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(54) **Title**: AUTOPHAGY-INHIBITING COMPOUNDS AND USES THEREOF

(57) **Abstract**: The present disclosure describes a compound for use in the treatment of cancer, infectious disease, and autoimmune disorders. The compounds herein can inhibit autophagy in an affected cell to promote cell death. Further, the compound can be used to overcome the drug-resistance of certain cells.

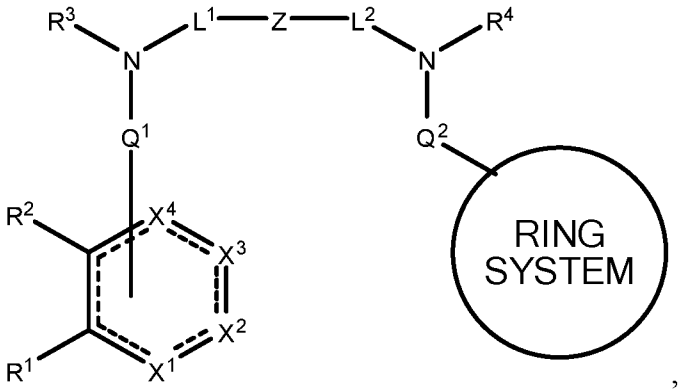
# AUTOPHAGY-INHIBITING COMPOUNDS AND USES THEREOF

## BACKGROUND

**[0001]** Tumors use various resistance mechanisms to defeat present therapies. One of the resistance mechanisms deployed by tumors relies on the activation of autophagy in tumor cells and stroma to provide nutrients to the growing tumor. Inhibition of autophagy can restore sensitivity of tumors to present therapies, provide for more effective therapeutic regimens and improve patient survival.

## SUMMARY OF THE INVENTION

**[0002]** In some embodiments, the invention provides a compound of the following formula:



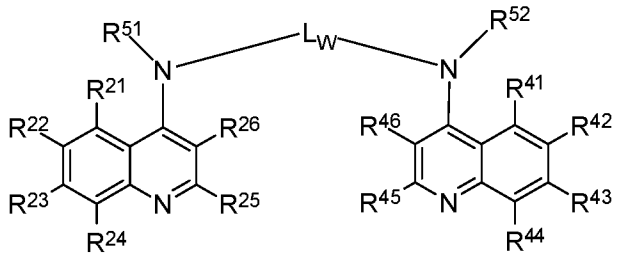

,

wherein: each ------- is independently a single bond or a double bond; RING SYSTEM is a cyclic group; $X^1$ is $CR^5$, $CR^5R^6$, N, $NR^5$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^2$ is $CR^7$, $CR^7R^8$, N, $NR^7$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^3$ is $CR^9$, $CR^9R^{10}$, N, $NR^9$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^4$ is $CR^{11}$, $CR^{11}R^{12}$, N, $NR^{11}$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$, wherein one of $X^1$, $X^2$, $X^3$, and $X^4$ is a carbon atom connected to $Q^1$; $Q^1$ is C=O, C=S, $C=CR^{13}R^{14}$, $C=NR^{13}$, or a bond; $Q^2$ is C=O, C=S, $C=CR^{15}R^{16}$, $C=NR^{15}$, or a bond; $L^1$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, oxo, or halogen, or $L^1$ together with Z forms a heterocycle; $L^2$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, oxo, or halogen, or a bond; Z is S, C=O, C(O)O, C=S, S=O, $SO_2$, $NHC(O)NR^{17}$, $OC(O)NR^{17}$, $C(O)NR^{17}$, $NR^{17}$, $CHR^{18}$, or cyclic group that is unsubstituted or substituted, or Z together with $L^1$ forms a

heterocycle; each of $R^1$ and $R^2$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring; each of $R^3$ and $R^4$ is independently alkyl, alkenyl, alkynyl, an acyl group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; each of $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, and $R^{12}$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H; each of $R^{13}$ and $R^{14}$ is independently alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^{13}$ and $R^{14}$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted; each of $R^{15}$ and $R^{16}$ is independently alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^{15}$ and $R^{16}$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted; $R^{17}$ is alkyl, alkenyl, an acyl group, a carboxaldehyde group, an ester group, an amine group, an amide

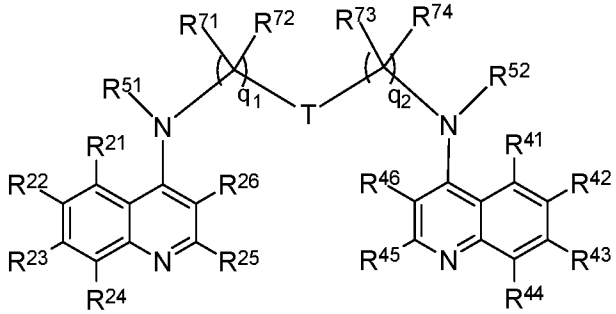
group, a carbonate group, a carbamate group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; and $R^{18}$ is $(C_3\text{-}C_{10})$-alkyl, $(C_3\text{-}C_{10})$-alkenyl, hydroxyl, $CH_2O$(aryl), $CH_2CH_2O$(aryl), alkoxy, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or halogen, wherein when $X^1$ is N, $X^3$ is CH, $R^1$ and $R^2$ together with the atoms to which they are bound form a mono-substituted aromatic six-membered carbocycle, and RING SYSTEM is a quinoline moiety that is substituted or unsubstituted or an isoquinoline moiety that is substituted or unsubstituted, or a pyridine moiety that is substituted or unsubstituted, then Z is not arylene or a 3,5-disubstituted piperidine group, and $R^{17}$ is not H, methyl, $CH_2$(aryl) or monosubstituted ethyl wherein the monosubstitution is with a heteroatom or aryl, or a pharmaceutically-acceptable salt or tautomer thereof.

**[0003]** In one aspect, the current disclosure provides a compound represented by a structure of Formula (XX):




(XX), or a salt thereof, wherein: $R^{21}$, $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{43}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, halogen, hydroxyl, nitro, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; $R^{51}$ and $R^{52}$ are independently selected from hydrogen and optionally substituted alkyl; and $L_W$ is an optionally substituted heterocycle or an optionally substituted carbocycle; or an optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted heteroalkylene, each one of which is interrupted by an optionally substituted heterocycle. In some embodiments, $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen and halogen. In some embodiments, $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently hydrogen. In some embodiments, $R^{23}$ and $R^{43}$ are independently selected from hydrogen, halogen, hydroxyl, and haloalkyl. In some embodiments, $R^{23}$ and $R^{43}$ are independently selected from F, Cl, Br, and I. In some embodiments, $R^{23}$ and $R^{43}$ are independently selected from F and Cl. In some embodiments, $R^{51}$ and $R^{52}$ are each hydrogen.

**[0004]** In some embodiments, $L_W$ is optionally substituted alkylene interrupted by an optionally substituted heterocycle. In some embodiments, $L_W$ is optionally substituted alkylene comprising 1-12 carbon atoms. In some embodiments, a compound of the current disclosure is represented by Formula (XXA):

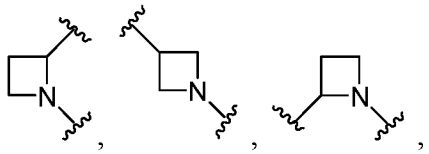


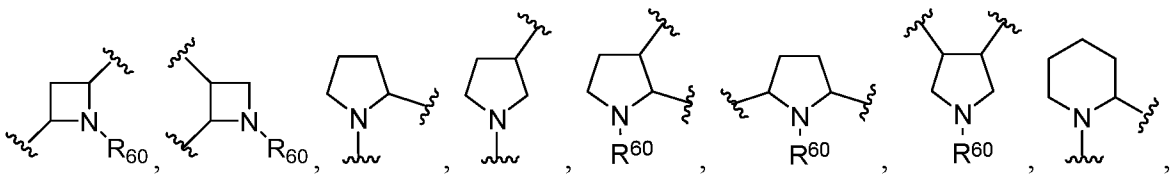
(XXA), wherein: $q_1$ is 0-5; $q_2$ is 0-5; $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ are independently selected at each occurrence from hydrogen, halogen, hydroxyl, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; and T is optionally substituted heterocycle.

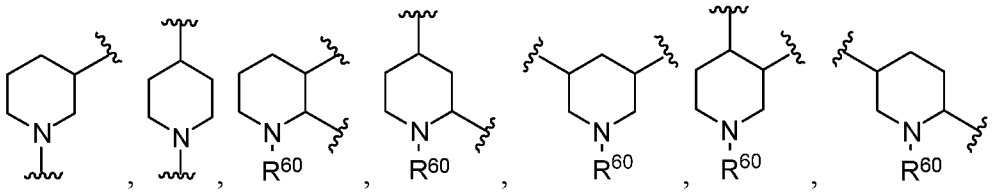
**[0005]** In certain embodiments, $L_W$ is further selected from an optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, and optionally substituted heteroalkylene, each one of which is interrupted by an optionally substituted carbocycle. In certain embodiments, $L_W$ is further selected from an optionally substituted alkylene interrupted by an optionally substituted carbocycle.

**[0006]** In some embodiments, each occurrence of $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ is independently selected from hydrogen, halogen, hydroxyl, cyano and optionally substituted alkyl. In some embodiments, $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ are each hydrogen. In some embodiments, $q_1$ is 1-3 and $q_2$ is 1-3. In some embodiments, $q_1$ is 2 and $q_2$ is 2; or $q_1$ is 2 and $q_2$ is 3; or $q_1$ is 1 and $q_2$ is 3.

**[0007]** In some embodiments, T is an optionally substituted 3- to 7-membered heterocycle. In some embodiments, T is optionally substituted saturated 3- to 7-membered heterocycle. In some embodiments, T is selected from piperidine, pyrrolidine, and azetidine, any of which is optionally substituted. In some embodiments, T is selected







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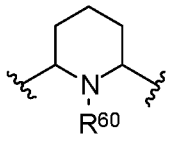
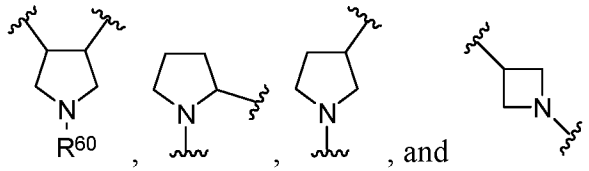
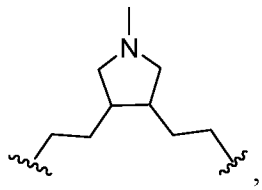


, wherein $R^{60}$ is hydrogen or optionally substituted alkyl. In some embodiments, T is selected from



. In some embodiments, $R^{60}$ is optionally substituted alkyl. In some embodiments, $L_W$ is selected from



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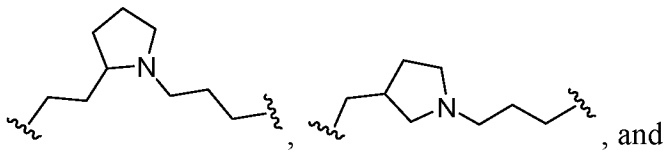
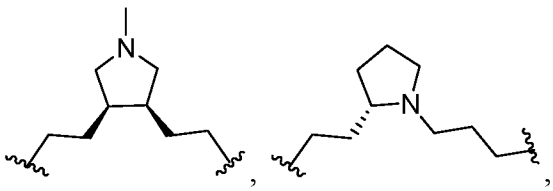


. In some embodiments, $L_W$ is selected from



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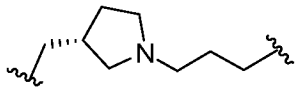

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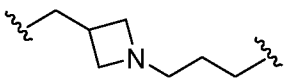
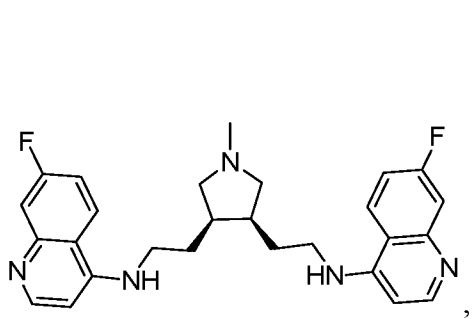


. In some embodiments, a compound of the current disclosure is represented by any one of the following formula:



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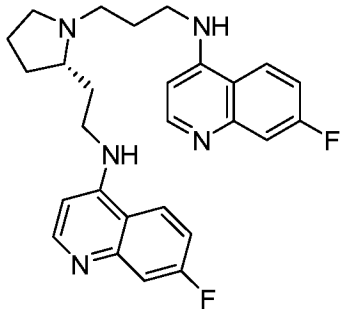

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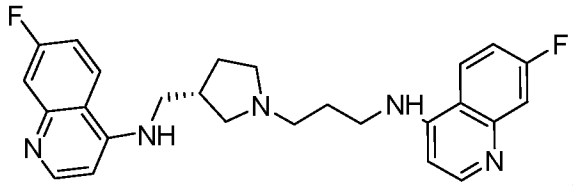

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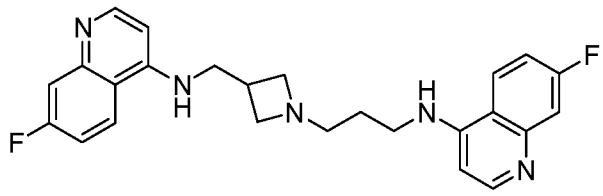


or a salt of anyone thereof.

**[0008]** In certain embodiments, a compound or salt of the disclosure kills human A375 melanoma cells with an $IC_{50}$ value of less than about 10 μM. In certain embodiments, a compound or salt of the disclosure does not inhibit hERG channel activity. In certain embodiments, a compound or salt of the disclosure exhibits a hERG $IC_{50}$ value of about 10 μM or more. The ratio of hERG $IC_{50}$ value to the cytotoxicity $IC_{50}$ value may be about about 5 or greater.

In some embodiments, the invention provides a pharmaceutical composition comprising: a) a therapeutically-effective amount of a compound herein; and b) a pharmaceutically-acceptable excipient.

**[0009]** In some embodiments, the disclosure provides a method of treating a condition, the method comprising administering to a subject in need thereof a therapeutically-effective amount of a compound or salt disclosed herein. In another aspect, the current disclosure provides a method of inducing autophagosomal aggregation, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or salt described herein. In another aspect, the current disclosure provides a method of inhibiting autophagy in tumor cells, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or salt described herein.

## DETAILED DESCRIPTION

Methods

**[0010]** The disclosure provides compounds that can be used in the treatment of, for example, cancer and parasitic infectious diseases. Tumor cells evolve during sequential treatment regimens to develop resistance to therapeutics over time, which can lead to aggressive diseases that are unresponsive to present therapies. Likewise, malaria parasites have evolved during decades of exposure to become resistant to chloroquine, once a mainstay therapy. The compound or salts of the present disclosure can be used as therapeutics to overcome

resistance in cancer cells and malarial parasites.

**[0011]** Normal and transformed mammalian cells possess different types of vesicles with different properties and functions that move throughout the cell in a coordinated manner. This intracellular vesicle trafficking maintains cellular functions including receptor-mediated endocytosis, phagocytosis, secretion, transcytosis and autophagy. Changes in intracellular vesicle movement and localization induced by environmental or genetic changes can change polypeptide maturation, protein and lipid metabolism, organelle turnover, antigen presentation, membrane protein translocation, neurotransmitter and hormone secretion, and intra- and intercellular signaling and thus alter cellular physiology. One of these phenotypes is that of a cell dependent on autophagy for survival.

**[0012]** Autophagy is a cellular catabolic process whereby, for example, dysfunctional organelles, protein aggregates, and cellular proteins are engulfed in autophagosomes for recycling to sustain cell survival. Autophagosomes containing damaged proteins and organelles fuse with lysosomes, highly acidic vesicles that contain hydrolytic enzymes that digest the autophagosome's cargo of proteins, nucleic acids, lipids and carbohydrates and thus allow the reutilization of nutrients for cell growth and proliferation. Destabilization of lysosomes can also result in the leakage of acid hydrolases including, for example, cathepsins, nucleases, proteases, glycosidases, lipases, phosphatases, and sulfatases into the cell interior, causing widespread damage to the cell and resulting in cell death.

**[0013]** Autophagy can be induced by, for example, hypoxia, the unfolded protein response, nuclear p53 activation, nutrient starvation, or reactive oxygen species. Autophagy can be induced by certain drugs including, for example, imatinib, cetuximab, TNF-related apoptosis-inducing ligand (TRAIL), proteasome inhibitors, vorinostat, arsenic trioxide, tamoxifen, cyclooxygenase inhibitors, nelfinavir, rapamycin, temsirolimus, everolimus, deforolimus, Torin1, PP242, AZD8055, WYE132, NVP-BEZ235, PI-103, metformin, fluoxetine, maprotiline, valproic acid, verapamil, minoxidil, and clonidine.

**[0014]** Autophagy can be inhibited by, for example, genetic ablation of ATGs (autophagy-related genes), 3-methyladenine, wortmannin, LY290002, chloroquine (CQ), hydroxychloroquine (HCQ), bafilomycin A1, monensin, clomipramine, or lucanthone.

**[0015]** Autophagy can be induced by, for example, the formation of the ULK1 (Unc-51 like autophagy activating kinase 1) serine/threonine kinase complex. The ULK1 complex contains ULK1, ATG13, and ATG17, and is able to integrate stress signals received through the mTORC1 complex. The mTOR pathway is activated downstream of the PI3K-AKT pathway, which can be dysregulated during cancer. Stress signals can cause inhibition of mTOR kinase

activity, preventing phosphorylation of autophagy-related genes including, for example, ATG13. When mTOR kinase activity is inhibited, ATG13 is able to associate with ULK1 to promote autophagosome formation.

**[0016]** Autophagosome formation involves, for example, vascular sorting protein 34 (Vsp34), a PI3 kinase that forms a complex with Beclin-1. The Beclin-1/Vsp34 complex can lead to production of Ptlns3P, which is important for the recruitment of other autophagy-related genes for formation of the autophagosome. During the initiation phase of autophagy, formation of the ATG5-ATG12-ATG16 complex promotes the recruitment and conversion of cytosolic-associated protein light chain 3 (LC3-I) protein to the membrane-bound, lipidated form, LC3-II. LC3 can be conjugated to phosphatidylethanolamine and incorporated into the membrane by an ATG7- and ATG3-dependent activation and transfer cascade initiated by cleavage of LC3 by the cysteine protease ATG4. Upon completion of autophagosome formation, and with the exception of a proportion of LC3-II that remains bound to the luminal membrane, the ATG proteins and LC3-II can be recycled in the cytosol. The presence of LC3-II in the membrane of autophagosomes allows the detection and detection and quantitation of autophagosomes in cells by histological techniques such as immunohistochemistry or immunofluorescence. Autophagosomes are revealed by light microscopy as punctate staining in the perinuclear region of cells.

**[0017]** Autophagy can have several functions within the cell. Autophagy can be a homeostatic mechanism used to rid the cell of damaged organelles and proteins to limit cell growth and genomic instability. Autophagy can also be a mechanism underlying cell death, as dying cells can contain features reflective of autophagy. By limiting genomic instability and degrading damaged proteins, autophagy can also be a tumor suppression mechanism. In cancer cells, autophagy can confer stress tolerance leading to promotion of tumor cell survival. Autophagy can also facilitate tumor dormancy, which can be mediated via senescence.

**[0018]** Tumor cells use autophagy as a resistance mechanism to survive the metabolic stress caused by the mismatch between increased proliferation induced by pathological growth-promoting signals, for example from aberrantly activated protein kinases, and simultaneous growth interference resulting from cellular exposure to cytotoxic drugs, hypoxia, and oxidative stress or genetic mutations that damage cellular constituents such as proteins, DNA or organelles, or limiting nutrient supplies caused, for example, by inadequate vascularization. Increased cellular self-digestion can also be induced by, for example, mTOR inhibitors, Bcl-2/Bcl-xL inhibitors via the release of Beclin from an inactivating complex with Bcl-2,

proteasome inhibitors that cause undigested proteins to accumulate in the cytoplasm and endoplasmic reticulum, AMP kinase activators, agents mimicking or inducing nutrient deprivation or by radiation exposure.

**[0019]** The increased proliferation of cancer cells can lead to higher metabolic demand and activation of autophagy. Cancer therapeutics can mimic nutrient deprivation and starvation, causing autophagy to be upregulated in response to treatment. The upregulation of autophagy can be associated with therapeutic resistance and is a mechanism by which tumor cells can escape death. The activation of autophagy in tumor cells by cytotoxic and metabolic stresses, including hypoxia and nutrient deprivation, can increase cellular biosynthesis and survival of the cancer cells.

**[0020]** Inhibition of autophagy in tumor cells can increase the efficacy of chemotherapeutics and overcome the autophagy-resistant phenotype of some tumor cells. A therapeutic that can interfere with lysosomal function and inhibit lysosome-autophagosome fusion would potentially cause autophagosome accumulation, stall organelle digestion, and prevent nutrient recycling, resulting in death of autophagy-dependent tumor cells.

**[0021]** The antimalarial drug chloroquine and the anti-rheumatic and anti-autoimmune therapeutic hydroxychloroquine are lysosomotropic 4-aminoquinolines that accumulate in acidic organelles such as lysosomes, phagosomes, late endosomes and fungal or protozoal vacuoles, reduce the acidity of their content, impair vesicle fusion and trafficking and inhibit autophagy, phagocytosis, and vesicle secretion. Chloroquine can improve patient survival in combination with carmustine and radiation in glioma patients. Hydroxy chloroquine can be used in combination with various anti-cancer therapies, for example: with bortezomib in multiple myeloma; with sunitinib, temozolomide (TMZ), temsirolimus, or vorinostat in solid tumors; with docetaxel in prostate cancer; with ixabepilone in metastatic breast cancer; with TMZ and radiotherapy (RT) in glioblastoma; with bevacizumab, carboplatin, and paclitaxel in lung cancer; and with gemcitabine in pancreatic cancer. Hydroxychloroquine can be used as a monotherapy in prostate and renal cell cancer.

**[0022]** Both chloroquine and hydroxychloroquine have low potency as autophagy inhibitors; thus, achievable patient dosing can be inadequate for achieving a durable clinical response in cancer patients due to limiting toxicities. This dose limitation hinders using these agents effectively in the setting of cancer combination therapies. Autophagy inhibitors with higher potency than chloroquine or hydroxychloroquine and more favorable absorption, distribution, metabolism, and excretion (ADME) and toxicology profiles can be valuable.

**[0023]** Malaria parasitic protozoans spend part of their lifecycle as merozoites inside human

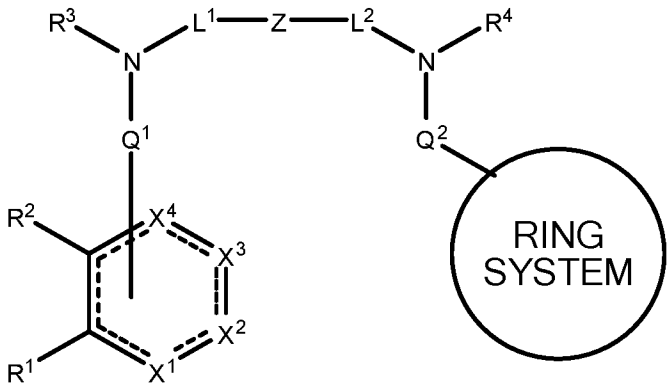
red blood cells where they feed on hemoglobin as a source of amino acids. The hemoglobin is degraded inside the acidic digestive vacuole of the parasite releasing the toxic cofactor protoporphyrin IX. Protoporphyrin IX is detoxified by crystallization to hemozoin inside the digestive vacuole of the parasite. Chloroquine-based compounds act as antimalarials by accumulating inside the digestive vacuole of the parasite, binding to protoporphyrin and inhibiting hemozoin formation. This increases the free protoporphyrin concentration in the vacuole to toxic levels which can kill the parasite.

**[0024]** In many parts of the world, chloroquine is no longer effective as a prophylactic or therapeutic for malaria infections due to the emergence of resistance. Resistance to chloroquine can be caused by carrier-mediated efflux of chloroquine from the digestive vacuole of the parasite. Newer compounds that inhibit hemozoin formation and are not substrates for the vacuolar chloroquine resistance transporter can kill chloroquine-resistant malarial strains and can be used in combination therapy regimens with drugs acting via other anti-protozoal mechanisms to hinder development of resistance.

Compounds

**[0025]** The present disclosure discloses compounds and salts for use in the treatment of, for example, cancer, autoimmune disease, or protozoal infection. The disclosed compounds and salts can be used, for example, to inhibit autophagy and induce cell death. The disclosed compounds and salts can be used in monotherapy or combination therapy with, for example, chemotherapy, radiation, or surgery. In some embodiments, the compound is a bisquinoline, a bisaminoquinoline, or a bisaminoaryl compound, any of which being symmetrical or unsymmetrical.

**[0026]** In some embodiments, the disclosure provides a compound of Formula I:




(I),

wherein: each ------- is independently a single bond or a double bond; RING SYSTEM is a cyclic group; $X^1$ is $CR^5$, $CR^5R^6$, N, $NR^5$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$;

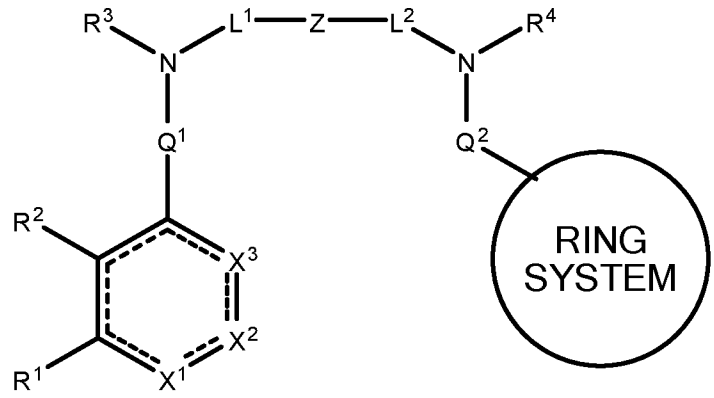
$X^2$ is $CR^7$, $CR^7R^8$, N, $NR^7$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^3$ is $CR^9$, $CR^9R^{10}$, N, $NR^9$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^4$ is $CR^{11}$, $CR^{11}R^{12}$, N, $NR^{11}$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$, wherein one of $X^1$, $X^2$, $X^3$, and $X^4$ is a carbon atom connected to $Q^1$; $Q^1$ is C=O, C=S, $C=CR^{13}R^{14}$, $C=NR^{13}$, or a bond; $Q^2$ is C=O, C=S, $C=CR^{15}R^{16}$, $C=NR^{15}$, or a bond; $L^1$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, oxo, or halogen, or $L^1$ together with Z forms a heterocyle; $L^2$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, oxo, or halogen, or a bond; Z is a cyclic or aliphatic cyclic group that is unsubstituted or substituted, O, S, C=O, C(O)O, C=S, S=O, $SO_2$, $NHC(O)NR^{17}$, $OC(O)NR^{17}$, $C(O)NR^{17}$, $NR^{17}$, or $CHR^{18}$, or Z together with $L^1$ forms a heterocyle; each of $R^1$ and $R^2$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring; each of $R^3$ and $R^4$ is independently alkyl, alkenyl, alkynyl, an acyl grouparyl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; each of $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, and $R^{12}$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H; each of $R^{13}$ and $R^{14}$ is independently alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl,

heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^{13}$ and $R^{14}$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted; each of $R^{15}$ and $R^{16}$ is independently alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^{15}$ and $R^{16}$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted; $R^{17}$ is alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; $R^{18}$ is alkyl, alkenyl, alkynyl, hydroxyl, alkoxy, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or halogen. In some embodiments, the formula above includes wherein when $X^1$ is N, $X^3$ is CH, $R^1$ and $R^2$ together with the atoms to which they are bound form a mono-substituted aromatic six-membered carbocycle, and RING SYSTEM is a quinoline moiety that is substituted or unsubstituted or an isoquinoline moiety that is substituted or unsubstituted or a pyridine moiety that is substituted or unsubstituted, then Z is not O, S, CHMe, CHEt, $CHCH_2OH$, 3,5-disubstituted piperidine, 1,3-cyclohexylene, or arylene, and $R^{18}$ is not H, Me, $CH_2CCH$, $CH_2CH_2OH$, methoxyethyl, methoxyethoxyethyl, or ethyl substituted with $NH_2$ or a primary, secondary, or tertiary amino group, $CH_2$(4-quinolinyl), $CH_2CH_2$(7-chloro-4-quinolinyl), or a pharmaceutically-acceptable salt or tautomer thereof.

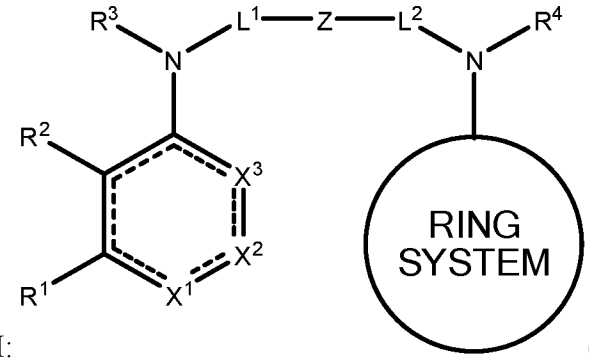
**[0027]** In some embodiments: Z is S, C=O, C(O)O, C=S, S=O, $SO_2$, $NHC(O)NR^{17}$, $OC(O)NR^{17}$, $C(O)NR^{17}$, $NR^{17}$, $CHR^{18}$, or a cyclic group that is unsubstituted or substituted and is connected to $L^1$ and $L^2$ such that $L^1$ and $L^2$ possess a 1,1- or 1,2- or 1,3- or 1,4-configuration on Z; $R^{17}$ is alkyl, alkenyl, an acyl group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, arylalkyl,

heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; and $R^{18}$ is $(C_3\text{-}C_{10})$-alkyl, $(C_3\text{-}C_{10})$-alkenyl, hydroxyl, $CH_2O$(aryl), $CH_2CH_2O$(aryl), a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or halogen, wherein when $X^1$ is N, $X^3$ is CH, $R^1$ and $R^2$ together with the atoms to which they are bound form a mono-substituted aromatic six-membered carbocycle, and RING SYSTEM is a quinoline moiety that is substituted or unsubstituted or an isoquinoline moiety that is substituted or unsubstituted, then $R^{17}$ is not H, substituted or unsubstituted methyl, or monosubstituted ethyl. In some embodiments, Z is not CHCH(OH)Me, 1,1-cyclohexylene, 1,2-cyclohexylene, CHOH, or CHO(aryl). In some embodiments, $R^{17}$ is not H, methyl, $CH_2$(aryl), $CH_2$(heteroaryl), or $CH_2$(heterocyclyl). In some embodiments, $R^{17}$ is not 2-hydroxyeth-1-yl, 2-methoxyeth-1-yl, 2-(ethoxymethoxy)eth-1-yl, or 2-aminoeth-1-yl, wherein the amino group of 2-aminoeth-1-yl is primary, secondary, or tertiary.

**[0028]** In some embodiments, the compound is of one of the following formulae, with the variables as described above:

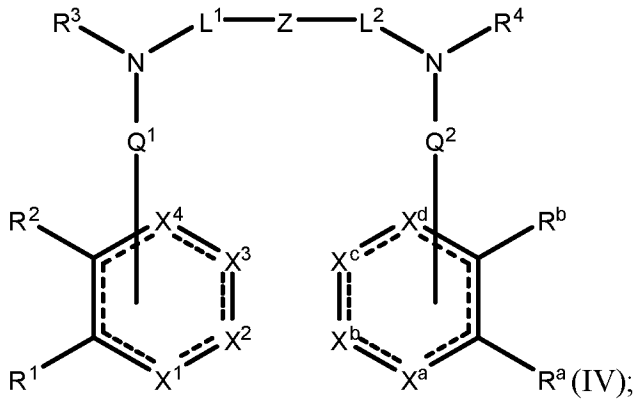
Formula II: 

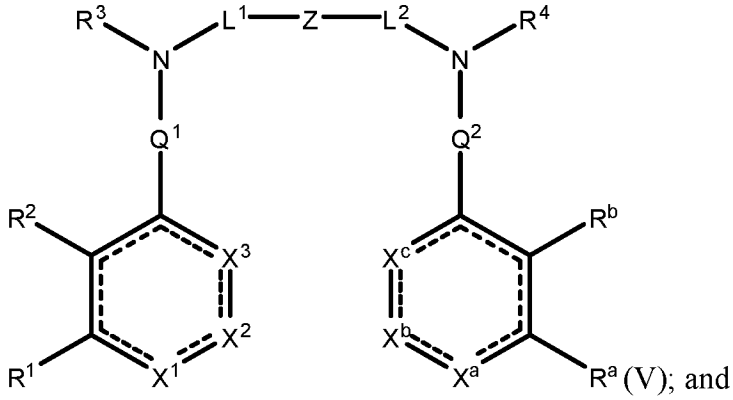
(II), and

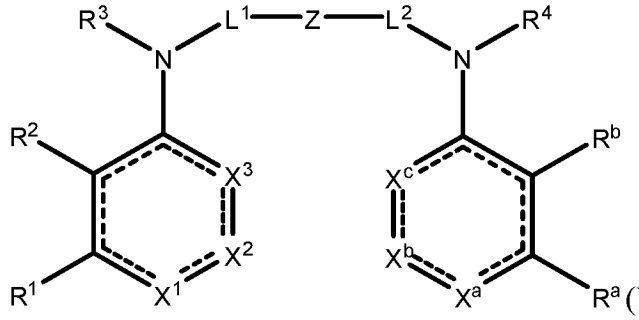
Formula III: 

(III).

**[0029]** Non-limiting examples of compounds of the disclosure include compounds of any of the following formulae:

Formula IV: 
(IV);

Formula V: 
(V); and

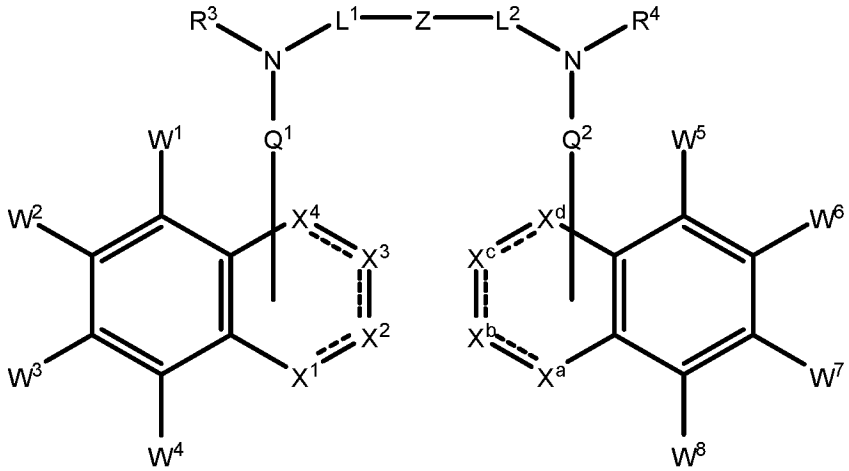
Formula VI: 
(VI),

wherein: $X^a$ is $CR^c$, $CR^cR^d$, N, $NR^c$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$; $X^b$ is $CR^e$, $CR^eR^f$, N, $NR^e$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$; $X^c$ is $CR^g$, $CR^gR^h$, N, $NR^g$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$; $X^d$ is $CR^i$, $CR^iR^j$, N, $NR^i$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$, wherein one of $X^a$, $X^b$, $X^c$, and $X^d$ is a carbon atom connected to $Q^2$; each of $R^a$ and $R^b$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^a$ and $R^b$ together with the atoms to which they are bound form

a ring that is substituted on at least one carbon atom of the ring; and each of $R^c$, $R^d$, $R^e$, $R^f$, $R^g$, $R^h$, $R^i$, and $R^j$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, and other variables are as defined above.

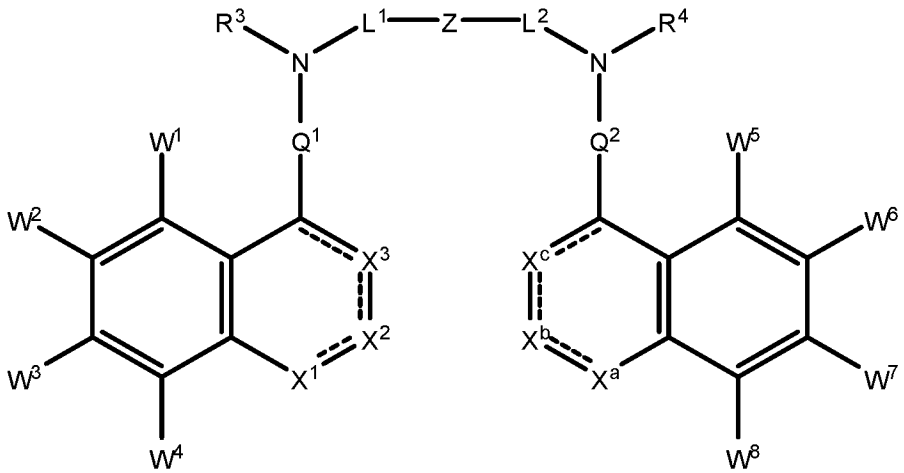
**[0030]** Non-limiting examples of compounds of the disclosure include compounds of any of the following formulae:

Formula VII:



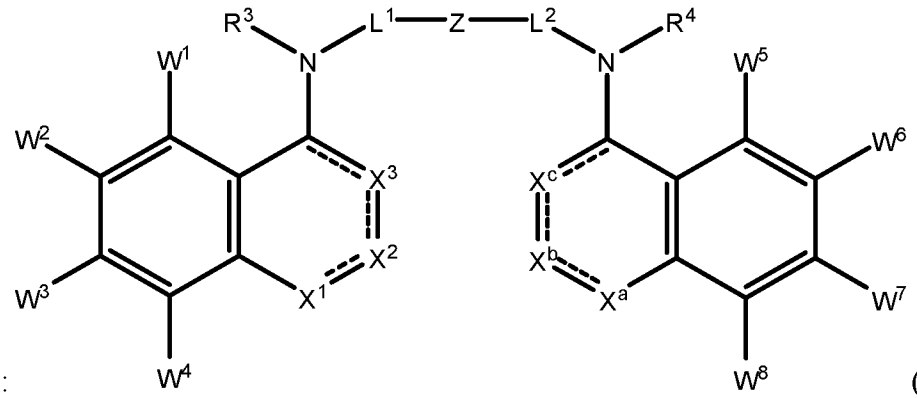
(VII);

Formula VIII:



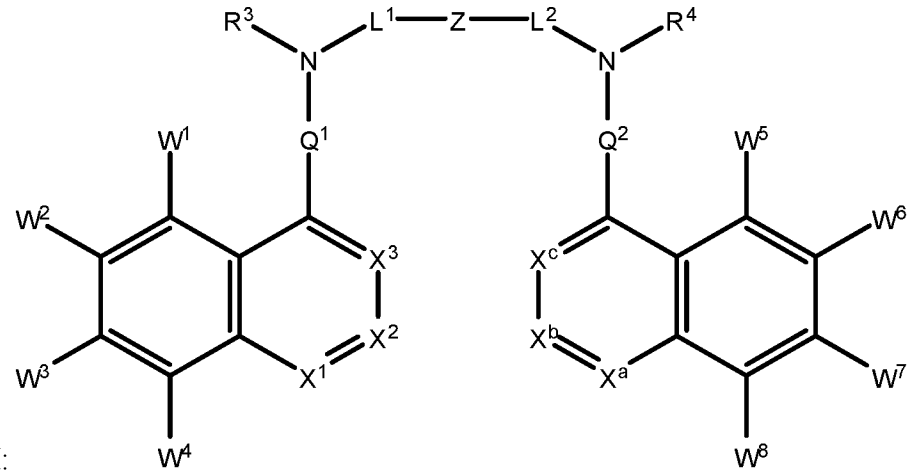
(VIII);

Formula IX:



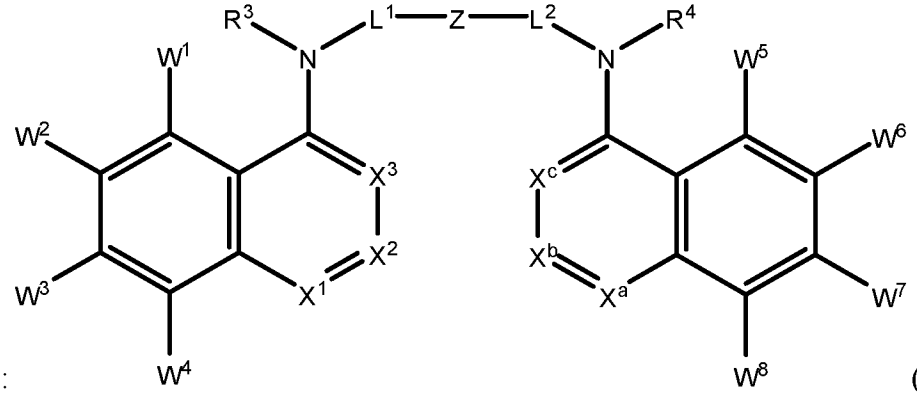
(IX);

Formula X:



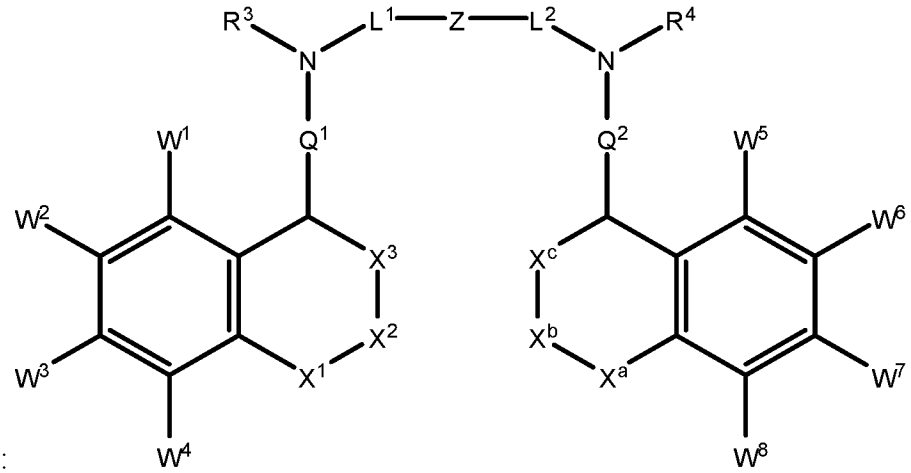
(X);

Formula XI:

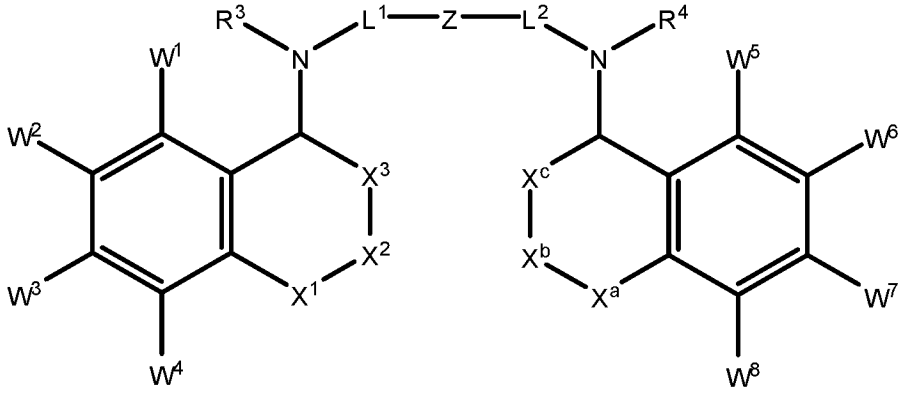


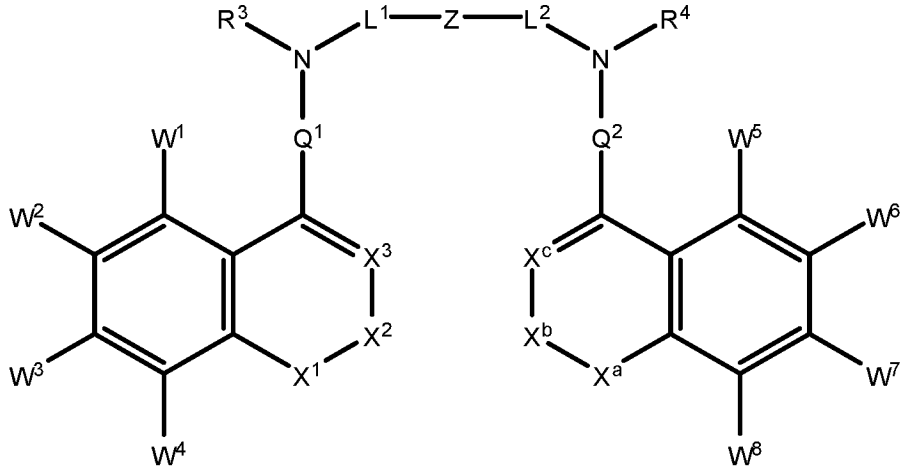
(XI);

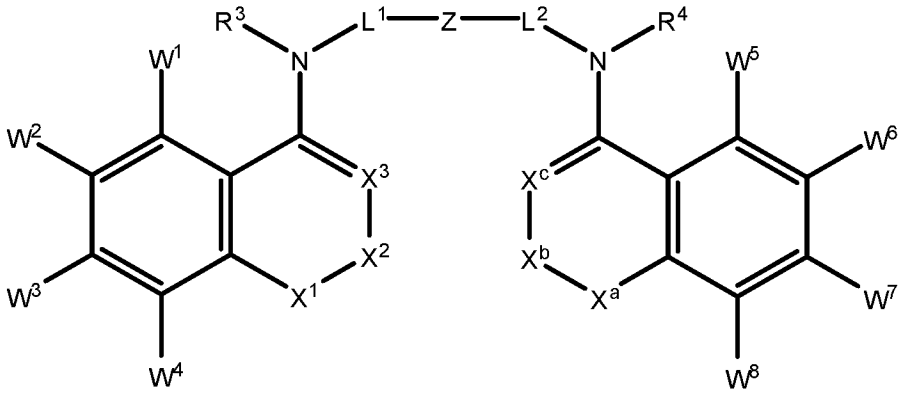
Formula XII:

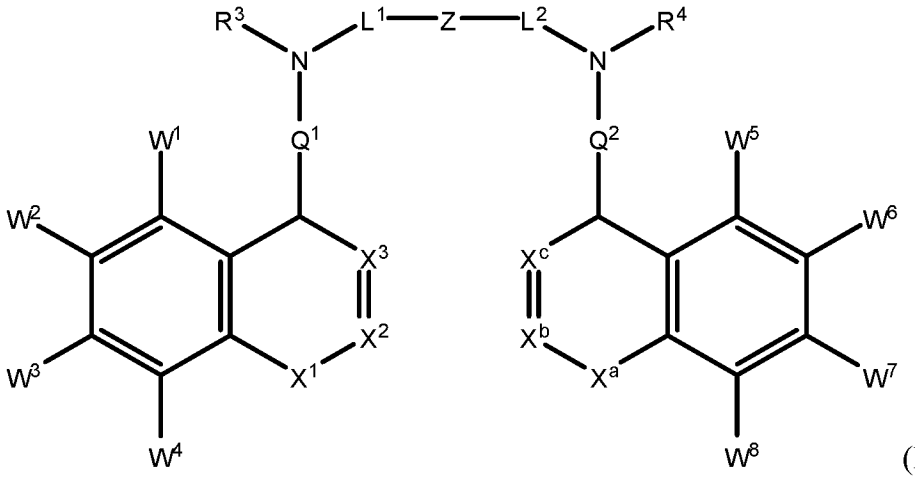


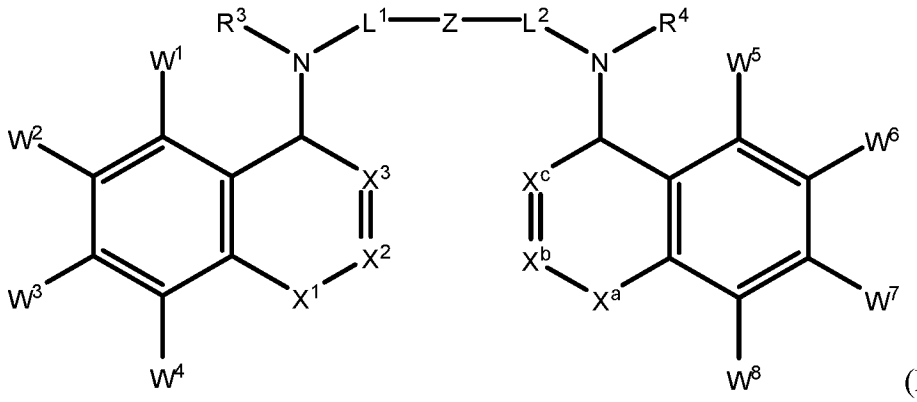
(XII);

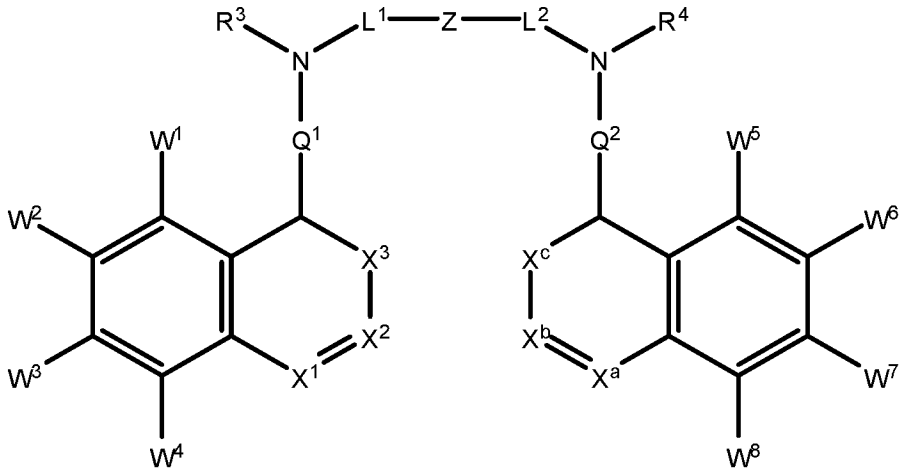
Formula XIII:  (XIII);

Formula XIV:  (XIV);

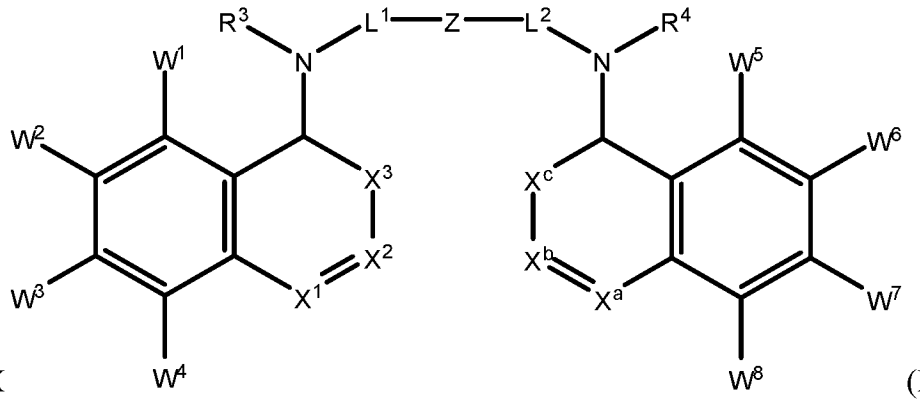
Formula XV:  (XV);

Formula XVI:  (XVI);

Formula XVII:  (XVII);

Formula XVIII: 

(XVIII); and

Formula XIX  (XIX),

wherein: each of $W^1$, $W^2$, $W^3$, $W^4$, $W^5$, $W^6$, $W^7$, and $W^8$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, and others variables are as defined above. In some embodiments,

each of $W^1$, $W^2$, $W^3$, $W^4$, $W^5$, $W^6$, $W^7$, and $W^8$ is independently alkyl, F, Cl, hydroxyl, or H. In some embodiments, $W^3$ and $W^7$ are both F. In some embodiments, $W^3$ and $W^7$ are both Cl. In some embodiments, each of $W^1$, $W^2$, $W^4$, $W^5$, $W^6$, and $W^8$ is H.

**[0031]** Non-limiting examples of cyclic groups or of a ring system include aromatic, non-aromatic, heterocyclic, carbocyclic, monocyclic, and polycyclic groups. A polycyclic group can be, for example, bicyclic, tricyclic, or tetracyclic. A polycyclic group can be, for example, fused, bridged, or spiro, or any combination thereof. Non-limiting examples of aromatic groups include heterocyclic, carbocyclic, monocyclic, and polycyclic rings. Any such group can be substituted or unsubstituted at any position, with any number of substituents. Non-limiting examples of substituents include: halogens, hydroxyl groups, sulfhydryl groups, amino groups, nitro groups, nitroso groups, cyano groups, azido groups, sulfoxide groups, sulfone groups, sulfonamide groups, carboxyl groups, carboxaldehyde groups, imine groups, alkyl groups, halo-alkyl groups, alkenyl groups, halo-alkenyl groups, alkynyl groups, halo-alkynyl groups, alkoxy groups, aryl groups, aryloxy groups, aralkyl groups, arylalkoxy groups, heterocyclyl groups, acyl groups, acyloxy groups, carbamate groups, amide groups, epoxides, ester groups, and any other substituent described herein.

**[0032]** In some embodiments, $X^1$ is $CR^5$, $CR^5R^6$, N, $NR^5$, O, S, C=O, or C=S. In some embodiments, $X^1$ is $CR^5$, N, $NR^5$, C=O, or C=S. In some embodiments, $X^1$ is $CR^5$, N, C=O, or C=S. In some embodiments, $X^1$ is $CR^5$, N, or C=O. In some embodiments, $X^1$ is $CR^5$ or N. In some embodiments, $X^1$ is $CR^5$. In some embodiments, $X^1$ is N. In some embodiments, $X^1$ is CH, CMe, or COH. In some embodiments, $X^2$ is $CR^7$, $CR^7R^8$, N, $NR^7$, O, S, C=O, or C=S. In some embodiments, $X^2$ is $CR^7$, N, $NR^7$, C=O, or C=S. In some embodiments, $X^2$ is $CR^7$, N, C=O, or C=S. In some embodiments, $X^2$ is $CR^7$, N, or C=O. In some embodiments, $X^2$ is $CR^7$ or N. In some embodiments, $X^2$ is $CR^7$. In some embodiments, $X^2$ is N. In some embodiments, $X^2$ is CH, CMe, or COH. In some embodiments, $X^3$ is $CR^9$, $CR^9R^{10}$, N, $NR^9$, O, S, C=O, or C=S. In some embodiments, $X^3$ is $CR^9$, N, $NR^9$, C=O, or C=S. In some embodiments, $X^3$ is $CR^9$, N, C=O, or C=S. In some embodiments, $X^3$ is $CR^9$, N, or C=O. In some embodiments, $X^3$ is $CR^9$ or N. In some embodiments, $X^3$ is $CR^9$. In some embodiments, $X^3$ is N. In some embodiments, $X^3$ is CH, CMe, or COH. In some embodiments, $X^4$ is $CR^{11}$, $CR^{11}R^{12}$, N, $NR^{11}$, O, S, C=O, or C=S. In some embodiments, $X^4$ is $CR^{11}$, N, $NR^{11}$, C=O, or C=S. In some embodiments, $X^4$ is $CR^{11}$, N, C=O, or C=S. In some embodiments, $X^4$ is $CR^{11}$, N, or C=O. In some embodiments, $X^4$ is $CR^{11}$ or N. In some embodiments, $X^4$ is $CR^{11}$. In some embodiments, $X^4$ is N. In some embodiments, $X^4$ is CH, CMe, or COH. In some embodiments, $X^a$ is $CR^c$, $CR^cR^d$, N, $NR^c$, O, S, C=O, or C=S. In

some embodiments, $X^a$ is $CR^c$, N, $NR^c$, C=O, or C=S. In some embodiments, $X^a$ is $CR^c$, N, C=O, or C=S. In some embodiments, $X^a$ is $CR^c$, N, or C=O. In some embodiments, $X^a$ is $CR^c$ or N. In some embodiments, $X^a$ is $CR^c$. In some embodiments, $X^a$ is N. In some embodiments, $X^a$ is CH, CMe, or COH. In some embodiments, $X^b$ is $CR^e$, $CR^eR^f$, N, $NR^e$, O, S, C=O, or C=S. In some embodiments, $X^b$ is $CR^e$, N, $NR^e$, C=O, or C=S. In some embodiments, $X^b$ is $CR^e$, N, C=O, or C=S. In some embodiments, $X^b$ is $CR^e$, N, or C=O. In some embodiments, $X^b$ is $CR^e$ or N. In some embodiments, $X^b$ is $CR^e$. In some embodiments, $X^b$ is N. In some embodiments, $X^b$ is CH, CMe, or COH. In some embodiments, $X^c$ is $CR^g$, $CR^gR^h$, N, $NR^g$, O, S, C=O, or C=S. In some embodiments, $X^c$ is $CR^g$, N, $NR^g$, C=O, or C=S. In some embodiments, $X^c$ is $CR^g$, N, C=O, or C=S. In some embodiments, $X^c$ is $CR^g$, N, or C=O. In some embodiments, $X^c$ is $CR^g$ or N. In some embodiments, $X^c$ is $CR^g$. In some embodiments, $X^c$ is N. In some embodiments, $X^c$ is CH, CMe, or COH. In some embodiments, $X^d$ is $CR^i$, $CR^iR^j$, N, $NR^i$, O, S, C=O, or C=S. In some embodiments, $X^d$ is $CR^i$, N, $NR^i$, C=O, or C=S. In some embodiments, $X^d$ is $CR^i$, N, C=O, or C=S. In some embodiments, $X^d$ is $CR^i$, N, or C=O. In some embodiments, $X^d$ is $CR^i$ or N. In some embodiments, $X^d$ is $CR^i$. In some embodiments, $X^d$ is N. In some embodiments, $X^d$ is CH, CMe, or COH.

**[0033]** In some embodiments, one, at least one, or no greater than one of $X^1$, $X^2$, $X^3$, $X^4$, $X^a$, $X^b$, $X^c$, and $X^d$ is N. In some embodiments, two, at least two, or no greater than two of $X^1$, $X^2$, $X^3$, $X^4$, $X^a$, $X^b$, $X^c$, and $X^d$ are N. In some embodiments, one, at least one, or no greater than one of $X^1$, $X^2$, $X^3$, $X^a$, $X^b$, and $X^c$ is N. In some embodiments, two, at least two, or no greater than two of $X^1$, $X^2$, $X^3$, $X^a$, $X^b$, and $X^c$ are N. In some embodiments, one, at least one, or no greater than one of $X^1$, $X^2$, $X^3$, $X^4$, $X^a$, $X^b$, $X^c$, and $X^d$ is CH. In some embodiments, two, at least two, or no greater than two of $X^1$, $X^2$, $X^3$, $X^4$, $X^a$, $X^b$, $X^c$, and $X^d$ are CH. In some embodiments, one, at least one, or no greater than one of $X^1$, $X^2$, $X^3$, $X^a$, $X^b$, and $X^c$ is CH. In some embodiments, two, at least two, or no greater than two of $X^1$, $X^2$, $X^3$, $X^a$, $X^b$, and $X^c$ are CH. In some embodiments, one, at least one, or no greater than one of $X^1$, $X^2$, $X^3$, $X^4$, $X^a$, $X^b$, $X^c$, and $X^d$ is C(alkyl), such as C(methyl). In some embodiments, two, at least two, or no greater than two of $X^1$, $X^2$, $X^3$, $X^4$, $X^a$, $X^b$, $X^c$, and $X^d$ are C(alkyl), such as C(methyl). In some embodiments, one, at least one, or no greater than one of $X^1$, $X^2$, $X^3$, $X^a$, $X^b$, and $X^c$ is C(alkyl), such as C(methyl). In some embodiments, two, at least two, or no greater than two of $X^1$, $X^2$, $X^3$, $X^a$, $X^b$, and $X^c$ are C(alkyl), such as C(methyl).

**[0034]** In some embodiments, the ------- bonds in a ring or in a molecule are chosen to provide an electron configuration that is an aromatic system, a six-electron system, a ten-

electron system, or a non-aromatic system.

**[0035]** In some embodiments, $Q^1$ is C=O, C=S, $C=CR^{13}R^{14}$, $C=NR^{13}$, or a bond. In some embodiments, $Q^1$ is C=O, $C=NR^{13}$, or a bond. In some embodiments, $Q^1$ is C=O. In some embodiments, $Q^1$ is $C=NR^{13}$, C=NH, C=N(alkyl), C=N(methyl), or C=N(ethyl). In some embodiments, $Q^1$ is a bond. In some embodiments, $Q^2$ is C=O, C=S, $C=CR^{15}R^{16}$, $C=NR^{15}$, or a bond. In some embodiments, $Q^2$ is C=O, $C=NR^{15}$, or a bond. In some embodiments, $Q^2$ is C=O. In some embodiments, $Q^2$ is $C=NR^{15}$, C=NH, C=N(alkyl), C=N(methyl), or C=N(ethyl). In some embodiments, $Q^2$ is a bond.

**[0036]** In some embodiments, $L^1$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted. In some embodiments, $L^1$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, unsubstituted or substituted amino, halogen, or any other substituent disclosed herein. In some embodiments, $L^1$ is an alkylene group or a heteroalkylene group. In some embodiments, $L^2$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, or halogen, or a bond. In some embodiments, $L^2$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, unsubstituted or substituted amino, halogen, or any other substituent disclosed herein. In some embodiments, $L^2$ is an alkylene group or a heteroalkylene group. In some embodiments, $L^2$ is a bond.

**[0037]** In some embodiments, $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted. In some embodiments, $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring. In some embodiments, $R^1$ and $R^2$ together with the atoms to which they are bound form a ring, which, together with the group to which the ring is fused, forms a quinoline moiety that is unsubstituted or substituted, for example, substituted on the benzo-portion of the quinoline moiety, substituted on the pyrido-portion of the quinoline moiety, or substituted at the 5-, 6-, 7-, or 8-position of the quinoline moiety. In some embodiments, $R^1$ and $R^2$ together with the atoms to which they are bound form a ring, which, together with the group to which the ring is fused, forms an isoquinoline moiety that is unsubstituted or substituted, for example, substituted on the benzo-portion of the isoquinoline moiety,

substituted on the pyrido-portion of the isoquinoline moiety, or substituted at the 5-, 6-, 7-, or 8-position of the isoquinoline moiety. In some embodiments, $R^a$ and $R^b$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted. In some embodiments, $R^a$ and $R^b$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring. In some embodiments, $R^a$ and $R^b$ together with the atoms to which they are bound form a ring, which, together with the group to which the ring is fused, forms a quinoline moiety that is unsubstituted or substituted, for example, substituted on the benzo-portion of the quinoline moiety, substituted on the pyrido-portion of the quinoline moiety, or substituted at the 5-, 6-, 7-, or 8-position of the quinoline moiety. In some embodiments, $R^a$ and $R^b$ together with the atoms to which they are bound form a ring, which, together with the group to which the ring is fused, forms an isoquinoline moiety that is unsubstituted or substituted, for example, substituted on the benzo-portion of the isoquinoline moiety, substituted on the pyrido-portion of the isoquinoline moiety, or substituted at the 5-, 6-, 7-, or 8-position of the isoquinoline moiety. A ring can be substituted with any number of positions with any number of substituents.

**[0038]** In some embodiments, each of $R^3$ and $R^4$ is independently alkyl, alkenyl, alkynyl, an acyl group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H. In some embodiments, each of $R^3$ and $R^4$ is independently H, methyl, ethyl, or acetyl.

**[0039]** In some embodiments, Z is a cyclic group that is unsubstituted or substituted, O, S, C=O, C(O)O, C=S, S=O, $SO_2$, $NHC(O)NR^{17}$, $OC(O)NR^{17}$, $C(O)NR^{17}$, $NR^{17}$, or $CHR^{18}$. In some embodiments, Z is S, C=O, C(O)O, C=S, S=O, $SO_2$, $NHC(O)NR^{17}$, $OC(O)NR^{17}$, $C(O)NR^{17}$, $NR^{17}$, $CHR^{18}$, or a cyclic group that is unsubstituted or substituted and is connected to $L^1$ and $L^2$ such that $L^1$ and $L^2$ possess a 1,1- or 1,2- or 1,3- or 1,4-configuration on Z. In some embodiments, Z is C=O, C(O)O, $C(O)NR^{17}$, $NR^{17}$, or $CHR^{18}$. In some embodiments, Z is C=O, $NR^{17}$, or $CHR^{18}$, for example, NH, N(alkyl), N(methyl), N(acyl), or N(acetyl).

**[0040]** Non-limiting examples of Z include rings that are geminally substituted, viscinally substituted, 1,1-disubstituted, 1,2-disubstituted, 1,3-disubstituted, or 1,4-disubstituted. Aromatic rings can be substituted *ortho*, *meta*, or *para*. The rings can be symmetrical or unsymmetrical, *cis*, *trans*, *syn*, or *anti* in configuration, and can be substituted at any number of positions with any number of substituents, such as those described herein. For example, a ring can have 3, 4, 5, 6, 7, 8, 9, or 10 members, any of which is carbon or a heteroatom, for example, N, O, S, P, Si, or B. A ring can be an acetal, a hemiacetal, an aminal, a hemiaminal,

a lactone, a lactam, a tetrahydrofuran, or a tetrahydropyran. Non-limiting examples include 1,1-disubstituted-1,3-dioxolane, with the 1,1-disubstitution being points of attachment to the remainder of the molecule, and 4,5-disubstituted-1,3-dioxolane, with the 4,5-disubstitution being points of attachment to the remainder of the molecule. Non-limiting examples include a tetrahydrofuran that is attached to the remainder of the molecule at any of the 2-, 3-, 4-, or 5-positions, and is unsubstituted or substituted at the other positions, for example, a 2,3-disubstituted tetrahydrofuran.

**[0041]** In some embodiments, $R^{17}$ is alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H. In some embodiments, $R^{17}$ is alkyl, alkenyl, an acyl group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H. In some embodiments, $R^{17}$ is H, alkyl, for example, methyl, acyl, for example, acetyl, ethyl, substituted ethyl, for example, 2-hydroxyeth-1-yl or 2-hydroxy-1-cyanoeth-1-yl. In some embodiments, $R^{17}$ is aryl, heterocyclyl, or heteroaryl, for example, a quinoline or isoquinoline moiety that is unsubstituted or substituted at any number of positions with any number of substituents, for example, substituted on the benzo-portion, substituted on the pyrido-portion, or substituted at the 5-, 6-, 7-, or 8-position. In some embodiments, $R^{17}$ is a quinoline or isoquinoline moiety that is identical to a quinoline or isoquinoline moiety that is present in another region of the molecule, for example, in RING SYSTEM.

**[0042]** In some embodiments, $R^{18}$ is alkyl, alkenyl, alkynyl, hydroxyl, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or halogen. In some embodiments, $R^{18}$ is $(C_3\text{-}C_{10})$-alkyl, $(C_3\text{-}C_{10})$-alkenyl, hydroxyl, $CH_2O$(aryl), $CH_2CH_2O$(aryl), a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or halogen. In some embodiments, $R^{18}$ is an amino group that is substituted or unsubstituted, for example, $NH_2$, NH(alkyl), NHMe, N(alkyl)(alkyl), $NMe_2$, NH(acyl),

NHC(O)Me, NMe(acyl), or NMeC(O)Me. In some embodiments, $R^{18}$ is alkyl-O-aryl, alkyl-O-heteroaryl, alkyl-O-heterocycle, alkyl-C(O)O-aryl, alkyl-C(O)O-heteroaryl, alkyl-C(O)O-heterocycle, alkyl-C(O)NH-aryl, alkyl-C(O)NH-heteroaryl, alkyl-C(O)NH-heterocycle, alkyl-NH-aryl, alkyl-NH-heteroaryl, or alkyl-NH-heterocycle. In some embodiments, $R^{18}$ is $CH_2O$(aryl), $CH_2CH_2O$(aryl), $CH_2O$(heteroaryl), $CH_2CH_2O$(heteroaryl), $CH_2O$(heterocycle), $CH_2CH_2O$(heterocycle), $CH_2O$(quinoline), $CH_2CH_2O$(quinoline), $CH_2O$(isoquinoline), or $CH_2CH_2O$(isoquinoline). A foregoing group, such as a quinoline or isoquinoline moiety, can be unsubstituted or substituted at any number of positions with any number of substituents, for example, substituted on the benzo-portion, substituted on the pyrido-portion, or substituted at the 5-, 6-, 7-, or 8-position. In some embodiments, the quinoline or isoquinoline moiety that is identical to a quinoline or isoquinoline moiety that is present in another region of the molecule, for example, in RING SYSTEM.

**[0043]** In some embodiments, $X^1$ is $CR^5$, N, or $NR^5$; $X^2$ is $CR^7$, N, C=O, or C=S; $X^3$ is $CR^9$, N, or $NR^9$; $X^a$ is $CR^c$, N, or $NR^c$; $X^b$ is $CR^e$, N, C=O, or C=S; $X^c$ is $CR^g$, N, or $NR^g$; $L^1$ is an alkylene group or a heteroalkylene group; $L^2$ is an alkylene group or a bond; Z is C=O, C(O)O, $C(O)NR^{17}$, $NR^{17}$, $CHR^{18}$, or a cyclic group that is unsubstituted or substituted and is connected to $L^1$ and $L^2$ such that $L^1$ and $L^2$ possess a 1,1- or 1,2- or 1,3- or 1,4-configuration on Z; $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring; each of $R^3$ and $R^4$ is independently alkyl, an acyl group, arylalkyl, heterocyclylalkyl, heteroarylalkyl, or H; $R^{17}$ is alkyl, alkenyl, an acyl group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or H; and $R^{18}$ is $(C_3$-$C_{10})$-alkyl, $(C_3$-$C_{10})$-alkenyl, hydroxyl, $CH_2O$(aryl), $CH_2CH_2O$(aryl), an amine group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

**[0044]** In some embodiments, $X^1$ is $CR^5$ or N; $X^2$ is $CR^7$; $X^3$ is $CR^9$ or N; $X^a$ is $CR^c$ or N; $X^b$ is $CR^e$; $X^c$ is $CR^g$ or N; $L^2$ is an unsubstituted alkylene group or a bond; each of $R^3$ and $R^4$ is independently alkyl, an acyl group, arylalkyl, heterocyclylalkyl, heteroarylalkyl, or H; and each of $R^5$, $R^7$, $R^9$, $R^c$, $R^e$, and $R^g$ is independently alkyl, an alkoxy group, halogen, hydroxyl, or H.

**[0045]** In some embodiments $L^2$ is methylene, ethylene, or a bond; each of $R^3$ and $R^4$ is independently alkyl, an acyl group, or H; and each of $R^5$, $R^7$, $R^9$, $R^c$, $R^e$, and $R^g$ is independently alkyl or H.

**[0046]** In some embodiments, Z is C=O, $NR^{17}$, $CHR^{18}$, or a cyclic group that is unsubstituted or substituted and is connected to $L^1$ and $L^2$ such that $L^1$ and $L^2$ possess a 1,1- or 1,2-or 1,3-

or1,4-configuration on Z; $R^{17}$ is alkyl, an acyl group, or heteroaryl; and $R^{18}$ is $CH_2O$(heteroaryl), $CH_2CH_2O$(heteroaryl) or an amine group.

**[0047]** In some embodiments, Z is NMe.

**[0048]** In some embodiments, $X^1$ is N; $X^2$ is CH or C(alkyl); $X^3$ is CH or C(alkyl); $X^a$ is N; $X^b$ is CH or C(alkyl); and $X^c$ is CH or C(alkyl).

**[0049]** In some embodiments, $X^1$ is CH or C(alkyl); $X^2$ is CH or C(alkyl); $X^3$ is N; $X^a$ is CH or C(alkyl); $X^b$ is CH or C(alkyl); and $X^c$ is N.

**[0050]** In some embodiments, $X^1$ is N; $X^2$ is CH or C(alkyl); $X^3$ is N; $X^a$ is N; $X^b$ is CH or C(alkyl); and $X^c$ is N.

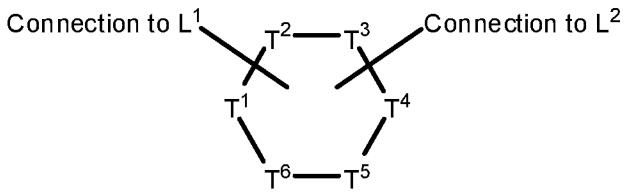
**[0051]** In some embodiments, $X^1$ is N; $X^2$ is CH; $X^3$ is CH; $X^a$ is N; $X^b$ is CH; and $X^c$ is CH.

**[0052]** In some embodiments, $X^1$ is CH; $X^2$ is CH; $X^3$ is N; $X^a$ is CH; $X^b$ is CH; and $X^c$ is N.

**[0053]** In some embodiments, $X^1$ is N; $X^2$ is CH; $X^3$ is N; $X^a$ is N; $X^b$ is CH; and $X^c$ is N.

**[0054]** In some embodiments, Z is, or is not, an aliphatic ring, a heterocycle, a carbocycle, arylene, 1,2-arylene, 1,3-arylene, 1,4-arylene, phenylene, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, heteroarylene, 1,2-heteroarylene, 1,3-heteroarylene, 1,4-heteroarylene, heterocyclylene, 1,2-heterocyclylene, 1,3-heterocyclylene, 1,4-heterocyclylene, dicyclohexylmethane-4,4-diyl, cyclohexane-1,1-diyl, cyclohexane-1,2-diyl, cyclohexane-1,3-diyl, cyclohexane-1,4-diyl, cyclopentane-1,2-diyl, or cyclopentane-1,3-diyl.

**[0055]** In some embodiments, Z is a ring of the following formula:




,

wherein: $T^1$ is N, O, S, C(O), NH, N(alkyl), N(acyl), alkylene, or alkenylene, any of which is substituted or unsubstituted; $T^2$ is N, O, S, C(O), NH, N(alkyl), N(acyl), alkylene, or alkenylene, any of which is substituted or unsubstituted, or is linked to $T^5$ by a bridge; $T^3$ is N, O, S, C(O), NH, N(alkyl), N(acyl), alkylene, or alkenylene, any of which is substituted or unsubstituted; $T^4$ is N, O, S, C(O), NH, N(alkyl), N(acyl), alkylene, or alkenylene, any of which is substituted or unsubstituted; $T^5$ is N, O, S, C(O), NH, N(alkyl), N(acyl), alkylene, or alkenylene, any of which is substituted or unsubstituted, or is linked to $T^2$ by a bridge; and $T^6$ is N, O, S, C(O), NH, N(alkyl), N(acyl), alkylene, or alkenylene, any of which is substituted or unsubstituted, or is a bond.

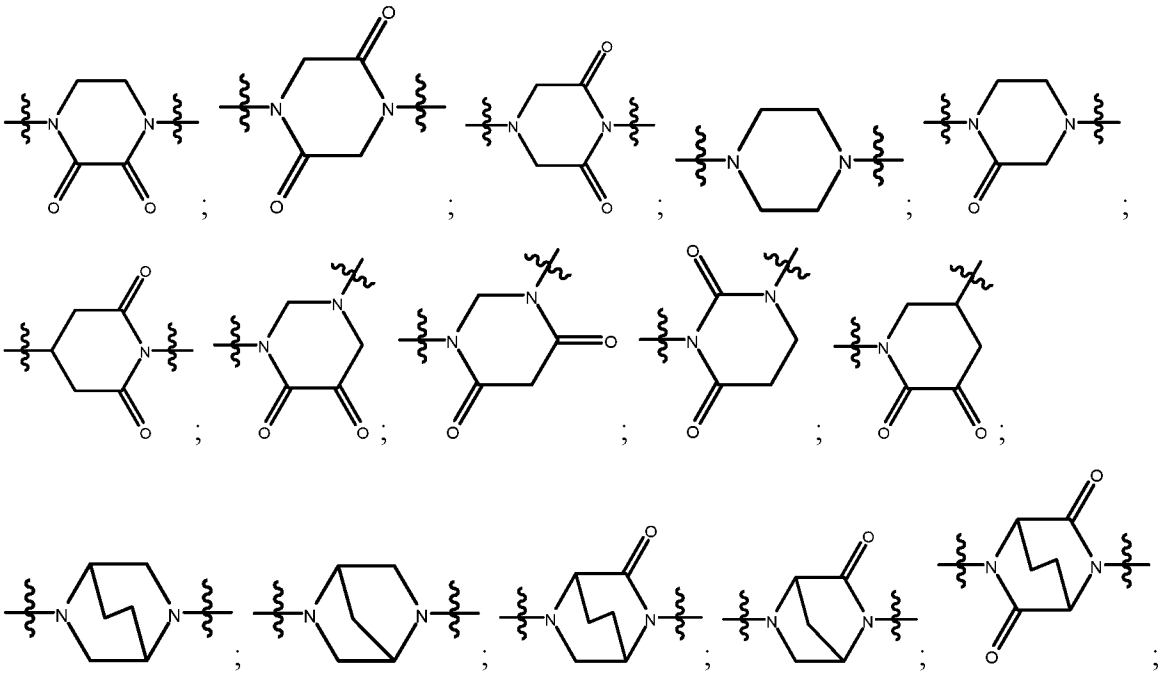
**[0056]** In some embodiments, $T^1$ is N, NH, N(alkyl), N(acyl), or alkylene, any of which is substituted or unsubstituted; $T^2$ is N, C(O), NH, N(alkyl), N(acyl), or alkylene, any of which

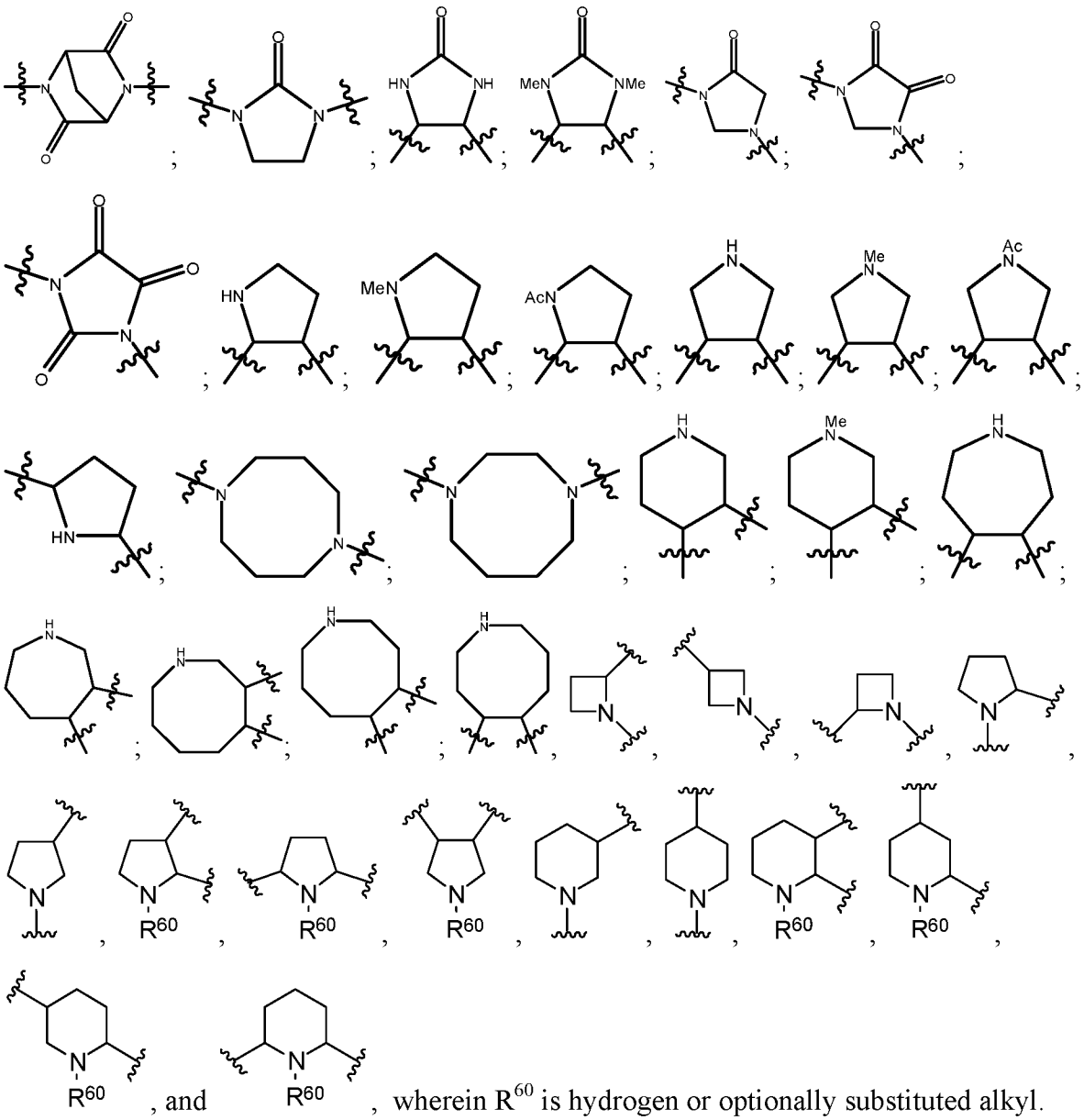
is substituted or unsubstituted, or is linked to $T^5$ by a bridge; $T^3$ is N, C(O), NH, N(alkyl), N(acyl), or alkylene, any of which is substituted or unsubstituted; $T^4$ is N, NH, N(alkyl), N(acyl), or alkylene, any of which is substituted or unsubstituted; $T^5$ is N, C(O), NH, N(alkyl), N(acyl), or alkylene, any of which is substituted or unsubstituted, or is linked to $T^2$ by a bridge; and $T^6$ is N, C(O), NH, N(alkyl), N(acyl), or alkylene, any of which is substituted or unsubstituted, or is a bond.

**[0057]** In some embodiments, $T^1$ is N, NH, or alkylene that is substituted or unsubstituted; $T^2$ is N, NH, or alkylene that is substituted or unsubstituted, or is linked to $T^5$ by a bridge; $T^3$ is N, C(O), NH, N(alkyl), N(acyl), or alkylene, any of which is substituted or unsubstituted; $T^4$ is N, NH, or alkylene that is substituted or unsubstituted; $T^5$ is C(O) or alkylene that is substituted or unsubstituted, or is linked to $T^2$ by a bridge; and $T^6$ is C(O), or alkylene that is substituted or unsubstituted, or is a bond.

**[0058]** In some embodiments, $T^1$ is N, NH, methylene, ethylene, or propylene; $T^2$ is N, NH, methylene, ethylene, or propylene, any of which is substituted or unsubstituted, or is linked to $T^5$ by a bridge; $T^3$ is N, C(O), NH, N(alkyl), N(acyl), methylene, ethylene, or propylene, any of which is substituted or unsubstituted; $T^4$ is N, NH, methylene, ethylene, or propylene; $T^5$ is C(O), methylene, ethylene, or propylene, or is linked to $T^2$ by a bridge; and $T^6$ is C(O), methylene, ethylene, or propylene, or is a bond.

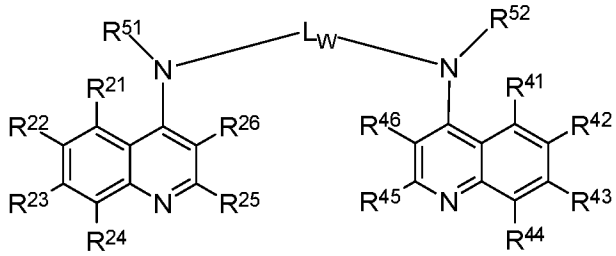
**[0059]** Non-limiting examples of Z include the following:





, and , wherein $R^{60}$ is hydrogen or optionally substituted alkyl.

**[0060]** A compound of the disclosure may be represented by a structure of Formula (XX):



(XX), or a salt thereof, wherein: $R^{21}$, $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{43}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, halogen, hydroxyl, nitro, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; $R^{51}$ and $R^{52}$ are independently selected from hydrogen and optionally substituted alkyl; and $L_W$ is optionally substituted carbocycle or optionally substituted heterocycle; or optionally substituted alkylene, optionally substituted alkenylene, optionally substituted

alkynylene, or optionally substituted heteroalkylene, each of which is interrupted by an optionally substituted heterocycle.

**[0061]** In some embodiments, $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, halogen and optionally substituted alkyl. In some embodiments, $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, and $R^{44}$ are each hydrogen and $R^{45}$ and $R^{46}$ are each halogen. In some embodiments, $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, F, Cl, Br, I, and $CF_3$. In some embodiments, one of $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ is $CF_3$. In some embodiments, at least one of $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ is a halogen. In some embodiments, $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are each hydrogen.

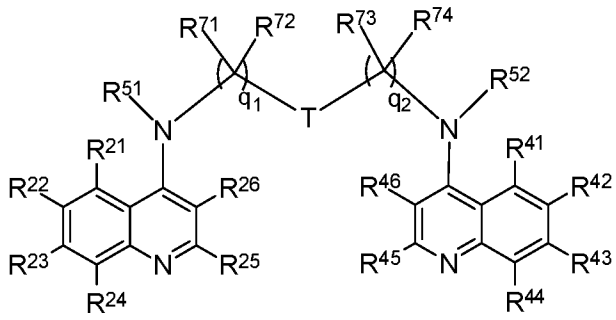
**[0062]** In some embodiments, $R^{23}$ and $R^{43}$ are independently selected from hydrogen, halogen, hydroxyl, and haloalkyl. In some embodiments, $R^{23}$ and $R^{43}$ are independently selected from hydrogen, F, Cl, Br, I, hydroxyl, and haloalkyl. In some embodiments, one of $R^{23}$ and $R^{43}$ is F, Cl, Br, I, or haloalkyl. In some embodiments, one of $R^{23}$ and $R^{43}$ is $CF_3$. In some embodiments, $R^{23}$ is F and $R^{43}$ is F. In some embodiments, $R^{23}$ is F and $R^{43}$ is Cl. In some embodiments, $R^{23}$ is Cl and $R^{43}$ is F. In some embodiments, $R^{23}$ is Cl and $R^{43}$ is Cl.

**[0063]** In some embodiments, $R^{51}$ and $R^{52}$ are selected from hydrogen and methyl. In some embodiments, $R^{51}$ and $R^{52}$ are each hydrogen.

**[0064]** In some embodiments, $L_W$ is optionally substituted alkylene interrupted by an optionally substituted heterocycle. In some embodiments, the optionally substituted alkylene of $L_W$ comprises 1-12 carbon atoms. In some embodiments, the optionally substituted alkylene of $L_W$ comprises 4-12 carbon atoms. In some embodiments, the optionally substituted alkylene of $L_W$ comprises 4-8 carbon atoms. In some embodiments, the optionally substituted alkylene of $L_W$ comprises 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms or10 carbon atoms. In certain embodiments, the number of carbon atoms of the alkylene chain of $L_W$ described in this paragraph include only the carbon atoms in the linear or branched alkyl chain of the alkylene.

**[0065]** In certain embodiments, $L_W$ is further selected from an optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, and optionally substituted heteroalkylene, each one of which is interrupted by an optionally substituted carbocycle. In certain embodiments, $L_W$ is further selected from an optionally substituted alkylene interrupted by an optionally substituted carbocycle.

**[0066]** A compound of the current disclosure may be represented by Formula (XXA):

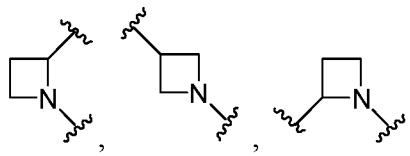
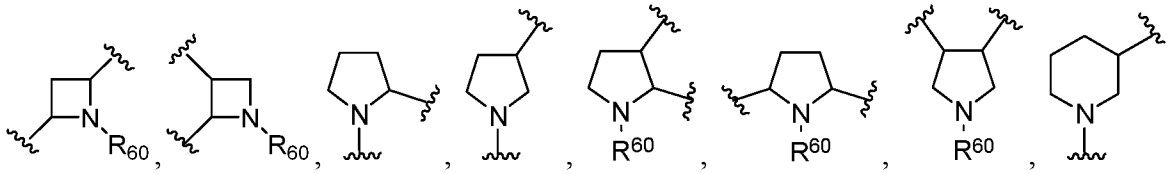


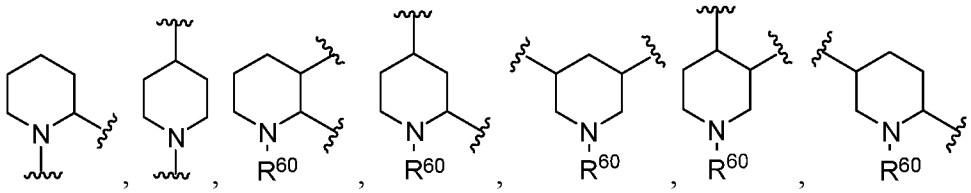
(XXA), wherein: $q_1$ is 0-5; $q_2$ is 0-5; $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ are independently selected from hydrogen, halogen, hydroxyl, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; and T is optionally substituted heterocycle.

**[0067]** In some embodiments, each occurrence of $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ are independently selected from hydrogen, halogen, hydroxyl, cyano and optionally substituted alkyl. In some embodiments, each occurrence of $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ is independently selected from hydrogen, halogen, and optionally substituted alkyl. In some embodiments, each occurrence of $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ is independently selected from hydrogen, F, Cl, Br, I, and $CF_3$. In some embodiments, each occurrence of $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ is independently hydrogen. In some embodiments, $q_1$ is 1-3 and $q_2$ is 1-3. In some embodiments, $q_1$ is 2 and $q_2$ is 2, or $q_1$ is 2 and $q_2$ is 3, or $q_1$ is 1 and $q_2$ is 3.

**[0068]** In some embodiments, T is optionally substituted 3- to 7-membered heterocycle. In some embodiments, T is optionally substituted 4- to 6-membered heterocycle. In some embodiments, T is optionally substituted 5-membered heterocycle or 6-membered heterocycle. In some embodiments, T is a saturated heterocycle. In some embodiments, T is an unsaturated heterocycle or an aromatic heterocycle.

**[0069]** In some embodiments, T is selected from aziridine, piperidine, pyrrolidine, azetidine, pyrrole, morpholine, imidazole, imidazoline, imidazolidine, pyridine, tetrahydrofuran, dihydrofuran, furan, thiophene, tetrahydrothiophene, oxazole, thiazole, tetrazole, quinolone, or isoquinoline, any of which is optionally substituted.

**[0070]** In some embodiments, T is selected from  , 



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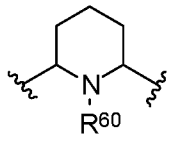
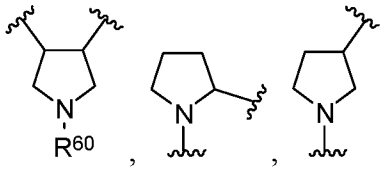
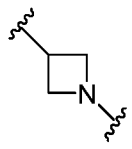
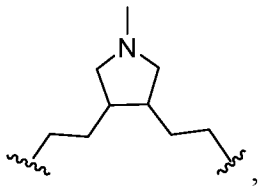


, wherein $R^{60}$ is hydrogen or optionally substituted alkyl. In some embodiments, $R^{60}$ is hydrogen. In some embodiments, $R^{60}$ is alkyl optionally substituted with one or more halo, hydroxyl, cyano, or nitro. In some embodiments, $R^{60}$ is methyl, ethyl, or propyl, any one of which is optionally substituted.

**[0071]** In some embodiments, T is selected from 

, and



. In some embodiments, $L_W$ is selected from 

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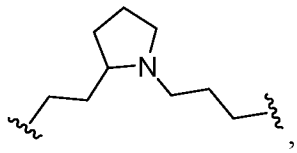
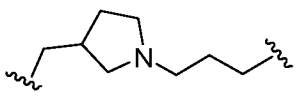
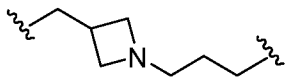
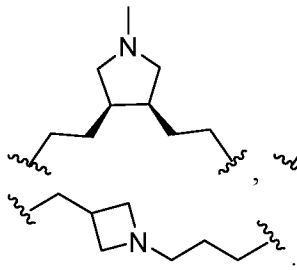


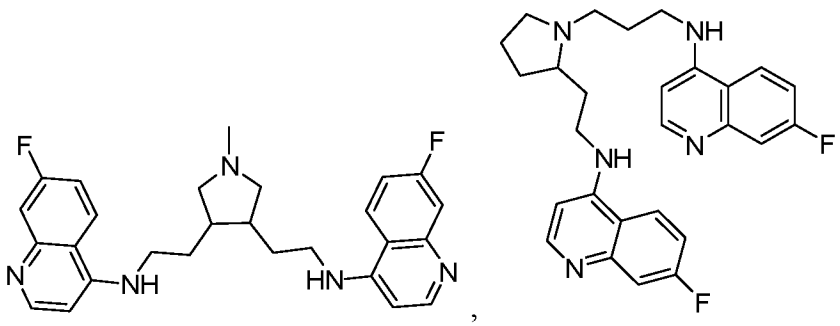
, 

, and 

. In some embodiments, $L_W$ is selected from



, and

**[0072]** In some embodiments, a compound of the current disclosure is represented by any one of the following formula: 

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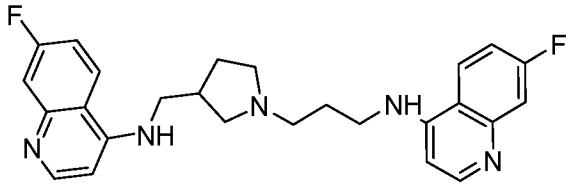
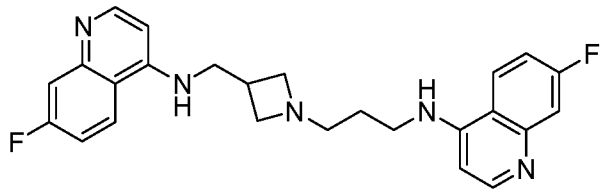
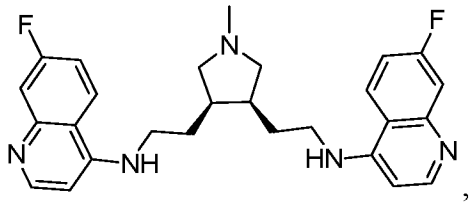
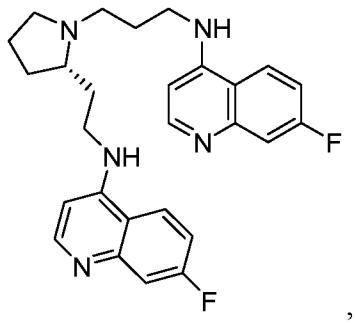

, or


or a salt of anyone therof.

**[0073]** In some embodiments, a compound of the current disclosure is represented by any one of the following formula: 
, 
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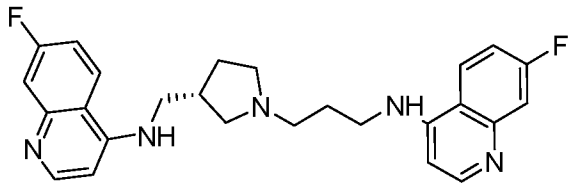
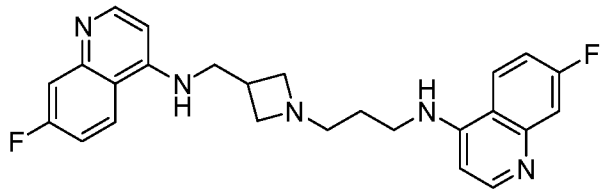
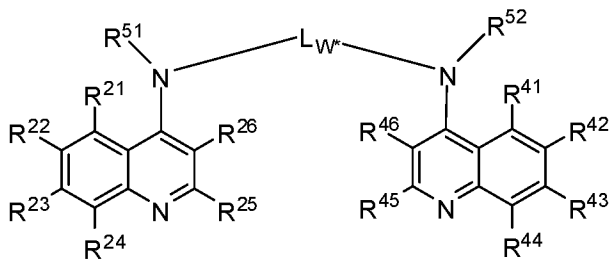
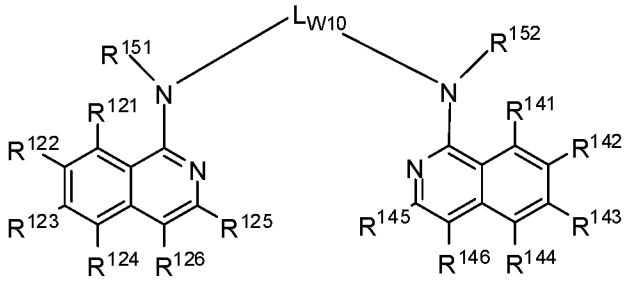

, or


or a salt of anyone therof.

**[0074]** In some embodiments, a compound of the current disclosure may be a compound represented by a structure of Formula (XXI): 
(XXI), or a salt thereof, wherein: $R^{21}$, $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{43}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, halogen, hydroxyl, nitro, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; $R^{51}$ and $R^{52}$ are independently selected from hydrogen and optionally substituted alkyl; and $L_{W*}$ is optionally substituted carbocycle or optionally substituted heterocycle; optionally substituted alkylene, optionally substituted

alkenylene, optionally substituted alkynylene, or optionally substituted heteroalkylene, each of which is interrupted by an optionally substituted carbocycle or an optionally substituted heterocycle. In certain embodiments, $L_{W*}$ is optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted heteroalkylene, each of which is interrupted by an optionally substituted carbocycle.

**[0075]** In some embodiments, a compound of the current disclosure may be represented by a structure of Formula (XXII):



(XXII), or a salt thereof, wherein: $R^{121}$, $R^{122}$, $R^{123}$, $R^{124}$, $R^{125}$, $R^{126}$, $R^{141}$, $R^{142}$, $R^{143}$, $R^{144}$, $R^{145}$, and $R^{146}$ are independently selected from hydrogen, halogen, hydroxyl, nitro, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; $R^{151}$ and $R^{152}$ are independently selected from hydrogen and optionally substituted alkyl; and $L_{W10}$ is optionally substituted heteroalkylene, optionally substituted heteroalkenylene, optionally substituted heteroalkynylene. In some embodiments, $L_{W10}$ is optionally substituted $C_{6-20}$ heteroalkylene, optionally substituted $C_{6-20}$ heteroalkenylene, or optionally substituted $C_{6-20}$ heteroalkynylene. In some embodiments, $L_{W10}$ is optionally substituted $C_{6-8}$ heteroalkylene. In certain embodiments, the heteroalkylene, heteroalkenylene, or heteroalkylnylene has from 1 to 3 heteroatoms.

**[0076]** In some embodiments, $R^{121}$, $R^{122}$, $R^{124}$, $R^{125}$, $R^{126}$, $R^{141}$, $R^{142}$, $R^{144}$, $R^{145}$, and $R^{146}$ are independently selected from hydrogen and F, Cl, Br, I, and optionally substituted alkyl. In some embodiments, $R^{121}$, $R^{122}$, $R^{124}$, $R^{125}$, $R^{126}$, $R^{141}$, $R^{142}$, $R^{144}$, $R^{145}$, and $R^{146}$ are each hydrogen. In some embodiments, $R^{123}$ and $R^{143}$ are independently selected from hydrogen, F, Cl, Br, I, hydroxyl, and haloalkyl. In some embodiments, $R^{123}$ and $R^{143}$ are independently selected from hydrogen, F, Cl, Br, I, hydroxyl, and $CF_3$. In some embodiments, $R^{123}$ and $R^{143}$ are independently selected from hydrogen, F, and $CF_3$. In some embodiments, $R^{123}$ and $R^{143}$ are independently selected from F, Cl, Br, and I. In some embodiments, $R^{123}$ is F and $R^{143}$ is F. In some embodiments, $R^{123}$ is Cl and $R^{143}$ is F. In some embodiments, $R^{123}$ is F and $R^{143}$ is Cl. In some embodiments, $R^{123}$ is Cl and $R^{143}$ is F. In some embodiments, $R^{123}$ is Cl and $R^{143}$ is Cl. In some embodiments, $R^{151}$ and $R^{152}$ are each hydrogen.

**[0077]** The disclosure contemplates the use of any form of any compound provided herein,

for example, any enantiomer, racemate, diastereomer, epimer, *meso*-compound, tautomer, atropisomer, zwitterion, geometric isomer, crystal form, solid form, powder form, polymorph, or mixture of any of the foregoing. If a compound can exist as one or a mixture of polymorphs, then any polymorph of the compound or mixture thereof is suitable for the uses provided herein.

Pharmaceutical Compositions

**[0078]** Combination therapies contemplate administering compositions of a compound of the disclosure and one or more anti-cancer therapies or ionizing radiation to a subject using any suitable dosing or scheduling regimen.

**[0079]** In various embodiments, combination therapies comprising a compound described herein may refer to (1) pharmaceutical compositions that comprise one or more compounds described herein in combination with one or more therapeutic agents (e.g., one or more therapeutic agents described herein); and (2) co-administration of one or more compounds described herein with one or more therapeutic agents wherein the compound described herein and therapeutic agent have not been formulated in the same composition, but may be present within the same kit or package, such as a blister pack or other multi-chamber package; connected, separately sealed containers (e.g., foil pouches) that can be separated by the user; or a kit where the compound(s) described herein and other therapeutic agent(s) are in separate vessels. When using separate formulations, the compound described herein may be administered at the same, intermittent, staggered, prior to, subsequent to, or combinations thereof, with the administration of another therapeutic agent.

**[0080]** In some embodiments, the disclosure provides a solid pharmaceutical composition for oral administration containing: (i) a compound of the current disclosure; and (ii) a pharmaceutical excipient suitable for oral administration. In some embodiments, the composition further contains: (iii) a third agent or a fourth agent. In some embodiments, each compound or agent is present in a therapeutically effective amount. In other embodiments, one or more compounds or agents is present in a sub-therapeutic amount.

**[0081]** In some embodiments, compounds in a composition may act synergistically to provide a provide a therapeutically effective pharmaceutical composition. In some embodiments, compounds in a composition may act more than additively. In some embodiments, compounds in a composition may act synergistically to provide a provide a

therapeutically effective pharmaceutical composition. In some embodiments, compounds in a composition may act more than additively.

**[0082]** In some embodiments, a compound of the current disclosure may be dosed with a cancer therapy drug or an anticancer agent. Composition comprising a compound of the current disclosure and a cancer therapy drug may have additive or synergistic effects. Non-limiting examples of cancer therapy drugs or anticancer agents include, but are not limited to, aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, bleomycin, daunorubicin, liposomal doxorubicin, doxorubicin, elsamitrucin, epirbucin, glarbuicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin, and zinostatin.

**[0083]** In some embodiments, a compound of the current disclosure may be administered with hydroxychloroquine. In some embodiments, a compound of the current disclosure may be administered with hydroxychloroquine and the treatment may have synergistic effects, or more than additive effects. In some embodiments, a compound of the current disclosure may be dosed with hydroxychloroquine and the treatment may have antagonistic effects, or less than additive effects. In some embodiments, a compound of the current disclosure may be administered with doxorubicin. In some embodiments, a compound of the current disclosure may be administered with doxorubicin and the treatment may have synergistic effects, or more than additive effects.

**[0084]** In some embodiments, a compound may be dosed with a known cancer therapy and the treatment may have synergistic effects, or more than additive effects. In some embodiments, a compound may be dosed with doxorubicin and the treatment may have synergistic effects, or more than additive effects.

**[0085]** In some embodiments, a subject has previously been shown to be non-responsive to administration of an anticancer agent. In some examples, the subject is then co-administered a combination therapy of a compound of the current disclosure and the same, or different, anticancer agent. A subject may be considered non-responsive to a treatment if symptoms of the disease state do not decrease in severity by more than 10%, the size of the tumor does not stay the same, or the size of the tumor increases by more than 10%. In some examples, a subject that had previously been shown to be non-responsive to a single agent therapy is responsive to a treatment comprising comprising two therapies, or two agents, wherein one of the agents is a compound of the current disclosure.

**[0086]** Compounds provided herein can be used in combination with one or more of alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics,

antiproliferatives, Aurora kinase inhibitors, other apoptosis promoters (for example, Bcl-xL, Bcl-w and Bfl-1) inhibitors, activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, dual variable domain binding proteins (DVDs), leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteosome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, etinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, and ubiquitin ligase inhibitors.

**[0087]** BiTE antibodies are bi-specific antibodies that direct T-cells to attack cancer cells by simultaneously binding both cells. The T-cell then attacks the target cancer cell. An example of a BiTE antibody is blinatumomab.

**[0088]** SiRNAs are molecules having endogenous RNA bases or chemically modified nucleotides. The modifications do not abolish cellular activity, but impart increased stability and/or increased cellular potency. Examples of chemical modifications comprise phosphorothioate groups, 2′-deoxynucleotide, 2′-$OCH_3$-containing ribonucleotides, 2′-F-ribonucleotides, 2′-methoxyethyl ribonucleotides, or combinations thereof. The siRNA can have varying lengths (e.g., 10-200 bps) and structures (*e.g.*, hairpins, single/double strands, bulges, nicks/gaps, mismatches) and are processed in cells to provide active gene silencing. A double-stranded siRNA (dsRNA) can have the same number of nucleotides on each strand (blunt ends) or asymmetric ends (overhangs). The overhang of 1-2 nucleotides can be present on the sense and/or the antisense strand, as well as present on the 5′- and/or the 3′-ends of a given strand.

**[0089]** Multivalent binding proteins are binding proteins comprising two or more antigen binding sites. Multivalent binding proteins are engineered to have the three or more antigen binding sites and are generally not naturally-occurring antibodies. A multispecific binding protein can bind two or more targets. Dual variable domain (DVD) binding proteins are

tetravalent or multivalent binding proteins comprising two or more antigen binding sites. Such DVDs can be monospecific (*i.e.*, capable of binding one antigen) or multispecific (*i.e.*, capable of binding two or more antigens). DVD-binding proteins comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides are referred to as DVD Igs. Each half of a DVD Ig comprises a heavy chain DVD polypeptide, a light chain DVD polypeptide, and two antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of 6 CDRs involved in antigen binding per antigen binding site.

**[0090]** Non-limiting examples of alkylating agents include: altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine, chlorambucil, laromustine, cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine, mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, bendamustine, treosulfan, and rofosfamide.

**[0091]** Non-limiting examples of angiogenesis inhibitors include: endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs, and vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors.

**[0092]** Non-limiting examples of antimetabolites include: pemetrexed disodium, 5-azacitidine, capecitabine, carmofur, cladribine, clofarabine, cytarabine, cytarabine ocfosfate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR, enocitabine, ethnylcytidine, fludarabine, 5-fluorouracil, leucovorin, gemcitabine, hydroxyurea, melphalan, mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, nelarabine, nolatrexed, ocfosfate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, and UFT.

**[0093]** Non-limiting examples of antimalarials include: ritonavir, chloroquine, hydroxychloroquine, primaquine, atovaquone, proguanil, artemether, lumefantrine, quinine sulfate, doxycycline, tetracycline, clindamycin, mefloquine, and quinidine.

**[0094]** Non-limiting examples of Bcr-Abl kinase inhibitors include: dasatinib, nilotinib, and imatinib.

**[0095]** Non-limiting examples of CDK inhibitors include: AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib, and ZK-304709.

**[0096]** Non-limiting examples of COX-2 inhibitors include: ABT-963, etoricoxib, valdecoxib, BMS347070, celecoxib, lumiracoxib, CT-3, deracoxib, JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl-1H-pyrrole), etoricoxib, NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, and rofecoxib.

**[0097]** Non-limiting examples of EGFR inhibitors include: ABX-EGF, anti-EGFR immunoliposomes, EGF-vaccine, EMD-7200, cetuximab, HR3, IgA antibodies, gefitinib, erlotinib, TP-38, EGFR fusion protein, and lapatinib.

**[0098]** Non-limiting examples of ErbB2 receptor inhibitors include: CP-724-714, canertinib, trastuzumab, lapatinib, petuzumab, TAK-165, ionafarnib, GW-282974, EKB-569, PI-166, dHER2 HER2 vaccine, APC-8024 HER-2 vaccine, anti-HER2/neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecific antibodies, mAB AR-209, and mAB 2B-1.

**[0099]** Non-limiting examples of histone deacetylase inhibitors include: depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, and valproic acid.

**[00100]** Non-limiting examples of HSP-90 inhibitors include: 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, human recombinant antibody to HSP-90, NCS-683664, PU24FC1, PU-3, radicicol, SNX-2112, or STA-9090 VER49009.

**[00101]** Non-limiting examples of inhibitors of inhibitors of apoptosis proteins include: HGS1029, GDC-0145, GDC-0152, LCL-161, and LBW-242.

**[00102]** Non-limiting examples of antibody-drug conjugates include: anti-CD22-MC-MMAF, anti-CD22-MC-MMAE, anti-CD22-MCC-DM1, CR-0,1-vcMMAE, PSMA-ADC, MEDI-547, SGN-19Am SGN-35, and SGN-75.

**[00103]** Non-limiting examples of activators of death receptor pathway include: TRAIL, antibodies or other agents that target TRAIL or death receptors (e.g., DR4 and DR5) such as apomab, conatumumab, ETR2-ST01, GDC0145, lexatumumab, HGS-1029, LBY-135, PRO-1762, and trastuzumab.

**[00104]** Non-limiting examples of kinesin inhibitors include: Eg5 inhibitors such as AZD4877, ARRY-520; and CENPE inhibitors such as GSK923295A.

**[00105]** Non-limiting examples of JAK-2 inhibitors include: lesaurtinib, XL019 or INCB018424.

**[00106]** Non-limiting examples of MEK inhibitors include: trametinib, ARRY-142886, ARRY-438162 PD-325901, CI-1040, and PD-98059.

**[00107]** Non-limiting examples of mTOR inhibitors include: AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus, ATP-competitive TORC1/TORC2 inhibitors, comprising PI-103, PP242, PP30, and Torin 1.

**[00108]** Non-limiting examples of non-steroidal anti-inflammatory drugs include: salsalate, diflunisal, ibuprofen, ketoprofen, nabumetone, piroxicam, ibuprofen cream, naproxen, diclofenac, indomethacin, sulindac, tolmetin, etodolac, ketorolac, and oxaprozin.

**[00109]** Non-limiting examples of PDGFR inhibitors include: C-451, CP-673, and CP-868596.

**[00110]** Non-limiting examples of platinum chemotherapeutics include: cisplatin, oxaliplatin, eptaplatin, lobaplatin, nedaplatin, carboplatin, satraplatin, and picoplatin.

**[00111]** Non-limiting examples of polo-like kinase inhibitors include: BI-2536.

**[00112]** Non-limiting examples of phosphoinositide-3 kinase (PI3K) inhibitors include: wortmannin, LY294002, XL-147, CAL-120, ONC-21, AEZS-127, ETP-45658, PX-866, GDC-0941, BGT226, BEZ235, and XL765.

**[00113]** Non-limiting examples of thrombospondin analogs include: ABT-510, ABT-567, ABT-898, and TSP-1.

**[00114]** Non-limiting examples of VEGFR inhibitors include: bevacizumab, ABT-869, AEE-788, ANGIOZYME™ (a ribozyme that inhibits angiogenesis, axitinib, AZD-2171, CP-547,632, IM-862, pegaptamib, sorafenib, pazopanib, vatalanib, sunitinib, VEGF trap, and vandetanib.

**[00115]** Non-limiting examples of antibiotics include: intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, bleomycin, daunorubicin, liposomal doxorubicin, doxorubicin, elsamitrucin, epirbucin, glarbuicin, idarubicin, mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, valrubicin, and zinostatin.

**[00116]** Non-limiting examples of topoisomerase inhibitors include: aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, irinotecan, camptothecin, dexrazoxine, diflomotecan, edotecarin, epirubicin, etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarbucin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, and topotecan.

**[00117]** Non-limiting examples of antibodies include: bevacizumab, CD40 antibodies, chTNT-1/B, denosumab, cetuximab, zanolimumab, IGF1R antibodies, lintuzumab,

edrecolomab, WX G250, rituximab, ticilimumab, trastuzumab, CD20 antibodies types I and II, pembrolizumab, ipilumimab, nivolumab, rituximab, and panitumumab.

**[00118]** Non-limiting examples of hormonal therapies include: anastrozole, exemestane, arzoxifene, bicalutamide, cetrorelix, degarelix, deslorelin, trilostane, dexamethasone, flutamide, raloxifene, fadrozole, toremifene, fulvestrant, letrozole, formestane, glucocorticoids, doxercalciferol, sevelamer carbonate, lasofoxifene, leuprolide acetate, megesterol, mifepristone, nilutamide, tamoxifen citrate, abarelix, prednisone, finasteride, rilostane, buserelin, luteinizing hormone releasing hormone (LHRH), histrelin implant, trilostane, modrastane, fosrelin, and goserelin.

**[00119]** Non-limiting examples of deltoids and retinoids include: seocalcitol, lexacalcitrol, fenretinide, aliretinoin, liposomal tretinoin, bexarotene, and LGD-1550.

**[00120]** Non-limiting examples of PARP inhibitors include: ABT-888, olaparib, KU-59436, AZD-2281, AG-014699, BSI-201, BGP-15, INO-1001, and ONO-2231.

**[00121]** Non-limiting examples of plant alkaloids include: vincristine, vinblastine, vindesine, and vinorelbine.

**[00122]** Non-limiting examples of proteasome inhibitors include: bortezomib, carfilzomib, MG132, and NPI-0052.

**[00123]** Non-limiting examples of immunologicals include: interferons or immune-enhancing agents. Interferons comprise interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, interferon gamma-1b, interferon gamma-nl. Other immune-enhancing agents comprise oxidized glutathione, tasonermin, tositumomab, alemtuzumab, CTLA4, decarbazine, denileukin, epratuzumab, lenograstim, lentinan, leukocyte alpha interferon, imiquimod, ipilumimab, melanoma vaccine, mitumomab, molgramostim, gemtuzumab ozogamicin, filgrastim, OncoVAC-CL, oregovomab, pemtumomab, sipuleucel-T, sargaramostim, sizofilan, teceleukin, Bacillus Calmette-Guerin, ubenimex, virulizin, Z-100, Tetrachlorodecaoxide (TCDO), aldesleukin, thymalfasin, daclizumab, and 90Y-Ibritumomab tiuxetan.

**[00124]** Non-limiting examples of biological response modifiers include: krestin, lentinan, sizofuran, picibanil, PF-3512676, and ubenimex.

**[00125]** Non-limiting examples of pyrimidine analogs include: cytarabine, cytosine arabinoside, doxifluridine, fludarabine, 5-fluorouracil, floxuridine, gemcitabine, ratitrexed, and triacetyluridine troxacitabine.

**[00126]** Non-limiting examples of purine analogs include: thioguanine, and mercaptopurine.

**[00127]** Non-limiting examples of antimitotic agents include: batabulin, epothilone D, N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone, paclitaxel, docetaxel, PNU100940, patupilone, XRP-9881 larotaxel, vinflunine, and epothilone.

**[00128]** Non-limiting examples of ubiquitin ligase inhibitors include: MDM2 inhibitors, such as nutlins, and NEDD8 inhibitors such as MLN4924.

**[00129]** Compounds of this disclosure can also be used as radiosensitizers that enhance the efficacy of radiotherapy. Non-limiting examples of radiotherapy include: external beam radiotherapy, teletherapy, brachytherapy and sealed, unsealed source radiotherapy.

**[00130]** Compounds of the disclosure can be combined with other anti-cancer agents such as ABI-007, ABT-100, Ad5CMV-p53 vaccine, lovastatin, poly I:poly C12U synthetic RNA, exisulind, pamidronic acid, arglabin, L-asparaginase, atamestane, tazarotene, combreastatin, mitumomab, cachectin, cachexin, canvaxin, CeaVac, celmoleukin, histamine, human papillomavirus vaccine, cyclophosphamide, hydroxydoxorubicin, vincristine, prednisone, cyproterone, combrestatin, DAB(389)EGF (catalytic and translocation domains of diphtheria toxin fused via a His-Ala linker to human epidermal growth factor), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, squalamine lactate, T4N5 liposome lotion, discodermolide, exatecan mesylate, enzastaurin, epithilone B, quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine, GASTRIMMUNE®, oblimersen sodium, GMK, GVAX®, halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, cintredekin besudotox, IL-13-pseudomonas exotoxin, IL-1alpha, IL-1beta, IL-2, interferon-α, interferon-γ, mifamurtide, lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine, AE-941, trimetrexate glucuronate, pentostatin, ranpirnase, vitespen, ONCOVAX®, rubitecan, OSIDEM®, oregovomab, paclitaxel, PANDIMEX™, panitumumab, falimarev, inalimarev, pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, catumaxomab, lenalidomide, efaproxiral, lanreotide, acitretin, staurosporine, talabostat, bexarotene, DHA-paclitaxel, canfosfamide, temilifene, temozolomide, tesmilifene, thalidomide, STn-KLH, 2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride, golnerminogene pradenovec, bosentan, tretinoin, tetrandrine, arsenic trioxide, virulizin, ukrain, vitaxin, motexafin gadolinium, atrasentan, paclitaxel poliglumex, trabectedin, ZD-6126, dexrazoxane, zolendronic acid, or zorubicin. Illustrative compounds of the disclosure have been tested for anti-cancer activity against human tumor cell lines and found to induce autophagosome aggregation and to be cytotoxic to tumor cells. The compounds can treat cancer in

combination therapy with clinically used anti-cancer agents, such as chemotherapeutics, targeted agents, immunotherapies, antibody-drug conjugates (ADCs), cellular therapies and anti-tumor vaccines. Compounds of the disclosure possess antimalarial activity against chloroquine- sensitive strains, and can be effective against chloroquine-sensitive and chloroquine-resistant malaria strains.

**[00131]** In some embodiments, a therapy of the disclosure is more effective as compared to a corresponding dosage of a chloroquine or hydroxychloroquine. A compound of the disclosure can be at least 1% more effective, at least 5% more effective, at least 10% more effective, at least 15% more effective, at least 20% more effective, at least 25% more effective, at least 30% more effective, at least 35% more effective, at least 40% more effective, at least 45% more effective, at least 50% more effective, at least 55% more effective, at least 60% more effective, at least 65% more effective, at least 70% more effective, at least 75% more effective, at least 80% more effective, at least 85% more effective, at least 95% more effective, or at least 100% more effective than chloroquine or hydroxychloroquine. In some embodiments, a compound of the disclosure is at least 0.5-fold more effective, at least 1-fold more effective, at least 2-fold more effective, at least 3-fold more effective, at least 4-fold more effective, at least 5-fold more effective, at least 6-fold more effective, at least 7-fold more effective, at least 8-fold more effective, at least 9-fold more effective, at least 10-fold more effective, at least 11-fold more effective, at least 12-fold more effective, at least 13-fold more effective, at least 14-fold more effective, at least 15-fold more effective, at least 16-fold more effective, at least 17-fold more effective, at least 18-fold more effective, at least 19-fold more effective, or at least 20-fold more effective, at least 21-fold more effective, at least 22-fold more effective, at least 23-fold more effective, at least 24-fold more effective, at least 25-fold more effective, at least 26-fold more effective, at least 27-fold more effective, at least 28-fold more effective, at least 29-fold more effective, at least 30-fold more effective, at least 31-fold more effective, at least 32-fold more effective, at least 33-fold more effective, at least 34-fold more effective, at least 35-fold more effective, at least 36-fold more effective, at least 37-fold more effective, at least 38-fold more effective, at least 39-fold more effective, at least 40-fold more effective, at least 41-fold more effective, at least 42-fold more effective, at least 43-fold more effective, at least 44-fold more effective, at least 45-fold more effective, at least 46-fold more effective, at least 47-fold more effective, at least 48-fold more effective, at least 49-fold more effective, at least 50-fold more effective, at least 51-fold more effective, at least 52-fold more effective, at least 53-fold more effective, at least 54-fold more effective, at least 55-fold more effective, at least 56-fold more effective, at least 57-fold more effective, at least

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**[00132]** Any compound herein can be purified. A compound herein can be least 1% pure, at least 2% pure, at least 3% pure, at least 4% pure, at least 5% pure, at least 6% pure, at least 7% pure, at least 8% pure, at least 9% pure, at least 10% pure, at least 11% pure, at least 12% pure, at least 13% pure, at least 14% pure, at least 15% pure, at least 16% pure, at least 17% pure, at least 18% pure, at least 19% pure, at least 20% pure, at least 21% pure, at least 22% pure, at least 23% pure, at least 24% pure, at least 25% pure, at least 26% pure, at least 27% pure, at least 28% pure, at least 29% pure, at least 30% pure, at least 31% pure, at least 32% pure, at least 33% pure, at least 34% pure, at least 35% pure, at least 36% pure, at least 37% pure, at least 38% pure, at least 39% pure, at least 40% pure, at least 41% pure, at least 42% pure, at least 43% pure, at least 44% pure, at least 45% pure, at least 46% pure, at least 47% pure, at least 48% pure, at least 49% pure, at least 50% pure, at least 51% pure, at least 52% pure, at least 53% pure, at least 54% pure, at least 55% pure, at least 56% pure, at least 57%

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Optional substituents for chemical groups

**[00133]** Non-limiting examples of optional substituents include hydroxyl groups, sulfhydryl groups, halogens, amino groups, nitro groups, nitroso groups, cyano groups, azido groups, sulfoxide groups, sulfone groups, sulfonamide groups, carboxyl groups, carboxaldehyde groups, imine groups, alkyl groups, halo-alkyl groups, alkenyl groups, halo-alkenyl groups, alkynyl groups, halo-alkynyl groups, alkoxy groups, aryl groups, aryloxy groups, aralkyl groups, arylalkoxy groups, heterocyclyl groups, acyl groups, acyloxy groups, carbamate groups, amide groups, urethane groups, and ester groups.

**[00134]** The term substituted refers to moieties having substituents replacing a hydrogen on one or more carbons or substitutable heteroatoms, e.g., NH, of the structure. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. In certain embodiments, substituted refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, the

heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms.

**[00135]** In some embodiments, optional substituents include any substituents described herein, for example: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazino (=N-$NH_2$), $-R^n-OR^m$, $-R^n-OC(O)-R^m$, $-R^n-OC(O)-OR^m$, $-R^n-OC(O)-N(R^m)_2$, $-R^n-N(R^m)_2$, $-R^n-C(O)R^m$, $-R^n-C(O)OR^m$, $-R^n-C(O)N(R^m)_2$, $-R^n-O-R^p-C(O)N(R^m)_2$, $-R^n-N(R^m)C(O)OR^m$, $-R^n-N(R^m)C(O)R^m$, $-R^n-N(R^m)S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tOR^m$ (where t is 1 or 2), and $-R^n-S(O)_tN(R^m)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, aralkyl, aralkenyl, aralkynyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, and heteroarylalkyl any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-$NH_2$), $-R^n-OR^m$, $-R^n-OC(O)-R^m$, $-R^n-OC(O)-OR^m$, $-R^n-OC(O)-N(R^m)_2$, $-R^n-N(R^m)_2$, $-R^n-C(O)R^m$, $-R^n-C(O)OR^m$, $-R^n-C(O)N(R^m)_2$, $-R^n-O-R^p-C(O)N(R^m)_2$, $-R^n-N(R^m)C(O)OR^m$, $-R^n-N(R^m)C(O)R^m$, $-R^n-N(R^m)S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tOR^m$ (where t is 1 or 2) and $-R^n-S(O)_tN(R^m)_2$ (where t is 1 or 2); wherein each $R^m$ is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, wherein each $R^m$, valence permitting, may be optionally substituted with alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), hydrazine (=N-$NH_2$), $-R^n-OR^m$, $-R^n-OC(O)-R^m$, $-R^n-OC(O)-OR^m$, $-R^n-OC(O)-N(R^m)_2$, $-R^n-N(R^m)_2$, $-R^n-C(O)R^m$, $-R^n-C(O)OR^m$, $-R^n-C(O)N(R^m)_2$, $-R^n-O-R^p-C(O)N(R^m)_2$, $-R^n-N(R^m)C(O)OR^m$, $-R^n-N(R^m)C(O)R^m$, $-R^n-N(R^m)S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tOR^m$ (where t is 1 or 2) and $-R^n-S(O)_tN(R^m)_2$ (where t is 1 or 2); and wherein each $R^n$ is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each $R^p$ is a straight or branched alkylene, alkenylene or alkynylene chain.

**[00136]** Non-limiting examples of alkyl and alkylene groups include straight, branched, and cyclic alkyl and alkylene groups. An alkyl or alkylene group can be, for example, a $C_1$, $C_2$, $C_3$, $C_4$, $C_5$, $C_6$, $C_7$, $C_8$, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$, $C_{13}$, $C_{14}$, $C_{15}$, $C_{16}$, $C_{17}$, $C_{18}$, $C_{19}$, $C_{20}$, $C_{21}$, $C_{22}$, $C_{23}$,

$C_{24}$, $C_{25}$, $C_{26}$, $C_{27}$, $C_{28}$, $C_{29}$, $C_{30}$, $C_{31}$, $C_{32}$, $C_{33}$, $C_{34}$, $C_{35}$, $C_{36}$, $C_{37}$, $C_{38}$, $C_{39}$, $C_{40}$, $C_{41}$, $C_{42}$, $C_{43}$, $C_{44}$, $C_{45}$, $C_{46}$, $C_{47}$, $C_{48}$, $C_{49}$, or $C_{50}$ group that is substituted or unsubstituted. In certain embodiments, alkyl includes straight chain and branched alkyl and alkylene includes straight chain and branched alkylene.

**[00137]** Non-limiting examples of straight alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl.

**[00138]** Branched alkyl groups include any straight alkyl group substituted with any number of alkyl groups. Non-limiting examples of branched alkyl groups include isopropyl, isobutyl, *sec*-butyl, and *t*-butyl.

**[00139]** Non-limiting examples of cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptlyl, and cyclooctyl groups. Cyclic alkyl groups also include fused-, bridged-, and *spiro*-bicycles and higher fused-, bridged-, and *spiro*-systems. A cyclic alkyl group can be substituted with any number of straight, branched, or cyclic alkyl groups.

**[00140]** Non-limiting examples of alkenyl and alkenylene groups include straight, branched, and cyclic alkenyl groups. The olefin or olefins of an alkenyl group can be, for example, *E*, *Z*, *cis*, *trans*, terminal, or *exo*-methylene. An alkenyl or alkenylene group can be, for example, a $C_2$, $C_3$, $C_4$, $C_5$, $C_6$, $C_7$, $C_8$, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$, $C_{13}$, $C_{14}$, $C_{15}$, $C_{16}$, $C_{17}$, $C_{18}$, $C_{19}$, $C_{20}$, $C_{21}$, $C_{22}$, $C_{23}$, $C_{24}$, $C_{25}$, $C_{26}$, $C_{27}$, $C_{28}$, $C_{29}$, $C_{30}$, $C_{31}$, $C_{32}$, $C_{33}$, $C_{34}$, $C_{35}$, $C_{36}$, $C_{37}$, $C_{38}$, $C_{39}$, $C_{40}$, $C_{41}$, $C_{42}$, $C_{43}$, $C_{44}$, $C_{45}$, $C_{46}$, $C_{47}$, $C_{48}$, $C_{49}$, or $C_{50}$ group that is substituted or unsubstituted. In certain embodiments, alkenyl includes straight chain and branched alkenyl and alkenylene includes straight chain and branched alkenylene.

**[00141]** Non-limiting examples of an alkylene, alkenylene or alkynylene interrupted by a carbocycle or heterocycle include straight or branched alkylene groups with a carbocycle or heterocycle at the terminal or internal position of the alkylene group, e.g., -heterocycle-$CH_2$-$CH_2$-$CH_2$-, -$CH_2$-heterocycle- $CH_2$-$CH_2$-, -$CH(CH_3)$-carbocycle-$CH_2$-$CH_2$-$CH_2$-,and -$CH_2$-$CH(CH_2$-$CH_3)$-$CH_2$-carbocycle-. The carbocycle or heterocycle may be bound to the remainder of the molecule through any stable bond, such as a single or double bond. Non-limiting examples of an alkylene interrupted with a heterocycle include -$CH_2$-pyridine-$CH_2$-$CH_2$-, -$CH_2$-$CH_2$-pyridine-$CH_2$-$CH_2$-, -$CH_2$-$CH_2$-pyrrole-$CH_2$-$CH_2$, and -piperidine-$CH_2$-$CH_2$. Non-limiting examples of an alkenylene interrupted with a heterocycle include -$CH_2$-pyridine-CH=CH-, -$CH_2$-$CH_2$-azetidine-CH=CH-, -CH=CH-piperidine-CH=CH-, and -piperidine-CH=CH-$CH_2$-$CH_2$-. Non-limiting examples of an alkynylene interrupted with a heterocycle include -$CH_2$-$CH_2$-pyridine-C≡C-, -$CH_2$-$CH_2$-azetidine-$CH_2$-C≡C-, and -C≡C-

$CH_2$-$CH_2$-piperidine-$CH_2$-.

**[00142]** Non-limiting examples of a heteroalkylene, heteroalkenylene or heteroalkynylene interrupted by a carbocycle or heterocycle include straight or branched heteroalkylene groups with a carbocycle of heterocycle at the terminal or internal position of the heteroalkylene group, e.g., -heterocycle- $CH_2$-NH-$CH_2$-, $CH_2$-heterocycle- O-$CH_2$-, -CH($CH_3$)-carbocycle-N($CH_3$)-$CH_2$-$CH_2$-, and -$CH_2$-N($CH_2$-$CH_3$)-$CH_2$-carbocycle-. The carbocycle or heterocycle may be bound to the remainder of the molecule through any stable bond, such as a single or double bond. Non-limiting examples of a heteroalkylene interrupted with a heterocycle include -$CH_2$-pyridine-NH-$CH_2$-, -$CH_2$-$CH_2$-pyridine-O-$CH_2$-, -$CH_2$-S-pyrrole-$CH_2$-$CH_2$, and -piperidine-N(CH3)-$CH_2$-. Non-limiting examples of heteroalkenylene interrupted with a heterocycle include -$CH_2$-O-pyridine-CH=CH-, -$CH_2$-N(H)-azetidine-CH=CH-, -CH=CH-piperidine-N=CH-, and -piperidine-CH=CH-O-$CH_2$-. Non-limiting examples of a heteroalkynylene interrupted with a heterocycle include -$CH_2$-O-pyridine-C≡C-, -$CH_2$-N(H)-azetidine-$CH_2$-C≡C-, and -C≡C-$CH_2$-S-piperidine-$CH_2$-.

**[00143]** Non-limiting examples of alkynyl or alkynylene groups include straight, branched, and cyclic alkynyl groups. The triple bond of an alkylnyl or alkynylene group can be internal or terminal. An alkylnyl or alkynylene group can be, for example, a $C_2$, $C_3$, $C_4$, $C_5$, $C_6$, $C_7$, $C_8$, $C_9$, $C_{10}$, $C_{11}$, $C_{12}$, $C_{13}$, $C_{14}$, $C_{15}$, $C_{16}$, $C_{17}$, $C_{18}$, $C_{19}$, $C_{20}$, $C_{21}$, $C_{22}$, $C_{23}$, $C_{24}$, $C_{25}$, $C_{26}$, $C_{27}$, $C_{28}$, $C_{29}$, $C_{30}$, $C_{31}$, $C_{32}$, $C_{33}$, $C_{34}$, $C_{35}$, $C_{36}$, $C_{37}$, $C_{38}$, $C_{39}$, $C_{40}$, $C_{41}$, $C_{42}$, $C_{43}$, $C_{44}$, $C_{45}$, $C_{46}$, $C_{47}$, $C_{48}$, $C_{49}$, or $C_{50}$ group that is substituted or unsubstituted. In certain embodiments, alkynyl includes straight chain and branched alkynyl and alkynylene includes straight chain and branched alkynylene.

**[00144]** A halo-alkyl group can be any alkyl group substituted with any number of halogen atoms, for example, fluorine, chlorine, bromine, and iodine atoms. A halo-alkenyl group can be any alkenyl group substituted with any number of halogen atoms. A halo-alkynyl group can be any alkynyl group substituted with any number of halogen atoms.

**[00145]** An alkoxy group can be, for example, an oxygen atom covalently bound to an alkyl, alkenyl, or alkynyl group. Non-limiting examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, and isobutoxy.

**[00146]** An aryl group can be heterocyclic or non-heterocyclic. An aryl group can be monocyclic or polycyclic. An aryl group can be substituted with any number of substituents described herein, for example, hydrocarbyl groups, alkyl groups, alkoxy groups, and halogen atoms. Non-limiting examples of aryl groups include phenyl, tolyl, naphthyl, pyrrolyl, pyridyl, imidazolyl, thiophenyl, and furyl. An aryl group can have a ring with any number of

members, for example from 5 to 14 members.

**[00147]** An exemplary aryloxy group is phenoxy.

**[00148]** An exemplary aralkyl group is benzyl.

**[00149]** An exemplary arylalkoxy is benzyloxy.

The term "carbocycle" as used herein refers to a saturated, unsaturated or aromatic ring in which each atom of the ring is carbon. Carbocycle includes 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated, and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, are included in the definition of carbocyclic. Exemplary carbocycles include cyclopentyl, cyclohexyl, cyclohexenyl, adamantyl, phenyl, indanyl, and naphthyl.

**[00150]** A heterocycle can be any ring containing a ring atom that is not carbon, for example, N, O, S, P, Si, B, or any other heteroatom. A heterocycle can be substituted with any number of substituents, for example, alkyl groups and halogen atoms. Heterocycles may be 3- to 10-membered monocyclic rings, 6- to 12-membered bicyclic rings, and 6- to 12-membered bridged rings. A heterocycle can be aromatic (heteroaryl) or non-aromatic. Each ring of a bicyclic heterocycle may be selected from saturated, unsaturated, and aromatic rings wherein at least one of the rings includes a heteroatom. In an exemplary embodiment, an aromatic ring, e.g., pyridyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, morpholine, piperidine or cyclohexene. Non-limiting examples of heterocycles include pyrrole, pyrrolidine, pyridine, piperidine, succinamide, maleimide, morpholine, imidazole, thiophene, furan, tetrahydrofuran, pyran, and tetrahydropyran. A heterocycle or heteroaryl group can have a ring with any number of members, for example 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 members.

**[00151]** Non-limiting examples of acyl include acetyl, benzoyl, benzyloxycarbonyl, phenoxycarbonyl, methoxycarbonyl, and ethoxycarbonyl.

**[00152]** A non-limiting example of an acyloxy group, or an ester group, is acetate.

**[00153]** An amide group may be represented as -C(O)N(group 1)(group 2), wherein each of group 1 and group 2 is independently H or any group described herein, non-limiting examples of which include alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, any of which is substituted or unsubstituted.

**[00154]** A carbamate group can be represented by -OC(O)N(group 1)(group 2)-, wherein

each of group 1 and group 2 may be independently H or any group described herein, non-limiting examples of which include alkyl, alkenyl, alkynyl, aryl, heteroaryl, or heterocyclyl, any of which is substituted or unsubstituted

**[00155]** Any group of a compound of the current disclosure may be optionally substituted, wherein each group, valence permitting, may be optionally substituted with straight or branched alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), or hydrazine (=N-$NH_2$).

Pharmaceutical Formulations

**[00156]** A pharmaceutical composition of the disclosure can be used, for example, before, during, or after treatment of a subject with another pharmaceutical agent, radiation therapy, or surgery.

**[00157]** A pharmaceutical composition of the disclosure can be a combination of any pharmaceutical compounds described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can be administered in therapeutically-effective amounts as pharmaceutical compositions by any form and route known in the art including, for example, intravenous, subcutaneous, intramuscular, oral, rectal, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, and topical administration.

**[00158]** A pharmaceutical composition can be administered in a local or systemic manner, for example, via injection of the compound directly into an organ, optionally in a depot or sustained release formulation. Pharmaceutical compositions can be provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. A rapid release form can provide an immediate release. An extended release formulation can provide a controlled release or a sustained delayed release.

**[00159]** For oral administration, pharmaceutical compositions can be formulated by combining the active compounds with pharmaceutically acceptable carriers or excipients. Such carriers can be used to formulate liquids, gels, syrups, elixirs, slurries, suspensions, pills, capsules, and tablets, for oral ingestion by a subject. Non-limiting examples of solvents used in an oral dissolvable formulation can include water, ethanol, isopropanol, saline, physiological saline, DMSO, dimethylformamide, potassium phosphate buffer, phosphate buffer saline (PBS), sodium phosphate buffer, 4-2-hydroxyethyl-1-piperazineethanesulfonic

acid buffer (HEPES), 3-(N-morpholino)propanesulfonic acid buffer (MOPS), piperazine-N,N′-bis(2-ethanesulfonic acid) buffer (PIPES), and saline sodium citrate buffer (SSC). Non-limiting examples of co-solvents used in an oral dissolvable formulation can include sucrose, urea, cremaphor, DMSO, and potassium phosphate buffer.

**[00160]** Pharmaceutical compositions of the disclosure suitable for oral administration can be presented as discrete dosage forms, such as hard or soft capsules, cachets, troches, lozenges, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion, or dispersible powders or granules, or syrups or elixirs. Such dosage forms can be prepared by any of the methods of pharmacy, which typically include the step of bringing the active ingredient(s) into association with the carrier. In general, the composition are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient(s) in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

**[00161]** This disclosure further encompasses anhydrous pharmaceutical composition and dosage forms comprising an active ingredient, since water can facilitate the degradation of some compounds. For example, water may be added (e.g., 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the disclosure can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the disclosure which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable

formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

**[00162]** An active ingredient can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the composition for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

**[00163]** Pharmaceutical preparations can be formulated for intravenous and intratumoral administration. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form or solubilized with drug carriers such as cyclodextrins or albumin or organic solvents such as propylene glycol, PEG 300, PEG 400, ethanol, glycerin, polysorbate 80, cremophor, or solutol HS 15. Suspensions of the active compounds can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. The suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

**[00164]** The active compounds can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, and ointments. Such pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

**[00165]** The compounds can also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention

enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone or PEG. In suppository forms of the compositions, a low-melting wax such as a mixture of fatty acid glycerides, optionally in combination with cocoa butter, is first melted.

**[00166]** In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the compounds described herein are administered in pharmaceutical compositions to a subject having a disease or condition to be treated. In some embodiments, the subject is a mammal such as a human. A therapeutically-effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compounds used, and other factors.

**[00167]** Pharmaceutical compositions can be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Formulation can be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising compounds described herein can be manufactured in a conventional manner, for example, by means of conventional mixing, dissolving, granulating, or emulsifying.

**[00168]** The pharmaceutical compositions can include at least one pharmaceutically acceptable carrier, diluent, or excipient and compounds described herein or pharmaceutically-acceptable salt form.

**[00169]** Methods for the preparation of compositions comprising the compounds described herein can include formulating the compounds with one or more inert, pharmaceutically-acceptable excipients. Liquid compositions include, for example, solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, for example, gels, suspensions and creams. The compositions can be in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions can also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives.

**[00170]** Compounds can be delivered via liposomal technology. The use of liposomes as drug carriers can increase the therapeutic index of the compounds. Liposomes are composed of natural phospholipids, and can contain mixed lipid chains with surfactant properties (e.g., egg phosphatidylethanolamine). A liposome design can employ surface ligands for attaching to unhealthy tissue. Non-limiting examples of liposomes include the multilamellar vesicle

(MLV), the small unilamellar vesicle (SUV), and the large unilamellar vesicle (LUV). Liposomal physicochemical properties can be modulated to optimize penetration through biological barriers and retention at the site of administration, and to prevent premature degradation and toxicity to non-target tissues. Optimal liposomal properties depend on the administration route: large-sized liposomes show good retention upon local injection, small-sized liposomes are better suited to achieve passive targeting. PEGylation reduces the uptake of the liposomes by the liver and spleen, and increases the circulation time, resulting in increased localization at the inflamed site due to the enhanced permeability and retention (EPR) effect. Additionally, liposomal surfaces can be modified to achieve selective delivery of the encapsulated drug to target cells. Non-limiting examples of targeting ligands include monoclonal antibodies, vitamins, peptides, and polysaccharides binding to receptors concentrated on the surface of cells associated with the disease.

**[00171]** Non-limiting examples of dosage forms suitable for use in the disclosure include capsules, tablets, liquids, elixirs, nanosuspensions, aqueous or oily suspensions, drops, syrups, and any combination thereof. Non-limiting examples of pharmaceutically-acceptable excipients suitable for use in the disclosure include granulating agents, binding agents, lubricating agents, disintegrating agents, sweetening agents, glidants, anti-adherents, anti-static agents, surfactants, anti-oxidants, gums, coating agents, coloring agents, flavoring agents, coating agents, plasticizers, preservatives, suspending agents, emulsifying agents, plant cellulosic material and spheronization agents, and any combination thereof.

**[00172]** Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), each of which is incorporated by reference in its entirety.

**[00173]** Compositions of the disclosure can be packaged as a kit. In some embodiments, a kit includes written instructions on the administration/use of the composition. The written material can be, for example, a label. The written material can suggest conditions methods of administration. The instructions provide the subject and the supervising physician with the best guidance for achieving the optimal clinical outcome from the administration of the therapy. The written material can be a label. In some embodiments, the label can be approved by a regulatory agency, for example the U.S. Food and Drug Administration (FDA),

the European Medicines Agency (EMA), or other regulatory agencies.

Pharmaceutically-Acceptable Salts

**[00174]** The disclosure provides the use of pharmaceutically-acceptable salts of any therapeutic compound described herein. Pharmaceutically-acceptable salts include, for example, acid-addition salts and base-addition salts. The acid that is added to the compound to form an acid-addition salt can be an organic acid or an inorganic acid. A base that is added to the compound to form a base-addition salt can be an organic base or an inorganic base. In some embodiments, a pharmaceutically-acceptable salt is a metal salt. In some embodiments, a pharmaceutically-acceptable salt is an ammonium salt.

**[00175]** Acid addition salts can arise from the addition of an acid to a compound of the disclosure. In some embodiments, the acid is organic. In some embodiments, the acid is inorganic. In some embodiments, the acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, nitrous acid, sulfuric acid, sulfurous acid, a phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, gentisinic acid, gluconic acid, glucaronic acid, saccaric acid, formic acid, benzoic acid, glutamic acid, pantothenic acid, acetic acid, propionic acid, butyric acid, fumaric acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, oxalic acid, or maleic acid. Acid addition salts can be, for example, monosalts, disalts, trisalts, tetrasalts, or higher salts. Such forms can have counterions that are all the same anion, or encompass a plurality of chemically-distinct anions.

**[00176]** In some embodiments, the salt is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, a nitrate salt, a nitrite salt, a sulfate salt, a sulfite salt, a phosphate salt, isonicotinate salt, a lactate salt, a salicylate salt, a tartrate salt, an ascorbate salt, a gentisinate salt, a gluconate salt, a glucaronate salt, a saccarate salt, a formate salt, a benzoate salt, a glutamate salt, a pantothenate salt, an acetate salt, a propionate salt, a butyrate salt, a fumarate salt, a succinate salt, a methanesulfonate (mesylate) salt, an ethanesulfonate salt, a benzenesulfonate salt, a p-toluenesulfonate salt, a citrate salt, an oxalate salt, or a maleate salt.

**[00177]** Metal salts can arise from the addition of an inorganic base to a compound of the disclosure. The inorganic base consists of a metal cation paired with a basic counterion, such as, for example, hydroxide, carbonate, bicarbonate, or phosphate. The metal can be an alkali metal, alkaline earth metal, transition metal, or main group metal. In some embodiments, the metal is lithium, sodium, potassium, cesium, cerium, magnesium, manganese, iron, calcium, strontium, cobalt, titanium, aluminum, copper, or zinc.

**[00178]** In some embodiments, a metal salt is a lithium salt, a sodium salt, a potassium salt, a cesium salt, a cerium salt, a magnesium salt, a manganese salt, an iron salt, a calcium salt, a strontium salt, a cobalt salt, a titanium salt, an aluminum salt, a copper salt, a cadmium salt, or a zinc salt.

**[00179]** Ammonium salts can arise from the addition of ammonia or an organic amine to a compound of the disclosure. In some embodiments, the organic amine is triethyl amine, diisopropyl amine, ethanol amine, diethanol amine, triethanol amine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, N-ethylpiperidine, dibenzylamine, piperazine, pyridine, pyrrazole, pipyrrazole, imidazole, pyrazine, or pipyrazine.

**[00180]** In some embodiments, an ammonium salt is a triethyl amine salt, a diisopropyl amine salt, an ethanol amine salt, a diethanol amine salt, a triethanol amine salt, a morpholine salt, an N-methylmorpholine salt, a piperidine salt, an N-methylpiperidine salt, an N-ethylpiperidine salt, a dibenzylamine salt, a piperazine salt, a pyridine salt, a pyrrazole salt, a pipyrrazole salt, an imidazole salt, a pyrazine salt, or a pipyrazine salt.

Dosage

**[00181]** Pharmaceutical compositions described herein can be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage can be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged pills, tablets, capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Multiple-dose reclosable containers can be used, for example, in combination with a preservative. Formulations for parenteral injection can be presented in unit dosage form, for example, in ampoules, or in multi-dose containers with a preservative.

**[00182]** A compound described herein can be present in a composition in a range of from about 1 mg to about 2000 mg; from about 10 mg to about 1000 mg, from about 25 mg to 500 mg, from about 50 mg to about 250 mg, from about 100 mg to about 200 mg, from about 1 mg to about 50 mg, from about 50 mg to about 100 mg, from about 100 mg to about 150 mg, from about 150 mg to about 200 mg, from about 200 mg to about 250 mg, from about 250 mg to about 300 mg, from about 300 mg to about 350 mg, from about 350 mg to about 400 mg, from about 400 mg to about 450 mg, from about 450 mg to about 500 mg, from about 500 mg to about 550 mg, from about 550 mg to about 600 mg, from about 600 mg to about 650 mg, from about 650 mg to about 700 mg, from about 700 mg to about 750 mg, from about 750 mg

to about 800 mg, from about 800 mg to about 850 mg, from about 850 mg to about 900 mg, from about 900 mg to about 950 mg, or from about 950 mg to about 1000 mg.

**[00183]** A compound described herein can be present in a composition in an amount of about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, or about 2000 mg.

**[00184]** A combination treatment according to the disclosure may be effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the agent selected, the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

**[00185]** In certain embodiments, a compound of the disclosure is represented by any one of the formula in Table 1:

**Table 1**

| Compound | Structure |
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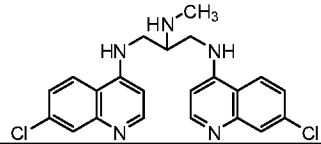
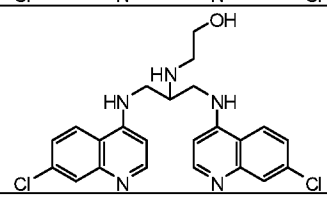
| 1 |  |
| 2 |  |

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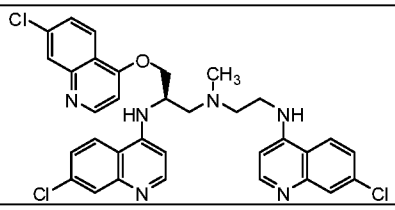
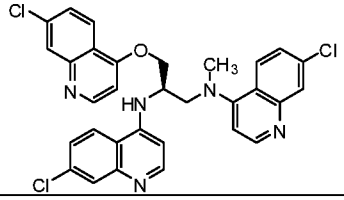
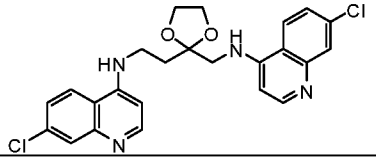
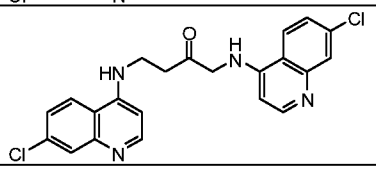
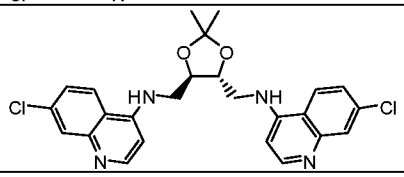
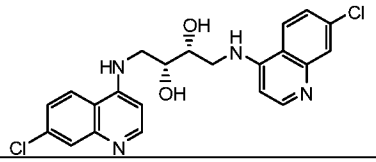
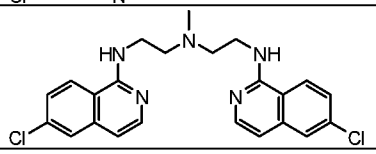
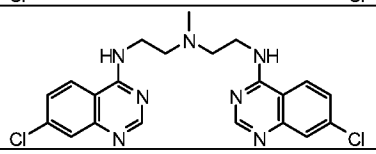
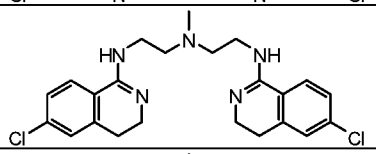
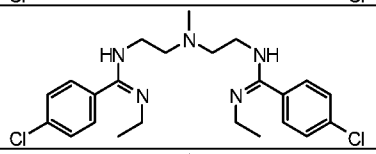
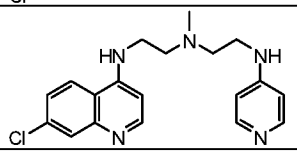
| 3 |  |
| 4 |  |
| 5 |  |
| 6 |  |
| 7 |  |
| 8 |  |
| 9 |  |
| 10 |  |
| 11 |  |
| 12 |  |
| 13 |  |

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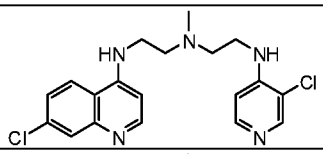
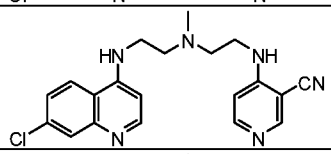
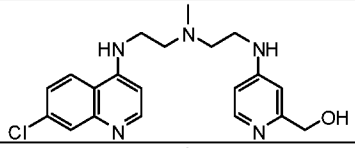
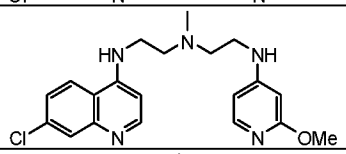
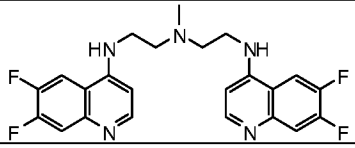
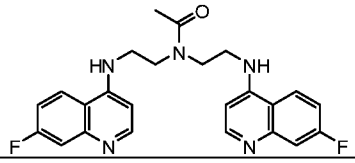
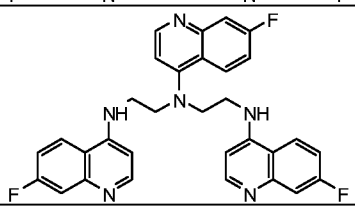
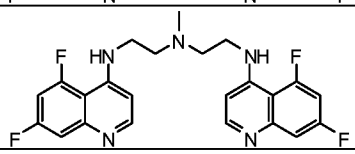
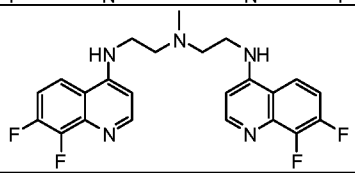
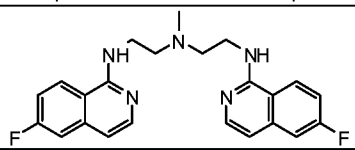
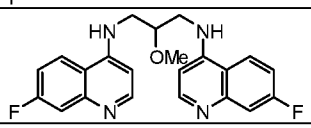
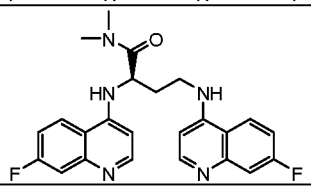
| 14 |  |
| 15 |  |
| 16 |  |
| 17 |  |
| 18 |  |
| 19 |  |
| 20 |  |
| 21 |  |
| 22 |  |
| 23 |  |
| 24 |  |
| 25 |  |

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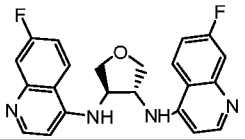
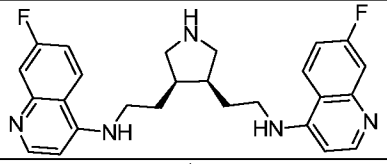
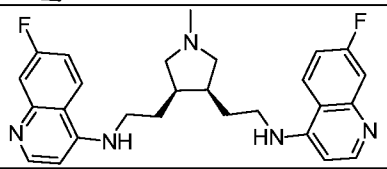
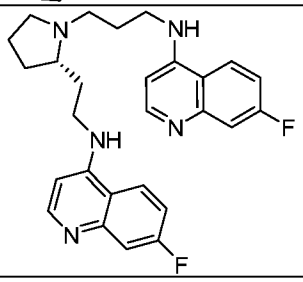
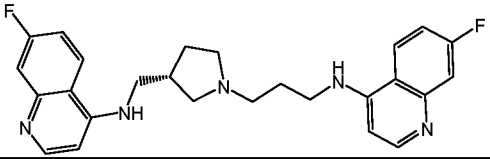
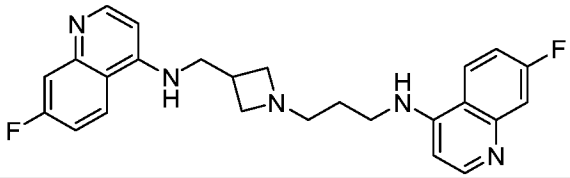
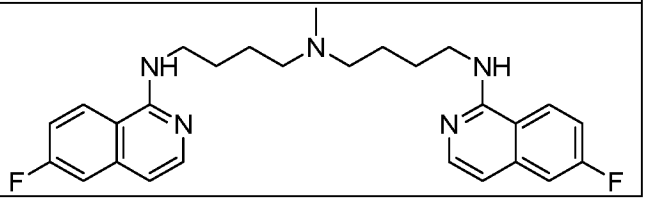
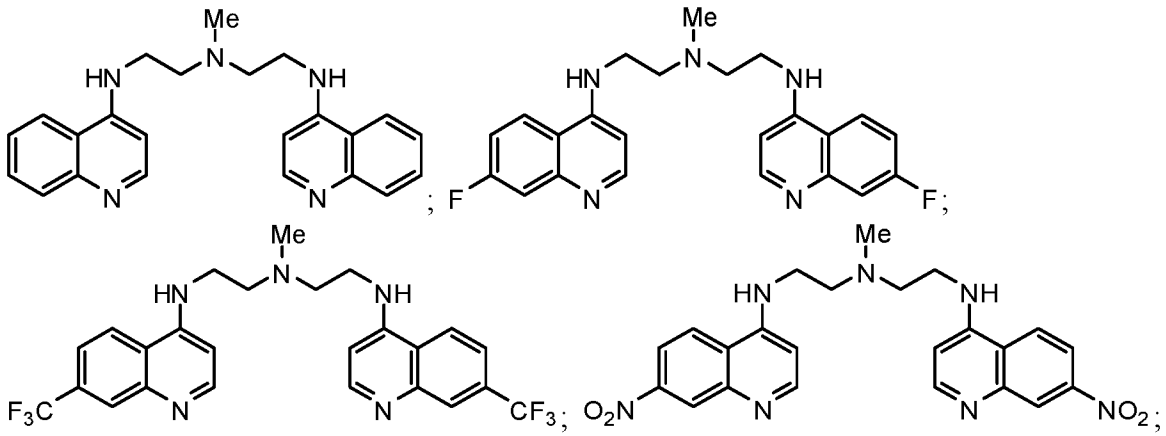
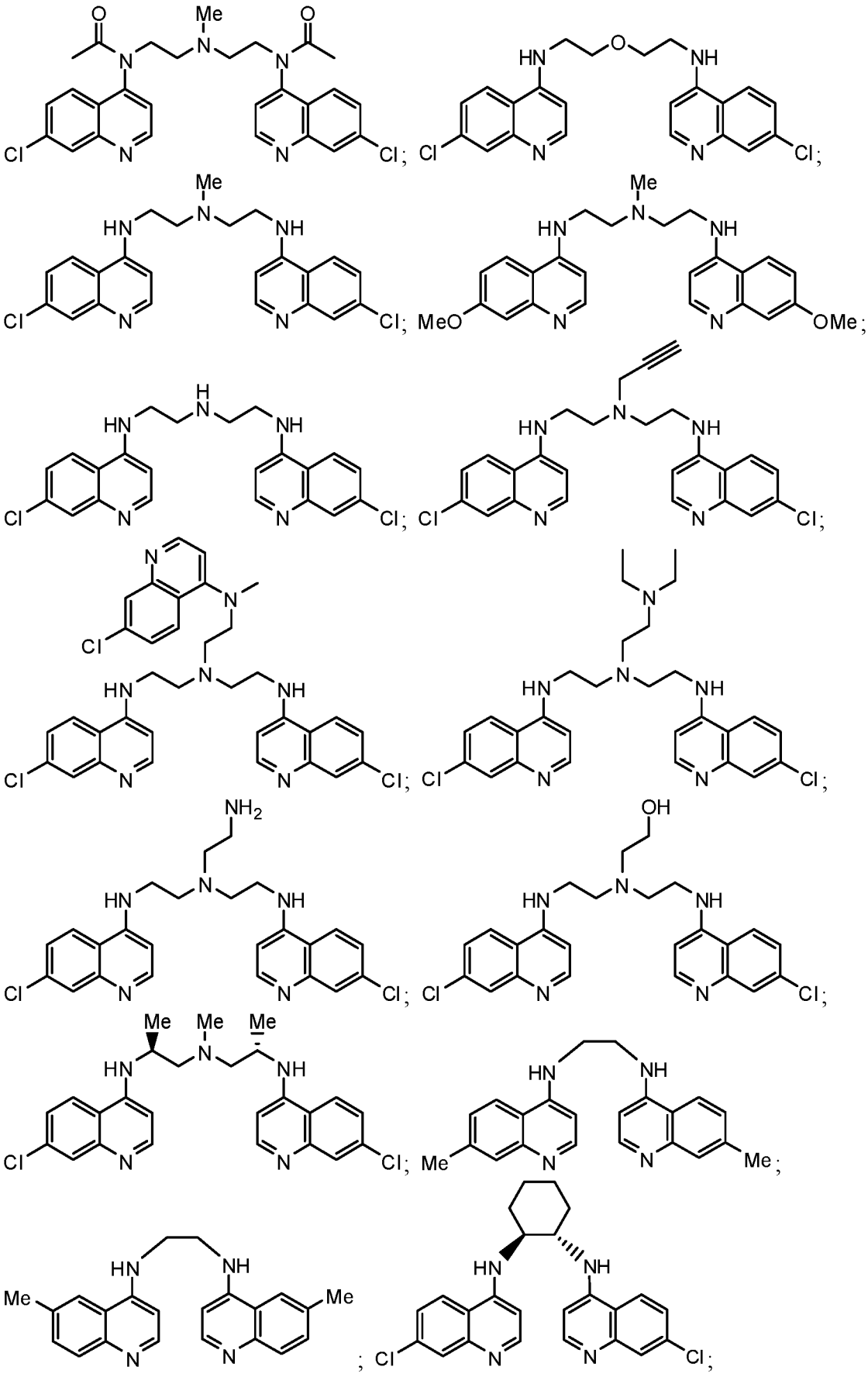
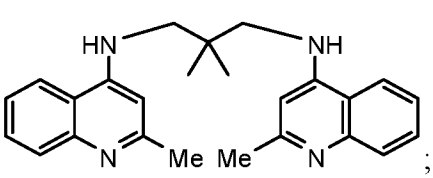
| 26 |  |
| 27 |  |
| 28 |  |
| 29 |  |
| 30 |  |
| 31 |  |
| 32 |  |

**[00186]** In some embodiments, a compound is, or is not, any one of the following:



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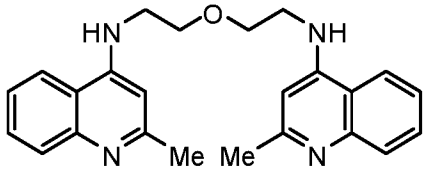
Me
Me
N
;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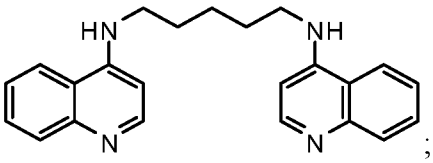
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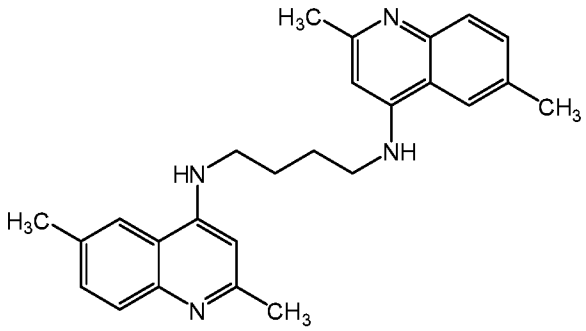
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CH3
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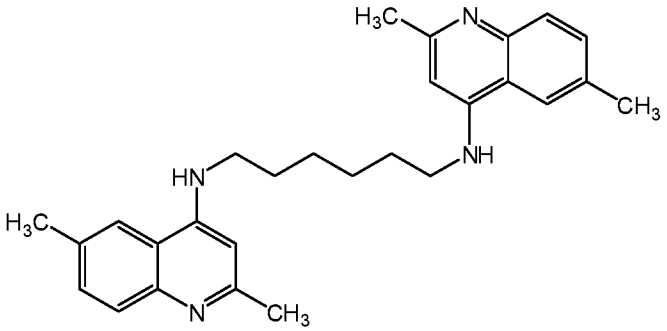
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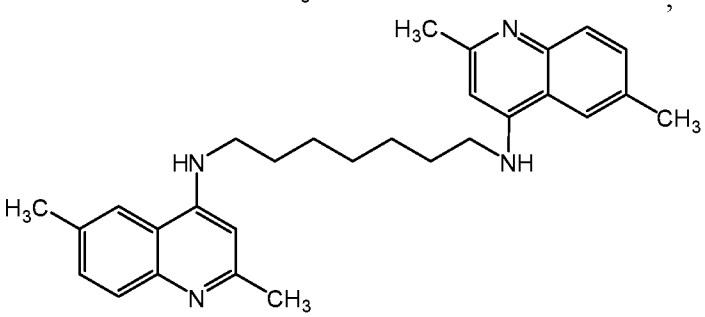
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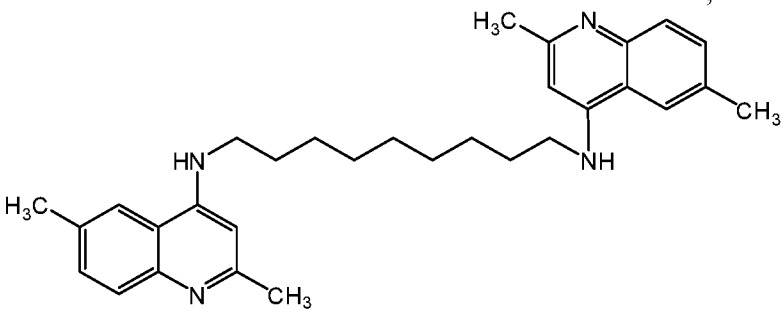
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CH3
HN
NH
H3C
N
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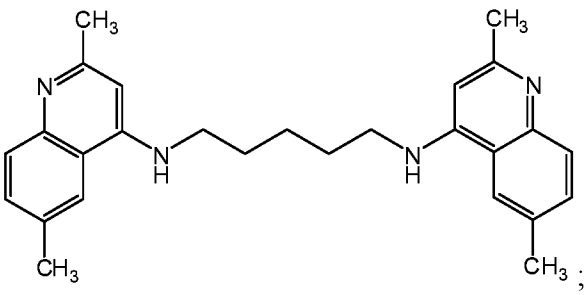
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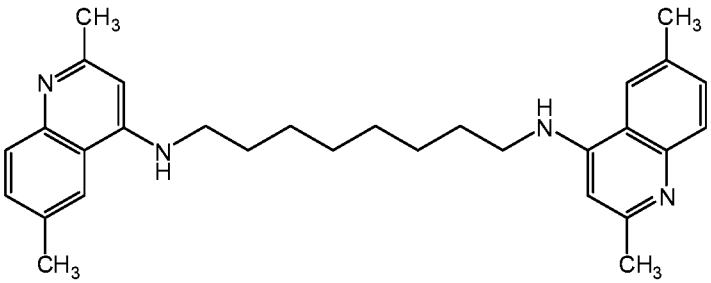
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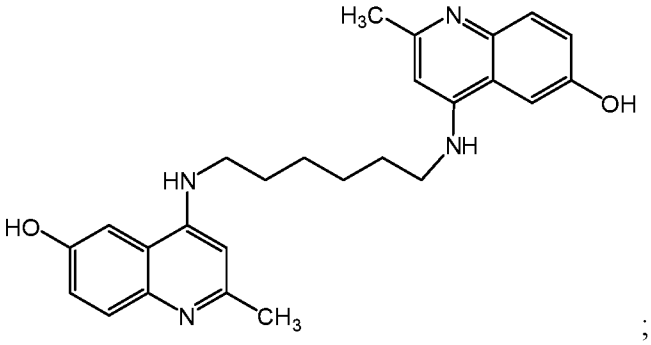
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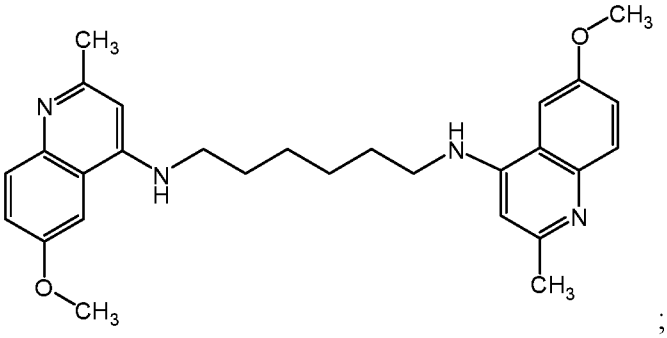
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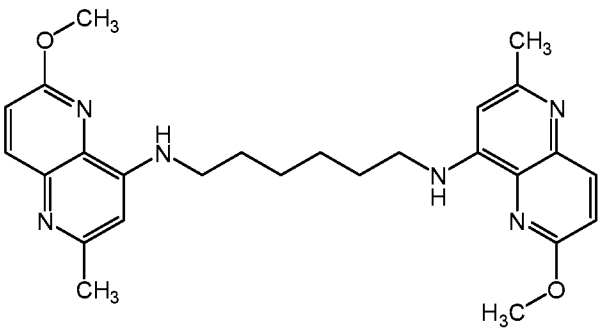
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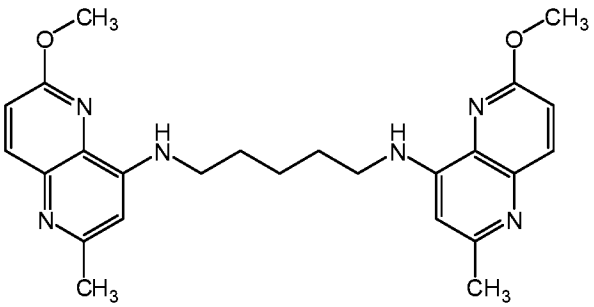
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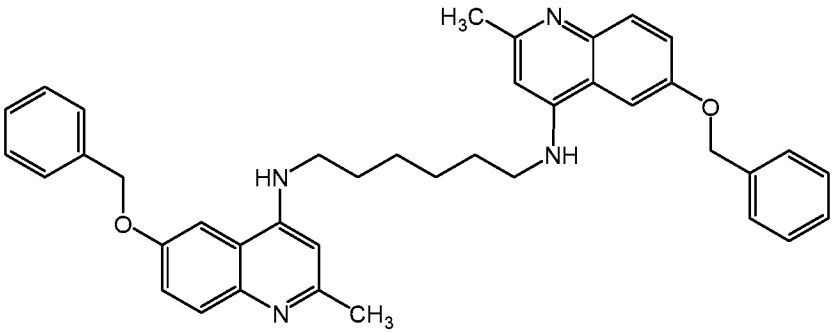

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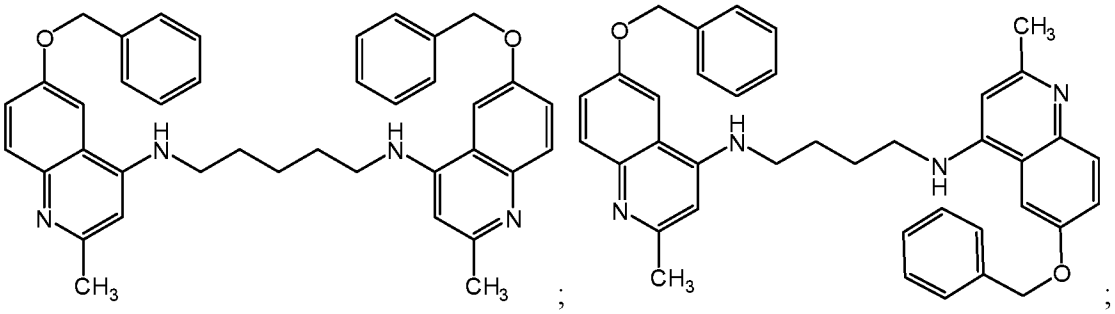

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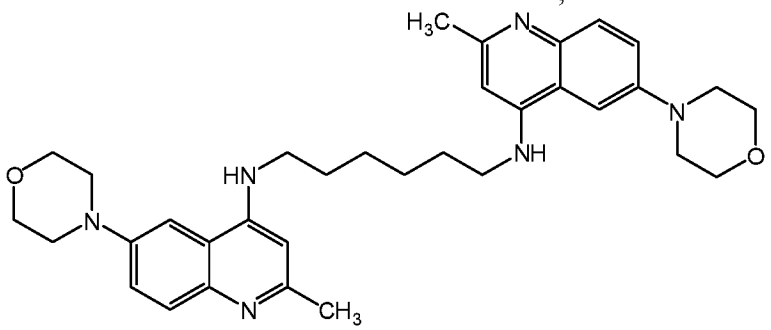

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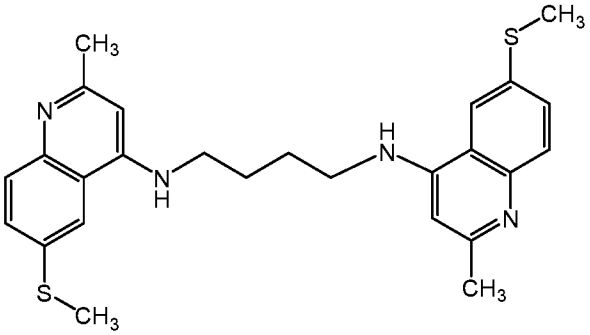

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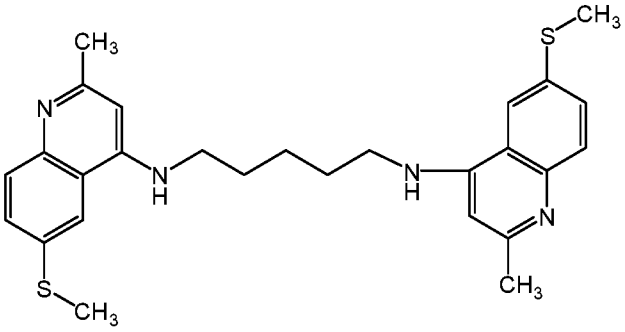

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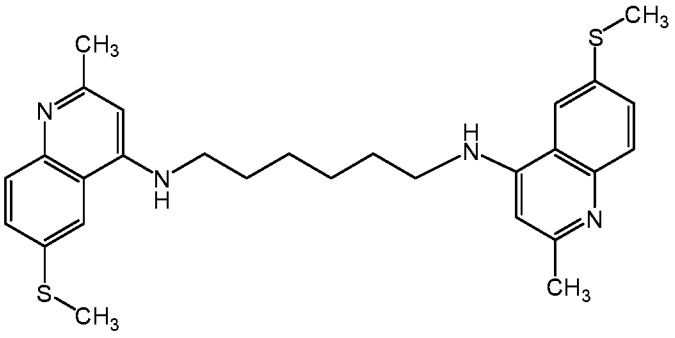
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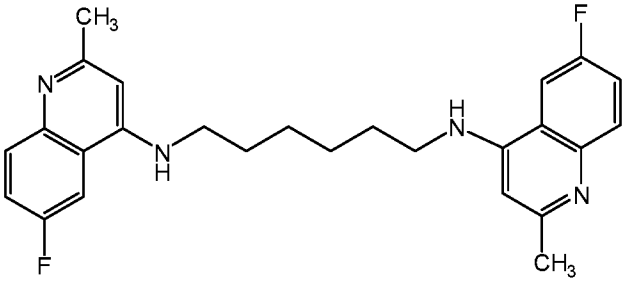
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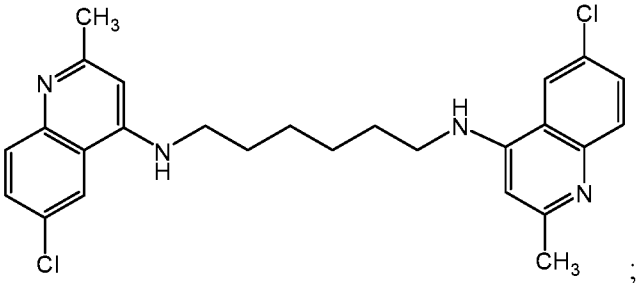
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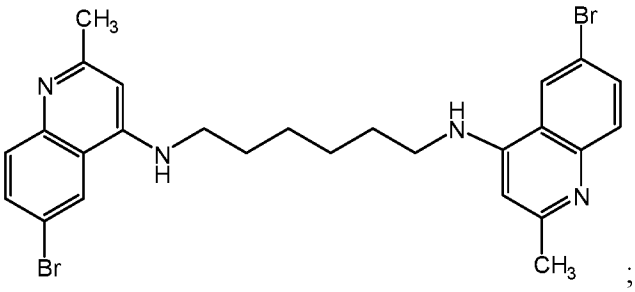
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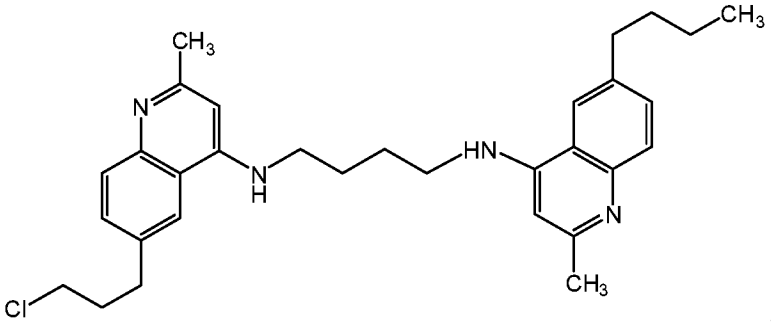
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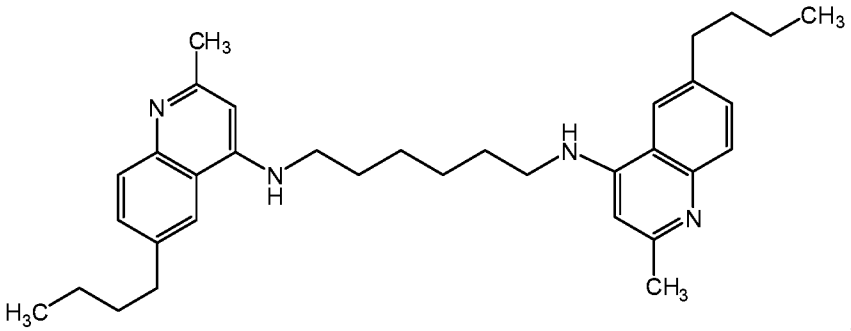
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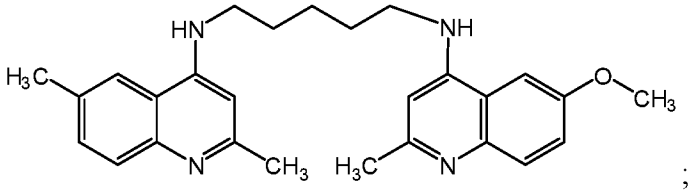
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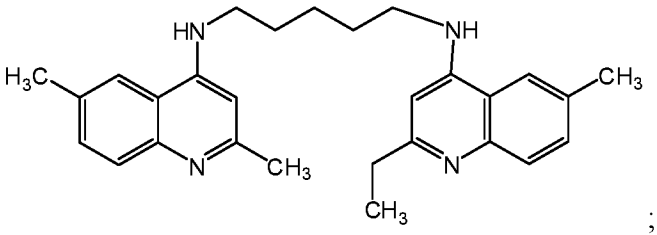
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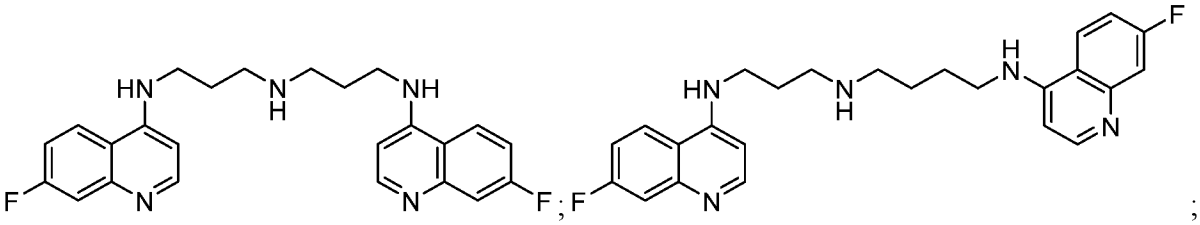
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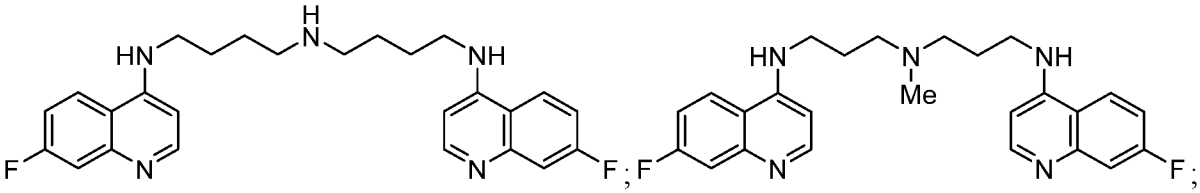
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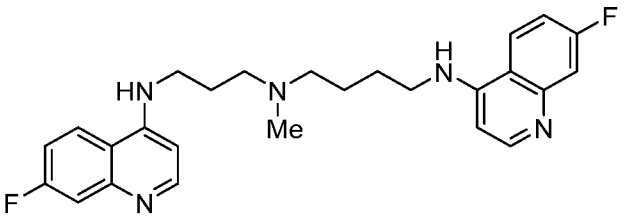
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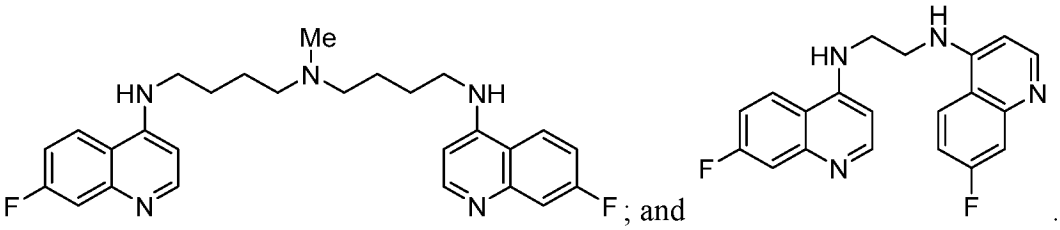

; and

Therapeutic Uses

**[00187]** In certain embodiments, a compound or salt of any of Formulas (I) to (XXII) may be used in the methods described herein. Subjects of the methods of the disclosure may be

elderly adults, adults, adolescents, pre-adolescents, children, toddlers, or infants. A subject can be a patient. A subject can be a non-human animal, for example, a horse, cow, sheep, goat, dog, cat, bird, rat, or mouse.

**[00188]** A compound of the disclosure can be used to treat, for example, malaria, amoebic liver abscess, toxoplasmosis, *Leishmania donovani*, Africa trypanosomiasis, avian malaria, or chikungunya fever. A compound of the disclosure can be used to treat malaria caused by *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium knowlesi*, or *Plasmodium malariae*.

**[00189]** A compound of the disclosure can be used to treat, for example, rheumatoid arthritis, lupus erythematosus, sarcoidosis, systemic scleroderma, pemphigus, lichen planus, polymyositis, porphyria cutanea tarda or Hashimoto's encephalopathy.

**[00190]** In some embodiments, a compound of the disclosure can be used in the treatment of cancer. Non-limiting examples of cancers include: acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, appendix cancer, astrocytomas, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancers, brain tumors, such as cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas, Burkitt lymphoma, carcinoma of unknown primary origin, central nervous system lymphoma, cerebellar astrocytoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, cutaneous T-cell lymphoma, desmoplastic small round cell tumor, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma, germ cell tumors, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gliomas, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) cancer, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell carcinoma, Kaposi sarcoma, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liposarcoma, liver cancer, lung cancers, such as non-small cell and small cell lung cancer, lymphomas, leukemias, macroglobulinemia, malignant fibrous histiocytoma of bone/osteosarcoma, medulloblastoma, melanomas, mesothelioma, metastatic squamous neck cancer with occult primary, mouth cancer, multiple endocrine neoplasia syndrome, myelodysplastic syndromes, myeloid leukemia, nasal cavity and paranasal sinus cancer, nasopharyngeal carcinoma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma/malignant fibrous histiocytoma of bone, ovarian cancer,

ovarian epithelial cancer, ovarian germ cell tumor, pancreatic cancer, pancreatic cancer islet cell, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineal astrocytoma, pineal germinoma, pituitary adenoma, pleuropulmonary blastoma, plasma cell neoplasia, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis and ureter transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcomas, skin cancers, Merkel cell carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach cancer, T-cell lymphoma, throat cancer, thymoma, thymic carcinoma, thyroid cancer, trophoblastic tumor (gestational), cancers of unknown primary site, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, and Wilms tumor.

**[00191]** Therapeutic outcomes can be improved by use of a method of classifying a patient for eligibility for treatment with a compound of the disclosure as a monotherapy or in a combination therapy with an anti-cancer agent, such as chemotherapeutics, targeted agents, immunotherapies, ADCs, cellular therapies, and anti-tumor vaccines. An illustrative diagnostic protocol includes: a) obtaining a test sample from a patient; b) determining the presence or absence of autophagy based on relevant markers in the test sample, for example, p62, LC3, and autophagic vesicles (AVs); and c) classifying the patient as being eligible for receiving treatment with a compound of the disclosure as a monotherapy or in a combination therapy based on the presence or absence of autophagy as determined in step b.

**[00192]** The test sample can be a tissue sample. For example, the tissue sample can be a peripheral blood sample, a tumor tissue or a suspected tumor tissue, a thin layer cytological sample, a fine needle aspirate sample, a bone marrow sample, a lymph node sample, a urine sample, an ascites sample, a lavage sample, an esophageal brushing sample, a bladder or lung wash sample, a spinal fluid sample, a brain fluid sample, a ductal aspirate sample, a nipple discharge sample, a pleural effusion sample, a fresh frozen tissue sample, a paraffin embedded tissue sample or an extract or processed sample produced from any of a peripheral blood sample, a tumor tissue or a suspected tumor tissue, a thin layer cytological sample, a fine needle aspirate sample, a bone marrow sample, a urine sample, an ascites sample, a lavage sample, an esophageal brushing sample, a bladder or lung wash sample, a spinal fluid sample, a brain fluid sample, a ductal aspirate sample, a nipple discharge sample, a pleural effusion sample, a fresh frozen tissue sample, or a paraffin embedded tissue sample.

**[00193]** The determination step can be performed, for example, by immunohistochemistry. For example, the immunohistochemistry can be performed with an antibody probe that detects either p62 or LC3. The determination step can be performed by immunofluorescence

with an antibody probe that detects either p62 or LC3. Alternatively, the determination step can be performed by electron microscopy with an antibody probe that detects either p62 or LC3 or by direct analysis of AVs.

**[00194]** The determination step can be performed by an analysis of immunohistochemistry or immunofluorescence with an antibody probe that detects LC3 or p62 by the following illustrative protocol: (i) the local LC3 or p62 immunohistochemical staining or immunofluorescence intensity is averaged for each pixel on the basis of the surrounding pixels (for example, 8, 12, 15, 20, or 25 pixels; about 2 square microns); (ii) pixels with an LC3 or p62 intensity level above the local mean are designated as punctate and the remaining pixels as diffuse; (iii) oversaturated pixels are excluded from the analysis; and (iv) the intensity of LC3 or p62 in each designation and the percentage of pixels assigned to the punctate category is then calculated. If one or more measures in (iv) crosses a threshold, then autophagy is determined to be present. The percentage threshold can be, for example, at least about 8 percent, at least about 9 percent, at least about 10 percent, at least about 11 percent, at least about 12 percent, at least about 13 percent, at least about 14 percent, or at least about 15 percent.

**[00195]** The determination step can be performed by electron microscopy by direct analysis of a morphological criteria for AVs, wherein the morphological criteria for AVs comprise: (i) circularity; (ii) contrast with structures that were white or lighter than the cytoplasm; (iii) vesicles with contents; (iv) vesicles more than 200 nanometers (nm) in size; or (v) vesicles more than 200 nm interior to the plasma membrane. The percentage of AVs with these criteria is then calculated. If one or more measures crosses a threshold, then autophagy is determined to be present.

**[00196]** The determination step can be done by an automated system, such as a software program or an intelligence system that is part of, or compatible with, equipment (*e.g.*, computer platform) on which an assay is carried out. This comparison or informational analysis can be done by a health care provider.

**[00197]** In the above method, the subject can also, contemporaneously therewith, be receiving treatment with anti-cancer agents such as chemotherapeutics, targeted agents, immunotherapies, ADCs, cellular therapies and anti-tumor vaccines or combinations thereof.In some embodiments, the disclosure provides a method of treating a cancer, an autoimmune disorder, or an infectious disease, the method comprising administering to a subject in need of relief thereof a composition comprising a therapeutically-effective amount of a compound of the disclosure.

**[00198]** In some embodiments, the disclosure provides a method of formulating a medicament for treatment of a cancer, an autoimmune disorder, or an infectious disease, wherein the medicament comprises a therapeutically-effective amount of a compound of the disclosure.

**[00199]** In some embodiments, the disclosure provides a use of a unit dosage form for treatment of a cancer, an autoimmune disorder, or an infectious disease, the unit dosage form comprising a therapeutically-effective amount of a compound of the disclosure.

**[00200]** In some embodiments, the disclosure provides a use of any compound herein for treating a condition. In some embodiments, the disclosure provides a use of any compound herein in formulating a medicament for treating a condition.

**[00201]** In some embodiments, the disclosure provides a use of a compound herein for treatment of cancer. In some embodiments, the disclosure provides a use of a compound herein for treatment of melanoma. The some embodiments, the melanoma is superficial spreading melanoma, nodular melanoma, lentigno maligna melanoma, or acral lentiginous melanoma.

**[00202]** In some embodiments, a compound described herein does not inhibit hERG channel activity. In some embodiments, the disclosure provides a use of a compound herein for inhibiting autophagy. In some embodiments, the disclosure provides a use of a compound herein for agragation of autophagosomes. In some embodiments, a compound herein does not induce cardiovascular disease, such as cardiac arrest, cardiac arrhythmia, or congestive heart failure.

## EXAMPLES

**EXAMPLE 1**: Promotion of autophagosome aggregation.

**[00203]** To determine whether a compound of the invention was able to induce autophagosome aggregation, the ability of the compounds to interfere with the fusion of lysosomes and autophagosomes was measured in an *in vitro* cell-based assay. The measurement was based on quantifying the presence of LC3 protein in autophagosomes by immunofluorescence (IF) using high-content screening. Autophagosome accumulation can lead to intense perinuclear punctate LC3 staining.

**[00204]** Human A375 melanoma cells were exposed to 10 different compound concentrations between 10 nM and 100 μM for 48 hours, and then fixed and labeled with an anti-LC3 antibody. The anti-LC3 antibody was detected with a secondary fluorescently

labeled antibody and the cells counterstained with a nuclear dye. Cultures were imaged using an automated fluorescent cell imager (ArrayScan VTI) and the cellular staining intensity for the LC3 antigen determined. In untreated control cells, the LC3 staining was distributed homogeneously at low intensity throughout the cell cytoplasm as determined by IF staining. The lowest compound concentration at which cellular punctate staining for LC3 increased above baseline was recorded as the threshold concentration for autophagy inhibition. The threshold concentration varied between 0.32 μM for compound 5 to >100 μM for compounds 8, 11 and 12 as shown in **TABLE 2**. Compound 5 was 10 times more potent than hydroxychloroquine and chloroquine; compounds 1, 4, 6 and 9 were 3 times more potent.

**TABLE 2**

| **Compound** | **A375 Autophagy Threshold (μM)** |
|---|---|
| Chloroquine | 3.2 |
| Hydroxychloroquine | 3.2 |
| 1 | 1 |
| 2 | 10 |
| 3 | none measurable[d] |
| 4 | 1 |
| 5 | 0.32 |
| 6[a] | 1 |
| 8[a] | >100 [c] |
| 9 | 1 |
| 10 | 10 |
| 11[b] | >100 [c] |
| 12[b] | >100 [c] |
| 13 | 10 |
| 14 | 3.2 |
| 15 | 10 |
| 16 | 32 |
| 17 | 3.2 |
| 18 | 3.2 |

| | |
|---|---|
| 19 | none measureable[d] |
| 20 | 10 |
| 21 | none measurable[d] |
| 22[b] | 10 |
| 23[a] | 3.2 |
| 24 | 3.2 |
| 25[a] | 10 |
| 26 | 3.2 |
| 29[b] | 1 |
| 30[b] | 1 |
| 31 | 1 |
| 32 | 1 |

a: assayed as a dihydrochloride salt

b: assayed as a trihydrochloride salt

c: highest concentration tested was 100 μM

d: no autophagosome accumulation despite measurable cytotoxicty

**EXAMPLE 2**: Antitumor cell efficacy of compounds of the invention.

**[00205]** Cytotoxic activity of the compounds against human tumor cells was measured using an *in vitro* cell culture viability assay. Human A375 melanoma cells were incubated with 10 different compound concentrations between 10 nM and 100 μM for 72 hours and stained with a resazurin-based cell viability reagent to quantify viable cells. Living cells can reduce the non-fluorescent resazurin to a highly fluorescent resorufin, which can be quantified with a spectrophotometric plate reader. The fluorescence signal was normalized between the signals of untreated viable cells and the background signal of dead cells. Then, the half-maximum concentration for the inhibition of resazurin staining was calculated as shown in **TABLE 3**.

**[00206]** The $IC_{50}$ concentrations of viability ranged from about 2 μM for compounds 3, 6, and 9 to about 100 μM and above for compounds 10, 11 and 12. Compounds 3, 6 and 9 were 8 to 13 times more cytotoxic than chloroquine or hydroxychloroquine.

| TABLE 3 | |
|---|---|
| **Compound** | **A375 Cytotoxicity $IC_{50}$ (μM)** |
| Chloroquine | 18 |
| Hydroxychloroquine | 23 |
| 1 | 6.9 |
| 2 | 20 |
| 3 | 1.8 |
| 4 | 4.9 |
| 5 | 4 |
| 6[a] | 2.2 |
| 8[a] | 18 |
| 9 | 1.8 |
| 10 | >100 |
| 11[b] | 92 |
| 12[b] | >100 |
| 13 | 16 |
| 14 | 8.5 |
| 15 | 28 |
| 16 | 51 |
| 17 | 9.7 |
| 18 | 6.1 |
| 19 | 12 |
| 20 | 12 |
| 21 | 4.9 |
| 22 | 13 |
| 23[b] | 5.6 |
| 24[a] | 7.2 |
| 25 | 38 |
| 26[a] | 4.5 |
| 27 | >100[c] |
| 28 | 9.9 |

| | |
|---|---|
| 29[b] | 1.6 |
| 30[b] | 0.93 |
| 31 | 0.82 |
| 32 | 2.1 |

a: assayed as a dihydrochloride salt

b: assayed as a trihydrochloride salt

**EXAMPLE 3:** Diminished inhibition of the cardiac hERG channel and improved safety margin

**[00207]** As a counter screen to eliminate compounds with the potential for undesirable cardiac arrhythmias in vivo, the compounds of the disclosure were profiled by automated patch clamp analysis for inhibition of the tail potassium current of the human hERG channel expressed in HEK293 cells. The half-maximum inhibitory concentration ($IC_{50}$) was estimated based on measurements of the potassium current at three different concentrations and expressed as safety margin of the hERG $IC_{50}$ divided by the $EC_{50}$ of cytotoxicity in A375 melanoma cells. hERG inhibition by chloroquine and hydroxychloroquine were measured as controls to generate data for the two reference compounds under identical assay conditions. The hERG $IC_{50}$ and the safety margin are shown in Table 4.

**[00208]** The safety margin measured was below 1 for the reference compounds chloroquine and hydroxychloroquine. The safety margin was improved to between 2 and 3 for compounds 8, 9 and 18. The safety margin was between 20 and 51 for compounds 29, 30 and 31. Compounds 29, 30, and 31 lack significant hERG-inhibitory activity relative to their potency as cytotoxic autophagy inhibitors. Compound 28 did not inhibit the cardiac hERG channel at the highest concentration tested (100 μM). Compounds 30 and 31 in particular have a safety margin in excess of 30. Thus these compounds of the disclosure are more potent than chloroquine and hydroxychloroquine as cytotoxic autophagy inhibitors and may possess better cardiac safety in vivo.

**Table 4**

| Compound | hERG IC50 ICso (μM) | hERG/A375 Safety Margin |
|---|---|---|
| CQ | 1.6 | 0.089 |

| | | |
|---|---|---|
| HCQ | 16 | 0.73 |
| 1 | 1.3 | 0.19 |
| 3 | 1.2 | 0.67 |
| 5 | 0.43 | 0.11 |
| 6[a] | 1.2 | 0.55 |
| 8[a] | 48 | 2.7 |
| 9 | 4 | 2.2 |
| 10 | 1.7 | <0.017 |
| 11[b] | 1.7 | 0.018 |
| 13 | 7.3 | 0.46 |
| 14 | 0.85 | 0.1 |
| 15 | 0.46 | 0.016 |
| 17 | 0.93 | 0.096 |
| 18 | 12 | 2 |
| 19 | 5.8 | 0.48 |
| 20 | 12 | 1 |
| 21 | 2.1 | 0.43 |
| 22 | 6.1 | 0.47 |
| 23[b] | 0.97 | 0.17 |
| 24[a] | 2.2 | 0.31 |
| 25 | 7.9 | 0.21 |
| 26[a] | 0.55 | 0.12 |
| 28 | >100[c] | >10 |
| 29[b] | 32 | 20 |
| 30[b] | 29 | 31 |
| 31 | 42 | 51 |
| 32 | 7.1 | 3.4 |

a: assayed as a dihydrochloride salt

b: assayed as a trihydrochloride salt

c: highest concentration tested was 100 μM

**EXAMPLE 4:** Metabolic stability towards human microsomal metabolism

**[00209]** The sensitivity of the compounds of the disclosure towards hepatic metabolism was assessed by measuring their stability in the presence of human liver microsomes. The test compounds were pre-incubated under agitation for 5 min at 37°C in phosphate buffer of pH 7.4 at a compound concentration of 100 nM and pooled human liver microsomes at a protein concentration of 100 µg/mL. The reaction was initiated by adding an NADPH-generating system and samples withdrawn immediately and after 15, 30, 45, and 60 min. The reaction in each sample was stopped by mixing the sample into acetonitrile/methanol. Samples were centrifuged to remove precipitated microsomal protein and supernatants were analyzed by HPLC-MS/MS analysis to determine the concentration of test compound. As controls for the quality of the microsomal preparation the stability of four reference compounds with known sensitivity towards hepatic metabolism were tested in each assay; comparison with historical stability data allowed determining that the assays met preset acceptance criteria. The half-life $t_{1/2}$ of the test compounds in the presence of liver microsomes was calculated from the chromatogram peak areas of the test compound assuming first order kinetics. The human microsomal intrinsic clearance ($CL_{int}$) was calculated from the half-life $t_{1/2}$ using the following equation:

$CL_{int}$ (µL/min/mg protein) = ln(2) / $t_{1/2}$ (min) / microsome protein concentration (mg/µL)

**[00210]** The measured values for human microsomal intrinsic clearance are shown in Table 5.

**[00211]** Several compounds of the disclosure (11, 13, 28, 29, and 30) had a human microsomal intrinsic clearance below a guidance value of good hepatic metabolic stability of 11 µL/min/mg similar to the reference compounds chloroquine and hydroxychloroquine.

**Table 5**

| Compound | Human Liver Microsomal $Cl_{int}$ (µL/min/mg) |
|---|---|
| CQ | 1.5 |
| HCQ | <1 |
| 1 | 590 |
| 3 | 490 |
| 4 | 1100 |
| 5 | 660 |

| | |
|---|---|
| 6[a] | 680 |
| 8[a] | 410 |
| 9 | 180 |
| 10 | 700 |
| 11[b] | <1 |
| 13 | 8.8 |
| 14 | 860 |
| 15 | 390 |
| 17 | 200 |
| 18 | 370 |
| 19 | 110 |
| 20 | 68 |
| 21 | 880 |
| 22 | 450 |
| 23[b] | 280 |
| 24[a] | 110 |
| 25 | 140 |
| 26[a] | 110 |
| 28 | <1 |
| 29[b] | <1 |
| 30[b] | 4.9 |
| 31 | 44 |
| 32 | 190 |

a: assayed as a dihydrochloride salt

b: assayed as a trihydrochloride salt

**EXAMPLE 5:** Reduced binding to human plasma protein

**[00212]** The affinity of the compounds of the disclosure towards binding to human plasma proteins was assessed by determining the fraction of free compound in an equilibrium binding assay. Human plasma was spiked with a concentrated stock solution of test compound to achieve a total concentration of 10 uM. The spiked plasma sample was added

into the sample compartment of a two-compartment dialysis chamber. The sample compartment was separated from the dialysate compartment by a semipermeable membrane impermeable to protein but permeable to the test compound. Immediately before adding assay buffer (phosphate buffered saline, PBS, pH 7.4) to the dialysate compartment, two aliquots of the spiked plasma sample were removed and added to wells containing acetonitrile as control samples and as basis for the recovery determination. The dialysis plate was then sealed and incubated at 37°C. After 4 hours of incubation, dialysis samples were taken from each compartment, diluted with the phosphate buffer followed by addition of acetonitrile. All control samples and dialysis samples were centrifuged to remove precipitated protein. The concentration of the test article was then determined in the sample supernatants by HPLC-MS/MS analysis. Three control compounds with known protein binding were measured in parallel to assure the quality of the assay. Protein binding (%), free fraction and recovery (%) were calculated from the chromatogram peak areas of the test compound as follows:

protein binding (%) = ( A(p) – A(b) ) x 100% / A(p)

free fraction = 1 - protein binding (%) / 100%

recovery (%) = ( A(p) + A(b) ) x 100% / A(c)

A(p) = Peak area of analyte in the protein matrix

A(b) = Peak area of analyte in the assay buffer

A(c) = Peak area of analyte in the control sample

**[00213]** Binding data for a compound are considered acceptable if recovery exceeds a minimum of 50%. The free fraction in human plasma measured for those samples tested and exceeding minimum recovery are shown in Table 6.

**[00214]** Over half of the compounds had a free fraction in excess of 0.03, a guidance value which when exceeded may reduce the likelihood of encountering untoward and potentially toxic increases the free plasma concentration in individual patients across human patient populations. Compounds 11, 13, 19, 25 and 30 showed similarly low protein binding as the reference compounds chloroquine and hydroxychloroquine.

**Table 6**

| **Compound** | **Human Plasma Free Fraction** |
|---|---|
| CQ | 0.48 |

| | |
|---|---|
| HCQ | 0.38 |
| 1 | 0.009 |
| 5 | 0.009 |
| 6[a] | 0.0025 |
| 8[a] | 0.009 |
| 9 | 0.0018 |
| 10 | 0.027 |
| 11[b] | 0.26 |
| 13 | 0.35 |
| 14 | 0.044 |
| 15 | 0.13 |
| 17 | 0.076 |
| 18 | 0.019 |
| 19 | 0.29 |
| 20 | 0.048 |
| 21 | 0.044 |
| 22 | 0.077 |
| 23[b] | 0.03 |
| 24[a] | 0.13 |
| 25 | 0.37 |
| 26[a] | 0.026 |
| 28 | 0.057 |
| 29[b] | 0.025 |
| 30[b] | 0.77 |
| 31 | 0.014 |
| 32 | 0.004 |

a: assayed as a dihydrochloride salt

b: assayed as a trihydrochloride salt

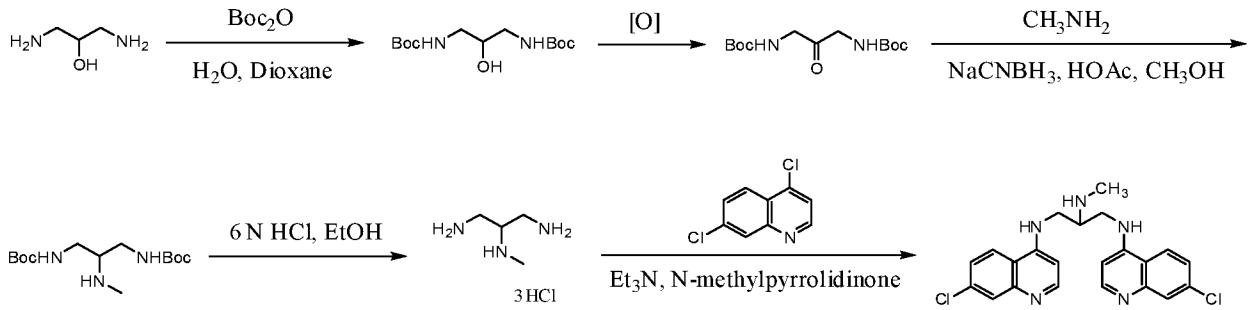
**Synthetic Routes**

**[00215]** NMR spectra were recorded on a Bruker ™ AV-300 300 MHz or a Bruker ™ AV-

500 500 MHz NMR spectrometer using $CDCl_3$, DMSO-d6 or $D_2O$ with TMS as an internal standard. Chemical shifts (δ) are reported as ppm relative to TMS. Coupling constants (J values) are reported in Hertz (Hz). Mass spectral data were obtained with a Bruker Esquire™ Liquid Chromatography - Ion Trap Mass Spectrometer.

**[00216]** Analytical HPLC analysis was performed on an Agilent ™ 1100 HPLC with a Phenomenex Luna ™ C18 (2) column (3 micron, 150 x 4.6 mm id) at a flow rate of 0.6 mL/min. Various gradients and run times were used. Analytes with concentrations of 0.5 - 1 mg/mL in $CH_3CN$/TFA were monitored at 254 nm and 214 nm. Mobile phases were based on $CH_3CN$/Milli-Q water gradients and contained 0.1% TFA: Mobile phase A: Milli-Q water with 0.1% TFA; Mobile phase B: $CH_3CN$ with 0.1% TFA; A non-limiting example of a solvent gradient that was used to analyze the final products was: 5% mobile phase B to 70% mobile phase B in 20 min, then to 95% mobile phase B in 5 min.

**EXAMPLE 6**: Synthesis of $N^1,N^3$-bis(7-chloroquinolin-4-yl)-$N^2$-methylpropane-1,2,3-triamine.




Step 1: Di-tert-butyl (2-hydroxypropane-1,3-diyl)dicarbamate

**[00217]** A solution of 1,3-diaminopropan-2-ol (3.0 g, 33.3 mmol) in water (7 mL) was added to a solution of di-*tert*-butyldicarbonate (16.0 g, 73.7 mmol) in dioxane (400 mL). The reaction mixture was stirred for 22 h at room temperature then concentrated *in vacuo*. The resulting solid was dissolved in $CH_2Cl_2$ (300 mL), washed with water (300 mL), and dried ($MgSO_4$). Concentration *in vacuo* gave di-tert-butyl (2-hydroxypropane-1,3-diyl)dicarbamate (9.0 g) as a faint-yellow oil, which was used without further purification. $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.09 (br, 2H), 3.78-3.73 (m, 1H), 3.55 (br, 1H), 3.34-3.12 (m, 4H), 1.46 (s, 18H).

Step 2: Di-tert-butyl (2-oxopropane-1,3-diyl)dicarbamate

**[00218]** Oxalyl chloride (1.67 mL, 19.2 mmol) was dissolved in $CH_2Cl_2$ (23 mL) and cooled to -78 °C before a solution of anhydrous DMSO (2.7 mL, 38.3 mmol) in $CH_2Cl_2$ (19.2 mL)

was added dropwise. After the mixture was stirred at -78 °C for 20 min, a solution of di-tert-butyl (2-hydroxypropane-1,3-diyl)dicarbamate (3.71 g, 12.8 mmol) in $CH_2Cl_2$ (12.1 mL) was added dropwise. The reaction mixture was stirred for 30 min at -78 °C before triethylamine (8.89 mL, 63.9 mmol) was added. The reaction mixture was stirred for 1 h at room temperature, diluted with $CH_2Cl_2$ (200 mL) and washed with $H_2O$ (100 mL x 2), 1N HCl (50 mL x 3), and brine (50 mL), and dried ($MgSO_4$). Concentration *in vacuo* gave di-*tert*-butyl (2-oxopropane-1,3-diyl)dicarbamate (3.45 g) as a pale-yellow solid, which was used without further purification. TLC (50% EtOAc/hexane): $R_f = 0.76$.

Step 3: di-tert-butyl (2-(methylamino)propane-1,3-diyl)dicarbamate

**[00219]** To a solution of di-*tert*-butyl (2-oxopropane-1,3-diyl)dicarbamate (1.2 g, 4.16 mmol), acetic acid (0.238 mL, 4.16 mmol), and methylamine (2 M in THF, 2.28 mL, 4.56 mmol) in MeOH (9 mL) was added $NaBH_3CN$ (0.29 g, 4.56 mmol). The reaction mixture was stirred at room temperature for 15.5 h and then concentrated *in vacuo*. The residue was poured into 0.1 N NaOH (100 mL) and extracted with $CH_2Cl_2$ (50 mL x 4). The organic extracts were combined, dried with $Na_2SO_4$, and concentrated *in vacuo*. Purification by silica-gel column chromatography with 5% and 10% $CH_3OH/CH_2Cl_2$ yielded di-*tert*-butyl (2-(methylamino)propane-1,3-diyl)dicarbamate (0.58 g, 40 % over 3 steps) as a pale yellow oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.13 (br, 2H), 3.28-3.03 (m, 5H), 2.6 (m, 1H), 2.45 (s, 3H), 1.46 (s, 18H).

Step 4: $N^2$-methylpropane-1,2,3-triamine

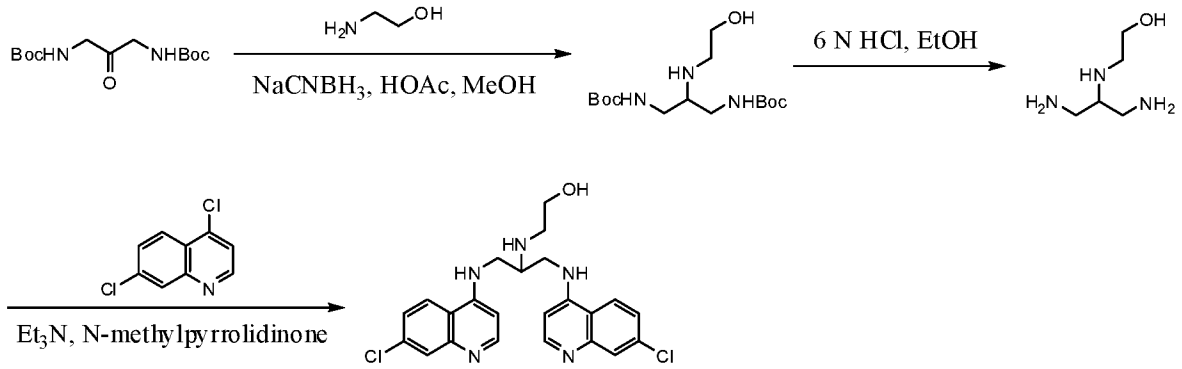
**[00220]** To a solution of di-*tert*-butyl (2-(methylamino)propane-1,3-diyl)dicarbamate (0.58 g, 1.91 mmol) in EtOH (6 mL) was added 6 N HCl (6 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was co-concentrated *in vacuo* with water to dryness to give $N^2$-methylpropane-1,2,3-triamine (3 HCl salt, 0.386 g, off- white solid), which was used without further purification. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8.53 (br, 5H), 3.69 (m, 1H), 3.33 (m, 4H, under water peak), 2.66 (s, 3H).

Step 5: $N^1$,$N^3$-bis(7-chloroquinolin-4-yl)-$N^2$-methylpropane-1,2,3-triamine

**[00221]** A reaction mixture of 4,7-dichloroquinoline (0.883 g, 3.64 mmol), triethylamine (1.27 mL, 9.1 mmol), and $N^2$-methylpropane-1,2,3-triamine (3 HCl salt, 0.386 g, 1.82 mmol) in N-methylpyrrolidinone (3.6 mL) was stirred at 130 °C for 17 h. The reaction mixture was cooled to room temperature, poured into $H_2O$ (15 mL) and extracted with EtOAc (25 mL x 6). The organic extracts were combined and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1) yielded the partially-pure product

(0.525 g, <95% pure based on analytical HPLC) as a pale-yellow solid. This partially-pure product (0.45 g) was stirred in 12 mL of $CH_3CN$/EtOH (4:1) at 73 °C for 15 minutes, the insoluble material (0.39 g) was collected via filtration after storage at 4 °C overnight, and washed with cold $CH_3CN$/EtOH (4:1) and $H_2O$. Further lyophilization of the solid collected (0.23 g) with $CH_3CN/H_2O$ after sonication afforded $N^1$,$N^3$-bis(7-chloroquinolin-4-yl)-$N^2$-methylpropane-1,2,3-triamine (0.21 g, 43.7% in 2 steps) as an off-white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.42 (3H, s); 3.08-3.18 (m, 1H); 3.40 (br d, J = 5.7, 4H); 6.50 (d, J = 5.4, 2H); 7.23 (br s, 2H); 7.43 (dd, J = 2.1, 9.0, 2H); 7.81 (d, J = 1.5, 2H); 8.26 (d, J = 9.0, 2H); 8.30 (d, J = 5.4, 2H). Mass spectrum (ESI) m/e = 426.2, 428.0 (M+1).

**EXAMPLE** 7: Synthesis of 2-((1,3-bis((7-chloroquinolin-4-yl)amino)propan-2-yl)amino)ethan-1-ol.




Step 1: di-tert-butyl (2-((2-hydroxyethyl)amino)propane-1,3-diyl)dicarbamate

**[00222]** To a solution of di-*tert*-butyl (2-oxopropane-1,3-diyl)dicarbamate (0.81 g, 2.8 mmol), acetic acid (0.21 mL, 3.6 mmol), and ethanolamine (2.4 mL, 4.05 mmol) in MeOH (7,5 mL) was added $NaBH_3CN$ (0.255 g, 4.05 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated *in vacuo*. The residue was poured into 0.1 N NaOH (100 mL) and extracted with $CH_2Cl_2$ (50 mL x 4). The organic extracts were combined, dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo*. Purification by silica gel column chromatography with 5%, 10% and 15% $CH_3OH/CH_2Cl_2$ yielded di-*tert*-butyl (2-((2-hydroxyethyl)amino)propane-1,3-diyl)dicarbamate (0.24 g, 25.6 %) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) δ 5.17 (br s, 2H), 3.67 (t, 2H), 3.20 (t, 4H), 2.9 (t, 2H), 2.7 (m, 1H), 1.46 (s, 18H).

Step 2: 2-((1,3-diaminopropan-2-yl)amino)ethan-1-ol

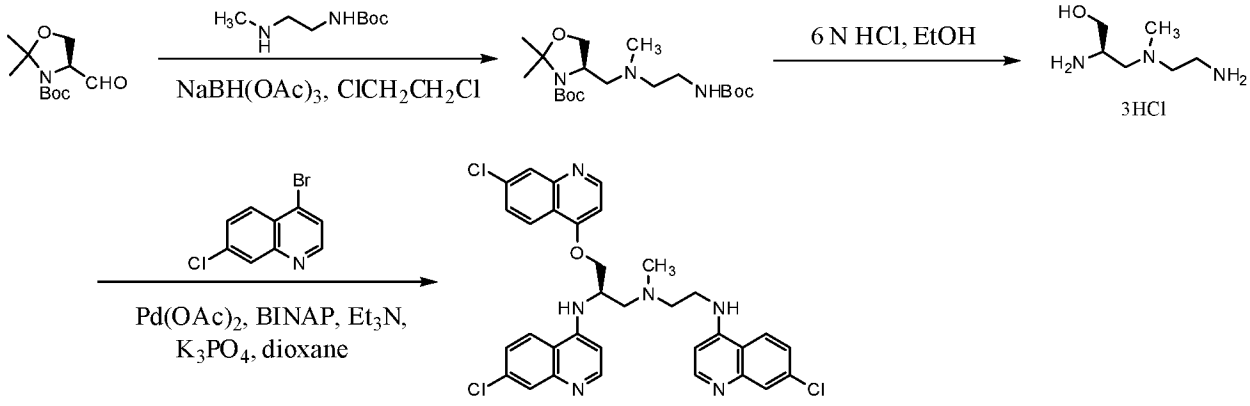
**[00223]** To a solution of di-*tert*-butyl (2-((2-hydroxyethyl)amino)propane-1,3-diyl)dicarbamate (0.24 g, 0.72 mmol) in EtOH (5 mL) was added 6N HCl (5 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was

concentrated *in vacuo* and the resulting residue was co-concentrated *in vacuo* with water to dryness to give 2-((1,3-diaminopropan-2-yl)amino)ethan-1-ol (HCl salt, 0.17 g, 92%) as a yellow foam, which was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.69 (br, 1H), 8.51 (br, 5H), 3.9-3.6 (m, 9H).

Step 3: 2-((1,3-bis((7-chloroquinolin-4-yl)amino)propan-2-yl)amino)ethan-1-ol

**[00224]** A reaction mixture of 4,7-dichloroquinoline (0.388 g, 1.60 mmol), triethylamine (0.56 mL, 4.0 mmol), and 2-((1,3-bis((7-chloroquinolin-4-yl)amino)propan-2-yl)amino)ethan-1-ol (3 HCl salt, 0.17 g, 0.80 mmol) in N-methylpyrrolidinone (1.6 mL) was stirred at 130 °C for 18 h. The reaction mixture was cooled to room temperature, poured into 0.1N NaOH (12 mL) and EtOAc (15 mL), and extracted with EtOAc (25 mL x 4). The organic extracts were combined and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1, 135:9:1, and 90:9:1) yielded partially-pure product (0.18 g, ~85% pure based on analytical HPLC) as a yellow solid. This partially-pure product (0.18 g) was sonicated in 5 mL of $CH_3CN$/EtOH (4:1), and the insoluble material was collected via filtration and washed with cold $CH_3CN$/EtOH (4:1) and $H_2O$. Further lyophilization with $CH_3CN$/$H_2O$ afforded 2-((1,3-bis((7-chloroquinolin-4-yl)amino)propan-2-yl)amino)ethan-1-ol (133 mg, 36.4%) as an off-white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.77 (br t, J = 5.3, 2H); 3.38-3.52 (m, 6H); 4.58 (br t, 1H); 6.51 (d, J = 5.4, 2H); 7.4 (br s,2H); 7.47 (dd, J = 2.1, 9.0, 2H); 7.78 (d, J = 2.1, 2H); 8.26 (d, J = 9.0, 2H); 8.32 (d, J = 5.4, 2H). Mass spectrum (ESI) m/e = 456.2, 458.0 (M+1).

**EXAMPLE 8**: Synthesis of (R)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine.




Step 1: tert-butyl (R)-4-(((2-((tert-butoxycarbonyl)amino)ethyl)(methyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate

**[00225]** To a solution of Garner's aldehyde (0.458 g, 2.0 mmol) in 1,2-dichloroethane (20 mL) was added *tert*-butyl (S)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate (0.365 g, 2.09 mmol). After stirring at room temperature for 5 min, $NaBH(OAc)_3$ (0.43 g, 2.03 mmol) was added in portions. The reaction mixture was stirred at room temperature for 3 h. Saturated $NaHCO_3$ (25 mL) was added, the organic phase was separated, and the aqueous phase was further extracted with $CH_2Cl_2$ (25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil. Purification by silica gel column chromatography with 1% and 5% $CH_3OH/CH_2Cl_2$ yielded *tert*-butyl (R)-4-(((2-((*tert*-butoxycarbonyl)amino)ethyl)(methyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate (0.684 g, 88%) as a colorless oil. $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.03, 4.86 (br, 1H), 4.0-3.83 (br, 1H), 3.94 (s, 2H), 3.18 (br, 2H), 2.6-2.4 (m, 4H), 2.28 (d, 3H, J = 6.9 Hz), 1.6-1.4 (m, 24H).

Step 2: (R)-2-Amino-3-((2-aminoethyl)(methyl)amino)propan-1-ol

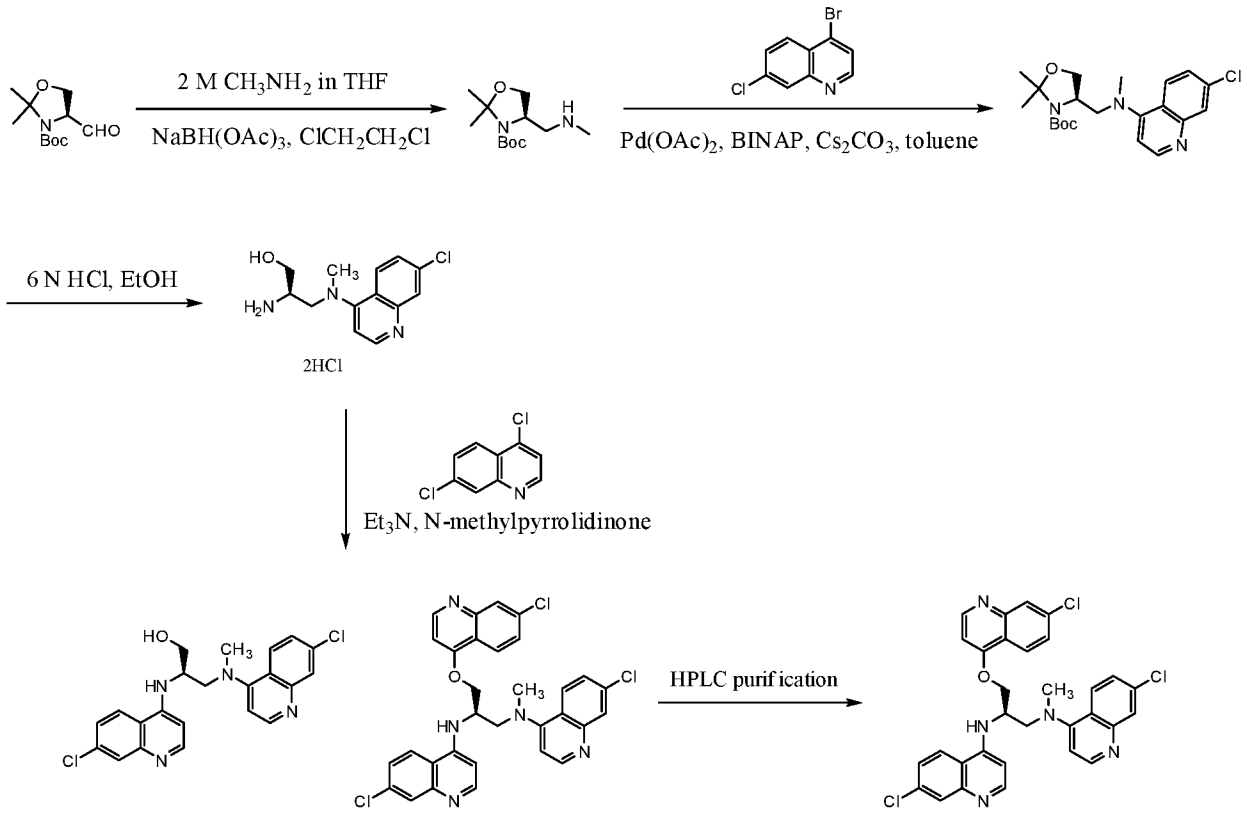
**[00226]** To a solution of *tert*-butyl (R)-4-(((2-((*tert*-butoxycarbonyl)amino)ethyl)(methyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate (0.669 g, 1.73 mmol) in EtOH (6 mL) was added 6 N HCl (6 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was co-concentrated *in vacuo* with water to give the HCl salt of (R)-2-amino-3-((2-aminoethyl)(methyl)amino)propan-1-ol as a yellow oil, which was used without further purification. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 8.4 (br, 1H), 8.0 (br, 6H incl. two salt protons), 3.9- 2.3 (m, 9H), 2.2 (s, 3H).

Step 3: (R)-$N^2$-(7-Chloroquinolin-4-yl)-$N^1$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine

**[00227]** A pressure tube was charged with 4-bromo-7-chloroquinoline (0.26 g, 1.07 mmol), $Pd(OAc)_2$ (11.5 mg, 0.05 mmol), 2,2-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (62.5 mg, 0.1 mmol), $K_3PO_4$ (0.38 g, 1.8 mmol), (R)-2-amino-3-((2-aminoethyl)(methyl)amino)propan-1-ol (HCl salt form, 92 mg, 0.358 mmol), triethylamine (0.15 mL, 0.29 mmol) and dioxane (5 mL). The reaction mixture was heated to 90 °C for 18 h, cooled to room temperature, then adsorbed onto silica gel. Purification by chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (190:9:1, then 90:9:1) and lyophilization with $H_2O$ containing a minimum amount of MeOH afforded (R)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine (0.10 g, 29.6%) as a pale-yellow solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 2.50 (s,

3H, overlay with DMSO); 2.80-3.00 (4H, m); 3.50-3.60 (2H, m); 4.31-4.42 (2H, m); 4.50-4.60 (m, 1H); 6.61 (d, J = 6.3, 1H); 6.83 (d, J = 5.7, 1H); 6.85 (d, J = 6.9, 1H); 7.24 (dd, J = 1.8, 9.0, 1H); 7.39 (dd, J = 2.0, 9.2, 1H); 7.45 (dd, J = 2.1, 8.7, 1H); 7.62 (d, J = 2.1, 1H); 7.73 (d, J = 2.1, 1H); 7.76-7.88 (m, 1H); 7.90 (d, J = 1.8, 1H); 7.95 (d, J = 9.0, 1H); 8.09 (d, J = 9.0, 1H); 8.29-8.32 (m, 3H); 8.44 (d, J = 6.0, 1H); 8.60 (d, J = 5.1, 1H). Mass spectrum (ESI) m/e = 631.7, 633.2 (M+1).

**EXAMPLE 9**: Synthesis of (R)-$N^1$,$N^2$-bis(7-chloroquinolin-4-yl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine.




Step 1: tert-butyl (R)-2,2-dimethyl-4-((methylamino)methyl)oxazolidine-3-carboxylate

**[00228]** To a solution of *tert*-butyl (S)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate (0.74 g, 3.23 mmol) in 1,2-dichloroethane (30 mL) was added methylamine (2 M in THF, 1.72 mL, 3.44 mmol). After stirring at room temperature for 5 min, $NaBH(OAc)_3$ (0.73 g, 3.44 mmol) was added in small portions. The reaction mixture was stirred at room temperature for 6 h. Saturated $NaHCO_3$ (25 mL) was added and the organic phase was separated. The aqueous phase was further extracted with $CH_2Cl_2$ (25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give *tert*-butyl (R)-2,2-dimethyl-4-

((methylamino)methyl)oxazolidine-3-carboxylate (0.71 g, 90 %) as a pale-yellow oil, which was used without further purification. TLC (10% MeOH/$CH_2Cl_2$): $R_f$ = 0.26.

Step 2: tert-butyl (R)-4-(((7-chloroquinolin-4-yl)(methyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate

**[00229]** A solution of *tert*-butyl (R)-2,2-dimethyl-4-((methylamino)methyl)oxazolidine-3-carboxylate (0.52 g, 2.1 mmol), 4-bromo-7-chloroquinoline (0.279 g, 2.1 mmol), $Pd(OAc)_2$ (67 mg), BINAP (166 mg), $Cs_2CO_3$ (0.97 g) in toluene (10 mL) was degassed with argon for 5 min. The reaction mixture was then heated to 80 °C for 41 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™ and concentrated *in vacuo*. Purification by silica gel chromatography using 30%, 40% and 50% EtOAc/hexane afforded *tert*-butyl (R)-4-(((7-chloroquinolin-4-yl)(methyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate (0.175 g, 20.5%) as a pale-yellow oily residue. Mass spectrum (ESI) m/e = 406.4 (M+1).

Step 3: (R)-2-amino-3-((7-chloroquinolin-4-yl)(methyl)amino)propan-1-ol

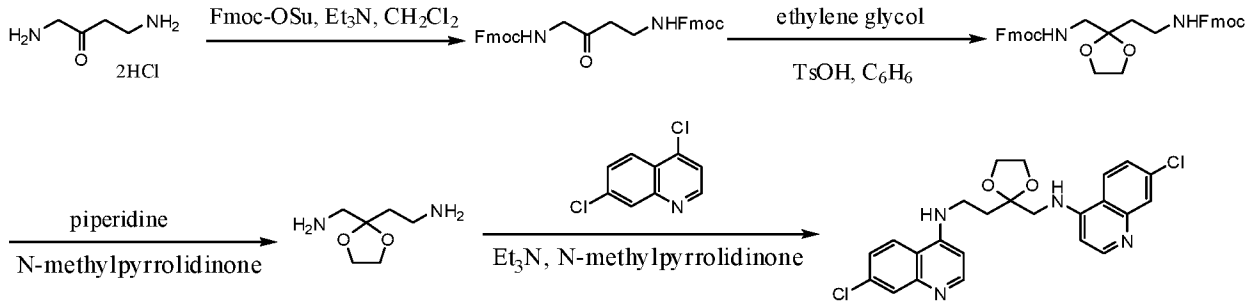
**[00230]** To a solution of *tert*-butyl (R)-4-(((7-chloroquinolin-4-yl)(methyl)amino)methyl)-2,2-dimethyloxazolidine-3-carboxylate (0.175 g, 0.43 mmol) in EtOH (3 mL) was added 6 N HCl (3 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the resulting residue was co-concentrated *in vacuo* with water to give (R)-2-amino-3-((7-chloroquinolin-4-yl)(methyl)amino)propan-1-ol (HCl salt, 0.152 g, pale-yellow solid), which was used without further purification. TLC ($CH_2Cl_2$/MeOH/$NH_4OH$, 135:9:1): $R_f$ = 0.23.

Step 4: (R)-$N^1$,$N^2$-bis(7-chloroquinolin-4-yl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine

**[00231]** A reaction mixture of 4,7-dichloroquinoline (0.109 g, 0.448 mmol), triethylamine (0.187 mL, 1.34 mmol), and (R)-2-amino-3-((7-chloroquinolin-4-yl)(methyl)amino)propan-1-ol (2 HCl salt, 0.152 g, 0.448 mmol) in N-methylpyrrolidinone (1 mL) was stirred at 130 °C for 19 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography on silica gel using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1, then 135:9:1) gave partially pure (R)-$N^1$,$N^2$-bis(7-chloroquinolin-4-yl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine (73.2 mg, brown residues) and (R)-3-((7-chloroquinolin-4-yl)(methyl)amino)-2-((7-chloroquinolin-4-yl)amino)propan-1-ol (48.3 mg, brown residues). HPLC purification using a C18 reverse phase semipreparative HPLC column with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in $CH_3CN$) as eluents gave (R)-$N^1$,$N^2$-bis(7-chloroquinolin-4-yl)-3-(7-chloroquinolin-4-yloxy)-$N^1$-

methylpropane-1,2 diamine (3TFA salt) as a faint-yellow solid after lyophilization. Further desalting and lyophilization afforded (R)-$N^1$,$N^2$-bis(7-chloroquinolin-4-yl)-3-((7-chloroquinolin-4-yl)oxy)-$N^1$-methylpropane-1,2-diamine (38.7 mg, 14.7%) as an off-white powder. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.13 (s, 3H); 3.84-4.39 (m, 4H); 4.68-4.80 (m, 1H); 6.81 (d, J = 5.4, 1H); 6.83 (d, J = 6.6, 1H); 6.88 (d, J = 5.4, 1H); 7.15 (d, J = 8.4. 1H); 7.33-7.39 (m, 2H); 7.43 (dd, J = 2.1, 9.0, 1H); 7.60 (d, J = 2.4, 1H); 7.80 (d, J = 1.8, 1H); 7.81 (d, J = 8.7, 1H); 7.90 (d, J = 2.1, 1H); 8.03 (d, J = 9.0, 1H); 8.16 (d, J =9.0, 1H); 8.37 (d, J = 5.1, 1H); 8.46 (d, J = 5.7, 1H); 8.61 (d, J = 5.1, 1H). Mass spectrum (ESI) m/e = 588.0, 590.0 (M+1).

**EXAMPLE 10**: Synthesis of 7-chloro-N-((2-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)quinolin-4-amine.




Step 1: Bis((9H-fluoren-9-yl)methyl) (2-oxobutane-1,4-diyl)dicarbamate

**[00232]** To a suspension of 1,4-diaminobutan-2-one dihydrochloride (1.0 g, 5.71 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C was added FMOC-Succinimide (4.0 g, 11.86 mmol), followed by the addition of $Et_3N$ (2.48 mL, 17.76 mmol). The reaction mixture was stirred at 0 °C for 1 h, then at room temperature for 1 h. The reaction was diluted with $CH_2Cl_2$ (100 mL), and washed with 0.1% HCl (20 mL) and water (20 mL). The organic layer was dried ($Na_2SO_4$), and concentrated *in vacuo*. Purification by silica gel chromatography using 15% and 30% EtOAc/$CH_2Cl_2$ yielded bis((9H-fluoren-9-yl)methyl) (2-oxobutane-1,4-diyl)dicarbamate (1.15 g, 36.9%) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.9-7.3 (m, 16H), 5.4 (br, 1H), 5.2 (br, 1H), 4.4 (t, 4H), 4.26 (m, 2H), 4.12 (m, 2H), 3.51 (m, 2H), 2.71 (m, 2H). Mass spectrum (ESI) m/e = 547.1 (M+1).

Step 2: (9H-fluoren-9-yl)methyl ((2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)carbamate

**[00233]** A mixture of bis((9H-fluoren-9-yl)methyl) (2-oxobutane-1,4-diyl)dicarbamate (1.15 g, 2.10 mmol), ethylene glycol (0.60 mL, 10.8 mmol) and p-toluenesulfonic acid

monohydrate (92 mg) in 1,2-dichloroethane (13.8 mL) and DMSO (0.3 mL) was stirred at 95 °C for 20 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography using 15% and 20% EtOAc/$CH_2Cl_2$ to yield (9H-fluoren-9-yl)methyl ((2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)carbamate (1.19 g, 96%) as a white solid. Mass spectrum (ESI) m/e = 591.3 (M+1).

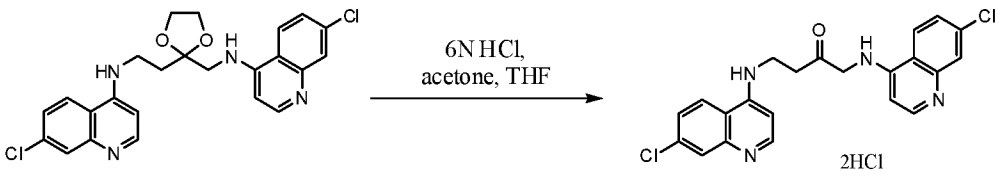
Step 3: 2-(2-(aminomethyl)-1,3-dioxolan-2-yl)ethan-1-amine

**[00234]** A mixture of (9H-fluoren-9-yl)methyl ((2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)carbamate (1.19 g, 2.02 mmol) and piperidine (5.4 mL, 55.0 mmol) in N-methylpyrrolidinone (10.8 mL) was stirred at room temperature for 1.5 h, concentrated *in vacuo*, and water (25 mL) and $CH_2Cl_2$ (50 mL) were added. The organic layers were further extracted with water (25 mL x 2). The combined aqueous extracts were washed with $CH_2Cl_2$ (25 mL), concentrated *in vacuo* and co-concentrated *in vacuo* with toluene twice to yield 2-(2-(aminomethyl)-1,3-dioxolan-2-yl)ethan-1-amine (5 g) as an orange liquid, which was used without further purification. TLC ($CH_2Cl_2$/MeOH/$NH_4OH$, 90:9:1): $R_f$ = 0.

Step 4: 7-chloro-N-((2-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)quinolin-4-amine

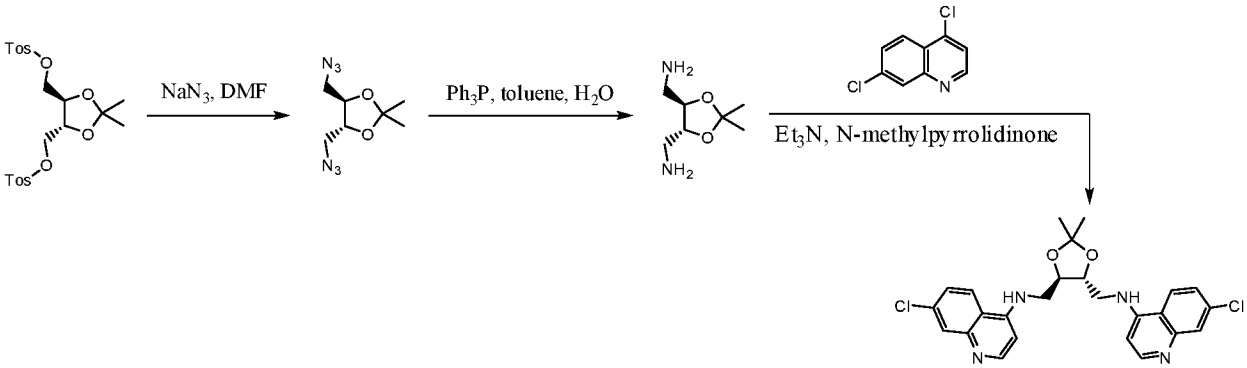
**[00235]** A mixture of 4,7-dichloroquinoline (0.8 g, 4.0 mmol), triethylamine (0.56 mL, 4.0 mmol), and 2-(2-(aminomethyl)-1,3-dioxolan-2-yl)ethan-1-amine (5 g) in N-methylpyrrolidinone (5.5 mL) was stirred at 130 °C for 18.5 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. Purification twice on silica gel using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1) gave 7-chloro-N-((2-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)quinolin-4-amine as an off-white solid (0.32 g, 33.8% in two steps). A small sample for testing (26 mg) was further purified as follows: sonication in $CH_3CN$ and EtOH; filtration and washing with EtOH, water and $CH_3CN$ or water and $CH_3CN$; then lyophilization with $H_2O$ and $CH_3CN$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 2.08-2.18 (m, 2H); 3.35-3.46 (m, 2H); 3.54 (d, J = 6.0, 2H); 3.98 (s, 4H); 6.46 (d, J = 5.4, 1H); 6.74 (d, J = 5.7, 1H); 7.26-7.35 (m, 2H); 7.44 (dd, J = 2.1, 9.0, 2H); 7.77 (d, J = 2.7, 1H); 7.78 (d, J = 2.4, 1H); 8.18 (d, J = 9.0, 1H); 8.30 (d, J = 9.0, 1H); 8.38 (d, J = 5.1, 1H); 8.39 (d, J = 5.1, 1H). Mass spectrum (ESI) m/e = 469.2 (M+1).

**EXAMPLE 11**: Synthesis of 1,4-bis((7-chloroquinolin-4-yl)amino)butan-2-one.




**[00236]** A solution of 7-chloro-N-((2-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1,3-dioxolan-2-yl)methyl)quinolin-4-amine (0.21 g, 0.45 mmol) in THF (50 mL), 6 N HCl (20 mL), and acetone (10 mL) was heated to 90 °C for 3 h then at 100 °C overnight. The reaction mixture was concentrated *in vacuo*, and the resulting residue was co-concentrated *in vacuo* to dryness with $CH_3CN$ twice. This solid was sonicated in $CH_3CN$ (10 mL), and the insoluble material was collected via filtration and washed with $CH_3CN$. Further lyophilization with $H_2O$ afforded 1,4-bis((7-chloroquinolin-4-yl)amino)butan-2-one (0.18 g, ~ 81%) as a white solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 3.16 (t, J = 6.0, 2H); 3.72-3.81 (m, 2H); 4.68 (d, J = 5.1, 2H); 6.80 (d, J = 6.9, 1H); 6.94 (d, J = 6.9, 1H); 7.77-7.85 (m, 2H); 7.97 (d, J = 2.1, 1H); 8.00 (d, J = 1.8, 1H); 8.51-8.61 (m, 4H); 9.38-9.40 (m, 1H); 9.50-9.60 (m, 1H). Mass spectrum (ESI) m/e = 425.2 (M+1).

**EXAMPLE 12**: Synthesis of N,N'-(((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(7-chloroquinolin-4-amine).




Step 1: (4R,5R)-4,5-bis(azidomethyl)-2,2-dimethyl-1,3-dioxolane

**[00237]** Na$N^3$ (0.456 g, 7.01 mmol) was added to a solution of ((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene) bis(4-methylbenzenesulfonate) (1.5 g, 3.19 mmol) in DMF (9 mL). The reaction mixture was stirred at 75 °C for 20 h, poured into water (50 mL), and extracted with $CH_2Cl_2$ (50 mL x 3). The organic extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by silica gel chromatography using 10% and 15% EtOAc/hexane yielded (4R,5R)-4,5-bis(azidomethyl)-2,2-dimethyl-1,3-dioxolane (0.71 g) as a colorless liquid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.1 (m, 2H), 3.65-3.30 (m, 4H), 1.5 (s, 6H).

Step 2: ((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine

**[00238]** To a solution of (4R,5R)-4,5-bis(azidomethyl)-2,2-dimethyl-1,3-dioxolane (0.26 g, 1.22 mmol) in toluene (9 mL) was added triphenylphosphine (0.92 g, 3.5 mmol). The reaction mixture was stirred at 125 °C for 15 min. Water (0.6 mL) was added and the reaction was heated to 125 °C and stirred overnight. After cooling to room temperature, the reaction mixture was extracted with water (10 mL). The extract was concentrated *in vacuo* to yield ((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine (0.184 g, 98% over 2 steps) as a yellow oil, which was used without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 3.8 (m, 2H), 3.0-2.8 (m, 4H), 1.6-1.4 (br s, 10H).

Step 3: N,N'-(((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(7-chloroquinolin-4-amine)

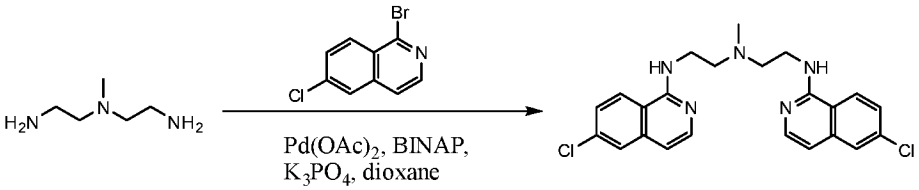
**[00239]** A reaction mixture of 4,7-dichloroquinoline (0.456 g, 2.3 mmol), triethylamine (0.32 mL, 2.3 mmol), and ((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanamine (0.184 g, 1.15 mmol) in N-methylpyrrolidinone (2.5 mL) was stirred at 130 °C for 21 h. The reaction mixture was cooled to room temperature and taken up in water (10 mL) and EtOAc (25 mL). The aqueous layer was extracted with EtOAc (25 mL x 2). The combined organic extracts were concentrated *in vacuo* and purified on silica gel using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1) to give N,N'-(((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(7-chloroquinolin-4-amine) as an off-white solid (0.26 g, 39%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.39 (d, 2H, J = 6 Hz), 8.3-8.1 (br, 2H; d, 2H, J = 9 Hz), 7.74 (d, 2H, J = 2 Hz), 7.41 (dd, 2H, J = 2 Hz, 9 Hz), 6.71 (d, 2H, J = 6 Hz), 4.33 (br s, 2H), 3.66 (br s, 4H), 1.36 (s, 6H). Mass spectrum (ESI) m/e = 483.1 (M+1).

**EXAMPLE 13**: Synthesis of (2R,3R)-1,4-bis((7-chloroquinolin-4-yl)amino)butane-2,3-diol.

**[00240]** To a suspension of N,N'-(((4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene))bis(7-chloroquinolin-4-amine) (0.26 g, 0.538 mmol) in EtOH (10 mL) was added 6 N HCl (10 mL). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo* and the resulting residue was co-concentrated *in vacuo* with EtOH once. The brownish solid was sonicated in $CH_3CN$ (10 mL) and EtOH (3 mL), and the insoluble material was collected via filtration and washed with $CH_3CN$ and cold EtOH. Further lyophilization with $H_2O$ and $CH_3CN$ afforded (2R,3R)-1,4-bis((7-chloroquinolin-4-

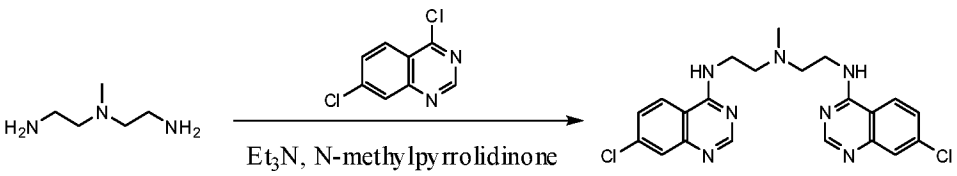
yl)amino)butane-2,3-diol (HCl salt, 230 mg, 82.7%) as an off-white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.65-3.76 (m, 4H); 3.92-4.04 (m, 2H); 5.48 (d, J = 5.7, 2H); 6.96 (d, J = 7.2, 2H); 7.78 (dd, J = 2.0, 9.2, 2H); 7.99 (d, J = 2.1, 2H); 8.56 (d, J = 7.2, 2H); 8.67 (d, J = 9.0, 2H); 9.56 (br t, 2H). Mass spectrum (ESI) m/e = 443.2 (M+1).

**EXAMPLE 14**: Synthesis of $N^1$-(6-chloroisoquinolin-1-yl)-$N^2$-(2-((6-chloroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine.




**[00241]** A mixture of 1-bromo-6-chloroisoquinoline (0.35 g, 1.44 mmol), $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (0.061 mL, 0.474 mmol), $Pd(OAc)_2$ (11 mg), BINAP (60 mg), $K_3PO_4$ (0.50 g) in 1,4-dioxane (4.8 mL) was degassed with argon for 5 min and then heated to90 °C for 17.5 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™ and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1, and 90:9:1) and lyophilization afforded $N^1$-(6-chloroisoquinolin-1-yl)-$N^2$-(2-((6-chloroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.156 g, 74 %) as a pale-yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.35 (br s, 3H); 2.63-2.76 (m, 4H); 3.57-3.67 (m, 4H); 6.83 (d, J = 5.7, 2H); 7.30-7.40 (m, 2H); 7.39 (br d, J = 8.7, 2H); 7.78 (d, J = 2.1, 2H); 7.86 (d, J = 5.7, 2H); 8.12 (d, J = 9.0, 2H). Mass spectrum (ESI) m/e = 440.1 (M+1).

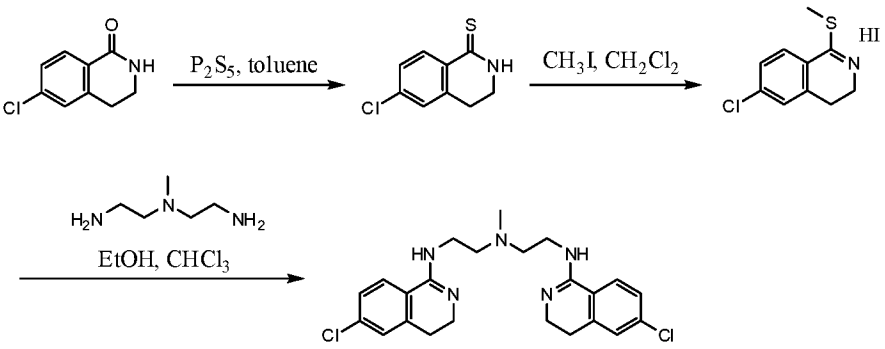
**EXAMPLE 15**: Synthesis of $N^1$-(7-chloroquinazolin-4-yl)-$N^2$-(2-((7-chloroquinazolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine.




**[00242]** A reaction mixture of 4,7-dichloroquinazoline (0.40 g, 2.01 mmol), triethylamine (0.28 mL, 2.0 mmol), and $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (0.129 mL, 1.01 mmol) in N-methylpyrrolidinone (2 mL) was stirred at 130 °C for 17 h. The reaction mixture was cooled to room temperature, $H_2O$ (5 mL) was added, and the reaction was stirred for

several hours. The insoluble material was collected via filtration and washed with $H_2O$. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, and 90:9:1) and lyophilization yielded $N^1$-(7-chloroquinazolin-4-yl)-$N^2$-(2-((7-chloroquinazolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.188 g, 42 %) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.36 (s, 3H); 2.64-2.76 (m, 4H); 3.58-3.67 (br q, 4H); 7.47 (dd, J = 2.1, 9.0, 2H); 7.66 (d, J = 2.1, 2H); 8.14 (d, J = 8.7, 2H); 8.21-8.29 (m, 2H); 8.42 (s, 2H). Mass spectrum (ESI) m/e = 442.1 (M+1).

**EXAMPLE 16**: Synthesis of $N^1$-(6-chloro-3,4-dihydroisoquinolin-1-yl)-$N^2$-(2-((6-chloro-3,4-dihydroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine.




Step 1: 6-chloro-3,4-dihydroisoquinoline-1(2H)-thione

**[00243]** A mixture of 6-chloro-3,4-dihydroisoquinolin-1(2H)-one (0.498 g, 2.74 mmol) and phosphorus pentasulfide (0.67 g, 3.0 mmol) in toluene (15 mL) was stirred at 70 °C for 21 h. The reaction was cooled to room temperature, filtered through Celite™, and concentrated *in vacuo*. Purification by silica gel chromatography using 2% $CH_3OH/CH_2Cl_2$ yielded 6-chloro-3,4-dihydroisoquinoline-1(2H)-thione (0.48 g, 89.3%) as a yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.55 (br s, 1H), 8.3 (d, 1H, J = 9 Hz), 7.42 (s, 1H), 7.41 (d, 1H, J = 9 Hz), 3.4 (m, 2H), 2.93 (t, 2H, J = 7 Hz).

Step 2: 6-chloro-1-(methylthio)-3,4-dihydroisoquinoline hydroiodide

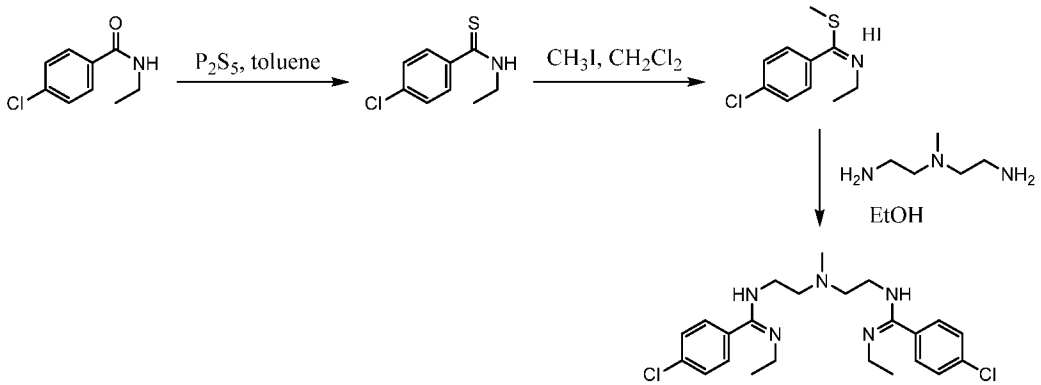
**[00244]** To a solution of 6-chloro-3,4-dihydroisoquinoline-1(2H)-thione (0.484 g, 2.45 mmol) in $CH_2Cl_2$ (6.5 mL) was added methyl iodide (0.45 mL, 7.32 mmol). The reaction mixture was stirred at room temperature for 18 h. The solvents were concentrated *in vacuo* and co-concentrated *in vacuo* with $CHCl_3$ twice to yield 6-chloro-1-(methylthio)-3,4-dihydroisoquinoline hydroiodide as a yellow solid, which was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.89 (d, 1H, J = 7 Hz), 7.65 (s, 1H), 7.56 (d, 1H, J = 7 Hz), 3.79 (t, 2H, J = 7 Hz), 3.01 (br, 2H), 2.72 (s, 3H).

Step 3: $N^1$-(6-chloro-3,4-dihydroisoquinolin-1-yl)-$N^2$-(2-((6-chloro-3,4-dihydroisoquinolin-1-

yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine

**[00245]** To a solution of 6-chloro-1-(methylthio)-3,4-dihydroisoquinoline hydroiodide in anhydrous ethanol (4.6 mL) and $CHCl_3$ (1.5 mL) was added $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (0.15 mL, 1.17 mmol). The reaction mixture was stirred at room temperature for 4.5 h and at 75 °C for 17 h. The reaction mixture was concentrated *in vacuo* and purified on silica gel using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, 90:9:1) to give the hydroiodide salt of $N^1$-(6-chloro-3,4-dihydroisoquinolin-1-yl)-$N^2$-(2-((6-chloro-3,4-dihydroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine as a colorless residue (0.715 g). The residue (0.415 g) was taken into 1N NaOH (10 mL) and EtOAc (15 mL). The aqueous layer was further extracted with EtOAc (10 mL x 2). The combined organic extracts were washed with water (5 mL), dried ($Na_2SO_4$), and concentrated *in vacuo* to yield a colorless oily residue, which was further treated with 6 N HCl (1 mL) in EtOH (5 mL). Concentration *in vacuo* and co-evaporation with EtOH, followed by lyophilization with $H_2O$ and $CH_3CN$ afforded $N^1$-(6-chloro-3,4-dihydroisoquinolin-1-yl)-$N^2$-(2-((6-chloro-3,4-dihydroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine as the HCl salt (273 mg, 73.4% in two steps) as a pale-yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.97-3.06 (m, 7H); 3.48-3.58 (m, 4H); 3.68-3.80 (m, 2H); 3.92-4.03 (m, 4H); 7.56 (d, J = 8.4, 2H); 7.65 (s, 2H); 8.22 (d, J = 8.4, 2H); 10.08 (br s, 2H); 10.47 (br s, 2H). Mass spectrum (ESI) m/e = 444.4 (M+1).

**EXAMPLE 17**: Synthesis of (1E,1'E)-N,N''-((methylazanediyl)bis(ethane-2,1-diyl))bis(4-chloro-N'-ethylbenzimidamide).




Step 1: 4-chloro-N-ethylbenzothioamide

**[00246]** A mixture of 4-chloro-N-ethylbenzamide (1.0 g, 5.45 mmol) and phosphorus pentasulfide (1.33 g, 6.0 mmol) in toluene (20 mL) was stirred at 70 °C overnight. The reaction mixture was cooled to room temperature, filtered through Celite™, and concentrated

*in vacuo*. Purification by silica gel chromatography using 20% EtOAc/hexane yielded 4-chloro-N-ethylbenzothioamide (1.0 g, 93.5%) as a yellow solid. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, 2H, J = 7 Hz), 7.5 (br s, 1H). 7.43 (d, 2H, J = 7 Hz), 3.5 (m, 2H), 1.28 (s, 3H).

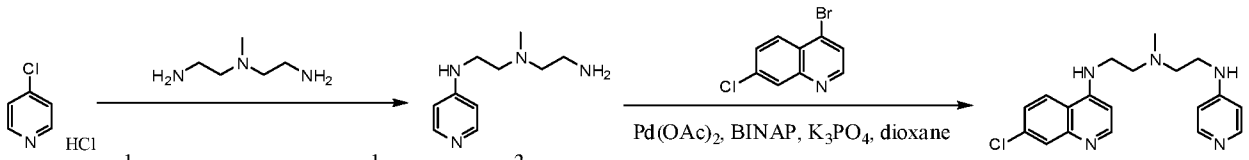
Step 2: Methyl (E)-4-chloro-N-ethylbenzimidothioate hydroiodide

**[00247]** To a solution of 4-chloro-N-ethylbenzothioamide (0.458 g, 2.29 mmol) in $CH_2Cl_2$ (6 mL) was added methyl iodide (0.42 mL, 6.8 mmol). The reaction mixture was stirred at room temperature for 22 h. The solvents were concentrated *in vacuo* and co-concentrated *in vacuo* with $CHCl_3$ twice to yield methyl (E)-4-chloro-N-ethylbenzimidothioate hydroiodide as an orange oil, which was used without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 7.74 (d, 2H, J = 9 Hz), 7.66 (d, 2H, J = 9 Hz), 3.71 (dd, 2H, J = 7.2 Hz, 14.7 Hz), 2.41 (s, 3H), 1.36 (t, 3H, J = 7 Hz).

Step 3: (1E,1'E)-N,N''-((methylazanediyl)bis(ethane-2,1-diyl))bis(4-chloro-N'-ethylbenzimidamide)

**[00248]** To a solution of methyl (E)-4-chloro-N-ethylbenzimidothioate hydroiodide in anhydrous ethanol (4.6 mL) and $CHCl_3$ (1.5 mL) was added $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (0.15 mL, 1.17 mmol). The reaction mixture was stirred at room temperature for 4.5 h and at 75 °C for 17 h. The reaction mixture was concentrated *in vacuo*. Purification and repurification on silica gel using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1, 90:9:1) gave the product hydroiodide as a colorless residue (0.20 g). This residue was taken into 1N NaOH (10 mL) and EtOAc (15 mL). The aqueous layer was further extracted with EtOAc (15 mL). The combined organic extracts were washed with 10% $Cs_2CO_3$ (10 mL) and saturated NaCl (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo* to yield a colorless oily residue, which was further treated with 6 N HCl (1 mL) in EtOH (5 mL). Concentration *in vacuo* and co-evaporation with EtOH, followed by lyophilization with $H_2O$ and $CH_3CN$, afforded (1E,1'E)-N,N''-((methylazanediyl)bis(ethane-2,1-diyl))bis(4-chloro-N'-ethylbenzimidamide) (HCl salt, 142.5 mg, 23.4% in 2 steps) as a pale-yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.14 (t, J = 7.2, 3H); 1.2 (q or overlapping t, J = 7.2, 3H); 2.54-2.60 (m, 1H); 2.72-2.80 (m, 2H); 2.92-3.01 (m, 1H); 3.10-3.22 (m, 3H), 3.50-3.72 (m, 6H); 3.94-4.06 (m, 2H); 7.69-7.78 (m, 8H); 9.75-10.16 (m, 4H incl. salt protons). Mass spectrum (ESI) m/e = 448.5 (M+1).

**EXAMPLE 18**: Synthesis of $N^1$-(7-chloroquinolin-4-yl)-$N^2$-methyl-$N^2$-(2-(pyridin-4-ylamino)ethyl)ethane-1,2-diamine.



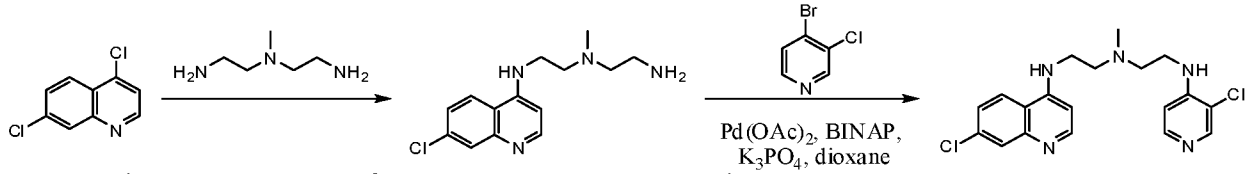

Step 1: $N^1$-(2-aminoethyl)-$N^1$-methyl-$N^2$-(pyridin-4-yl)ethane-1,2-diamine

**[00249]** A mixture of 4-chloropyridine hydrochloride (1.0 g, 6.67 mmol) and $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (8.59 mL, 66.7 mmol) was stirred at 200 °C for 4 h in a sealed tube. The reaction mixture was cooled to room temperature, diluted with $H_2O$ (25 mL), and extracted with $CH_2Cl_2$ (25 mL x 5). The combined extracts were dried ($Na_2SO_4$) and concentrated *in vacuo* to afford $N^1$-(2-aminoethyl)-$N^1$-methyl-$N^2$-(pyridin-4-yl)ethane-1,2-diamine (0.95 g, 53.8%) as a yellow oil, which was used without further purification. TLC ($CH_2Cl_2$/MeOH/$NH_4OH$, 6:4:0.2): $R_f$ = 0.

Step 2: $N^1$-(7-chloroquinolin-4-yl)-$N^2$-methyl-$N^2$-(2-(pyridin-4-ylamino)ethyl)ethane-1,2-diamine

**[00250]** A mixture of 4-bromo-7-chloroquinoline (0.56 g, 2.32 mmol), $N^1$-(2-aminoethyl)-$N^1$-methyl-$N^2$-(pyridin-4-yl)ethane-1,2-diamine (0.45 g, 2.32 mmol), $Pd(OAc)_2$ (57 mg), BINAP (0.313 g), and $K_3PO_4$ (2.65 g) in 1,4-dioxane (25 mL) was degassed with argon for 5 min and then stirred at 90 °C for 21 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™, and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (90:9:1) afforded $N^1$-(7-chloroquinolin-4-yl)-$N^2$-methyl-$N^2$-(2-(pyridin-4-ylamino)ethyl)ethane-1,2-diamine ((0.54 g, 47.9% in two steps) as a pale-yellow oil. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.31 (s, 3H); 2.61 (J = 6.6, 2H); 2.70 (t, J = 6.5, 2H); 3.15 (q, J = 5.7, 2H); 3.38 (q, J = 5.7, 2H); 6.37 (t, J = 6.3, 1H); 6.46 (dd, J = 1.5, 5.1, 2H); 6.49 (d, J = 5.7, 1H); 7.12 (t, J = 5.7, 2H); 7.42 (dd, J = 2.1, 9.0, 1H); 7.78 (d, J = 2.1, 1H); 7.98 (d, J = 6.3, 2H); 8.18 (d, J = 9.0, 1H); 8.38 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 356.2 (M+1).

**EXAMPLE 19**: <u>$N^1$-(3-chloropyridin-4-yl)-$N^2$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine.</u>




Step 1: $N^1$-(2-aminoethyl)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-methylethane-1,2-diamine

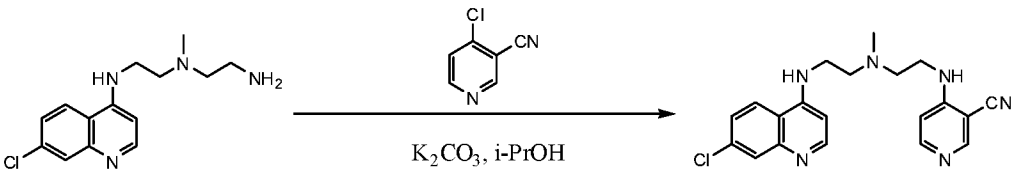
**[00251]** A reaction mixture of 4,7-dichloroquinoline (2.5 g, 10.3 mmol) and $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (4.65 mL, 36.1 mmol) was stirred at 90 °C for 1 h

and at 135 °C for 3 h. The reaction mixture was cooled to room temperature and taken up in 1N NaOH (30 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (50 mL x 7). The combined organic extracts were washed with water (30 mL) and dried ($Na_2SO_4$). Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1, 70:30:1, and 25:25:1) afforded $N^1$-(2-aminoethyl)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-methylethane-1,2-diamine (2.63 g, 92%) as a pale-yellow oil. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.25 (s, 3H); 2.40 (t, J = 6.2, 2H); 2.55-2.60 (m, 4H); 2.9-3.4 (m, 2H, overlay with $H_2O$); 3.30-3.41 (m, 2H); 6.49 (d, J = 5.4, 1H); 7.20-7.30 (m, 1H); 7.41 (dd, J = 2.4, 9.0, 1H); 7.78 (d, J = 2.1, 1H); 8.23 (d, J = 9.0, 1H); 8.40 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 279.1 (M+1).

Step 2: $N^1$-(3-chloropyridin-4-yl)-$N^2$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine

**[00252]** A mixture of 4-bromo-3-chloropyridine (0.171 g, 0.886 mmol), $N^1$-(2-aminoethyl)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-methylethane-1,2-diamine (0.247 g, 0.886 mmol), $Pd(OAc)_2$ (22 mg), BINAP (0.12 g), and $K_3PO_4$ (1.0 g) in 1,4-dioxane (8.9 mL) was degassed with argon for 5 min and then stirred at 100 °C for 16.5 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™, and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (270:9:1, and 180:9:1) afforded $N^1$-(3-chloropyridin-4-yl)-$N^2$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.276 g, 80%) as a pale-yellow oil, and further lyophilization with $CH_3CN/H_2O$ gave an off-white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.32 (s, 3H); 2.66 (t, J = 6.3, 2H); 2.72 (t, J = 6.6, 2H); 3.26 (q, J = 5.7, 2H); 3.40 (q, J = 6.0, 2H); 6.04 (t, J = 5.0, 1H); 6.50 (d, J = 5.4, 1H); 6.64 (d, J = 5.7, 1H); 7.24 (t, J = 4.8, 1H); 7.43 (dd, J = 2.1, 9.0, 1H); 7.78 (d, J = 2.1, 1H); 8.02 (d, J = 5.7, 1H); 8.11 (s, 1H); 8.20 (d, J = 9.3, 1H); 8.38 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 390.1 (M+1).

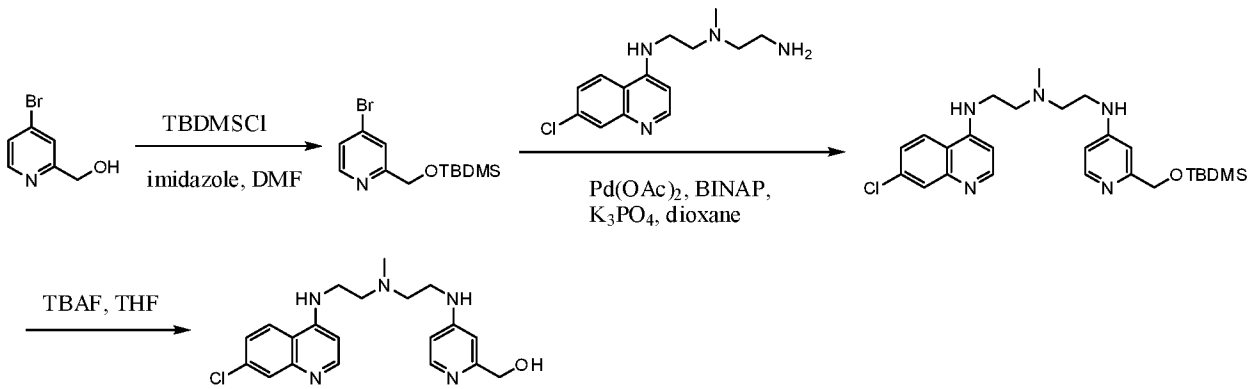
**EXAMPLE 20**: Synthesis of 4-((2-((2-((7-chloroquinolin-4-yl)amino)ethyl)(methyl)amino)ethyl)amino)nicotinonitrile.




**[00253]** A reaction mixture of 4-chloronicotinonitrile (0.124 g, 0.897 mmol), $N^1$-(2-aminoethyl)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-methylethane-1,2-diamine (0.25 g, 0.897 mmol),

and potassium carbonate (0.248 g, 1.79 mmol) in 2-propanol (2.5 mL) was stirred at 100 °C for 22.5 h in a sealed tube. The reaction mixture was cooled to room temperature, taken up in water (15 mL) and EtOAc (10 mL) and the phases were separated. The aqueous layer was extracted with EtOAc (10 mL x 4) and the combined extracts were dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (270:9:1 and 180:9:1) afforded 4-((2-((2-((7-chloroquinolin-4-yl)amino)ethyl)(methyl)amino)ethyl)amino)nicotinonitrile (0.217 g, 63.5%) as a colorless oil. A white solid was obtained after lyophilization with $CH_3CN/H_2O$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.33 (s, 3H); 2.65 (t, J = 6.5, 2H); 2.71 (t, J = 6.6, 2H); 3.25-3.42 (m, 4H overlay with $H_2O$); 6.49 (d, J = 5.4, 1H); 6.72 (d, J = 6.0, 1H; 6.86 (t, J = 5.1); 7.22 (br t, 1H); 7.43 (dd, J = 2.4, 9.0, 1H); 7.78 (d, J = 2.1, 1H); 8.18 (d, J = 8.7, 1H); 8.19 (d, J = 6.6, 1H); 8.39 (1H, s); 8.39 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 381.1 (M+1).

**EXAMPLE 21**: Synthesis of (4-((2-((2-((7-chloroquinolin-4-yl)amino)ethyl)(methyl)amino)ethyl)amino)pyridin-2-yl)methanol.




Step 1: 4-bromo-2-(((tert-butyldimethylsilyl)oxy)methyl)pyridine

**[00254]** To a solution of (4-bromopyridin-2-yl)methanol (0.50 g, 2.66 mmol) in DMF (5 mL) was added imidazole (0.18 g, 2.7 mmol) and *tert*-butyldimethylsilyl chloride (0.41 g, 2.7 mmol). The reaction mixture was stirred at room temperature for 4.5 h, poured into 0.1 N NaOH (50 mL), and hexane (50 mL). The aqueous layers were extracted with hexane (25 mL x 2). The combined extracts were dried ($Na_2SO_4$) and concentrated *in vacuo* to dryness to give 4-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (0.57 g, 71%) as a pale-yellow liquid, which was used without further purification. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, 1H, J = 5 Hz), 7.70 (s, 1H), 7.35 (d, 1H, J = 5 Hz), 4.83 (s, 2H), 0.98 (s, 9H), 0.15 (s, 6H).

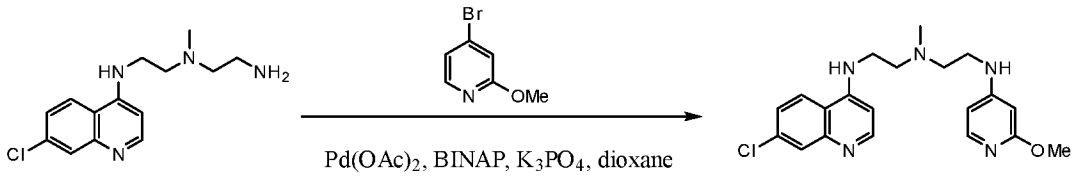
Step 2: $N^1$-(2-(((tert-butyldimethylsilyl)oxy)methyl)pyridin-4-yl)-$N^2$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine

**[00255]** A mixture of 4-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine (0.256 g, 0.847 mmol), $N^1$-(2-aminoethyl)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-methylethane-1,2-diamine (0.236 g, 0.847 mmol), $Pd(OAc)_2$ (21 mg), BINAP (0.115 g), and $K_3PO_4$ (0.965 g) in 1,4-dioxane (8.5 mL) was degassed with argon for 5 min and then stirred at 100 °C for 21 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™, and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, 135:9:1, and 90:9:1) afforded $N^1$-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-4-yl)-$N^2$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.288 g, 69.9%) as a faint-yellow oily residue. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.38 (d, 1H, J = 5.4 Hz), 8.16 (d, 1H, J = 9 Hz), 7.90 (d, 1H, J = 5.7 Hz), 7.78 (d, 1H, J = 2 Hz), 7.41 (dd, 1H, J = 2 Hz, 9 Hz), 7.12 (t, 1H), 6.6 (m, 1H), 6.56 (br, 1H), 6.48 (d, 1H, J = 6 Hz), 6.34 (m, 1H), 4.53 (s, 2H), 3.5-3.1 (m, 4H), 2.69 (t, 2H, J = 6 Hz), 2.61 (t, 2H, J = 6 Hz), 2.31 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Step 3: (4-((2-((2-((7-chloroquinolin-4-yl)amino)ethyl)(methyl)amino)ethyl)amino)pyridin-2-yl)methanol

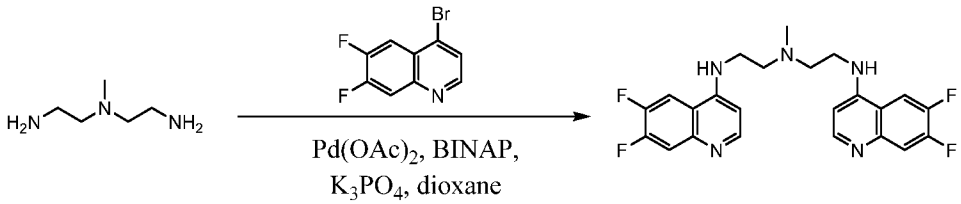
**[00256]** A solution of $N^1$-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridin-4-yl)-$N^2$-(2-((7-chloroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.288 g, 0.59 mmol) in THF (3 mL) was treated with tetrabutylammonium fluoride solution (1.0 M in THF; 1.19 mL, 1.19 mmol) at room temperature for 2.5 h, and concentrated *in vacuo* to dryness. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1, and 70:30:1) twice and lyophilization with $CH_3CN/H_2O$ afforded a white solid (0.184 g, NMR analysis indicated about 12% tetrabutylammonium hydroxide existed). This partially-pure product (0.184 g) was sonicated in $H_2O$ (5 mL), and the insoluble material was collected via centrifugation at 4 °C. Further washing with $H_2O$ (5 mL x 5) via sonication at room temperature, centrifugation at 4 °C, and lyophilization with $CH_3CN/H_2O$ afforded (4-((2-((2-((7-chloroquinolin-4-yl)amino)ethyl)(methyl)amino)ethyl)amino)pyridin-2-yl)methanol (156 mg, 68.5%) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.31 (s, 3H); 2.62 (t, J = 6.6, 2H); 2.70 (t, J = 6.6, 2H) 3.18 (br q, 2H), 3.38 (br q, 2H); 4.39 (s, 2H); 6.57 (br t, 1H); 5.25 (br t, 1H); 6.36 (dd, J = 2.3, 5.9, 1H); 6.49 (d, J = 5.7, 1H); 6.64 (d, J = 2.4, 1H); 7.14 (br t, 1H); 7.43 (dd, J = 2.4, 9.0, 1H); 7.78 (d, J = 2.1, 1H); 7.90 (d, J = 9.0, 1H); 8.18 (d, J = 9.0, 1H); 8.39 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 386.2 (M+1).

**EXAMPLE 22**: Synthesis of $N^1$-(7-chloroquinolin-4-yl)-$N^2$-(2-((2-methoxypyridin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine.




**[00257]** A mixture of 4-bromo-2-methoxypyridine (0.188 g, 0.997 mmol), $N^1$-(2-aminoethyl)-$N^2$-(7-chloroquinolin-4-yl)-$N^1$-methylethane-1,2-diamine (0.278 g, 0.997 mmol), $Pd(OAc)_2$ (24.5 mg), BINAP (0.135 g), and $K_3PO_4$ (1.14 g) in 1,4-dioxane (10 mL) was degassed with argon for 5 min and then stirred at 100 °C for 20 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™, and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (270:9:1, and 180:9:1) afforded $N^1$-(7-chloroquinolin-4-yl)-$N^2$-(2-((2-methoxypyridin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.26 g, 67%) as a pale-yellow solid after lyophilization with $CH_3CN/H_2O$. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.31 (s,3H); 2.60 (t, J = 6.3, 2H); 2.69 (t, J = 6.6, 2H); 3.12 (q, J = 5.9, 2H); 3.38 (q, J = 6.0, 2H); 3.72 (s, 3H); 5.78 (d, J = 2.1, 1H); 6.20 (dd, J = 2.0, 5.9, 1H); 6.26 (t, J = 5.0, 1H); 6.50 (d, J = 5.4, 1H); 7.14 (br t, 1H); 7.41 (dd, J = 2.1, 9.0, 1H); 7.62 (d, J = 5.7, 1H); 7.78 (d, J = 2.4, 1H); 8.17 (d, J = 9.0, 1H); 8.39 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 386.6 (M+1).

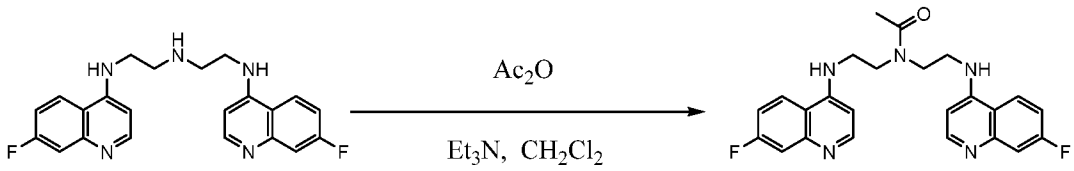
**EXAMPLE 23**: $N^1$-(6,7-difluoroquinolin-4-yl)-$N^2$-(2-((6,7-difluoroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine.




**[00258]** A mixture of 4-bromo-6,7-difluoroquinoline (0.40 g, 1.65 mmol), $N^1$-(2-aminoethyl)-$N^1$-methylethane-1,2-diamine (0.092 mL, 0.75 mmol), $Pd(OAc)_2$ (16 mg), BINAP (89 mg), and $K_3PO_4$ (0.75 g) in 1,4-dioxane (7.5 mL) was degassed with argon for 5 min and then stirred at 120 °C for 20 h in a sealed tube. The reaction mixture was cooled to room temperature, filtered through Celite™, and concentrated *in vacuo*. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, 135:9:1, and 90:9:1) and lyophilization afforded $N^1$-(6,7-difluoroquinolin-4-yl)-$N^2$-(2-((6,7-difluoroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.157 g, 47%) as a pale-yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.38 (s, 3H); 2.73 (t, J = 6.2, 4H); 3.28-3.38 (m, 4H, overlay with $H_2O$); 6.43 (d, J = 5.4, 2H); 6.98 (br t, 2H); 7.66 (dd, J = 8.3, 12.1, 2H); 8.16 (dd, J = 8.9,

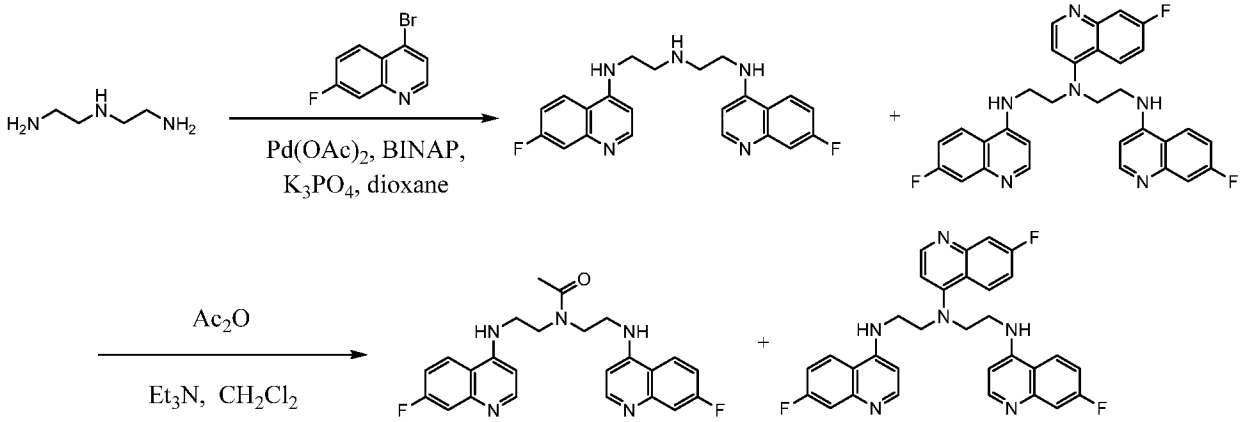
12.8, 2H); 8.32 (d, J = 6.0, 2H). Mass spectrum (ESI) m/e = 444.1 (M+1).

**EXAMPLE 24**: N,N-bis(2-((7-fluoroquinolin-4-yl)amino)ethyl)acetamide.




**[00259]** To a suspension of crude $N^1$-(7-fluoroquinolin-4-yl)-$N^2$-(2-((7-fluoroquinolin-4-yl)amino)ethyl)ethane-1,2-diamine (0.19 g) in $CH_2Cl_2$ (5 mL) at 0 °C was added $Et_3N$ (0.2 mL, 1.45 mmol) and $Ac_2O$ (0.137 mL, 1.45 mmol). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo* and co-concentrated *in vacuo* with MeOH twice. HPLC purification using a C18 reverse phase semipreparative HPLC column with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in $CH_3CN$) as eluents and a gradient of 5% B to 40% B over 40 min gave the purified compound (78 mg) as a white solid after lyophilization. Further desalting and lyophilization afforded N,N-bis(2-((7-fluoroquinolin-4-yl)amino)ethyl)acetamide (26 mg) as a white powder. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.98 (s, 3H); 3.40-3.72 (m, 8H); 6.46 (d, J = 5.4, 1H); 6.53 (d, J = 5.4, 1H); 7.30-7.39 (m, 2H); 7.42-7.45 (m, 2H); 7.44-7.48 (m, 2H); 8.18 (dd, J = 6.2, 9.2, 1H); 8.21 (dd, J = 6.2, 9.2, 1H); 8.34 (d, J = 4.5, 1H); 8.36 (d, J = 5.1, 1H). Mass spectrum (ESI) m/e = 436.2 (M+1).

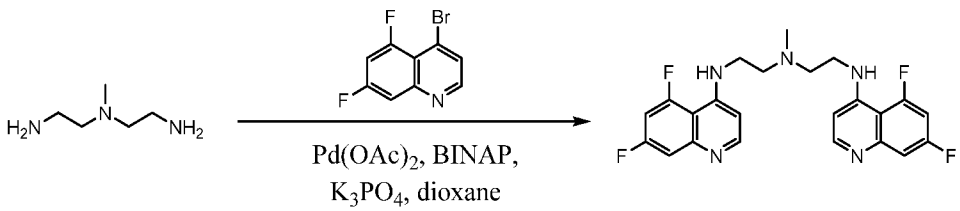
**EXAMPLE 25**: $N^1$,$N^2$-bis(7-fluoroquinolin-4-yl)-$N^1$-(2-((7-fluoroquinolin-4-yl)amino)ethyl)ethane-1,2-diamine.




**[00260]** A reaction mixture of 4-bromo-7-fluoroquinoline (1.5 g, 6.64 mmol), triethylamine (0.925 mL, 6.64 mmol), $N^1$-(2-aminoethyl)ethane-1,2-diamine (0.36 mL, 3.32 mmol), and N-methylpyrrolidinone (6.6 mL) was stirred at 130 °C for 21.5 h, and the temperature was

increased to 140 °C for another 20.5 h. After the reaction mixture was cooled to room temperature, EtOAc (10 mL) and water (30 mL) were added with stirring at 0 °C for 2 h. The temperature was raised to room temperature, and overnight, an oil formed. Oil and supernatant were separated, the supernatant was concentrated *in vacuo* to dryness, and both oil and dried supernatant were purified by two separate silica gel chromatographic separations. Two eluents ($CH_2Cl_2$/MeOH/$NH_4OH$ (180:9:1 and 90:9:1) were used in each separation. Both supernatant and oil yielded crude mixtures of $N^1$-(7-fluoroquinolin-4-yl)-$N^2$-(2-((7-fluoroquinolin-4-yl)amino)ethyl)ethane-1,2-diamine and $N^1$,$N^2$-bis(7-fluoroquinolin-4-yl)-$N^1$-(2-((7-fluoroquinolin-4-yl)amino)ethyl)ethane-1,2-diamine as yellow solids, which were combined for a total amount of 0.65 g (0.47 g from the supernatant and 0.18 g from the oil). To a suspension of this mixture (0.26 g) in $CH_2Cl_2$ (5 mL) at 0 °C was added $Et_3N$ (0.18 mL, 1.3 mmol) and $Ac_2O$ (0.093 mL, 0.99 mmol). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo,* and thereafter co-concentrated *in vacuo* with MeOH. HPLC purification using a C18 reverse phase semipreparative HPLC column with solvent A (0.1% of TFA in water) and solvent B (0.1% of TFA in $CH_3CN$) as eluents and gradient of 5% B to 40% B over 40 min provided the trifluoroacetate salt of $N^1$,$N^2$-bis(7-fluoroquinolin-4-yl)-$N^1$-(2-((7-fluoroquinolin-4-yl)amino)ethyl)ethane-1,2-diamine as a white powder (140 mg). Further desalting and lyophilization afforded the free base (50 mg) as white powder. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.51-3.61 (m, 4H); 3.77 (t, J = 6.3, 4H); 6.37 (d, J = 5.7, 2H); 7.15 (d, J = 5.1, 1H); 7.22-7.38 (m, 3H); 7.4-7.5 (m, 2H); 7.45 (dd, J = 2.7, 10.5, 2H); 7.54 (dd, J = 2.7, 10.5, 1H); 8.04 (dd, J = 6.6, 9.3, 1H); 8.15 (dd, J = 6.0, 9.3. 2H); 8.26 (d, J = 5.7, 2H); 8.54 (d, J = 5.1, 1H). Mass spectrum (ESI) m/e = 539.2 (M+1).

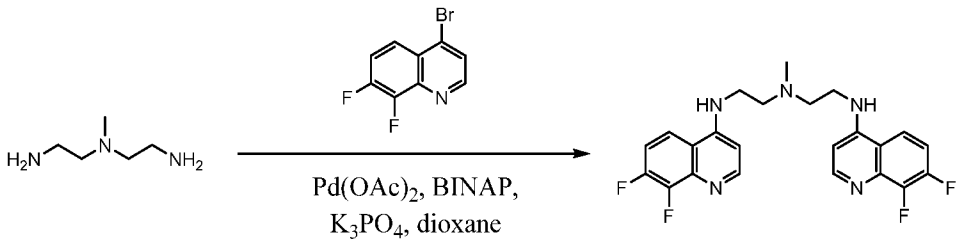
**EXAMPLE 26:** N1-(5,7-difluoroquinolin-4-yl)-N2-(2-((5,7-difluoroquinolin-4-yl)amino)ethyl)-N2-methylethane-1,2-diamine




**[00261]** A mixture of 4-bromo-5,7-difluoroquinoline (0.50 g, 2.23 mmol), N-methyl-2,2'-diaminodiethyl amine (0.097 mL, 0.75 mmol), $Pd(OAc)_2$ (16 mg), BINAP (89 mg), $K_3PO_4$ (0.75 g) in 1,4-dioxane (7.5 mL) was degassed with argon for a few minutes and then stirred

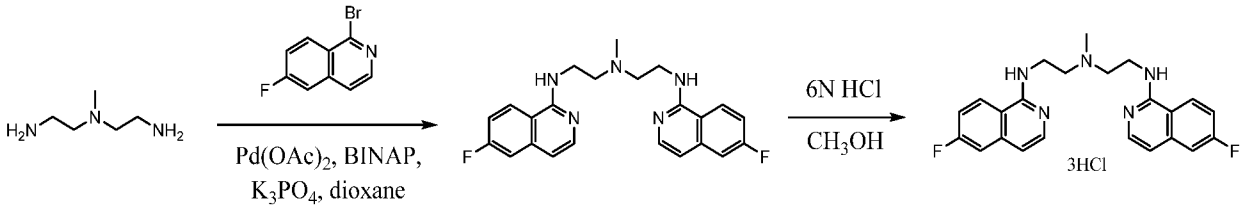
at 120 °C for 18 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1) and lyophilization afforded $N^1$-(5,7-difluoroquinolin-4-yl)-$N^2$-(2-((5,7-difluoroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.159 g, 47.9%) as a pale-brownish solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.34 (s, 3H); 2.74 (t, J = 6.0, 4H); 3.28-3.38 (m, 4H, overlay with $H_2O$); 6.46 (d, J = 5.4, 2H); 6.79-6.90 (m, 2H); 7.00-7.08 (m, 2H); 7.28 (dd, J = 2.1, 10.2, 2H); 8.32 (d, J = 5.4, 2H). Mass spectrum (ESI) m/e = 444.1 (M+1).

**EXAMPLE 27**: $N^1$-(7,8-difluoroquinolin-4-yl)-$N^2$-(2-((7,8-difluoroquinolin-4-yl)amino)ethyl)-N2-methylethane-1,2-diamine




**[00262]** A mixture of 4-bromo-7,8-difluoroquinoline (0.50 g, 2.23 mmol), N-methyl-2,2'-diaminodiethyl amine (0.097 mL, 0.75 mmol), $Pd(OAc)_2$ (16 mg), BINAP (89 mg), $K_3PO_4$ (0.75 g) in 1,4-dioxane (7.5 mL) was degassed with argon for a few minutes and then stirred at 120 °C for 18 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_3OH/CH_2Cl_2$ (10%, 15%, and 20%), and further purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1) and lyophilization afforded $N^1$-(7,8-difluoroquinolin-4-yl)-$N^2$-(2-((7,8-difluoroquinolin-4-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.20 g, 60%) as a yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.37 (s, 3H); 2.73 (t, J = 6.5, 4H); 3.38 (q, J = 6.0, 4H); 6.50 (d, J = 5.7, 2H); 7.21 (br t, J = 5.1, 2H); 7.35-7.44 (m, 2H); 7.91-7.97 (m, 2H); 8.38 (d, J = 5.4, 2H). Mass spectrum (ESI) m/e = 444.1 (M+1).

**EXAMPLE 28:** $N^1$-(6-fluoroisoquinolin-1-yl)-$N^2$-(2-((6-fluoroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine



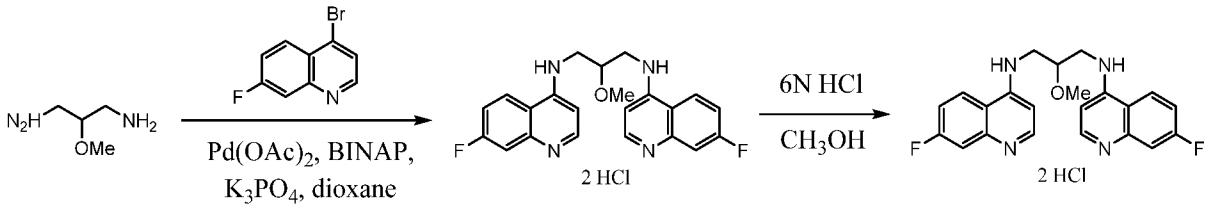

Step 1: $N^1$-(6-fluoroisoquinolin-1-yl)-$N^2$-(2-((6-fluoroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine

**[00263]** A mixture of 1-bromo-6-fluoro-isoquinoline (0.50 g, 2.23 mmol), N-methyl-2,2'-diaminodiethyl amine (0.097 mL, 0.75 mmol), $Pd(OAc)_2$ (16 mg), BINAP (89 mg), $K_3PO_4$ (0.75 g) in 1,4-dioxane (7.5 mL) was degassed with argon for a few minutes and then stirred at 120 °C for 19 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, 90:9:1), and further purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (135:9:1) and lyophilization afforded $N^1$-(6-fluoroisoquinolin-1-yl)-$N^2$-(2-((6-fluoroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine (0.16 g, 52%) as a pale-brownish solid. $^1$H NMR (300 MHz, DMSO-d6) δ 2.34 (s, 3H); 2.69 (t, 4H); 3.60 (q, J = 6.3, 4H); 6.84 (d, J = 5.7, 2H); 7.25-7.35 (m, 2H); 7.33 (br t, J= 5.3, 2H); 7.46 (dd, J = 2.7, 10.2, 2H); 7.85 (d, J = 5.7, 2H); 8.21 (dd, J = 5.6, 9.2, 2H). Mass spectrum (ESI) m/e = 408.1 (M+1).

Step 2: $N^1$-(6-fluoroisoquinolin-1-yl)-$N^2$-(2-((6-fluoroisoquinolin-1-yl)amino)ethyl)-$N^2$-methylethane-1,2-diamine trihydrochloride

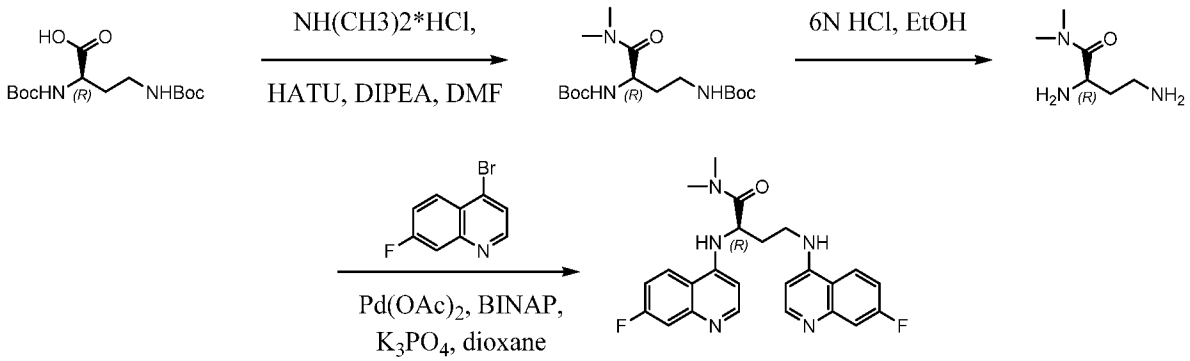
**[00264]** 74 mg of the free base was dissolved in methanol (1 mL), treated with 6N HCl (1 mL) via sonication and evaporated to dryness. The resulting residues were sonicated in $CH_3CN$ (10 mL). The insoluble material was collected via filtration, washed with $CH_3CN$ and lyophilized with water to afford the trihydrochloride salt (71 mg) as a white solid. $^1$H NMR (300 MHz, $D_2O$) δ 3.06 (s, 3H); 3.59 (t, J = 5.4, 4H); 3.86 (t, J = 5.3, 4H); 6.84 (d, J = 6.9, 2H); 7.19-7.29 (m, 6H); 7.93 (dd, J = 5.0, 7.9, 2H). Mass spectrum (ESI) m/e = 408.1 (M+1).

**EXAMPLE 29:** $N^1$,$N^3$-bis(7-fluoroquinolin-4-yl)-2-methoxypropane-1,3-diamine




**[00265]** A mixture of 4-bromo-7-fluoroquinoline (0.50 g, 2.23 mmol), 2-methoxypropane-1,3-diamine (0.078 g, 0.75 mmol), $Pd(OAc)_2$ (16 mg), BINAP (89 mg), $K_3PO_4$ (0.75 g) in 1,4-dioxane (7.5 mL) was degassed with argon for a few minutes and then stirred at 120 °C for 19 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, and 135:9:1) yielded 0.23 g of the free base as a pale-yellow solid. Further conversion to its hydrochloride salt by treatment with 6N HCl in $CH_3OH$, filtration to collect the isolable material in $CH_3CN$ and lyophilization afforded $N^1,N^3$-bis(7-fluoroquinolin-4-yl)-2-methoxypropane-1,3-diamine dihydrochloride (0.216 g, 61.7%) as a white solid. $^1H$ NMR (300 MHz, DMSO-d6) δ 3.39 (s, 3H); 3.77-3.88 (m, 4H); 3.85-3.96 (m, 1H); 7.03 (d, J = 7.2, 2H); 7.65-7.73 (m, 4H); 8.58 (d, J = 7.2, 2H); 8.84 (J = 5.7, 9.0, 2H); 9.75 (br t, 2H). Mass spectrum (ESI) m/e = 395.2 (M+1).

**EXAMPLE 30:** (R)-2,4-bis((7-fluoroquinolin-4-yl)amino)-N,N-dimethylbutanamide




Step 1: di-tert-butyl (4-(dimethylamino)-4-oxobutane-1,3-diyl)(R)-dicarbamate

**[00266]** To a solution of (R)-2,4-bis-tert-butoxycarbonylamino-butyric acid (0.33 g, 1.0 mmol) in DMF (5 mL) at 0 °C was added dimethylamine hydrochloride (0.154 g, 1.9 mmol), followed by HATU (0.715 g, 1.9 mmol) and DIPEA (0.89 mL, 5.1 mmol). After stirring under argon at 0 °C for 0.5 h and then at room temperature overnight, the reaction mixture was taken up in EtOAc (30 mL) and 10% $KHSO_4$ (15 mL). The aqueous layers were extracted with EtOAc (15 mL x 1), and the organic extracts were washed with brine (10 mL),

dried with $Na_2SO_4$ and evaporated. Further silica-gel chromatography with 50% EtOAc/hexane afforded the dimethylamide as a colorless oil (0.35 g).

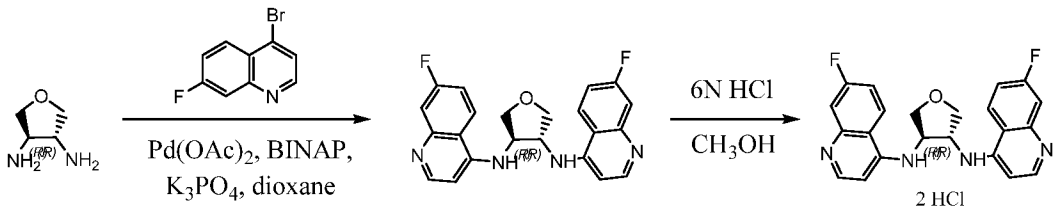
Step 2: (R)-2,4-diamino-N,N-dimethylbutanamide

**[00267]** The dimethylamide (0.35 g) was treated with 6N HCl (5 mL) in EtOH (5 mL) at room temperature for 20 hours, and evaporated to dryness to yield the deprotected diamine as a white solid (0.22 g), which was used in the next step without further purification.

Step 3: (R)-2,4-bis((7-fluoroquinolin-4-yl)amino)-N,N-dimethylbutanamide

**[00268]** A mixture of 4-bromo-7-fluoroquinoline (0.50 g, 2.23 mmol), diamine (0.164 g, 0.75 mmol), $Pd(OAc)_2$ (18 mg), BINAP (89 mg), and $K_3PO_4$ (1.07 g) in 1,4-dioxane (7.5 mL) was degassed with argon for one minute and then stirred at 120 °C for 22 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_3OH/CH_2Cl_2/NH_4OH$ (180:9:1, 135:9:1, and 90:9:1) yielded (R)-2,4-bis((7-fluoroquinolin-4-yl)amino)-N,N-dimethylbutanamide as a pale-brownish solid (0.167 g, 51%). $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 2.18-2.27 (m, 2H); 2.86 (s, 3H); 3.05 (s, 3H); 3.44-3.52 (m, 2H); 4.74-4.84 (m, 1H); 6.35 (d, J = 5.3, 1H); 6.52 (d, J = 5.4, 1H); 7.31-7.51 (m, 4H); 7.34-7.45 (m, 2H); 8.30 (dd, J = 6.2, 9.2, 1H); 8.35 (d, J = 4.5, 1H); 8.36 (d, J = 4.8, 1H); 8.54 (dd, J = 6.2, 9.2, 1H). Mass spectrum (ESI) m/e = 436.2 (M+1).

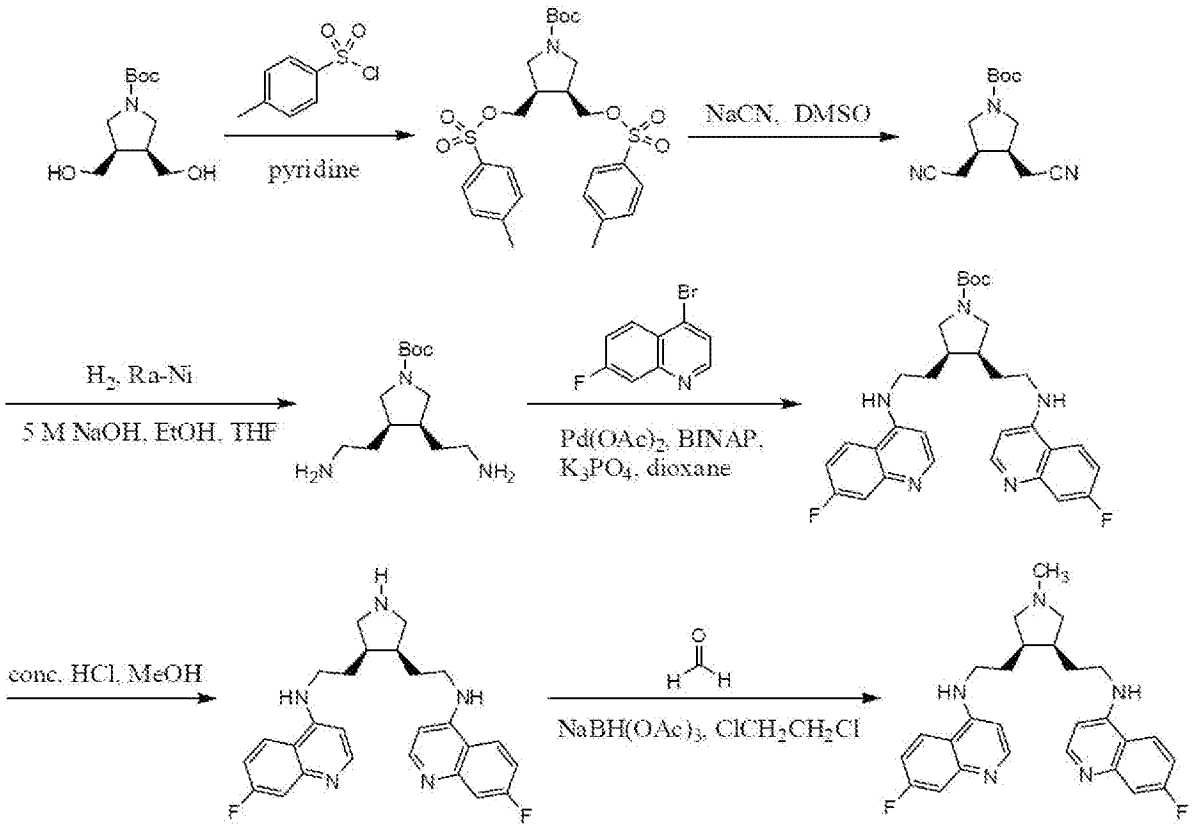
**EXAMPLE 31:** (3R,4R)-$N^3$,$N^4$-bis(7-fluoroquinolin-4-yl)tetrahydrofuran-3,4-diamine




**[00269]** A mixture of 4-bromo-7-fluoroquinoline (0.50 g, 2.23 mmol), (3R,4R)-tetrahydrofuran-3,4-diamine (0.087 g, 0.85 mmol), $Pd(OAc)_2$ (18 mg), BINAP (89 mg), $K_3PO_4$ (0.75 g) in 1,4-dioxane (7.5 mL) was degassed with argon for one minute and then stirred at 120 °C for 22 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_3OH/CH_2Cl_2/NH_4OH$ (180:9:1, 135:9:1, and 90:9:1) yielded the free base as a yellow solid. Further conversion to its hydrochloride salt by treatment with 6N HCl in $CH_3OH$, evaporation of $CH_3OH$, sonication of the salt in $CH_3CN$ and collection by filtration, and subsequent lyophilization from water afforded (3R,4R)-$N^3$,$N^4$-bis(7-fluoroquinolin-4-

yl)tetrahydrofuran-3,4-diamine dihydrochloride (0.239 g, 60%) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 4.00 (dd, J = 4.1, 9.5, 2H); 4.41 (dd, J = 6.0, 9.6, 2H); 4.95-5.06 (m, 2H); 6.89 (d, J = 7.2, 2H); 7.72-7.82 (m, 4H); 8.60 (d, J = 7.2, 2H); 8.90-8.94 (m, 2H); 9.42-9.52 (m, 2H). Mass spectrum (ESI) m/e = 393.1 (M+1).

**EXAMPLE 32:** Synthesis of N,N'-(((3S,4R)-pyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine) and N,N'-(((3S,4R)-1-methylpyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine).




Step 1: (3S, 4R)-tert-butyl 3,4-bis(tosyloxymethyl)pyrrolidine-1-carboxylate

**[00270]** To a solution of tert-butyl (3R, 4S)-3,4-bis(hydroxymethyl)pyrrolidine-1-carboxylate (2.0 g, 8.65 mmol) in pyridine (10 mL) at 0°C was added 4-methylbenzenesulfonyl chloride (2.27 g, 11.9 mmol) in small portions. The reaction mixture was stirred at room temperature under argon overnight, and concentrated. The resulting residues were dissolved in $CH_2Cl_2$ (100 mL) and washed with saturated $NaHCO_3$ solution (50 mL) and saturated NaCl solution (50 mL), dried over $Na_2SO_4$. Evaporation to dryness yielded the desired product (3.8 g) as a brown oil which was used in the next step without purification.

Step 2: (3S,4R)-tert-butyl 3,4-bis(cyanomethyl)pyrrolidine-1-carboxylate

**[00271]** To a solution of (3S, 4R)-tert-butyl 3,4-bis(tosyloxymethyl)pyrrolidine-1-carboxylate (3.8 g, 7.1 mmol) in DMSO (26 mL) was added sodium cyanide (0.69 g, 14.2 mmol). The reaction mixture was stirred at 90°C under argon for 10 hours. After being cooled to room temperature, the reaction mixture was treated with 50 mL of a solution of saturated $FeSO_4$ at room temperature overnight and then extracted with EtOAc (100 mL x 1, 50 mL x 2). The combined organic extracts were washed with saturated NaCl solution (50 mL) and dried over $Na_2SO_4$. Silica-gel chromatography (25% and 50% EtOAc/Hexane) gave the desired pure product (0.74 g, 34.3% overall yield for steps 1 & 2) as a faint-yellow oil.

Step 3: (3S,4R)-tert-butyl 3,4-bis(2-aminoethyl)pyrrolidine-1-carboxylate

**[00272]** To a solution of (3S,4R)-tert-butyl 3,4-bis(cyanomethyl)pyrrolidine-1-carboxylate (0.32 g, 1.29 mmol) in EtOH (24.5 mL) and THF (6.0 mL) was sequentially added 5 M NaOH (2.5 mL) and Raney Nickel (3.1 mL). The reaction mixture was placed under an atmosphere of hydrogen and stirred at room temperature for 22 hours, followed by filtration with Celite and washing with MeOH. The resulting filtrate was concentrated under reduced pressure. This afforded a residue which was partitioned between $CH_2Cl_2$ (10 mL) and water (10 mL). The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 10 mL). Combined organic extracts were washed with brine (10 mL) and dried over $Na_2SO_4$. Evaporation to dryness afforded the product as a pale-yellow oil (0.31 g, 94 %).

Step 4: (3S,4R)-tert-butyl 3,4-bis(2-(7-fluoroquinolin-4-ylamino)ethyl)pyrrolidine-1-carboxylate

**[00273]** A mixture of 4-bromo-7-fluoroquinoline (0.348 g, 3.45 mmol), (3S,4R)-tert-butyl 3,4-bis(2-aminoethyl)pyrrolidine-1-carboxylate (0.29 g, 1.14 mmol), $Pd(OAc)_2$ (24.7 mg), BINAP (134 mg), and $K_3PO_4$ (1.12 g) in 1,4-dioxane (11 mL) was degassed with argon for one minute and then stirred at 120°C for 19 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, and 90:9:1) gave the partial pure product (0.45 g) as a yellow solid, which was used in the next step without further purification.

Step 5: N,N'-(2,2'-((3S,4R)-pyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine)

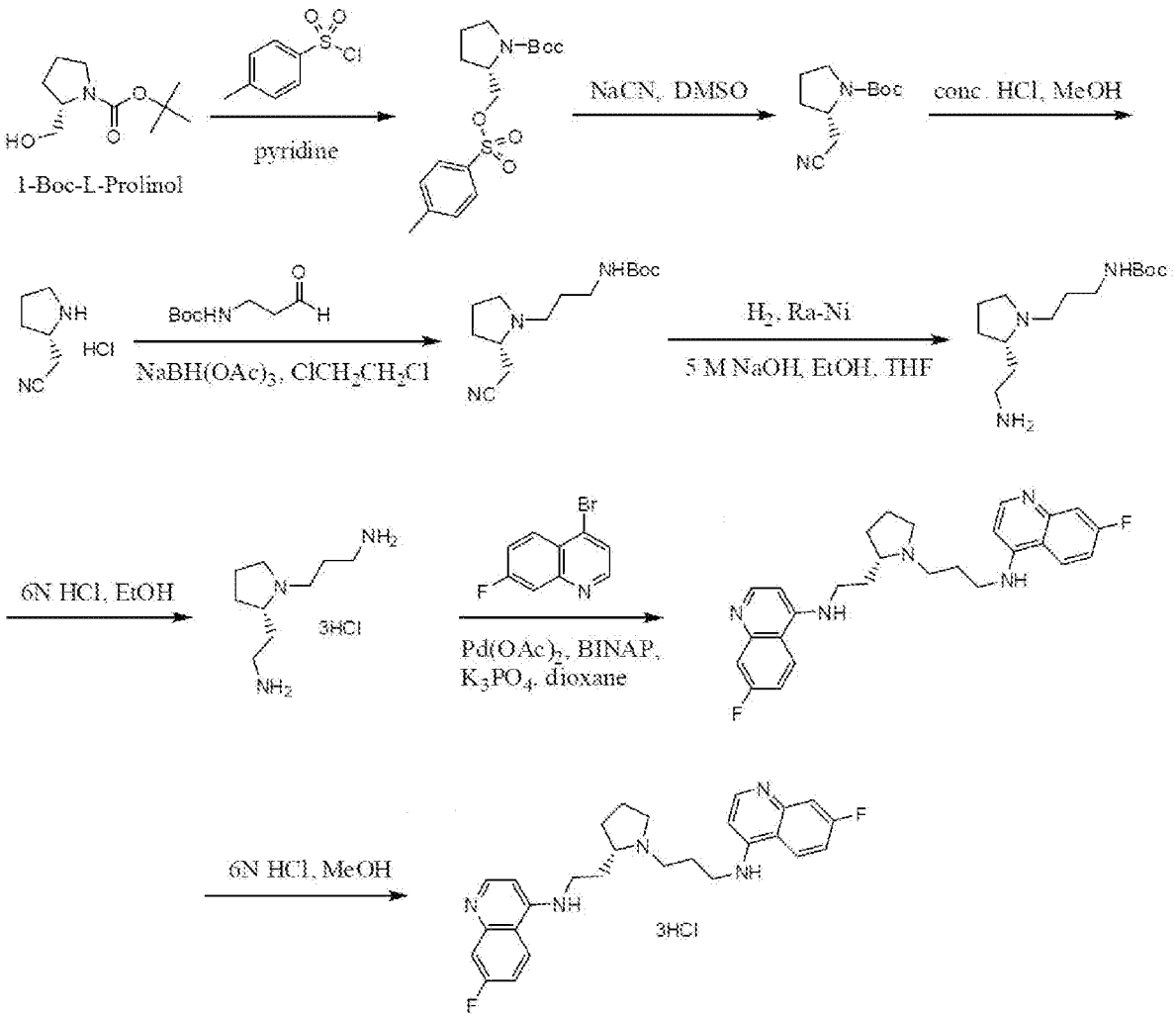
**[00274]** To a solution (3S,4R)-tert-butyl 3,4-bis(2-(7-fluoroquinolin-4-ylamino)ethyl)pyrrolidine-1-carboxylate (0.45 g, 0.82 mmol) in EtOH (5 mL) was added 6 N HCl (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the resulting residue was co-evaporated with EtOH

twice to dryness. The resulting yellow residues were taken up into water (25 mL), washed with $CH_2Cl_2$ (10 mL x 3), and then adjusted to pH > 12 with 1N NaOH. The resulting yellow precipitate was collected by filtration. Washing with cold water afforded the product as a pale yellow solid (0.35 g). A small amount of this solid was lyophilized with $CH_3CN/H_2O$ to yield N,N'-(2,2'-((3S,4R)-pyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine) as white powder (3.3 mg). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.48-1.62 (m, 2H); 1.74-1.88 (m, 2H); 2.06-2.20 (m, 2H); 2.26-2.37 (m, 1H); 2.57-2.64 (m, 2H); 2.98-3.04 (m, 2H); 3.18-3.28, 4H); 6.39 (d, J = 5.4, 0.5H); 6.40 (d, J = 5.4, 1.5H); 7.29 (br t, 2H); 7.31 (dt, J = 2.7, 8.6, 2H); 7.44 (dd, J = 2.7, 10.8, 2H); 8.29 (dd, J = 6.3, 9.3, 2H); 8.31 (d, J = 5.4, 0.5H); 8.32 (d, J = 5.1, 1.5H). Mass spectrum (ESI) m/e = 448.2 (M+1).

Step 6: N,N'-(((3S,4R)-1-methylpyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine)

**[00275]** To a solution of N,N'-(2,2'-((3S,4R)-pyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine) (0.35 g, 0.78 mmol) in $CH_2Cl_2$ (16 mL) and $CH_3OH$ (1 mL) was added 37 wt% formaldehyde (0.104 mL, 1.56 mmol), followed by $NaBH(OAc)_3$ (0.66 g, 3.1 mmol). The reaction mixture was stirred at room temperature overnight, and 2N NaOH (45 mL) was added. This reaction mixture was stirred at room temperature for another 1 hour before extracting with $CHCl_3$ (50 mL x 5). The combined organic extracts were evaporated to dryness. Purification by silica-gel column chromatography with $CH_3OH/CH_2Cl_2/NH_4OH$ (90:9:1) and lyophilization with $CH_3CN/H_2O$ yielded N,N'-(((3S,4R)-1-methylpyrrolidine-3,4-diyl)bis(ethane-2,1-diyl))bis(7-fluoroquinolin-4-amine) (0.124 g, 34%) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.48-1.63 (2H, m); 1.79-1.92 (2H, m); 2.08 (t, J = 7.8, 2H); 2.26 (s, 3H); 2.26-2.34 (2H, m); 2.93 (dd, J = 6.6, 8.7, 2H), 3.19-3.27 (m, 4H); 6.41 (d, J = 5.4, 2H); 7.26 (br t, 2H); 7.31 (dt, J = 2.7, 8.7, 2H); 7.44 (dd, J = 2.7, 10.8, 2H); 8.28 (dd, J = 6.3, 9.3, 2H); 8.35 (d, J = 5.4, 2H). Mass spectrum (ESI) m/e = 462.2 (M+1).

**EXAMPLE 33:** Synthesis of (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine trihydrochloride.




Step 1: (S)-tert-butyl 2-(tosyloxymethyl)pyrrolidine-1-carboxylate

**[00276]** To a solution of 1-Boc-L-prolinol (2.0 g, 9.94 mmol) in pyridine (7 mL) at 0°C was added 4-methylbenzenesulfonyl chloride (2.27 g, 11.9 mmol) in small portions. The reaction mixture was stirred at room temperature under argon overnight, and concentrated. The resulting residues were dissolved in $CH_2Cl_2$ (50 mL) and washed with saturated $NaHCO_3$ (50 mL) and saturated NaCl (25 mL) solutions, followed by drying over $Na_2SO_4$. Evaporation to dryness yielded the desired product (4.2 g) as a pale-yellow oil which was used in the next step without purification.

Step 2: (S)-tert-butyl 2-(cyanomethyl)pyrrolidine-1-carboxylate

**[00277]** To a solution of (S)-tert-butyl 2-(tosyloxymethyl)pyrrolidine-1-carboxylate (4.2 g) in DMSO (36 mL) was added sodium cyanide (0.97 g, 19.9 mmol). The reaction mixture was stirred at 90°C under argon overnight. After cooled to room temperature, the reaction mixture was treated with saturated $FeSO_4$ solution (50 mL) at room temperature for another 5 hours and then extracted with EtOAc (50 mL x 3). The combined organic extracts were washed

with saturated NaCl solution (30 mL) and dried over $Na_2SO_4$. Silica-gel chromatography with 25% EtOAc/Hexane gave the desired product (1.77 g, 84.7% overall yield for steps 1 & 2) as a colorless oil.

Step 3: tert-butyl 3-oxopropylcarbamate

**[00278]** To a solution of (S)-tert-butyl 2-(cyanomethyl)pyrrolidine-1-carboxylate (1.77 g, 4.45 mmol) in methanol (18 mL) was added 12N HCl (1.8 mL). The reaction mixture was stirred at 40°C overnight. The solvent was removed under reduced pressure, the resulting residue was co-evaporated with toluene twice and high vacuum to give (S)-2-(pyrrolidin-2-yl)acetonitrile hydrochloride (1.35 g) as a white solid, which was used in the next step without further purification.

Step 4: (S)-tert-butyl 3-(2-(cyanomethyl)pyrrolidin-1-yl)propylcarbamate

**[00279]** To a solution of tert-butyl 3-oxopropylcarbamate (0.33 g, 1.9 mmol) in 1,2-dichloroethane (19 mL) was added (S)-2-(pyrrolidin-2-yl)acetonitrile hydrochloride (0.291 g, 2.0 mmol), followed by $NaBH(OAc)_3$ (0.636 g, 3.0 mmol). The reaction mixture was stirred at room temperature under argon overnight, saturated $NaHCO_3$ (20 mL) was added. The organic phase was separated, and the aqueous phase was further extracted with $CH_2Cl_2$ (20 mL x 2). The combined organic phase was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), then dried with $MgSO_4$ and concentrated under reduced pressure. Purification by silica-gel column chromatography with $CH_3OH/CH_2Cl_2/NH_4OH$ (180:9:1) yielded the desired product (0.274 g, 51 %) as a colorless oil.

Step 5: (S)-tert-butyl 3-(2-(2-aminoethyl)pyrrolidin-1-yl)propylcarbamate

**[00280]** To a solution of (S)-tert-butyl 3-(2-(cyanomethyl)pyrrolidin-1-yl)propylcarbamate (0.264 g, 0.987 mmol) in EtOH (16 mL) and THF (4 mL) was sequentially added 5 M NaOH (1.6 mL) and Raney Nickel (2 mL). The reaction mixture was placed under an atmosphere of hydrogen, stirred at room temperature overnight, and then filtered via Celite and washed with MeOH. The resulting filtrate was concentrated under reduced pressure. The afforded residue was partitioned between $CH_2Cl_2$ (10 mL) and water (10 mL). The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 10 mL). Combined organic extracts were washed with brine (10 mL) and dried over $Na_2SO_4$. Evaporation to dryness afforded the product as a colorless oil (0.234 g, 87%).

Step 6: (S)-3-(2-(2-aminoethyl)pyrrolidin-1-yl)propan-1-amine trihydrochloride

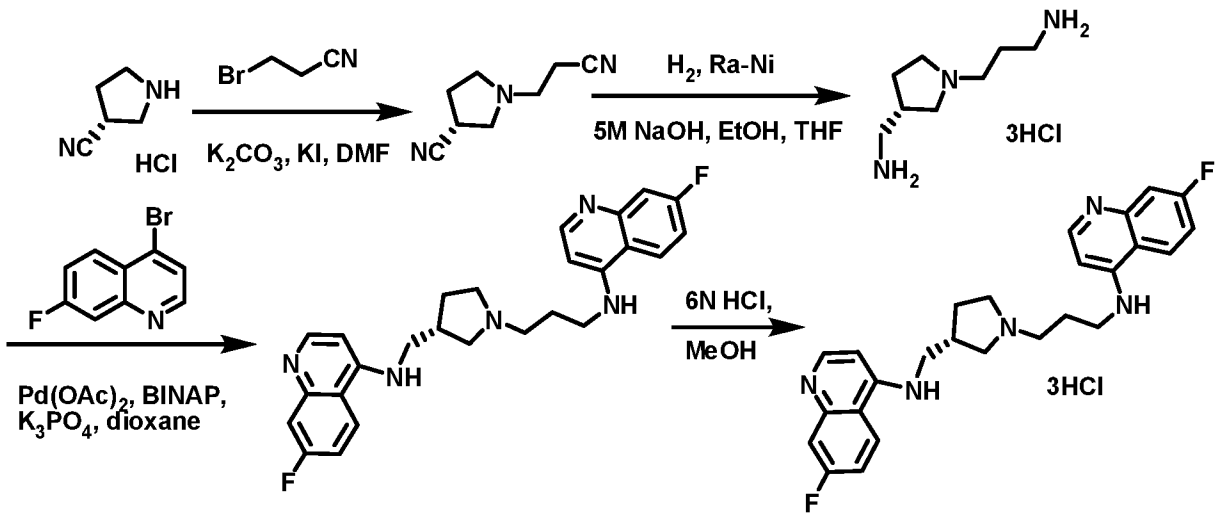
**[00281]** To a solution of (S)-tert-butyl 3-(2-(2-aminoethyl)pyrrolidin-1-yl)propylcarbamate (0.23 g, 0.85 mmol) in EtOH (5 mL) was added 6 N HCl (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the

resulting residue was co-evaporated with EtOH twice and high vacuum gave (S)-3-(2-(2-aminoethyl)pyrrolidin-1-yl)propan-1-amine trihydrochloride (0.30 g) as a colorless oil, which was used in the next step without further purification.

Step 7: (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine trihydrochloride

**[00282]** A mixture of 4-bromo-7-fluoroquinoline (0.348 g, 1.54 mmol), (S)-3-(2-(2-aminoethyl)pyrrolidin-1-yl)propan-1-amine trihydrochloride (0.15 g, 0.53 mmol), $Pd(OAc)_2$ (11 mg), BINAP (61 mg), and $K_3PO_4$ (0.83 g) in 1,4-dioxane (5.1 mL) was degassed with argon for one minute and then stirred at 120°C for 20 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, and 90:9:1) gave the partial pure product (0.17 g) as a brownish residue, which was further washed four times with $CH_3CN$ at 0°C. (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine was obtained as a yellow foam. The free base was converted to its hydrochloride salt by treatment with 6N HCl in $CH_3OH$ and double lyophilization with $CH_3CN/H_2O$ yielding (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine trihydrochloride (0.147 g, 48.5%) as a yellow solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 1.71-1.85 (m, 1H); 1.92-2.03 (m, 2H); 2.08-2.23 (m, 3H); 2.30-2.47 (m, 2H); 3.05-3.18 (m, 2H); 3.41-3.56 (m, 2H), 3.54-3.72 (m, 5H); 6.95 (d, 1H, J = 7.8); 6.98 (d, J = 8.7, 1H); 7.62-7.75 (m, 4H); 8.58 (d, J = 5.7), 2H); 8.78-8.96 (2H, m); 9.62-9.80 (m, 2H). Mass spectrum (ESI) m/e = 462.2 (M+1).

**EXAMPLE 34:** Synthesis of (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine trihydrochloride.




Step 1: (R)-1-(2-cyanoethyl)pyrrolidine-3-carbonitrile

**[00283]** To a suspension of (R)-pyrrolidine-3-carbonitrile hydrochloride (0.5 g, 3.77 mmol) in DMF (12 mL) was added 3-bromopropanenitrile (0.51 g, 3.77 mmol), potassium carbonate (2.1 g, 15 mmol) and potassium iodide (0.63 g, 3.77 mmol). The reaction mixture was stirred at room temperature overnight and at 85°C for 24 h, and then water (25 mL) was added. The mixture was extracted with EtOAc (25 mL x 3). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$ and evaporated. Purification by silica gel chromatography using $CH_3OH/CH_2Cl_2$ (2.5% and 5%) gave the desired product (0.43 g, 76.8%) as a brown liquid.

Step 2: (S)-3-(3-(aminomethyl)pyrrolidin-1-yl)propan-1-amine trihydrochloride

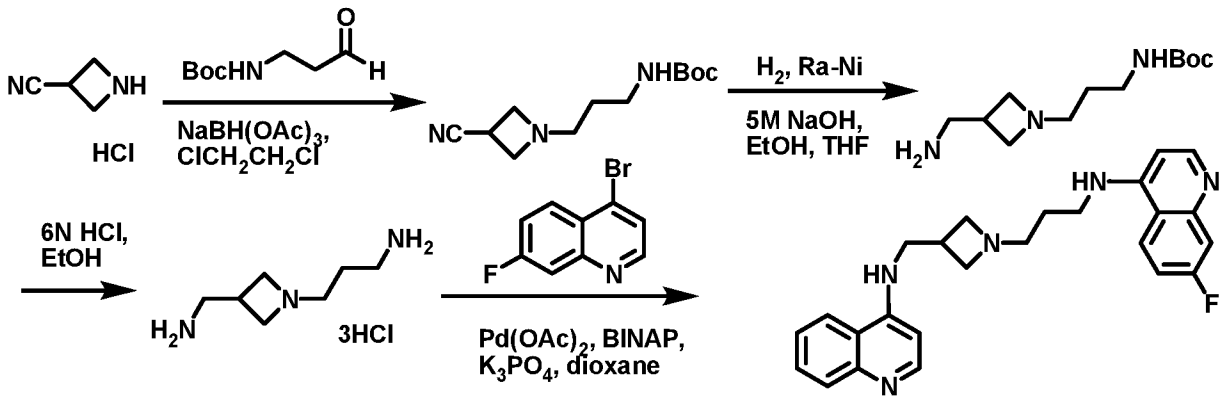
**[00284]** To a solution of (R)-1-(2-cyanoethyl)pyrrolidine-3-carbonitrile (0.23 g, 1.54 mmol) in EtOH (24.5 mL) and THF (6.0 mL) was sequentially added 5 M NaOH (2.46 mL) and Raney Nickel (3.1 mL). The reaction mixture was placed under an atmosphere of hydrogen and stirred at room temperature overnight, and then filtered via Celite and washed through with MeOH. The resulting filtrate was concentrated under reduced pressure. This afforded a residue which was partitioned between $CH_2Cl_2$ (10 mL) and water (10 mL). The aqueous layer was further washed with $CH_2Cl_2$, acidified at 0°C with 2N HCl. and evaporated to dryness. The resulting solid was extracted with 50% $MeOH/CH_2Cl_2$. Evaporation to dryness afforded the product as a faint-yellow oily residue (0.4 g, 97.6%).

Step 3: (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine trihydrochloride

**[00285]** A mixture of 4-bromo-7-fluoroquinoline (0.394 g, 1.74 mmol), (S)-3-(3-(aminomethyl)pyrrolidin-1-yl)propan-1-amine trihydrochloride (0.154 g, 0.578 mmol), $Pd(OAc)_2$ (12.7 mg), BINAP (69 mg), and $K_3PO_4$ (0.945 g) in 1,4-dioxane (5.8 mL) was degassed with argon for one minute and then stirred at 120°C for 20 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, and 90:9:1) gave the pure product (0.11 g) as a pale-yellow foam and the partial pure product (21.4 mg) as a yellow residue. The partially pure product was further washed with $CH_3CN$ at 0°C and yielded (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine (16.8 mg) as a white solid. Pure and purified (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine were combined and converted to the trihydrochloride salt by treatment with 6N HCl in $CH_3OH$ and double lyophilization with $CH_3CN/H_2O$. (S)-7-fluoro-N-(3-(2-(2-((7-fluoroquinolin-4-yl)amino)ethyl)pyrrolidin-1-yl)propyl)quinolin-4-amine trihydrochloride (0.153 g, 47.5%) was obtained as a yellow solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 1.73-2.02 (m, 1H); 2.08-2.32 (m, 3H); 2.78-3.25 (m, 5H); 3.48-

3.61 (m, 1H); 3.63-3.80 (m, 5H); 6.96 (d, J = 7.2, 1H); 6.99 (d, J = 7.5, 0.5H); 7.05 (d, J = 7.2, 0.5 H); 7.62-7.69 (m, 1.5H; 7.65-7.77 (m, 4H); 7.67-7.82 (m, 0.5H); 8.60 (d, J = 6.9, 2H); 8.78-8.89 (2H, m). Mass spectrum (ESI) m/e = 448.2 (M+1).

**EXAMPLE 35:** Synthesis of 7-fluoro-N-(3-(3-(((7-fluoroquinolin-4-yl)amino)methyl)azetidin-1-yl)propyl)quinolin-4-amine.




Step 1: tert-butyl 3-(3-cyanoazetidin-1-yl)propylcarbamate

**[00286]** To a solution of tert-butyl 3-oxopropylcarbamate (0.30 g, 1.73 mmol) in 1,2-dichloroethane (19 mL) was added azetidine-3-carbonitrile hydrochloride (0.205 g, 1.73 mmol), followed by addition of $NaBH(OAc)_3$ (0.55 g, 2.6 mmol). The reaction mixture was stirred at room temperature under argon overnight and a solution of saturated $NaHCO_3$ (20 mL) added. The organic phase was separated, and the aqueous phase was further extracted with $CH_2Cl_2$ (20 mL x 2). The combined organic phase was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, and finally was concentrated under reduced pressure. Purification by silica-gel column chromatography with $CH_3OH/CH_2Cl_2/NH_4OH$ (180:9:1) yielded the desired product (0.24 g, 58 %) as a colorless oil.

Step 2: tert-butyl 3-(3-(aminomethyl)azetidin-1-yl)propylcarbamate

**[00287]** To a solution of tert-butyl 3-(3-cyanoazetidin-1-yl)propylcarbamate (0.24 g, 1.0 mmol) in EtOH (15.9 mL) and THF (3.9 mL) was sequentially added 5 M NaOH (1.6 mL) and Raney Nickel (2 mL). The reaction mixture was placed under an atmosphere of hydrogen, stirred at room temperature overnight, and then filtered via Celite and washed with MeOH. The resulting filtrate was concentrated under reduced pressure. The residue was partitioned between $CH_2Cl_2$ (10 mL) and water (10 mL). The aqueous layer was further extracted with $CH_2Cl_2$ (2 × 10 mL). Combined organic extracts were washed with brine (10 mL) and dried over $Na_2SO_4$. Evaporation to dryness afforded the product as an oil (0.22 g, 90%).

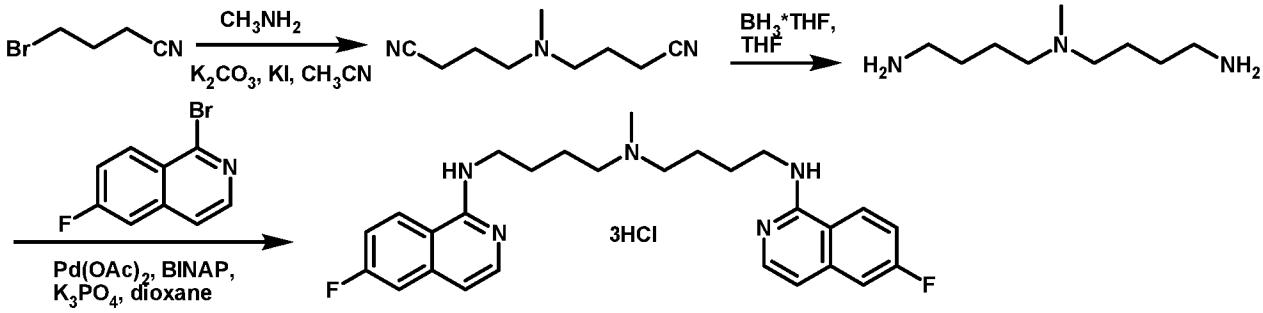
Step 3: 3-(3-(aminomethyl)azetidin-1-yl)propan-1-amine trihydrochloride

**[00288]** To a solution of tert-butyl 3-(3-(aminomethyl)azetidin-1-yl)propylcarbamate (0.22 g, 0.90 mmol) in EtOH (5 mL) was added 6 N HCl (5 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, the resulting residue was co-evaporated with EtOH twice and high vacuum gave 3-(3-(aminomethyl)azetidin-1-yl)propan-1-amine trihydrochloride (0.19 g) as a yellow foam, which was used in the next step without further purification.

Step 4: 7-fluoro-N-(3-(3-(((7-fluoroquinolin-4-yl)amino)methyl)azetidin-1-yl)propyl)quinolin-4-amine

**[00289]** A mixture of 4-bromo-7-fluoroquinoline (0.52 g, 2.30 mmol), 3-(3-(aminomethyl)azetidin-1-yl)propan-1-amine trihydrochloride (0.19 g, 0.768 mmol), $Pd(OAc)_2$ (16.9 mg), BINAP (91.7 mg), and $K_3PO_4$ (1.26 g) in 1,4-dioxane (7.7 mL) was degassed with argon for one minute and then stirred at 120°C for 20 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Double purification by silica gel chromatography using $CH_2Cl_2/CH_3OH/NH_4OH$ (180:9:1, and 90:9:1) yielded 7-fluoro-N-(3-(3-(((7-fluoroquinolin-4-yl)amino)methyl)azetidin-1-yl)propyl)quinolin-4-amine (58.8 mg, 18%) as a white solid. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 1.60-1.73 (m, 2H); 2.72-2.86 (m, 1H); 2.97 (t, J = 6.2, 2H); 3.23-3.37 (m, 6H); 3.48 (t, J = 6.2, 2H); 7.28-7.36 (m, 2H); 7.32-7.37 (m, 2H); 7.42-7.48 (2H); [6.43 (d, J = 5.7, 1H); 6.46 (d, J = 5.4, 1H)] or [6.44 (d, J = 9.6, 1H); 6.46 (d, J = 9.3, 1H)]; 8.23-8.33 (m,2H); 8.38 (d, J = 5.4, 1H); 8.39 (d, J = 5.4, 1H). Mass spectrum (ESI) m/e = 434.2 (M+1).

**EXAMPLE 36:** $N^1$-(6-fluoroisoquinolin-1-yl)-$N^4$-(4-((6-fluoroisoquinolin-1-yl)amino)butyl)-$N^4$-methylbutane-1,4-diamine trihydrochloride




*Step 1: N-methyl-bis-(3-cyanopropyl)amine*

**[00290]** To a solution of 4-bromobutyronitrile (1.3 g, 8.0 mmol) in $CH_3CN$ (12 mL) was added N-methylamine (2 M in THF; 2 mL, 4 mmol), potassium carbonate (1.66 g, 12 mmol) and potassium iodide (1.33 g, 8.0 mmol). The reaction mixture was stirred at 85°C for 21 h in

a sealed tube, and the solvents was removed with a rotary evaporator. The resulting residues were taken up in dichloromethane (25 mL) and water (25 mL). The aqueous layers were extracted with dichloromethane (25 mL). The combined organic extracts were washed with brine (25 mL), dried ($Na_2SO_4$) and evaporated to give N-methyl-bis-(3-cyanopropyl)amine as a yellow oil (0.79 g), which was used in the next step without further purification.

*Step 2: N-methyl-bis-(3-aminopropyl)amine*

**[00291]** The crude N-methyl-bis-(3-cyanopropyl)amine (0.79 g) was dissolved in anhydrous THF (7.2 mL), and borane-THF (0.9 M in THF, 8 equiv.) was added. The reaction mixture was heated at reflux for 2 h under argon, and quenched with 6 N HCl and methanol. After evaporation, the remaining white solid (1.65 g) was dissolved in water (15 mL), basified to pH >13 and extracted with $CH_2Cl_2$/MeOH (15:1; 5 x 16 mL). The combined organic extracts were dried ($Na_2SO_4$) and concentrated to give N-methyl-bis-(3-aminopropyl)amine as a faint-yellow oil (0.35 g), which was used in the next step without further purification.

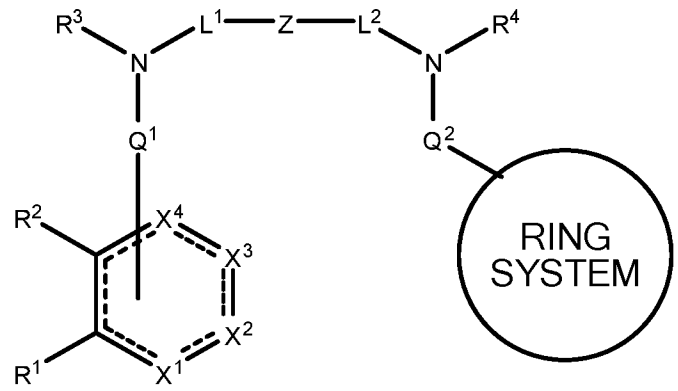
*Step 3: $N^1$-(6-fluoroisoquinolin-1-yl)-$N^4$-(4-((6-fluoroisoquinolin-1-yl)amino)butyl)-$N^4$-methylbutane-1,4-diamine trihydrochloride*

**[00292]** A mixture of 1-bromo-6-fluoro-isoquinoline (0.45 g, 1.99 mmol), N-methyl-bis-(3-aminopropyl)amine (114 mg, 0.66 mmol), $Pd(OAc)_2$ (14.5 mg), BINAP (79 mg), and $K_3PO_4$ (0.66 g) in 1,4-dioxane (6.6 mL) was degassed with argon for one minute and then stirred at 120°C for 18 hours in a sealed tube. The reaction mixture was cooled to room temperature, filtered via Celite and evaporated. Double purification by silica gel chromatography using $CH_2Cl_2$/$CH_3OH$/$NH_4OH$ (180:9:1, and 90:9:1), further conversion to its hydrochloride salt by treatment with 6N HCl in $CH_3OH$ and lyophilization with $CH_3CN$/$H_2O$ afforded $N^1$-(6-fluoroisoquinolin-1-yl)-$N^4$-(4-((6-fluoroisoquinolin-1-yl)amino)butyl)-$N^4$-methylbutane-1,4-diamine trihydrochloride (79 mg, 21%) as a yellow solid. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.75-1.92 (m, 8H); 2.76 (s, 3H); 3.08-3.23 (m, 4H); 3.70 (br q, J = 6.0, 4H); 6.78 (d, J = 6.6, 2H); 7.21 (d, J = 7.2, 2H); 7.71 (dt, J = 2.7, 8.9, 2H); 7.83 (dd, J = 2.6, 9.5, 2H); 9.00 (dd, J = 5.4, 9.3, 2H); 10.20 (br t, 2H); 10.32 (br s, 1H). Mass spectrum (ESI) m/e = 464.2 (M+1).

## EMBODIMENTS

**[00293]** The following non-limiting embodiments provide illustrative examples of the disclosure, but do not limit the scope of the disclosure.

**[00294]** Embodiment 1. A compound of the following formula:

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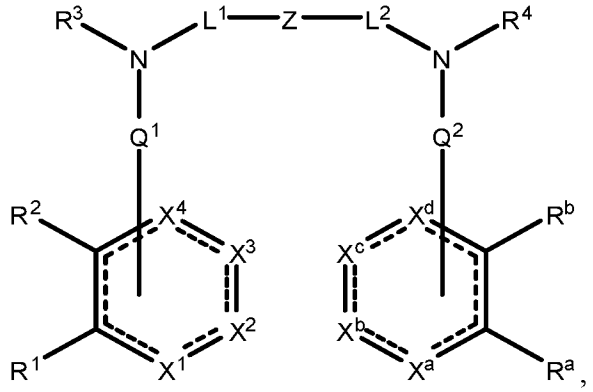
wherein: each ------- is independently a single bond or a double bond; RING SYSTEM is a cyclic group; $X^1$ is $CR^5$, $CR^5R^6$, N, $NR^5$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^2$ is $CR^7$, $CR^7R^8$, N, $NR^7$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^3$ is $CR^9$, $CR^9R^{10}$, N, $NR^9$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$; $X^4$ is $CR^{11}$, $CR^{11}R^{12}$, N, $NR^{11}$, O, S, C=O, C=S, or a carbon atom connected to $Q^1$, wherein one of $X^1$, $X^2$, $X^3$, and $X^4$ is a carbon atom connected to $Q^1$; $Q^1$ is C=O, C=S, $C=CR^{13}R^{14}$, $C=NR^{13}$, or a bond; $Q^2$ is C=O, C=S, $C=CR^{15}R^{16}$, $C=NR^{15}$, or a bond; $L^1$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, oxo, or halogen, or $L^1$ together with Z forms a heterocycle; $L^2$ is an alkylene group, a heteroalkylene group, an alkenylene group, a heteroalkenylene group, an alkynylene group, or a heteroalkynylene group, any of which is unsubstituted or substituted with alkyl, hydroxyl, oxo, or halogen, or a bond; Z is S, C=O, C(O)O, C=S, S=O, $SO_2$, $NHC(O)NR^{17}$, $OC(O)NR^{17}$, $C(O)NR^{17}$, $NR^{17}$, $CHR^{18}$, or cyclic group that is unsubstituted or substituted, or Z together with $L^1$ forms a heterocycle; each of $R^1$ and $R^2$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring; each of $R^3$ and $R^4$ is independently alkyl, alkenyl, alkynyl, an acyl group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; each of $R^5$, $R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$, and $R^{12}$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an

acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H; each of $R^{13}$ and $R^{14}$ is independently alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^{13}$ and $R^{14}$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted; each of $R^{15}$ and $R^{16}$ is independently alkyl, alkenyl, alkynyl, an acyl group, an ether group, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^{15}$ and $R^{16}$ together with the atoms to which they are bound form a ring that is substituted or unsubstituted; $R^{17}$ is alkyl, alkenyl, an acyl group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or H; and $R^{18}$ is $(C_3\text{-}C_{10})$-alkyl, $(C_3\text{-}C_{10})$-alkenyl, hydroxyl, $CH_2O$(aryl), $CH_2CH_2O$(aryl), alkoxy, a carboxylic acid group, a carboxaldehyde group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, or halogen, wherein when $X^1$ is N, $X^3$ is CH, $R^1$ and $R^2$ together with the atoms to which they are bound form a mono-substituted aromatic six-membered carbocycle, and RING SYSTEM is a quinoline moiety that is substituted or unsubstituted or an isoquinoline moiety that is substituted or unsubstituted, then Z is not arylene or a 3,5-disubstituted piperidine group, and $R^{17}$ is not H, methyl, $CH_2$(aryl) or monosubstituted ethyl wherein the monosubstitution is with a heteroatom or aryl, or a pharmaceutically-acceptable salt or tautomer thereof.

**[00295]** Embodiment 2. The compound of embodiment 1, wherein the compound possesses an axis of rotational symmetry at Z.

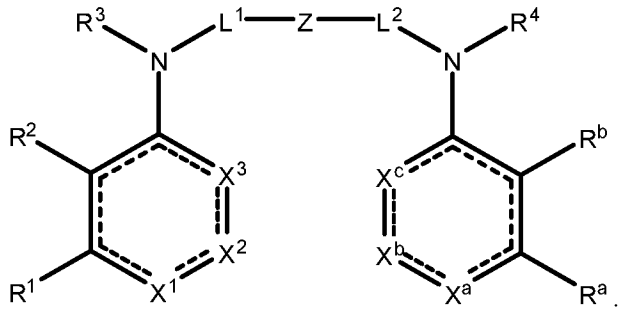
**[00296]** Embodiment 3. The compound of any one of embodiments 1 and 2, wherein the compound possesses a plane symmetry perpendicular to Z.

**[00297]** Embodiment 4. The compound of any one of embodiments 1-3, wherein the compound has the formula:



wherein: $X^a$ is $CR^c$, $CR^cR^d$, N, $NR^c$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$; $X^b$ is $CR^e$, $CR^eR^f$, N, $NR^e$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$; $X^c$ is $CR^g$, $CR^gR^h$, N, $NR^g$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$; $X^d$ is $CR^i$, $CR^iR^j$, N, $NR^i$, O, S, C=O, C=S, or a carbon atom connected to $Q^2$, wherein one of $X^a$, $X^b$, $X^c$, and $X^d$ is a carbon atom connected to $Q^2$; each of $R^a$ and $R^b$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H, or $R^a$ and $R^b$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring; and each of $R^c$, $R^d$, $R^e$, $R^f$, $R^g$, $R^h$, $R^i$, and $R^j$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl, nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H.

**[00298]** Embodiment 5. The compound of any one of embodiments 1-4, wherein the compound has the formula:



**[00299]** Embodiment 6. The compound of any one of embodiments 1-5, wherein: $X^1$ is $CR^5$, N, or $NR^5$; $X^2$ is $CR^7$, N, C=O, or C=S; $X^3$ is $CR^9$, N, or $NR^9$; $X^a$ is $CR^c$, N, or $NR^c$; $X^b$ is $CR^e$, N, C=O, or C=S; $X^c$ is $CR^g$, N, or $NR^g$; $L^1$ is an alkylene group or a heteroalkylene group; $L^2$ is an alkylene group or a bond; Z is C=O, C(O)O, $C(O)NR^{17}$, $NR^{17}$, $CHR^{18}$, or a cyclic group that is unsubstituted or substituted and is connected to $L^1$ and $L^2$ such that $L^1$ and $L^2$ possess a 1,1- or 1,2-configuration on Z; $R^1$ and $R^2$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring; each of $R^3$ and $R^4$ is independently alkyl, an acyl group, arylalkyl, heterocyclylalkyl, heteroarylalkyl, or H; $R^{17}$ is alkyl, alkenyl, an acyl group, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl, or H; and $R^{18}$ is $(C_3$-$C_{10})$-alkyl, $(C_3$-$C_{10})$-alkenyl, hydroxyl, $CH_2O$(aryl), $CH_2CH_2O$(aryl), an amine group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

**[00300]** Embodiment 7. The compound of any one of embodiments 1-6, wherein: $X^1$ is $CR^5$ or N; $X^2$ is $CR^7$; $X^3$ is $CR^9$ or N; $X^a$ is $CR^c$ or N; $X^b$ is $CR^e$; $X^c$ is $CR^g$ or N; $L^2$ is an unsubstituted alkylene group or a bond; each of $R^3$ and $R^4$ is independently alkyl, an acyl group, arylalkyl, heterocyclylalkyl, heteroarylalkyl, or H; and each of $R^5$, $R^7$, $R^9$, $R^c$, $R^e$, and $R^g$ is independently alkyl, an alkoxy group, halogen, hydroxyl, or H.

**[00301]** Embodiment 8. The compound of any one of embodiments 4-7, wherein $R^a$ and $R^b$ together with the atoms to which they are bound form a ring that is substituted on at least one carbon atom of the ring.

**[00302]** Embodiment 9. The compound of any one of embodiments 1-8, wherein: $L^2$ is methylene, ethylene, or a bond; each of $R^3$ and $R^4$ is independently alkyl, an acyl group, or H; and each of $R^5$, $R^7$, $R^9$, $R^c$, $R^e$, and $R^g$ is independently alkyl or H.

**[00303]** Embodiment 10. The compound of any one of embodiments 1-9, wherein: Z is C=O, $NR^{17}$, $CHR^{18}$, or a cyclic group that is unsubstituted or substituted and is connected

to $L^1$ and $L^2$ such that $L^1$ and $L^2$ possess a 1,1- or 1,2-configuration on Z; $R^{17}$ is alkyl, an acyl group, or heteroaryl; and $R^{18}$ is $CH_2O$(heteroaryl), $CH_2CH_2O$(heteroaryl) or an amine group.

**[00304]** Embodiment 11. The compound of any one of embodiments 1-10, wherein Z is NMe.

**[00305]** Embodiment 12. The compound of any one of embodiments 1-11, wherein: $X^1$ is N; $X^2$ is CH or C(alkyl); $X^3$ is CH or C(alkyl); $X^a$ is N; $X^b$ is CH or C(alkyl); and $X^c$ is CH or C(alkyl).

**[00306]** Embodiment 13. The compound of any one of embodiments 1-11, wherein: $X^1$ is CH or C(alkyl); $X^2$ is CH or C(alkyl); $X^3$ is N; $X^a$ is CH or C(alkyl); $X^b$ is CH or C(alkyl); and $X^c$ is N.

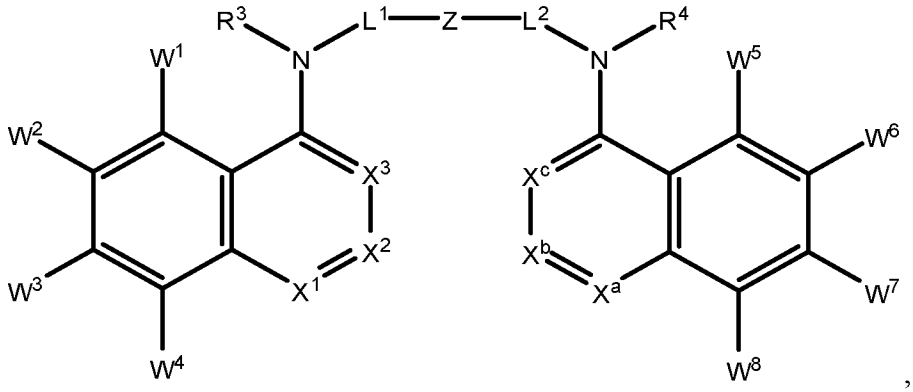
**[00307]** Embodiment 14. The compound of any one of embodiments 1-11, wherein: $X^1$ is N; $X^2$ is CH or C(alkyl); $X^3$ is N; $X^a$ is N; $X^b$ is CH or C(alkyl); and $X^c$ is N.

**[00308]** Embodiment 15. The compound of any one of embodiments 1-11, wherein: $X^1$ is N; $X^2$ is CH; $X^3$ is CH; $X^a$ is N; $X^b$ is CH; and $X^c$ is CH.

**[00309]** Embodiment 16. The compound of any one of embodiments 1-11, wherein: $X^1$ is CH; $X^2$ is CH; $X^3$ is N; $X^a$ is CH; $X^b$ is CH; and $X^c$ is N.

**[00310]** Embodiment 17. The compound of any one of embodiments 1-11, wherein: $X^1$ is N; $X^2$ is CH; $X^3$ is N; $X^a$ is N; $X^b$ is CH; and $X^c$ is N.

**[00311]** Embodiment 18. The compound of any one of embodiments 1-17, wherein the compound has the formula:




,

wherein: each of $W^1$, $W^2$, $W^3$, $W^4$, $W^5$, $W^6$, $W^7$, and $W^8$ is independently alkyl, alkenyl, alkynyl, an alkoxy group, an acyl group, an acyloxy group, an ether group, a carboxylic acid group, a carboxaldehyde group, an imine group, an ester group, an amine group, an amide group, a carbonate group, a carbamate group, a thioether group, a thioester group, a thioacid group, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, any of which is substituted or unsubstituted, halogen, hydroxyl, sulfhydryl,

nitro, nitroso, cyano, azido, a sulfoxide group, a sulfone group, a sulfonamide group, a sulfonic acid group, or H.

**[00312]** Embodiment 19. The compound of embodiment 18, wherein each of $W^1$, $W^2$, $W^3$, $W^4$, $W^5$, $W^6$, $W^7$, and $W^8$ is independently alkyl, F, Cl, hydroxyl, or H.

**[00313]** Embodiment 20. The compound of embodiment 19, wherein each of $W^1$, $W^2$, $W^4$, $W^5$, $W^6$, and $W^8$ is H.

**[00314]** Embodiment 21. The compound of any one of embodiments 18-20, wherein $W^3$ and $W^7$ are both F.

**[00315]** Embodiment 22. The compound of any one of embodiments 18-20, wherein $W^3$ and $W^7$ are both Cl.

**[00316]** Embodiment 23. A pharmaceutical composition comprising, in unit dosage form: a) a therapeutically-effective amount of a compound of any one of embodiments 1-22; and b) a pharmaceutically-acceptable excipient.

**[00317]** Embodiment 24. The pharmaceutical composition of embodiment 23, wherein the therapeutically-effective amount is from about 10 mg to about 1000 mg.

**[00318]** Embodiment 25. The pharmaceutical composition of any one of embodiments 23-24, further comprising an anti-malarial agent.

**[00319]** Embodiment 26. The pharmaceutical composition of any one of embodiments 23-25, further comprising an anti-cancer therapeutic.

**[00320]** Embodiment 27. A method of treating a condition, the method comprising administering to a subject in need thereof a therapeutically-effective amount of a compound of any one of claims 1-22.

**[00321]** Embodiment 28. The method of embodiment 27, wherein the compound inhibits autophagy in a cell of the subject.

**[00322]** Embodiment 29. The method of any one of embodiments 27-28, wherein the condition is cancer.

**[00323]** Embodiment 30. The method of any one of embodiments 27-28, wherein the condition is caused by a parasitic protozoan.

**[00324]** Embodiment 31. The method of any one of embodiments 27-28, wherein the condition is malaria.

**[00325]** Embodiment 32. The method of any one of embodiments 27-31, wherein the administration is oral.

**[00326]** Embodiment 33. The method of any one of embodiments 27-31, wherein the administration is intravenous.

**[00327]** Embodiment 34. The method of any one of embodiments 27-31, wherein the administration is subcutaneous.

**[00328]** Embodiment 35. The method of any one of embodiments 27-31, wherein the administration is intratumoral.

**[00329]** Embodiment 36. The method of any one of embodiments 27-35, wherein the therapeutically-effective amount is from about 10 mg to about 1000 mg.

**[00330]** Embodiment 37. The method of any one of embodiments 27-36, the method further comprising administration of an anti-malarial agent.

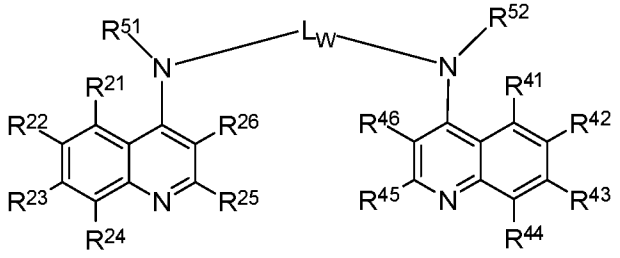
**[00331]** Embodiment 38. The method of any one of embodiments 27-37, the method further comprising administration of an anti-cancer therapeutic.

**[00332]** Embodiment 39. The method of any one of embodiments 27-38, wherein the subject is human.

## CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by a structure of Formula (XX):




(XX),

or a salt thereof, wherein:

$R^{21}$, $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{43}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, halogen, hydroxyl, nitro, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted;

$R^{51}$ and $R^{52}$ are independently selected from hydrogen and optionally substituted alkyl; and

$L_W$ is an optionally substituted heterocycle or an optionally substituted carbocycle; or an optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted heteroalkylene, each one of which is interrupted by an optionally substituted heterocycle.

2. The compound or salt of claim 1, wherein $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen and halogen.

3. The compound or salt of claim 2, wherein $R^{21}$, $R^{22}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently hydrogen.

4. The compound or salt of claims 1-3, wherein $R^{23}$ and $R^{43}$ are independently selected from hydrogen, halogen, hydroxyl, and haloalkyl.

5. The compound or salt of claim 4, wherein $R^{23}$ and $R^{43}$ are independently selected from F, Cl, Br, and I.

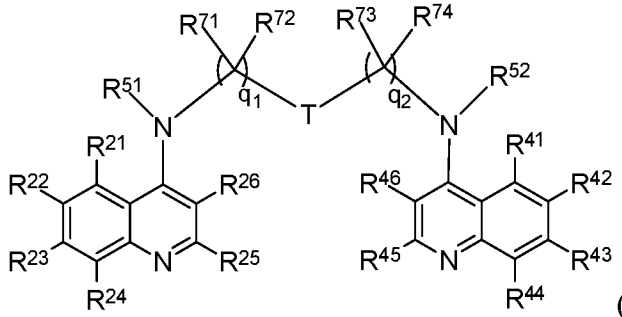
6. The compound or salt of claim 5, wherein $R^{23}$ and $R^{43}$ are independently selected from F and Cl.

7. The compound or salt of any of claims 1-6, wherein $R^{51}$ and $R^{52}$ are independently hydrogen.

8. The compound or salt of any of claims 1-7, wherein $L_W$ is optionally substituted alkylene interrupted by an optionally substituted heterocycle.

9. The compound or salt of any of claims 1-8, wherein the optionally substituted alkylene of $L_W$ comprises 1-12 carbon atoms.

10. The compound or salt of any of claims 1-9, represented by Formula (XXA):



(XXA),

wherein:

$q_1$ is 0-5;

$q_2$ is 0-5;

$R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ are independently selected from hydrogen, halogen, hydroxyl, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted; and

T is optionally substituted heterocycle.

11. The compound or salt of claim 10, wherein each occurrence of $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ is independently selected from hydrogen, halogen, hydroxyl, cyano and optionally substituted alkyl.

12. The compound or salt of claim 11, wherein $R^{71}$, $R^{72}$, $R^{73}$, and $R^{74}$ are independently hydrogen.

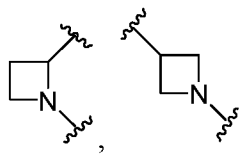
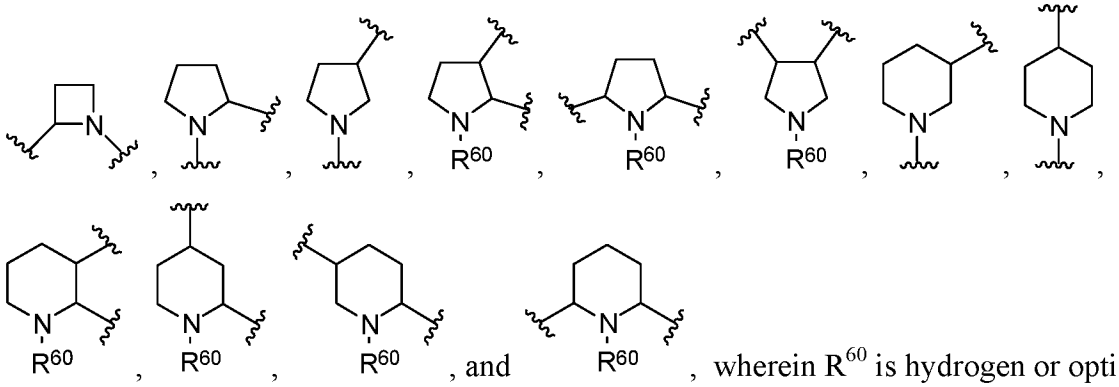
13. The compound or salt of claim 10, wherein $q_1$ is 1-3 and $q_2$ is 1-3.

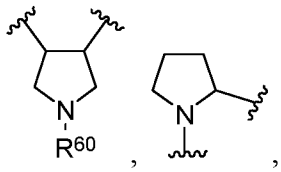
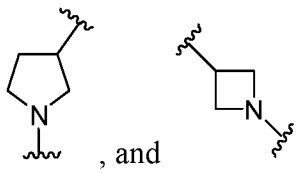
14. The compound or salt of claim 13, wherein $q_1$ is 2 and $q_2$ is 2; or $q_1$ is 2 and $q_2$ is 3; or $q_1$ is 1 and $q_2$ is 3.

15. The compound or salt of claim 10, wherein T is optionally substituted 3- to 7-membered heterocycle.

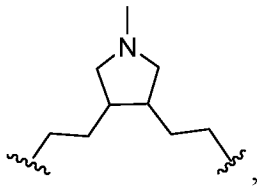
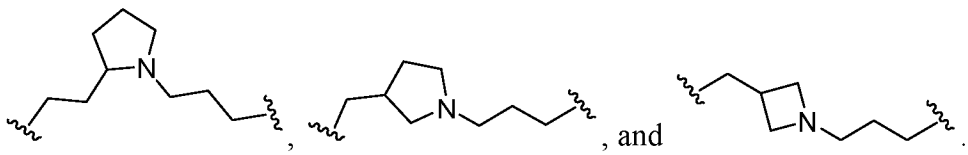
16. The compound or salt of claim 15, wherein T is optionally substituted saturated 3- to 7-membered heterocycle.

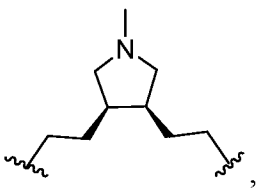
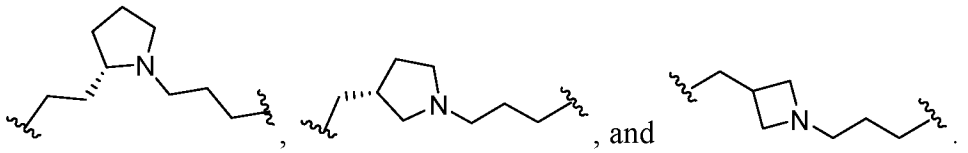
17. The compound or salt of claim 16, wherein T is selected from piperidine, pyrrolidine, and azetidine, any of which is optionally substituted.

18. The compound or salt of claim 10, wherein T is selected from  ,  , and , wherein $R^{60}$ is hydrogen or optionally substituted alkyl.

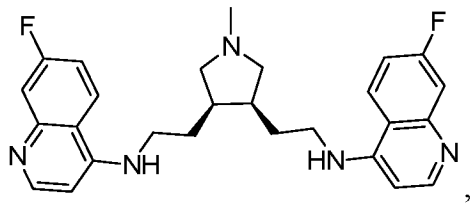
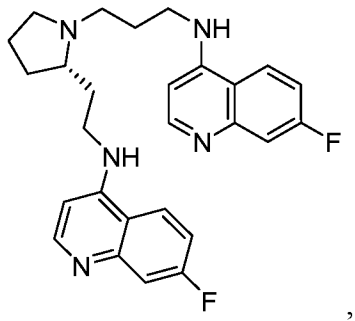
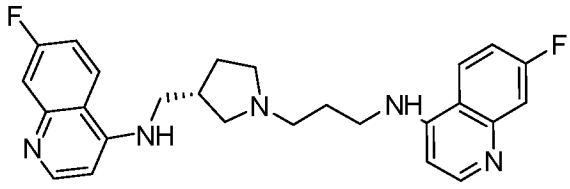
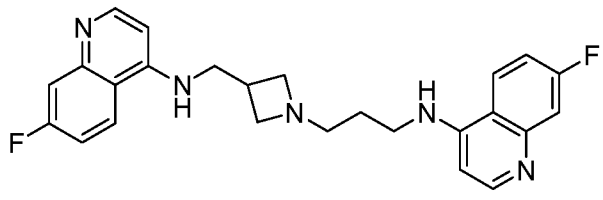
19. The compound or salt of claim 18, wherein T is selected from  ,  , and .

20. The compound or salt of claim 18, wherein $R^{60}$ is optionally substituted alkyl.

21. The compound or salt of claim 19, wherein $L_W$ is selected from  ,  , and .

22. The compound or salt of claim 21, wherein $L_W$ is selected from  ,  , and .

23. The compound of any of the preceding claims, wherein when a group is optionally substituted, the optional substituents are selected at each occurrence from: halogen, hydroxy, oxo (=O), thioxo (=S), cyano (-CN), nitro ($-NO_2$), imino (=N-H), oximo (=N-OH), $-R^n-OR^m$, $-R^n-OC(O)-R^m$, $-R^n-OC(O)-OR^m$, $-R^n-OC(O)-N(R^m)_2$, $-R^n-N(R^m)_2$, $-R^n-C(O)R^m$, $-R^n-C(O)OR^m$, $-R^n-C(O)N(R^m)_2$, $-R^n-O-R^p-C(O)N(R^m)_2$, $-R^n-N(R^m)C(O)OR^m$, $-R^n-N(R^m)C(O)R^m$, $-R^n-N(R^m)S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tR^m$ (where t is 1 or 2), $-R^n-S(O)_tOR^m$ (where t is 1 or 2), and $-R^n-S(O)_tN(R^m)_2$ (where t is 1 or 2); and alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, and heteroaryl, any of which may be optionally substituted by alkyl, alkenyl, alkynyl, halogen, haloalkyl, haloalkenyl, haloalkynyl, oxo (=O), thioxo (=S), cyano (-CN), and nitro ($-NO_2$); wherein each $R^m$ is independently selected from hydrogen, alkyl, cycloalkyl, aryl, and heteroaryl, wherein each $R^m$, valence permitting, may be optionally substituted with halogen, oxo (=O), thioxo (=S), cyano (-CN), and nitro ($-NO_2$); and wherein each $R^n$ is independently selected from a direct bond or a straight or branched alkylene, alkenylene, or alkynylene chain, and each $R^p$ a straight or branched alkylene, alkenylene or alkynylene chain.

24. The compound or salt of any of claims 1-23, wherein the compound is represented by any one of the following formula:  ,  ,  , or  or a salt thereof.

25. A pharmaceutical composition comprising a compound or salt of any of claims 1-24 and a pharmaceutically acceptable excipient.

26. The compound or salt of any of claims 1-24, wherein the compound or salt kills human A375 melanoma cells with an $IC_{50}$ value of less than about 10 μM.

27. The compound or salt of any of claims 1-24, wherein the compound or salt does not inhibit hERG channel activity.

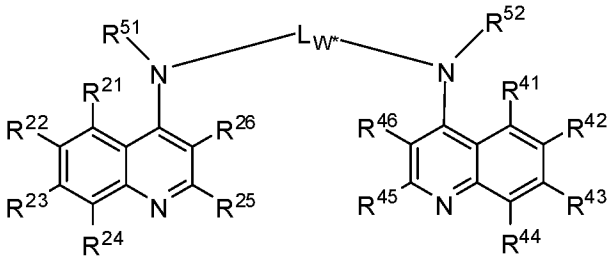
28. The compound or salt of any of claims 1-24, wherein the compound or salt exhibits a hERG $IC_{50}$ value of about 10 μM or more.

29. The compound or salt of claim 28, wherein the ratio of hERG $IC_{50}$ value to the cytotoxicity $IC_{50}$ value is about 5 or more.

30. A method of inducing autophagosomal aggregation, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or salt of any of claims 1-24.

31. A method of inhibiting autophagy in tumor cells, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or salt of any of claims 1-24.

32. A method of inhibiting autophagy in tumor cells, comprising administering to a patient in need thereof a therapeutically effective amount of a compound represented by a structure of Formula (XXI):



(XXI),

or a salt thereof, wherein:

$R^{21}$, $R^{22}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{41}$, $R^{42}$, $R^{43}$, $R^{44}$, $R^{45}$, and $R^{46}$ are independently selected from hydrogen, halogen, hydroxyl, nitro, cyano; alkyl, alkoxy, and amine, any of which is optionally substituted;

$R^{51}$ and $R^{52}$ are independently selected from hydrogen and optionally substituted alkyl; and

$L_{W*}$ is optionally substituted carbocycle or optionally substituted heterocycle; optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, or optionally substituted heteroalkylene, each of which is interrupted by an optionally substituted carbocycle or an optionally substituted heterocycle.