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(54) Title: COMPOUNDS FOR THE INHIBITION OF A PROLYL ISOMERASE AND METHODS OF USE THEREOF

FIG. 1A



(57) Abstract: There are provided compounds for the inhibition of Pin 1 and/or FKBP and methods of use thereof.



COMPOUNDS FOR THE INHIBITION OF A PROLYL ISOMERASE AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/435,572 filed December 16, 2016, which is incorporated herein by reference in its entirety.

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

[0002] The Sequence Listing written in file 048536-591001WO Sequence Listing_ST25.TXT, created on December 11, 2017, 769 bytes, machine format IBM-PC, MS-Windows operating system, is hereby incorporated by reference.

BACKGROUND

[0003] Peptidyl-prolyl isomerases (PPIases) are a family of proteins that catalyze the cis-trans isomerization of proline bonds. The PPIase super-family includes the FK506-binding proteins (FKBPs), cyclophilins and parvulins. The macrocyclic natural products FK506 and rapamycin inhibit the FKBP class of PPIases and the cyclophilins are inhibited by the macrocyclic natural product, cyclosporin. However, there are not any known inhibitors of peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1). None of the natural or synthetic inhibitors of other PPIase families bind Pin1. Pin1 has emerged as a promising drug target in cancer and neurodegeneration.

[0004] PPIases have emerged as important targets in cancer, neurodegeneration, mental illnesses and neuropathic pain. Targeting the peptidyl-prolyl isomerases has been a challenge as most inhibitors have overlapping specificity for multiple family members and are lacking cellular activity. Disclosed herein are novel, selective inhibitors for the peptidyl-prolyl isomerase Pin1 to overcome this challenge.

[0005] Developing selective Pin1 inhibitors has posed a significant challenge because its active site is shallow and requires candidate compounds to possess a highly electronegative group (e.g. phosphate) to bind. Pin1 inhibitors that contain these electronegative substituents often lack membrane permeability and have poor pharmacokinetics. Macrocyclic natural products, including FK506 and rapamycin, possess exceptional activity and are biologically active.

[0006] Accordingly, there is a need in the art for inhibitors of the peptidyl-prolyl isomerase, Pin1, for the treatment of Pin1-dependent diseases, such as cancer or neurodegeneration. Provided herein are solutions to these and other problems in the art.

BRIEF SUMMARY

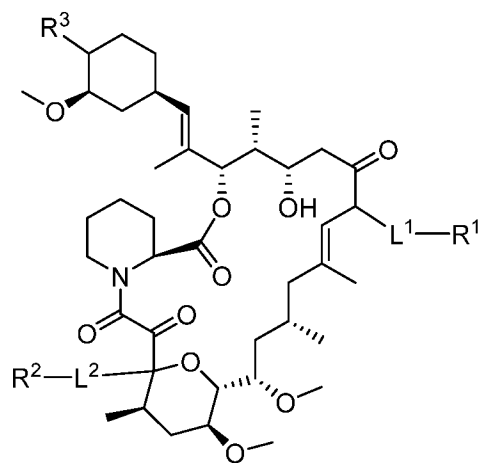
[0007] Disclosed herein, *inter alia*, are selective inhibitors of Pin 1 which can utilize a chemotype known to possess exceptional biological activity, addressing the limited cellular activity of previous Pin 1 inhibitors.

[0008] In a first aspect, there is provided a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound including a macrolide with a pipecolyl moiety, or a pharmaceutically acceptable salt thereof.

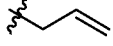
[0009] In another aspect, there is provided an FK506 binding protein (FKBP) inhibitor compound including a macrolide with a pipecolyl moiety, or a pharmaceutically acceptable salt thereof.

[0010] In another aspect, there is provided a macrolide compound covalently attached to an electronegative group at a position equivalent to C-10 of FK506, or a pharmaceutically acceptable salt thereof.

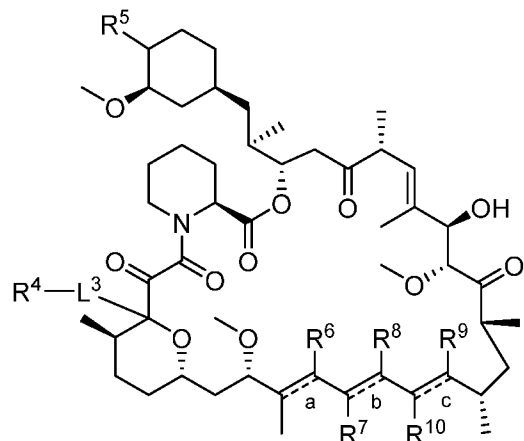
[0011] In another aspect, there is provided a compound of structural Formula (I):



(I), or a pharmaceutically acceptable salt thereof. In the compounds of structural Formula (I): n_1 , n_2 and n_3 are independently an integer from 0 to 4. m_1 , m_2 , m_3 , v_1 , v_2 and v_3 are independently 1 or 2. L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted

heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, 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^{1L} , R^{2L} , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} and R^{3D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, 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^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. $X^{1.1}$, $X^{2.1}$ and $X^{3.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$. When L^2 is $-O-$, L^1 is a bond, R^1 is  or $-CH_2CH_3$ and R^3 is hydroxyl, then R^2 is not hydrogen.

[0012] In another aspect, there is provided a compound of structural Formula (II):



(II), or a pharmaceutically acceptable salt thereof. In the

compounds of structural Formula (II), $\text{--}\overset{\text{a}}{\text{--}}$, $\text{--}\overset{\text{b}}{\text{--}}$ and $\text{--}\overset{\text{c}}{\text{--}}$ are independently single bonds or double bonds. n_4 , n_5 , n_6 , n_7 , n_8 , n_9 and n_{10} are independently an integer from 0 to 4. m_4 , m_5 , m_6 , m_7 , m_8 , m_9 , m_{10} , v_4 , v_5 , v_6 , v_7 , v_8 , v_9 and v_{10} are independently 1 or 2. L^3 is a bond, --O-- , --S-- , $\text{--NR}^{3L}\text{--}$, $\text{--NR}^{3L}\text{C(O)--}$, --C(O)-- , --C(O)O-- , --S(O)-- , $\text{--S(O)}_2\text{--}$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^4 is hydrogen, halogen, $\text{--CX}^{4.1}_3$, $\text{--CHX}^{4.1}_2$, $\text{--CH}_2\text{X}^{4.1}$, --CN , $\text{--SO}_{n_4}\text{R}^{4A}$, $\text{--SO}_{v_4}\text{NR}^{4B}\text{R}^{4C}$, $\text{--NHNR}^{4B}\text{R}^{4C}$, $\text{--ONR}^{4B}\text{R}^{4C}$, $\text{--NHC(O)NHN}^{4B}\text{R}^{4C}$, $\text{--NHC(O)NR}^{4B}\text{R}^{4C}$, --N(O)_{m_4} , $\text{--NR}^{4B}\text{R}^{4C}$, --C(O)R^{4D} , --C(O)OR^{4D} , $\text{--C(O)NR}^{4B}\text{R}^{4C}$, --OR^{4A} , $\text{--NR}^{4B}\text{SO}_2\text{R}^{4A}$, $\text{--NR}^{4B}\text{C(O)R}^{4D}$, $\text{--NR}^{4B}\text{C(O)OR}^{4D}$, $\text{--NR}^{4B}\text{OR}^{4D}$, $\text{--OCX}^{4.1}_3$, $\text{--OCHX}^{4.1}_2$, 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^5 is hydrogen, halogen, $\text{--CX}^{5.1}_3$, $\text{--CHX}^{5.1}_2$, $\text{--CH}_2\text{X}^{5.1}$, --CN , $\text{--SO}_{n_5}\text{H}$, $\text{--SO}_{v_5}\text{NH}_2$, --NHNH_2 , --ONH_2 , --NHC(O)NHNH_2 , --NHC(O)NH_2 , --N(O)_{m_5} , --NH_2 , --C(O)H , --C(O)OH , --C(O)NH_2 , --OH , $\text{--NHSO}_2\text{H}$, --NHC(O)H , --NHC(O)OH , --NHOH , $\text{--OCX}^{5.1}_3$, $\text{--OCHX}^{5.1}_2$, 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^6 is hydrogen, halogen, $\text{--CX}^{6.1}_3$, $\text{--CHX}^{6.1}_2$, $\text{--CH}_2\text{X}^{6.1}$, --CN , $\text{--SO}_{n_6}\text{H}$, $\text{--SO}_{v_6}\text{NH}_2$, --NHNH_2 , --ONH_2 , --NHC(O)NHNH_2 , --NHC(O)NH_2 , --N(O)_{m_6} , --NH_2 , --C(O)H , --C(O)OH , --C(O)NH_2 , --OH , $\text{--NHSO}_2\text{H}$, --NHC(O)H , --NHC(O)OH , --NHOH , $\text{--OCX}^{6.1}_3$, $\text{--OCHX}^{6.1}_2$, 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^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, $-CN$, $-SO_{n7}H$, $-SO_{v7}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m7}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$, 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^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, $-CN$, $-SO_{n8}H$, $-SO_{v8}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m8}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, 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^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, $-CN$, $-SO_{n9}H$, $-SO_{v9}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m9}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, 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^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, $-CN$, $-SO_{n10}H$, $-SO_{v10}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m10}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, 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^{3L} , R^{4A} , R^{4B} , R^{4C} and R^{4D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, 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^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl. $X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$. When $\overset{a}{\text{---}}$, $\overset{b}{\text{---}}$ and $\overset{c}{\text{---}}$ are double bonds, L^3 is $-O-$ and R^6 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, then R^4 is not hydrogen.

[0013] In another aspect, there is provided a pharmaceutical composition, including a compound described herein, including in an aspect or embodiment, and a pharmaceutically acceptable excipient.

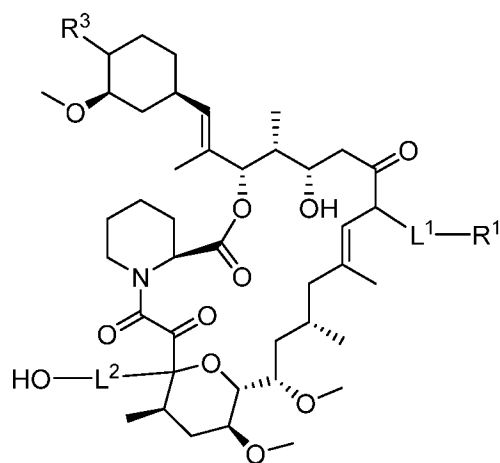
[0014] In another aspect, there is provided a method of inhibiting Pin1, including contacting Pin1 with a compound as set forth herein, including embodiments thereof.

[0015] In another aspect, there is provided a method of inhibiting an FK506 binding protein (FKBP), including contacting the FKBP with a compound as set forth herein, including embodiments thereof.

[0016] In another aspect, there is provided a method of treating a Pin-1 associated disease or disorder, including administering to a patient in need thereof a compound as set forth herein, including embodiments thereof.

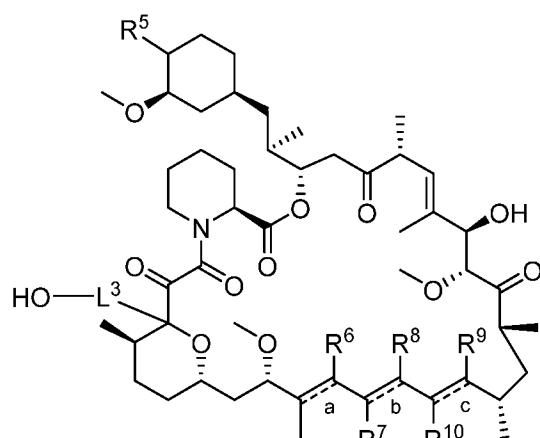
[0017] In another aspect, there is provided a method of treating an FKBP51-mediated disease or disorder, including administering to a patient in need thereof a compound as set forth herein, including embodiments thereof.

[0018] In another aspect, there is provided a method of preparing a compound of structural Formula (I) as set forth herein, including contacting a compound of structural Formula (Ic) with ammonia:



(Ic). L¹, L², R¹, and R³ are as described herein.

[0019] In another aspect, there is provided a method of preparing a compound of structural Formula (II) as set forth herein, including contacting a compound of structural Formula (IIc) with



ammonia:

and R¹⁰ are as described herein.

(IIc). $\frac{-a-}{-b-}$, $\frac{-b-}{-c-}$, L³, R⁵, R⁶, R⁷, R⁸, R⁹,

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIGS. 1A-1B. Structure of Pin1 with key features highlighted. A) Ribbon diagram. The active site pocket within the PPIase domain is composed of antiparallel β -sheets that position a short α -helix. The WW domain consists of two, short antiparallel β -sheets connected to the PPIase domain by a flexible linker (not resolved in this structure). FIG. 1B) Surface representation of the active site. The hydrophobic proline pocket (gray) orients substrate to interact with the catalytic cysteine and the cationic groove that binds phosphate groups. (Protein Data Bank reference, PDB: 1PIN).

[0021] FIG. 2. Natural product inhibitors of Pin1.

[0022] FIG. 3. Representative pipecolic acid-based phosphopeptide inhibitor of Pin1. The phosphopeptide, pintide, is bound to Pin1 (shown as the surface electrostatic map). Significantly, the pipecolate ring is anchored in the proline binding pocket, positioning the phosphate group to interact with the cationic groove. Further affinity is gained via the naphthyl interaction with the hydrophobic shelf of the active site.

[0023] FIG. 4. Small molecule Pin1 inhibitors based on pipecolic acid, demonstrating resemblance to FKBP inhibitors, such as SLF.

[0024] FIG. 5. Bi-aryl amides potently bind Pin1. Bi-aryl amides potently bind Pin1. Co-crystallization with 65c (PDB: 3IKG) revealed a new binding orientation with the phenyl ring oriented in the proline-binding pocket and the phosphate group oriented between Arg-68 and Arg-69. (PDB: 3IKG).

[0025] FIG. 6. Optimization of the bi-aryl amide scaffold to enhance cellular permeability. The phosphate group was replaced with a carboxylic acid, which retained a similar binding pose as (compound 4.5a) with the orientation of the carboxylate facing Lys-63 as in the phosphopeptide inhibitors. (PDB: 4TYO).

[0026] FIG. 7. Alternative bi-aryl scaffold engages peripheral residues of the Pin1 cationic groove. Spanning the phosphate-binding region (Lys-63, Arg-68, Arg-69) enhances affinity for Pin1, even without engagement of the hydrophobic shelf.

[0027] FIGS. 8A-8B. Overlay of the bound conformation of FK506 compared to the pintide phosphopeptide, highlighting the potential modification site. FIG. 8A) Aligning the pipercolate ring in FK506 to the pintide phosphopeptide demonstrates the binding pose similarity of each compound and proximity to the cationic phosphate binding site. FIG. 8B) FK506 and Rapamycin shown with the FKBP binding motif highlighted. The tertiary hydroxyl is highlighted (FIG. 8A, third panel; black arrow in FIG. 8B).

[0028] FIG. 9. Semisynthetic modification of FK506 and rapamycin, demonstrating modification of the tertiary hydroxyl of FK506 and Rapamycin into a primary amine for further derivatization.

[0029] FIG. 10. Conversion of FK506 into FK-NH₂. Within 30 minutes, a significant portion of FK506 is converted into the amine-containing derivative. Order of curves: top peak to bottom at about 3.4 min: control, 30min, 60min, 90min, 120min, 180min.

[0030] FIG. 11. Reaction rate of the FK506 conversion. Data were fit to a one-phase exponential.

[0031] FIG. 12. Comparison of FK-NH₂ and FK506 by MS. In the converted FK-NH₂, the parent amine is readily ionized, unlike in FK506.

[0032] FIG. 13. Downfield region of the FK-NH₂ ¹³C NMR spectrum. The C10 peak corresponding to the tertiary hydroxyl attachment point is typically at 97ppm (left highlight), but appears shifted after conversion to the amine (right highlight).

[0033] FIG. 14. Determination of concentration effects on the conversion of FK506. HPLC traces are shown of the reaction after two hours in various concentrations of ammonia without and with peak highlighting (left and right, respectively). Increasing ammonia concentration results in formation of a new species that is less polar than FK-NH₂.

[0034] FIG. 15. Solvent dramatically effects the conversion of FK506. Alcohols are heavily preferred in the conversion of FK506, with other polar and protic solvents leading to only minimal product formation after three hours. Bins (left to right): DCM, Dioxane, DMPU, EtOH, TFE, IPA, m N-BuOH, MeOH. Order within each bin: FK-NH₂ (left), FK506 (right).

[0035] FIG. 16. Deuterated methanol slightly enhances the rate of reaction. Bins (left to right): Methanol(-d) at 30min, 60min, 240min; Methanol at 30min, 60min, 240min.

[0036] FIG. 17. Semisynthetic scheme to derivatize FK-NH₂. i) 2M ammonia, ethanol; ii) FK-NH₂, 3-chlorobenzyl bromide (3eq), DIPEA (6 eq), DMAP (0.1eq), DCM. Order within each bin: FK-NH₂ (left), FK506 (right).

[0037] FIGS. 18A-18B. The phosphopeptide WFYpSPFLE binds to Pin1 and is competed by **34**. FIG. 18A) Wild-type Pin1 and the PPIase domain (see B legend) bind with good affinity to the phosphopeptide tracer. The smaller PPIase domain has a lower ΔmP corresponding to its smaller molecular mass. FIG. 18B) The phosphopeptide tracer is competed by **34**, which contains an electronegative sulfamic acid group that likely engages the Pin1 cationic groove. Experiments are the average of at least two experiments with duplicate measurements. Error is SEM.

[0038] FIGS. 19A-19B. Competitive binding to FKBP12 of FK506 derivatives. A) Modification of FK506 at this position dramatically reduces affinity for FKBP12 depending on the functional group properties. B) K_i calculations of the FK506 derivatives in comparison to FK506. Results are the average of triplicates, and error is SEM.

[0039] FIGS. 20A-20I. MS spectra for compounds 15 (FIG. 20A), 16 (FIG. 20A), 18 (FIG. 20A), 19 (FIG. 20A), 22 (FIG. 20A), 24 (FIG. 20A), 27 (FIG. 20A), 29 (FIG. 20A), and 34 (FIG. 20A). Axes: relative abundance (y-axis); m/z (x-axis).

[0040] FIG. 21. Binding of FK506 to natural target FKBP12.

[0041] FIG. 22. Schematic of multiple binding functionality incorporated into a compound.

[0042] FIG. 23. Computational model showing binding functionality incorporated into a compound.

DETAILED DESCRIPTION

DEFINITIONS

[0043] 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.

[0044] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$.

[0045] 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., $\text{C}_1\text{-C}_{10}$ means one to ten carbons). Alkyl is an uncyclized chain. Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, 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 ($-\text{O}-$). An alkyl moiety may be an alkenyl moiety. An alkyl moiety may be an alkynyl moiety. An alkyl moiety may be fully saturated. An alkenyl may include more than one double bond and/or one or more triple bonds in addition to the one or more double bonds. An alkynyl may include more than one triple bond and/or one or more double bonds in addition to the one or more triple bonds.

[0046] The term “alkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkyl, as exemplified, but not limited by, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred herein. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms. The term “alkenylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene.

[0047] 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., 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-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 eight optionally different heteroatoms (e.g., O, N, S, Si, or P).

[0048] Similarly, the term “heteroalkylene,” by itself or as part of another substituent, means, unless otherwise stated, a divalent radical derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., 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 -C(O)₂R'- represents both -C(O)₂R'- and -R'C(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 -C(O)R', -C(O)NR', -NR'R'', -OR', -SR', and/or -SO₂R'. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R'' or the like, it will be understood that the terms heteroalkyl and -NR'R'' are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity.

Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0049] 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. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems are bridged monocyclic rings or fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. In embodiments, fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. In embodiments, cycloalkyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted by one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkyl ring systems are a monocyclic cycloalkyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the base ring.

[0050] 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. In embodiments, monocyclic cycloalkenyl ring systems are cyclic hydrocarbon groups containing from 3 to 8 carbon atoms, where such groups are unsaturated (i.e., containing at least one annular carbon carbon double bond), but not aromatic. Examples of monocyclic cycloalkenyl ring systems include cyclopentenyl and cyclohexenyl. In embodiments, bicyclic cycloalkenyl rings are bridged monocyclic rings or a fused bicyclic rings. In embodiments, bridged monocyclic rings contain a monocyclic cycloalkenyl ring where two non adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (i.e., a bridging group of the form $(CH_2)_w$, where w is 1, 2, or 3). Representative examples of bicyclic cycloalkenyls include, but are not limited to, norbornenyl and bicyclo[2.2.2]oct 2 enyl. In embodiments, fused bicyclic cycloalkenyl ring systems contain a monocyclic cycloalkenyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. In embodiments, the bridged or fused bicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkenyl ring. In embodiments, cycloalkenyl groups are optionally substituted with one or two groups which are independently oxo or thia. In embodiments, multicyclic cycloalkenyl rings contain a monocyclic cycloalkenyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two ring systems independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. In embodiments, the multicyclic cycloalkenyl is attached to the parent molecular moiety through any carbon atom contained within the base ring. In embodiments, multicyclic cycloalkenyl rings contain a monocyclic cycloalkenyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl.

[0051] In embodiments, a heterocycloalkyl is a heterocyclyl. The term “heterocyclyl” as used herein, means a monocyclic, bicyclic, or multicyclic heterocycle. The heterocyclyl monocyclic

heterocycle is a 3, 4, 5, 6 or 7 membered ring containing at least one heteroatom independently selected from the group consisting of O, N, and S where the ring is saturated or unsaturated, but not aromatic. The 3 or 4 membered ring contains 1 heteroatom selected from the group consisting of O, N and S. The 5 membered ring can contain zero or one double bond and one, two or three heteroatoms selected from the group consisting of O, N and S. The 6 or 7 membered ring contains zero, one or two double bonds and one, two or three heteroatoms selected from the group consisting of O, N and S. The heterocyclyl monocyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heterocyclyl monocyclic heterocycle. Representative examples of heterocyclyl monocyclic heterocycles include, but are not limited to, azetidiny, azepany, aziridiny, diazepany, 1,3 dioxany, 1,3 dioxolany, 1,3 dithiolany, 1,3 dithiany, imidazoliny, imidazolidiny, isothiazoliny, isothiazolidiny, isoxazoliny, isoxazolidiny, morpholiny, oxadiazoliny, oxadiazolidiny, oxazoliny, oxazolidiny, piperaziny, piperidiny, pyran, pyrazoliny, pyrazolidiny, pyrroliny, pyrrolidiny, tetrahydrofurany, tetrahydrothieny, thiadiazoliny, thiadiazolidiny, thiazoliny, thiazolidiny, thiomorpholiny, 1,1 dioxidothiomorpholiny (thiomorpholine sulfone), thiopyran, and trithiany. The heterocyclyl bicyclic heterocycle is a monocyclic heterocycle fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycle, or a monocyclic heteroaryl. The heterocyclyl bicyclic heterocycle is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the monocyclic heterocycle portion of the bicyclic ring system. Representative examples of bicyclic heterocyclyls include, but are not limited to, 2,3 dihydrobenzofuran 2 yl, 2,3 dihydrobenzofuran 3 yl, indolin 1 yl, indolin 2 yl, indolin 3 yl, 2,3 dihydrobenzothien 2 yl, decahydroquinoliny, decahydroisoquinoliny, octahydro 1H indolyl, and octahydrobenzofurany. In embodiments, heterocyclyl groups are optionally substituted with one or two groups which are independently oxo or thia. In certain embodiments, the bicyclic heterocyclyl is a 5 or 6 membered monocyclic heterocyclyl ring fused to a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the bicyclic heterocyclyl is optionally substituted by one or two groups which are independently oxo or thia. Multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems

independently selected from the group consisting of a phenyl, a bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic cycloalkenyl, and a monocyclic or bicyclic heterocyclyl. The multicyclic heterocyclyl is attached to the parent molecular moiety through any carbon atom or nitrogen atom contained within the base ring. In embodiments, multicyclic heterocyclyl ring systems are a monocyclic heterocyclyl ring (base ring) fused to either (i) one ring system selected from the group consisting of a bicyclic aryl, a bicyclic heteroaryl, a bicyclic cycloalkyl, a bicyclic cycloalkenyl, and a bicyclic heterocyclyl; or (ii) two other ring systems independently selected from the group consisting of a phenyl, a monocyclic heteroaryl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, and a monocyclic heterocyclyl. Examples of multicyclic heterocyclyl groups include, but are not limited to 10H-phenothiazin-10-yl, 9,10-dihydroacridin-9-yl, 9,10-dihydroacridin-10-yl, 10H-phenoxazin-10-yl, 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl, 1,2,3,4-tetrahydropyrido[4,3-g]isoquinolin-2-yl, 12H-benzo[b]phenoxazin-12-yl, and dodecahydro-1H-carbazol-9-yl.

[0052] 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.

[0053] 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.

[0054] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent, which can be a single ring or multiple rings (preferably from 1 to 3 rings) that are fused together (i.e., a fused ring aryl) or linked covalently. A fused ring aryl refers to multiple rings fused together wherein at least one of the fused rings is an aryl ring. The term “heteroaryl” refers to aryl groups (or rings) that contain at least one heteroatom such as N, O, or S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Thus, the term “heteroaryl” includes fused ring heteroaryl groups (i.e., multiple rings fused together wherein at least one of the fused rings is a heteroaromatic ring). A 5,6-fused ring heteroarylene refers to two

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

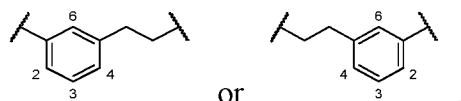
[0055] Spirocyclic rings are two or more rings wherein adjacent rings are attached through a single atom. The individual rings within spirocyclic rings may be identical or different. Individual rings in spirocyclic rings may be substituted or unsubstituted and may have different substituents from other 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.

[0056] The symbol “” denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0057] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom.

[0058] 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:



[0059] 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, -N₃, -CF₃, -CCl₃, -CBr₃, -Cl₃, -CN, -CHO, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -SO₂CH₃, -SO₃H, -OSO₃H, -SO₂NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, substituted or unsubstituted C₁-C₅ alkyl or substituted or unsubstituted 2 to 5 membered heteroalkyl). In embodiments, the alkylarylene is unsubstituted.

[0060] 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.

[0061] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''''R''''', -CN, -NO₂, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to (2m'+1), where m' is the total number of carbon

atoms in such radical. R, R', R'', R''', and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted heteroaryl, substituted or unsubstituted alkyl, alkoxy, or thioalkoxy groups, or arylalkyl groups. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' group when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R'' includes, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0062] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are varied and are selected from, for example: -OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR'C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR'', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -NR'NR''R''', -ONR'R'', -NR'C(O)NR''NR''R''', -CN, -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, -NR'SO₂R'', -NR'C(O)R'', -NR'C(O)-OR'', -NR'OR'', in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''', and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. When a compound described herein includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''', and R'''' groups when more than one of these groups is present.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] As used herein, the terms “heteroatom” or “ring heteroatom” are meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0067] A “substituent group,” as used herein, means a group selected from the following moieties:

(A) oxo,

halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCH_2$, $-OCHF_2$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl), and

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

(i) oxo,

halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$,

-OCHI₂, -OCHF₂, 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, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from:

(a) oxo,

halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -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, 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, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, substituted with at least one substituent selected from: oxo,

halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -CN, -OH, -NH₂, -COOH, -CONH₂, -NO₂, -SH, -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, 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).

[0068] 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.

[0069] A “lower substituent” or “lower substituent group,” as used herein, means a group selected from all of the substituents described above for a “substituent group,” wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C₁-C₈ alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C₃-C₇ cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 3 to 7 membered heterocycloalkyl, each substituted or unsubstituted aryl is a substituted or unsubstituted C₆-C₁₀ aryl, and each substituted or unsubstituted heteroaryl is a substituted or unsubstituted 5 to 9 membered heteroaryl.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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).

[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 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.

[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 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.

[0076] 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.

[0077] 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.

[0078] A “nitrogen-containing functional group”, as used herein, means any substituent group containing nitrogen atom. In embodiments, the nitrogen-containing functional group is an amino group, primary amino group, secondary amino group, tertiary amino group, ammonium ion, primary ketamine, secondary ketamine, primary aldimine, secondary aldimine, imide, azide, diimide, cyanate, isocyanate, nitrate, nitrile, isonitrile, nitrosooxy group, nitro group, nitroso group, oxime,

nitrogen-containing 2 to 8 membered heteroalkyl, nitrogen-containing 3 to 8 membered heterocycloalkyl, or nitrogen-containing 5 to 9 membered heteroaryl.

[0079] Certain compounds disclosed herein 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 presently disclosed compounds 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.

[0080] 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.

[0081] 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.

[0082] It will be apparent to one skilled in the art that certain compounds may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope hereof.

[0083] 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 hereof.

[0084] 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 hereof.

[0085] 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.

[0086] 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.

[0087] "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.

[0088] The terms "a" or "an," as used in herein means one or more. In addition, the phrase "substituted with a[n]," as used herein, means the specified group may be substituted with one or more of any or all of the named substituents. For example, where a group, such as an alkyl or heteroaryl group, is "substituted with an unsubstituted $\text{C}_1\text{-C}_{20}$ alkyl, or unsubstituted 2 to 20 membered heteroalkyl," the group may contain one or more unsubstituted $\text{C}_1\text{-C}_{20}$ alkyls, and/or one or more unsubstituted 2 to 20 membered heteroalkyls.

[0089] 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 R^{13} substituents are present, each R^{13} substituent may be distinguished as $\text{R}^{13\text{A}}$, $\text{R}^{13\text{B}}$, $\text{R}^{13\text{C}}$, $\text{R}^{13\text{D}}$, etc.,

wherein each of R^{13A} , R^{13B} , R^{13C} , R^{13D} , etc. is defined within the scope of the definition of R^{13} and optionally differently.

[0090] A “detectable moiety” as used herein refers to a moiety that can be covalently or noncovalently attached to a compound (e.g. biomolecule) that can be detected for instance, using techniques known in the art. In embodiments, the detectable moiety is covalently attached. The detectable moiety may provide for imaging of the attached compound or biomolecule. The detectable moiety may indicate the contacting between two compounds. Exemplary detectable moieties are fluorophores, antibodies, reactive dyes, radio-labeled moieties, magnetic contrast agents, and quantum dots. Exemplary fluorophores include fluorescein, rhodamine, GFP, coumarin, FITC, Alexa fluor, Cy3, Cy5, BODIPY, and cyanine dyes. Exemplary radionuclides include Fluorine-18, Gallium-68, and Copper-64. Exemplary magnetic contrast agents include gadolinium, iron oxide and iron platinum, and manganese.

[0091] 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.

[0092] A “test compound” as used herein refers to an experimental compound used in a screening process to identify activity, non-activity, or other modulation of a particularized biological target or pathway.

[0093] The term “pharmaceutically acceptable salts” is meant to include salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When

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

[0094] Thus, the compounds of the present invention may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, propionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g. methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

[0095] 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. In embodiments, 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. The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compounds differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but, unless specifically indicated, the salts disclosed herein are equivalent to the parent form of the compound for the purposes of the present disclosure.

[0096] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Prodrugs of the compounds described herein may be converted *in vivo* after administration. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment, such as, for example, when contacted with a suitable enzyme or chemical reagent.

[0097] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0098] “Pharmaceutically acceptable excipient” and “pharmaceutically acceptable carrier” refer to a substance that aids the administration of an active agent to and absorption by a subject and can be included in the compositions of the present invention without causing a significant adverse toxicological effect on the patient. Non-limiting examples of pharmaceutically acceptable excipients include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, and colors, and the like. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention. One of skill in the art will recognize that other pharmaceutical excipients are useful in the present invention.

[0099] 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.

[0100] The terms “peptidyl-prolyl cis/trans isomerase” or “PPIase” refer to a protein or proteins (including homologs, isoforms, and functional fragments thereof) that isomerizes the peptide bond of prolines. The term includes any recombinant or naturally-occurring form of a PPIase and variants thereof that maintain PPIase activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype Pin 1). The term includes any mutant form of PPIase variants (e.g., frameshift mutations) thereof that maintain PPIase activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to the wildtype PPIase).

[0101] The term “peptidyl-prolyl cis-trans isomerase NIMA-interacting 1” (“Pin 1”) refer to a protein or proteins (including homologs, isoforms, and functional fragments thereof) that isomerizes only phospho-Serine/Threonine-Proline motifs. The enzyme binds to a subset of proteins and thus plays a role as a post phosphorylation control in regulating protein function. The term includes any recombinant or naturally-occurring form of Pin 1 variants thereof that maintain Pin 1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype Pin 1). The term includes any mutant form of Pin 1 variants (e.g., frameshift mutations) thereof that maintain Pin 1 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype Pin 1). In embodiments, the term “Pin 1” refers to NCBI Accession No. NP_006212, and proteins having sequence homology to Pin 1 of at least 80%, e.g., 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or even 100%.

[0102] A “Pin 1 inhibitor” refers to a compound (e.g., compounds described herein) that reduces the activity of Pin 1 when compared to a control, such as absence of the compound or a compound with known inactivity.

[0103] A “Pin-1 mediated disease or disorder” refers to a disease or disorder associated with modulated levels of expression of Pin-1 or levels of DNA/RNA encoding Pin-1 in a subject and/or changes in cellular regulation mediated by Pin-1.

[0104] The terms “FKBP” or “FK506 binding protein” refer to a family of proteins (including homologs, isoforms, and functional fragments thereof) that have prolyl isomerase activity and are related to the cyclophilins in function. The terms include any recombinant or naturally-occurring

form of FKBP variants thereof that maintain FKBP activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype FKBP). The term includes any mutant form of FKBP variants (e.g., frameshift mutations) thereof that maintain FKBP activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype FKBP).

[0105] The terms “FK506-binding protein 5” “FKBP5,” “FKBP51,” “FKBP54,” “P54” and “Pdg-10” refer to a specific enzyme of the FKBP family of proteins (including homologs, isoforms, and functional fragments thereof). The terms include any recombinant or naturally-occurring form of FKBP5 and variants thereof that maintain FKBP5 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype FKBP5). The term includes any mutant form of FKBP5 variants (e.g., frameshift mutations) thereof that maintain FKBP5 activity (e.g. within at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or 100% activity compared to wildtype FKBP5). In embodiments, the term “FKBP5” refers to Entrez 2289, UniProt Q13451, NM_004117, NM_004117.3, NP_004108.1, or NP_004108.

[0106] In embodiments, the term “FKBP38” refers to NCBI Accession No. NP_36313, and proteins having sequence homology to FKBP38 of at least 80%, e.g., 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or even 100%. In embodiments, the term “FKBP51” refers to NCBI Accession No. AAC51189, and proteins having sequence homology to FKBP51 of at least 80%, e.g., 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or even 100%. In embodiments, the term “FKBP52” refers to NCBI Accession No. AAC36111, and proteins having sequence homology to FKBP52 of at least 80%, e.g., 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or even 100%. In embodiments, term “FKBP12” refers to NCBI Accession No. NP_463460, and proteins having sequence homology to FKBP12 of at least 80%, e.g., 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or even 100%.

[0107] An “FKBP inhibitor” refers to a compound (e.g., compounds described herein) that reduces the activity of an FKBP (e.g., FKBP51, FKBP52 and/or FKBP38) when compared to a control, such as absence of the compound or a compound with known inactivity.

[0108] The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues, wherein the polymer may optionally be conjugated to a moiety that does not consist of amino acids. The terms apply to amino acid polymers in which one or more

amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. In embodiments, the terms “polypeptide,” “peptide,” and “protein”, used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include genetically coded and non-genetically coded amino acids, chemically or biochemically modified or derivatized amino acids, and polypeptides having modified polypeptide backbones. The terms include fusion proteins, including, but not limited to, fusion proteins with a heterologous amino acid sequence; fusion proteins with heterologous and homologous leader sequences, with or without N-terminus methionine residues; immunologically tagged proteins; and the like.

[0109] A polypeptide, or a cell is “recombinant” when it is artificial or engineered, or derived from or contains an artificial or engineered protein or nucleic acid (*e.g.* non-natural or not wild type). For example, a polynucleotide that is inserted into a vector or any other heterologous location, *e.g.*, in a genome of a recombinant organism, such that it is not associated with nucleotide sequences that normally flank the polynucleotide as it is found in nature is a recombinant polynucleotide. A protein expressed *in vitro* or *in vivo* from a recombinant polynucleotide is an example of a recombinant polypeptide. Likewise, a polynucleotide sequence that does not appear in nature, for example a variant of a naturally occurring gene, is recombinant.

[0110] “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.

[0111] 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.

[0112] As defined herein, the term “activation”, “activate”, “activating” and the like in reference to a protein refers to conversion of a protein into a biologically active derivative from an initial inactive or deactivated state. The terms reference activation, or activating, sensitizing, or up-

regulating signal transduction or enzymatic activity or the amount of a protein decreased in a disease.

[0113] 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. In embodiments, an agonist is a molecule that interacts with a target to cause or promote an increase in the activation of the target. In embodiments, activators are molecules that increase, activate, facilitate, enhance activation, sensitize, or up-regulate, e.g., a gene, protein, ligand, receptor, or cell.

[0114] As defined herein, the term “inhibition”, “inhibit”, “inhibiting” and the like in reference to a protein-inhibitor interaction means negatively affecting (e.g. decreasing) the activity or function of the protein 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).

[0115] 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. An antagonist prevents, reduces, inhibits, or neutralizes

the activity of an agonist, and an antagonist can also prevent, inhibit, or reduce constitutive activity of a target, e.g., a target receptor, even where there is no identified agonist. In embodiments, inhibitors are molecules that decrease, block, prevent, delay activation, inactivate, desensitize, or down-regulate, e.g., a gene, protein, ligand, receptor, or cell. An inhibitor may also be defined as a molecule that reduces, blocks, or inactivates a constitutive activity. An “antagonist” is a molecule that opposes the action(s) of an agonist.

[0116] 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.*).

[0117] The terms “disease,” “disorder” or “condition” refer to a state of being or health status of a patient or subject capable of being treated with the compounds or methods provided herein. The disease may be a cancer. The disease may be cancer. The disease may be a mental illness (*e.g.* schizophrenia). The disease may be depression. The disease may be pain (*e.g.* chronic pain or neuropathic pain). In some further instances, “cancer” refers to human cancers and carcinomas, sarcomas, adenocarcinomas, lymphomas, leukemias, *etc.*, including solid and lymphoid cancers, kidney, breast, lung, bladder, colon, ovarian, prostate, pancreas, stomach, brain, head and neck, skin, uterine, testicular, glioma, esophagus, and liver cancer, including hepatocarcinoma, lymphoma, including B-acute lymphoblastic lymphoma, non-Hodgkin’s lymphomas (*e.g.*, Burkitt’s, Small Cell, and Large Cell lymphomas), Hodgkin’s lymphoma, leukemia (including MDS, AML, ALL, ATLL and CML), or multiple myeloma.

[0118] As used herein, the term "cancer" refers to all types of cancer, neoplasm, or malignant tumors found in mammals, including leukemias, lymphomas, carcinomas and sarcomas. Exemplary cancers that may be treated with a compound or method provided herein include brain cancer, glioma, glioblastoma, neuroblastoma, prostate cancer, colorectal cancer, pancreatic cancer, Medulloblastoma, melanoma, cervical cancer, gastric cancer, ovarian cancer, lung cancer, cancer of the head, Hodgkin's Disease, and Non-Hodgkin's Lymphomas. Exemplary cancers that may be treated with a compound or method provided herein include cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, ovary, pancreas,

rectum, stomach, uterus, Hodgkin's Disease, and Non-Hodgkin's Lymphoma. Additional examples include, thyroid carcinoma, cholangiocarcinoma, pancreatic adenocarcinoma, skin cutaneous melanoma, colon adenocarcinoma, rectum adenocarcinoma, stomach adenocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, breast invasive carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, non-small cell lung carcinoma, mesothelioma, melanoma, medulloblastoma, multiple myeloma, metastatic bone cancer, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, malignant pancreatic insulanoma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, or prostate cancer.

[0119] “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. In embodiments, treating does not include preventing.

[0120] “Treating” and “treatment” as used herein include prophylactic treatment. Treatment methods include administering to a subject a therapeutically effective amount of a compound described herein. 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 the compound, 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.

[0121] 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. In embodiments, prevent refers to slowing the progression of the disease, disorder or condition or inhibiting progression thereof to a harmful or otherwise undesired state.

[0122] “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, such as bovines, rats, mice, dogs, monkeys, goats, sheeps, cows, deers, and other animals. In some embodiments, a patient is human.

[0123] 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). The therapeutically effective amount can be ascertained by measuring relevant physiological effects, and it can be adjusted in connection with the dosing regimen and diagnostic analysis of the subject’s condition, and the like. By way of example, measurement of the serum level of a CCR4 inhibitor (or, e.g., a metabolite thereof) at a particular time post-administration may be indicative of whether a therapeutically effective amount has been administered.

[0124] 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.

[0125] 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. Adjusting the dose to achieve maximal therapeutic window efficacy or toxicity in humans based on the methods described above and other methods is well within the capabilities of the ordinarily skilled artisan.

[0126] 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.

[0127] 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.

[0128] “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).

[0129] The term “modulate” is used in accordance with its plain ordinary meaning and refers to the act of changing or varying one or more properties. “Modulation” refers to the process of changing or varying one or more properties. For example, as applied to the effects of a modulator on a target protein, to modulate means to change by increasing or decreasing a property or function of the target molecule or the amount of the target molecule. In embodiments, the terms “modulate,” “modulation” and the like refer to the ability of a molecule (e.g., an activator or an inhibitor) to increase or decrease the function or activity of PPIases, either directly or indirectly, relative to the absence of the molecule.

[0130] 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.

[0131] The phrase “in a sufficient amount to affect a change” means that there is a detectable difference between a level of an indicator measured before (e.g., a baseline level) and after administration of a particular therapy. Indicators include any objective parameter (e.g., serum concentration) or subjective parameter (e.g., a subject’s feeling of well-being).

[0132] The “activity” of a molecule may describe or refer to the binding of the molecule to a ligand or to a receptor; to catalytic activity; to the ability to stimulate gene expression or cell signaling, differentiation, or maturation; to antigenic activity; to the modulation of activities of other molecules; and the like. The term “proliferative activity” encompasses an activity that promotes, that is necessary for, or that is specifically associated with, for example, normal cell division, as well as cancer, tumors, dysplasia, cell transformation, metastasis, and angiogenesis.

[0133] The term “substantially pure” indicates that a component makes up greater than about 50% of the total content of the composition, and typically greater than about 60% of the total polypeptide content. More typically, “substantially pure” refers to compositions in which at least 75%, at least 85%, at least 90% or more of the total composition is the component of interest. In some cases, the polypeptide will make up greater than about 90%, or greater than about 95% of the total content of the composition (percentage in a weight per weight basis).

[0134] The terms “specifically binds” and “selectively binds,” when referring to a ligand/receptor, antibody/antigen, or other binding pair, indicates a binding reaction which is determinative of the presence of the protein in a heterogeneous population of proteins and other biologics. Thus, under designated conditions, a specified ligand binds to a particular receptor and does not bind in a significant amount to other proteins present in the sample.

[0135] 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.

[0136] The terms “nucleic acid,” “nucleic acid molecule,” “polynucleotide” and the like are used interchangeably herein to refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Non-limiting examples of polynucleotides include linear and circular nucleic acids, DNA, RNA, messenger RNA (mRNA), complementary DNA (cDNA), recombinant polynucleotides, vectors, probes, primers and the like.

[0137] As used herein, the terms “variants” and “homologs” are used interchangeably to refer to amino acid or nucleic acid sequences that are similar to reference amino acid or nucleic acid sequences, respectively. The term encompasses naturally-occurring variants and non-naturally-occurring variants. Naturally-occurring variants include homologs (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one species to another), and allelic variants (polypeptides and nucleic acids that differ in amino acid or nucleotide sequence, respectively, from one individual to another within a species). Thus, variants and homologs encompass naturally occurring amino acid and nucleic acid sequences encoded thereby and their isoforms, as well as splice variants of a protein or gene. The terms also encompass nucleic acid sequences that vary in one or more bases from a naturally-occurring nucleic acid sequence but still translate into an amino acid sequence that corresponds to the naturally-occurring protein due to degeneracy of the genetic code. Non-naturally-occurring variants and homologs include polypeptides and nucleic acids that comprise a change in amino acid or nucleotide sequence, respectively, where the change in sequence is artificially introduced; for example, the change is generated in the laboratory by human intervention (“hand of man”). Therefore, non-naturally occurring variants and homologs may also refer to those that differ from the naturally-occurring sequences by one or more conservative substitutions and/or tags and/or conjugates.

[0138] As used herein, the term “administering” means oral administration, administration as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intracranial, intranasal or subcutaneous administration, or the implantation of a slow-release device, *e.g.*, a mini-osmotic pump, to a subject. Administration is by any route, including parenteral and transmucosal (*e.g.*, buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, *e.g.*, intravenous, intramuscular, intra-arteriole,

intradermal, subcutaneous, intraperitoneal, intraventricular, and intracranial. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, transdermal patches, *etc.* By "co-administer" it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies (e.g. anti-cancer agent, chemotherapeutic, or treatment for a mental illness or pain). The compound of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compound individually or in combination (more than one compound or agent). Thus, the preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation). The compositions of the present invention can be delivered by transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, cachets, gels, syrups, slurries, suspensions, *etc.*, suitable for ingestion by the patient. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes. The compositions of the present invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997). In another embodiment, the formulations of the compositions of the present invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing receptor ligands attached to the liposome, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries receptor ligands specific for target cells, or are otherwise preferentially directed to a

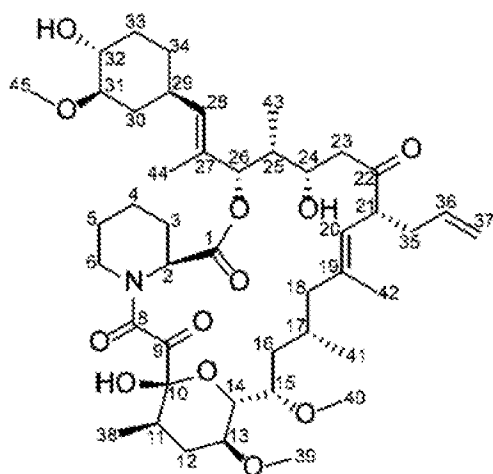
specific organ, one can focus the delivery of the compositions of the present invention into the target cells in vivo. (See, *e.g.*, Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989). The compositions of the present invention can also be delivered as nanoparticles.

[0139] By “co-administer” it is meant that a composition described herein is administered at the same time, just prior to, or just after the administration of one or more additional therapies. The compounds of the invention can be administered alone or can be coadministered to the patient. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The compositions of the present invention can be delivered transdermally, by a topical route, or formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

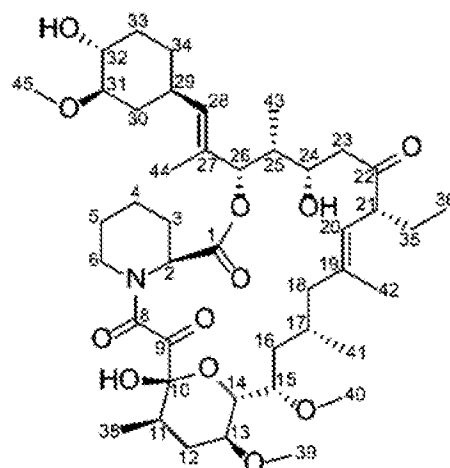
[0140] The compounds described herein can be used in combination with one another, with other active agents known to be useful in treating cancer (e.g. colon cancer), mental illness, pain or depression.

[0141] In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 hours, 2 days, 4 days, 1 week or 1 month of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In some embodiments, the compounds described herein may be combined with treatments for cancer (e.g. colon cancer), mental illness (e.g. schizophrenia), pain (e.g. chronic pain or neuropathic pain) or depression.

[0142] As used herein, numbering of atoms for FK506, ascomycin and rapamycin follows:

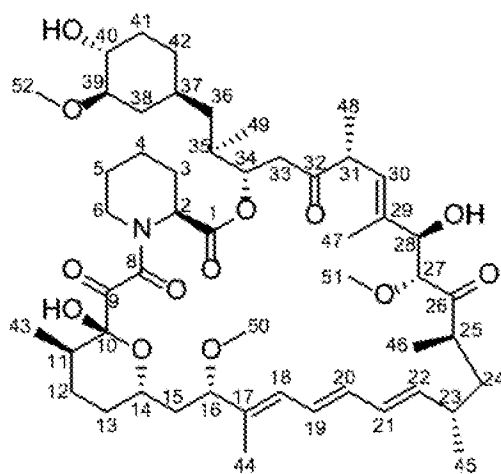


FK506:



; ascomycin:

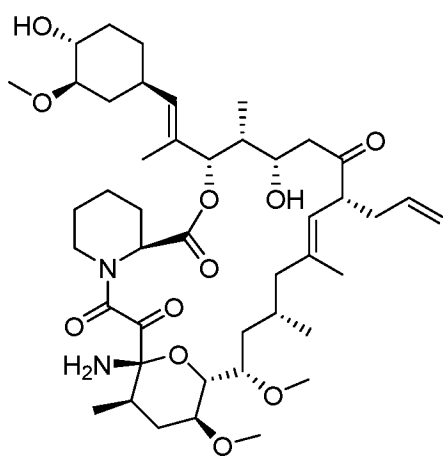
and



rapamycin:

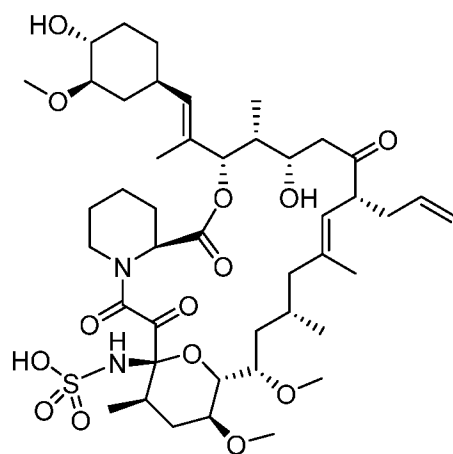
[0143] As used herein, the phrase “a position equivalent to C10 of FK506” means a carbon position on a macrolide compound (e.g. FK506, rapamycin, ascomycin or derivative or variant thereof) that is chemically or functionally equivalent to the C10 of FK506 (e.g. the C10 of rapamycin (or variant or derivative thereof) or the C10 of ascomycin (or variant or derivative thereof)). Thus, in embodiments, the position equivalent to C10 of FK506 is the C10 position of rapamycin, or a variant, derivative or pharmaceutically acceptable salt thereof, or C10 position of ascomycin, or a variant, derivative or pharmaceutically acceptable salt thereof. Accordingly, the phrase “a position equivalent to C10 of FK506,” “C10 of FK506,” “C10 of an FK506,” “C10 of ascomycin,” and/or “C10 of rapamycin” are used interchangeably.

[0144] As used herein, compounds FK-NH₂, “2a,” “2c” and “2d” have the structures following:



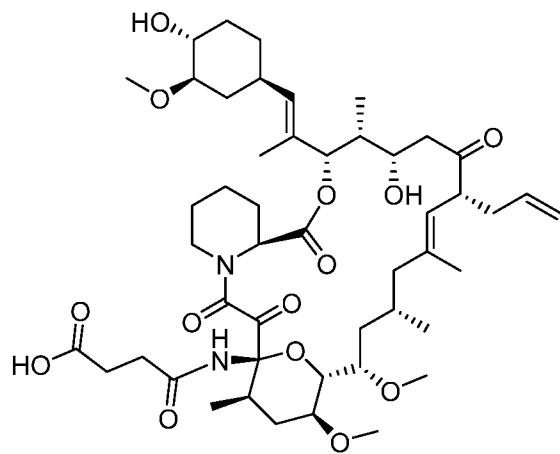
FK-NH2:

,



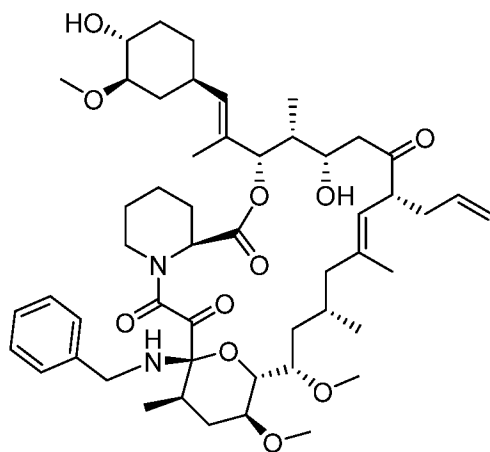
Compound "2a":

,



Compound "2c":

, and



Compound "2d":

COMPOUNDS

[0145] In a first aspect, there is provided a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound, including a macrolide with a pipercolyl moiety, or a pharmaceutically acceptable salt thereof.

[0146] In embodiments, the compound is an FK506 compound, or a derivative thereof, covalently bound to a nitrogen-containing functional group at the C-10 position. In embodiments, the nitrogen-containing functional group is an amino group. In embodiments, the nitrogen-containing functional group is a primary amino group. In embodiments, the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

[0147] In embodiments, the compound is an FK506 compound, or a derivative thereof, covalently bound to a substituted or unsubstituted amino at the C10 position in place of the –OH present in FK506. In embodiments, the amino is unsubstituted. In embodiments, the amino is mono-substituted. In embodiments, the amino is di-substituted. In embodiments, the amino is tri-substituted. In embodiments, the amino is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted amino 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.

[0148] In embodiments, the compound is an FK506 compound, or a derivative thereof, including an electronegative group at the C-10 position. In embodiments, the electronegative group is not –OH. In embodiments, the electronegative group is not a substituted hydroxyl (e.g., substituted with a substituent group, size-limited substituent group, or lower substituent group).

[0149] In embodiments, the compound is an FK506 compound, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position. In embodiments, the linker is covalently bound to an electronegative group. In embodiments, the electronegative group is a phosphate isostere. In embodiments, the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group. In embodiments, the compound is an FK506 compound, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position, in place of the –OH in FK506. In embodiments, the linker is covalently bound to an electronegative moiety. In embodiments, the electronegative moiety is a phosphate isostere moiety. In embodiments, the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

[0150] Further to any aspect above or embodiments thereof, in embodiments the FK-506 compound is an ascomycin derivative or variant. As indicated, the term “FK-506” or “FK506” refers, in the usual and customary sense, to (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-5,6,8,11,12,13,14,15,16, 17,18,19,24,25,26,26a-Hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propen-1-yl)-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone. In embodiments the derivative of the FK-506 compound is an ascomycin compound.

[0151] In embodiments the compound is an ascomycin, or a derivative thereof, covalently bound to a nitrogen-containing functional group at the C10 position. In embodiments, the nitrogen-containing functional group is an amino group. In embodiments, the nitrogen-containing functional group is a primary amino group. In embodiments, the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

[0152] In embodiments, the compound is an ascomycin, or a derivative thereof, including an electronegative group at the C-10 position. In embodiments, the electronegative group is not –OH. In embodiments, the electronegative group is not a substituted hydroxyl (e.g., substituted with a substituent group, size-limited substituent group, or lower substituent group).

[0153] In embodiments, the compound is an ascomycin, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position. In embodiments, the linker is covalently bound to an electronegative group. In embodiments, the electronegative group is a phosphate isostere. In embodiments, the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group. In embodiments, the compound is ascomycin, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position, in place of the –OH in FK506. In embodiments, the linker is covalently bound to an electronegative moiety. In embodiments, the electronegative moiety is a phosphate isostere moiety. In embodiments, the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

[0154] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including a nitrogen-containing functional group at the C-10 position. In embodiments, the nitrogen-containing functional group is an amino group. In embodiments, the nitrogen-containing functional group is a primary amino group. In embodiments, the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

[0155] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including an electronegative group at the C-10 position. In embodiments, the electronegative group is not –OH. In embodiments, the electronegative group is not a substituted hydroxyl (e.g., substituted with a substituent group, size-limited substituent group, or lower substituent group).

[0156] In embodiments, the compound is a rapamycin compound, or a derivative thereof, covalently bound to a substituted or unsubstituted amino at the C10 position in place of the –OH present in rapamycin. In embodiments, the amino is unsubstituted. In embodiments, the amino is mono-substituted. In embodiments, the amino is di-substituted. In embodiments, the amino is tri-substituted. In embodiments, the amino is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted amino 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.

[0157] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position. In embodiments, the linker is covalently bound to an electronegative group. In embodiments, the electronegative group is a phosphate isostere. In embodiments, the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group. In embodiments, the compound is a rapamycin compound, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position, in place of the –OH in rapamycin. In embodiments, the linker is covalently bound to an electronegative moiety. In embodiments, the electronegative moiety is a phosphate isostere moiety. In embodiments, the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a

sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

[0158] The term “electronegative group” is used according to its plain, ordinary meaning and refers to a chemical substituent (e.g., an atom or a functional group) that attracts electrons or electron density towards itself. The terms “electronegative group” and “electronegative substituent” are used synonymously. Examples of electronegative atoms include, but are not limited to, nitrogen, oxygen, phosphorus, sulfur, chlorine, bromine and fluorine. The foregoing groups bearing these atoms, (e.g., -NO₂, -CN, -CO₂H, etc.) may be said to be “electronegative groups.” For a more in depth discussion of electronegative groups, see Taft, R. W. *Progress in Physical Organic Chemistry*, Volume 13. New York: John Wiley & Sons, 1981, which is incorporated herein by reference in its entirety for all purposes.

[0159] In embodiments, the electronegative group is a phosphate isostere. The term “phosphate isostere” is used according to its plain, ordinary meaning and refers to a chemical substituent with similar physical or chemical properties as a phosphate, which produces similar biological properties (e.g. in a method disclosed herein) to a phosphate. In embodiments, the phosphate isostere is a phosphonate, a tetrahedral sulphate, or a tetrahedral sulphonate. For a more in depth discussion of useful phosphate isosteres, see Elliott et al., “The use of phosphate bioisosteres in medicinal chemistry and chemical biology,” *Med. Chem. Commun.*, 2012,3, 735-751, which is incorporated herein by reference in its entirety for all purposes.

[0160] In embodiments, the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

[0161] In another aspect, there is provided an FK506 binding protein (FKBP) inhibitor compound, including a macrolide with a pipicolyl moiety, or a pharmaceutically acceptable salt thereof.

[0162] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including a nitrogen-containing functional group at the C-10 position. In embodiments, the nitrogen-containing functional group is an amino group. In embodiments, the nitrogen-containing

functional group is a primary amino group. In embodiments, the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

[0163] In embodiments, the compound is a rapamycin compound, or a derivative thereof, comprising an electronegative group at the C-10 position.

[0164] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position. In embodiments, the linker is covalently bound to an electronegative group. In embodiments, the electronegative group is a phosphate isostere. In embodiments, the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

[0165] In another aspect, there is provided a macrolide compound covalently attached to an electronegative group at a position equivalent to C-10 of FK506 or a pharmaceutically acceptable salt thereof.

[0166] In embodiments, the macrolide compound is an FK506 compound derivative, a rapamycin compound derivative or an ascomycin compound derivative.

[0167] In another aspect, there is provided an FK506 binding protein (FKBP) inhibitor compound, including a macrolide with a pipecolyl moiety, or a pharmaceutically acceptable salt thereof.

[0168] In embodiments, the FK506 binding protein (FKBP) inhibitor compound is a rapamycin compound, or a derivative thereof, covalently bound to a substituted or unsubstituted amino at the C10 position in place of the –OH present in rapamycin. In embodiments, the amino is unsubstituted. In embodiments, the amino is mono-substituted. In embodiments, the amino is di-substituted. In embodiments, the amino is tri-substituted. In embodiments, the amino is substituted with at least one substituent group, size-limited substituent group, or lower substituent group; wherein if the substituted amino 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.

[0169] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including an electronegative group at the C-10 position. In embodiments, the electronegative group is not –OH. In embodiments, the electronegative group is not a substituted hydroxyl (e.g., substituted with a substituent group, size-limited substituent group, or lower substituent group).

[0170] In embodiments, the compound is a rapamycin compound, or a derivative thereof, including an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position, in place of the –OH in rapamycin. In embodiments, the linker is covalently bound to an electronegative moiety. In embodiments, the electronegative moiety is a phosphate isostere moiety. In embodiments, the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

[0171] In another aspect, there is provided a macrolide compound covalently attached to an electronegative group at a position equivalent to C10 of FK506 or a pharmaceutically acceptable salt thereof. In embodiments, the electronegative group is not –OH. In embodiments, the electronegative group is not a substituted hydroxyl (e.g., substituted with a substituent group, size-limited substituent group, or lower substituent group). In embodiments, the macrolide compound is an FK506 compound derivative, a rapamycin compound derivative, or an ascomycin compound derivative.

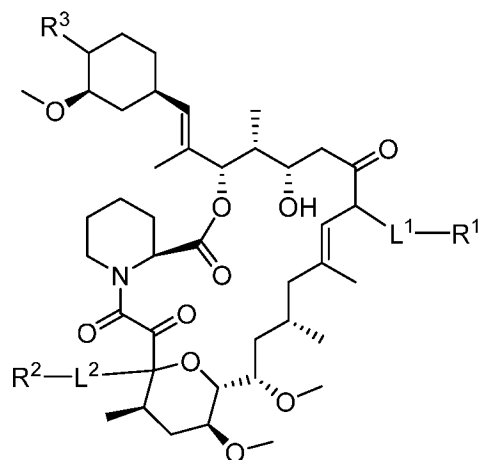
[0172] In embodiments, the macrolide compound is capable of inhibiting a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) protein. In embodiments, the K_D for inhibition is less than 1000 nM, 100 nM, 10 nM, or even 1 nM. In embodiments, the K_D for inhibition is in the range 0.1-1000 nM, 0.1-100 nM, 0.1-10 nM, or even 0.1-1 nM.

[0173] In embodiments, the macrolide compound is capable of inhibiting an FK506 binding protein. In embodiments, the K_D for inhibition is less than 1000 nM, 100 nM, 10 nM, or even 1 nM. In embodiments, the K_D for inhibition is in the range 0.1-1000 nM, 0.1-100 nM, 0.1-10 nM, or even 0.1-1 nM.

[0174] In embodiments, the electronegative group is a phosphate isostere.

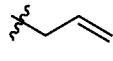
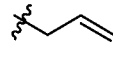
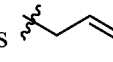
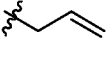
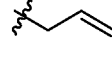
[0175] In embodiments, the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

[0176] In an aspect is provided a compound of structural Formula (I):



(I), or a pharmaceutically acceptable salt thereof. n_1 , n_2 and n_3 are independently an integer from 0 to 4. m_1 , m_2 , m_3 , v_1 , v_2 and v_3 are independently 1 or 2. L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$,

$-\text{ONR}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{NHC}(\text{O})\text{NHN}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{NHC}(\text{O})\text{NR}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{N}(\text{O})_{\text{m}2}$, $-\text{NR}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{C}(\text{O})\text{R}^{2\text{D}}$,
 $-\text{C}(\text{O})\text{OR}^{2\text{D}}$, $-\text{C}(\text{O})\text{NR}^{2\text{B}}\text{R}^{2\text{C}}$, $-\text{OR}^{2\text{A}}$, $-\text{NR}^{2\text{B}}\text{SO}_2\text{R}^{2\text{A}}$, $-\text{NR}^{2\text{B}}\text{C}(\text{O})\text{R}^{2\text{D}}$, $-\text{NR}^{2\text{B}}\text{C}(\text{O})\text{OR}^{2\text{D}}$, $-\text{NR}^{2\text{B}}\text{OR}^{2\text{D}}$,
 $-\text{OCX}^{2.1}_3$, $-\text{OCHX}^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,
substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or
unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^3 is hydrogen, halogen, $-\text{CX}^{3.1}_3$,
 $-\text{CHX}^{3.1}_2$, $-\text{CH}_2\text{X}^{3.1}$, $-\text{CN}$, $-\text{SO}_{\text{n}3}\text{R}^{3\text{A}}$, $-\text{SO}_{\text{v}3}\text{NR}^{3\text{B}}\text{R}^{3\text{C}}$, $-\text{NHN}^{3\text{B}}\text{R}^{3\text{C}}$, $-\text{ONR}^{3\text{B}}\text{R}^{3\text{C}}$,
 $-\text{NHC}(\text{O})\text{NHN}^{3\text{B}}\text{R}^{3\text{C}}$, $-\text{NHC}(\text{O})\text{NR}^{3\text{B}}\text{R}^{3\text{C}}$, $-\text{N}(\text{O})_{\text{m}3}$, $-\text{NR}^{3\text{B}}\text{R}^{3\text{C}}$, $-\text{C}(\text{O})\text{R}^{3\text{D}}$, $-\text{C}(\text{O})\text{OR}^{3\text{D}}$,
 $-\text{C}(\text{O})\text{NR}^{3\text{B}}\text{R}^{3\text{C}}$, $-\text{OR}^{3\text{A}}$, $-\text{NR}^{3\text{B}}\text{SO}_2\text{R}^{3\text{A}}$, $-\text{NR}^{3\text{B}}\text{C}(\text{O})\text{R}^{3\text{D}}$, $-\text{NR}^{3\text{B}}\text{C}(\text{O})\text{OR}^{3\text{D}}$, $-\text{NR}^{3\text{B}}\text{OR}^{3\text{D}}$, $-\text{OCX}^{3.1}_3$,
 $-\text{OCHX}^{3.1}_2$, 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. $\text{R}^{1\text{L}}$, $\text{R}^{2\text{L}}$, $\text{R}^{1\text{A}}$, $\text{R}^{1\text{B}}$, $\text{R}^{1\text{C}}$, $\text{R}^{1\text{D}}$, $\text{R}^{2\text{A}}$, $\text{R}^{2\text{B}}$, $\text{R}^{2\text{C}}$, $\text{R}^{2\text{D}}$, $\text{R}^{3\text{A}}$,
 $\text{R}^{3\text{B}}$, $\text{R}^{3\text{C}}$ and $\text{R}^{3\text{D}}$, are independently hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$, $-\text{CBr}_3$, $-\text{CI}_3$, $-\text{COOH}$,
 $-\text{CONH}_2$, 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. $\text{R}^{1\text{B}}$ and $\text{R}^{1\text{C}}$, $\text{R}^{2\text{B}}$ and $\text{R}^{2\text{C}}$, $\text{R}^{3\text{B}}$ and $\text{R}^{3\text{C}}$ substituents
bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted
heterocycloalkyl or substituted or unsubstituted heteroaryl. $\text{X}^{1.1}$, $\text{X}^{2.1}$ and $\text{X}^{3.1}$ are independently
 $-\text{Cl}$, $-\text{Br}$, $-\text{I}$ or $-\text{F}$.

[0177] In embodiments, when L^2 is $-\text{O}-$, L^1 is a bond, R^1 is  or $-\text{CH}_2\text{CH}_3$ and R^3 is
hydroxyl, then R^2 is not hydrogen. In embodiments, when L^2 is $-\text{O}-$ then R^2 is not hydrogen. In
embodiments, when R^1 is  then R^2 is not hydrogen. In embodiments, when R^1 is $-\text{CH}_2\text{CH}_3$
then R^2 is not hydrogen. In embodiments, when R^3 is hydroxyl then R^2 is not hydrogen. In
embodiments, when L^2 and L^1 are independently a bond, R^1 is  or $-\text{CH}_2\text{CH}_3$ and R^3 is
hydroxyl, then R^2 is not hydroxyl. In embodiments, when L^2 is a bond then R^2 is not hydroxyl. In
embodiments, when L^1 is a bond then R^2 is not hydroxyl. In embodiments, when R^1 is $-\text{CH}_2\text{CH}_3$
then R^2 is not hydroxyl. In embodiments, when R^1 is  then R^2 is not hydroxyl. In
embodiments, when R^3 is hydroxyl then R^2 is not hydroxyl. In embodiments, L^2 is not $-\text{O}-$. In
embodiments, L^1 is not a bond. In embodiments, R^1 is not  or $-\text{CH}_2\text{CH}_3$. In embodiments,

R^1 is not unsubstituted alkyl. In embodiment, R^3 is not hydroxyl. In embodiments, R^2 is not hydrogen.

[0178] In embodiments, L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0179] In embodiments, L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene), substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene), substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0180] In embodiments, L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, R^{11} -substituted or unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene), R^{11} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene), R^{11} -substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene), R^{11} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene), R^{11} -substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene), or R^{11} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0181] In embodiments, L^1 is R^{11} -substituted or unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene). In embodiments, L^1 is R^{11} -substituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene). In embodiments, L^1 is an unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene).

[0182] In embodiments, L^1 is R^{11} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene). In embodiments, L^1 is R^{11} -substituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene). In embodiments, L^1 is an unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene).

[0183] In embodiments, L^1 is R^{11} -substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene). In embodiments, L^1 is R^{11} -substituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene). In embodiments, L^1 is an unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene).

[0184] In embodiments, L^1 is R^{11} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^1 is R^{11} -substituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^1 is an unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene).

[0185] In embodiments, L^1 is R^{11} -substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene). In embodiments, L^1 is R^{11} -substituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene). In embodiments, L^1 is an unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene).

[0186] In embodiments, L^1 is R^{11} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^1 is R^{11} -substituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^1 is an unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0187] In embodiments, L^1 is a bond and R^1 is (R)-ethyl. In embodiments, L^1 is a bond and R^1 is ethylene. In embodiments, L^1 is a bond and R^1 is propylene.

[0188] In embodiments, L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0189] In embodiments, L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene), substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene), substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0190] In embodiments, L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, R^{14} -substituted or unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene), R^{14} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene), R^{14} -substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene), R^{14} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene), R^{14} -substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene), or R^{14} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0191] In embodiments, L^2 is R^{14} -substituted or unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene). In embodiments, L^2 is R^{14} -substituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene). In embodiments, L^2 is an unsubstituted alkylene (e.g., C_1 - C_8 alkylene, C_1 - C_6 alkylene, or C_1 - C_4 alkylene).

[0192] In embodiments, L^2 is R^{14} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene). In embodiments, L^2 is R^{14} -substituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene). In embodiments, L^2 is an unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene).

[0193] In embodiments, L^2 is R^{14} -substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene). In embodiments, L^2 is R^{14} -substituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene). In embodiments, L^2 is an unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene).

[0194] In embodiments, L^2 is R^{14} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^2 is R^{14} -substituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^2 is an unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene).

[0195] In embodiments, L^2 is R^{14} -substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene). In embodiments, L^2 is R^{14} -substituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene). In embodiments, L^2 is an unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene).

[0196] In embodiments, L^2 is R^{14} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^2 is R^{14} -substituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^2 is an unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0197] In embodiments, L^2 is a bond; and R^2 is NH_2 . In embodiments, L^2 is a bond, $-NR^{2L}-$, $-NR^{2L}C(O)-$, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^2 is $-NR^{2L}-$. In embodiments, L^2 is $-NR^{2L}C(O)-$. In embodiments, L^2 is substituted or unsubstituted alkylene. In embodiments, L^2 is substituted or unsubstituted heteroalkylene. In embodiments, L^2 is a bond, $-NR^{2L}-$, $-NR^{2L}C(O)-$. In embodiments, L^2 is a bond. In embodiments, L^2 is $-NH-$. In embodiments, L^2 is $-NHC(O)-$. In embodiments, L^2 is $-NHCH_2-$. In embodiments, L^2 is $-NHCH_2CH_2-$.

[0198] In embodiments, R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-SO_{nl}R^{1A}$, $-SO_{vl}NR^{1B}R^{1C}$, $-NHN R^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHN R^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{ml}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, R^{17} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{17} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{17} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{17} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{17} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{17} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0199] In embodiments, R^1 is R^{17} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^1 is R^{17} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^1 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0200] In embodiments, R^1 is R^{17} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^1 is R^{17} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^1 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0201] In embodiments, R^1 is R^{17} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^1 is R^{17} -substituted cycloalkyl (e.g., C_3 -

C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0202] In embodiments, R¹ is R¹⁷-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹ is R¹⁷-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0203] In embodiments, R¹ is R¹⁷-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹ is R¹⁷-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0204] In embodiments, R¹ is R¹⁷-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹ is R¹⁷-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹ is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0205] In embodiments, R² is hydrogen, halogen, -CX^{2.1}₃, -CHX^{2.1}₂, -CH₂X^{2.1}, -CN, -SO_{n2}R^{2A}, -SO_{v2}NR^{2B}R^{2C}, -NHN^{2B}R^{2C}, -ONR^{2B}R^{2C}, -NHC(O)NHN^{2B}R^{2C}, -NHC(O)NR^{2B}R^{2C}, -N(O)_{m2}, -NR^{2B}R^{2C}, -C(O)R^{2D}, -C(O)OR^{2D}, -C(O)NR^{2B}R^{2C}, -OR^{2A}, -NR^{2B}SO₂R^{2A}, -NR^{2B}C(O)R^{2D}, -NR^{2B}C(O)OR^{2D}, -NR^{2B}OR^{2D}, -OCX^{2.1}₃, -OCHX^{2.1}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.

[0206] In embodiments, R² is hydrogen, halogen, -CX^{2.1}₃, -CHX^{2.1}₂, -CH₂X^{2.1}, -CN, -SO_{n2}R^{2A}, -SO_{v2}NR^{2B}R^{2C}, -NHN^{2B}R^{2C}, -ONR^{2B}R^{2C}, -NHC(O)NHN^{2B}R^{2C}, -NHC(O)NR^{2B}R^{2C}, -N(O)_{m2}, -NR^{2B}R^{2C}, -C(O)R^{2D}, -C(O)OR^{2D}, -C(O)NR^{2B}R^{2C}, -OR^{2A}, -NR^{2B}SO₂R^{2A}, -NR^{2B}C(O)R^{2D}, -NR^{2B}C(O)OR^{2D}, -NR^{2B}OR^{2D}, -OCX^{2.1}₃, -OCHX^{2.1}₂, R²⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R²⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R²⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆

cycloalkyl), R²⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R²⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R²⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0207] In embodiments, R² is R²⁰-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R² is R²⁰-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R² is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R² is an unsubstituted ethyl. In embodiments, R² is an unsubstituted C₃ alkyl. In embodiments, R² is an unsubstituted C₄ alkyl.

[0208] In embodiments, R² is R²⁰-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R² is R²⁰-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R² is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0209] In embodiments, R² is R²⁰-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R² is R²⁰-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R² is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0210] In embodiments, R² is R²⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R² is R²⁰-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R² is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0211] In embodiments, R² is R²⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R² is R²⁰-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R² is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0212] In embodiments, R^2 is R^{20} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^2 is R^{20} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^2 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0213] In embodiments, R^2 is a phosphate isostere group. In embodiments, R^2 is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group. In embodiments, R^2 is a tetrazole group. In embodiments, R^2 is a triazole group. In embodiments, R^2 is a carboxylic acid group. In embodiments, R^2 is a phosphonate group. In embodiments, R^2 is a boranophosphate group. In embodiments, R^2 is a sulfate group. In embodiments, R^2 is a sulfamic acid group. In embodiments, R^2 is a sulphonate group. In embodiments, R^2 is a nitro group. In embodiments, R^2 is a thiazolidinone group. In embodiments, R^2 is a thiazolidinone group. In embodiments, R^2 is a squaric acid group. In embodiments, R^2 is a hydroxyl group. In embodiments, R^2 is a boronic acid group. In embodiments, R^2 is halogen. In embodiments, R^2 is unsubstituted C_5 - C_6 cycloalkyl. In embodiments, R^2 is substituted or unsubstituted phenyl.

[0214] In embodiments, R^2 is $-COOH$. In embodiments, R^2 is hydrogen. In embodiments, R^2 is $-C(O)R^{2D}$. In embodiments, R^2 is $-SO_3H$. In embodiments, R^2 is substituted or unsubstituted alkyl. In embodiments, R^2 is substituted alkyl. In embodiments, R^2 is substituted methyl. In embodiments, R^2 is R^{20} -substituted alkyl. In embodiments, R^2 is R^{20} -substituted methyl. In embodiments, R^2 is unsubstituted methyl. In embodiments, R^2 is substituted ethyl. In embodiments, R^2 is R^{20} -substituted ethyl. In embodiments, R^2 is unsubstituted ethyl. In embodiments, R^2 is substituted n-propyl. In embodiments, R^2 is R^{20} -substituted n-propyl. In embodiments, R^2 is unsubstituted n-propyl. In embodiments, R^2 is substituted or unsubstituted C_1 - C_8 alkyl. In embodiments, R^2 is substituted C_1 - C_8 alkyl. In embodiments, R^2 is R^{20} -substituted C_1 - C_8 alkyl. In embodiments, R^2 is substituted or unsubstituted heteroalkyl. In embodiments, R^2 is substituted heteroalkyl. In embodiments, R^2 is R^{20} -substituted heteroalkyl. In embodiments, R^2 is substituted or unsubstituted 5 to 8 membered heteroalkyl. In embodiments, R^2 is substituted 5 to 8 membered heteroalkyl. In embodiments, R^2 is R^{20} -substituted 5 to 8 membered heteroalkyl. In embodiments, R^2 is substituted

or unsubstituted 10 to 15 membered heteroalkyl. In embodiments, R^2 is substituted 10 to 15 membered heteroalkyl. In embodiments, R^2 is R^{20} -substituted 10 to 15 membered heteroalkyl. In embodiments, R^2 is substituted or unsubstituted cycloalkyl. In embodiments, R^2 is substituted cycloalkyl. In embodiments, R^2 is substituted cyclohexyl. In embodiments, R^2 is unsubstituted cyclohexyl. In embodiments, R^2 is R^{20} -substituted cycloalkyl. In embodiments, R^2 is R^{20} -substituted cyclohexyl. In embodiments, R^2 is substituted C_3 - C_8 cycloalkyl. In embodiments, R^2 is unsubstituted C_3 - C_8 cycloalkyl. In embodiments, R^2 is R^{20} -substituted C_3 - C_8 cycloalkyl. In embodiments, R^2 is substituted or unsubstituted aryl. In embodiments, R^2 is substituted aryl. In embodiments, R^2 is substituted phenyl. In embodiments, R^2 is unsubstituted phenyl. In embodiments, R^2 is R^{20} -substituted aryl. In embodiments, R^2 is R^{20} -substituted phenyl.

[0215] In embodiments, R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_m$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, 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.

[0216] In embodiments, R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_m$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, R^{23} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{23} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{23} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{23} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0217] In embodiments, R^3 is R^{23} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^3 is R^{23} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^3 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0218] In embodiments, R^3 is R^{23} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^3 is R^{23} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^3 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0219] In embodiments, R^3 is R^{23} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^3 is R^{23} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^3 is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0220] In embodiments, R^3 is R^{23} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^3 is R^{23} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^3 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0221] In embodiments, R^3 is R^{23} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^3 is R^{23} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^3 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0222] In embodiments, R^3 is R^{23} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^3 is R^{23} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^3 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0223] In embodiments, R^3 is hydroxyl group.

[0224] In embodiments, R^{1L} , R^{2L} , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} and R^{3D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, 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.

[0225] In embodiments, R^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0226] In embodiments, R^{1L} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{11L} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{11L} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{11L} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{11L} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{11L} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{11L} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0227] In embodiments, R^{2L} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{14L} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{14L} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{14L} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{14L} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{14L} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{14L} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0228] In embodiments, R^{1A} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{17A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{17A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{17A} -substituted or unsubstituted cycloalkyl (e.g.,

C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{17A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{17A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{17A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0229] In embodiments, R^{2A} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{20A}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{20A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{20A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{20A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{20A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{20A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0230] In embodiments, R^{3A} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{23A}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23A}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23A}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23A}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23A}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{23A}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0231] In embodiments, R^{1B} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{17B}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{17B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{17B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{17B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{17B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or

phenyl), or R^{17B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{1B} and R^{1C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{17B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{17B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0232] In embodiments, R^{2B} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{20B}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{20B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{20B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{20B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{20B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{20B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{2B} and R^{2C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{20B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{20B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0233] In embodiments, R^{3B} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{23B}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23B}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23B}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{23B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{3B} and R^{3C} substituents

bonded to the same nitrogen atom may optionally be joined to form a R^{23B} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{23B} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0234] In embodiments, R^{1C} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{17C} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{17C} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{17C} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{17C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{17C} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{17C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{1B} and R^{1C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{17C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{17C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0235] In embodiments, R^{2C} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{20C} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{20C} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{20C} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{20C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{20C} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{20C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{2B} and R^{2C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{20C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered

heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{20C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0236] In embodiments, R^{3C} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{23C} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{23C} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23C} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{23C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23C} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{23C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{3B} and R^{3C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{23C} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{23C} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0237] In embodiments, R^{1D} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{17D} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{17D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{17D} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{17D} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{17D} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{17D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0238] In embodiments, R^{2D} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, R^{20D} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{20D} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{20D} -substituted or unsubstituted cycloalkyl (e.g., C_3 -

C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{20D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{20D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{20D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0239] In embodiments, R^{2D} is substituted or unsubstituted alkyl. In embodiments, R^{2D} is substituted alkyl. In embodiments, R^{2D} is substituted methyl. In embodiments, R^{2D} is R^{20D}-substituted alkyl. In embodiments, R^{2D} is R^{20D}-substituted methyl. In embodiments, R^{2D} is substituted ethyl. In embodiments, R^{2D} is R^{20D}-substituted ethyl. In embodiments, R^{2D} is unsubstituted ethyl. In embodiments, R^{2D} is unsubstituted methyl. In embodiments, R^{2D} is substituted n-propyl. In embodiments, R^{2D} is R^{20D}-substituted n-propyl. In embodiments, R^{2D} is unsubstituted n-propyl. In embodiments, R^{2D} is substituted or unsubstituted C₁-C₈ alkyl. In embodiments, R^{2D} is substituted C₁-C₈ alkyl. In embodiments, R^{2D} is R^{20D}-substituted C₁-C₈ alkyl. In embodiments, R^{2D} is -CF₃. In embodiments, R^{2D} is substituted or unsubstituted aryl. In embodiments, R^{2D} is substituted aryl. In embodiments, R^{2D} is substituted phenyl. In embodiments, R^{2D} is unsubstituted phenyl. In embodiments, R^{2D} is substituted or unsubstituted phenyl.

[0240] In embodiments, R^{20D} is halogen. In embodiments, R^{20D} is -Cl. In embodiments, R^{20D} is -F. In embodiments, R^{20D} is -Br. In embodiments, R^{20D} is oxo. In embodiments, R^{20D} is -COOH. In embodiments, R^{20D} is -OH. In embodiments, R^{20D} is -SO₃H. In embodiments, R^{20D} is substituted or unsubstituted aryl. In embodiments, R^{20D} is substituted aryl. In embodiments, R^{20D} is substituted phenyl. In embodiments, R^{20D} is unsubstituted phenyl. In embodiments, R^{20D} is substituted or unsubstituted phenyl.

[0241] In embodiments, R^{3D} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{23D}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{23D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{23D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{23D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{23D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or

phenyl), or R^{23D}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0242] R¹¹ is independently oxo,

halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -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, R¹²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R¹²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R¹²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R¹²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R¹²-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R¹²-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0243] In embodiments, R¹¹ is R¹²-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is R¹²-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹¹ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0244] In embodiments, R¹¹ is R¹²-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹¹ is R¹²-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹¹ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0245] In embodiments, R¹¹ is R¹²-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is R¹²-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹¹ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0246] In embodiments, R¹¹ is R¹²-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered

heterocycloalkyl). In embodiments, R^{11} is R^{12} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{11} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0247] In embodiments, R^{11} is R^{12} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{11} is R^{12} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{11} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0248] In embodiments, R^{11} is R^{12} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{11} is R^{12} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{11} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0249] R^{12} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{13} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{13} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{13} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{13} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{13} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{13} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0250] In embodiments, R^{12} is R^{13} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{12} is R^{13} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{12} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0251] In embodiments, R^{12} is R^{13} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{12} is R^{13} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{12} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0252] In embodiments, R^{12} is R^{13} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{12} is R^{13} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{12} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0253] In embodiments, R^{12} is R^{13} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{12} is R^{13} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{12} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0254] In embodiments, R^{12} is R^{13} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{12} is R^{13} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{12} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0255] In embodiments, R^{12} is R^{13} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{12} is R^{13} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{12} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0256] R^{14} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{15} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{15} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to

4 membered heteroalkyl), R¹⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R¹⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R¹⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R¹⁵-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0257] In embodiments, R¹⁴ is R¹⁵-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹⁴ is R¹⁵-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹⁴ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0258] In embodiments, R¹⁴ is R¹⁵-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹⁴ is R¹⁵-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹⁴ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0259] In embodiments, R¹⁴ is R¹⁵-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹⁴ is R¹⁵-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹⁴ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0260] In embodiments, R¹⁴ is R¹⁵-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹⁴ is R¹⁵-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹⁴ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0261] In embodiments, R¹⁴ is R¹⁵-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹⁴ is R¹⁵-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹⁴ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0262] In embodiments, R^{14} is R^{15} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{14} is R^{15} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{14} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0263] R^{15} is independently oxo,

halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{16} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{16} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{16} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{16} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{16} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{16} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0264] In embodiments, R^{15} is R^{16} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{15} is R^{16} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{15} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0265] In embodiments, R^{15} is R^{16} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{15} is R^{16} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{15} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0266] In embodiments, R^{15} is R^{16} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{15} is R^{16} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{15} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0267] In embodiments, R^{15} is R^{16} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{15} is R^{16} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{15} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0268] In embodiments, R^{15} is R^{16} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{15} is R^{16} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{15} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0269] In embodiments, R^{15} is R^{16} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{15} is R^{16} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{15} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0270] R^{17} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{18} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{18} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{18} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{18} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{18} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{18} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0271] In embodiments, R^{17} is R^{18} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{17} is R^{18} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or

C₁-C₄ alkyl). In embodiments, R¹⁷ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0272] In embodiments, R¹⁷ is R¹⁸-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹⁷ is R¹⁸-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹⁷ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0273] In embodiments, R¹⁷ is R¹⁸-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹⁷ is R¹⁸-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹⁷ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0274] In embodiments, R¹⁷ is R¹⁸-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹⁷ is R¹⁸-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹⁷ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0275] In embodiments, R¹⁷ is R¹⁸-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹⁷ is R¹⁸-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R¹⁷ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0276] In embodiments, R¹⁷ is R¹⁸-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹⁷ is R¹⁸-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R¹⁷ is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0277] R¹⁸ is independently oxo,

halogen, -CCl₃, -CBr₃, -CF₃, -Cl₃, -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,

R¹⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R¹⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R¹⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R¹⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R¹⁹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R¹⁹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0278] In embodiments, R¹⁸ is R¹⁹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹⁸ is R¹⁹-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R¹⁸ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0279] In embodiments, R¹⁸ is R¹⁹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹⁸ is R¹⁹-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R¹⁸ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0280] In embodiments, R¹⁸ is R¹⁹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹⁸ is R¹⁹-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R¹⁸ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0281] In embodiments, R¹⁸ is R¹⁹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹⁸ is R¹⁹-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R¹⁸ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0282] In embodiments, R^{18} is R^{19} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{18} is R^{19} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{18} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0283] In embodiments, R^{18} is R^{19} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{18} is R^{19} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{18} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0284] R^{20} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-CI_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCI_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{21} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{21} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{21} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{21} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{21} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{21} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0285] In embodiments, R^{20} is R^{21} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{20} is R^{21} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{20} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0286] In embodiments, R^{20} is R^{21} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{20} is R^{21} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{20} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0287] In embodiments, R^{20} is R^{21} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{20} is R^{21} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{20} is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0288] In embodiments, R^{20} is R^{21} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{20} is R^{21} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{20} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0289] In embodiments, R^{20} is R^{21} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{20} is R^{21} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{20} is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0290] In embodiments, R^{20} is R^{21} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{20} is R^{21} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{20} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0291] In embodiments, R^{20} is substituted or unsubstituted aryl. In embodiments, R^{20} is substituted or unsubstituted phenyl. In embodiments, R^{20} is substituted phenyl. In embodiments, R^{20} is unsubstituted phenyl. In embodiments, R^{20} is substituted or unsubstituted C₁₀-C₁₂ aryl. In embodiments, R^{20} is substituted C₁₀-C₁₂ aryl. In embodiments, R^{20} is unsubstituted C₁₀-C₁₂ aryl. In embodiments, R^{20} is substituted or unsubstituted fluorenyl. In embodiments, R^{20} is substituted fluorenyl. In embodiments, R^{20} is unsubstituted fluorenyl. In embodiments, R^{20} is halogen. In embodiments, R^{20} is -Cl. In embodiments, R^{20} is -F. In embodiments, R^{20} is -Br. In embodiments, R^{20} is oxo. In embodiments, R^{20} is -COOH. In embodiments, R^{20} is -OH. In embodiments, R^{20} is -SO₃H. In embodiments, R^{20} is R^{21} -substituted or unsubstituted aryl. In embodiments, R^{20} is R^{21} -substituted or unsubstituted phenyl. In embodiments, R^{20} is R^{21} -substituted phenyl. In embodiments, R^{20} is R^{21} -substituted fluorenyl.

[0292] R^{21} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{22} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{22} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{22} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{22} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{22} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{22} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0293] In embodiments, R^{21} is R^{22} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{21} is R^{22} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{21} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0294] In embodiments, R^{21} is R^{22} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{21} is R^{22} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{21} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0295] In embodiments, R^{21} is R^{22} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{21} is R^{22} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{21} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0296] In embodiments, R^{21} is R^{22} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{21} is R^{22} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In

embodiments, R^{21} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0297] In embodiments, R^{21} is R^{22} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{21} is R^{22} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{21} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0298] In embodiments, R^{21} is R^{22} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{21} is R^{22} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{21} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0299] In embodiments, R^{21} is halogen. In embodiments, R^{21} is $-Cl$. In embodiments, R^{21} is $-F$.

[0300] R^{23} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{24} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{24} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{24} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{24} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{24} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{24} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0301] In embodiments, R^{23} is R^{24} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{23} is R^{24} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{23} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0302] In embodiments, R^{23} is R^{24} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{23} is

R^{24} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{23} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0303] In embodiments, R^{23} is R^{24} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{23} is R^{24} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{23} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0304] In embodiments, R^{23} is R^{24} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{23} is R^{24} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{23} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0305] In embodiments, R^{23} is R^{24} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{23} is R^{24} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{23} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0306] In embodiments, R^{23} is R^{24} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{23} is R^{24} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{23} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0307] R^{24} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{25} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{25} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{25} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{25} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8

membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{25} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{25} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0308] In embodiments, R^{24} is R^{25} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{24} is R^{25} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{24} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0309] In embodiments, R^{24} is R^{25} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{24} is R^{25} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{24} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0310] In embodiments, R^{24} is R^{25} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{24} is R^{25} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{24} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

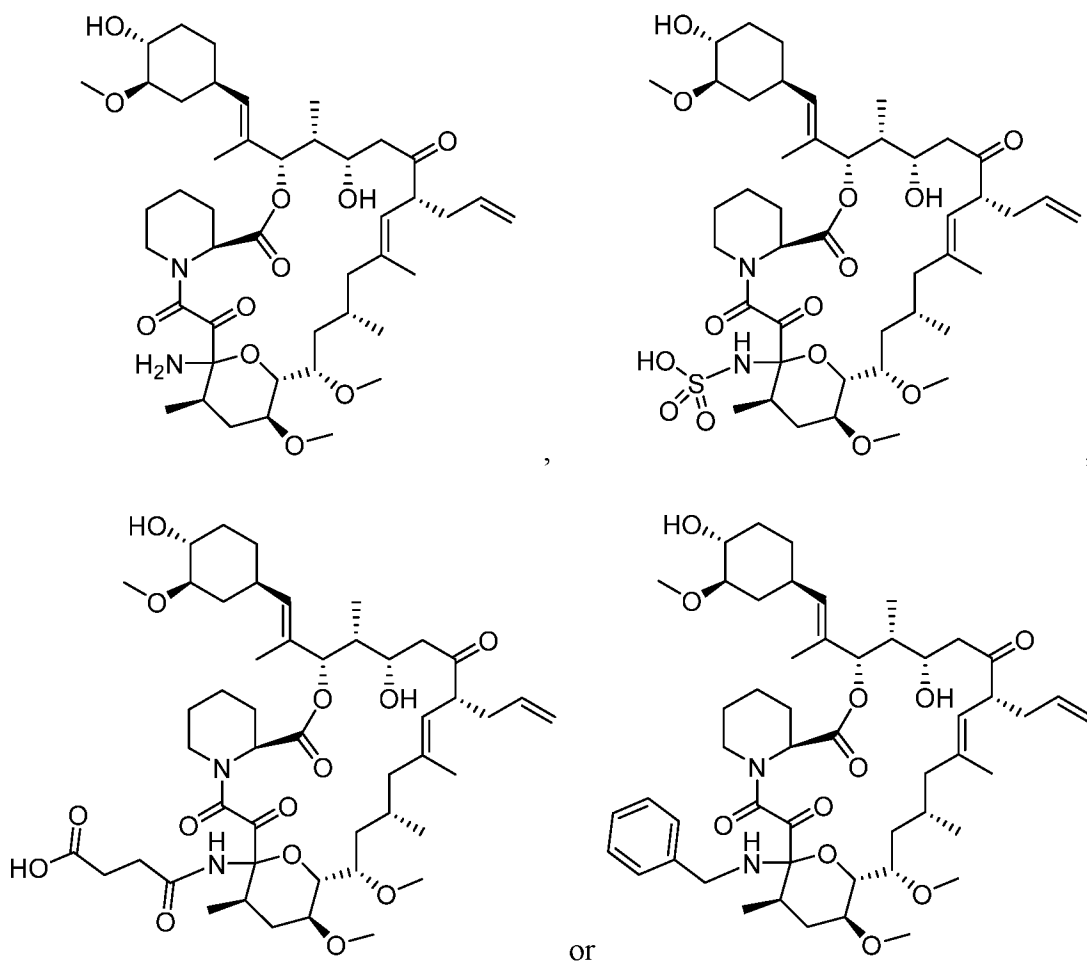
[0311] In embodiments, R^{24} is R^{25} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{24} is R^{25} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{24} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0312] In embodiments, R^{24} is R^{25} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{24} is R^{25} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{24} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

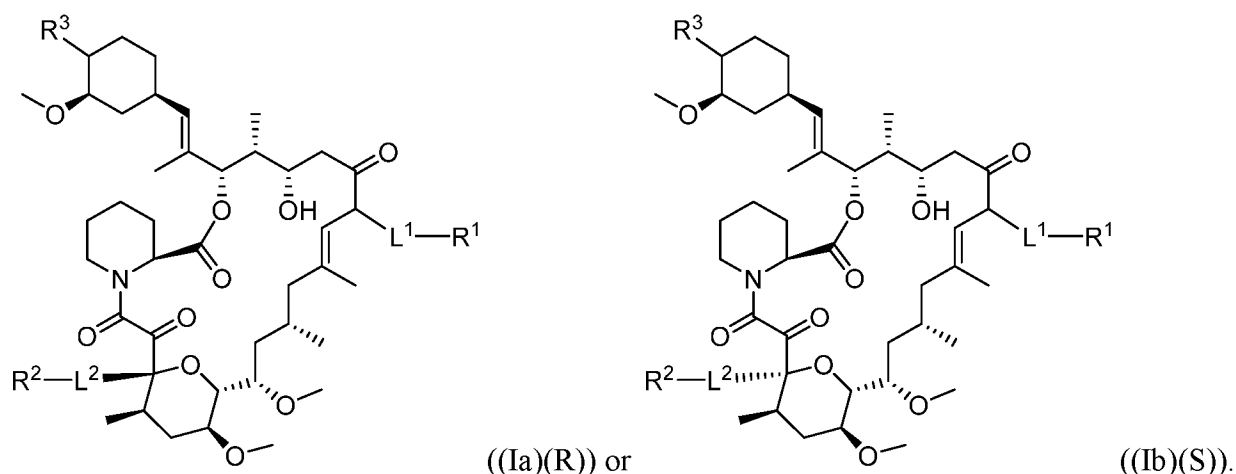
[0313] In embodiments, R^{24} is R^{25} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{24} is R^{25} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6

membered heteroaryl). In embodiments, R^{24} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0314] In embodiments, the compound is



[0315] In embodiments, the compound is



[0316] R^{11L} , R^{13} , R^{14L} , R^{16} , R^{17A} , R^{17B} , R^{17C} , R^{17D} , R^{19} , R^{20A} , R^{20B} , R^{20C} , R^{20D} , R^{22} , R^{23A} , R^{23B} , R^{23C} , R^{23D} and R^{25} are independently hydrogen, oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHl_2$, $-OCHF_2$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0317] In embodiments, $X^{1.1}$, $X^{2.1}$ and $X^{3.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$. In embodiments, $X^{1.1}$ is $-Cl$. In embodiments, $X^{1.1}$ is $-F$. In embodiments, $X^{1.1}$ is $-Br$. In embodiments, $X^{1.1}$ is $-I$. In embodiments, $X^{2.1}$ is $-Cl$. In embodiments, $X^{2.1}$ is $-F$. In embodiments, $X^{2.1}$ is $-Br$. In embodiments, $X^{2.1}$ is $-I$. In embodiments, $X^{3.1}$ is $-Cl$. In embodiments, $X^{3.1}$ is $-F$. In embodiments, $X^{3.1}$ is $-Br$. In embodiments, $X^{3.1}$ is $-I$.

[0318] In embodiments, the symbol $n1$ is an integer from 0 to 4. In embodiments, $n1$ is 0. In embodiments, $n1$ is 1. In embodiments, $n1$ is 2. In embodiments, $n1$ is 3. In embodiments, $n1$ is 4.

[0319] In embodiments, the symbols $m1$ and $v1$ are independently 1 or 2. In embodiments, $m1$ is 1. In embodiments, $m1$ is 2. In embodiments, $v1$ is 1. In embodiments, $v1$ is 2.

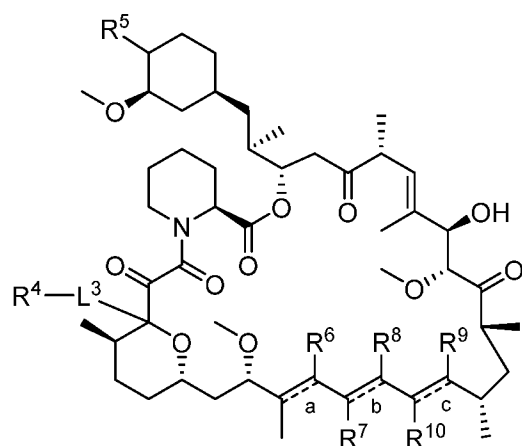
[0320] In embodiments, the symbol n_2 is an integer from 0 to 4. In embodiments, n_2 is 0. In embodiments, n_2 is 1. In embodiments, n_2 is 2. In embodiments, n_2 is 3. In embodiments, n_2 is 4.

[0321] In embodiments, the symbols m_2 and v_2 are independently 1 or 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.

[0322] In embodiments, the symbol n_3 is an integer from 0 to 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.

[0323] In embodiments, the symbols m_3 and v_3 are independently 1 or 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.

[0324] In another aspect, there is provided a compound of structural Formula (II): ***



(II), or a pharmaceutically acceptable salt thereof. $\text{--}\overset{a}{\text{--}}$,

$\text{--}\overset{b}{\text{--}}$ and $\text{--}\overset{c}{\text{--}}$ are independently single bonds or double bonds. $n_4, n_5, n_6, n_7, n_8, n_9$ and n_{10} are independently an integer from 0 to 4. $m_4, m_5, m_6, m_7, m_8, m_9, m_{10}, v_4, v_5, v_6, v_7, v_8, v_9$ and v_{10} are independently 1 or 2. L^3 is a bond, $-\text{O}-$, $-\text{S}-$, $-\text{NR}^{3L}-$, $-\text{NR}^{3L}\text{C}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene. R^4 is hydrogen, halogen, $-\text{CX}^{4.1}_3$, $-\text{CHX}^{4.1}_2$, $-\text{CH}_2\text{X}^{4.1}$, $-\text{CN}$, $-\text{SO}_{n_4}\text{R}^{4A}$, $-\text{SO}_{v_4}\text{NR}^{4B}\text{R}^{4C}$, $-\text{NHN}^{4B}\text{R}^{4C}$, $-\text{ONR}^{4B}\text{R}^{4C}$, $-\text{NHC}(\text{O})\text{NHN}^{4B}\text{R}^{4C}$, $-\text{NHC}(\text{O})\text{NR}^{4B}\text{R}^{4C}$, $-\text{N}(\text{O})_{m_4}$, $-\text{NR}^{4B}\text{R}^{4C}$, $-\text{C}(\text{O})\text{R}^{4D}$, $-\text{C}(\text{O})\text{OR}^{4D}$, $-\text{C}(\text{O})\text{NR}^{4B}\text{R}^{4C}$, $-\text{OR}^{4A}$, $-\text{NR}^{4B}\text{SO}_2\text{R}^{4A}$, $-\text{NR}^{4B}\text{C}(\text{O})\text{R}^{4D}$, $-\text{NR}^{4B}\text{C}(\text{O})\text{OR}^{4D}$, $-\text{NR}^{4B}\text{OR}^{4D}$, $-\text{OCX}^{4.1}_3$, $-\text{OCHX}^{4.1}_2$, 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^5 is hydrogen, halogen, $-\text{CX}^{5.1}_3$, $-\text{CHX}^{5.1}_2$, $-\text{CH}_2\text{X}^{5.1}$,

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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^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$.

[0325] In embodiments, when $\text{--}\overset{\text{a}}{\text{--}}$, $\text{--}\overset{\text{b}}{\text{--}}$ and $\text{--}\overset{\text{c}}{\text{--}}$ are double bonds, L^3 is $-O-$ and R^6 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, then R^4 is not hydrogen. In embodiments, when $\text{--}\overset{\text{a}}{\text{--}}$ is a double bond then R^4 is not hydrogen. In embodiments, when $\text{--}\overset{\text{b}}{\text{--}}$ is a double bond then R^4 is not hydrogen. In embodiments, when $\text{--}\overset{\text{c}}{\text{--}}$ is a double bond then R^4 is not hydrogen. In embodiments, when L^3 is $-O-$ then R^4 is not hydrogen. In embodiments, when R^6 is hydrogen then R^4 is not hydrogen. In embodiments, when R^7 is hydrogen then R^4 is not hydrogen. In embodiments, when R^8 is hydrogen then R^4 is not hydrogen. In embodiments, when R^9 is hydrogen then R^4 is not hydrogen. In embodiments, when R^{10} is hydrogen then R^4 is not hydrogen. In embodiments, when $\text{--}\overset{\text{a}}{\text{--}}$, $\text{--}\overset{\text{b}}{\text{--}}$ and $\text{--}\overset{\text{c}}{\text{--}}$ are double bonds, L^3 is a bond and R^6 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, then R^4 is not hydroxyl. In embodiments, when $\text{--}\overset{\text{a}}{\text{--}}$ is a double bond then R^4 is not hydroxyl. In embodiments, when $\text{--}\overset{\text{b}}{\text{--}}$ is a double bond then R^4 is not hydroxyl. In embodiments, when $\text{--}\overset{\text{c}}{\text{--}}$ is a double bond then R^4 is not hydroxyl. In embodiments, when L^3 is a bond then R^4 is not hydroxyl. In embodiments, when R^6 is hydrogen then R^4 is not hydroxyl. In embodiments, when R^7 is hydrogen then R^4 is not hydroxyl. In embodiments, when R^8 is hydrogen, then R^4 is not hydroxyl. In embodiments, when R^9 is hydrogen then R^4 is not hydroxyl. In embodiments, when R^{10} is hydrogen then R^4 is not hydroxyl.

[0326] In embodiments, L^3 is a bond, $-O-$, $-S-$, $-\text{NR}^{3L}-$, $-\text{NR}^{3L}\text{C}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene.

[0327] In embodiments, L^3 is a bond, $-O-$, $-S-$, $-NR^{3L}-$, $-NR^{3L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, or C_1-C_4 alkylene), substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene), substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_3-C_6 cycloalkylene, or C_5-C_6 cycloalkylene), substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene), substituted or unsubstituted arylene (e.g., C_6-C_{10} arylene, C_{10} arylene, or phenylene), or substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0328] In embodiments, L^3 is a bond, $-O-$, $-S-$, $-NR^{3L}-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, R^{26} -substituted or unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, or C_1-C_4 alkylene), R^{26} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene), R^{26} -substituted or unsubstituted cycloalkylene (e.g., C_3-C_8 cycloalkylene, C_3-C_6 cycloalkylene, or C_5-C_6 cycloalkylene), R^{26} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene), R^{26} -substituted or unsubstituted arylene (e.g., C_6-C_{10} arylene, C_{10} arylene, or phenylene), or R^{26} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^3 is a bond.

[0329] In embodiments, L^3 is R^{26} -substituted or unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, or C_1-C_4 alkylene). In embodiments, L^3 is R^{26} -substituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, or C_1-C_4 alkylene). In embodiments, L^3 is an unsubstituted alkylene (e.g., C_1-C_8 alkylene, C_1-C_6 alkylene, or C_1-C_4 alkylene).

[0330] In embodiments, L^3 is R^{26} -substituted or unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene). In embodiments, L^3 is R^{26} -substituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene). In embodiments, L^3 is an unsubstituted heteroalkylene (e.g., 2 to 8 membered heteroalkylene, 2 to 6 membered heteroalkylene, or 2 to 4 membered heteroalkylene).

[0331] In embodiments, L^3 is R^{26} -substituted or unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene). In embodiments, L^3 is R^{26} -substituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene). In embodiments, L^3 is an unsubstituted cycloalkylene (e.g., C_3 - C_8 cycloalkylene, C_3 - C_6 cycloalkylene, or C_5 - C_6 cycloalkylene).

[0332] In embodiments, L^3 is R^{26} -substituted or unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^3 is R^{26} -substituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene). In embodiments, L^3 is an unsubstituted heterocycloalkylene (e.g., 3 to 8 membered heterocycloalkylene, 3 to 6 membered heterocycloalkylene, or 5 to 6 membered heterocycloalkylene).

[0333] In embodiments, L^3 is R^{26} -substituted or unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene). In embodiments, L^3 is R^{26} -substituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene). In embodiments, L^3 is an unsubstituted arylene (e.g., C_6 - C_{10} arylene, C_{10} arylene, or phenylene).

[0334] In embodiments, L^3 is R^{26} -substituted or unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^3 is R^{26} -substituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene). In embodiments, L^3 is an unsubstituted heteroarylene (e.g., 5 to 10 membered heteroarylene, 5 to 9 membered heteroarylene, or 5 to 6 membered heteroarylene).

[0335] In embodiments, L^3 is $-NR^{3L}$ or a bond. In embodiments, L^3 is $-NR^{3L}C(O)-$, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^3 is substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene. In embodiments, L^3 is a bond, $-NR^{3L}-$, $-NR^{3L}C(O)-$. In embodiments, L^3 is a bond. In embodiments, L^3 is $-NH-$. In embodiments, L^3 is $-NHC(O)-$. In embodiments, L^3 is $-NHCH_2-$. In embodiments, L^3 is $-NHCH_2CH_2-$.

[0336] In embodiments, R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, 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.

[0337] In embodiments, R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, R^{29} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{29} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{29} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{29} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{29} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{29} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0338] In embodiments, R^4 is $-CN$, $-C(O)NH_2$, $-CF_3$, $-CH_3$ or $-C(CH_3)_2OH$. In embodiments, R^4 is $-CN$. In embodiments, R^4 is $-C(O)NH_2$. In embodiments, R^4 is $-CF_3$. In embodiments, R^4 is $-CH_3$. In embodiments, R^4 is $-C(CH_3)_2OH$.

[0339] In embodiments, R^4 is R^{29} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^4 is R^{29} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^4 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0340] In embodiments, R^4 is R^{29} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^4 is R^{29} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^4 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0341] In embodiments, R^4 is R^{29} -substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^4 is R^{29} -substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^4 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0342] In embodiments, R^4 is R^{29} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^4 is R^{29} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^4 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0343] In embodiments, R^4 is R^{29} -substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^4 is R^{29} -substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^4 is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0344] In embodiments, R^4 is R^{29} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^4 is R^{29} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^4 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0345] In embodiments, R^4 is a phosphate isostere group. In embodiments, R^4 is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group. In embodiments, R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. In embodiments, R^4 is substituted or unsubstituted alkyl. In embodiments, R^4 is substituted or unsubstituted aryl. In embodiments, R^4 is substituted or unsubstituted benzyl.

[0346] In embodiments, R^4 is -COOH. In embodiments, R^4 is hydrogen. In embodiments, R^4 is -C(O) R^{4D} . In embodiments, R^4 is -SO₃H. In embodiments, R^4 is substituted or unsubstituted alkyl. In embodiments, R^4 is substituted alkyl. In embodiments, R^4 is substituted methyl. In embodiments,

R^4 is R^{29} -substituted alkyl. In embodiments, R^4 is R^{29} -substituted methyl. In embodiments, R^4 is unsubstituted methyl. In embodiments, R^4 is substituted ethyl. In embodiments, R^4 is R^{29} -substituted ethyl. In embodiments, R^4 is unsubstituted ethyl. In embodiments, R^4 is substituted n-propyl. In embodiments, R^4 is R^{29} -substituted n-propyl. In embodiments, R^4 is unsubstituted n-propyl. In embodiments, R^4 is substituted or unsubstituted C_1 - C_8 alkyl. In embodiments, R^4 is substituted C_1 - C_8 alkyl. In embodiments, R^4 is R^{29} -substituted C_1 - C_8 alkyl. In embodiments, R^4 is substituted or unsubstituted heteroalkyl. In embodiments, R^4 is substituted heteroalkyl. In embodiments, R^4 is R^{29} -substituted heteroalkyl. In embodiments, R^4 is substituted or unsubstituted 5 to 8 membered heteroalkyl. In embodiments, R^4 is substituted 5 to 8 membered heteroalkyl. In embodiments, R^4 is R^{29} -substituted 5 to 8 membered heteroalkyl. In embodiments, R^4 is substituted or unsubstituted 10 to 15 membered heteroalkyl. In embodiments, R^4 is substituted 10 to 15 membered heteroalkyl. In embodiments, R^4 is R^{29} -substituted 10 to 15 membered heteroalkyl. In embodiments, R^4 is substituted or unsubstituted cycloalkyl. In embodiments, R^4 is substituted cycloalkyl. In embodiments, R^4 is substituted cyclohexyl. In embodiments, R^4 is unsubstituted cyclohexyl. In embodiments, R^4 is R^{29} -substituted cycloalkyl. In embodiments, R^4 is R^{29} -substituted cyclohexyl. In embodiments, R^4 is substituted C_3 - C_8 cycloalkyl. In embodiments, R^4 is unsubstituted C_3 - C_8 cycloalkyl. In embodiments, R^4 is R^{29} -substituted C_3 - C_8 cycloalkyl. In embodiments, R^4 is substituted or unsubstituted aryl. In embodiments, R^4 is substituted aryl. In embodiments, R^4 is substituted phenyl. In embodiments, R^4 is unsubstituted phenyl. In embodiments, R^4 is R^{29} -substituted aryl. In embodiments, R^4 is R^{29} -substituted phenyl.

[0347] In embodiments, R^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-SO_{n5}H$, $-SO_{v5}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m5}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, 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.

[0348] In embodiments, R^5 is substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^5 is substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as

described herein, or “lower substituent group” as described herein. In embodiments, R^5 is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0349] In embodiments, R^5 is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^5 is substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^5 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0350] In embodiments, R^5 is substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^5 is substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^5 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0351] In embodiments, R^5 is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^5 is substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^5 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0352] In embodiments, R^5 is substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^5 is substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^5 is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0353] In embodiments, R^5 is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^5 is substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^5 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0354] In embodiments, R^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-SO_{n6}H$, $-SO_{v6}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m6}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, 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.

[0355] In embodiments, R^6 is substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^6 is substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^6 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0356] In embodiments, R^6 is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^6 is substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^6 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0357] In embodiments, R^6 is substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^6 is substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as

described herein. In embodiments, R^6 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0358] In embodiments, R^6 is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^6 is substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^6 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0359] In embodiments, R^6 is substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^6 is substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^6 is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0360] In embodiments, R^6 is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^6 is substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^6 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0361] In embodiments, R^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}_1$, $-CN$, $-SO_{n7}H$, $-SO_{v7}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m7}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$, 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.

[0362] In embodiments, R^7 is substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R^7 is substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^7 is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0363] In embodiments, R^7 is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^7 is substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^7 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0364] In embodiments, R^7 is substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^7 is substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^7 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0365] In embodiments, R^7 is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^7 is substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^7 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0366] In embodiments, R^7 is substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^7 is substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as

described herein, or “lower substituent group” as described herein. In embodiments, R^7 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0367] In embodiments, R^7 is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^7 is substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^7 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0368] In embodiments, R^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, $-CN$, $-SO_{n8}H$, $-SO_{v8}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m8}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, 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.

[0369] In embodiments, R^8 is substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^8 is substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^8 is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0370] In embodiments, R^8 is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^8 is substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^8 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0371] In embodiments, R^8 is substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^8 is substituted cycloalkyl (e.g., C_3 - C_8

cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R⁸ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0372] In embodiments, R⁸ is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R⁸ is substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R⁸ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0373] In embodiments, R⁸ is substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R⁸ is substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R⁸ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0374] In embodiments, R⁸ is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R⁸ is substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R⁸ is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0375] In embodiments, R⁹ is hydrogen, halogen, -CX^{9.1}₃, -CHX^{9.1}₂, -CH₂X^{9.1}, -CN, -SO_{n9}H, -SO_{v9}NH₂, -NHNH₂, -ONH₂, -NHC(O)NHNH₂, -NHC(O)NH₂, -N(O)_{m9}, -NH₂, -C(O)H, -C(O)OH, -C(O)NH₂, -OH, -NHSO₂H, -NHC(O)H, -NHC(O)OH, -NHOH, -OCX^{9.1}₃, -OCHX^{9.1}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.

[0376] In embodiments, R^9 is substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R^9 is substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^9 is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0377] In embodiments, R^9 is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^9 is substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^9 is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0378] In embodiments, R^9 is substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^9 is substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^9 is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0379] In embodiments, R^9 is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^9 is substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^9 is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0380] In embodiments, R^9 is substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^9 is substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^9 is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0381] In embodiments, R^9 is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^9 is substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^9 is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0382] In embodiments, R^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, $-CN$, $-SO_{n10}H$, $-SO_{v10}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m10}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, 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.

[0383] In embodiments, R^{10} is substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{10} is substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^{10} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0384] In embodiments, R^{10} is substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{10} is substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In

embodiments, R^{10} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0385] In embodiments, R^{10} is substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R^{10} is substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^{10} is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0386] In embodiments, R^{10} is substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{10} is substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^{10} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0387] In embodiments, R^{10} is substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R^{10} is substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^{10} is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0388] In embodiments, R^{10} is substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{10} is substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl) that is substituted with e.g., a “substituent group” as described herein, a “size-limited substituent” as described herein, or “lower substituent group” as described herein. In embodiments, R^{10} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0389] In embodiments, R^{3L} , R^{4A} , R^{4B} , R^{4C} and R^{4D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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.

[0390] In embodiments, R^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0391] In embodiments, R^{3L} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, R^{26L} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{26L} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{26L} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{26L} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{26L} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{26L} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0392] In embodiments, R^{4A} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, R^{29A} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{29A} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{29A} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{29A} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{29A} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{29A} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0393] In embodiments, R^{4B} is hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, R^{29B} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{29B} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{29B} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{29B} -substituted or unsubstituted

heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{29B}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{29B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{29B}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{29B}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0394] In embodiments, R^{4C} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{29C}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{29C}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{29C}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{29C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{29C}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R^{29C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a R^{29C}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl) or R^{29C}-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0395] In embodiments, R^{4D} is hydrogen, halogen, -CF₃, -CCl₃, -CBr₃, -CI₃, -COOH, -CONH₂, R^{29D}-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R^{29D}-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{29D}-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R^{29D}-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{29D}-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or

phenyl), or R^{29D} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0396] In embodiments, R^{4D} is substituted or unsubstituted alkyl. In embodiments, R^{4D} is substituted alkyl. In embodiments, R^{4D} is substituted methyl. In embodiments, R^{4D} is R^{29D} -substituted alkyl. In embodiments, R^{4D} is R^{29D} -substituted methyl. In embodiments, R^{4D} is substituted ethyl. In embodiments, R^{4D} is R^{29D} -substituted ethyl. In embodiments, R^{4D} is unsubstituted ethyl. In embodiments, R^{4D} is unsubstituted methyl. In embodiments, R^{4D} is substituted n-propyl. In embodiments, R^{4D} is R^{29D} -substituted n-propyl. In embodiments, R^{4D} is unsubstituted n-propyl. In embodiments, R^{4D} is substituted or unsubstituted C_1 - C_8 alkyl. In embodiments, R^{4D} is substituted C_1 - C_8 alkyl. In embodiments, R^{4D} is R^{29D} -substituted C_1 - C_8 alkyl. In embodiments, R^{4D} is $-CF_3$. In embodiments, R^{4D} is substituted or unsubstituted aryl. In embodiments, R^{4D} is substituted aryl. In embodiments, R^{4D} is substituted phenyl. In embodiments, R^{4D} is unsubstituted phenyl. In embodiments, R^{4D} is substituted or unsubstituted phenyl.

[0397] R^{26} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{27} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{27} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{27} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{27} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{27} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{27} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0398] In embodiments, R^{26} is R^{27} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{26} is R^{27} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{26} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0399] In embodiments, R^{26} is R^{27} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{26} is R^{27} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{26} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0400] In embodiments, R^{26} is R^{27} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{26} is R^{27} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{26} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0401] In embodiments, R^{26} is R^{27} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{26} is R^{27} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{26} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0402] In embodiments, R^{26} is R^{27} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{26} is R^{27} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{26} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0403] In embodiments, R^{26} is R^{27} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{26} is R^{27} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{26} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0404] R^{27} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{28} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{28} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to

4 membered heteroalkyl), R^{28} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{28} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{28} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{28} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0405] In embodiments, R^{27} is R^{28} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{27} is R^{28} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{27} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0406] In embodiments, R^{27} is R^{28} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{27} is R^{28} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{27} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0407] In embodiments, R^{27} is R^{28} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{27} is R^{28} -substituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{27} is an unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl).

[0408] In embodiments, R^{27} is R^{28} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{27} is R^{28} -substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R^{27} is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0409] In embodiments, R^{27} is R^{28} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{27} is R^{28} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{27} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0410] In embodiments, R^{27} is R^{28} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{27} is R^{28} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{27} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0411] R^{29} is independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, R^{30} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), R^{30} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R^{30} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), R^{30} -substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R^{30} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or R^{30} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0412] In embodiments, R^{29} is R^{30} -substituted or unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{29} is R^{30} -substituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl). In embodiments, R^{29} is an unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl).

[0413] In embodiments, R^{29} is R^{30} -substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{29} is R^{30} -substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R^{29} is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0414] In embodiments, R^{29} is R^{30} -substituted or unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl). In embodiments, R^{29} is R^{30} -substituted cycloalkyl (e.g., C_3 -

C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R²⁹ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0415] In embodiments, R²⁹ is R³⁰-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R²⁹ is R³⁰-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R²⁹ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0416] In embodiments, R²⁹ is R³⁰-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²⁹ is R³⁰-substituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl). In embodiments, R²⁹ is an unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl).

[0417] In embodiments, R²⁹ is R³⁰-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R²⁹ is R³⁰-substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R²⁹ is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0418] In embodiments, R²⁹ is substituted or unsubstituted aryl. In embodiments, R²⁹ is substituted or unsubstituted phenyl. In embodiments, R²⁹ is substituted phenyl. In embodiments, R²⁹ is unsubstituted phenyl. In embodiments, R²⁹ is substituted or unsubstituted C₁₀-C₁₂ aryl. In embodiments, R²⁹ is substituted C₁₀-C₁₂ aryl. In embodiments, R²⁹ is unsubstituted C₁₀-C₁₂ aryl. In embodiments, R²⁹ is substituted or unsubstituted fluorenyl. In embodiments, R²⁹ is substituted fluorenyl. In embodiments, R²⁹ is unsubstituted fluorenyl. In embodiments, R²⁹ is halogen. In embodiments, R²⁹ is -Cl. In embodiments, R²⁹ is -F. In embodiments, R²⁹ is -Br. In embodiments, R²⁹ is oxo. In embodiments, R²⁹ is -COOH. In embodiments, R²⁹ is -OH. In embodiments, R²⁹ is -SO₃H. In embodiments, R²⁹ is R³⁰-substituted or unsubstituted aryl. In embodiments, R²⁹ is R³⁰-substituted or unsubstituted phenyl. In embodiments, R²⁹ is R³⁰-substituted phenyl. In embodiments, R²⁹ is R³⁰-substituted fluorenyl.

[0419] R³⁰ is independently oxo, halogen, -CCl₃, -CBr₃, -CF₃, -CI₃, -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, R³¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl), R³¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), R³¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl), R³¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), R³¹-substituted or unsubstituted aryl (e.g., C₆-C₁₀ aryl, C₁₀ aryl, or phenyl), or R³¹-substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0420] In embodiments, R³⁰ is R³¹-substituted or unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R³⁰ is R³¹-substituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl). In embodiments, R³⁰ is an unsubstituted alkyl (e.g., C₁-C₈ alkyl, C₁-C₆ alkyl, or C₁-C₄ alkyl).

[0421] In embodiments, R³⁰ is R³¹-substituted or unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R³⁰ is R³¹-substituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl). In embodiments, R³⁰ is an unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl).

[0422] In embodiments, R³⁰ is R³¹-substituted or unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R³⁰ is R³¹-substituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl). In embodiments, R³⁰ is an unsubstituted cycloalkyl (e.g., C₃-C₈ cycloalkyl, C₃-C₆ cycloalkyl, or C₅-C₆ cycloalkyl).

[0423] In embodiments, R³⁰ is R³¹-substituted or unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R³⁰ is R³¹-substituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl). In embodiments, R³⁰ is an unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl).

[0424] In embodiments, R^{30} is R^{31} -substituted or unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{30} is R^{31} -substituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl). In embodiments, R^{30} is an unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl).

[0425] In embodiments, R^{30} is R^{31} -substituted or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{30} is R^{31} -substituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{30} is an unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0426] In embodiments, R^{30} is halogen. In embodiments, R^{30} is $-Cl$. In embodiments, R^{30} is $-F$.

[0427] R^{26L} , R^{28} , R^{29A} , R^{29B} , R^{29C} , R^{29D} and R^{31} are independently hydrogen, oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10} aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl). In embodiments, R^{26L} , R^{28} , R^{29A} , R^{29B} , R^{29C} , R^{29D} and R^{31} are independently oxo, halogen, $-CCl_3$, $-CBr_3$, $-CF_3$, $-Cl_3$, $-CN$, $-OH$, $-NH_2$, $-COOH$, $-CONH_2$, $-NO_2$, $-SH$, $-SO_3H$, $-SO_4H$, $-SO_2NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCCl_3$, $-OCF_3$, $-OCBr_3$, $-OCl_3$, $-OCHCl_2$, $-OCHBr_2$, $-OCHI_2$, $-OCHF_2$, unsubstituted alkyl (e.g., C_1 - C_8 alkyl, C_1 - C_6 alkyl, or C_1 - C_4 alkyl), unsubstituted heteroalkyl (e.g., 2 to 8 membered heteroalkyl, 2 to 6 membered heteroalkyl, or 2 to 4 membered heteroalkyl), unsubstituted cycloalkyl (e.g., C_3 - C_8 cycloalkyl, C_3 - C_6 cycloalkyl, or C_5 - C_6 cycloalkyl), unsubstituted heterocycloalkyl (e.g., 3 to 8 membered heterocycloalkyl, 3 to 6 membered heterocycloalkyl, or 5 to 6 membered heterocycloalkyl), unsubstituted aryl (e.g., C_6 - C_{10} aryl, C_{10}

aryl, or phenyl), or unsubstituted heteroaryl (e.g., 5 to 10 membered heteroaryl, 5 to 9 membered heteroaryl, or 5 to 6 membered heteroaryl).

[0428] In embodiments, R^{29D} is halogen. In embodiments, R^{29D} is $-Cl$. In embodiments, R^{29D} is $-F$. In embodiments, R^{29D} is $-Br$. In embodiments, R^{29D} is oxo. In embodiments, R^{29D} is $-COOH$. In embodiments, R^{29D} is $-OH$. In embodiments, R^{29D} is $-SO_3H$. In embodiments, R^{29D} is substituted or unsubstituted aryl. In embodiments, R^{29D} is substituted aryl. In embodiments, R^{29D} is substituted phenyl. In embodiments, R^{29D} is unsubstituted phenyl. In embodiments, R^{29D} is substituted or unsubstituted phenyl.

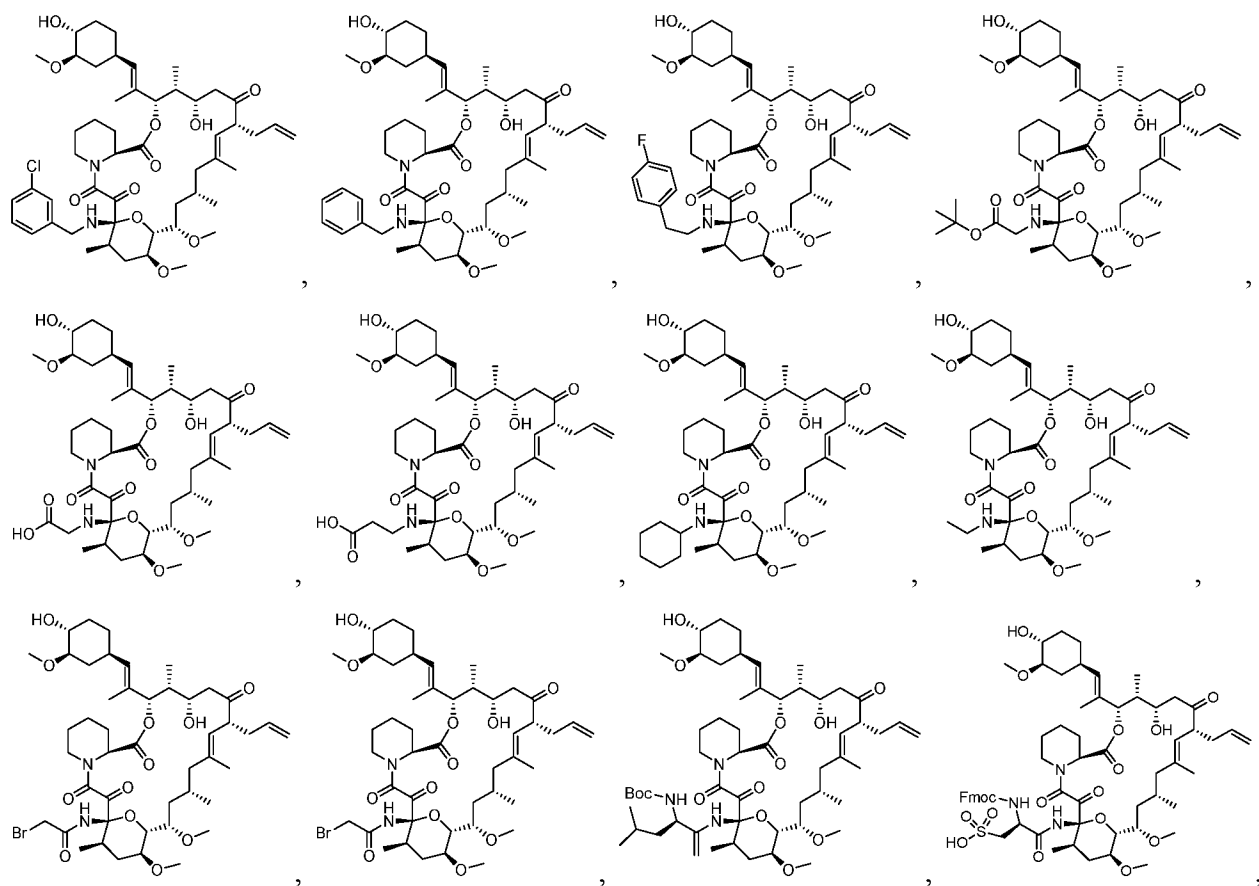
[0429] In embodiments, $X^{4.1}$ is $-Cl$. In embodiments, $X^{4.1}$ is $-F$. In embodiments, $X^{4.1}$ is $-Br$. In embodiments, $X^{4.1}$ is $-I$. In embodiments, $X^{5.1}$ is $-Cl$. In embodiments, $X^{5.1}$ is $-F$. In embodiments, $X^{5.1}$ is $-Br$. In embodiments, $X^{5.1}$ is $-I$. In embodiments, $X^{6.1}$ is $-Cl$. In embodiments, $X^{6.1}$ is $-F$. In embodiments, $X^{6.1}$ is $-Br$. In embodiments, $X^{6.1}$ is $-I$. In embodiments, $X^{7.1}$ is $-Cl$. In embodiments, $X^{7.1}$ is $-F$. In embodiments, $X^{7.1}$ is $-Br$. In embodiments, $X^{7.1}$ is $-I$. In embodiments, $X^{8.1}$ is $-Cl$. In embodiments, $X^{8.1}$ is $-F$. In embodiments, $X^{8.1}$ is $-Br$. In embodiments, $X^{8.1}$ is $-I$. In embodiments, $X^{9.1}$ is $-Cl$. In embodiments, $X^{9.1}$ is $-F$. In embodiments, $X^{9.1}$ is $-Br$. In embodiments, $X^{9.1}$ is $-I$. In embodiments, $X^{10.1}$ is $-Cl$. In embodiments, $X^{10.1}$ is $-F$. In embodiments, $X^{10.1}$ is $-Br$. In embodiments, $X^{10.1}$ is $-I$.

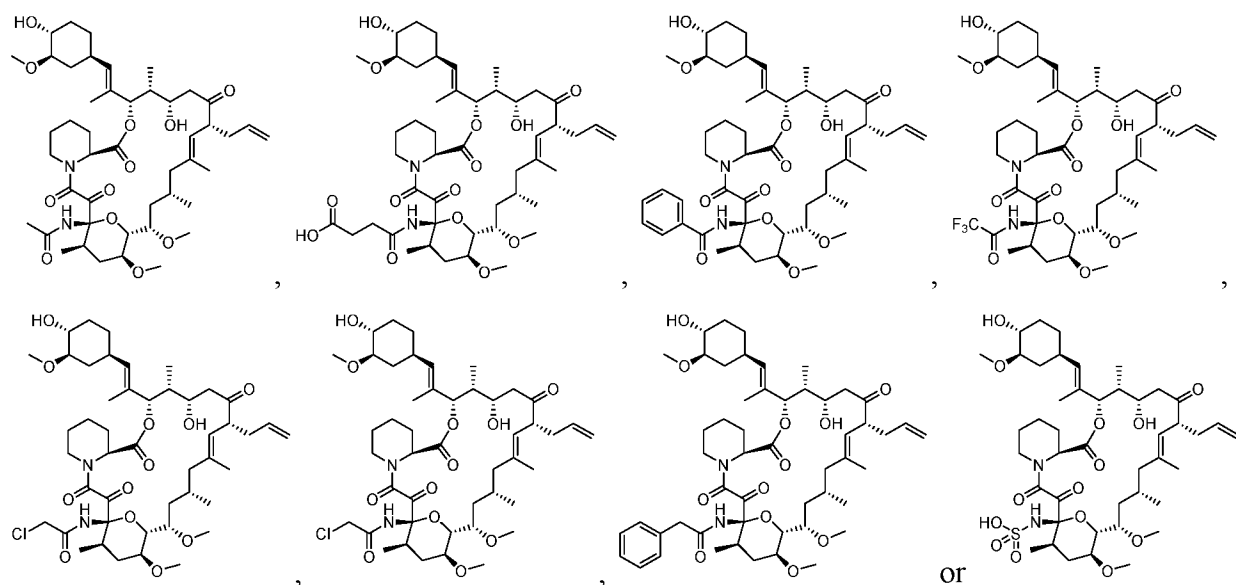
[0430] In embodiments, the symbol $n4$ is an integer from 0 to 4. In embodiments, $n4$ is 0. In embodiments, $n4$ is 1. In embodiments, $n4$ is 2. In embodiments, $n4$ is 3. In embodiments, $n4$ is 4. In embodiments, the symbol $n5$ is an integer from 0 to 4. In embodiments, $n5$ is 0. In embodiments, $n5$ is 1. In embodiments, $n5$ is 2. In embodiments, $n5$ is 3. In embodiments, $n5$ is 4. In embodiments, the symbol $n6$ is an integer from 0 to 4. In embodiments, $n6$ is 0. In embodiments, $n6$ is 1. In embodiments, $n6$ is 2. In embodiments, $n6$ is 3. In embodiments, $n6$ is 4. In embodiments, the symbol $n7$ is an integer from 0 to 4. In embodiments, $n7$ is 0. In embodiments, $n7$ is 1. In embodiments, $n7$ is 2. In embodiments, $n7$ is 3. In embodiments, $n7$ is 4. In embodiments, the symbol $n8$ is an integer from 0 to 4. In embodiments, $n8$ is 0. In embodiments, $n8$ is 1. In embodiments, $n8$ is 2. In embodiments, $n8$ is 3. In embodiments, $n8$ is 4. In embodiments, the symbol $n9$ is an integer from 0 to 4. In embodiments, $n9$ is 0. In embodiments, $n9$ is 1. In embodiments, $n9$ is 2. In embodiments, $n9$ is 3. In embodiments, $n9$ is 4. In

embodiments, the symbol n10 is an integer from 0 to 4. In embodiments, n10 is 0. In embodiments, n10 is 1. In embodiments, n10 is 2. In embodiments, n10 is 3. In embodiments, n10 is 4.

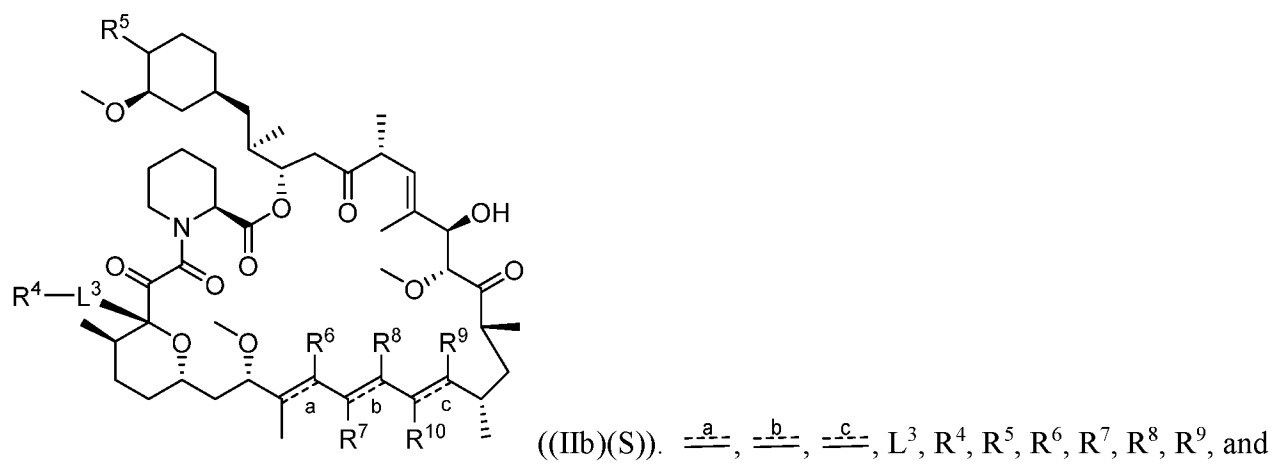
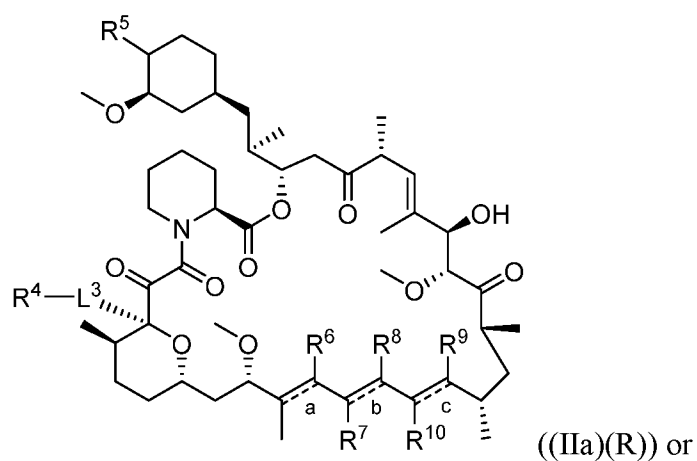
[0431] In embodiments, the symbols m4, m5, m6, m7, m8, m9, m10, v4, v5, v6, v7, v8, v9 and v10 are independently 1 or 2. In embodiments, m4 is 1. In embodiments, m4 is 2. In embodiments, v4 is 1. In embodiments, v4 is 2. In embodiments, m5 is 1. In embodiments, m5 is 2. In embodiments, v5 is 1. In embodiments, v5 is 2. In embodiments, m6 is 1. In embodiments, m6 is 2. In embodiments, v6 is 1. In embodiments, v6 is 2. In embodiments, m7 is 1. In embodiments, m7 is 2. In embodiments, v7 is 1. In embodiments, v7 is 2. In embodiments, m8 is 1. In embodiments, m8 is 2. In embodiments, v8 is 1. In embodiments, v8 is 2. In embodiments, m9 is 1. In embodiments, m9 is 2. In embodiments, v9 is 1. In embodiments, v9 is 2. In embodiments, m10 is 1. In embodiments, m10 is 2. In embodiments, v10 is 1. In embodiments, v10 is 2.

[0432] In embodiments, the compound is





[0433] In embodiments, the compound is



R^{10} are as described herein.

[0434] 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).

[0435] 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.

[0436] 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.

[0437] 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.

[0438] 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.

[0439] In another aspect, there is provided a pharmaceutical composition, including a compound described herein (e.g., compound of any aspect disclosed herein and embodiments thereof), and a pharmaceutically acceptable excipient.

METHODS

[0440] In another aspect, there is provided a method of inhibiting Pin 1, including contacting Pin 1 with a compound as described herein, including embodiments thereof.

[0441] In another aspect, there is provided a method of inhibiting an FK506 binding protein (FKBP), including contacting the FKBP with a compound as described herein, including embodiments thereof.

[0442] In embodiments, the FKBP is FKBP38, FKBP51 or FKBP52. In embodiments, the FKBP is FKBP51.

[0443] In another aspect, there is provided a method of treating a Pin 1-mediated disease or disorder, including administering to a patient in need thereof a compound as described herein, including embodiments thereof.

[0444] In embodiments, the Pin 1-mediated disease or disorder is cancer. In embodiments, the cancer is prostate cancer, brain cancer, breast cancer, ovarian cancer, cervical cancer or skin cancer (e.g., melanoma). In embodiments, the cancer is prostate cancer. In embodiments, the cancer is brain cancer. In embodiments, the cancer is breast cancer. In embodiments, the cancer is ovarian cancer. In embodiments, the cancer is cervical cancer. In embodiments, the cancer is skin cancer. In embodiments, the skin cancer is melanoma.

[0445] In embodiments, the Pin 1-mediated disease or disorder is a neurodegenerative disease. In embodiments, the neurodegenerative disease is a tauopathy. In embodiments, the neurodegenerative disease is Primary age-related tauopathy (PART)/Neurofibrillary tangle-predominant senile dementia, Chronic traumatic encephalopathy, including dementia pugilistica, Progressive supranuclear palsy, Corticobasal degeneration, Frontotemporal dementia and parkinsonism linked to chromosome 17, LYTIC-BODIG disease (Parkinson-dementia complex of Guam), Ganglioglioma and gangliocytoma, Meningioangiomas, Postencephalitic parkinsonism, Subacute sclerosing panencephalitis, encephalopathy, tuberous sclerosis, Hallervorden-Spatz disease, lipofuscinosis, Parkinsons Disease, Alzheimers Disease, Huntington's Disease, Pick's Disease, schizophrenia or corticobasal degeneration.

[0446] In embodiments, the Pin 1-mediated disease or disorder is depression. In embodiments, the method further includes administering to the subject an anti-depressant.

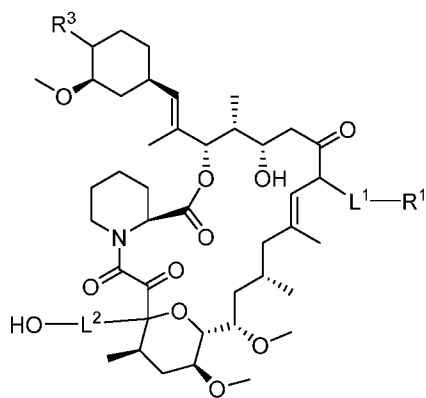
[0447] In embodiments, the Pin 1-mediated disease or disorder is pain. In embodiments, the pain is chronic pain or neuropathic pain.

[0448] Further to any aspect of treating a Pin 1-mediated disease or disorder, or embodiment thereof, in embodiments the method further includes administering to the subject a chemotherapeutic agent.

[0449] In another aspect, there is provided a method of treating an FKBP51-mediated disease or disorder, including administering to a patient in need thereof a compound as described herein, including embodiments thereof.

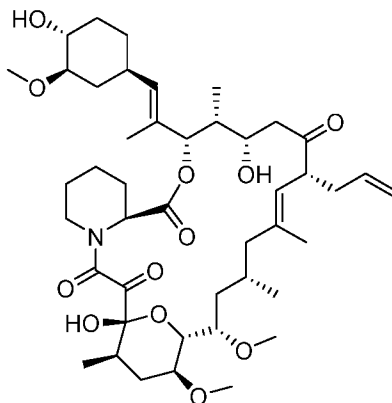
METHOD OF PREPARING

[0450] In another aspect, there is provided a method of preparing a compound of structural Formula (I) as described herein, including contacting a compound of structural Formula (Ic) with ammonia:

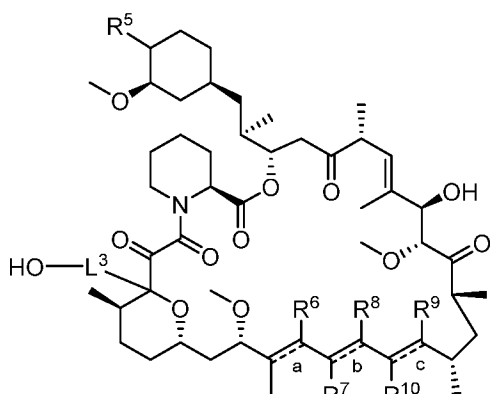


(Ic), wherein L¹, L², R¹, and R³ are as described herein.

[0451] In embodiments, the compound of Formula (Ic) is



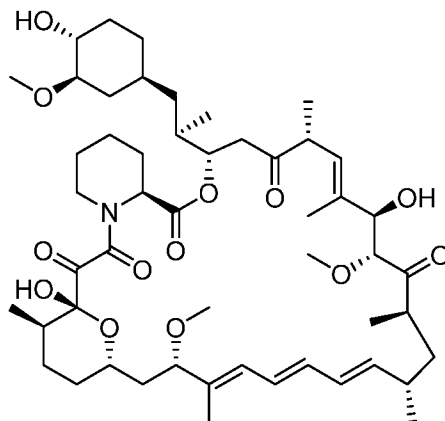
[0452] In another aspect, there is provided a method of preparing a compound of structural Formula (II) as described herein, including contacting a compound of structural Formula (IIc) with ammonia:



(IIc). $\text{---}\overset{\text{a}}{\text{---}}$, $\text{---}\overset{\text{b}}{\text{---}}$, $\text{---}\overset{\text{c}}{\text{---}}$, L^3 , R^5 , R^6 , R^7 , R^8 , R^9 , and R^{10}

are as described herein.

[0453] In embodiments, the compound of Formula (IIc) is



EXAMPLES

[0454] Example 1 - Novel Design of Inhibitors Targeting the PPIase Pin1

[0455] Pin1 is unique among the prolyl isomerases (PPIases) because it only binds to prolines that directly follow phosphorylated serine or threonine residues (pS/T-P motif). This activity is important as the phosphate of the pS/T-P motif sterically hinders the local peptide backbone and dramatically slows the spontaneous *cis*-trans isomerization of the proline. Thus, Pin1 activity becomes essential for isomerization of this motif on a relevant physiological time scale. Moreover, Pin1's clients include multiple cell cycle regulators, modulators of stress responses, and transcription factors. In these clients, isomerization of pS/T-P motifs is used as an essential regulatory switch, often in tandem with proline-directed kinases. Accordingly, misregulation or overexpression of Pin1 is implicated in numerous diseases, including cancer and neurodegeneration, making Pin1 an especially attractive target. However, attempts to discover Pin1 inhibitors have had limited success. The requirement for a highly electronegative group in the Pin1 active site, mimicking the pS/T-P interaction, seems to render many potential inhibitors inactive in cell and animal models because of poor permeability. Accordingly, a useful hypothesis is that the excellent pharmacological properties of FK506 can make it a suitable chemical scaffold for engineering Pin1 inhibitors. We reasoned that these molecules might take advantage of the mechanisms to yield potent, selective and long-lived inhibitors. However, FK506 itself has little affinity for Pin1, possibly because it lacks the key, electronegative region essential for Pin1 binding. To overcome this potential hurdle, we have designed a novel semisynthetic strategy to modify FK506 at a position likely to improve affinity and

selectivity for Pin1. We found that installing a sulfamic acid at the C10-position of the macrocyclic ring significantly improved the affinity for Pin1 (>100-fold) *in vitro*. This molecule is designed to yield the first high-affinity membrane-permeable inhibitors of Pin1, which should prove to be a powerful chemical probe of this PPIase.

[0456] Pin1 Plays a Diverse Role in Cellular Homeostasis. Pin1 has a unique role among all of the PPIases in that it only recognizes prolines immediately following phosphorylated serine or threonine residues (known as the pS/T-P motif) [1]. This unique feature of Pin1 bindings is mediated by a cationic groove formed by Lys-63, Arg-68 and Arg-69, which makes contact with the pS/T group (FIG. 1) [2]. In turn, isomerization of bound substrate is thought to be mediated by the nearby residue Cys-113 [3]. Like other PPIases, Pin1 also has a hydrophobic “shelf” adjacent to the proline pocket that it uses to gain additional contacts.

[0457] In addition to its PPIase domain, Pin1 has an N-terminal WW domain, that seems to contribute to the binding of phosphopeptide substrates. The WW domain does not possess intrinsic isomerase activity, and the reason for overlapping substrate preference with the PPIase domain is unclear. It is thought that the WW domain may initially localize with relevant clients, but the hand-off mechanism to the PPIase domain for isomerization is unknown.

[0458] Pin1 and its orthologs have been discovered in all eukaryotes and they are known to be critical for cell cycle regulation and cellular homeostasis. In *Saccharomyces cerevisiae*, the Pin1 homolog Ess1 is essential [4], and complementation with human Pin1 rescues viability [1]. One essential activity of Pin1 is in regulation of the cell cycle, through its activity on numerous phosphorylation-dependent regulatory pathways. Pin1 works in tandem with ‘proline-directed’ kinases and phosphatases, binding and isomerizing the peptide backbone of the pS/T-P motifs to alter the prolyl *cis*/trans conformation. This is especially important in the context of pS/T-P motifs, as they have been shown to isomerize 8-fold slower than their non-phosphorylated counterparts [5]. This slow rate is driven by specific contacts between the phosphate moiety and the amide backbone [6]. Since proline isomerization already represents a significant bottleneck in protein dynamics phosphoprotein substrates of Pin1 require the specific isomerase activity of this chaperone to function. Pin1-mediated conformational changes have been implicated in activating transcription factors, facilitating dephosphorylation or degradation of clients, stabilizing protein-protein interactions and targeting proteins for specific subcellular localization [7].

[0459] The Role of Pin1 in Disease. The importance of Pin1 for cellular homeostasis and the progression through mitosis suggests that misregulation of this protein may lead to a variety of disease states. Indeed, Pin1 has been implicated in both cancer and neurodegeneration. Pin1 interacts with multiple oncogenes, such as p53, and often enhances their oncogenic activity. Significant Pin1 overexpression has been found in numerous cancer types, including prostate, brain, breast, ovary, cervical and melanomas [8]. Conversely, low Pin1 expression has been correlated to increased neuronal vulnerability and enhanced degeneration of neurons and neurofibrillary tangle formation during AD-like pathologies [9]. Pin1 is often sequestered into paired helical filaments (PHF) of hyperphosphorylated tau [10] while soluble Pin1 is deactivated by oxidative stress at its catalytic cysteine [11]. Thus, Pin1 expression and activity is often inversely correlated with disease; it is upregulated and highly active in cancer, or downregulated and inactive in neurodegenerative diseases [12]. For these reasons, Pin1 inhibitors are of significant interest as potential anti-cancer therapeutics, where modulation of Pin1 levels have been shown to be effective at preventing tumorigenesis. Further, Pin1 inhibition may have some therapeutic benefit in certain neurodegenerative diseases, such as in tauopathies, where specific destabilizing mutations in tau have exhibited a decrease in pathogenesis when Pin1 levels are reduced [13].

[0460] Natural Product Inhibitors of Pin1. Finding high affinity, cell permeable inhibitors has been an active and ongoing pursuit for many years [14]. Discovered as the first Pin1 inhibitor, Juglone (FIG. 2) functions by covalent modification of Cys-113 in the active site [15]. Juglone (5-hydroxy-1,4-naphthalenedione) is produced by the Black Walnut tree and its inhibition of Pin1 activity has been suggested to contribute to the toxicity of Black Walnuts. However, the exact binding interaction of Juglone is unclear and this compound has proven to have other cellular targets, possibly acting non-specifically [16]. To date, no inhibitors are known to mimic this mode of inhibition. Interestingly, Juglone does not inhibit the FKBP or cyclophilins, whereas Pin1 has not been shown to have any appreciable affinity for the natural products, rapamycin, FK506 or cyclosporin. This observation is perhaps surprising, due to the similarity between active sites across the PPIases. However, Pin1 is unique among the PPIases because of its phospho-peptide binding activity through a positively charged surface. Thus, Pin1 inhibitors must navigate this feature of the pocket by including highly electronegative substituents. The challenge is that these same features often reduce membrane permeability. Other natural product derivatives (FIG. 2) have been shown to inhibit Pin1 while also engaging the phosphate-binding region, providing an alternate approach

towards novel scaffolds. Dexamethasone-21-phosphate is a synthetic corticosteroid prodrug found to modestly inhibit Pin1 activity ($K_D = 2.2 \mu\text{M}$) [17]. By NMR and X-ray crystallography, dexamethasone-21-phosphate was shown to bind across the proline pocket to the cationic groove formed by Lys-63, Arg-68 and Arg-69. Using a similar screening strategy, the vitamin A derivative all-trans retinoic acid (ATRA) was found to be a submicromolar inhibitor of Pin1 ($K_D = 0.8 \mu\text{M}$) and bound similarly to dexamethasone-21-phosphate [18]. The cyclohexene ring is anchored into the proline binding pocket with the alkene chain extending the carboxylic acid into the cationic phosphate-binding region. Treatment with ATRA suppresses proliferation of mouse embryonic fibroblasts and leads to Pin1 degradation but has no effect in Pin1 knockout cells or those harboring inactivating mutations in the binding site. In a model of acute promyelocytic leukemia (APL), ATRA facilitates degradation of the fusion oncoprotein promyelocytic leukemia-retinoic acid receptor α (PML-RAR- α) and was shown to be due to the inhibition of the stabilizing effect of Pin1. This was further demonstrated in a breast cancer model where Pin1 is highly expressed and possesses pro-oncogenic activity. Inhibition of Pin1 by ATRA limited tumorigenicity of MDA-MBA-231 cells injected into mice in a dose-dependent manner. Inhibitors based on these natural products may be a promising starting point.

[0461] Peptidomimetics Demonstrate the Necessity for Charged Substituents in Pin1 Inhibitors. Because of the challenges with the Pin1 site, early inhibitors were primarily based on peptides. Although these molecules haven't been useful as probes in cells or animals, they have illustrated the features of the active site. In one approach, a combinatorial library of 5-mer N-acetylated peptides incorporating unnatural amino acids surrounding a phosphothreonine residue was screened against the PPIase domain of Pin1. The strongest hit contained a pipicolate core not unlike those found to strongly inhibit FKBP that is central to the binding region of FK506 and rapamycin. Optimization of the peptide resulted in "pintide" (Ac-Phe-D-Thr(PO_3H_2)-Pip-Nal-Gln- NH_2 ; FIG. 3), which had a $K_i \approx 18 \text{ nM}$. Addition of the WW domain in the full-length protein did not alter binding preference [19]. Crystallization of the L- and D-peptide versions of pintide yielded surprising results, with nearly identical conformations of the stereoisomers. In both structures, the electronegative phosphate group was anchored into the phosphate recognition pocket, contacting Lys-63 and Arg-69. The pipicolate core rested in the proline-binding pocket, making hydrophobic contacts with Leu-122, Met-130 and Phe-134. The naphthylalanine side chain extends up and stacks on a hydrophobic shelf formed by Leu-122 and the top of the Met-130 side chain [20]. Based on these structures, the

reasons for the large difference in binding affinity are not obvious. Strikingly, the Pin1 active site occupied by these peptides adopted a conformation that is reminiscent of FKBP when bound to rapamycin, with both pipercolic rings in nearly identical orientations. However, rapamycin has no measureable affinity for Pin1 so the affinity of the peptides for Pin1 may originate through the phosphate-binding surface.

[0462] Early Design of Small Molecule Pin1 Inhibitors. Guided by the Pin1 crystal structure, FKBP ligands were modeled in the Pin1 active site to design novel small molecules. The first compound was found to be a low micromolar inhibitor ($K_i \approx 1.7 \mu\text{M}$), which was promising for a *de novo* lead (FIG. 4) [21]. Attempts to optimize the charge by replacing the phosphate with a sulfate resulted in a significant drop in potency ($9.5 \mu\text{M}$). Re-installing the phosphate and appending a propylbenzene to the carbinol center improved potency to $0.8 \mu\text{M}$ and inhibited cell cycle progression of CA46 cells at $15 \mu\text{M}$ (**4.4a**). The pipercolyl ester found in FK506 and rapamycin was replaced with a phenylalaninol phosphate as the minimum binding epitope. A pilot chemical screen identified a bi-aryl amide scaffold, which inhibited Pin at 100 nM (FIG. 5). Derivatization and co-crystallization of (**4.5a**) revealed a new binding pose, with the compound rotated to allow the phenyl group to dock into the hydrophobic proline pocket and placing the benzothiophene on the hydrophobic shelf formed by Leu-122 and Met-130. The phosphate group was rotated slightly and bound in-between Arg-68 and Arg-69, losing the interaction with Lys-63 as in the previous phosphopeptide inhibitors. This suggests that there is some flexibility in orienting the phosphate group in these compounds, with the positive charge being spread throughout a large region of the active site. Carboxylate-based scaffold was the subject of a limited SAR series [22]. In addition to modifications of the phenyl ring system, phosphate bioisosteres, such as tetrazoles, acylaminothiazols and acylsulfonamides, were tried in replacement of the carboxylic acid. The tetrazole retained the same activity as the carboxylate. It was hypothesized that export by P-glycoprotein efflux pumps may be responsible for the limited activity of this series. The amidyl carboxylate moiety in particular was implicated in recognition by P-glycoprotein, and it was concluded that further optimization of the scaffold was necessary to achieve improved cellular activity.

[0463] In an alternate approach, engagement of peripheral residues flanking the cationic phosphate-binding region was shown to be effective in the development of Pin1 inhibitors (FIG. 7).

An initial fragment-based screen was performed to inhibit Pin1 isomerase activity on a model substrate and confirmed in a follow-up NMR platform [23]. Optimization of the primary hit (**4.7a**) resulted in a phenyl-imidazole fragment substituted at the 3-position (**4.7b**; FIG. 7), a site shown previously to be effective in engaging the proline pocket. Subsequent modification of the central imidazole ring resulted in a series of amide substituted 3-chloro-phenyl-imidazole inhibitors with modest affinity for Pin1 (**4.7c**, $IC_{50} \approx 2.0 \mu M$) that were cell penetrant and able to inhibit cell division and Pin1-mediated cyclin D1 expression at micromolar levels. Furthermore, these compounds had a unique binding mode in Pin1, flanking Lys-63, Arg-68 and Arg-69 in the phosphate recognition pocket. It is worth noting that these fragments do not engage the hydrophobic shelf, as seen with other potent Pin1 inhibitors (**4.5a**, **4.5b**).

[0464] Together, these small molecules are the first Pin1 inhibitors that possess cellular activity.. Critical to the design of these small molecules, they all engage the cationic phosphate-binding site. Additional affinity is gained from either interacting with the hydrophobic shelf or residues adjacent to the phosphate binding site.

[0465] Remodeling FK506 and Rapamycin for Anti-Pin1 Activity. Without wishing to be bound by theory, it is believed that FK506 effectively drives the partitioning of HIV protease inhibitors into relevant cells. We wondered if a similar strategy may overcome the major problems that have plagued discovery of Pin1 inhibitors. As discussed above, early investigation into Pin1 inhibitors involved modifying the core scaffold of FKBP ligands based on the pipecolate core, which resulted in a series of compounds with good affinity. We wondered if the favorable properties of FK506 could be leveraged to drive the permeability of analogs containing electronegative groups.

[0466] To design an initial model, we created an overlay of the Pin1 active site with bound FK506 and compared it to the known co-crystal structures of Pin1 with inhibitors containing a pipecolate core. Analysis of these structures suggested that FK506 analogs might bind to Pin1 if the cationic groove could be sufficiently occupied (FIGS. 8A-8B). Likewise, modified analogs of rapamycin were predicted to have a similar interaction.

[0467] Analyzing the structure of both FK506 and Rapamycin highlighted the tertiary hydroxyl as being a potential point for modification. During our initial investigations into the feasibility of engineering Pin1-specific FK506/rapamycin derivatives, we rediscovered an obscure report on modifying the natural products at this position [24]. Specifically, the authors showed that treatment

of either of these macrocycles with methanolic ammonia converts the tertiary hydroxyl into a primary amine by an undetermined mechanism (FIG. 9). We predicted that the primary amine substitution at this position would create an orthogonally reactive handle for further derivatization. However, we first wanted to systematically explore the chemistry of this reaction, as it had remained underexplored.

[0468] Results

[0469] Semisynthetic Modification of FK506 and Rapamycin. Using the previously reported conditions, FK506 was treated with methanolic ammonia (2M) and monitored by HPLC (FIG. 10). Within 30 minutes, we saw conversion of FK506 into a more polar product (**13**, herein FK-NH₂), which we attributed to the primary amine. At the same time, we noticed that the unreacted FK506 peak appeared to develop a slightly more polar shoulder and that a small number of minor side products were produced. It had previously been suggested that treatment of FK506 with ammonia could also result in formation of the imine at the adjacent carbonyl, so we hypothesize that the “shoulder” might be the less polar imine. However, we have not been able to isolate enough of this compound for an in-depth characterization by NMR and MS. Similarly, we reasoned that the excess ammonia could be modifying FK506 with both the amine and imine, which would explain the other trace product slightly more polar than the FK-NH₂ peak. With these caveats, we quantified the HPLC traces to determine the amount of product formation and fit the data to a first order exponential (FIG. 11). We observed approximately 60% product formation.

[0470] Next, we characterized the presumed FK-NH₂ product by MS and NMR. The molecular mass was observed by MS (FIG. 12. M+H⁺: 803.63, expected: 803.50). This represents a slight decrease in mass (~ 1 amu) compared to FK506. However, the imine would also exhibit the same mass loss, so we turned to NMR. Due to the complexity of the compound and the large number of hydrogens (70 in FK-NH₂), we opted for ¹³C NMR. Guided by previous peak assignments, we observed that the C10 peak was significantly shifted (FIG. 13) [25]. Rather, this carbon was shifted upfield, consistent with attachment of an amine. Interestingly, we observed a slight double peak in the shifted spectrum, possibly due to tautomerization of FK506 in this region of the molecule. We are currently pursuing small molecule X-ray crystallography to further confirm the structure and its absolute stereochemistry as we continue the conversion of FK-NH₂ to desired products.

[0471] Solvent Screen of the FK506 Substitution Reaction. First, we attempted to optimize the concentration of ammonia to improve yield and minimize residual starting material in subsequent reactions. This led to a characteristic change in the observed peak shapes that progressed as concentration was increased (FIG. 14). At 1M ammonia, little reaction was observed that consisted of primarily unreacted FK506 and only a small amount of the FK-NH₂ product forming (box 1). The 2M reaction progressed as normal, with increased formation of FK-NH₂ (box 1) and appearance of the imine “shoulder” (box 3) that overlapped with the FK506 peak. Higher concentration 3.5M ammonia largely converted FK506 (box 4) with a mixture of FK-NH₂ (box 1) and a previously not seen side product (box 2). Likewise, 7M ammonia produced only the new peak (box 2), with no FK-NH₂ formation occurring.

[0472] Using the 2M ammonia conditions, we proceeded to optimize solvent conditions. For these experiments, we chose a series of solvents to represent a range of properties from polar (DMPU) to nonpolar (DCM), as well as protic (methanol) to aprotic (DMPU, dioxane, DCM) solvents. Notably, to this point we were performing the reactions by first diluting a stock 7M ammonia in methanol solution, which is commercially available, to a final concentration of 2M. For the solvent screens we used the same strategy, which resulted in a solvent mixture consisting of the co-solvent plus residual methanol as a by-product of the dilution. None of the solvent mixtures supported conversion to FK-NH₂, even at longer reaction times (FIG. 15). This result suggested that solvent effects were critical to the reaction. Because of the reasonable effectiveness of methanol, we next focused on an additional series of alcohols. All of the alcohols supported conversion to FK-NH₂, with ethanol being slightly preferred (FIG. 15). Performing the reaction in trifluoroethanol did not lead to significant conversion, which we hypothesized could be due to the lower pK_a of the free hydroxyl compared to ethanol (12.5 versus 15.9, respectively). Consistent for the role of the hydroxyl pK_a, the reaction progressed slightly faster in methan(ol-d). From these optimization studies, we selected ethanol with 2M ammonia (75% yield) for subsequent experiments.

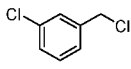
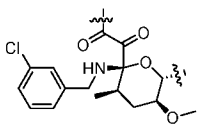
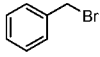
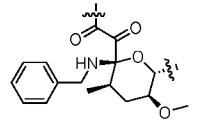
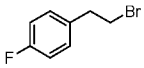
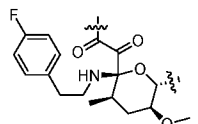
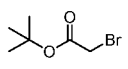
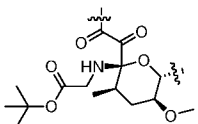
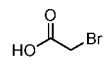
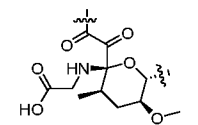
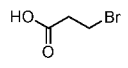
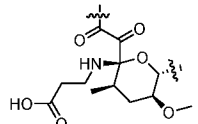
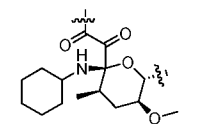
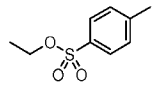
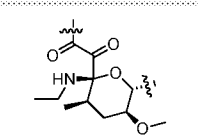
[0473] Investigating the Reactivity of amino-FK506 and amino-Rapamycin. Our first attempts at derivatization of FK-NH₂ involved a simple alkylation of the amine using 3-chlorobenzyl bromide (product **15**; FIG. 17). The yield was low, with optimization of the reaction resulting in approximately 10% product formation. In part, we chose to begin with the 3-chlorobenzyl bromide reagent. By ¹H NMR the 3-chlorobenzene ring was easily visible, as neither FK506 nor FK-NH₂

have any aromatic protons, and the chlorine isotopic signature was observed by MS. This confirmed that the desired product was formed.

[0474] To test the scope of the reaction, we performed alkylations with benzyl (compounds **16** and **17**), alkyl (compounds **21** and **22**) and carboxyl-containing groups (compounds **18-20**; Table 4.1).

Table 1. Alkylations and conditions of FK-NH2.

The pyranose fragment is shown where modification occurs. Yield is approximate as determined by product appearance in MS compared to residual starting material.

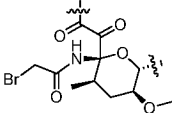
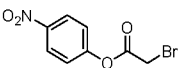
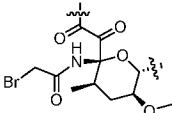
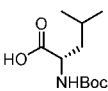
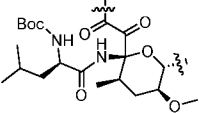
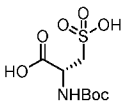
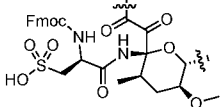
Compound ID	Reactant	Desired Product	Yield	Conditions
15			12%	a,b,h
16			10%	a,b,e,f,g
17			trace	d,e,f
18			25%	a,b,h
19			N/A	a,g
20			N/A	a
21			N/A	a,c,e,h
22			5%	a,b,d,e,f,g

^aDMF, DIEA^bDCM, DIEA, DMAP^cTHF, DIEA^dToluene, DIEA^eDMF, Pyridine^fDMF, DIEA, DMAP, 50°C^gDCM, DIEA, DMAP, 50°C^hDMF, Cs₂CO₃

[0475] Based on these results, we explored amide formation as an alternative (compounds **23-26**; Table 2). Some conversion was observed with the p-nitrophenol ester.

Table 2. Amide formations and conditions of FK-NH2.

The pyranose fragment is shown where modification occurs. Yield is approximate as determined by product appearance in MS compared to residual starting material.

Compound ID	Reactant	Desired Product	Yield	Conditions
23			N/A	a,b
24			5%	a,b,c,d,e
25			trace	d,e
26			N/A	d,e

^aDMF, DIEA, DMAP

^bDCM, DIEA, DMAP

^cDMF, Pyridine

^dDMF, DIEA, DMAP, 50°C

^eDCM, DIEA, DMAP, 50°

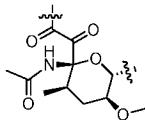
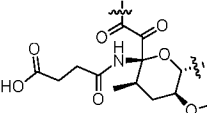
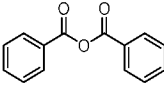
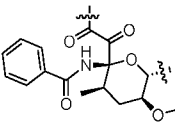
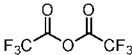
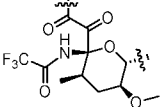
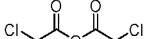
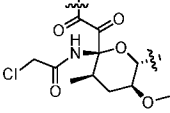
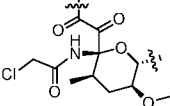
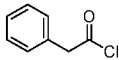
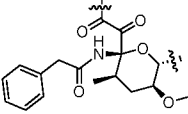
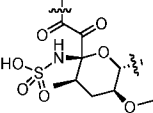
^fDMF, DIEA, HATU

[0476] Thus, we moved to progressively more reactive amide coupling conditions (Table 3). In neat acetic anhydride FK-NH2 proceeded to the desired product (**27**) in quantitative yield. Initial attempts with succinic anhydride (**28**) were frustrated by addition of multiple succinates, but optimization of reaction conditions allowed for reduction in the number of equivalents that afforded the desired compound. Similar profiles were observed with anhydride reactions yielding **29** and **31**. The one outlier was observed with trifluoroacetic anhydride (**30**). We are actively pursuing **31**, as installation of a reactive electrophile would be an additional strategy to append a variety of

substituents to the molecule to create potential Pin1 inhibitors. A small series of acid chlorides are being explored as an alternate to the anhydrides. The reaction to produce **34** was chosen in an attempt to synthesize the sulfamic acid as a direct phosphate bioisostere and proceeded in low to modest yield (~25%). Further attempts to characterize this compound are underway.

Table 3. FK-NH2 amide formation using anhydrides and acyl chlorides.

The pyranose fragment is shown where modification occurs. Yield is approximate as determined by product appearance in MS compared to residual starting material.

Compound ID	Reactant	Desired Product	Yield	Conditions
27			100%	a,e,f
28			100%	b,c,d,e,f
29			100%	b,c,e,f
30			N/A	f
31			100%	f
32			trace	f
33			N/A	d,e,f
34			25%	c,d

^aNeat^bDMF, DIEA^cDCM, DIEA^dDCM, DIEA, DMAP^eDMF, DIEA, 50°C^fDCM, DIEA, DMAP, 50°C

[0477] In summary, a series of FK-NH₂ derivatives have been prepared in modest yields. Reactions in nonpolar conditions seem to be heavily favored and the anhydrides were significantly more reactive than other approaches. This synthetic route provides an entry into FK506 analogs designed to bind Pin1.

[0478] Binding of FK506 Derivatives to FKBP12 and Pin1 by Fluorescence Polarization. To test binding to Pin1, we chose to employ a fluorescence polarization assay. This assay was based on our FP approach to measurement of binding to FKBP12. We found that a fluorescein-tagged substrate (WFYpSPFLE) bound with tight affinity to wild-type Pin1 ($K_D = 10.1 \pm 4.1$ nM, FIG. 18A), which was in good agreement with the known phosphopeptide substrates. Binding to the PPIase domain was considerably weaker ($K_D = 427 \pm 98$), as the WW domain is known to contribute to binding. Purified compounds were titrated in a competition format against static tracer and Pin1 protein. One compound appeared to be active in this format, the sulfamic acid **34**, which possessed sub-micromolar activity for the wild-type construct ($K_i^{WT} = 931$ nM, $K_i^{PPIase} = 4350$ nM, FIG. 18B). This was promising, as this compound would be most likely to engage the Pin1 cationic groove via electrostatic interactions with the charged sulfonate moiety.

[0479] Next, we tested the effects of our modification on FKBP12 binding. Based on the known FK506 binding interaction, we would expect many of these derivatives to have significantly impaired affinity for FKBP12. To test this, we used an FKBP12 binding assay to measure K_i values for the new FK506 analogs (FIG. 19). We found that small alkyl substitutions, such as in **19**, were reasonably well tolerated. Larger functional groups (such as in compounds **15** and **24**) resulted in a significant drop in affinity, as expected. Lastly, the sulfamic acid substitution in **34** had nearly a 500-fold loss of potency. This result is encouraging as it shows that Pin1 binding can be favored at the expense of FKBP12 binding.

[0480] The work disclosed herein is inspired by the natural mechanisms of FK506 and rapamycin. Despite their high molecular mass and chemical complexity, they possess excellent pharmacological

properties, specifically membrane permeability. Early studies on bifunctional molecules took advantage of this trait, and our investigation into this mechanism found that appending a PPIase ligand to HIV protease inhibitors could significantly improve its cellular partitioning. The early small molecules of Pin1 were based on the pipecolate scaffold found in FK506 and rapamycin, suggesting that the core recognition motif might be conserved. In addition, it was found that the bound conformation of pipecolate-containing Pin1 inhibitors is highly reminiscent of FK506 bound to FKBP12. Despite these similarities, FK506 has no measurable affinity for Pin1, likely because it lacks the electronegative functional group that is unique to Pin1 binding. We decided to pursue the semisynthetic modification of FK506 to impart Pin1 binding. We found that FK506 could be converted to FK-NH₂ at a region that is predicted to be in close proximity to the phosphate-binding region of the Pin1 active site. Indeed, compound **34** had affinity for Pin1 *in vitro* with FKBP12 binding considerably reduced.

[0481] One of the goals of this study was to optimize the route for creation of FK-NH₂. We found that the concentration of ammonia was critical; 1M ammonia resulted in the reaction stalling without significant conversion, while concentrations above 2M caused undesirable side-product formation. Dramatic solvent effects were also observed, with suitable conversion only occurring in alcohols. We found that FK-NH₂ would revert to FK506 during purification, so we moved to a one-pot strategy for subsequent derivatization. It was immediately apparent that the installed amine of FK-NH₂ had limited reactivity, because direct alkylation with alkyl halides or amide coupling with activated carboxylic acids or acyl chlorides was only moderately effective. However, we found that anhydrides allowed robust product formation in excellent yields (~100% in most cases). These systematic studies are expected to facilitate the creation of a larger collection of potential Pin1 inhibitors, with the next series of FK-NH₂ derivatives bearing substituents designed for Pin1 binding.

[0482] In collaboration, we are pursuing crystal structures of the free molecules as well as co-crystallized with Pin1. Pin1 has been well validated as a target in a variety of cell lines, including its impact on cell viability in numerous human cancers, so we propose to use these established models to test the cellular activity of the molecules.

[0483] Methods

[0484] Plasmid Generation and Protein Purification. Wild-type Pin1 was obtained in the pMCSG7 vector for bacterial expression and purification. The PPIase domain (45-163) of Pin1 was cloned into the pMCSG7 vector using ligation independent cloning (Fwd:

5'-TAC TTC CAA TCC AAT GCA AAA AAC GGG CAG G-3' (SEQ ID NO:1), Rev: 5'-TTA TCC ACT TCC AAT GTT ACT CAG TGC GGA GGA TGA-3' (SEQ ID NO:2)) for bacterial expression and purification.

[0485] The Pin1 constructs were transformed into E. coli BL21 cells and grown in Terrific Broth for six hours at 37 °C, followed by induction with 1 mM IPTG at 20 °C for 12 hours. Cells were collected, lysed by sonication (25 mM Tris, 500 mM NaCl, 10 mM imidazole, 10% glycerol, pH 8.0) and was bound on Ni-NTA resin. Resin was washed once with wash buffer 1 (25 mM Tris, 500 mM NaCl, 30 mM imidazole, 3% ethanol, 10% glycerol, pH 8.0), once with wash buffer 2 (25mM Tris, 100mM NaCl, 30mM imidazole, 3% ethanol, 10% glycerol, pH 8.0), once with wash buffer 3 (25mM Tris, 300mM NaCl, 30mM imidazole, 10% glycerol, pH 8.0) and eluted (25 mM Tris, 300 mM NaCl, 300 mM Imidazole, 10% glycerol, pH 8.0). Eluted protein was dialyzed overnight (10mM HEPES, 100mM NaCl, 5% glycerol, pH 7.5) and purified by Size Exclusion Chromatography using a SD75 column with the dialysis buffer.

[0486] Pin1 Fluorescence Polarization Assay. Binding to Pin1 was measured by fluorescence polarization. The assay was performed at 60 µL final volume in MOPS (pH 7.5) with 0.01% Triton X-100 using Corning 384-well flat-bottom black plates. For initial binding analysis of the fluorescent compound, recombinant Pin1 was serially diluted 3-fold from 80 µM initial concentration and then 30 µL added to each well for a top concentration of 40 µM. Fluorescent phosphopeptide WFYpSPFLE was initially dissolved in DMSO at 100 µM then dissolved into assay buffer and 30 µL of this solution was added to each well to give a final concentration of 75 nM. The plate was covered and equilibrated at room temperature for 30 minutes then read on a SpectraMax M5 at wavelength 488/515 ex/em.

[0487] Competition experiments were performed under similar conditions. Separate solutions of Pin1 and fluorescent peptide were prepared and then 15 µL of each were added to each well. The final concentrations used in the assay were 50nM and 1000nM for wild-type Pin1 and the Pin1 PPIase domain, respectively. Compounds were initially dissolved in DMSO to 10 mM, serially diluted 2-fold, then diluted to 400 µM with assay buffer and 30 µL was added to each well to a final

top concentration of 200 μ M and 2% DMSO. The assay was equilibrated at room temperature for 30 minutes and then read as before.

[0488] Synthetic Methods.

[0489] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-amino-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetrone (13)*

[0490] To a solution of FK506 (**1**) (25mg, 0.031mmol, 1eq) in 2.5mL ethanol was added 1mL 7M ammonia in methanol to a final concentration of 2M (excess). The reaction was allowed to stir for 3 hours before solvent and ammonia were removed by evaporation. The crude product was dried under high vacuum for 30 minutes to afford **13** as an oily, translucent solid (75% yield). Expected MW: 802.50, Found M+H⁺: 803.63.

[0491] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-((3-chlorobenzyl)amino)-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (15)*

[0492] To a solution of (**13**) (12.5mg, 0.016mmol, 1eq) in 2mL DCM was added DMAP (0.6mg, 0.005mmol, 0.3eq) and allowed to stir under N₂. 3-chlorobenzyl bromide (9.9mg, 0.048mmol, 3eq) was added dropwise followed by the addition of DIEA (12.4mg, 0.096mmol, 6eq). After 24 hours, the solvent was removed by evaporation and the crude product dissolved in 1mL methanol and purified by HPLC (25% yield). Expected MW: 926.51, Found M+ACN⁺: 968.93.

[0493] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-benzylamino-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (16)*

[0494] To a solution of (**13**) (20mg, 0.025mmol, 1eq) in 2mL DMF was added DMAP (1.0mg, 0.008mmol, 0.3eq) and allowed to stir under N₂. Benzyl bromide (42.8mg, 0.25mmol, 10eq) was added dropwise followed by the addition of DIEA (64.8mg, 0.5mmol, 20eq). The reaction

temperature was raised to 50°C. After 24 hours, the crude product was purified by HPLC (10% yield). Expected MW: 892.54, Found M+H⁺: 893.62.

[0495] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-((2-(tert-butoxy)-2-oxoethyl)amino)-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (18)*

[0496] To a solution of **(13)** (25mg, 0.031mmol, 1eq) in 2mL DCM was added DMAP (1.2mg, 0.010mmol, 0.3eq) and allowed to stir under N₂. Tert-Butyl bromoacetate (18.1mg, 0.093mmol, 3eq) was added dropwise followed by the addition of DIEA (24.1mg, 0.186mmol, 6eq). After 24 hours, the solvent was removed by evaporation and the crude product dissolved in 1mL methanol and purified by HPLC (25% yield). Expected MW: 916.57, Found M+ACN⁺: 959.01.

[0497] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-((carboxymethyl)amino)-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (19)*

[0498] The protected derivative **(18)** (5mg, 0.005mmol, 1eq) was dissolved in a solution of DCM:TFA:TIPS:H₂O (45:45:5:5) and stirred for 30 minutes. TIPS was included as a cation scavenger. Solvent was evaporated and the crude product was purified by HPLC (5% yield). Expected MW: 860.50, Found M+H⁺: 861.04.

[0499] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-23,25-dimethoxy-1-ethylamino-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (22)*

[0500] To a solution of **(13)** (25mg, 0.031mmol, 1eq) in 2mL DMF was added DMAP (1.2mg, 0.010mmol, 0.3eq) and allowed to stir under N₂. Ethyl p-toluenesulfonate (124.2mg, 0.62mmol, 20eq) was added dropwise followed by the addition of DIEA (160.6mg, 1.24mmol, 40eq). The reaction temperature was raised to 50°C. After 24 hours, the crude product was purified by HPLC (5% yield). Expected MW: 830.53, Found M+Na⁺: 853.58.

[0501] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-(2-bromoacetamido)-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (24)*

[0502] To a solution of **(13)** (12.5mg, 0.016mmol, 1eq) in 2mL DMF was added DMAP (0.6mg, 0.005mmol, 0.3eq) and allowed to stir under N₂. 4-Nitrophenyl bromoacetate (4.2mg, 0.016mmol, 1eq) was added dropwise followed by the addition of DIEA (6.2mg, 0.048mmol, 3eq). The reaction temperature was raised to 50°C. After 24 hours, the crude product was purified by HPLC (5% yield). Expected MW: 924.42, Found M+ACN⁺: 966.99.

[0503] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-acetamido-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (27)*

[0504] To **(13)** (12.5mg, 0.016mmol, 1eq) was added 1mL neat acetic anhydride and stirred under N₂. After 3 hours, the reaction was diluted with toluene and solvent was evaporated. This was repeated in total 3 times to remove as much unreacted acetic anhydride as possible. The crude product was dissolved in methanol and purified by HPLC (42% yield). Expected MW: 844.51, Found M+Na⁺: 867.58.

[0505] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-1-benzamido-23,25-dimethoxy-14-hydroxy-13,19,21,27-tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxo-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (29)*

[0506] To a solution of **(13)** (12.5mg, 0.016mmol, 1eq) in 2mL DCM was added DMAP (0.6mg, 0.005mmol, 0.3eq) and allowed to stir under N₂. Benzoic anhydride (18.1mg, 0.08mmol, 5eq) was added dropwise followed by the addition of DIEA (20.7mg, 0.16mmol, 10eq). After 24 hours, the solvent was removed, crude product was dissolved in 1mL methanol and purified by HPLC (10% yield). Expected MW: 924.42, Found M+ACN⁺: 966.99.

[0507] *(1R,9S,12S,13R,14S,17R,18E,21S,23S,24R,25S,27R)-12-[(1E)-1-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]prop-1-en-2-yl]-23,25-dimethoxy-14-hydroxy-1-sulfoamino-13,19,21,27-*

tetramethyl-17-(prop-2-en-1-yl)-11,28-dioxa-4-azatricyclo[22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetrone (34)

[0508] To a solution of **(13)** (12.5mg, 0.016mmol, 1eq) in 2mL DCM was added DMAP (0.6mg, 0.005mmol, 0.3eq) and allowed to stir under N₂. Chlorosulfonic acid (2.8mg, 0.024mmol, 1.5eq) was added dropwise followed by the addition of DIEA (20.7mg, 0.16mmol, 10eq). After 24 hours, the reaction had gone cloudy and solvent was removed. The crude product was dissolved in 1mL methanol and purified by HPLC (25% yield). Expected MW: 882.45, Found M-H⁺: 881.87.

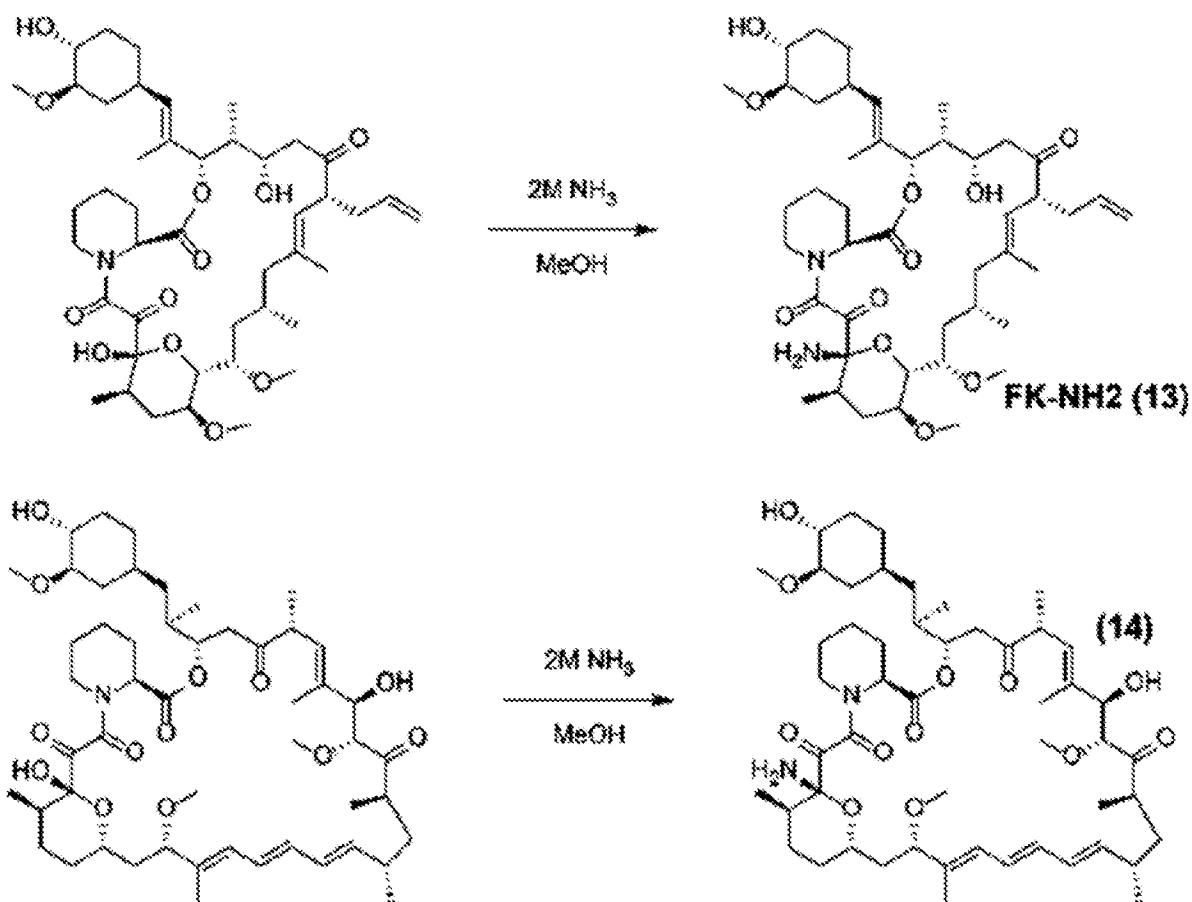
[0509] References

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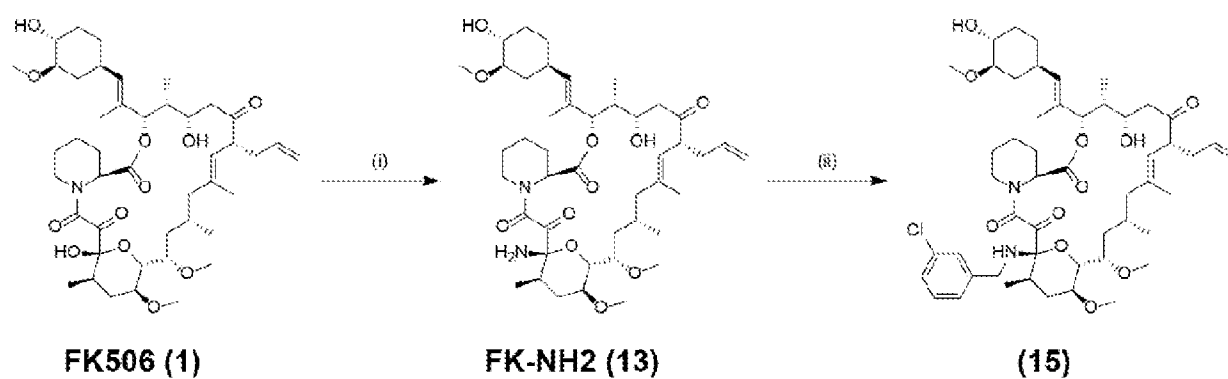
[0511] *Example 2 - Modification of FK506/Rapamycin Natural Products.*

[0512] Synthetic schemes for FK-NH₂ (13) and compound (14) follow:



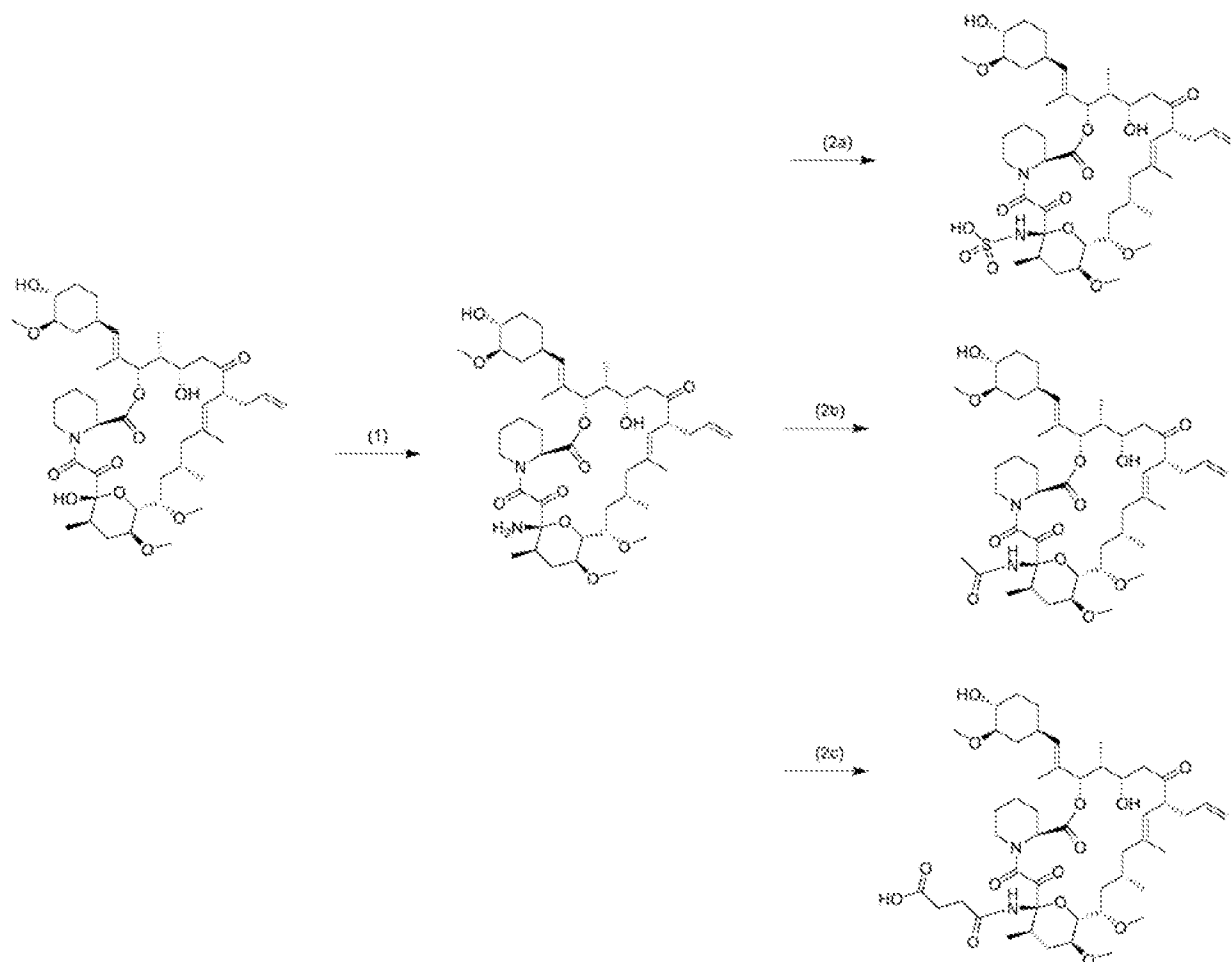
[0513] *Example 3 – General Synthetic Scheme.*

[0514] A general synthetic scheme for compounds FK-NH₂ (13) and (15) follows:



[0515] *Example 4 - Representative Synthetic Scheme*

[0516] A representative synthetic scheme for compounds disclosed herein follows.



[0517] 1) To a solution of FK506/rapamycin (25mg, 0.031 mmol, 1eq) is added ethanol (2.14 mL) and 7M ammonia in methanol 0.857 to a final concentration of 2M ammonia. The solution is stirred for 3hrs and the solvent is removed by evaporation.

[0518] 2) Generally, the crude product from (1) (25mg, 0.031mmol, 1eq) was carried forward and dissolved in 3mL dichloromethane followed by addition of dimethylaminopyridine (0.4mg, 0.003mmol, 0.1eq) and diisopropylethylamine (12mg, 0.093mmol, 3eq). The reactant (a, b, c, or d) was added and the reaction was stirred overnight. After completion, solvent was evaporated and the product was purified by HPLC. Legend: a) Chlorosulfonic acid; b) Acetic anhydride; c) Succinic anhydride; d) Any suitable anhydride, acyl halide, alkyl halide, alkyl tosylate, alkyl triflate

[0519] References.

[0520] [1]. Skytte, D.M., Frydenvang, K., Hansen, L., Nielsen, P.G. & Jaroszewski, J.W. Synthesis and characterization of an epimer of tacrolimus, an immunosuppressive drug. *Journal of natural products* 73, 776-779 (2010); [2]. Marinec, P.S., et al. Synthesis of orthogonally reactive FK506 derivatives via olefin cross metathesis. *Bioorganic & medicinal chemistry* 17, 5763-5768 (2009); [3]. Guo, Z.-F., Zhang, R. & Liang, F.-S. Facile functionalization of FK506 for biological studies by the thiol-ene 'click' reaction. *RSC Advances* 4, 11400-11403 (2014); [4]. Bayle, J.H., et al. Rapamycin analogs with differential binding specificity permit orthogonal control of protein activity. *Chemistry & biology* 13, 99-107 (2006); [5]. Ruan, B., et al. Binding of rapamycin analogs to calcium channels and FKBP52 contributes to their neuroprotective activities. *Proceedings of the National Academy of Sciences of the United States of America* 105, 33-38 (2008); [6]. Sedrani, R., Thai, B., France, J. & Cottens, S. Dihydroxylation of the Triene Subunit of Rapamycin. *The Journal of Organic Chemistry* 63, 10069-10073 (1998); [7]. Karanam, B.V., et al. Disposition of L-732,531, a potent immunosuppressant, in rats and baboons. *Drug metabolism and disposition: the biological fate of chemicals* 26, 949-957 (1998); [8]. Zimmer, R., et al. Synthetic Modifications of Ascomycin. V.* Access to Novel Ascomycin Derivatives by Replacement of the Cyclohexylvinylidene Subunit. *Croat. Chem. Acta* 78, 17-27 (2005); [9]. Gupta, A.K. & Chow, M. Pimecrolimus: a review. *Journal of the European Academy of Dermatology and Venereology : JEADV* 17, 493-503 (2003); [10]. Faivre, S., Kroemer, G. & Raymond, E. Current development of mTOR inhibitors as anticancer agents. *Nature reviews. Drug discovery* 5, 671-688 (2006); [11]. Sedrani, R., Cottens, S., Kallen, J. & Schuler, W. Chemical modification of rapamycin: the discovery of SDZ RAD. *Transplantation proceedings* 30, 2192-2194 (1998); [12]. Rivera, V.M., et al. Ridaforolimus (AP23573; MK-8669), a potent mTOR inhibitor, has broad antitumor activity and can be optimally administered using intermittent dosing regimens. *Molecular cancer therapeutics* 10, 1059-1071 (2011).

[0521] *Example 5 - Binding of a Modified FK506 Derivative to Pin1.*

[0522] FK-NH₂ substituted with chlorosulfonic acid to generate a sulfamic containing derivative (reaction 2a of Example above) binds to the peptidyl-prolyl isomerase Pin1. Pin1 binds to a fluorescent peptide which is then competed away by compound 2a. See FIG.18B. Unmodified FK506 has no affinity for Pin1 and is not capable of inhibiting the binding interaction with the

fluorescent peptide. Compound 2a is capable of competing the fluorescent peptide away from the wild type protein as well as just the isolated peptidyl-prolyl isomerase domain.

[0523] For wild type shown in FIG. 18B, IC_{50} and Span are 7.065 and 104.0, respectively. For PPIase domain, IC_{50} and Span are 15.25 and 47.49, respectively.

[0524] *Example 6 -- Binding of a Modified FK506 Derivative to FKBP12.*

[0525] The parent compound, FK506 binds to its native target FKBP12 with high affinity. Modification of FK506 to FK-NH₂, followed by substitution with chlorosulfonic acid to generate a sulfamic containing derivative (reaction 2a above) has significantly weaker binding to FKBP12. See FIG. 21. Similar to the Pin1 binding assay, the peptidyl-prolyl isomerase FKBP12 binds to a fluorescent ligand which is then competed away by FK506 and only weakly competed by the modified compound 2a. This suggests that compound 2a may be selective for Pin1 over the original target, FKBP12.

EMBODIMENTS

Embodiment 1. A peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound, or a pharmaceutically acceptable salt thereof, comprising a macrolide with a pipecolyl moiety.

Embodiment 2. The compound of embodiment 1, wherein the compound is an FK506 compound, or a derivative thereof, covalently bound to a nitrogen-containing functional group at the C-10 position.

Embodiment 3. The compound of embodiment 2, wherein the nitrogen-containing functional group is an amino group.

Embodiment 4. The compound of embodiment 2, wherein the nitrogen-containing functional group is a primary amino group.

Embodiment 5. The compound of embodiment 2, wherein the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

Embodiment 6. The compound of embodiment 1, wherein the compound is an FK506 compound, or a derivative thereof, comprising an electronegative group at the C-10 position.

Embodiment 7. The compound of embodiment 1, wherein the compound is an FK506 compound, or a derivative thereof, comprising an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position.

Embodiment 8. The compound of embodiment 7, wherein the linker is covalently bound to an electronegative group.

Embodiment 9. The compound of embodiment 5, 6 or 8, wherein the electronegative group is a phosphate isostere.

Embodiment 10. The compound of embodiment 5, 6, 8 or 9, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

Embodiment 11. The compound of any one of embodiments 1-10, wherein the FK-506 compound is an ascomycin derivative or variant.

Embodiment 12. The compound of embodiment 1, wherein the compound is a rapamycin compound, or a derivative thereof, comprising a nitrogen-containing functional group at the C-10 position.

Embodiment 13. The compound of embodiment 12, wherein the nitrogen-containing functional group is an amino group.

Embodiment 14. The compound of embodiment 12, wherein the nitrogen-containing functional group is a primary amino group.

Embodiment 15. The compound of embodiment 12, wherein the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

Embodiment 16. The compound of embodiment 1, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an electronegative group at the C-10 position.

Embodiment 17. The compound of embodiment 1, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position.

Embodiment 18. The compound of embodiment 17, wherein the linker is covalently bound to an electronegative group.

Embodiment 19. The compound of embodiment 15, 16 or 18, wherein the electronegative group is a phosphate isostere.

Embodiment 20. The compound of embodiment 15, 16, 18 or 19, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

Embodiment 21. An FK506 binding protein (FKBP) inhibitor compound, or a pharmaceutically acceptable salt thereof, comprising a macrolide with a piperidyl moiety.

Embodiment 22. The compound of embodiment 21, wherein the compound is a rapamycin compound, or a derivative thereof, comprising a nitrogen-containing functional group at the C-10 position.

Embodiment 23. The compound of embodiment 22, wherein the nitrogen-containing functional group is an amino group.

Embodiment 24. The compound of embodiment 22, wherein the nitrogen-containing functional group is a primary amino group.

Embodiment 25. The compound of embodiment 22, wherein the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

Embodiment 26. The compound of embodiment 21, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an electronegative group at the C-10 position.

Embodiment 27. The compound of embodiment 21, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position.

Embodiment 28. The compound of embodiment 27, wherein the linker is covalently bound to an electronegative group.

Embodiment 29. The compound of embodiment 25, 26 or 28, wherein the electronegative group is a phosphate isostere.

Embodiment 30. The compound of embodiment 25, 26, 28 or 29, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

Embodiment 31. A macrolide compound covalently attached to an electronegative group at a position equivalent to C-10 of FK506 or a pharmaceutically acceptable salt thereof.

Embodiment 32. The compound of embodiment 31, wherein the macrolide compound is an FK506 compound derivative, a rapamycin compound derivative or an ascomycin compound derivative.

Embodiment 33. The compound of embodiment 31, wherein the macrolide compound is capable of inhibiting a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) protein.

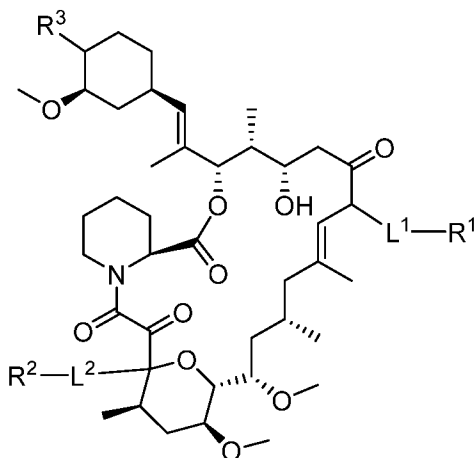
Embodiment 34. The compound of embodiment 31, wherein the macrolide compound is capable of inhibiting an FK506 binding protein.

Embodiment 35. The compound of any one of embodiments 31-34, wherein the electronegative group is a phosphate isostere.

Embodiment 36. The compound of any one of embodiments 31-34, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a

sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

Embodiment 37. A compound of structural Formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein:

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

m_1 , m_2 , m_3 , v_1 , v_2 and v_3 are independently 1 or 2;

L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

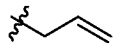
L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1B}R^{1C}$, $-NHNr^{1B}R^{1C}$, $-ONR^{1B}R^{1C}$, $-NHC(O)NHNr^{1B}R^{1C}$, $-NHC(O)NR^{1B}R^{1C}$, $-N(O)_{m1}$, $-NR^{1B}R^{1C}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1B}R^{1C}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, 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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, 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;

L^{1L} , L^{2L} , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} and R^{3D} , are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, $-COOH$, $-CONH_2$, 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^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and

$X^{1.1}$, $X^{2.1}$ and $X^{3.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$, wherein when L^2 is $-O-$, L^1 is a bond, R^1 is  or $-CH_2CH_3$ and R^3 is hydroxyl, then R^2 is not hydrogen.

Embodiment 38. The compound of embodiment 37, wherein:

L^2 is a bond; and

R^2 is NH_2 .

Embodiment 39. The compound of embodiment 37, wherein L^2 is $-NR^{2L}$.

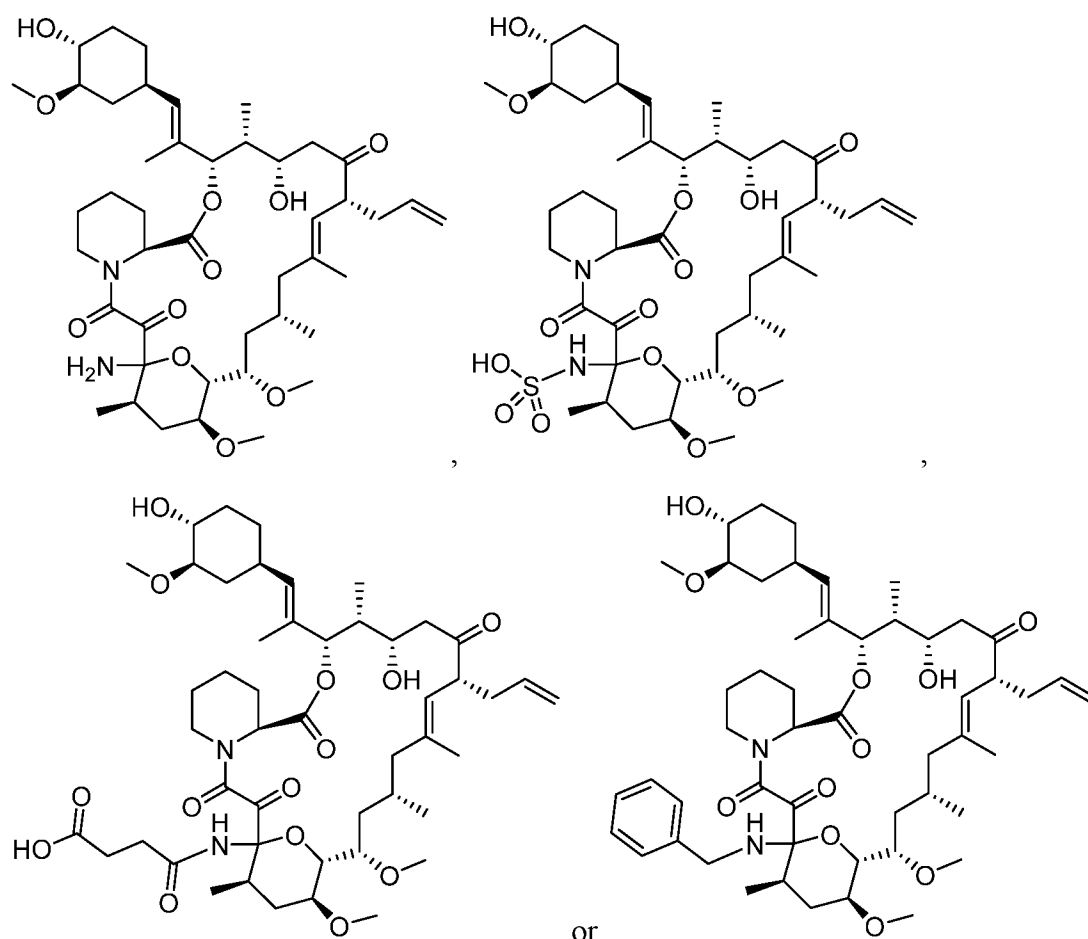
Embodiment 40. The compound of embodiment 37, wherein L^2 is $-NR^{2L}C(O)-$, alkylene or heteroalkylene.

Embodiment 41. The compound of any one of embodiments 39, 40 or 41, wherein R^2 is a phosphate isostere.

Embodiment 42. The compound of any one of embodiments 39, 40 or 41, wherein R^2 is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

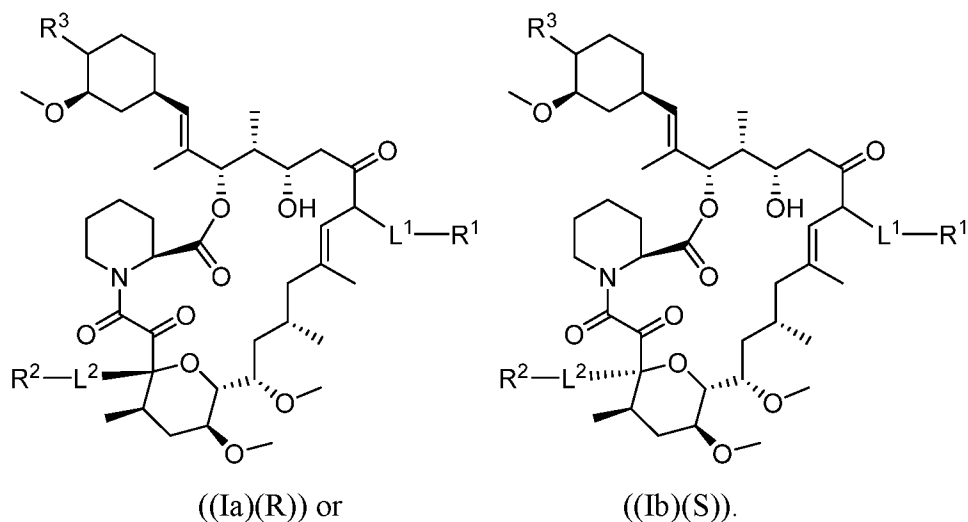
Embodiment 43. The compound of any one of embodiments 37-42, wherein:
 L^1 is a bond; and
 R^1 is (R)-ethyl.

Embodiment 44. The compound of embodiment 37, wherein the compound is

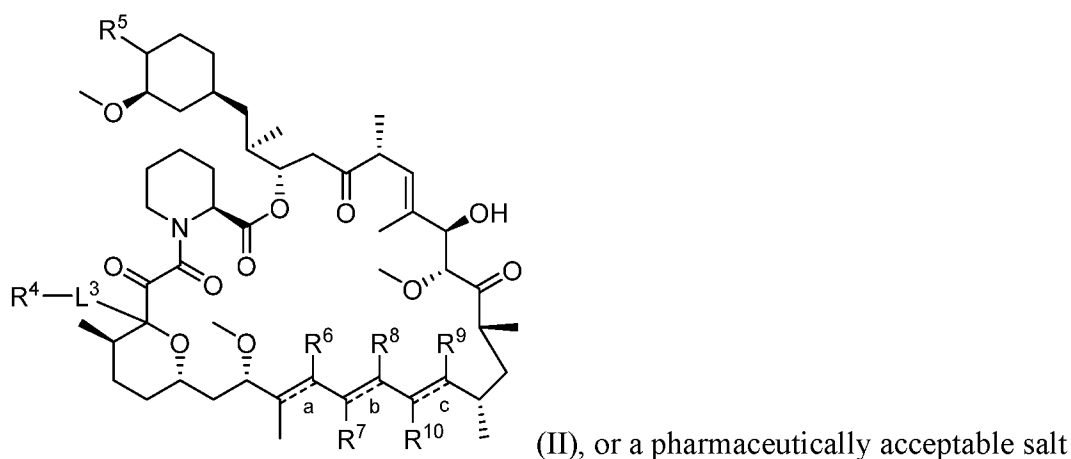


Embodiment 45. The compound of embodiment 37, wherein the compound

is



Embodiment 46. A compound of structural Formula (II):



thereof, wherein:

$\text{--}\underline{\underline{a}}\text{--}$, $\text{--}\underline{\underline{b}}\text{--}$ and $\text{--}\underline{\underline{c}}\text{--}$ are independently single bonds or double bonds;

n₄, n₅, n₆, n₇, n₈, n₉ and n₁₀ are independently an integer from 0 to 4;

m₄, m₅, m₆, m₇, m₈, m₉, m₁₀, v₄, v₅, v₆, v₇, v₈, v₉ and v₁₀ are independently 1 or 2;

L³ is a bond, --O-- , --S-- , $\text{--NR}^{3\text{L}}\text{--}$, $\text{--NR}^{3\text{L}}\text{C(O)--}$, --C(O)-- , --C(O)O-- , --S(O)-- , $\text{--S(O)}_2\text{--}$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene,

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

R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-SO_{n5}H$, $-SO_{v5}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m5}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, 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^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-SO_{n6}H$, $-SO_{v6}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m6}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, 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^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, $-CN$, $-SO_{n7}H$, $-SO_{v7}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m7}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$, 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^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, $-CN$, $-SO_{n8}H$, $-SO_{v8}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m8}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, 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^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, $-CN$, $-SO_{n9}H$, $-SO_{v9}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m9}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, 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^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, $-CN$, $-SO_{n10}H$, $-SO_{v10}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m10}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, 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^{3L} , R^{4A} , R^{4B} , R^{4C} and R^{4D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and

$X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$, wherein when $\text{--}\overset{\text{a}}{\text{C}}\text{--}$, $\text{--}\overset{\text{b}}{\text{C}}\text{--}$ and $\text{--}\overset{\text{c}}{\text{C}}\text{--}$ are double bonds, L^3 is $-O-$ and R^6 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, then R^4 is not hydrogen.

Embodiment 47. The compound of embodiment 46, wherein L^3 is $-NR^{3L}$ or a bond.

Embodiment 48. The compound of embodiment 46, wherein L^3 is $-NR^{3L}C(O)-$, alkylene or heteroalkylene.

Embodiment 49. The compound of any one of embodiments 46, 47 or 48, wherein R^4 is a phosphate isostere.

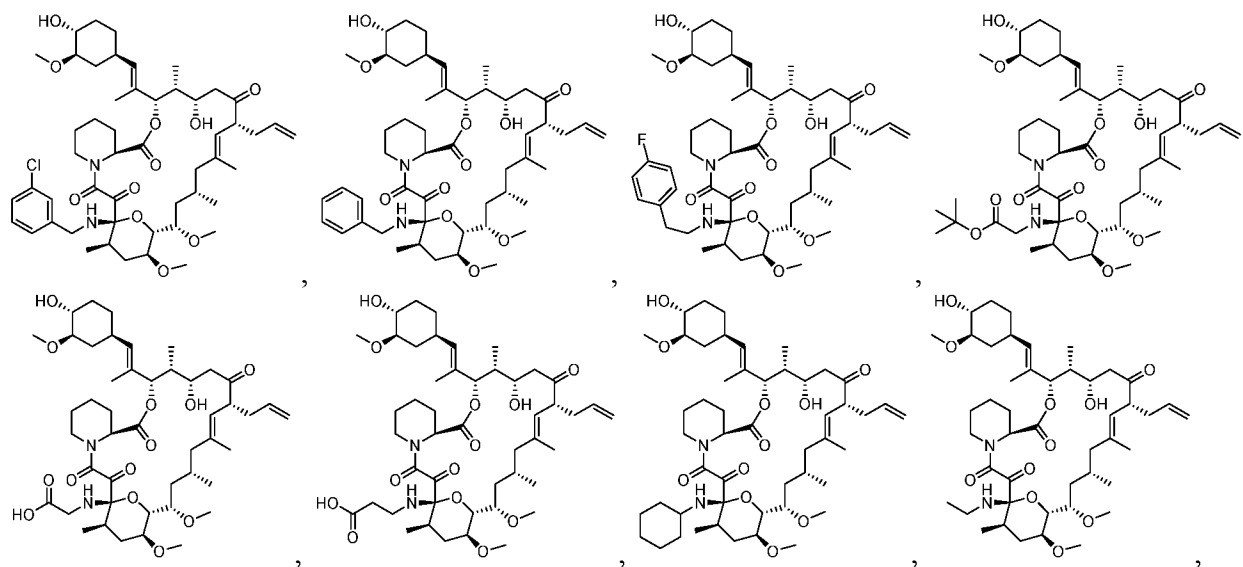
Embodiment 50. The compound of any one of embodiments 46, 47 or 48, wherein R^4 is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

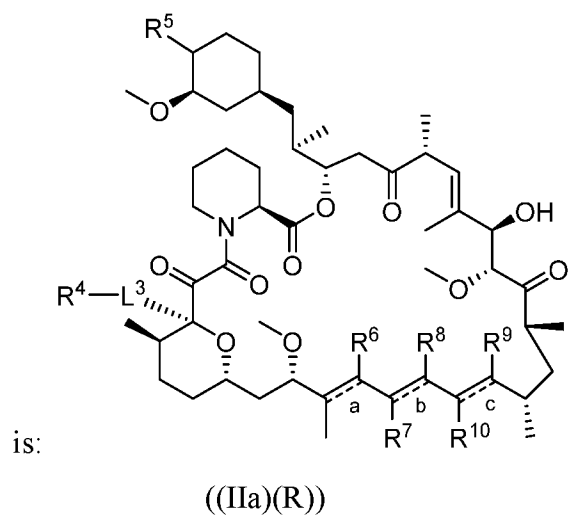
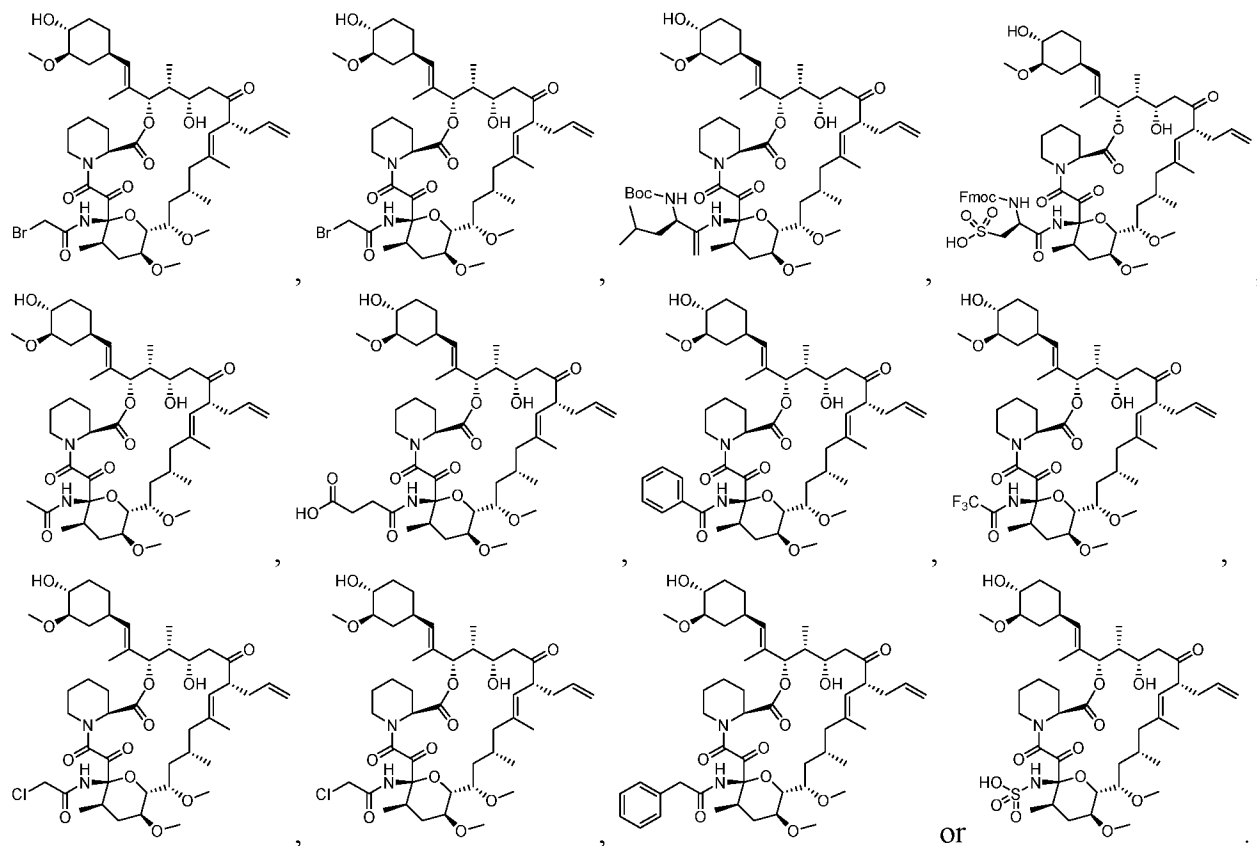
Embodiment 51. The compound of any one of embodiment 46, 47 or 48, wherein R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

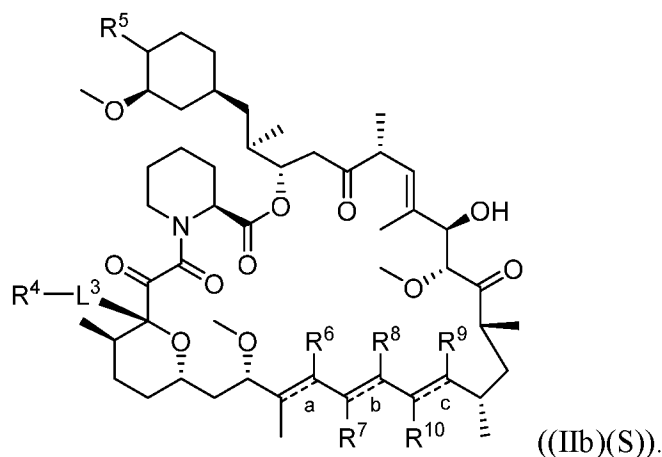
Embodiment 52. The compound of embodiment 46, wherein L^3 is substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

Embodiment 53. The compound of embodiment 46 or 52, wherein the R^4 is substituted or unsubstituted aryl.

Embodiment 54. The compound of embodiment P46***, wherein the compound is







Embodiment 56. A pharmaceutical composition, comprising a compound of any one of claims 1 to 55 and a pharmaceutically acceptable excipient.

Embodiment 57. A method of inhibiting Pin 1, comprising contacting Pin 1 with a compound of any one of embodiments 1-20, 31-33 or 35-55.

Embodiment 58. A method of inhibiting an FK506 binding protein (FKBP), comprising contacting the FKBP with a compound of any one of embodiments 20-32, 34-36 or 46-55.

Embodiment 59. The method of embodiment 58, wherein the FKBP is FKBP38, FKBP51 or FKBP52.

Embodiment 60. The method of embodiment 58, wherein the FKBP is FKBP51.

Embodiment 61. A method of treating a Pin 1-mediated disease or disorder, comprising administering to a patient in need thereof a compound of one of embodiments 1-20, 31-33 or 35-55

Embodiment P62. The method of embodiment 61, wherein the Pin 1-mediated disease or disorder is cancer.

Embodiment 63. The method of embodiment 62, wherein the cancer is prostate cancer, brain cancer, breast cancer, ovarian cancer cervical cancer or skin cancer.

Embodiment 64. The method of embodiment 62 or 63, further comprising administering to the subject a chemotherapeutic agent.

Embodiment 65. A method of treating an FKBP51-mediated disease or disorder, comprising administering to a patient in need thereof a compound of any one of embodiments 20-32, 34-36 or 46-55.

Embodiment 66. The method of embodiment 65, wherein the disease or disorder is depression or mental illness.

Embodiment 67. The method of embodiment 66, wherein the disease or disorder is depression.

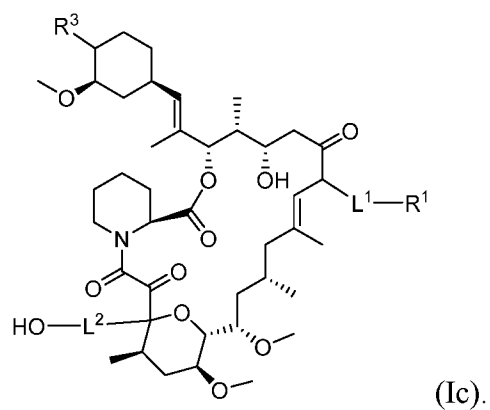
Embodiment 68. The method of embodiment 67, further comprising administering to the subject an anti-depressant.

Embodiment 69. The method of embodiment 66, wherein the mental illness is schizophrenia.

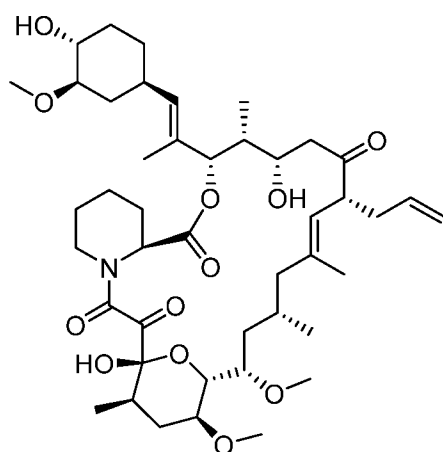
Embodiment 70. The method of embodiment 66, wherein the disease or disorder is pain.

Embodiment 71. The method of embodiment 70, wherein the pain is chronic pain or neuropathic pain.

Embodiment 72. A method of preparing a compound of structural Formula (I) of embodiment 37, comprising contacting a compound of structural Formula (Ic) with ammonia:

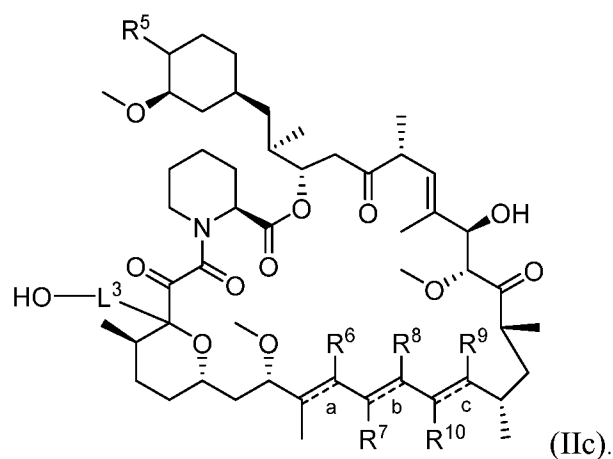


Embodiment 73. The method of embodiment 72, wherein the compound of

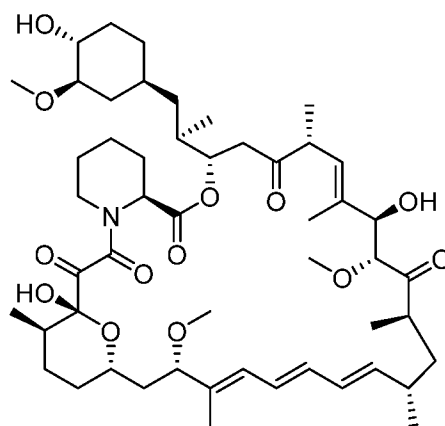


Formula (Ic) is

Embodiment 74. A method of preparing a compound of structural Formula (II) of embodiment 46, comprising contacting a compound of structural Formula (IIc) with ammonia:



Embodiment 75. The method of embodiment 74, wherein the compound of Formula (IIc) is



FURTHER EMBODIMENTS

N1. A peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound, comprising a macrolide with a pipicolyl moiety, or a pharmaceutically acceptable salt thereof.

N2. The compound of embodiment N1, wherein the compound is an FK506 derivative, comprising a substituted or unsubstituted amino at the C10 position in place of the –OH present in FK506.

N3. The compound of embodiment N2, wherein the amino is unsubstituted.

N4. The compound of embodiment N2, wherein the amino is mono-substituted.

N5. The compound of embodiment N2, wherein the substituted or unsubstituted amino is an electronegative moiety.

N6. The compound of embodiment N1, wherein the compound is an FK506 derivative comprising an electronegative moiety in place of the –OH of FK506 at the C-10 position.

N7. The compound of embodiment N1, wherein the compound is an FK506 derivative comprising a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl in place of the –OH of FK506 at the C-10 position.

N8. The compound of embodiment N7, wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is substituted with an electronegative moiety.

N9. The compound of embodiment N5, wherein the electronegative moiety is a phosphate isostere moiety.

N10. The compound of embodiment N5, wherein the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

N11. The compound of embodiment N2, wherein the FK506 derivative is an ascomycin derivative.

N12. The compound of embodiment N1, wherein the compound is a rapamycin derivative, comprising a substituted or unsubstituted amino at the C10 position in place of the –OH present in rapamycin.

N13. The compound of embodiment N12, wherein the amino is unsubstituted.

N14. The compound of embodiment N12, wherein the amino is mono-substituted.

N15. The compound of embodiment N12, wherein the substituted or unsubstituted amino is an electronegative moiety.

N16. The compound of embodiment N1, wherein the compound is a rapamycin comprising an electronegative moiety in place of the –OH of rapamycin at the C-10 position.

N17. The compound of embodiment N1, wherein the compound is a rapamycin derivative comprising a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl in place of the –OH of rapamycin at the C-10 position

N18. The compound of embodiment N17, wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is substituted with an electronegative moiety.

N19. The compound of embodiment N15, wherein the electronegative moiety is a phosphate isostere moiety.

N20. The compound of embodiment N15, wherein the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

N21. An FK506 binding protein (FKBP) inhibitor compound, comprising a macrolide with a piperidyl moiety, or a pharmaceutically acceptable salt thereof.

N22. The compound of embodiment N21, wherein the compound is a rapamycin derivative, comprising a substituted or unsubstituted amino at the C10 position in place of the –OH present in rapamycin.

N23. The compound of embodiment N22, wherein the amino is unsubstituted.

N24. The compound of embodiment N22, wherein the amino is mono-substituted.

N25. The compound of embodiment N22, wherein the substituted or unsubstituted amino is an electronegative moiety.

N26. The compound of embodiment N21, wherein the compound is a rapamycin comprising an electronegative moiety in place of the –OH of rapamycin at the C-10 position.

N27. The compound of embodiment N21, wherein the compound is a rapamycin derivative comprising a substituted or unsubstituted alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl in place of the –OH of rapamycin at the C-10 position.

N28. The compound of embodiment N27, wherein the alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl is substituted with an electronegative moiety.

N29. The compound of embodiment N25, wherein the electronegative moiety is a phosphate isostere moiety.

N30. The compound of embodiment N25, wherein the electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

N31. A macrolide comprising an electronegative moiety at a position equivalent to C10 of FK506 or a pharmaceutically acceptable salt thereof.

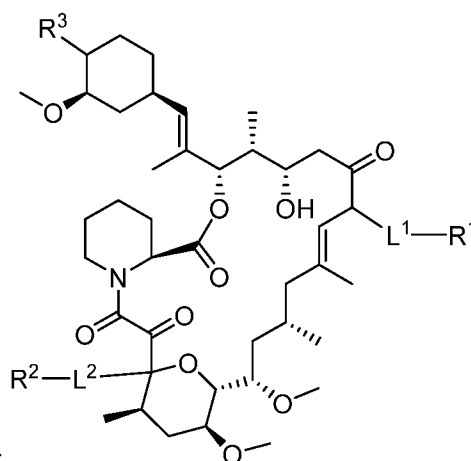
N32. The compound of embodiment N31, wherein the macrolide is an FK506 derivative, a rapamycin derivative or an ascomycin derivative.

N33. The compound of embodiment N31, wherein the macrolide is capable of inhibiting a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) protein.

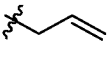
N34. The compound of embodiment N31, wherein the macrolide is capable of inhibiting an FK506 binding protein.

N35. The compound of embodiment N31, wherein the electronegative moiety is a phosphate isostere moiety.

N36. The compound of embodiment N31, electronegative moiety is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.



N37. A compound of structural Formula (I): (I), or a pharmaceutically acceptable salt thereof, wherein: n₁, n₂ and n₃ are independently an integer from 0 to 4; m₁, m₂, m₃, v₁, v₂ and v₃ are independently 1 or 2; L¹ is a bond, -O-, -S-, -NR^{1L}-, -NR^{1L}C(O)-, -C(O)-, -C(O)O-, -S(O)-, -S(O)₂-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; L² is a bond, -O-, -S-, -NR^{2L}-, -NR^{2L}C(O)-, -C(O)-, -C(O)O-, -S(O)-, -S(O)₂-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R¹ is hydrogen, halogen, -CX^{1.1}₃, -CHX^{1.1}₂, -CH₂X^{1.1}, -CN, -SO_{n1}R^{1A}, -SO_{v1}NR^{1B}R^{1C}, -NHN^{1B}R^{1C}, -ONR^{1B}R^{1C}, -NHC(O)NHN^{1B}R^{1C}, -NHC(O)NR^{1B}R^{1C}, -N(O)_{m1}, -NR^{1B}R^{1C}, -C(O)R^{1D}, -C(O)OR^{1D}, -C(O)NR^{1B}R^{1C}, -OR^{1A}, -NR^{1B}SO₂R^{1A}, -NR^{1B}C(O)R^{1D}, -NR^{1B}C(O)OR^{1D}, -NR^{1B}OR^{1D}, -OCX^{1.1}₃, -OCHX^{1.1}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^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2B}R^{2C}$, $-NHN R^{2B}R^{2C}$, $-ONR^{2B}R^{2C}$, $-NHC(O)NHN R^{2B}R^{2C}$, $-NHC(O)NR^{2B}R^{2C}$, $-N(O)_{m2}$, $-NR^{2B}R^{2C}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2B}R^{2C}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-SO_{n3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, 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^{1L} , R^{2L} , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} and R^{3D} , are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $X^{1.1}$, $X^{2.1}$ and $X^{3.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$; when L^2 is $-O-$, L^1 is a bond, R^1 is  or $-CH_2CH_3$ and R^3 is hydroxyl, then R^2 is not hydrogen.

N38. The compound of embodiment N37, wherein: L^2 is a bond; and R^2 is $-NH_2$.

N39. The compound of embodiment N37, wherein L^2 is $-NR^{2L}-$.

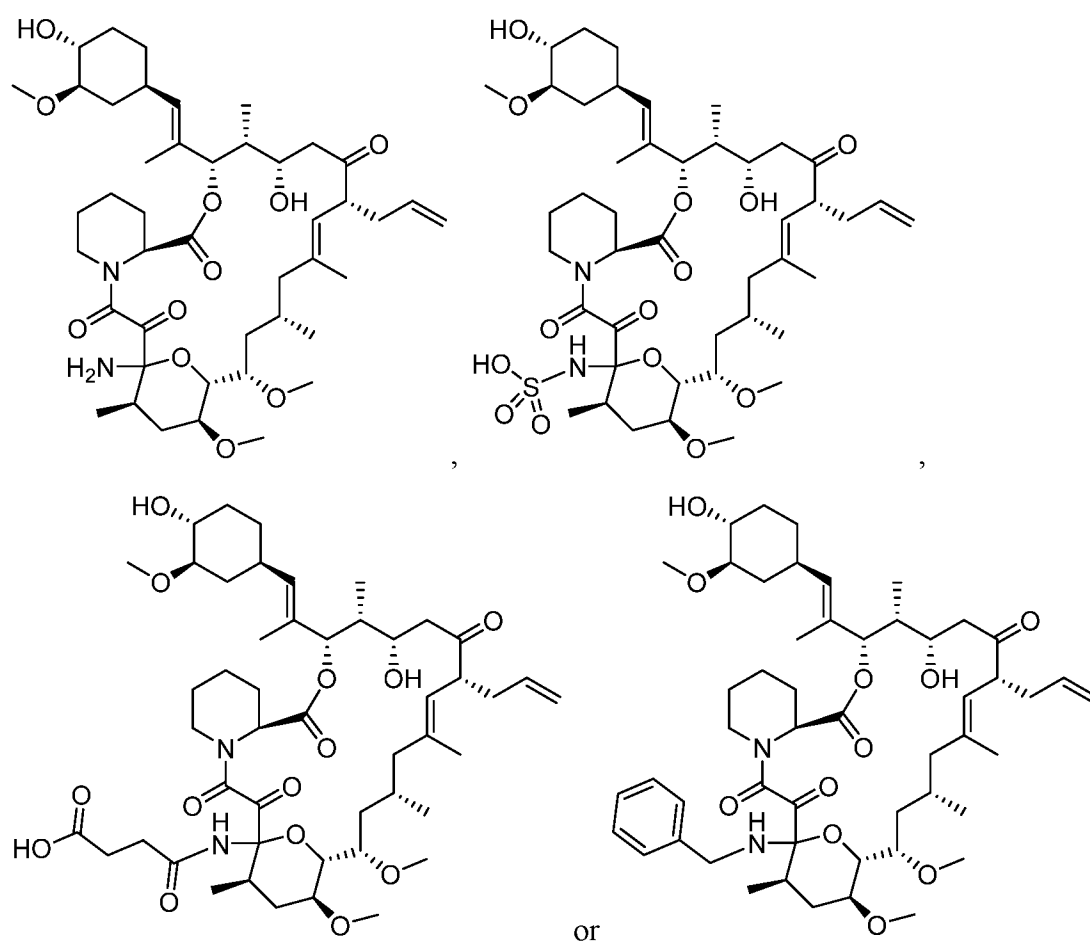
N40. The compound of embodiment N37, wherein L^2 is $-NR^{2L}C(O)-$, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

N41. The compound of embodiment N39, wherein R^2 is a phosphate isostere moiety.

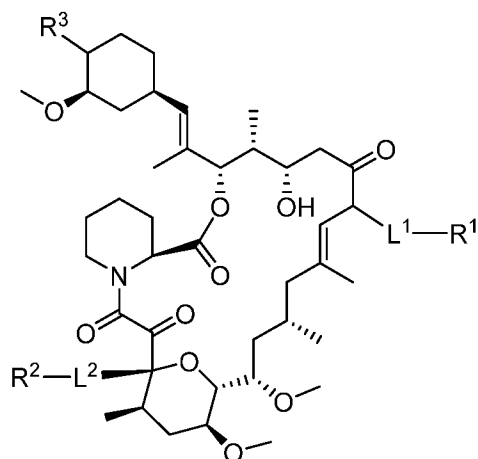
N42. The compound of embodiment N39, wherein R^2 is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

N43. The compound of embodiment N37, wherein: L^1 is a bond; and R^1 is (R)-ethyl.

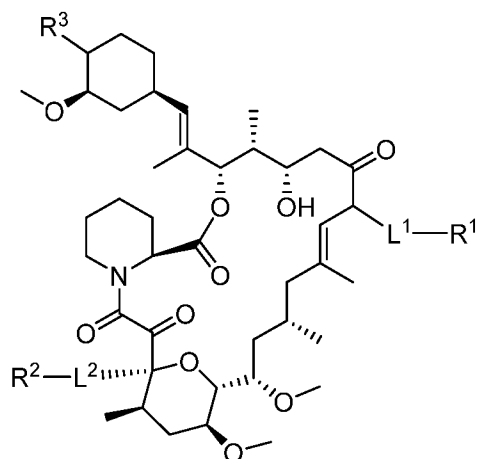
N44. The compound of embodiment N37, wherein the compound is



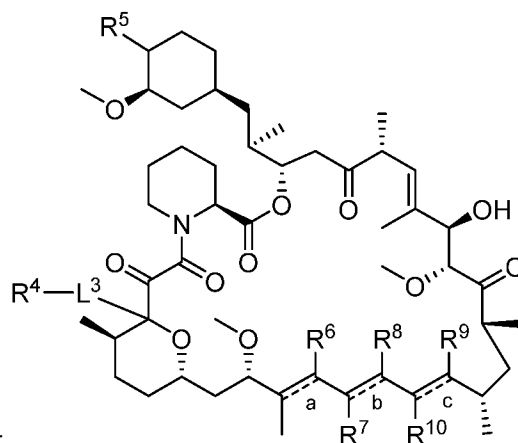
N45. The compound of embodiment N37, wherein the compound is:



((Ia)(R)) or



((Ib)(S)).



N46. A compound of structural Formula (II):

(II), or a pharmaceutically acceptable salt thereof, wherein: $\frac{-a-}{-}$, $\frac{-b-}{-}$ and $\frac{-c-}{-}$ are independently single bonds or double bonds; n_4 , n_5 , n_6 , n_7 , n_8 , n_9 and n_{10} are independently an integer from 0 to 4; m_4 , m_5 , m_6 , m_7 , m_8 , m_9 , m_{10} , v_4 , v_5 , v_6 , v_7 , v_8 , v_9 and v_{10} are independently 1 or 2; L^3 is a bond, $-O-$, $-S-$, $-NR^{3L}-$, $-NR^{3L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene; R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-SO_{n_4}R^{4A}$, $-SO_{v_4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m_4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-SO_{n5}H$, $-SO_{v5}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m5}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHOSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, 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^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-SO_{n6}H$, $-SO_{v6}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m6}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHOSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, 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^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, $-CN$, $-SO_{n7}H$, $-SO_{v7}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m7}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHOSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$, 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^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, $-CN$, $-SO_{n8}H$, $-SO_{v8}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m8}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHOSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, 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^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, $-CN$, $-SO_{n9}H$, $-SO_{v9}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m9}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHOSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, 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^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, $-CN$, $-SO_{n10}H$, $-SO_{v10}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m10}$,

$-\text{NH}_2$, $-\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{OH}$, $-\text{NH}\text{SO}_2\text{H}$, $-\text{NHC}(\text{O})\text{H}$, $-\text{NHC}(\text{O})\text{OH}$, $-\text{NHOH}$,
 $-\text{OCX}^{10.1}_3$, $-\text{OCHX}^{10.1}_2$, 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; $\text{R}^{3\text{L}}$,
 $\text{R}^{4\text{A}}$, $\text{R}^{4\text{B}}$, $\text{R}^{4\text{C}}$ and $\text{R}^{4\text{D}}$ are independently hydrogen, halogen, $-\text{CF}_3$, $-\text{CCl}_3$,
 $-\text{CBr}_3$, $-\text{Cl}_3$, $-\text{COOH}$, $-\text{CONH}_2$, 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; $\text{R}^{4\text{B}}$
and $\text{R}^{4\text{C}}$ substituents bonded to the same nitrogen atom may optionally be joined to form a
substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and $\text{X}^{4.1}$,
 $\text{X}^{5.1}$, $\text{X}^{6.1}$, $\text{X}^{7.1}$, $\text{X}^{8.1}$, $\text{X}^{9.1}$ and $\text{X}^{10.1}$ are independently $-\text{Cl}$, $-\text{Br}$, $-\text{I}$ or $-\text{F}$; wherein when $\text{--}\overset{\text{a}}{\text{--}}$, $\text{--}\overset{\text{b}}{\text{--}}$
and $\text{--}\overset{\text{c}}{\text{--}}$ are double bonds, L^3 is $-\text{O}-$ and R^6 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, then
 R^4 is not hydrogen.

N47. The compound of embodiment N46, wherein L^3 is $-\text{NR}^{3\text{L}}-$ or a bond.

N48. The compound of embodiment N46, wherein L^3 is $-\text{NR}^{3\text{L}}\text{C}(\text{O})-$, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

N49. The compound of embodiment N46, wherein R^4 is a phosphate isostere moiety.

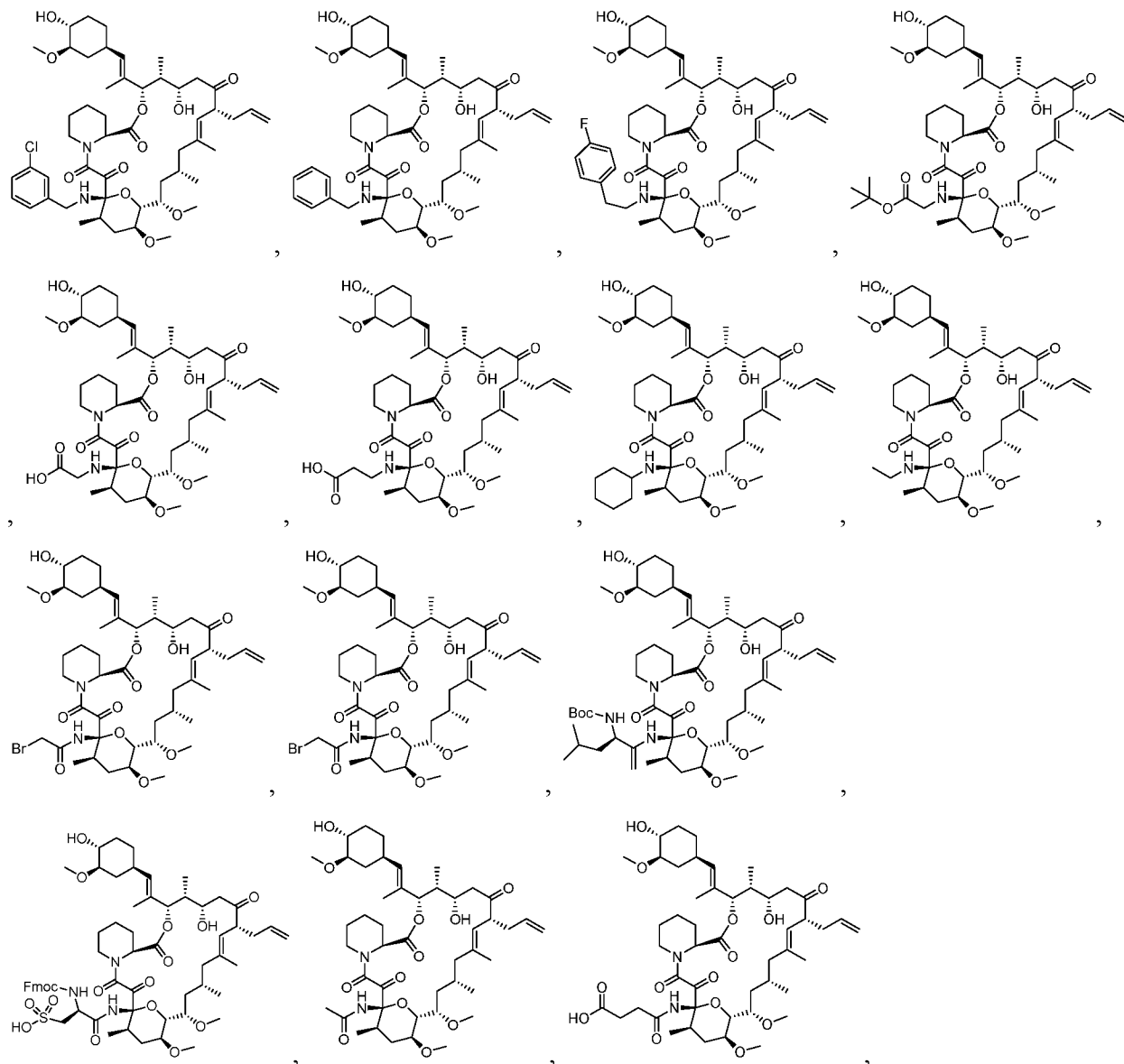
N50. The compound of embodiment N46, wherein R^4 is a tetrazole moiety, a triazole moiety, a carboxylic acid moiety, a phosphonate moiety, a boranophosphate moiety, a sulfate moiety, a sulfamic acid moiety, a sulphonate moiety, a nitro moiety, a thiazolidinone moiety, a squaric acid moiety, a hydroxyl moiety or a boronic acid moiety.

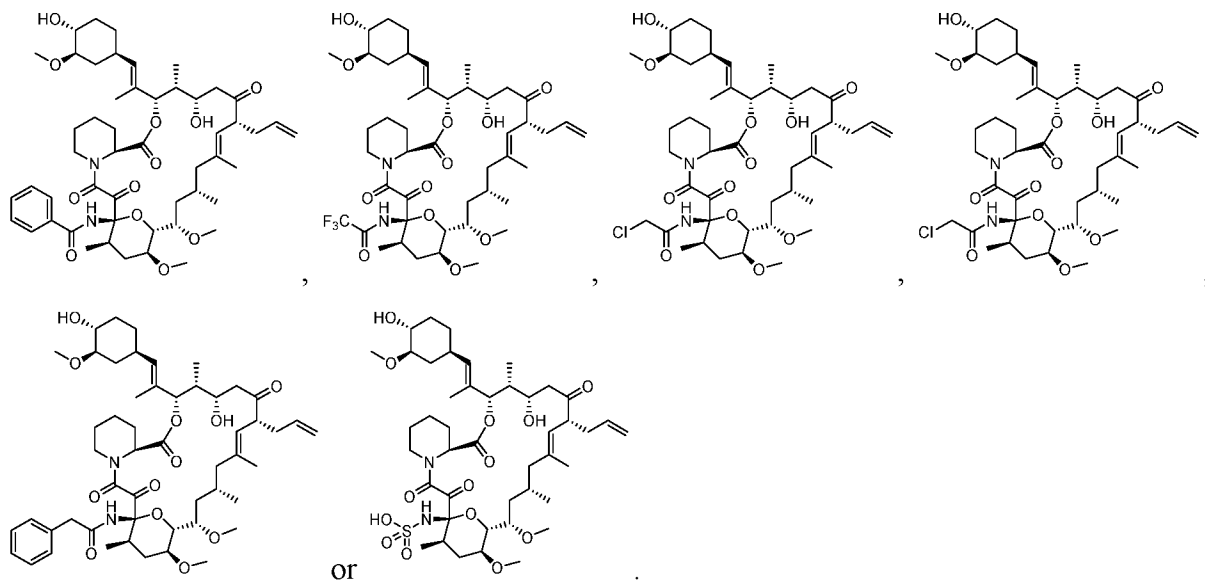
N51. The compound of embodiment N46, wherein R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

N52. The compound of embodiment N46, wherein L^3 is substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

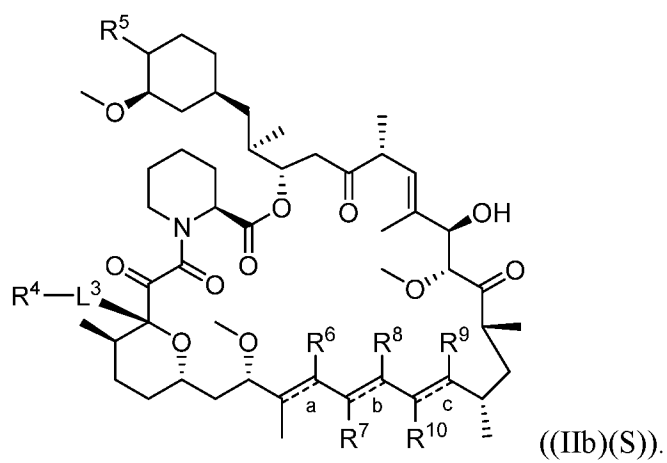
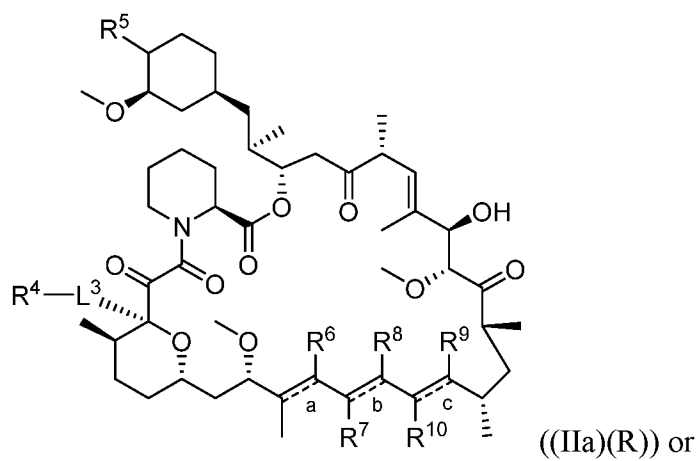
N53. The compound of embodiment N46, wherein the R^4 is substituted or unsubstituted aryl.

N54. The compound of embodiment N46, wherein the compound is





N55. The compound of embodiment N46, wherein the compound is:



N56. A pharmaceutical composition, comprising a compound of embodiment N1 and a pharmaceutically acceptable excipient.

N57. A method of inhibiting Pin 1, comprising contacting Pin 1 with a compound of embodiment N1.

N58. A method of inhibiting an FK506 binding protein (FKBP), comprising contacting the FKBP with a compound of embodiment N1.

N59. The method of embodiment N58, wherein the FKBP is FKBP38, FKBP51 or FKBP52.

N60. The method of embodiment N58, wherein the FKBP is FKBP51.

N61. A method of treating a Pin 1-mediated disease or disorder, comprising administering to a patient in need thereof a compound of embodiment N1.

N62. The method of embodiment N61, wherein the Pin 1-mediated disease or disorder is cancer.

N63. The method of embodiment N62, wherein the cancer is prostate cancer, brain cancer, breast cancer, ovarian cancer cervical cancer or skin cancer.

N64. The method of embodiment N62, further comprising administering to the subject a chemotherapeutic agent.

N65. A method of treating an FKBP51-mediated disease or disorder, comprising administering to a patient in need thereof a compound of embodiment N1.

N66. The method of embodiment N65, wherein the disease or disorder is depression or mental illness.

N67. The method of embodiment N66, wherein the disease or disorder is depression.

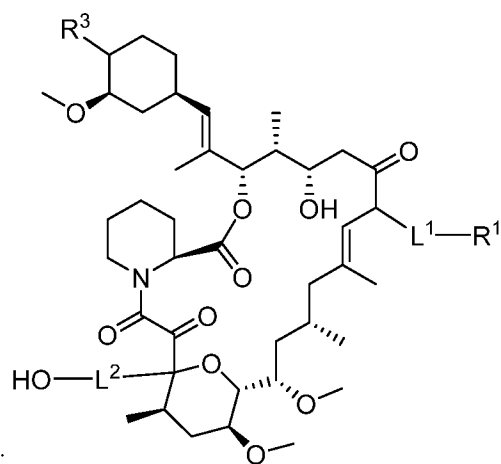
N68. The method of embodiment N67, further comprising administering to the subject an anti-depressant.

N69. The method of embodiment N66, wherein the mental illness is schizophrenia.

N70. The method of embodiment N65, wherein the disease or disorder is pain.

N71. The method of embodiment N70, wherein the pain is chronic pain or neuropathic pain.

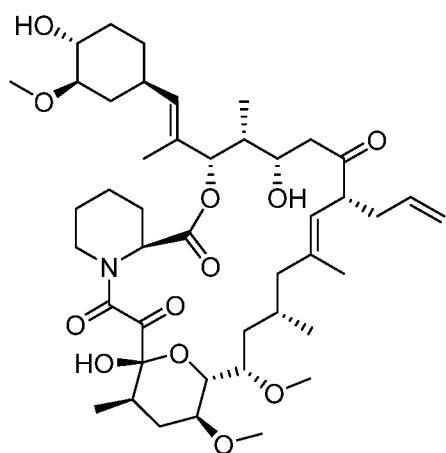
N72. A method of preparing a compound of embodiment N37, comprising contacting a



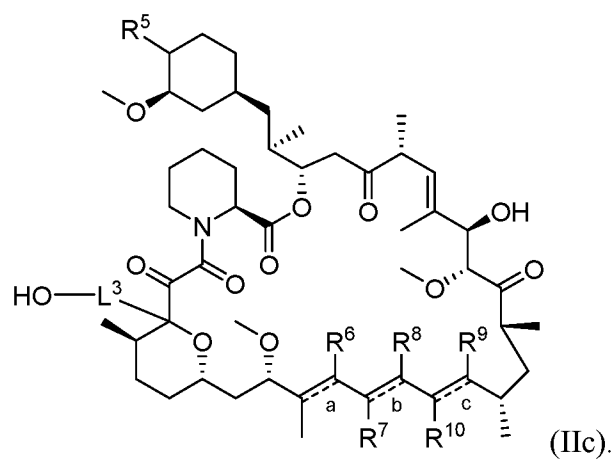
compound of structural Formula (Ic) with ammonia:

(Ic).

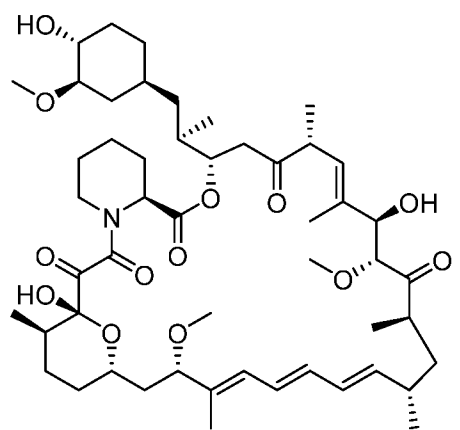
N73. The method of embodiment N72, wherein the compound of Formula (Ic) is



N74. A method of preparing a compound of embodiment N46, comprising contacting a compound of structural Formula (IIc) with ammonia:



N75. The method of embodiment N74, wherein the compound of Formula (IIc) is



WHAT IS CLAIMED IS:

1. A peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound, comprising a macrolide with a pipercolyl moiety, or a pharmaceutically acceptable salt thereof.
2. The compound of claim 1, wherein the compound is an FK506 compound, covalently bound to a nitrogen-containing functional group at the C-10 position, or a derivative thereof.
3. The compound of claim 2, wherein the nitrogen-containing functional group is an amino group.
4. The compound of claim 2, wherein the nitrogen-containing functional group is a primary amino group.
5. The compound of claim 2, wherein the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.
6. The compound of claim 1, wherein the compound is an FK506 compound, or a derivative thereof, comprising an electronegative group at the C-10 position.
7. The compound of claim 1, wherein the compound is an FK506 compound, or a derivative thereof, comprising an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position.
8. The compound of claim 7, wherein the linker is covalently bound to an electronegative group.
9. The compound of claim 5, wherein the electronegative group is a phosphate isostere group.
10. The compound of claim 5, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group,

a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

11. The compound of claim 1, wherein the FK506 compound is an ascomycin derivative or variant.

12. The compound of claim 1, wherein the compound is a rapamycin compound, or a derivative thereof, comprising a nitrogen-containing functional group at the C-10 position.

13. The compound of claim 12, wherein the nitrogen-containing functional group is an amino group.

14. The compound of claim 12, wherein the nitrogen-containing functional group is a primary amino group.

15. The compound of claim 12, wherein the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

16. The compound of claim 1, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an electronegative group at the C-10 position.

17. The compound of claim 1, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position.

18. The compound of claim 17, wherein the linker is covalently bound to an electronegative group.

19. The compound of claim 15, wherein the electronegative group is a phosphate isostere group.

20. The compound of claim 15, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a

boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

21. An FK506 binding protein (FKBP) inhibitor compound, comprising a macrolide with a pipecolyl moiety, or a pharmaceutically acceptable salt thereof.

22. The compound of claim 21, wherein the compound is a rapamycin compound, or a derivative thereof, comprising a nitrogen-containing functional group at the C-10 position.

23. The compound of claim 22, wherein the nitrogen-containing functional group is an amino group.

24. The compound of claim 22, wherein the nitrogen-containing functional group is a primary amino group.

25. The compound of claim 22, wherein the nitrogen-containing functional group is an electronegative group or is covalently bound to an electronegative group.

26. The compound of claim 21, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an electronegative group at the C-10 position.

27. The compound of claim 21, wherein the compound is a rapamycin compound, or a derivative thereof, comprising an alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene or heteroarylene linker at the C-10 position.

28. The compound of claim 27, wherein the linker is covalently bound to an electronegative group.

29. The compound of claim 25, wherein the electronegative group is a phosphate isostere group.

30. The compound of claim 25, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a

boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

31. A macrolide compound covalently attached to an electronegative group at a position equivalent to C-10 of FK506 or a pharmaceutically acceptable salt thereof.**covers FK506?*

32. The compound of claim 31, wherein the macrolide compound is an FK506 compound derivative, a rapamycin compound derivative or an ascomycin compound derivative.

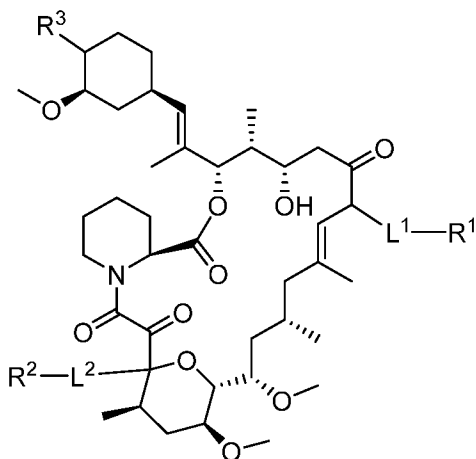
33. The compound of claim 31, wherein the macrolide compound is capable of inhibiting a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) protein.

34. The compound of claim 31, wherein the macrolide compound is capable of inhibiting an FK506 binding protein.

35. The compound of claim 31, wherein the electronegative group is a phosphate isostere group.

36. The compound of claim 31, wherein the electronegative group is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

37. A compound of structural Formula (I):



(I), or a pharmaceutically acceptable salt thereof,

wherein:

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

m_1 , m_2 , m_3 , v_1 , v_2 and v_3 are independently 1 or 2;

L^1 is a bond, $-O-$, $-S-$, $-NR^{1L}-$, $-NR^{1L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

L^2 is a bond, $-O-$, $-S-$, $-NR^{2L}-$, $-NR^{2L}C(O)-$, $-C(O)-$, $-C(O)O-$, $-S(O)-$, $-S(O)_2-$, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^1 is hydrogen, halogen, $-CX^{1.1}_3$, $-CHX^{1.1}_2$, $-CH_2X^{1.1}$, $-CN$, $-SO_{n1}R^{1A}$, $-SO_{v1}NR^{1BR^{1C}}$, $-NHN R^{1BR^{1C}}$, $-ONR^{1BR^{1C}}$, $-NHC(O)NHN R^{1BR^{1C}}$, $-NHC(O)NR^{1BR^{1C}}$, $-N(O)_{m1}$, $-NR^{1BR^{1C}}$, $-C(O)R^{1D}$, $-C(O)OR^{1D}$, $-C(O)NR^{1BR^{1C}}$, $-OR^{1A}$, $-NR^{1B}SO_2R^{1A}$, $-NR^{1B}C(O)R^{1D}$, $-NR^{1B}C(O)OR^{1D}$, $-NR^{1B}OR^{1D}$, $-OCX^{1.1}_3$, $-OCHX^{1.1}_2$, 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;

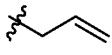
R^2 is hydrogen, halogen, $-CX^{2.1}_3$, $-CHX^{2.1}_2$, $-CH_2X^{2.1}$, $-CN$, $-SO_{n2}R^{2A}$, $-SO_{v2}NR^{2BR^{2C}}$, $-NHN R^{2BR^{2C}}$, $-ONR^{2BR^{2C}}$, $-NHC(O)NHN R^{2BR^{2C}}$, $-NHC(O)NR^{2BR^{2C}}$, $-N(O)_{m2}$, $-NR^{2BR^{2C}}$, $-C(O)R^{2D}$, $-C(O)OR^{2D}$, $-C(O)NR^{2BR^{2C}}$, $-OR^{2A}$, $-NR^{2B}SO_2R^{2A}$, $-NR^{2B}C(O)R^{2D}$, $-NR^{2B}C(O)OR^{2D}$, $-NR^{2B}OR^{2D}$, $-OCX^{2.1}_3$, $-OCHX^{2.1}_2$, substituted or

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

R^3 is hydrogen, halogen, $-CX^{3.1}_3$, $-CHX^{3.1}_2$, $-CH_2X^{3.1}$, $-CN$, $-SO_{m3}R^{3A}$, $-SO_{v3}NR^{3B}R^{3C}$, $-NHN R^{3B}R^{3C}$, $-ONR^{3B}R^{3C}$, $-NHC(O)NHN R^{3B}R^{3C}$, $-NHC(O)NR^{3B}R^{3C}$, $-N(O)_{m3}$, $-NR^{3B}R^{3C}$, $-C(O)R^{3D}$, $-C(O)OR^{3D}$, $-C(O)NR^{3B}R^{3C}$, $-OR^{3A}$, $-NR^{3B}SO_2R^{3A}$, $-NR^{3B}C(O)R^{3D}$, $-NR^{3B}C(O)OR^{3D}$, $-NR^{3B}OR^{3D}$, $-OCX^{3.1}_3$, $-OCHX^{3.1}_2$, 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^{1L} , R^{2L} , R^{1A} , R^{1B} , R^{1C} , R^{1D} , R^{2A} , R^{2B} , R^{2C} , R^{2D} , R^{3A} , R^{3B} , R^{3C} and R^{3D} , are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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^{1B} and R^{1C} , R^{2B} and R^{2C} , R^{3B} and R^{3C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and

$X^{1.1}$, $X^{2.1}$ and $X^{3.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$;

wherein when L^2 is $-O-$, L^1 is a bond, R^1 is  or $-CH_2CH_3$ and R^3 is hydroxyl, then R^2 is not hydrogen.

38. The compound of claim 37, wherein:

L^2 is a bond; and

R^2 is $-NH_2$.

39. The compound of claim 37, wherein L^2 is $-NR^{2L}-$.

40. The compound of claim 37, wherein L^2 is $-NR^{2L}C(O)-$, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

41. The compound of claim 39, wherein R^2 is a phosphate isostere group.

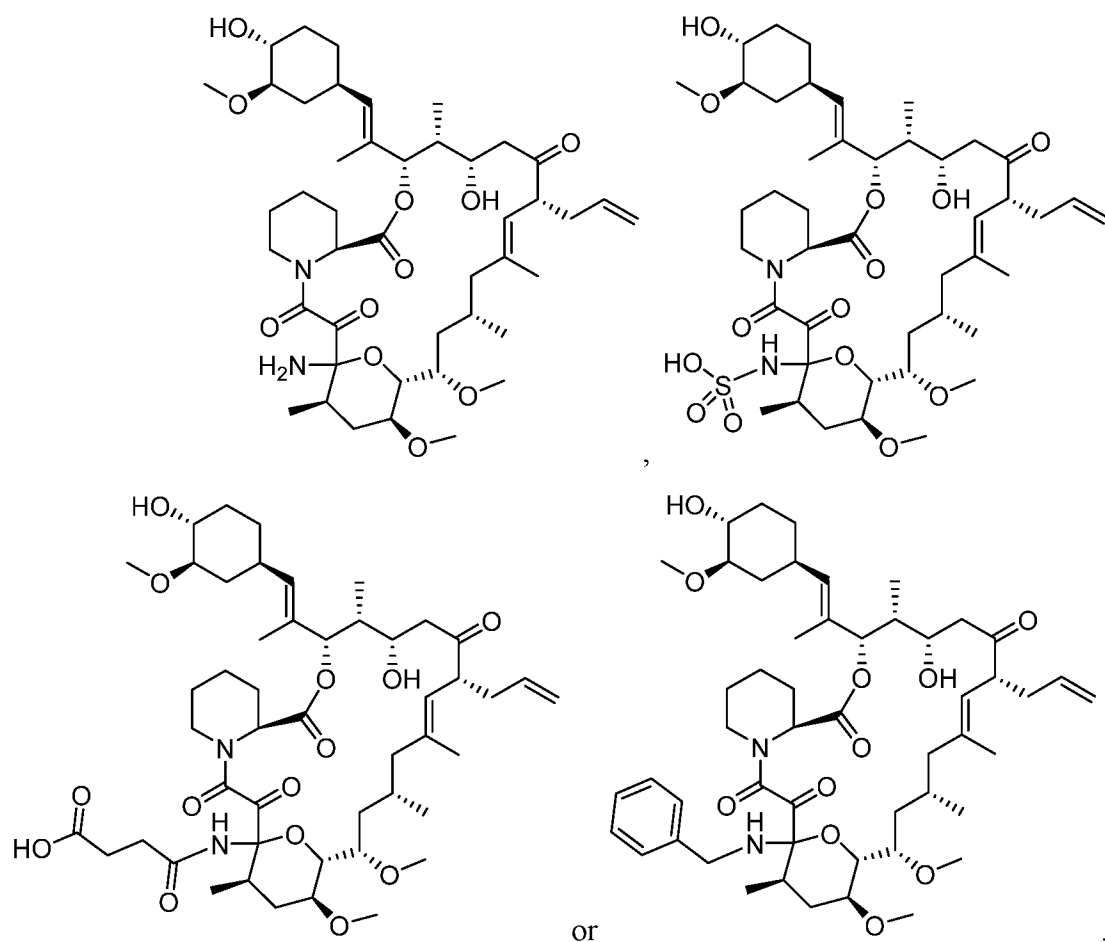
42. The compound of claim 39, wherein R^2 is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group, a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

43. The compound of claim 37, wherein:

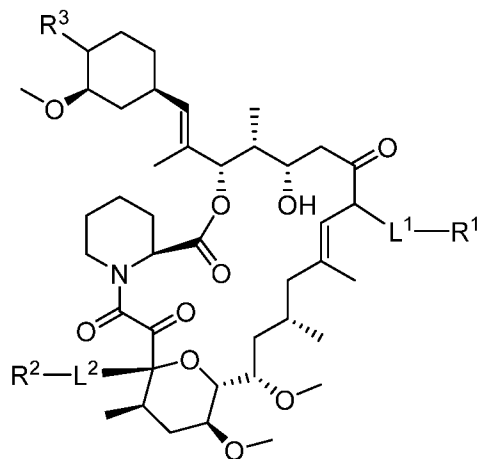
L^1 is a bond; and

R^1 is (R)-ethyl.

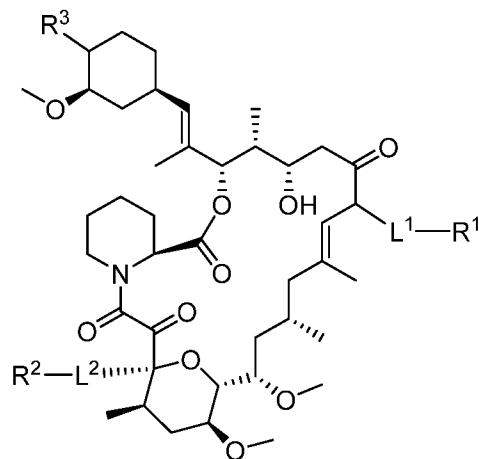
44. The compound of claim 37, wherein the compound is



45. The compound of claim 37, wherein the compound is:

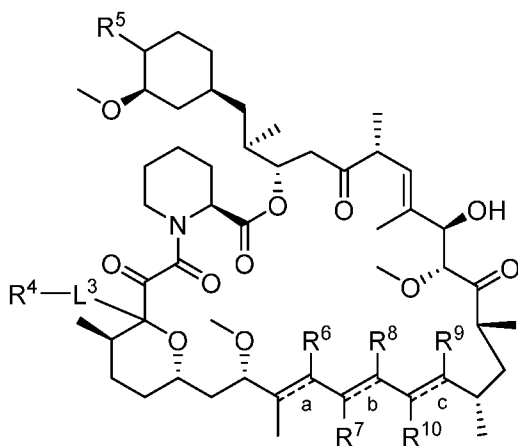


((Ia)(R)) or



((Ib)(S)).

46. A compound of structural Formula (II):



(II), or a pharmaceutically acceptable salt

thereof, wherein:

$\text{--}\overset{\text{a}}{\text{--}}$, $\text{--}\overset{\text{b}}{\text{--}}$ and $\text{--}\overset{\text{c}}{\text{--}}$ are independently single bonds or double bonds;

n₄, n₅, n₆, n₇, n₈, n₉ and n₁₀ are independently an integer from 0 to 4;

m₄, m₅, m₆, m₇, m₈, m₉, m₁₀, v₄, v₅, v₆, v₇, v₈, v₉ and v₁₀ are independently

1 or 2;

L³ is a bond, -O-, -S-, -NR^{3L}-, -NR^{3L}C(O)-, -C(O)-, -C(O)O-, -S(O)-, -S(O)₂-, substituted or unsubstituted alkylene, substituted or unsubstituted heteroalkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted heterocycloalkylene, substituted or unsubstituted arylene, or substituted or unsubstituted heteroarylene;

R^4 is hydrogen, halogen, $-CX^{4.1}_3$, $-CHX^{4.1}_2$, $-CH_2X^{4.1}$, $-CN$, $-SO_{n4}R^{4A}$, $-SO_{v4}NR^{4B}R^{4C}$, $-NHN R^{4B}R^{4C}$, $-ONR^{4B}R^{4C}$, $-NHC(O)NHN R^{4B}R^{4C}$, $-NHC(O)NR^{4B}R^{4C}$, $-N(O)_{m4}$, $-NR^{4B}R^{4C}$, $-C(O)R^{4D}$, $-C(O)OR^{4D}$, $-C(O)NR^{4B}R^{4C}$, $-OR^{4A}$, $-NR^{4B}SO_2R^{4A}$, $-NR^{4B}C(O)R^{4D}$, $-NR^{4B}C(O)OR^{4D}$, $-NR^{4B}OR^{4D}$, $-OCX^{4.1}_3$, $-OCHX^{4.1}_2$, 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^5 is hydrogen, halogen, $-CX^{5.1}_3$, $-CHX^{5.1}_2$, $-CH_2X^{5.1}$, $-CN$, $-SO_{n5}H$, $-SO_{v5}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m5}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{5.1}_3$, $-OCHX^{5.1}_2$, 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^6 is hydrogen, halogen, $-CX^{6.1}_3$, $-CHX^{6.1}_2$, $-CH_2X^{6.1}$, $-CN$, $-SO_{n6}H$, $-SO_{v6}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m6}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{6.1}_3$, $-OCHX^{6.1}_2$, 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^7 is hydrogen, halogen, $-CX^{7.1}_3$, $-CHX^{7.1}_2$, $-CH_2X^{7.1}$, $-CN$, $-SO_{n7}H$, $-SO_{v7}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m7}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{7.1}_3$, $-OCHX^{7.1}_2$, 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^8 is hydrogen, halogen, $-CX^{8.1}_3$, $-CHX^{8.1}_2$, $-CH_2X^{8.1}$, $-CN$, $-SO_{n8}H$, $-SO_{v8}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m8}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{8.1}_3$, $-OCHX^{8.1}_2$, 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^9 is hydrogen, halogen, $-CX^{9.1}_3$, $-CHX^{9.1}_2$, $-CH_2X^{9.1}$, $-CN$, $-SO_{n9}H$, $-SO_{v9}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m9}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{9.1}_3$, $-OCHX^{9.1}_2$, 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^{10} is hydrogen, halogen, $-CX^{10.1}_3$, $-CHX^{10.1}_2$, $-CH_2X^{10.1}$, $-CN$, $-SO_{n10}H$, $-SO_{v10}NH_2$, $-NHNH_2$, $-ONH_2$, $-NHC(O)NHNH_2$, $-NHC(O)NH_2$, $-N(O)_{m10}$, $-NH_2$, $-C(O)H$, $-C(O)OH$, $-C(O)NH_2$, $-OH$, $-NHSO_2H$, $-NHC(O)H$, $-NHC(O)OH$, $-NHOH$, $-OCX^{10.1}_3$, $-OCHX^{10.1}_2$, 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^{3L} , R^{4A} , R^{4B} , R^{4C} and R^{4D} are independently hydrogen, halogen, $-CF_3$, $-CCl_3$, $-CBr_3$, $-Cl_3$, $-COOH$, $-CONH_2$, 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^{4B} and R^{4C} substituents bonded to the same nitrogen atom may optionally be joined to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl; and

$X^{4.1}$, $X^{5.1}$, $X^{6.1}$, $X^{7.1}$, $X^{8.1}$, $X^{9.1}$ and $X^{10.1}$ are independently $-Cl$, $-Br$, $-I$ or $-F$; wherein when $\overset{\text{a}}{\text{--}}\text{--}$, $\overset{\text{b}}{\text{--}}\text{--}$ and $\overset{\text{c}}{\text{--}}\text{--}$ are double bonds, L^3 is $-O-$ and R^6 , R^7 , R^8 , R^9 and R^{10} are independently hydrogen, then R^4 is not hydrogen.

47. The compound of claim 46, wherein L^3 is $-NR^{3L}-$ or a bond.

48. The compound of claim 46, wherein L^3 is $-NR^{3L}C(O)-$, substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

49. The compound of claim 46, wherein R^4 is a phosphate isostere group.

50. The compound of claim 46, wherein R^4 is a tetrazole group, a triazole group, a carboxylic acid group, a phosphonate group, a boranophosphate group, a sulfate group,

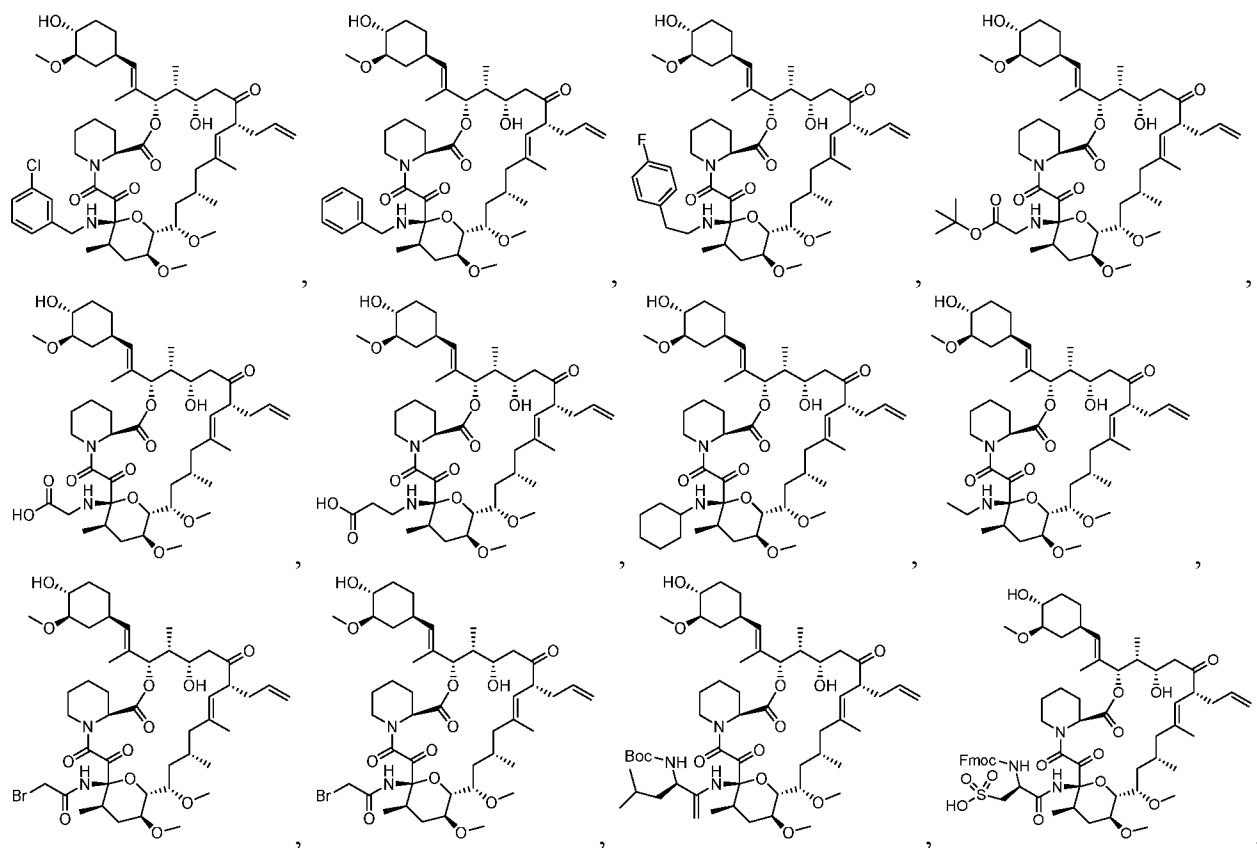
a sulfamic acid group, a sulphonate group, a nitro group, a thiazolidinone group, a squaric acid group, a hydroxyl group or a boronic acid group.

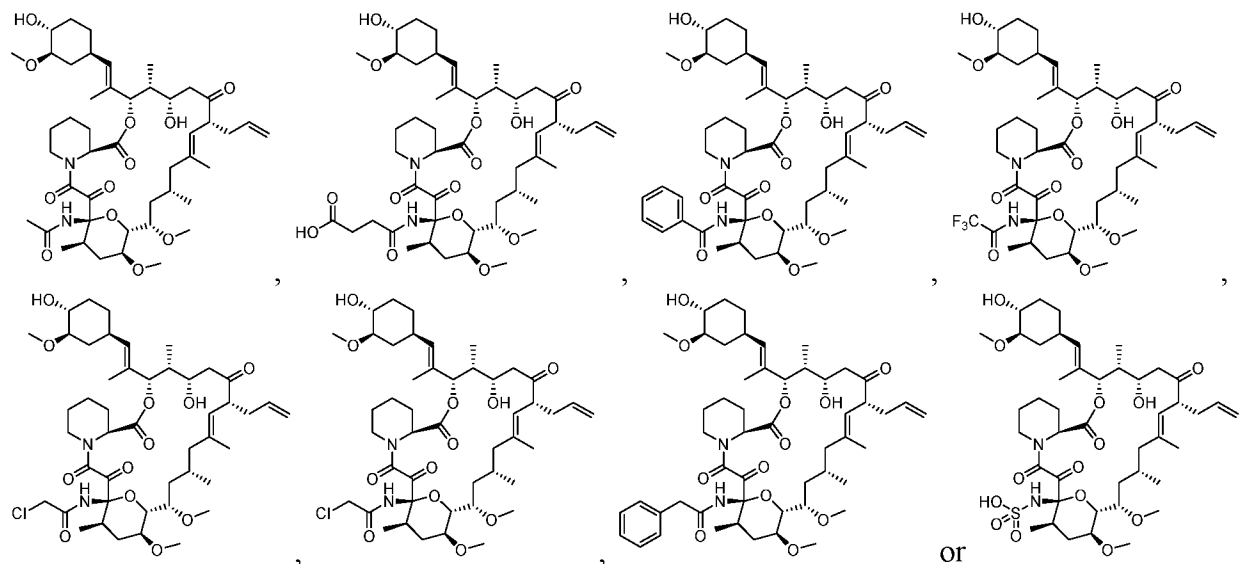
51. The compound of claim 46, wherein R^4 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl.

52. The compound of claim 46, wherein L^3 is substituted or unsubstituted alkylene or substituted or unsubstituted heteroalkylene.

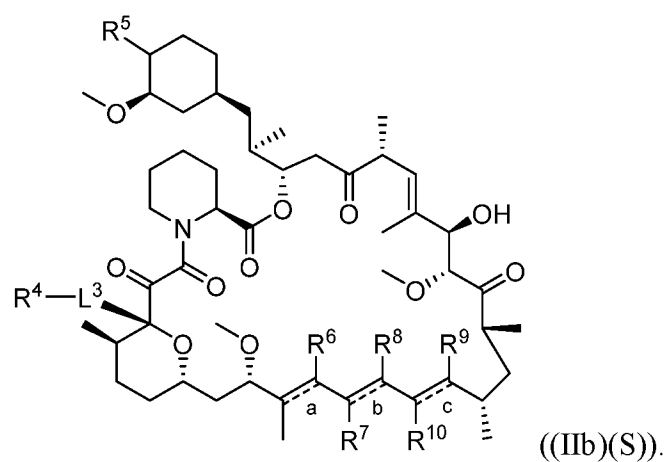
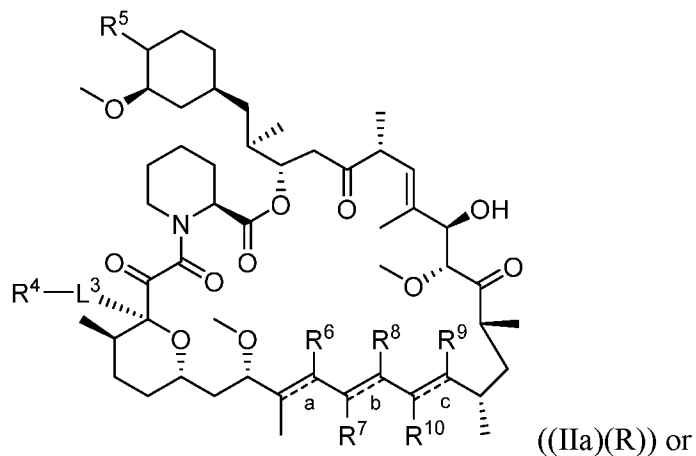
53. The compound of claim 46, wherein the R^4 is substituted or unsubstituted aryl.

54. The compound of claim 46, wherein the compound is





55. The compound of claim 46, wherein the compound is:



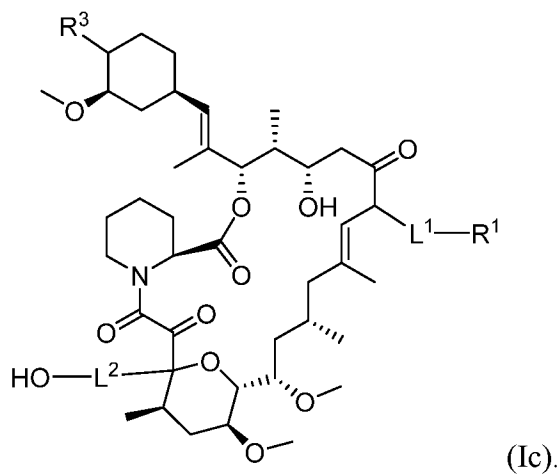
56. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

57. A method of inhibiting Pin 1, comprising contacting Pin 1 with a compound of claim 1.
58. A method of inhibiting an FK506 binding protein (FKBP), comprising contacting the FKBP with a compound of claim 2.
59. The method of claim 58, wherein the FKBP is FKBP38, FKBP51 or FKBP52.
60. The method of claim 58, wherein the FKBP is FKBP51.
61. A method of treating a Pin 1-mediated disease or disorder, comprising administering to a patient in need thereof a compound of claim 2.
62. The method of claim 61, wherein the Pin 1-mediated disease or disorder is cancer.
63. The method of claim 62, wherein the cancer is prostate cancer, brain cancer, breast cancer, ovarian cancer cervical cancer or skin cancer.
64. The method of claim 62, further comprising administering to the subject a chemotherapeutic agent.
65. A method of treating an FKBP51-mediated disease or disorder, comprising administering to a patient in need thereof a compound of claim 2.
66. The method of claim 65, wherein the disease or disorder is depression or mental illness.
67. The method of claim 66, wherein the disease or disorder is depression.
68. The method of claim 67, further comprising administering to the subject an anti-depressant.
69. The method of claim 66, wherein the mental illness is schizophrenia.

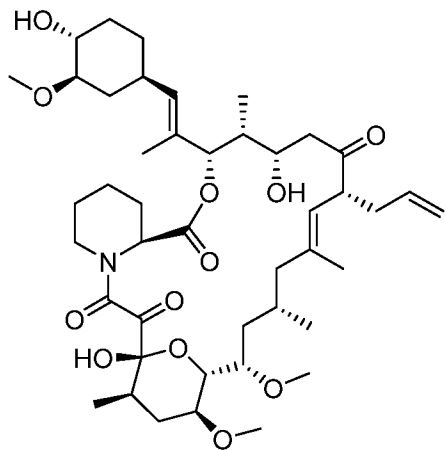
70. The method of claim 65, wherein the disease or disorder is pain.

71. The method of claim 70, wherein the pain is chronic pain or neuropathic pain.

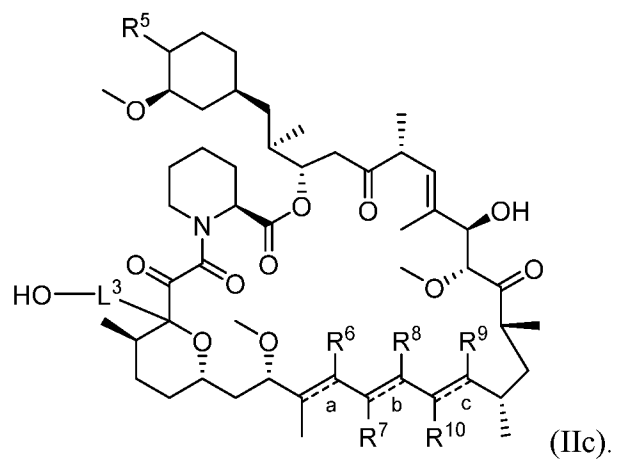
72. A method of preparing a compound of claim 37, comprising contacting a compound of structural Formula (Ic) with ammonia:



73. The method of claim 72, wherein the compound of Formula (Ic) is



74. A method of preparing a compound of claim 46, comprising contacting a compound of structural Formula (IIc) with ammonia:



75. The method of claim 74, wherein the compound of Formula (IIc) is

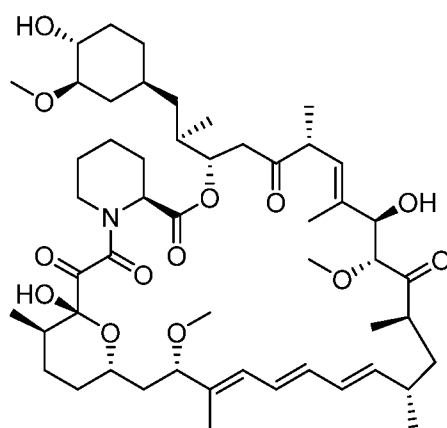


FIG. 1A

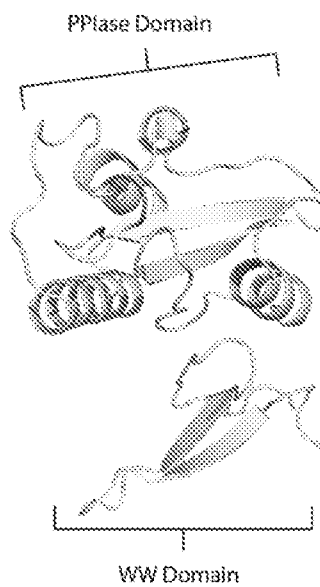


FIG. 1B

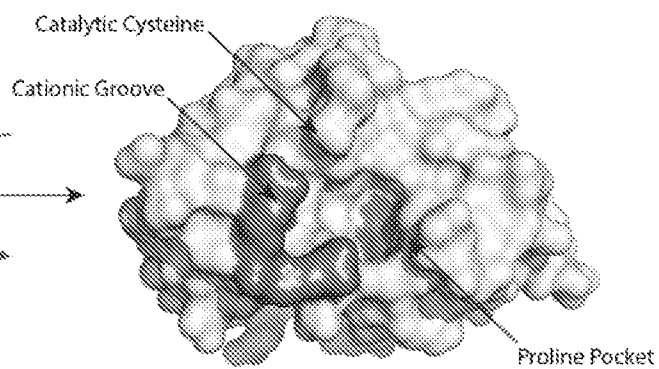


FIG. 2

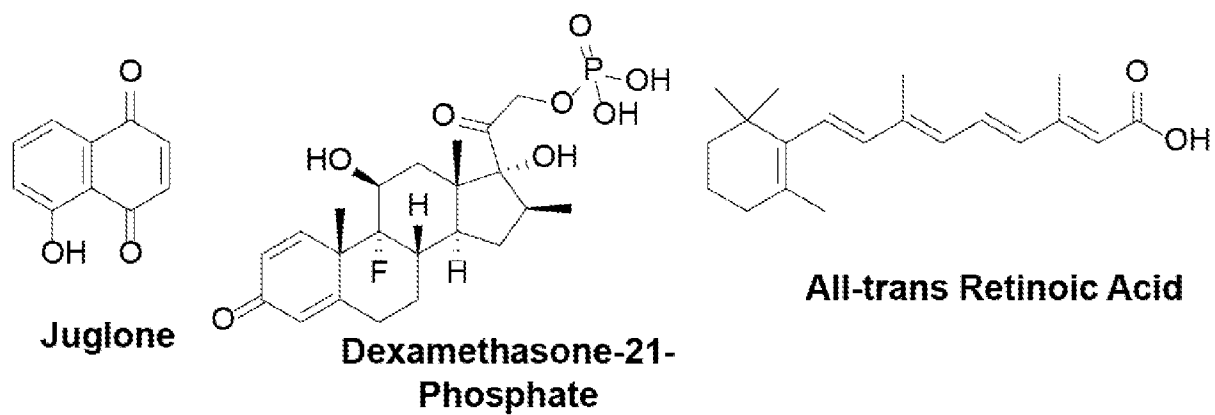


FIG. 3

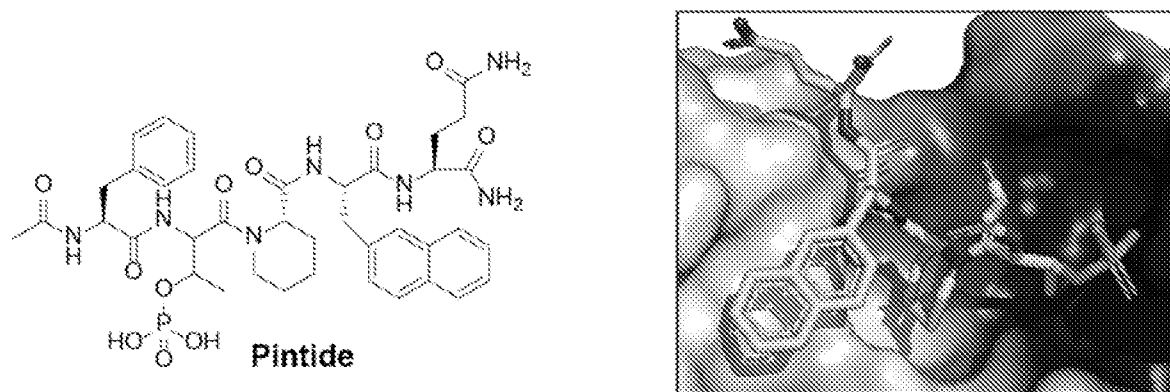


FIG. 4

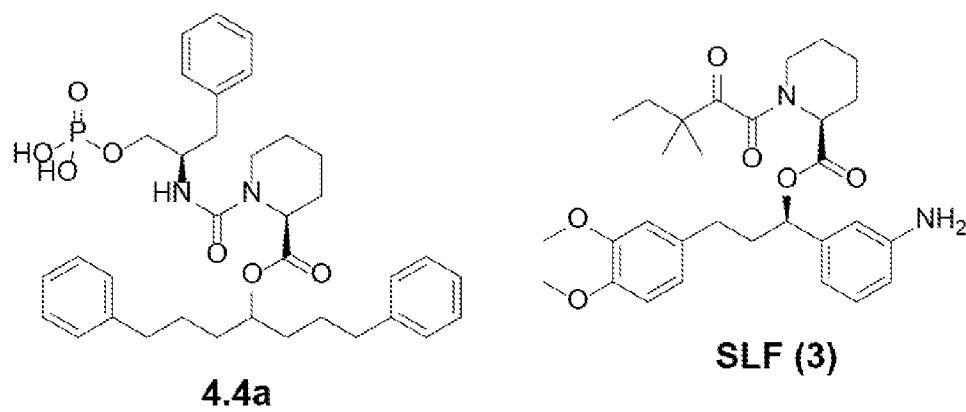


FIG. 5

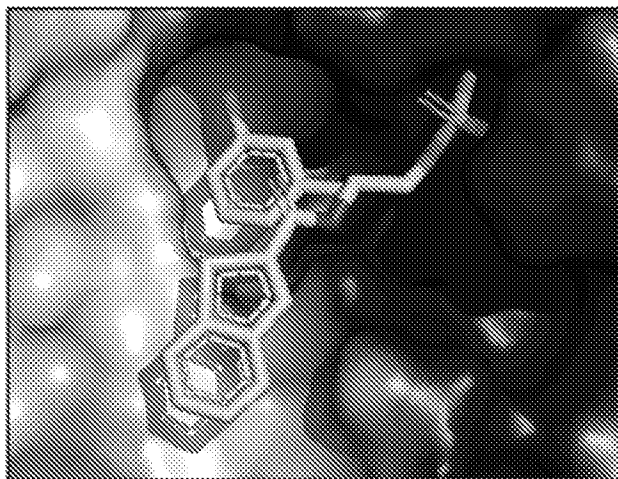
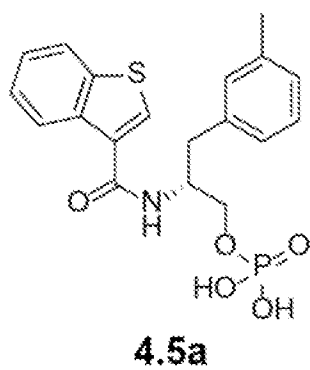


FIG. 6

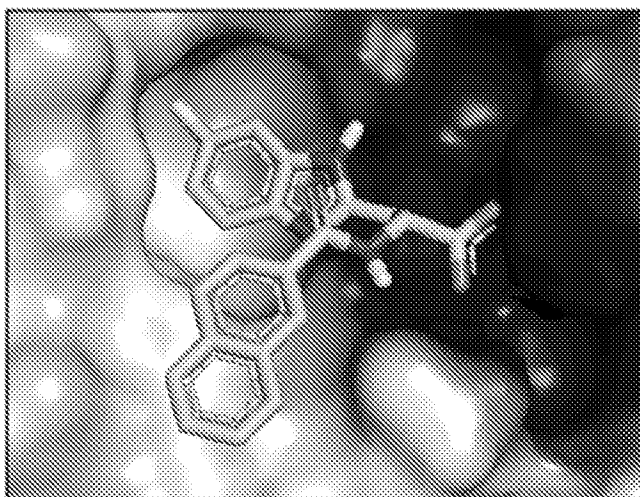
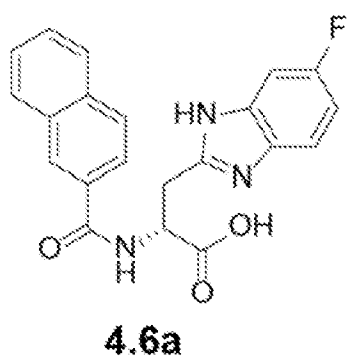


FIG. 7

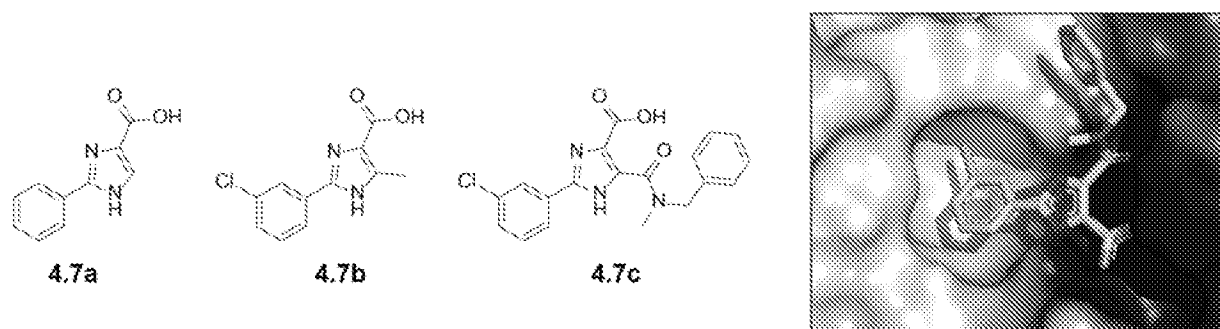


FIG. 8A

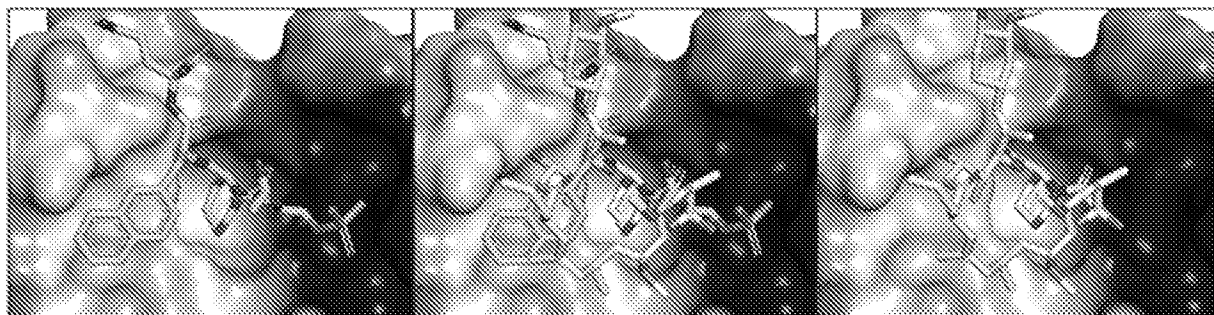


FIG. 8B

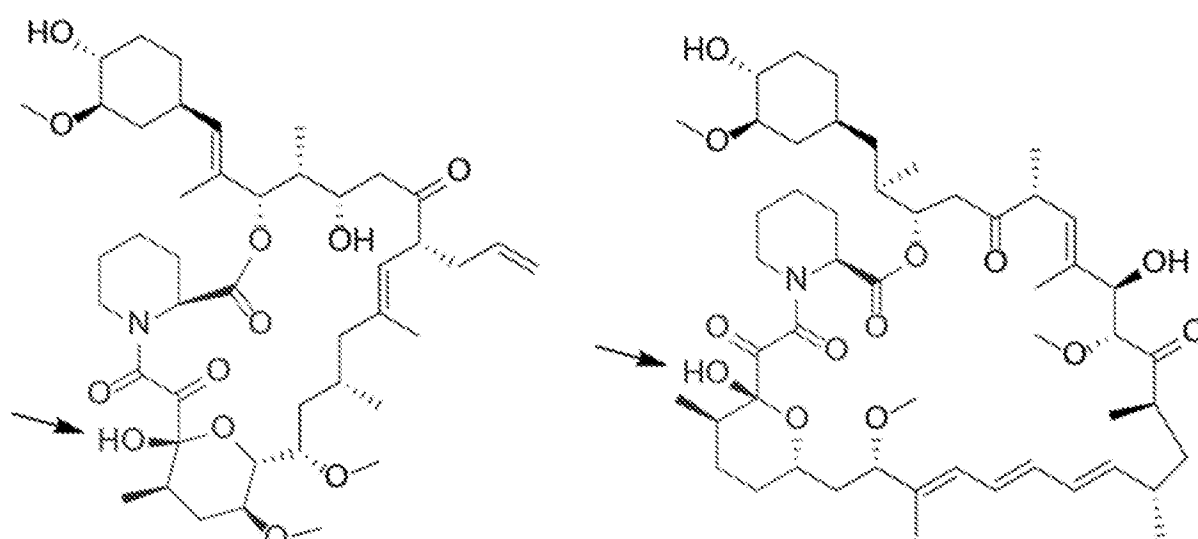


FIG. 9

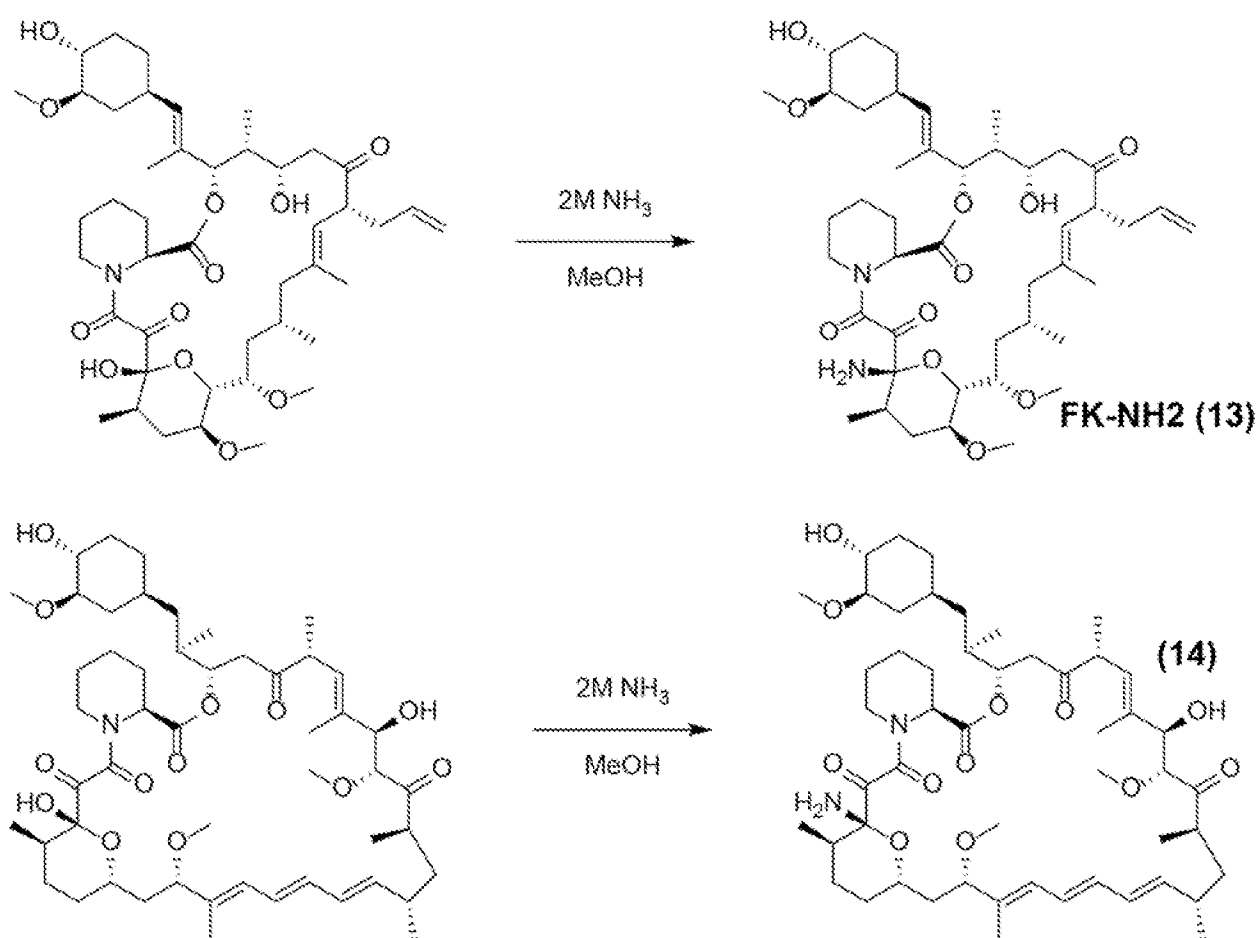


FIG. 10

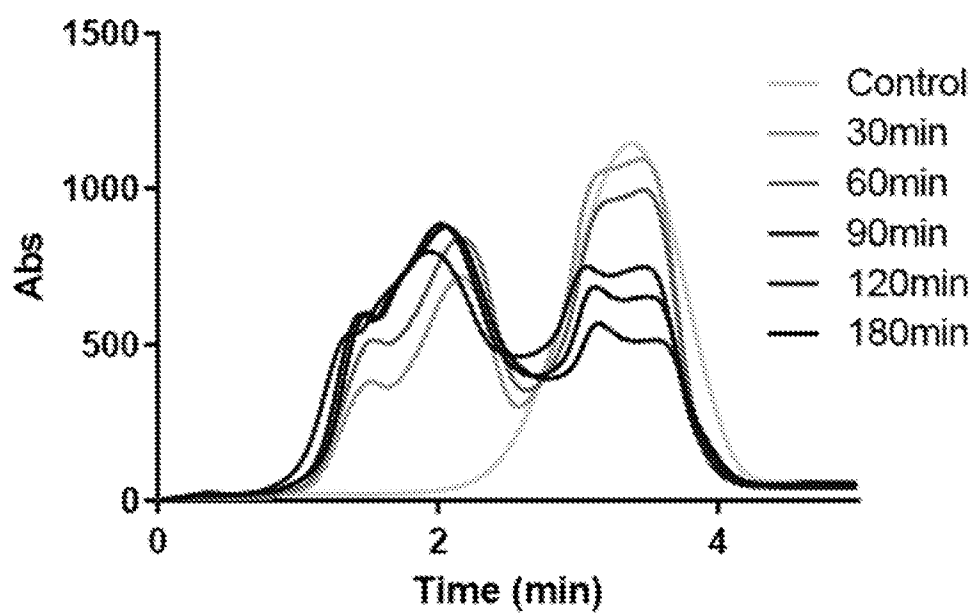
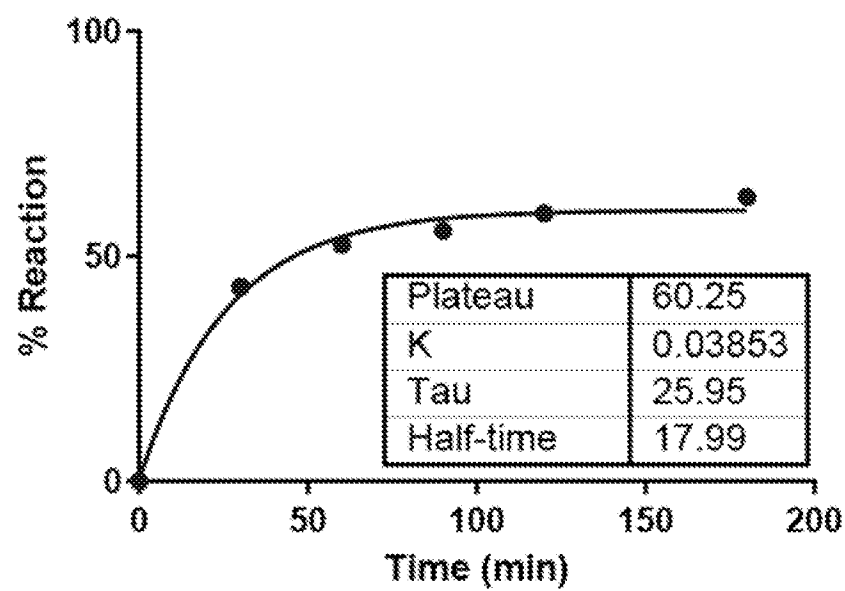


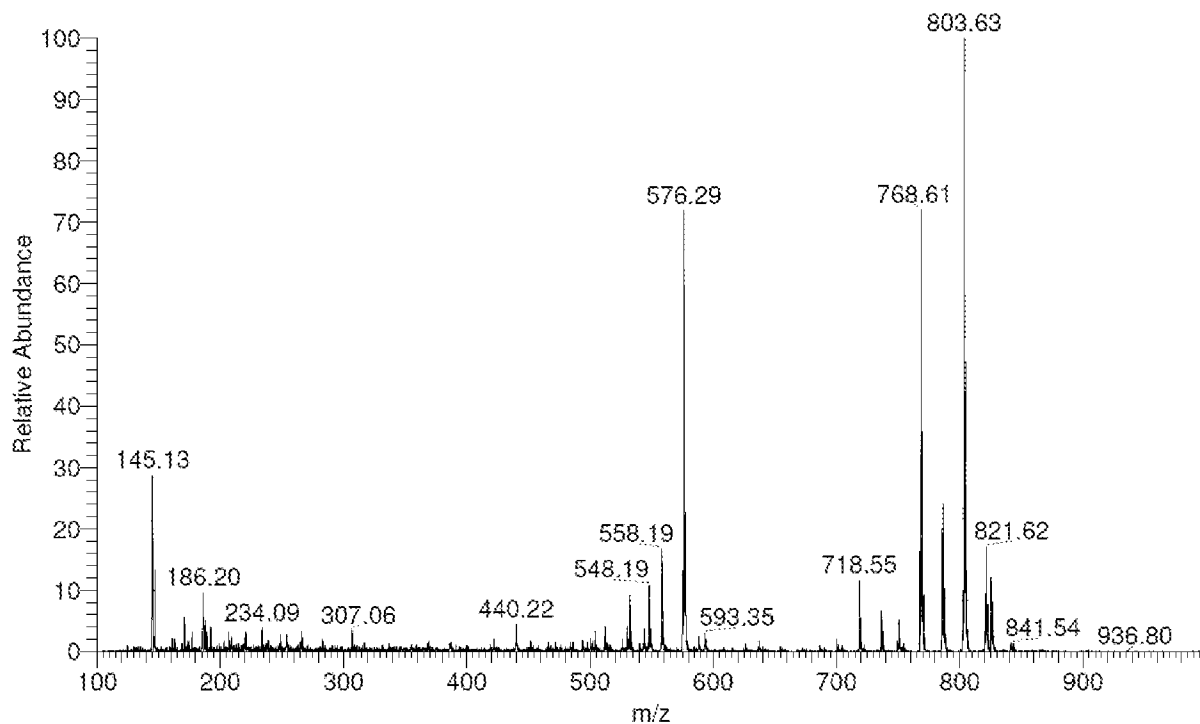
FIG. 11



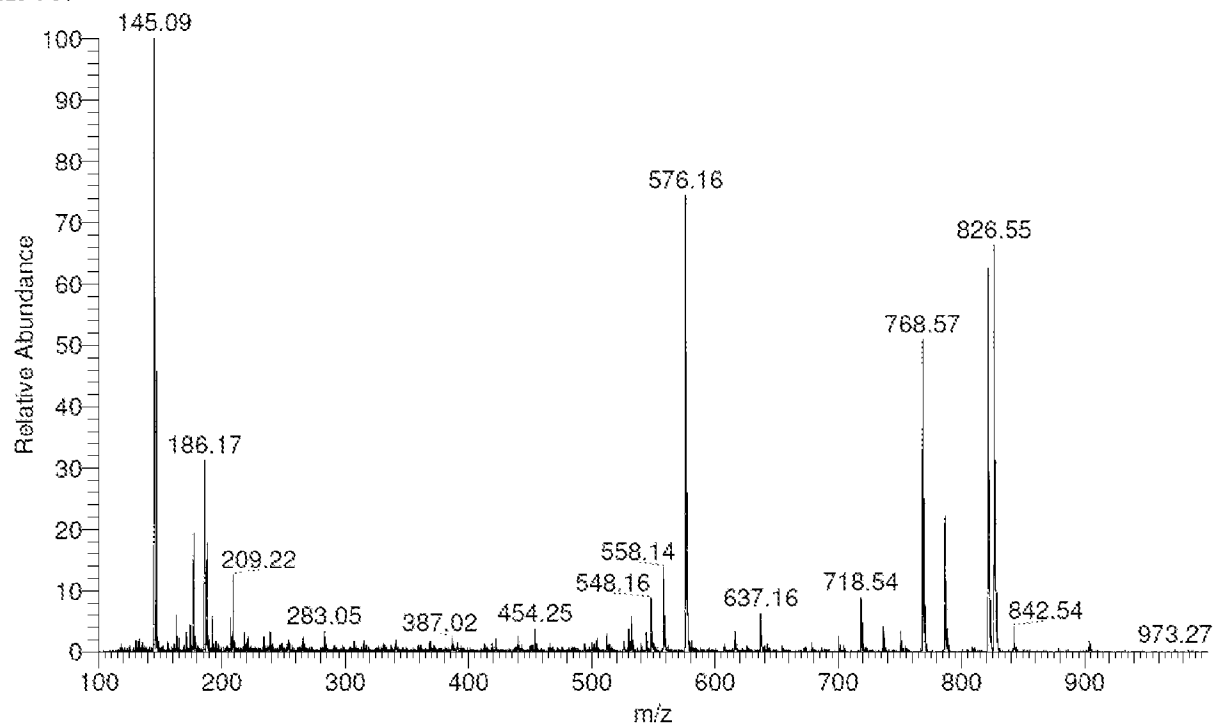
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FIG. 12

FK-NH2:



FK506:



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FIG. 13

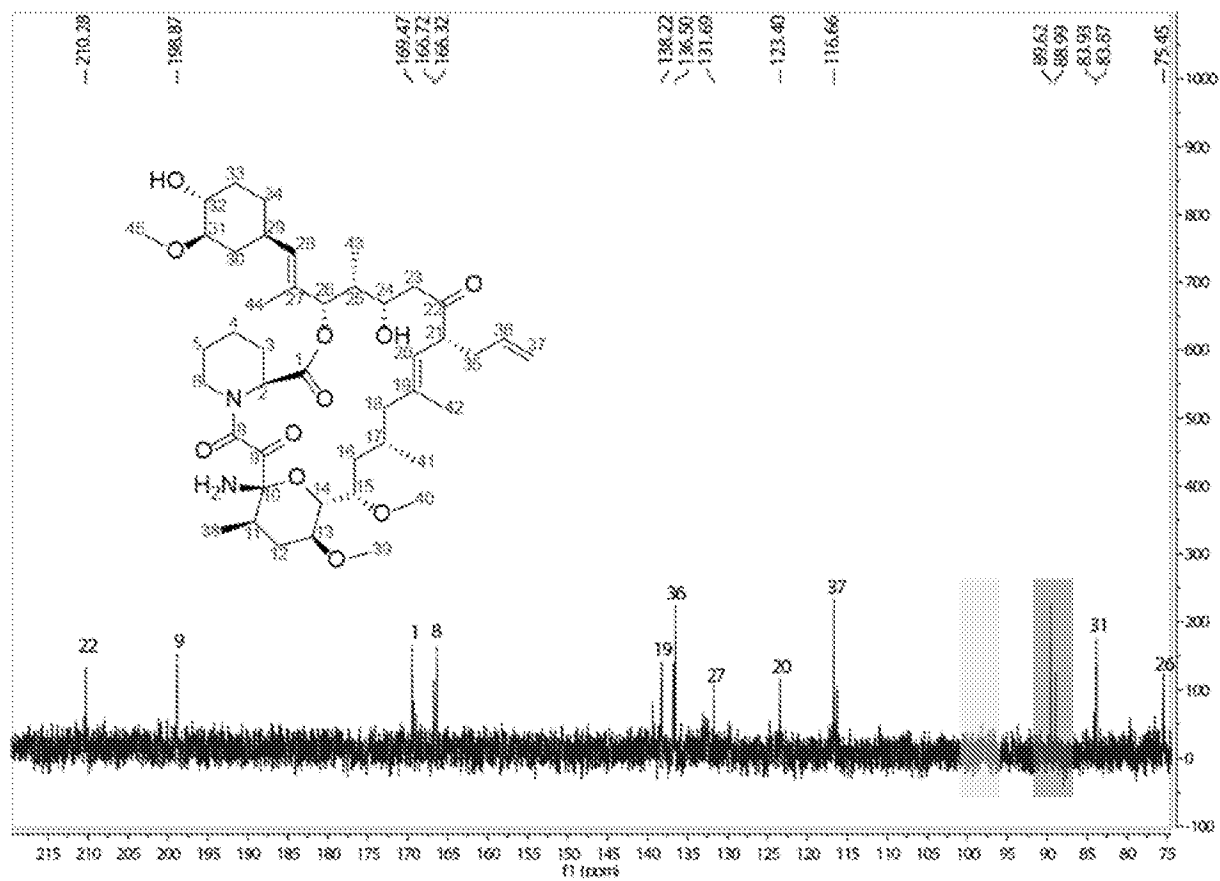


FIG. 14

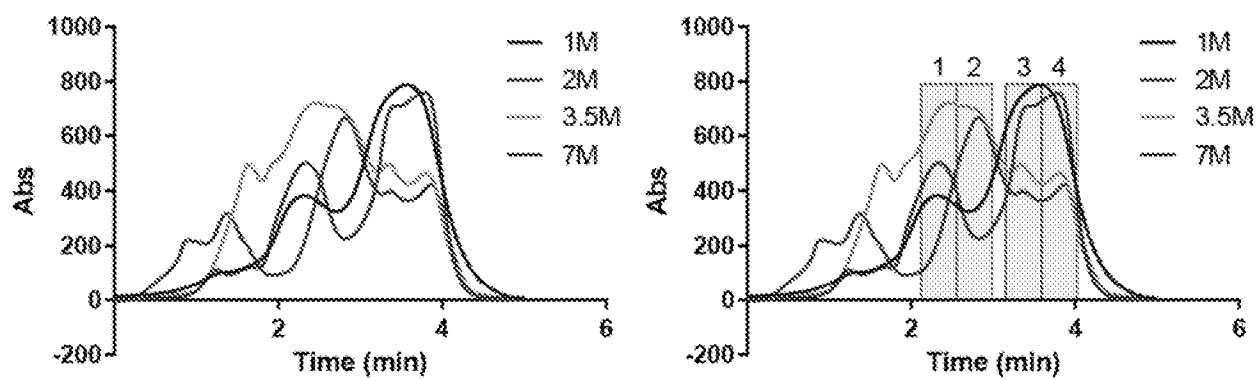


FIG. 15

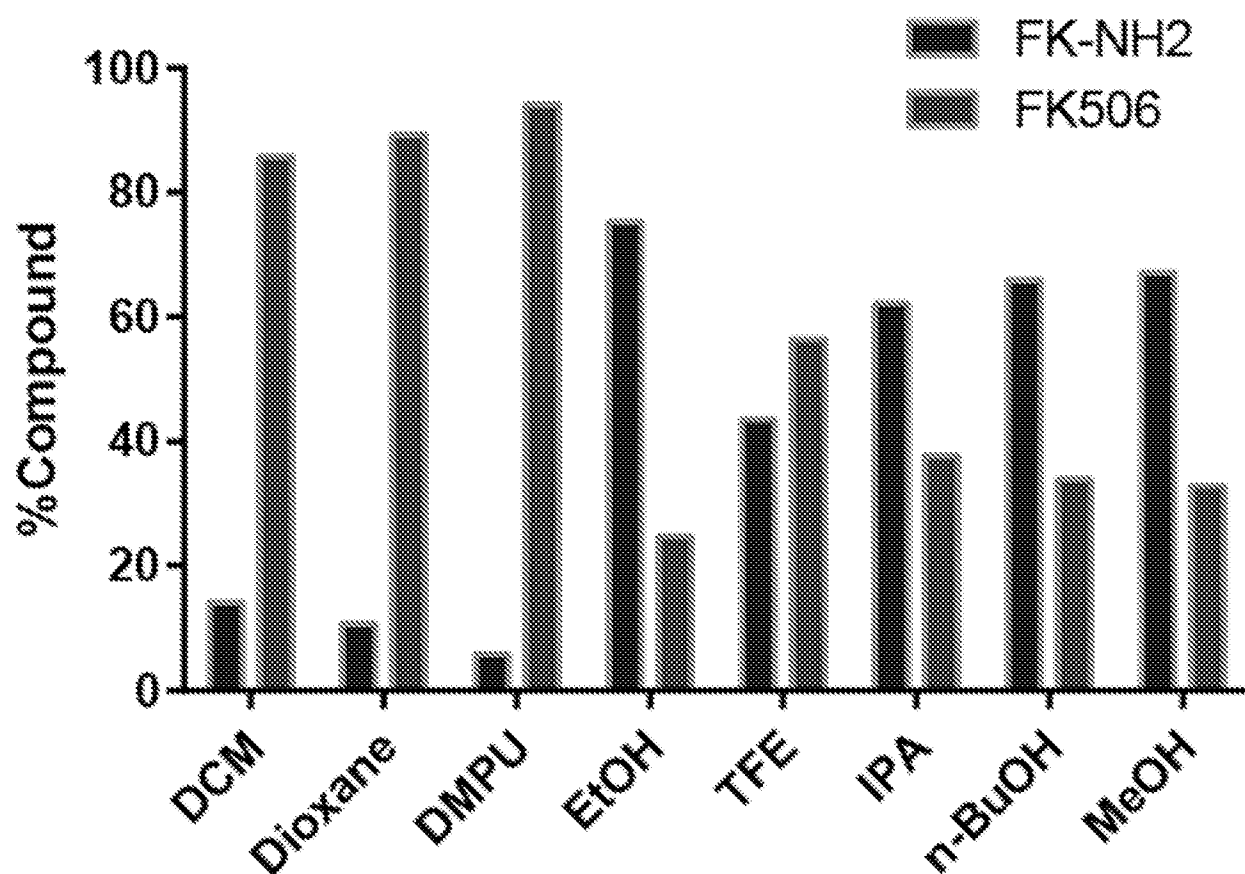


FIG. 16

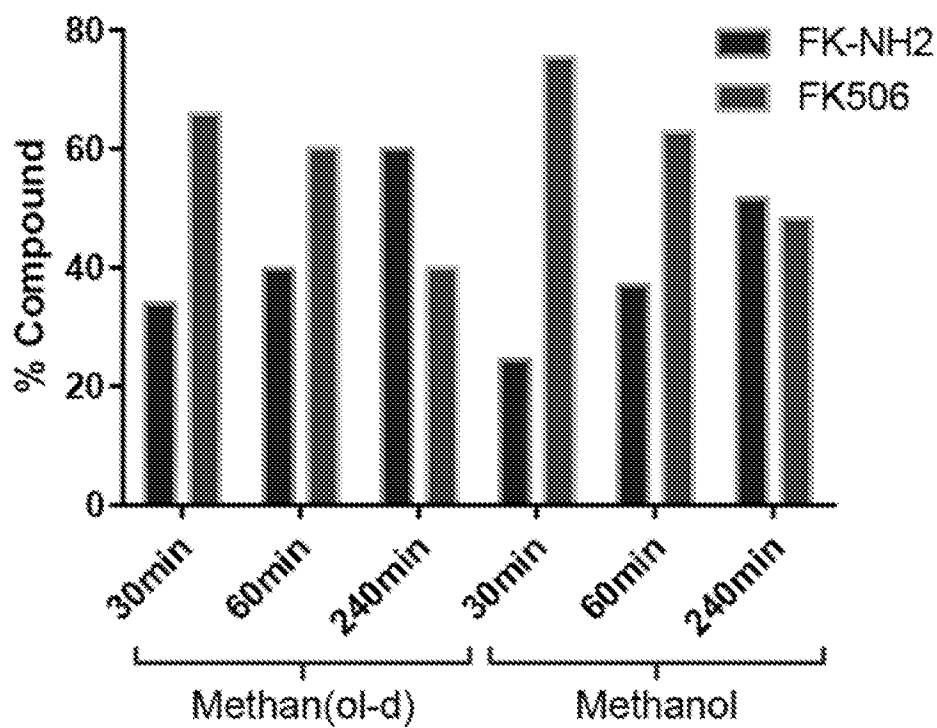


FIG. 17

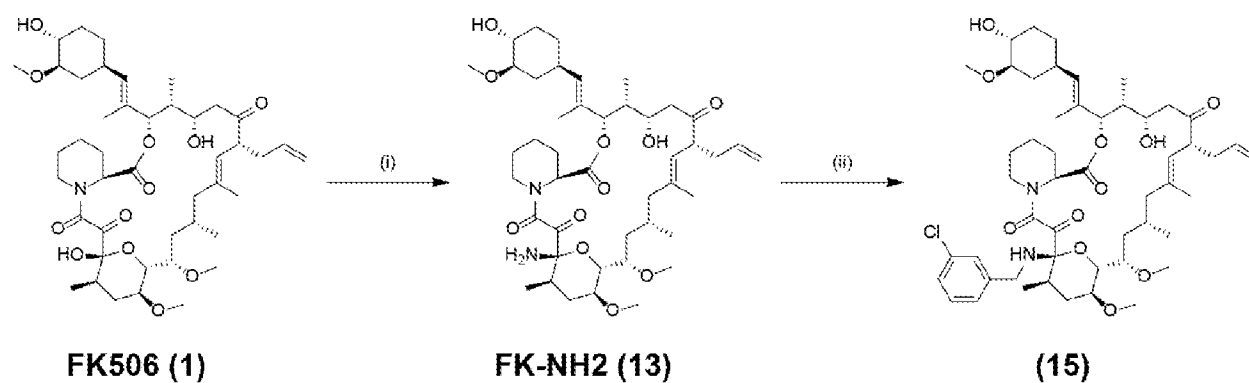


FIG. 18A

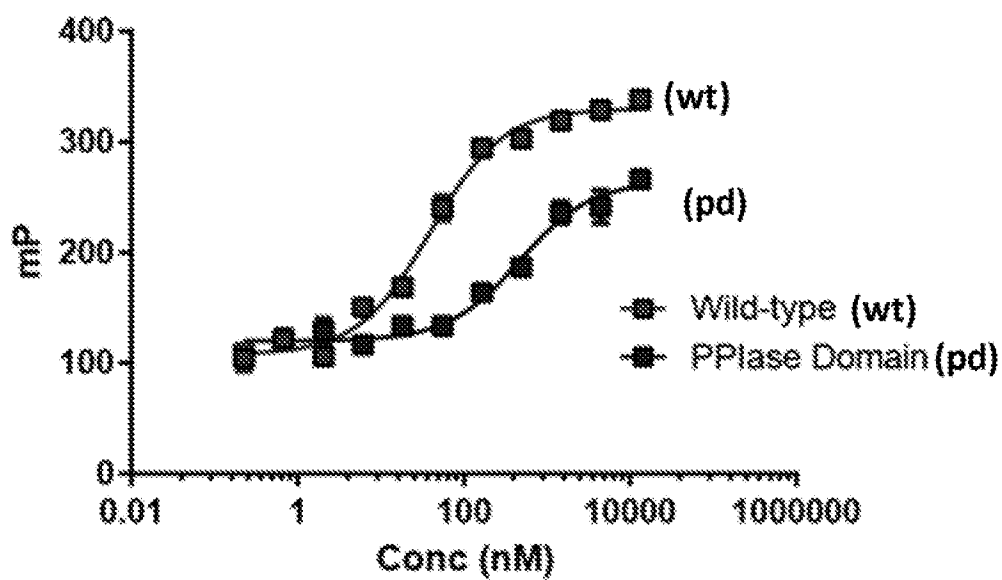
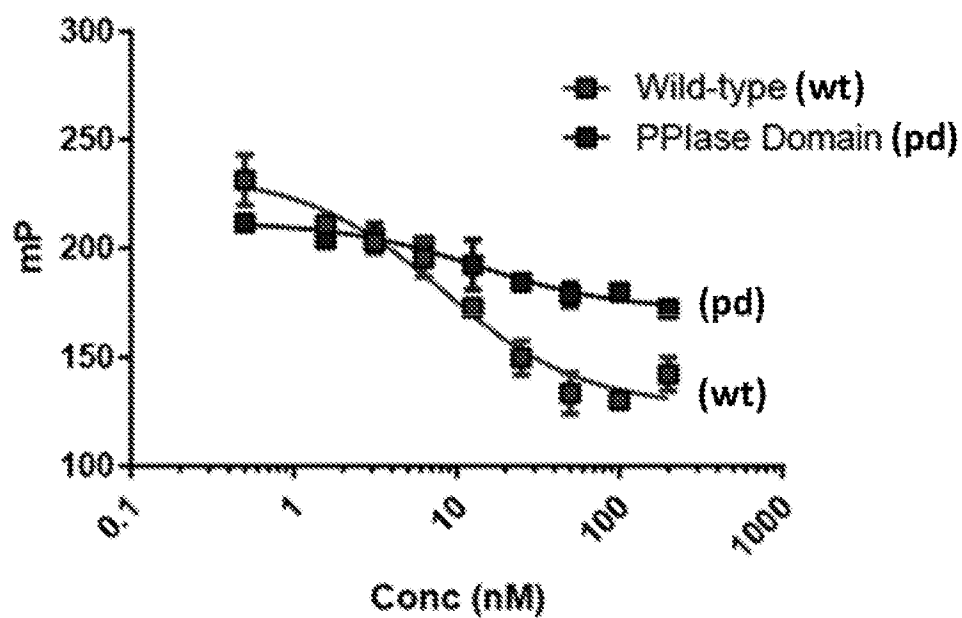


FIG.18B



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FIG. 19A

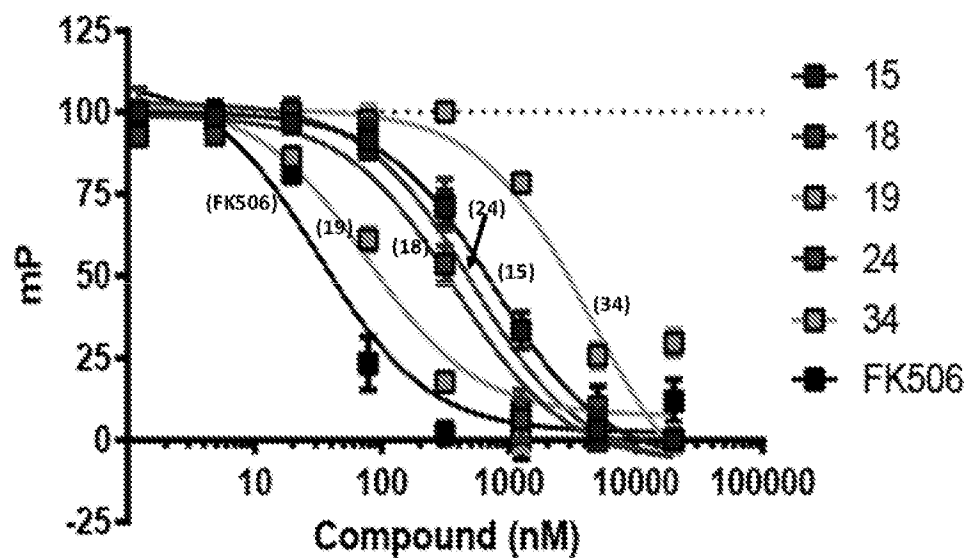
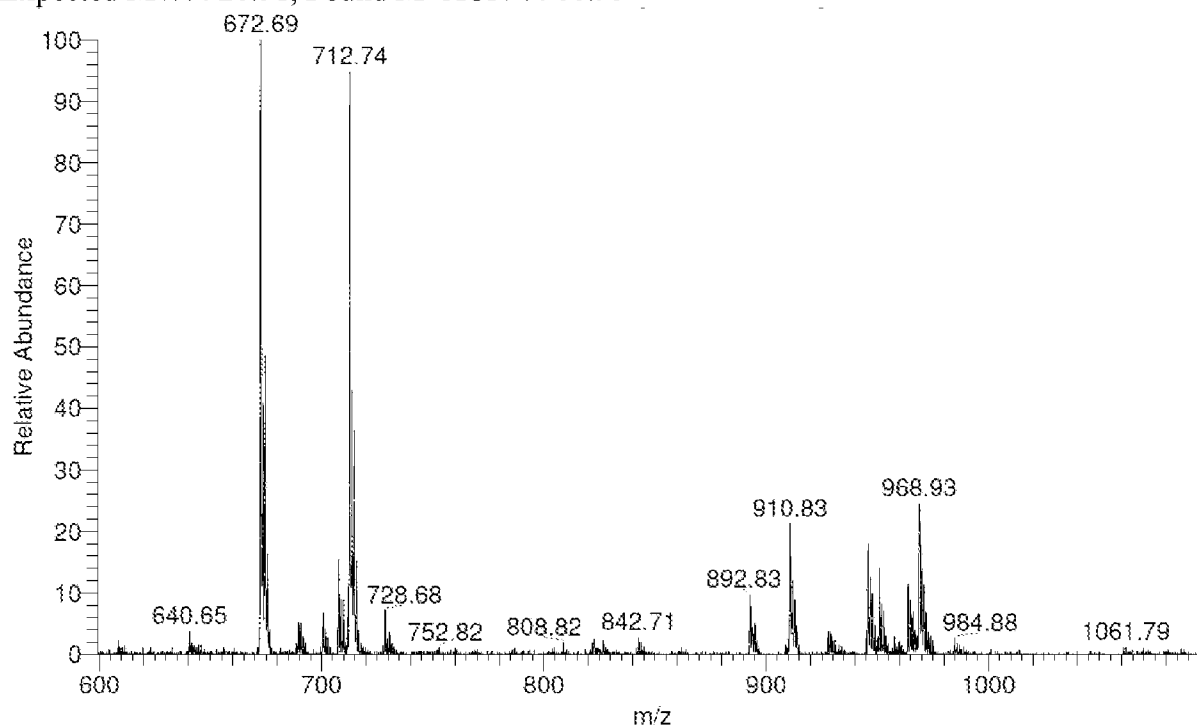


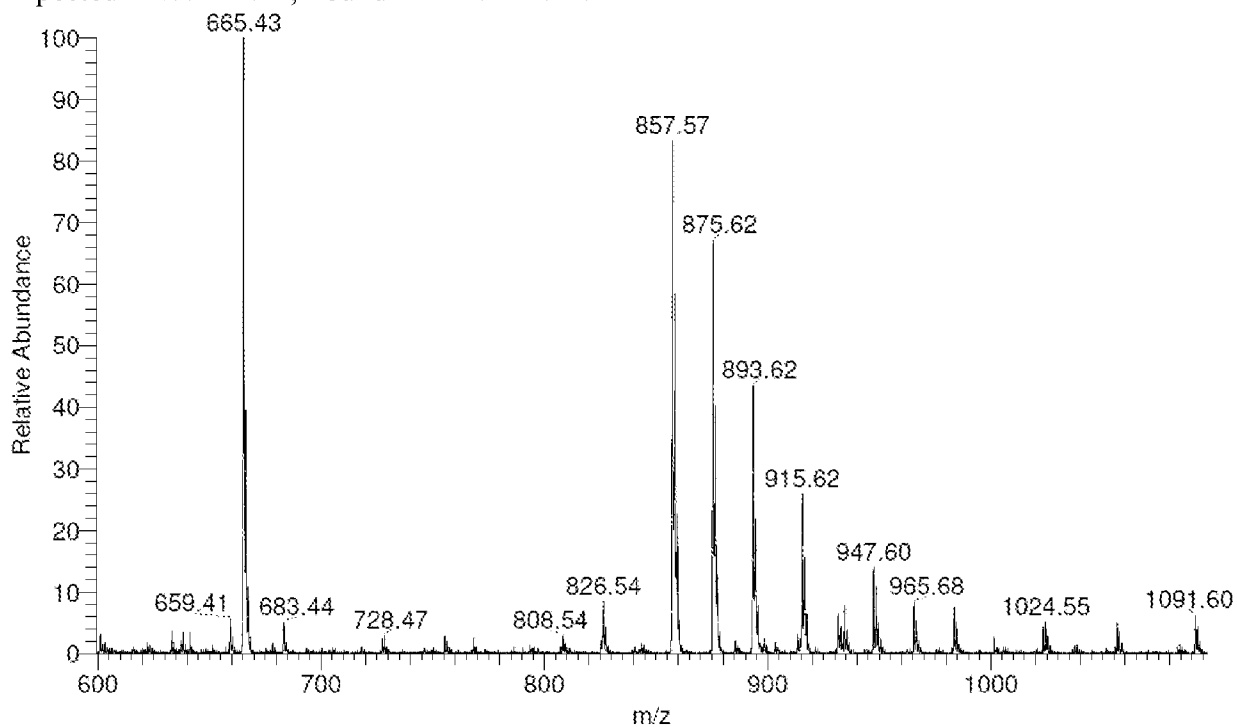
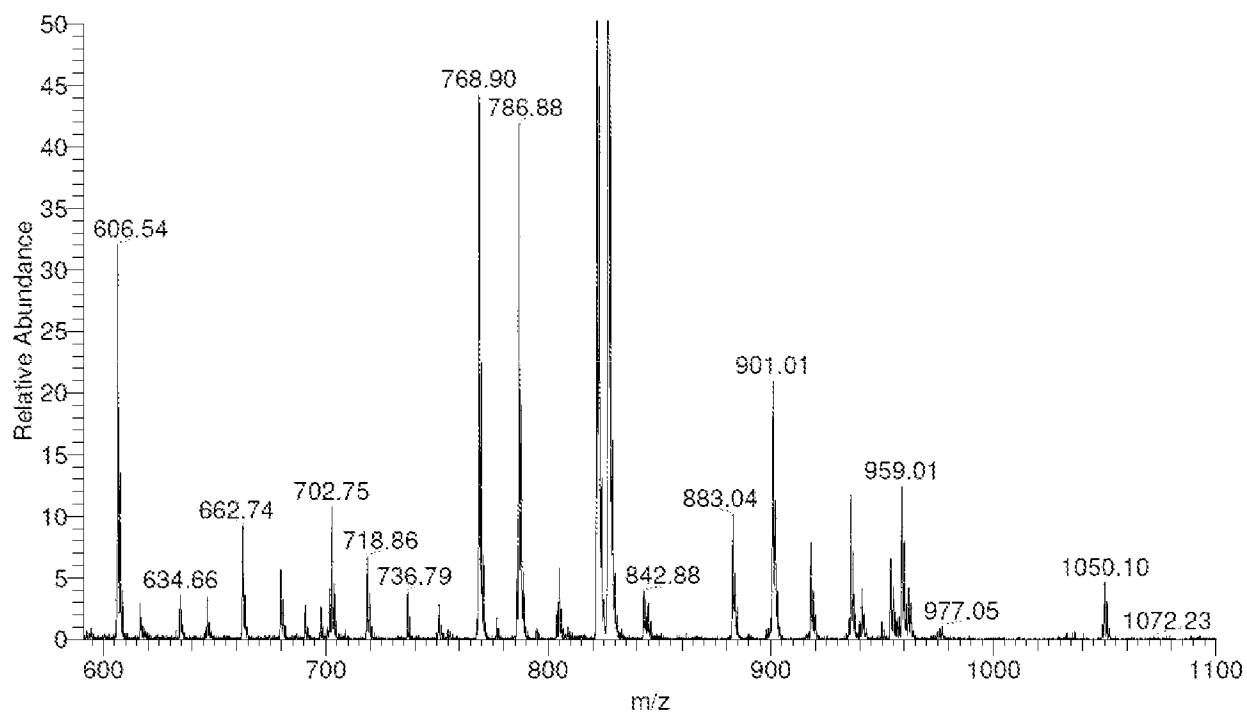
FIG. 19B

	K_i (nM)
15	187 ± 75
18	90.5 ± 50.5
19	17.1 ± 13.0
24	124 ± 93
34	1330 ± 740
FK	4.20 ± 6.40

FIG. 20A.

*Compound 15:*Expected MW: 926.51, Found $M+ACN^+$: 968.93

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FIG. 20B*Compound 16:*Expected MW: 892.54, Found $M+H^+$: 893.62.**FIG. 20C***Compound 18:*Expected MW: 916.57, Found $M+ACN^+$: 959.01.

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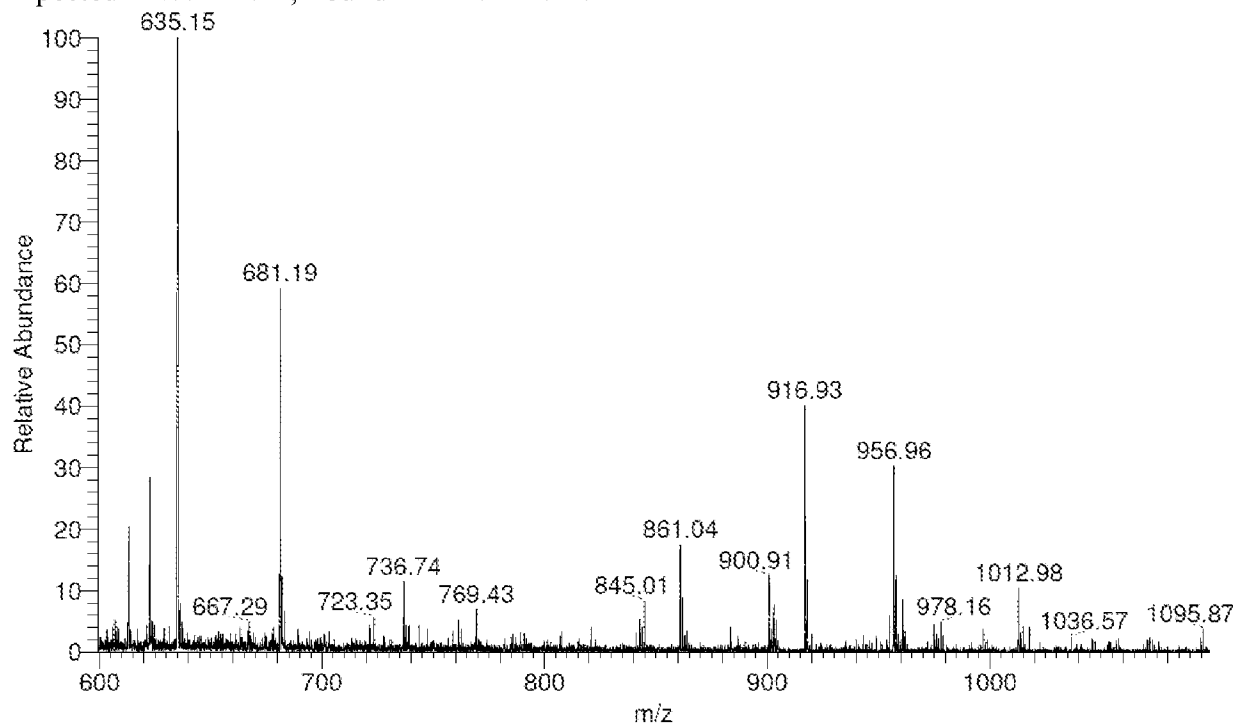
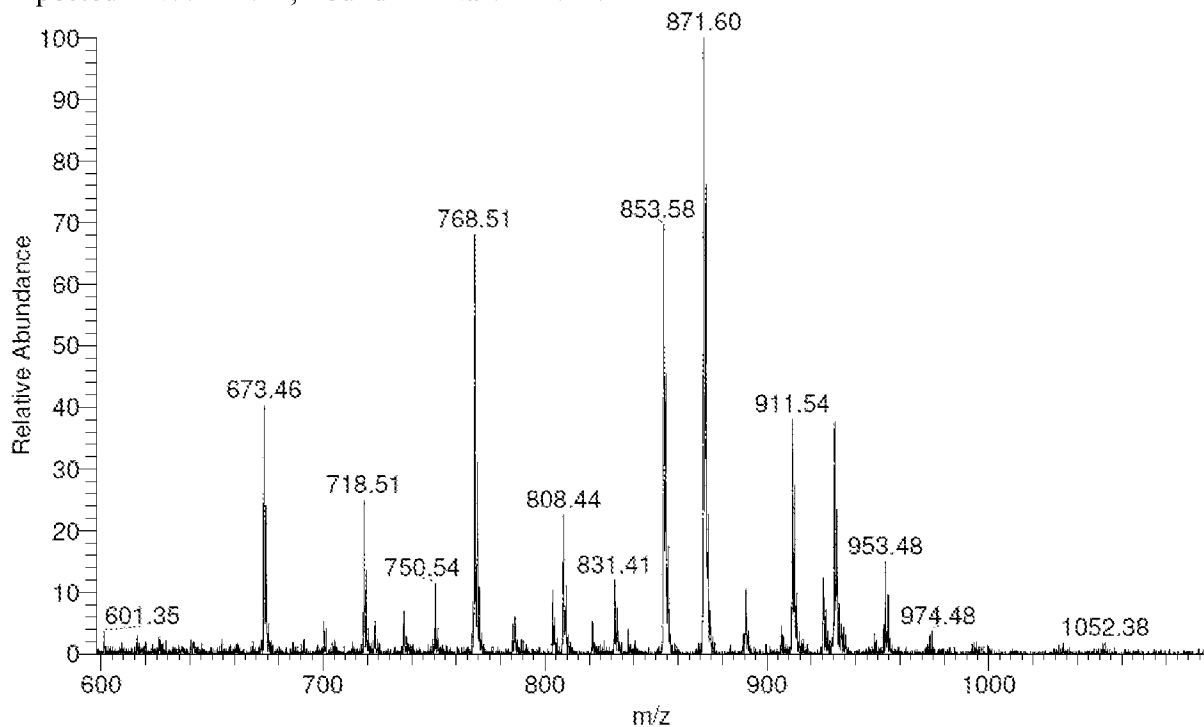
FIG. 20D*Compound 19:*Expected MW: 860.50, Found $M+H^+$: 861.04.**FIG. 20E***Compound 22:*Expected MW: 830.53, Found $M+Na^+$: 853.58.

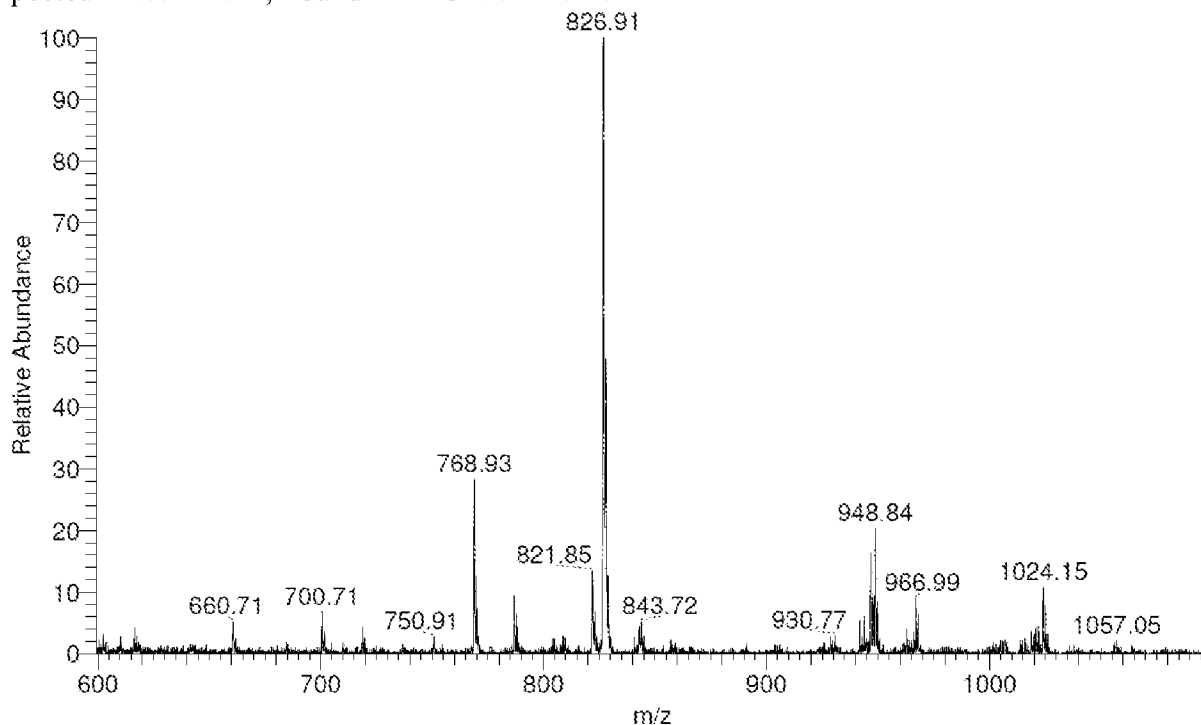
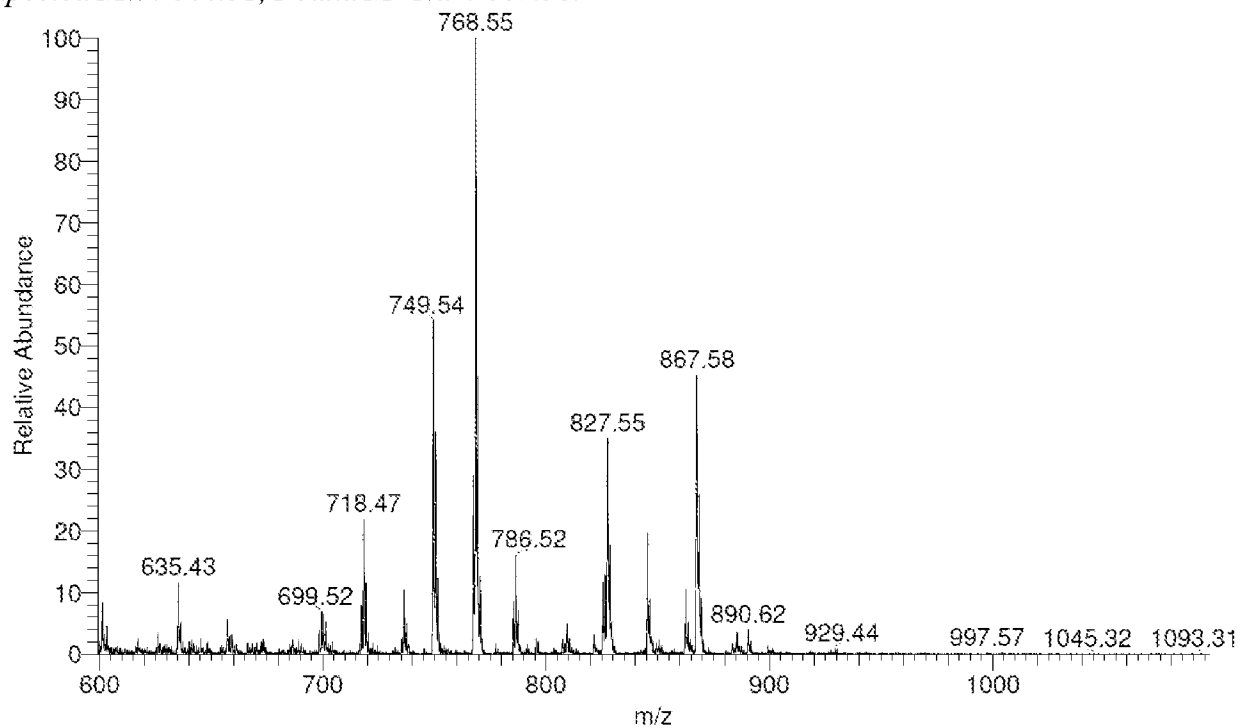
FIG. 20F*Compound 24:*Expected MW: 924.42, Found $M+ACN^+$: 966.99.**FIG. 20G***Compound 27:*Expected MW: 844.51, Found $M+Na^+$: 867.58.

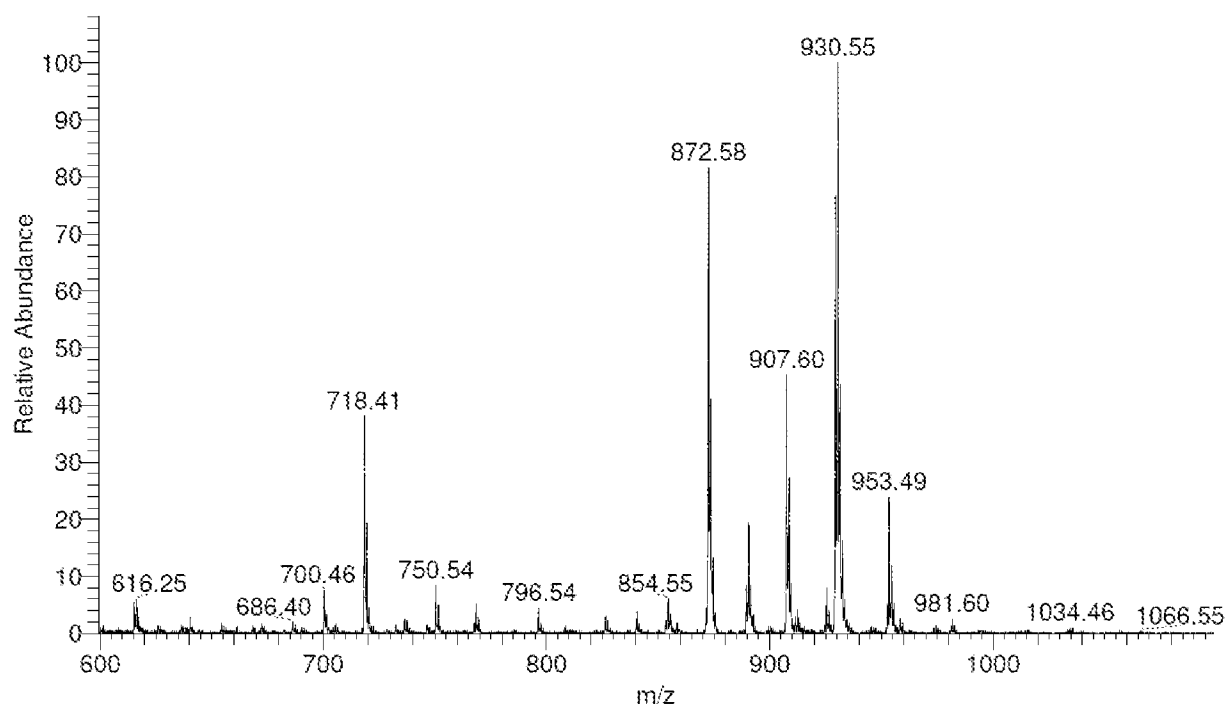
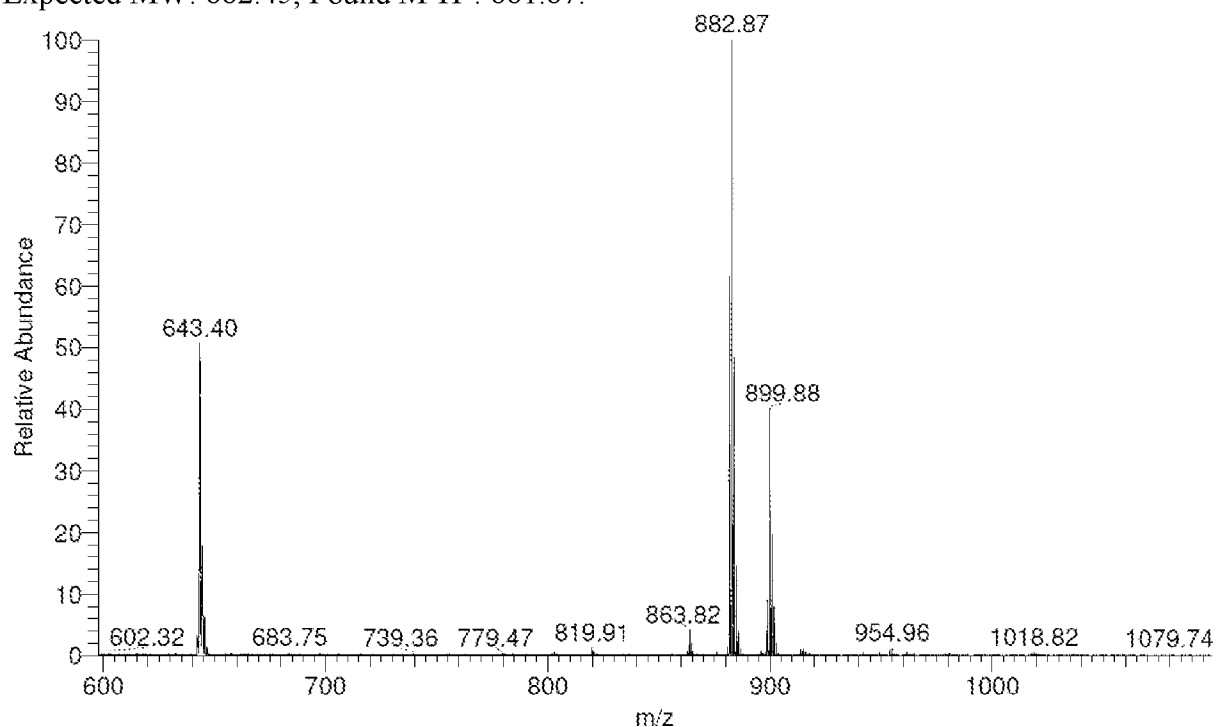
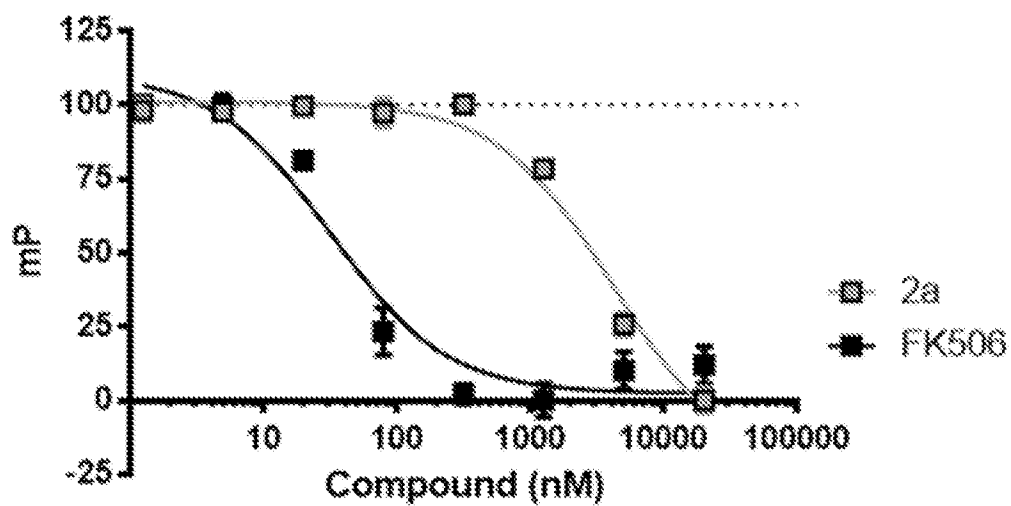
FIG. 20H*Compound 29:*Expected MW: 924.42, Found $M+ACN^+$: 966.99.**FIG. 20I***Compound 34:*Expected MW: 882.45, Found $M-H^+$: 881.87.

FIG. 21



2a	FK506
4270	31.64
125.9	108.2

FIG. 22

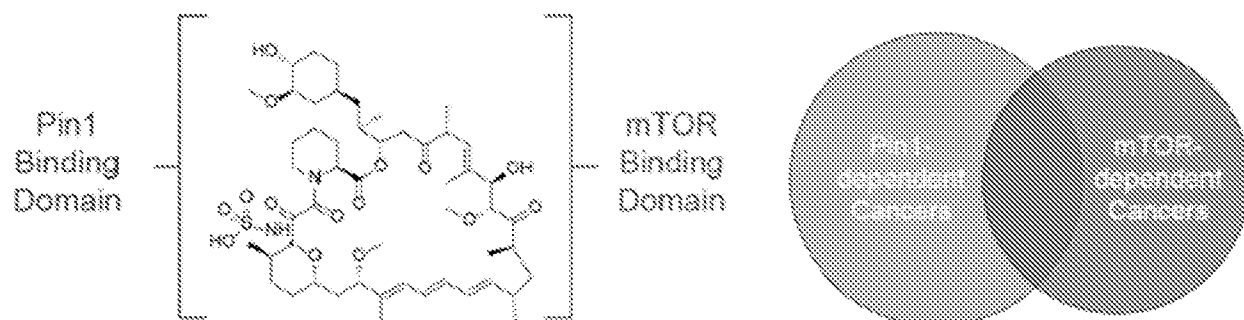
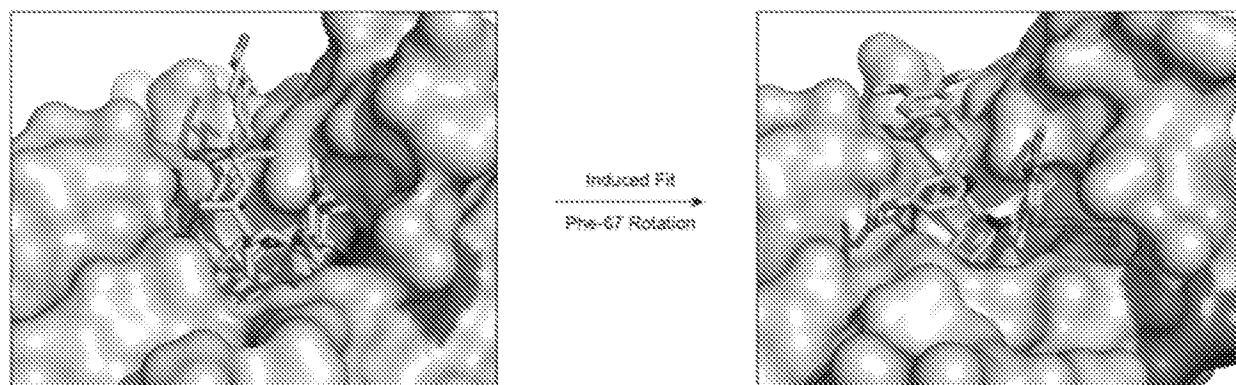


FIG. 23



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/66862

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 1/15, C12N 15/09, C12N 15/61 (2018.01)

CPC - C12N 15/67, C12N 9/20, C12N 9/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---	Liu et al. 'Membrane Permeable Cyclic Peptidyl Inhibitors against Human Peptidylprolyl Isomerase Pin1', Journal of Medicinal Chemistry, 24 February 2010 (24.02.2010), Vol.53, pages 2494-2501; p2497, p2498	1, 56-57 ----- 7-8, 17-18
X --- Y --- A	Rostam et al. 'Peptidyl-prolyl isomerases: Functionality and potential therapeutic targets in cardiovascular disease', Clinical and Experimental Pharmacology and Physiology, 05 November 2014 (05.11.2014), Vol.42, pages 117-124; Abstract, p117, p118, p119, p121	1, 11 ----- 2-4, 6, 12-14, 16, 58-71 ----- 5, 7-10, 15, 17-20
Y --- A	Donald et al. 'C10 N-Acyl modified FK-506: A possible hybrid analogue of the transition state of peptidyl-prolyl cis-trans isomerization', Tetrahedron Letters, 05 March 2001 (05.03.2001), Vol.32, pages 1375-1378; p1375, p1376, p1377	2-4, 6, 12-14, 16, 58-71 ----- 1, 5, 7-10, 15, 17-20
Y	Maiaru et al. 'The stress regulator FKBP51 drives chronic pain by modulating spinal glucocorticoid signaling', Science Translational Medicine, 10 February 2016 (10.02.2016), Vol.8, pages 1-10; Abstract, p1	66-68, 70-71
Y	Sinclair et al. 'Dysregulation of glucocorticoid receptor co-factors FKBP5, BAG1 and PTGES3 in prefrontal cortex in psychotic illness', Scientific Reports, 18 December 2013 (18.12.2013), Vol.3, pages 1-10; p3	66, 69
A	Wang et al. 'Peptidyl-Prolyl Isomerase Inhibitors', Peptide Science, 09 March 2006 (09.03.2006), Vol.84, pages 125-146; p133, p140	5, 9-11, 15, 19-20
A	US 5,296,489 A (Donald et al.) 22 March 1994 (22.03.1994); entire document	1-20, 56-71

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 April 2018

Date of mailing of the international search report

02 MAY 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/66862

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.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1 20 and 56-71

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/66862

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-20 and 56-71, directed to a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound, comprising a macrolide with a pipecolyl moiety

Group II: Claims 21-36, directed to FK506 binding protein (FKBP) inhibitor compound, comprising a macrolide with a pipecolyl moiety.

Group III: Claims 37-55, 72-75, directed to compound of formula I or II

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding technical features for the following reasons:

Special Technical Features

Group I includes the special technical features of a to a peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin 1) inhibitor compound that are not required by Groups II-III

Group II includes the special technical features of FK506 binding protein (FKBP) inhibitor compound that are not required by Groups I and III

Group III includes the special technical features of compound of formula I or II that are not required by Groups I-II

Shared Technical Features

Groups I-III share the technical feature of a macrolide

Groups I-II share the technical feature of with a pipecolyl moiety

However, these shared technical feature does not represent a contribution over prior art as being anticipated by US 7,507,752 B2 to He et al. (hereinafter 'He') which discloses macrolide with a pipecolyl moiety (col 35, ln 1-3, meridamycin analogues that have pipecolyl moiety)

Therefore, Groups I-III lack unity under PCT Rule 13 because they do not share a same or corresponding technical feature.

Note:

claim 31: At the end of claim 31, the term "**covers FK506?*" appears to be a typo. For the purposes of completing this lack of unity analysis, the term has been ignored