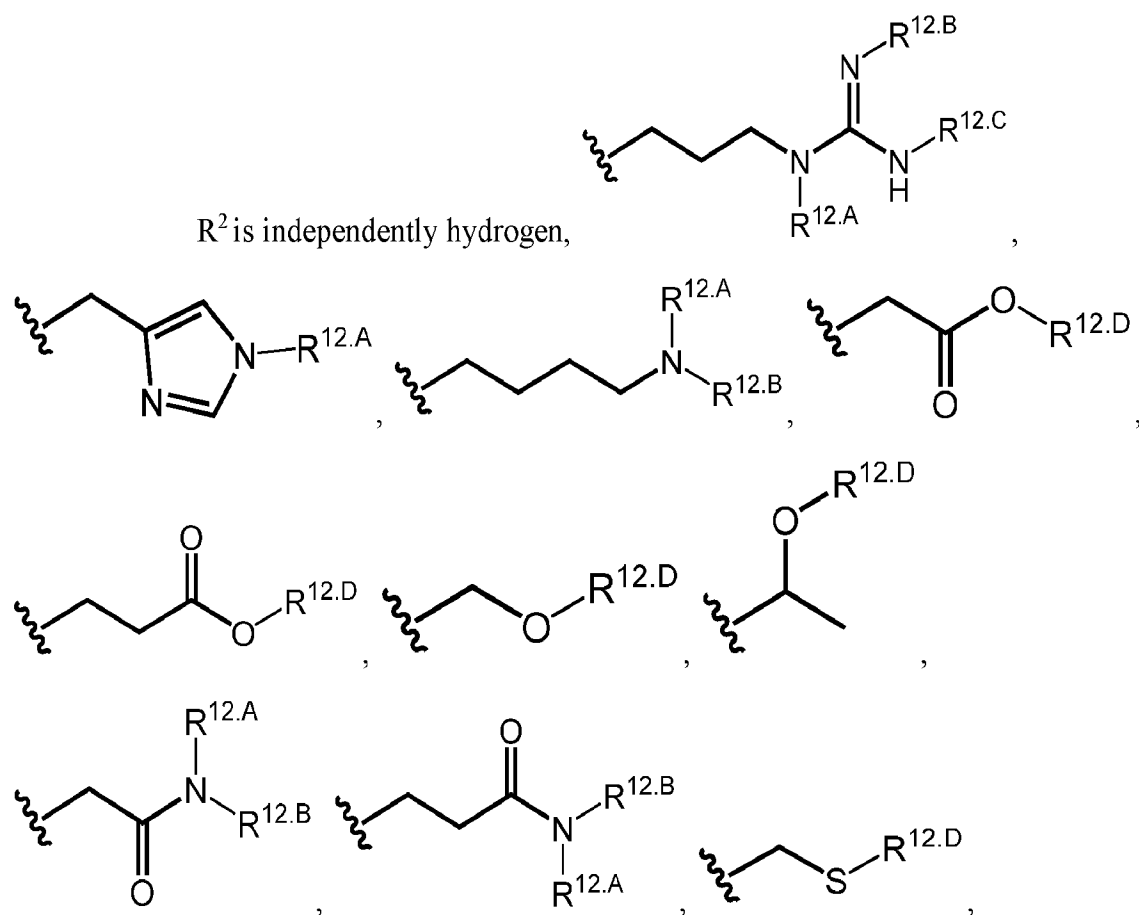
$R^{11.A}$, $R^{11.B}$, and $R^{11.C}$ are each independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

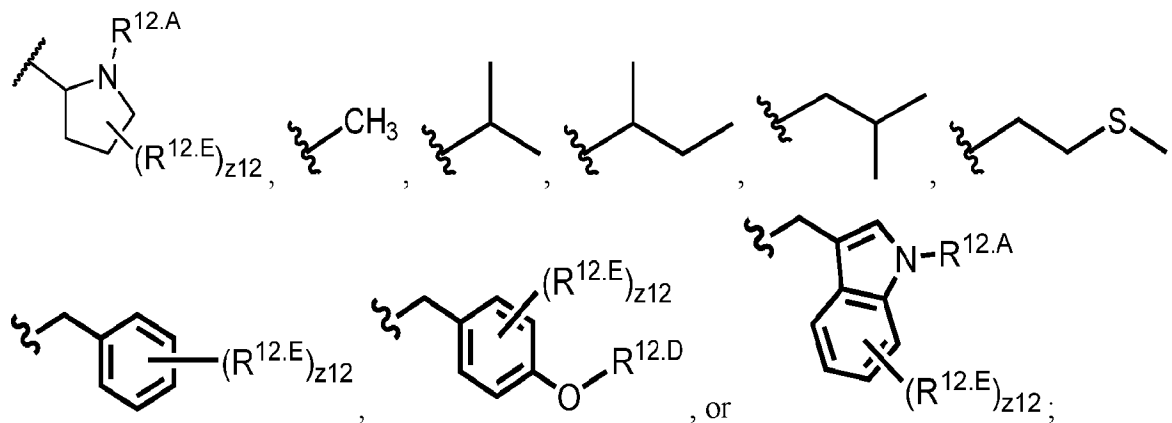
$R^{11.D}$ is independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or

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

$R^{11.E}$ is independently halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, $-OCH_2Cl$, $-OCH_2Br$, $-OCH_2I$, $-OCH_2F$, $-CN$, $-SH$, $-SCH_3$, $-SCF_3$, $-SCHF_2$, $-SCH_2F$, $-SCCl_3$, $-SCHCl_2$, $-SCH_2Cl$, $-SCBr_3$, $-SCHBr_2$, $-SCH_2Br$, $-SCI_3$, $-SCHI_2$, $-SCH_2I$, $-SOCH_3$, $-SO_2CH_3$, $-NH_2$, $-NHCH_3$, $-OH$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

z_{30e} is an integer from 0 to 7;





$R^{12.A}$, $R^{12.B}$, and $R^{12.C}$ are each independently hydrogen, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $CHCl_2$, $-CHBr_2$, $-CHF_2$, $-CHI_2$, $-CH_2Cl$, $-CH_2Br$, $-CH_2F$, $-CH_2I$, $-CN$, substituted 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^{12,D} is independently hydrogen, halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -CN, substituted 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^{12E} is independently halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CHCl₂, -CHBr₂, -CHF₂, -CHI₂, -CH₂Cl, -CH₂Br, -CH₂F, -CH₂I, -OCCl₃, -OCF₃, -OCBr₃, -OCI₃, -OCHCl₂, -OCHBr₂, -OCHI₂, -OCHF₂, -OCH₂Cl, -OCH₂Br, -OCH₂I, -OCH₂F, -CN, -SH, -SCH₃, -SCF₃, -SCHF₂, -SCH₂F, -SCCl₃, -SCHCl₂, -SCH₂Cl, -SCBr₃, -SCHBr₂, -SCH₂Br, -SCI₃, -SCHI₂, -SCH₂I, -SOCH₃, -SO₂CH₃, -NH₂, -NHCH₃, -OH, -N₃, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

z12 is an integer from 0 to 7.

21. The method of any one of claims 1 to 17, wherein

R¹ is independently -L¹⁴-R¹⁵.

L¹⁴ is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene;

R¹⁵ is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

R² is independently -L¹⁶-R¹⁷;

L¹⁶ is a bond, -NH-, -O-, -S-, -SO₂-, -C(O)-, -C(O)NH-, -NHC(O)-, -NHC(O)NH-, -C(O)O-, -OC(O)-, -SO₂NH-, -NHSO₂-, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene; and

R¹⁷ is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

22. The method of claim 21, wherein L¹⁴ and L¹⁶ are independently substituted or unsubstituted alkylene.

23. The method of claim 21, wherein L¹⁴ and L¹⁶ are independently substituted or unsubstituted methylene.

24. The method of any one of claims 21 to 23, wherein

L¹⁴ is R¹⁴-substituted or unsubstituted methylene;

R¹⁴ is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

L¹⁶ is R¹⁶-substituted or unsubstituted methylene; and

R¹⁶ is independently substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

25. The method of any one of claims 21 to 23, wherein

L¹⁴ is R¹⁴-substituted or unsubstituted methylene;

R¹⁴ is independently substituted or unsubstituted phenyl;

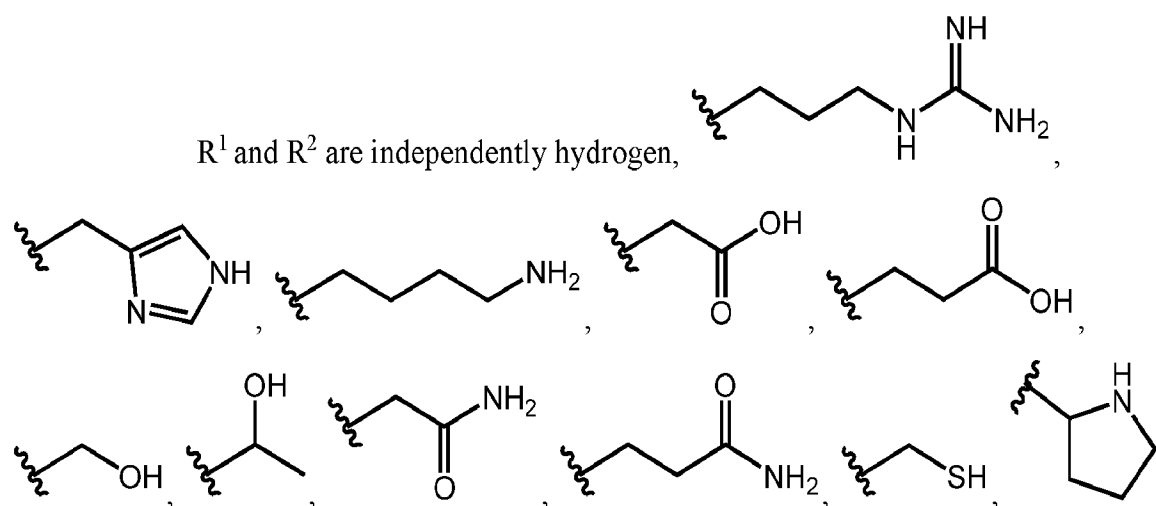
L¹⁶ is R¹⁶-substituted or unsubstituted methylene; and

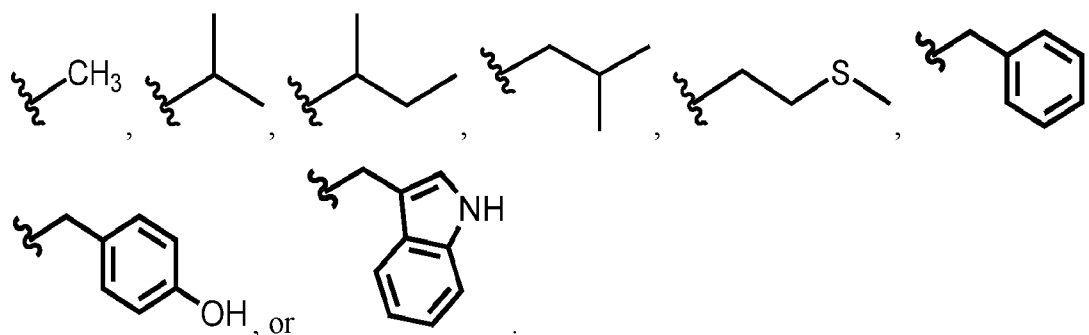
R¹⁶ is independently substituted or unsubstituted phenyl.

26. The method of any one of claims 21 to 25, wherein R¹⁵ and R¹⁷ are independently substituted or unsubstituted phenyl, substituted or unsubstituted pyridyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted triazinyl, substituted or unsubstituted naphthyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted quinoxalinyl, substituted or unsubstituted phthalazinyl, substituted or unsubstituted quinazolinyl, substituted or unsubstituted cinnolinyl, substituted or unsubstituted 1,8-naphthyridinyl, substituted or unsubstituted pyrido[3,2-d]pyrimidinyl, substituted or unsubstituted pyrido[4,3-d]pyrimidinyl, substituted or unsubstituted pyrido[3,4-b]pyrazinyl, substituted or unsubstituted pyrido[2,3-b]pyrazinyl, or substituted or unsubstituted pteridinyl.

27. The method of any one of claims 21 to 25, wherein R¹⁵ and R¹⁷ are independently unsubstituted phenyl, unsubstituted pyridyl, unsubstituted pyridazinyl, unsubstituted pyrimidinyl, unsubstituted pyrazinyl, unsubstituted triazinyl, unsubstituted naphthyl, unsubstituted quinolinyl, unsubstituted isoquinolinyl, unsubstituted quinoxalinyl, unsubstituted phthalazinyl, unsubstituted quinazolinyl, unsubstituted cinnolinyl, unsubstituted 1,8-naphthyridinyl, unsubstituted pyrido[3,2-d]pyrimidinyl, unsubstituted pyrido[4,3-d]pyrimidinyl, unsubstituted pyrido[3,4-b]pyrazinyl, unsubstituted pyrido[2,3-b]pyrazinyl, or unsubstituted pteridinyl.

28. The method of any one of claims 1 to 17, wherein:





29. The method of any one of claims 1 to 28, wherein:

R³, R⁴, R⁵, and R⁶ are independently hydrogen, substituted or unsubstituted C₁-C₆ alkyl, substituted or unsubstituted 2 to 6 membered heteroalkyl, substituted or unsubstituted C₃-C₆ cycloalkyl, or substituted or unsubstituted 3 to 6 membered heterocycloalkyl.

30. The method of any one of claims 1 to 28, wherein:

R³, R⁴, R⁵, and R⁶ are independently hydrogen or substituted or unsubstituted C₁-C₆ alkyl.

31. The method of any one of claims 1 to 28, wherein

R³, R⁴, R⁵, and R⁶ are independently hydrogen, unsubstituted methyl, unsubstituted ethyl, or unsubstituted propyl.

32. The method of any one of claims 1 to 28, wherein:

R³, R⁴, R⁵, and R⁶ are independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

33. The method of claim 6, wherein:

R¹ and R² are independently substituted or unsubstituted C₁-C₆ alkyl or substituted or unsubstituted 2 to 6 membered heteroalkyl;

z1 is an integer from 1 to 5; and

R³, R⁴, R⁵, and R⁶ are independently hydrogen, unsubstituted methyl, or unsubstituted ethyl.

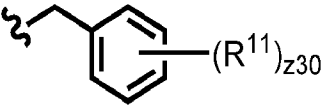
34. The method of claim 6, wherein:

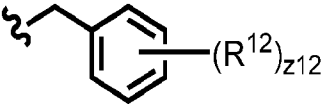
R^1 and R^2 are independently substituted or unsubstituted C_1 - C_4 alkyl;

z_1 is an integer from 1 to 5; and

R^3 , R^4 , R^5 , and R^6 are independently hydrogen.

35. The method of claim 6, wherein

R^1 is independently  ;

R^2 is independently  ;

z_1 is an integer from 1 to 5;

R^3 , R^4 , R^5 , and R^6 are independently hydrogen;

z_{30} is an integer from 0 to 5;

z_{12} is an integer from 0 to 5;

each R^{11} is independently halogen, $-CX^{11}_3$, $-CHX^{11}_2$, $-CH_2X^{11}$, $-OCX^{11}_3$,

$-OCH_2X^{11}$, $-OCHX^{11}_2$, $-CN$, $-SO_{n11}R^{11D}$, $-SO_{v11}NR^{11A}R^{11B}$, $-NR^{11C}NR^{11A}R^{11B}$, $-ONR^{11A}R^{11B}$,

$-NHC(O)NR^{11C}NR^{11A}R^{11B}$, $-NHC(O)NR^{11A}R^{11B}$, $-N(O)_{m11}$, $-NR^{11A}R^{11B}$, $-C(O)R^{11C}$,

$-C(O)-OR^{11C}$, $-C(O)NR^{11A}R^{11B}$, $-OR^{11D}$, $-NR^{11A}SO_2R^{11D}$, $-NR^{11A}C(O)R^{11C}$, $-NR^{11A}C(O)OR^{11C}$,

$-NR^{11A}OR^{11C}$, $-N_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

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

R^{11A} , R^{11B} , R^{11C} , and R^{11D} , are each independently

hydrogen, $-CX_3$, $-CHX_2$, $-CH_2X$, $-CN$, $-OH$, $-OCX_3$, $-OCHX_2$, $-OCH_2X$, $-COOH$, $-CONH_2$,

substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or

unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^{11A} and R^{11B} substituents bonded

to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted

heterocycloalkyl or substituted or unsubstituted heteroaryl;

R^{12} is independently halogen, $-CX^{12}_3$, $-CHX^{12}_2$, $-CH_2X^{12}$, $-OCX^{12}_3$, $-OCH_2X^{12}$,

$-OCHX^{12}_2$, $-CN$, $-SO_{n12}R^{12D}$, $-SO_{v12}NR^{12A}R^{12B}$, $-NR^{12C}NR^{12A}R^{12B}$, $-ONR^{12A}R^{12B}$,

$-NHC(O)NR^{12C}NR^{12A}R^{12B}$, $-NHC(O)NR^{12A}R^{12B}$, $-N(O)_{m12}$, $-NR^{12A}R^{12B}$, $-C(O)R^{12C}$,

$-C(O)-OR^{12C}$, $-C(O)NR^{12A}R^{12B}$, $-OR^{12D}$, $-NR^{12A}SO_2R^{12D}$, $-NR^{12A}C(O)R^{12C}$, $-NR^{12A}C(O)OR^{12C}$,

$-\text{NR}^{12\text{A}}\text{OR}^{12\text{C}}$, $-\text{N}_3$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

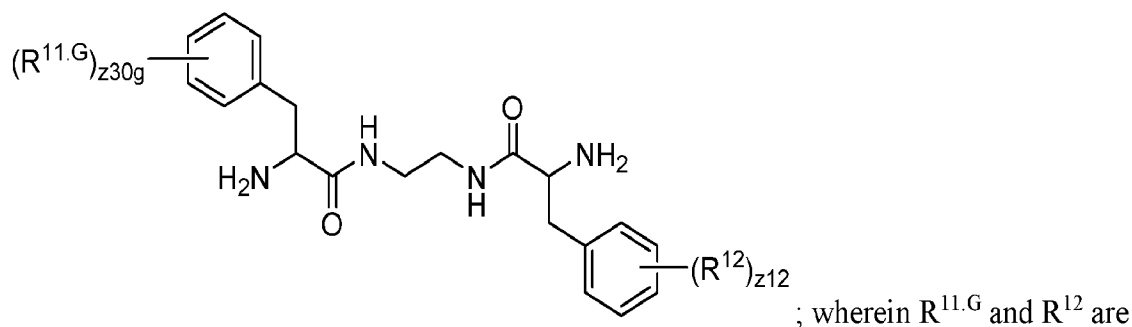
$\text{R}^{12\text{A}}$, $\text{R}^{12\text{B}}$, $\text{R}^{12\text{C}}$, $\text{R}^{12\text{D}}$, are each independently hydrogen, $-\text{CX}_3$, $-\text{CHX}_2$, $-\text{CH}_2\text{X}$, $-\text{CN}$, $-\text{OH}$, $-\text{OCX}_3$, $-\text{OCHX}_2$, $-\text{OCH}_2\text{X}$, $-\text{COOH}$, $-\text{CONH}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; $\text{R}^{12\text{A}}$ and $\text{R}^{12\text{B}}$ substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl;

X , X^{11} , and X^{12} are independently $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$;

n_{11} and n_{12} are independently an integer from 0 to 4; and

m_{11} , m_{12} , v_{11} , and v_{12} are independently 1 or 2.

36. The method of claim 6, wherein the compound has the formula

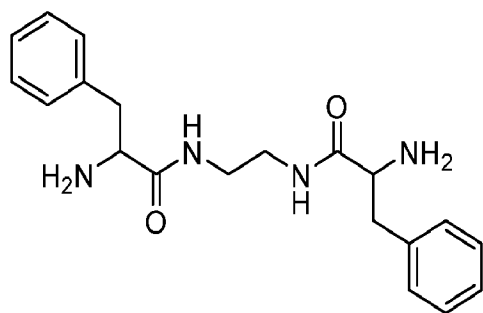


independently halogen, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CF}_3$, $-\text{Cl}_3$, CHCl_2 , $-\text{CHBr}_2$, $-\text{CHF}_2$, $-\text{CHI}_2$, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{Br}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{I}$, $-\text{OCCl}_3$, $-\text{OCF}_3$, $-\text{OCBr}_3$, $-\text{OCl}_3$, $-\text{OCHCl}_2$, $-\text{OCHBr}_2$, $-\text{OCHI}_2$, $-\text{OCHF}_2$, $-\text{OCH}_2\text{Cl}$, $-\text{OCH}_2\text{Br}$, $-\text{OCH}_2\text{I}$, $-\text{OCH}_2\text{F}$, $-\text{CN}$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{SCF}_3$, $-\text{SCHF}_2$, $-\text{SCH}_2\text{F}$, $-\text{SCCl}_3$, $-\text{SCHCl}_2$, $-\text{SCH}_2\text{Cl}$, $-\text{SCBr}_3$, $-\text{SCHBr}_2$, $-\text{SCH}_2\text{Br}$, $-\text{SCI}_3$, $-\text{SCHI}_2$, $-\text{SCH}_2\text{I}$, $-\text{SOCH}_3$, $-\text{SO}_2\text{CH}_3$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{OH}$, $-\text{N}_3$, substituted or unsubstituted C_1 - C_6 alkyl, or substituted or unsubstituted 2 to 6 membered heteroalkyl;

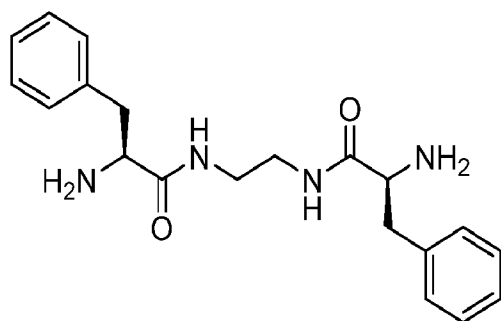
z_{30g} is an integer from 0 to 2; and

z_{12} is an integer from 0 to 2.

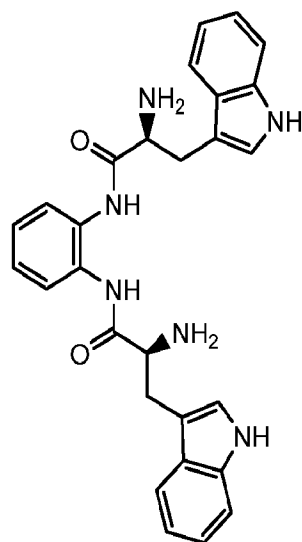
37. The method of claim 6, wherein the compound has the formula



38. The method of claim 6, wherein the compound has the formula



39. The method of claim 14, wherein the compound has the formula



40. The method of claim 14, wherein the compound has the formula

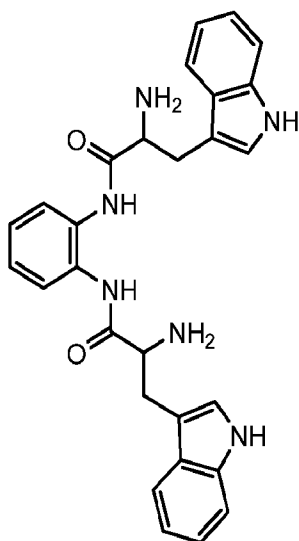


FIG. 1A

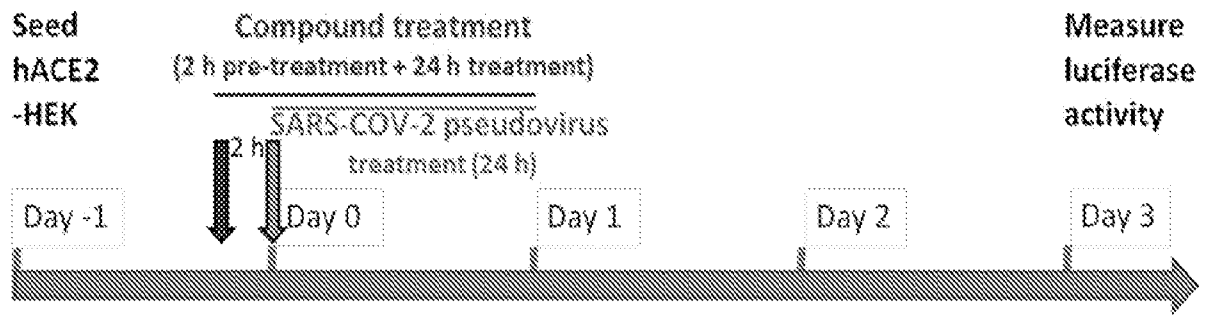


FIG. 1B

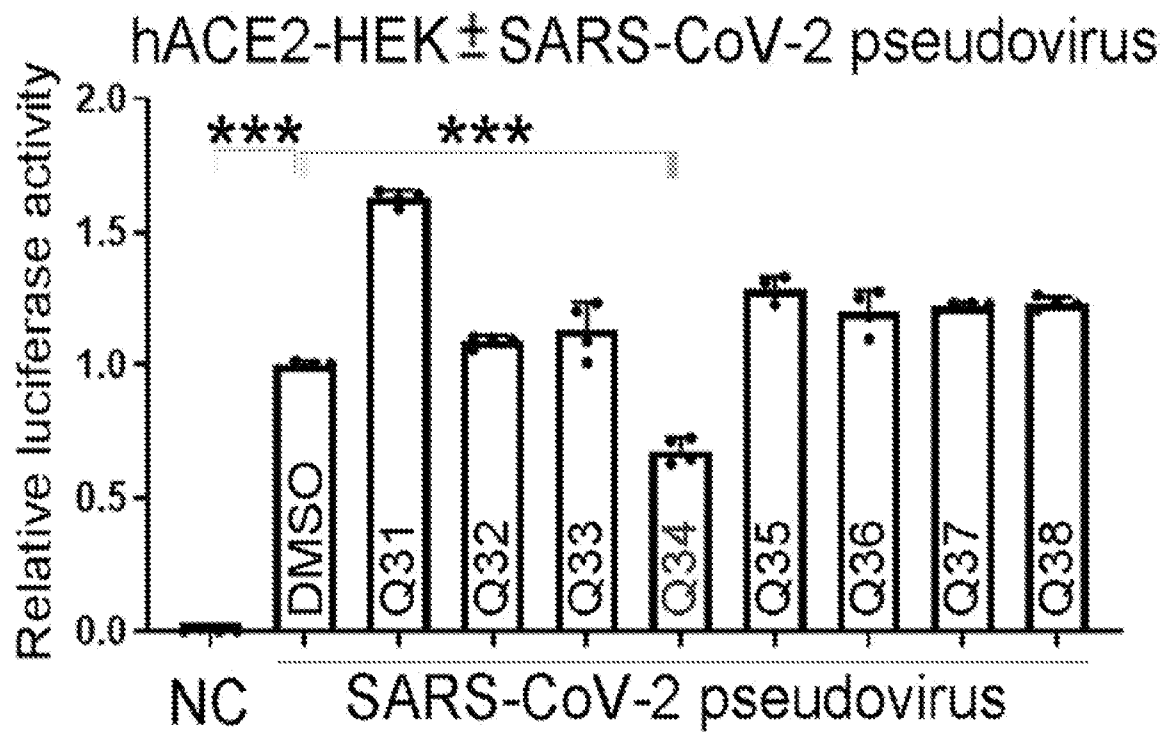


FIG. 1C

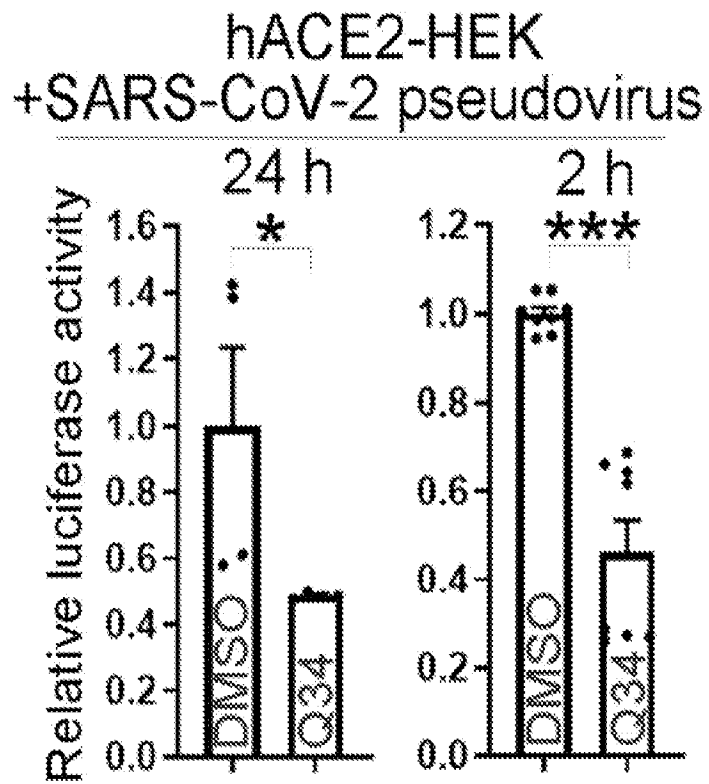


FIG. 1D

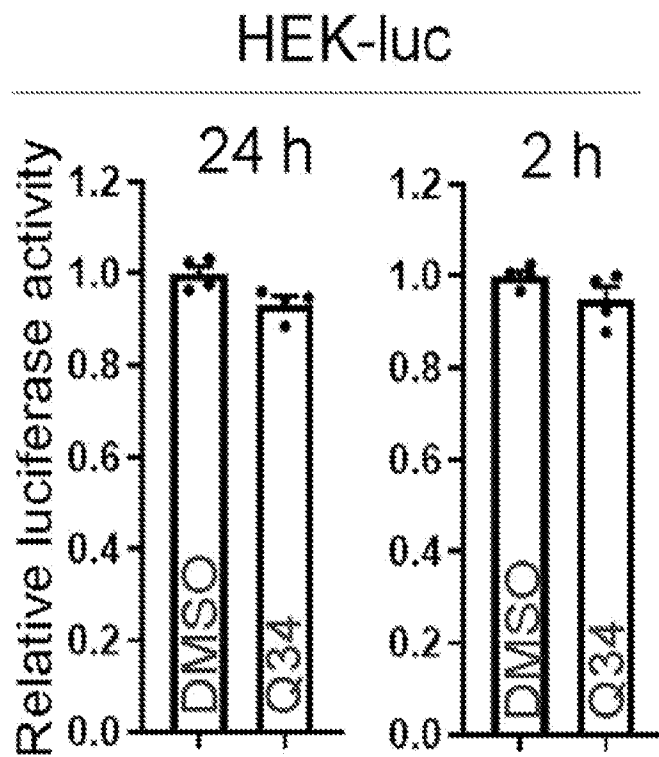


FIG. 2A

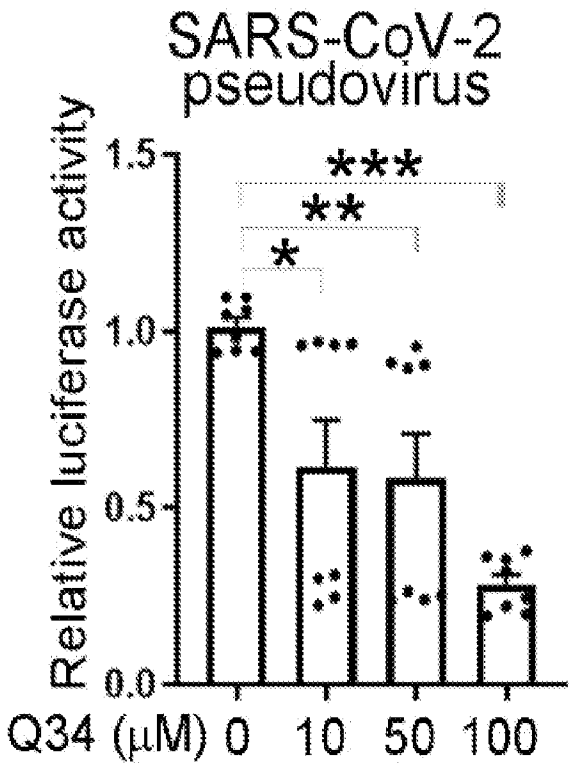


FIG. 2B

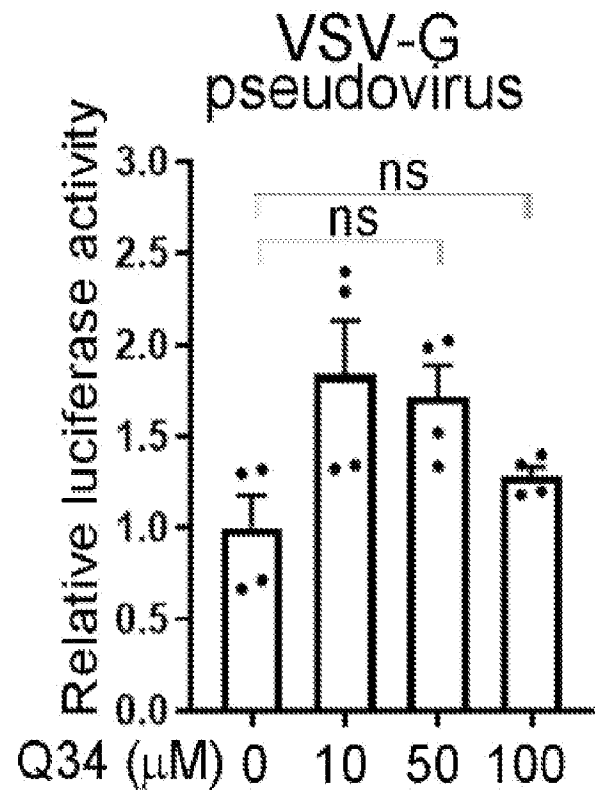


FIG. 2C

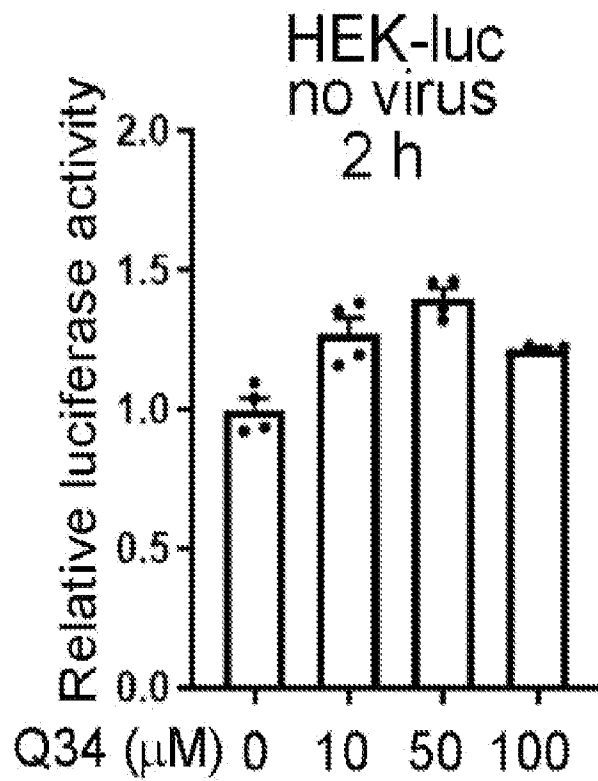


FIG. 2D

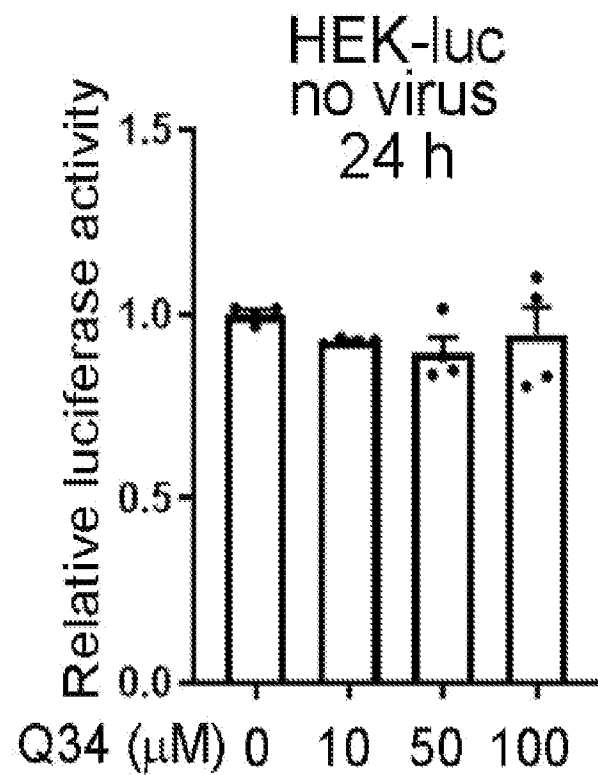


FIG. 3

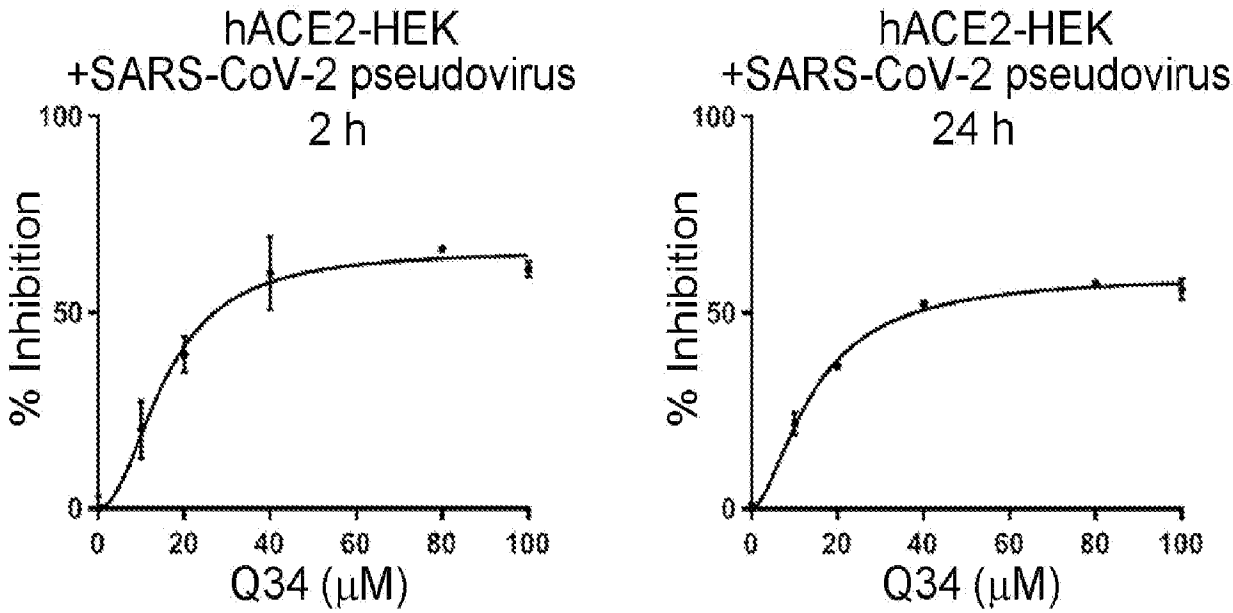


FIG. 4A

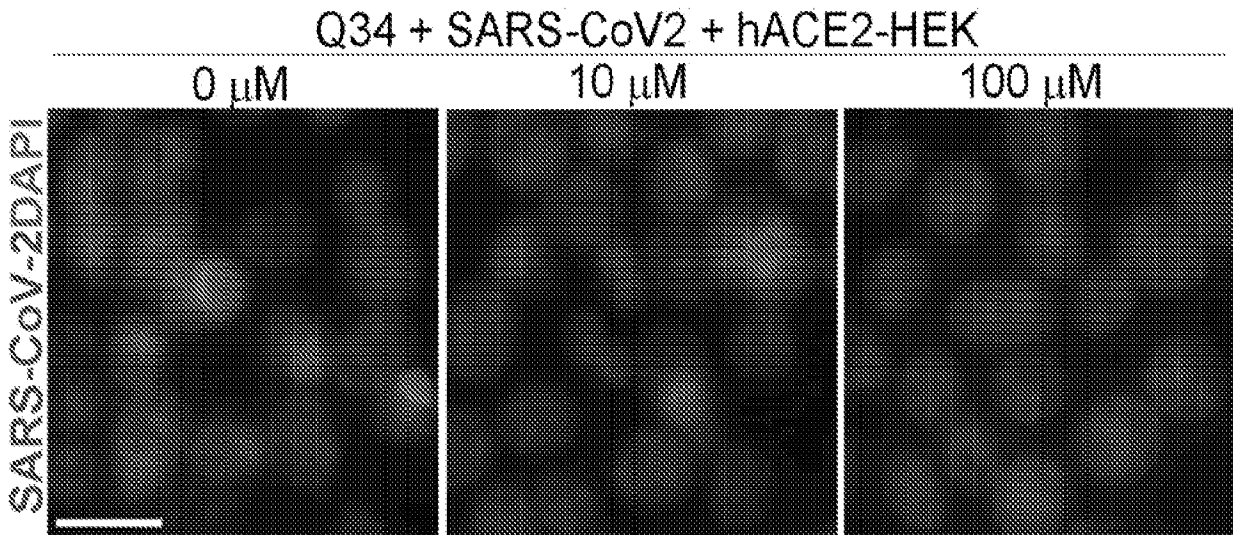


FIG. 4B

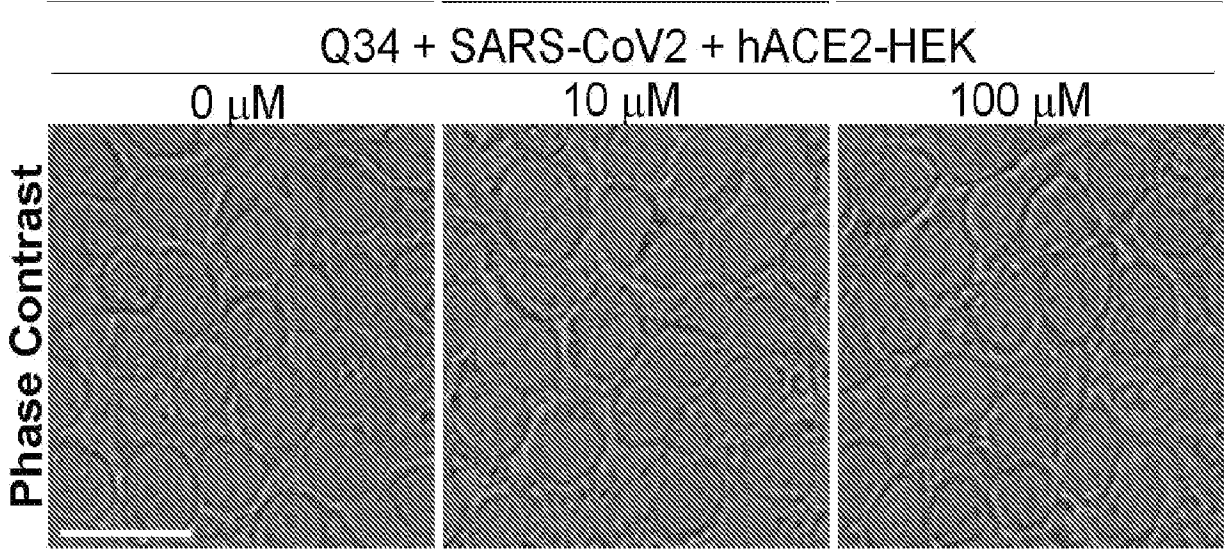


FIG. 4C

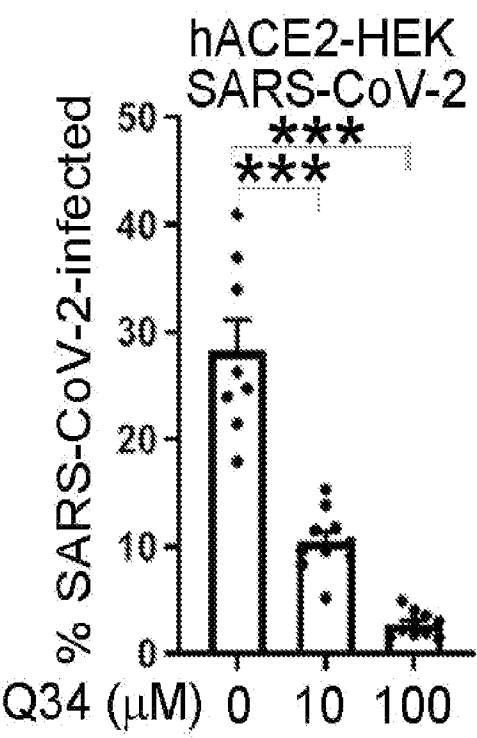


FIG. 4D

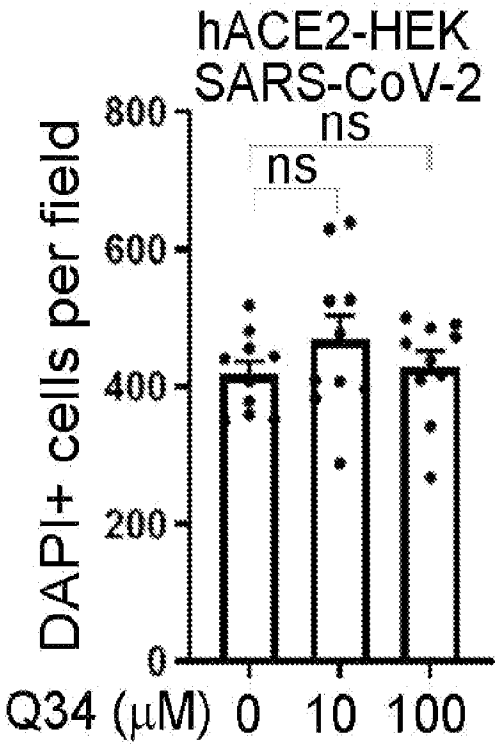


FIG. 4E

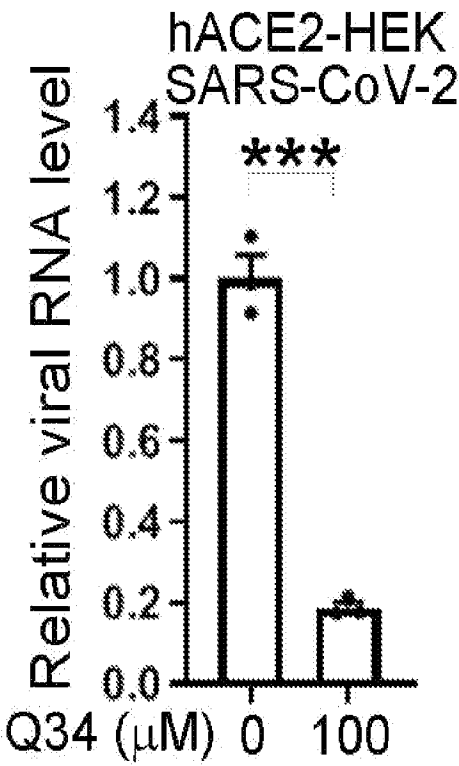


FIG. 5A

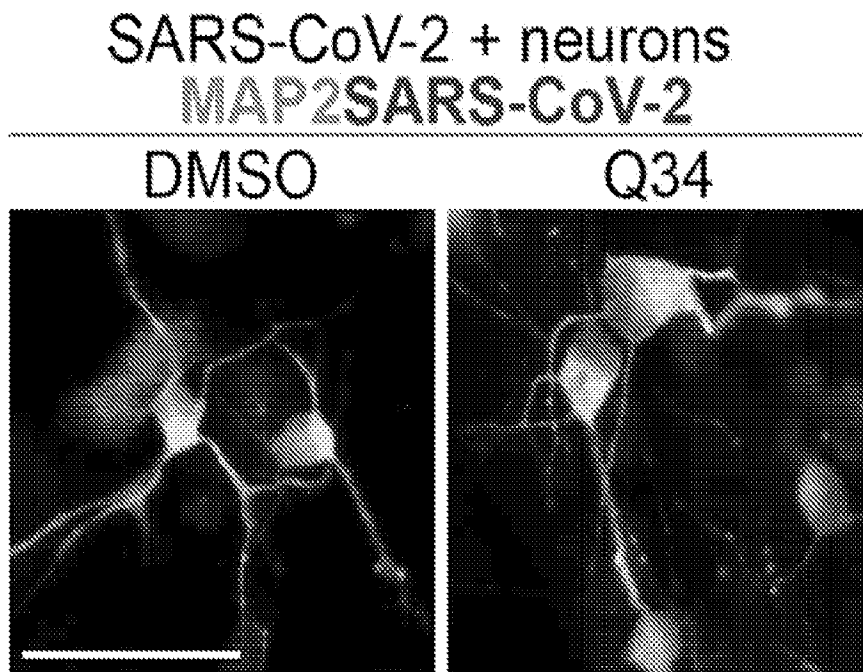


FIG. 5B

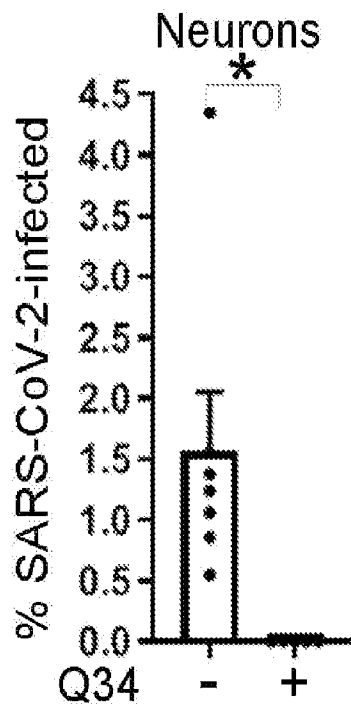


FIG. 5C

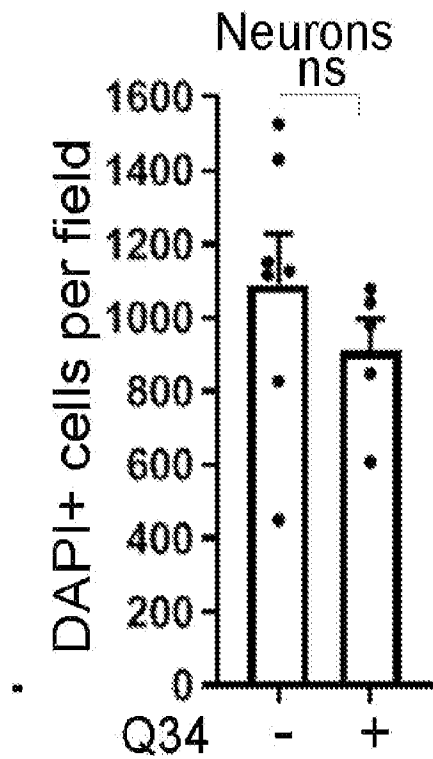


FIG. 5D

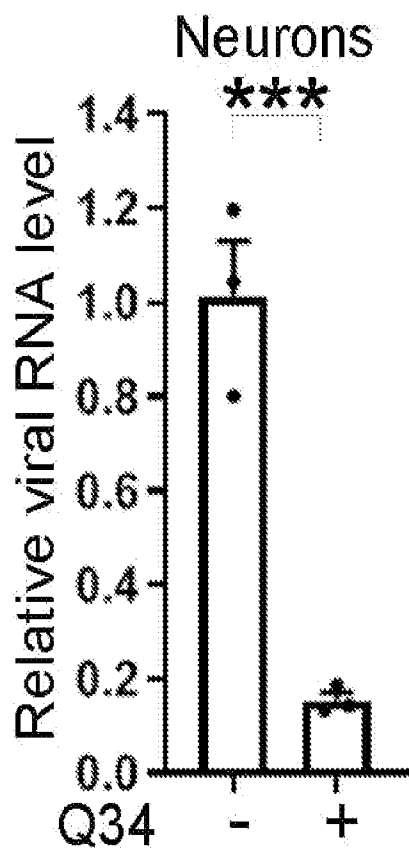


FIG. 5E

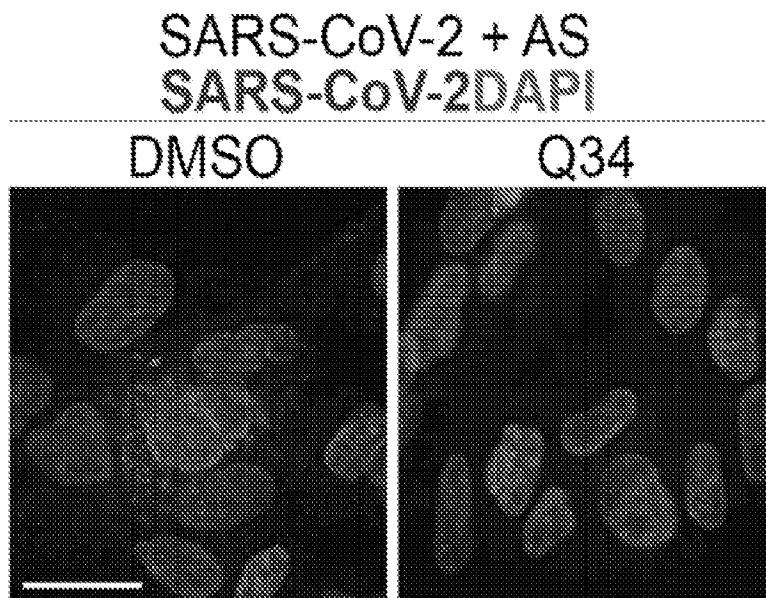


FIG. 5F

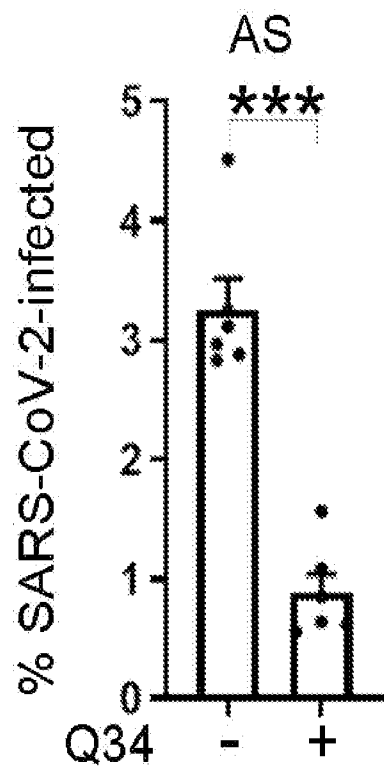


FIG. 5G

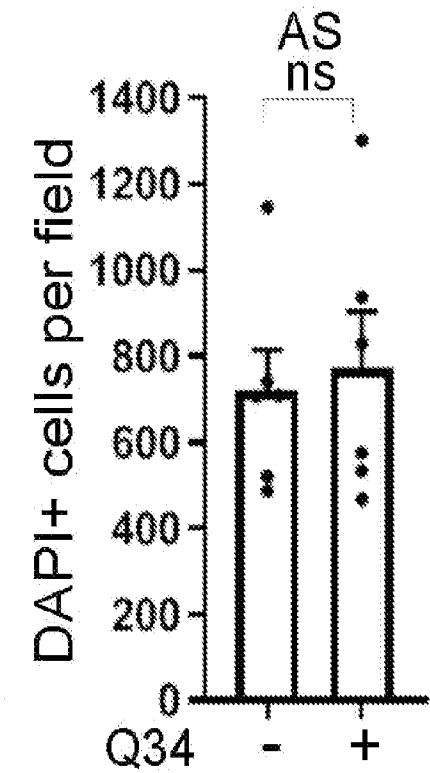


FIG. 5H

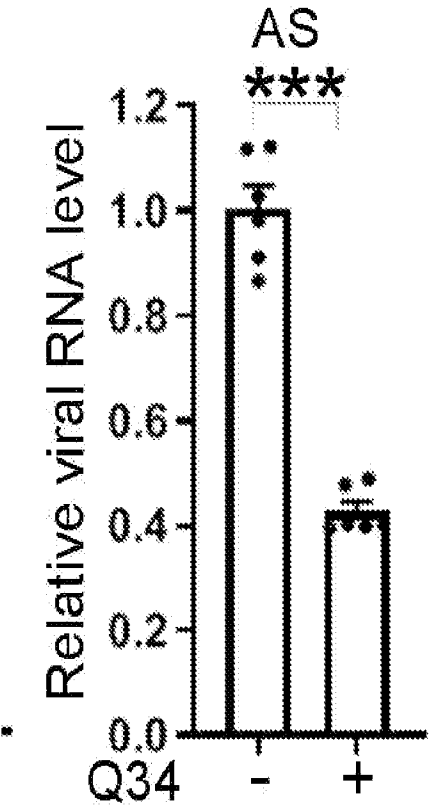


FIG. 6A

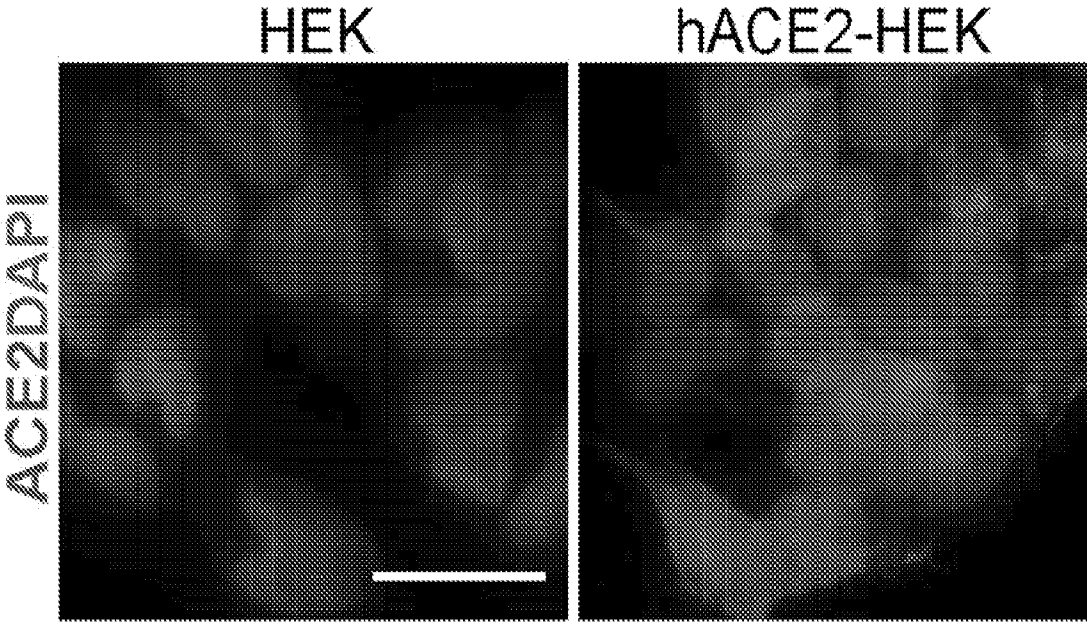


FIG. 6B

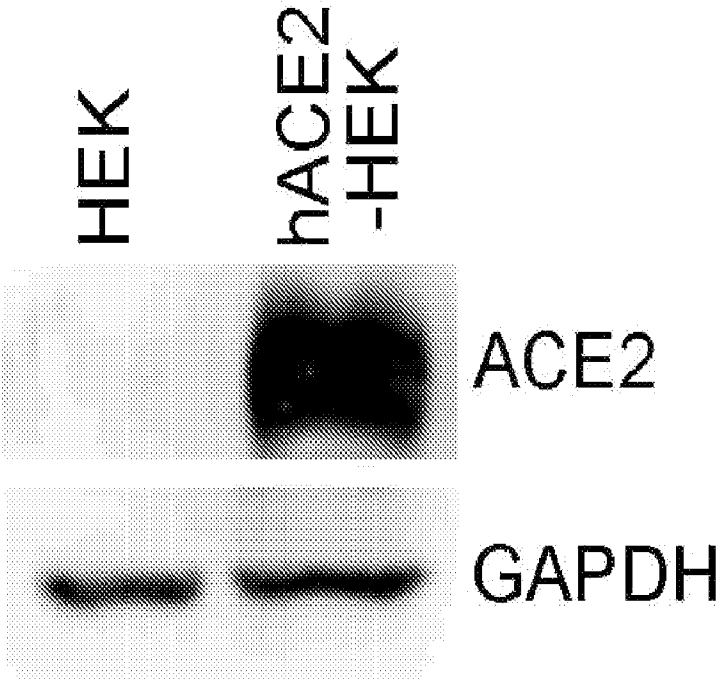


FIG. 7A

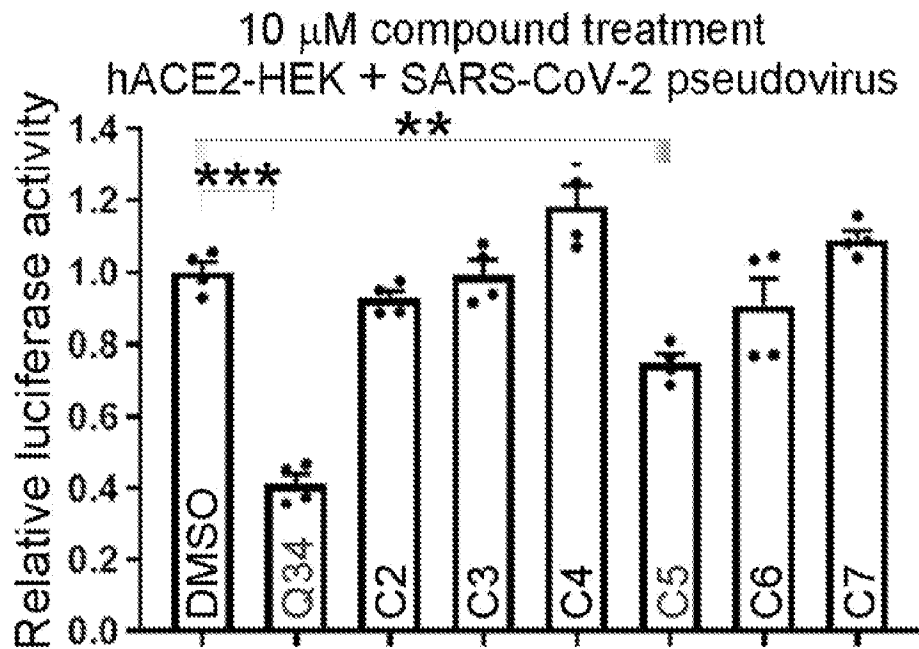


FIG. 7B

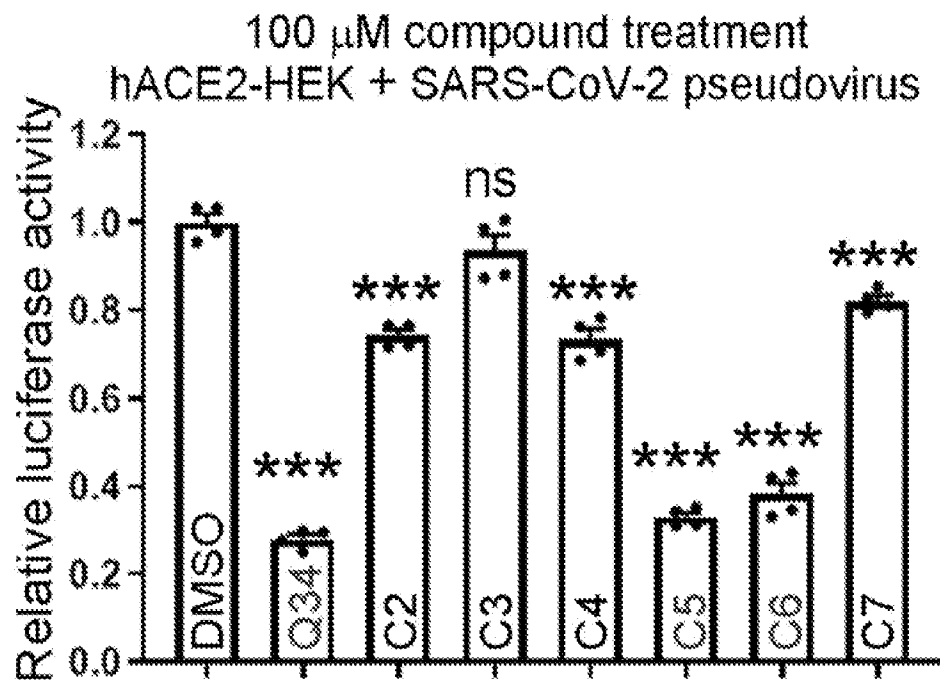


FIG. 7C

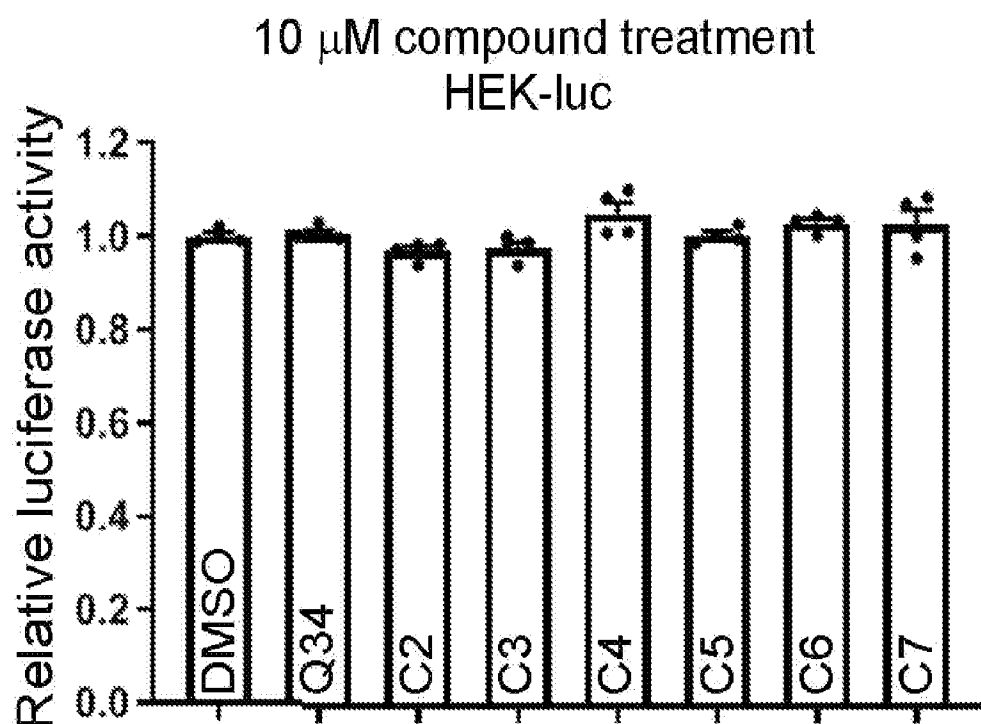


FIG. 7D

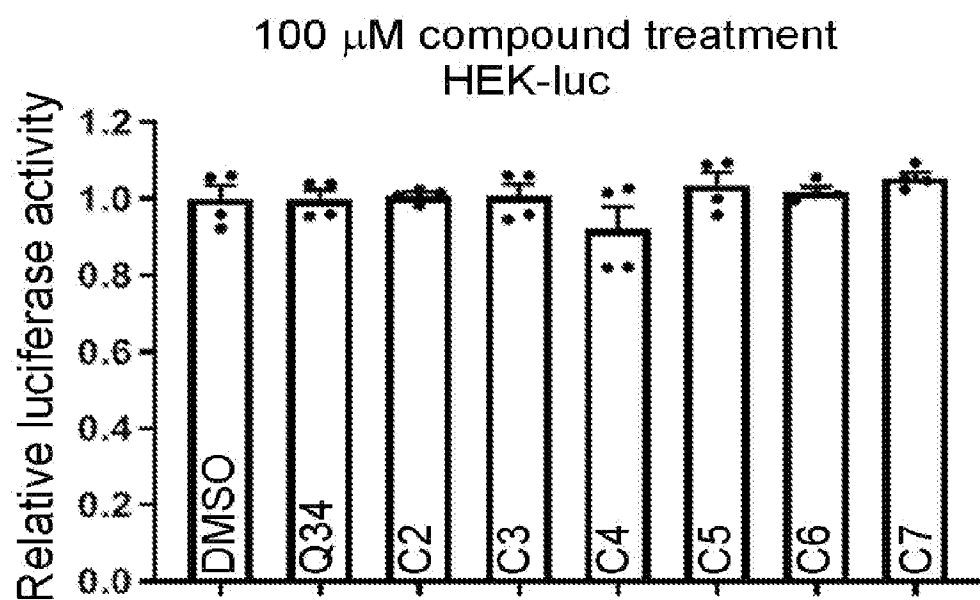


FIG. 7E

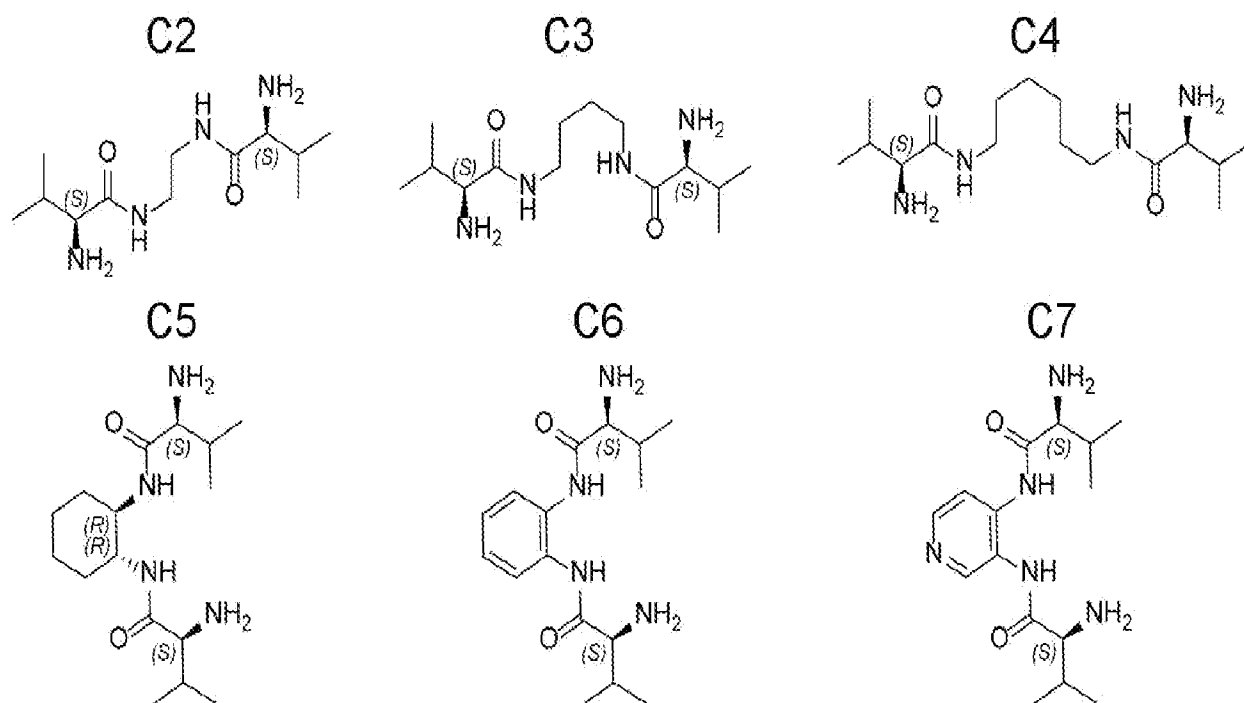
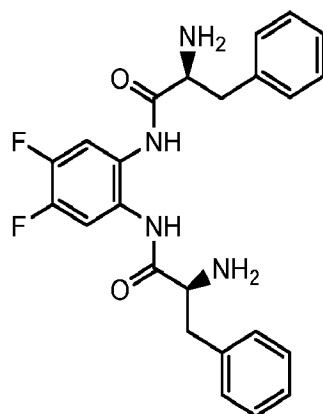
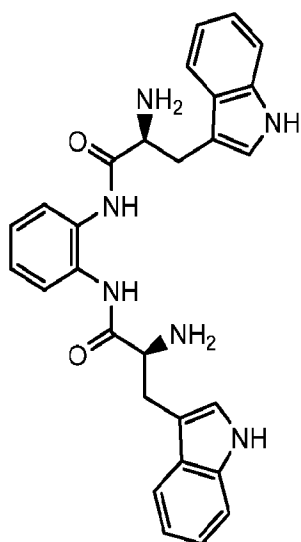


FIG. 8

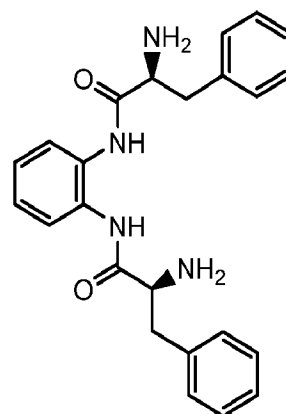
C11



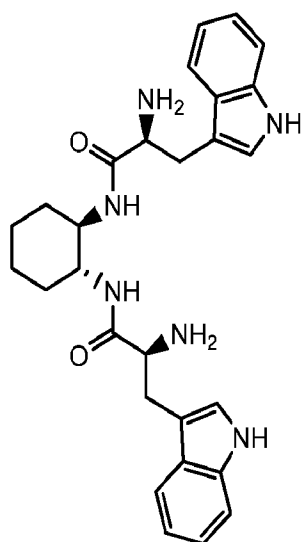
C12



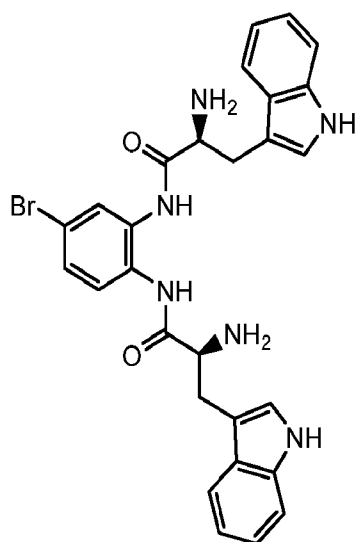
C13



C14



C15



C16

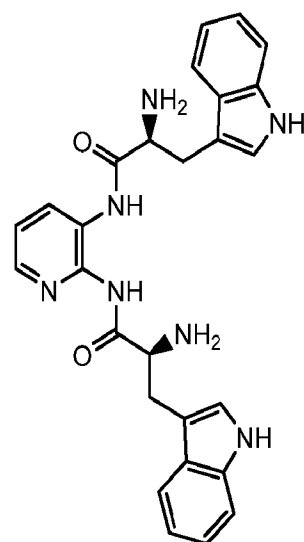


FIG. 9A

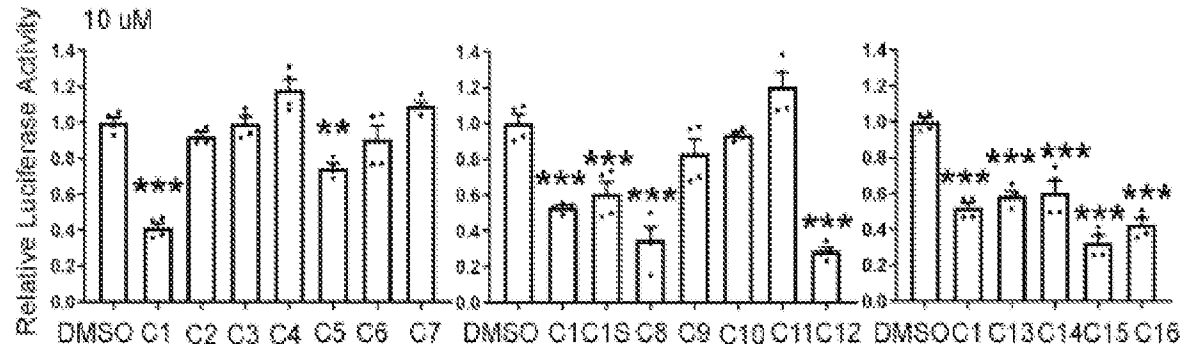


FIG. 9B

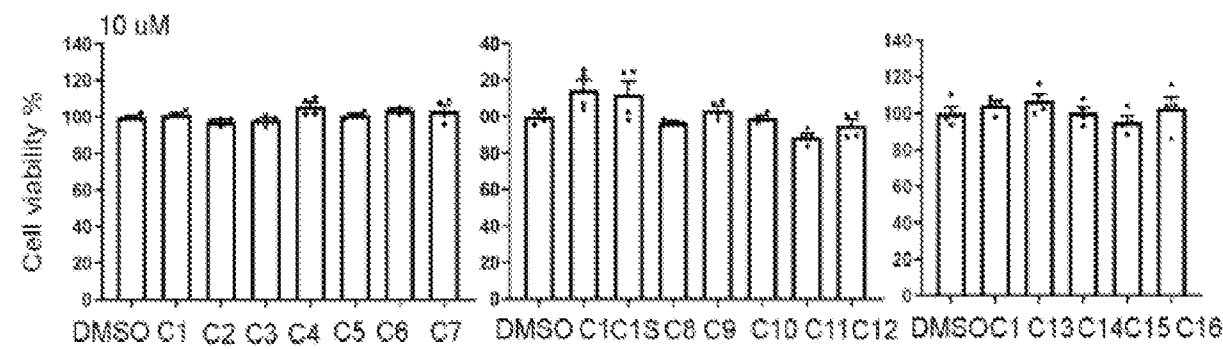


FIG. 9C

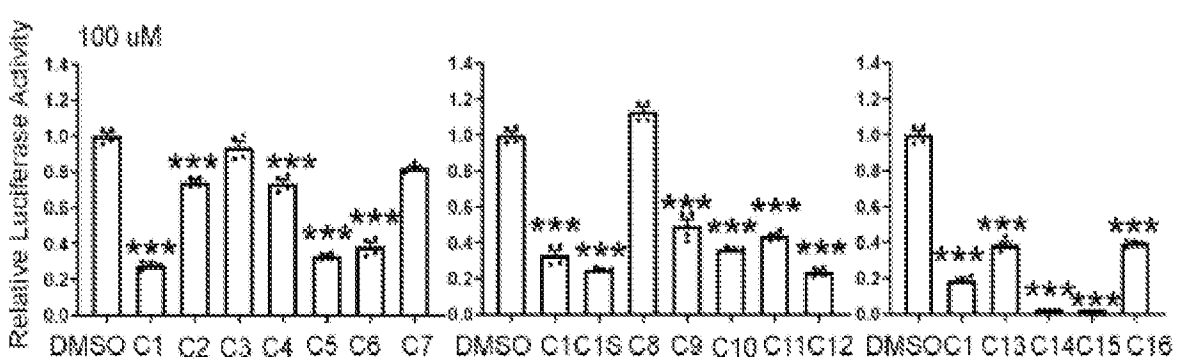


FIG.9D

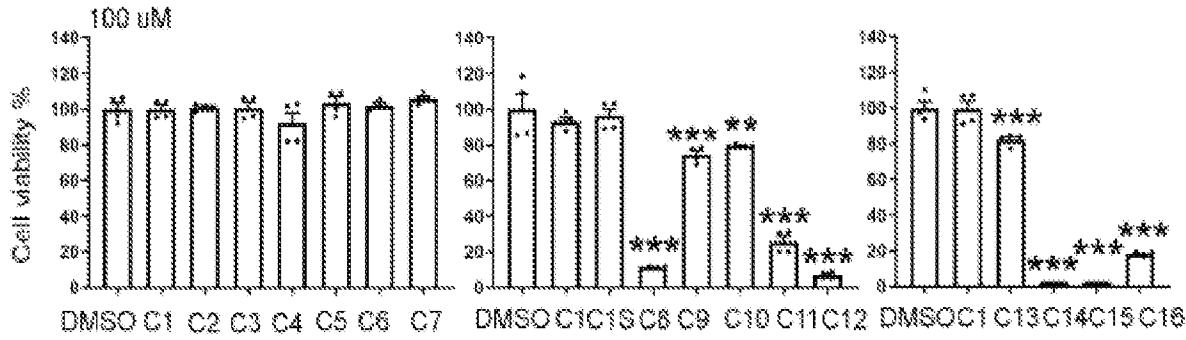


FIG. 10A

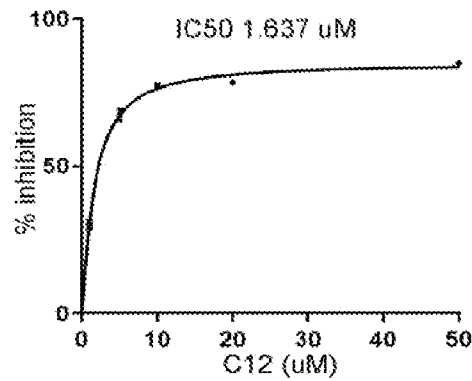


FIG. 10B

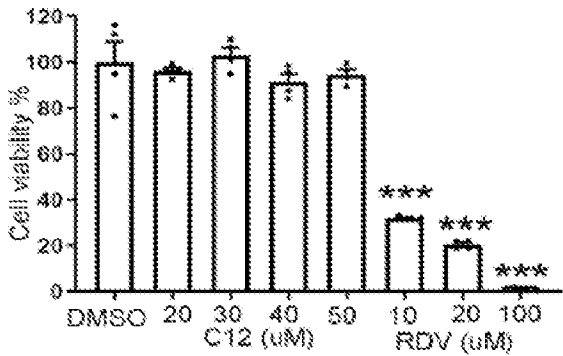


FIG. 10C

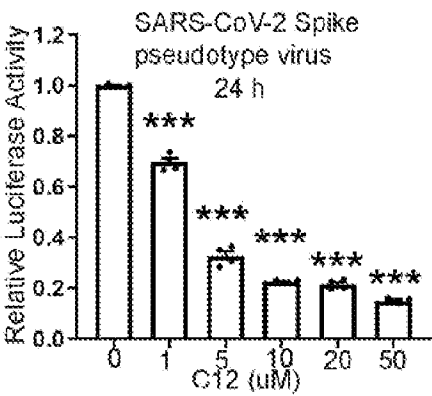


FIG. 10D

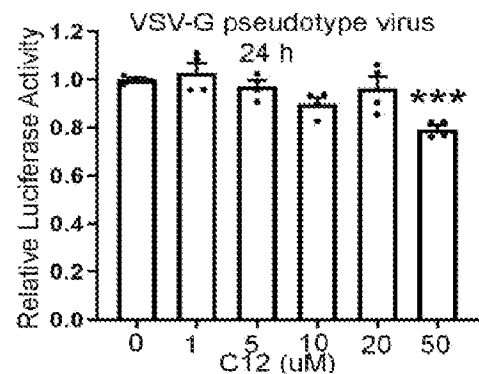


FIG. 10E

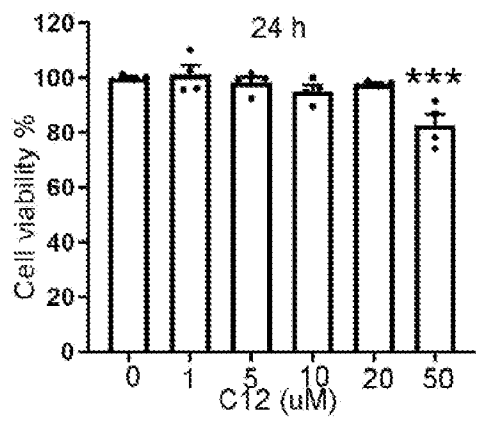


FIG. 10F

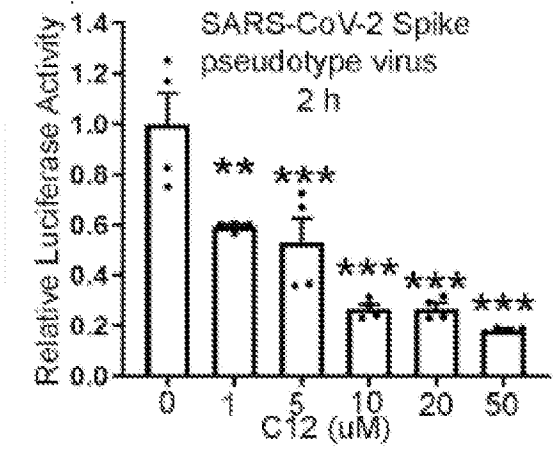


FIG. 10G

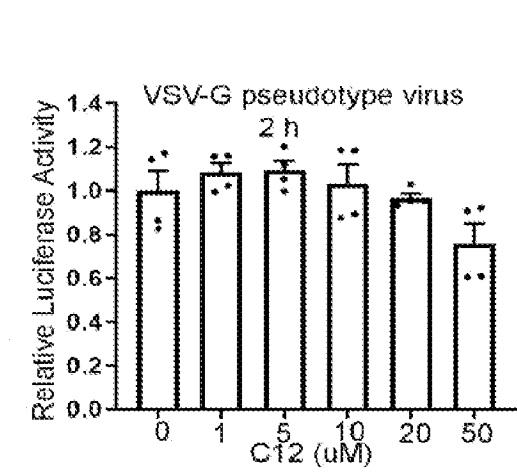


FIG. 10H

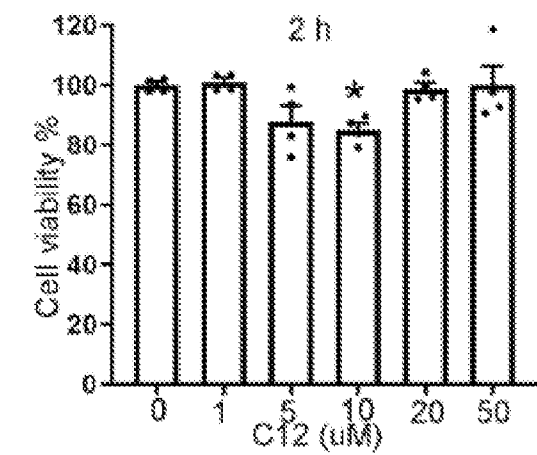


FIG. 11A

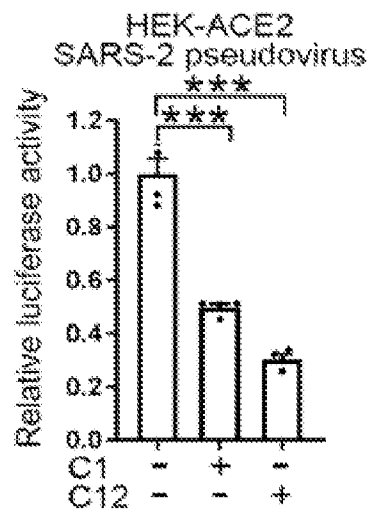


FIG. 11B

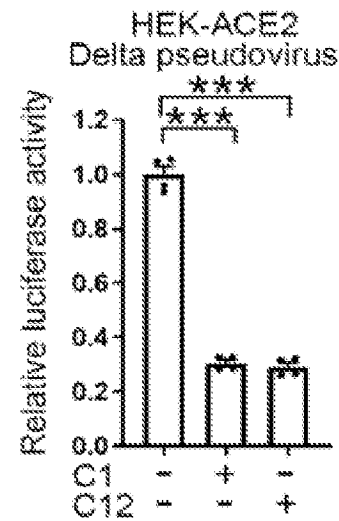


FIG. 12A

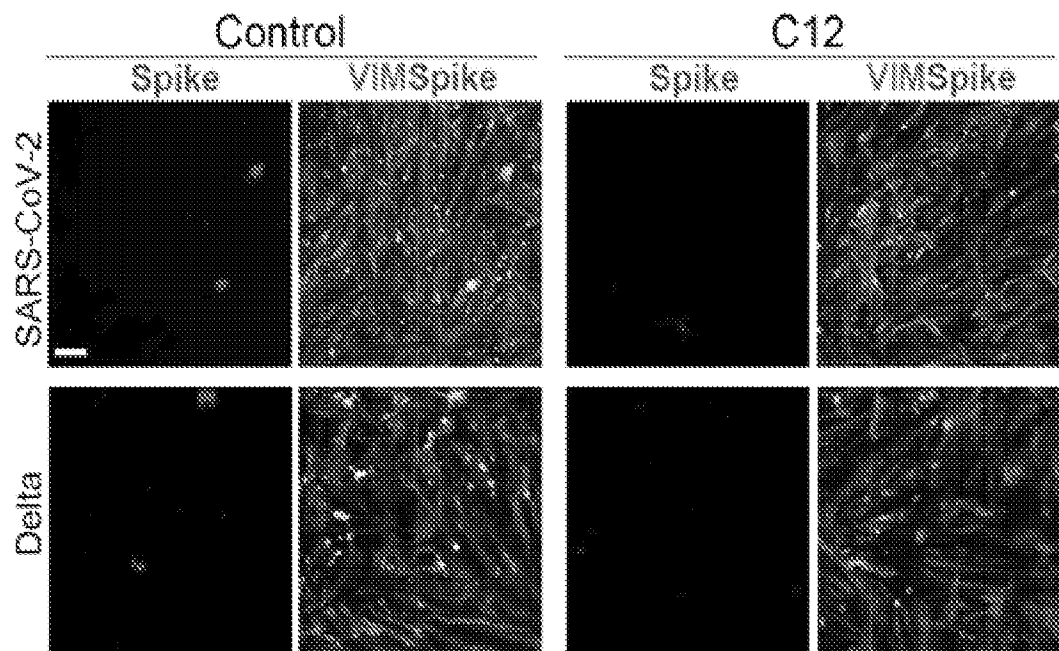


FIG. 12B

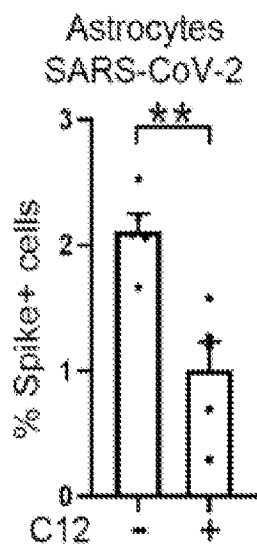


FIG. 12C

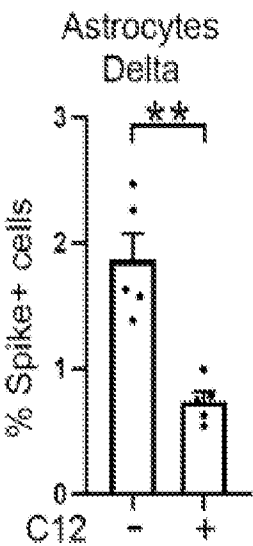


FIG. 12D

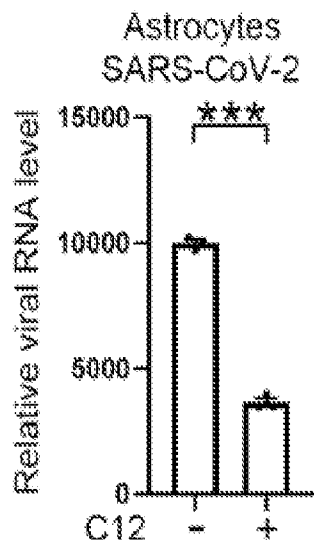


FIG. 12E

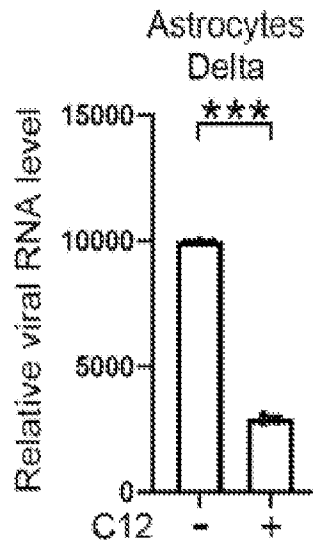


FIG. 13A

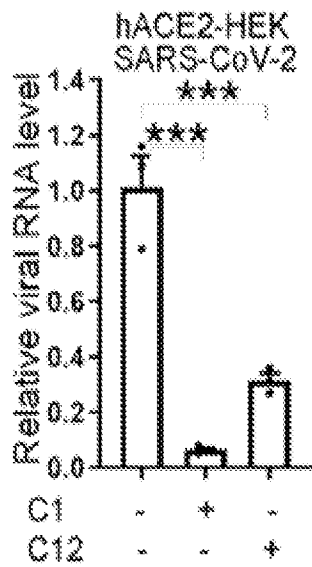


FIG. 13B

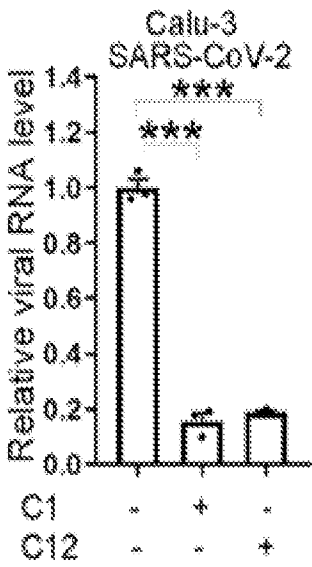


FIG. 13C

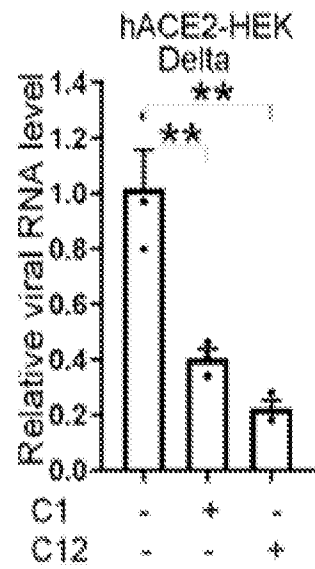


FIG. 13D

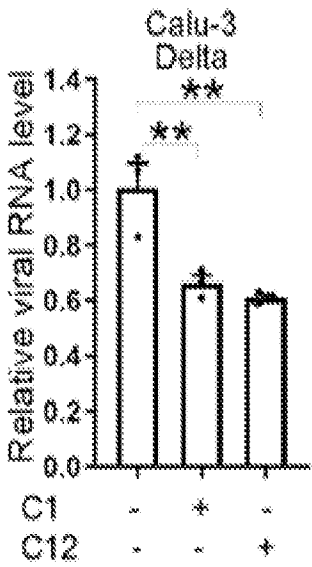


FIG. 14A

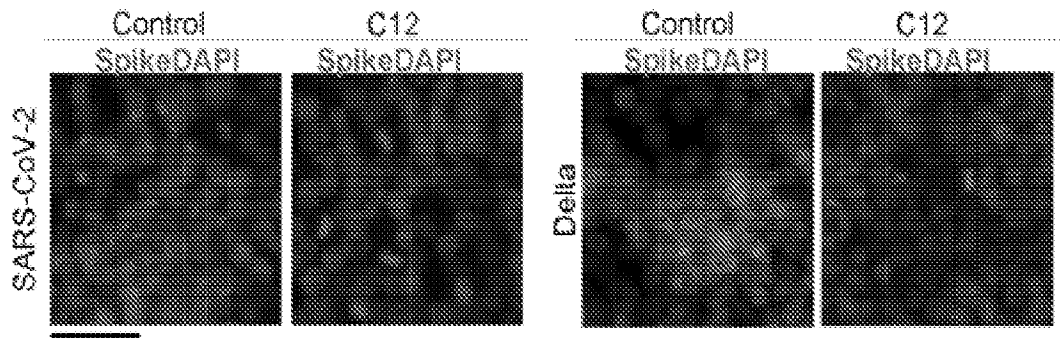


FIG. 14B

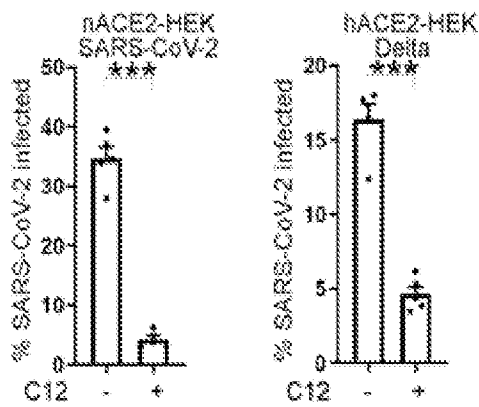


FIG. 14C

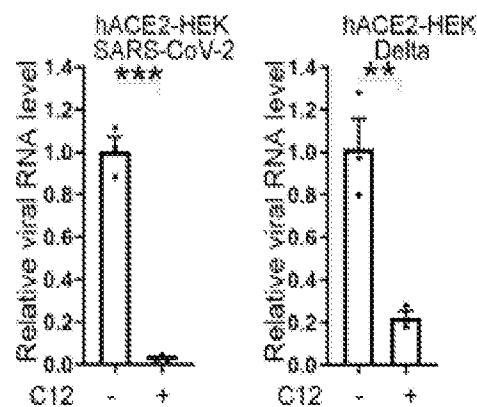


FIG. 15A

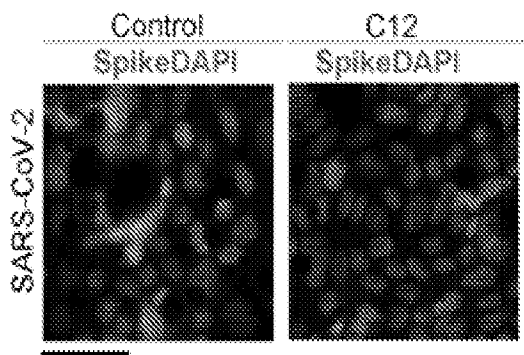


FIG. 15B

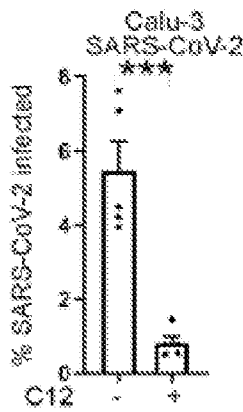


FIG. 15C

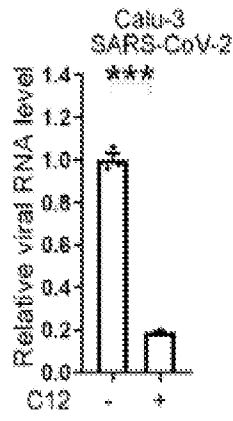
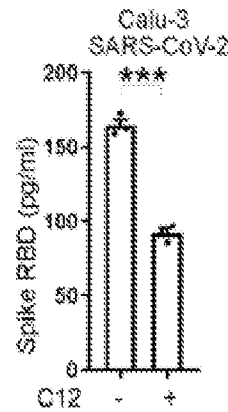


FIG. 15D



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US22/76355

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C07K 5/065; A61K 38/05; A61P 31/14 (2022.01)

ADD.

CPC - INV. C07K 5/06078; A61K 38/05; A61P 31/14

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NATIONAL LIBRARY OF MEDICINE / NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION. "PUBCHEM CID 3420953" 1-7. . Web. 2005; page 2	1-2, 3/1-2, 4/1-2, 5/1-2, 6/1-2, 7/6/1-2, 8/1-2, 9/8/1-2, 10/8/1-2, 11/8/1-2, 12/8/1-2, 13/8/1-2, 14/1-2, 15/14/1-2, 16/14/1-2, 17/15/14/1-2, 33/6/1-2, 34/6/1-2, 35/6/1-2, 36/6/1-2, 37/6/1-2, 38/6/1-2, 39/14/1-2, 40/14/1-2
A	NATIONAL LIBRARY OF MEDICINE / NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION. "PUBCHEM CID 10904681" 1-10. . Web. 2006; page 2	1-2, 3/1-2, 4/1-2, 5/1-2, 6/1-2, 7/6/1-2, 8/1-2, 9/8/1-2, 10/8/1-2, 11/8/1-2, 12/8/1-2, 13/8/1-2, 14/1-2, 15/14/1-2, 16/14/1-2, 17/15/14/1-2, 33/6/1-2, 34/6/1-2, 35/6/1-2, 36/6/1-2, 37/6/1-2, 38/6/1-2, 39/14/1-2, 40/14/1-2
A	NATIONAL LIBRARY OF MEDICINE / NATIONAL CENTER FOR BIOTECHNOLOGY	1-2, 3/1-2, 4/1-2, 5/1-2,

☒ 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

"D" document cited by the applicant in the international application

"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 November 2022 (12.11.2022)

Date of mailing of the international search report

DEC 13 2022

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US22/76355

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	INFORMATION. "PUBCHEM CID 138706621" 1-6. . Web. 2019; page 2	6/1-2, 7/6/1-2, 8/1-2, 9/8/1-2, 10/8/1-2, 11/8/1-2, 12/8/1-2, 13/8/1-2, 14/1-2, 15/14/1-2, 16/14/1-2, 17/15/14/1-2, 33/6/1-2, 34/6/1-2, 35/6/1-2, 36/6/1-2, 37/6/1-2, 38/6/1-2, 39/14/1-2, 40/14/1-2
A	US 2021/0008150 A1 (EMORY UNIVERSITY) 14 January 2021; paragraphs [0185]-[0186], [0335], [0486]	1, 3/1, 4/1, 5/1, 6/1, 7/6/1, 8/1, 9/8/1, 10/8/1, 11/8/1, 12/8/1, 13/8/1, 14/1, 15/14/1, 16/14/1, 17/15/14/1, 33/6/1, 34/6/1, 35/6/1, 36/6/1, 37/6/1, 38/6/1, 39/14/1, 40/14/1
A	ALAGUMUTHU. "Structure-Based Design of Novel Peptidomimetics Targeting the SARS-CoV-2 Spike Protein" 177-185. Cellular and Molecular Bioengineering. Web. April 2021; abstract; page 181, figure 3; page 183, column 1, first paragraph	2, 3/2, 4/2, 5/2, 6/2, 7/6/2, 8/2, 9/8/2, 10/8/2, 11/8/2, 12/8/2, 13/8/2, 14/2, 15/14/2, 16/14/2, 17/15/14/2, 33/6/2, 34/6/2, 35/6/2, 36/6/2, 37/6/2, 38/6/2, 39/14/2, 40/14/2
A	LARUE. "Rationally Designed ACE2-Derived Peptides Inhibit SARS-CoV 2" A-I. Bioconjugate Chemistry. Web. 2020; abstract; page B, column 1, third paragraph; page B, column 2, table 1; page F, column 1, second paragraph	2, 3/2, 4/2, 5/2, 6/2, 7/6/2, 8/2, 9/8/2, 10/8/2, 11/8/2, 12/8/2, 13/8/2, 14/2, 15/14/2, 16/14/2, 17/15/14/2, 33/6/2, 34/6/2, 35/6/2, 36/6/2, 37/6/2, 38/6/2, 39/14/2, 40/14/2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US22/76355

Box No. I 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter:1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US22/76355

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 18-32
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.