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(54) Title: COMPOUNDS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

(57) Abstract: In one aspect, the invention relates to NMDA receptor modulators, derivatives thereof, and related compounds, which are useful as inhibitors of the NMDA receptor; synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of treating or preventing neurological and psychiatric disorders associated with NMDA receptor dysfunction using the compounds and compositions. This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

COMPOUNDS FOR THE TREATMENT OF NEUROLOGICAL DISORDERS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This Application claims the benefit of U.S. Provisional Application No. 61/645,040, filed on March 9, 2013, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Neurological disorders are disorders that affect the nervous system. They can be categorized according to the structure or primary location affected, the nature of the dysfunction, or the primary cause (e.g., genetic disorder, injury, infection). Some neurologic disorders, like Parkinson's disease and stroke, are well-known, while others are very rare. One recent study by the World Health Organization (WHO) found that neurologic disorders account for almost 11% of total global disease burden worldwide. Collectively, the burden of neurologic disorders is hard to overstate, and include direct health care costs, disability, quality of life, and lost productivity. Alzheimer's disease alone drains more than $148 billion from the U.S. economy each year. The burden of neurologic disorder is expected to increase on a global basis, as demographic changes in the world's most populous countries will result in a significant increase in the number of persons with neurodegenerative diseases over the next few decades.

[0003] Glutamate (L-glutamic acid) is the principal excitatory neurotransmitter in the mammalian central nervous system, exerting its effects through both ionotropic and metabotropic glutamate receptors (*Br. J. Pharmacol.* 2009, 157:1301). The ionotropic glutamate receptors (iGluRs) comprise three receptor families: NMDA (*N*-methyl-D-aspartate), AMPA (2-amino-3-(methyl-3-hydroxyisoxazol-4-yl)propanoic acid), and kainate receptors. Ionotropic glutamate receptors form ligand-gated ion channels in the plasma membranes of neuronal cells, and mediate excitatory synaptic transmission in the central nervous system. Upon binding, a neurotransmitter or agonist ligand induces activation of the receptor and opening of the ion channel, allowing the flow of ions across the cell membrane (*Br. J. Pharmacol.* 2009, 157:1301, *Pharmacol. Rev.* 2010, 62:405, *Nature* 1987, 325:529).

[0004] The NMDA subtype of glutamate-gated ion channels comprise heterotetrametric assemblies composed of combinations of two or more of the three subunit subtypes, GluN1, GluN2 (A, B, C, and D), and GluN3 (A and B). Additionally, genes that encode for certain subunits of ionotropic glutamate receptors can undergo alternative splicing (*e.g.* GluN1-1a, GluN1-1b, GluN1-2a, GluN1-2b, GluN1-3a, GluN1-3b, GluN1-4a, and GluN1-4b) to generate diverse subunit compositions, which are critical in determining biological and

pharmacological properties of the NMDA receptor. Moreover, a functional channel requires the co-expression of at least one GluN1 subunit and one or more GluN2 subunits. Generally, this results in a NMDA receptor comprising a tetramer with two GluN1 and two identical or different GluN2 subunits. In rare cases, cells express the GluN3 subunit, which co-assembles with GluN1 or GluN1 and GluN2 to form GluN1–GluN3 or GluN1–GluN2–GluN3 tetrameric complexes (*Pharmacol. Rev.* 2010, 62:405). While GluN1 subunits are expressed virtually uniformally in all neurons and at all developmental stages, the GluN2 subunits exhibit different regional distribution and developmental patterns, and can provide a more selective therapeutic target (*Neuron* 1994, 12:529).

[0005] NMDA receptor subunits share a common modular design, each representing a functional unit, including: the extracellular area containing two large bi-lobed domains, the amino terminal domain (ATD) and the ligand binding domain (LBD), which binds glycine in GluN1 and GluN3, and glutamate in GluN2, the membrane domain comprising three transmembrane segments and a re-entrant loop that forms the ion channel, and the C-terminal cytoplasmic domain. As a result, the NMDA receptor has multiple binding and regulatory sites in addition to an ion channel, which also contains several internal binding sites. To function, the NMDA receptor requires co-activation by the binding of a co-agonist, glycine or D-serine, at GluN1 subunits, in addition to glutamate binding on GluN2 subunits. At resting membrane potentials, NMDA conductance is markedly reduced due to a voltage-dependent block of the channel pore by magnesium ions. Depolarization releases this channel block and permits passage of calcium and monovalent ions such as sodium ions (*Curr. Opin. Pharmacol.* 2007, 7:39, *Trends Pharmacol. Sci.* 2011, 32:726). This highly modular organization of the extracellular, intracellular, and transmembrane domains can potentially provide numerous regulatory sites at various protein-protein interfaces to modulate NMDA receptor activity (*Pharmacol. Rev.* 2010, 62:405, *Mol. Pharm.* 2011, 80:782, *J. Pharmacol. Exp. Ther.* 2010, 3355: 614, *J. Med. Chem.* 2010, 53:5476).

[0006] Without wishing to be bound by a particular theory, NMDA receptors have been implicated in a myriad of biological functions in the nervous system, indicating a potential role for the NMDA receptor in a variety of disease processes in mammals (*Trends Pharmacol. Sci.* 2011, 32:726). Therefore, ligands of NMDA receptors can be used for the treatment or prevention of acute and/or chronic neurological and/or psychiatric disorders associated with glutamate dysfunction, such as chronic pain and neuropathic pain (*Neurotherapeutics: J. Am. Soc. Exp. Neurotherapeutics* 2009, 6:693), neurodegenerative disorders (*Exp. Opin. Drug Metab. Toxicol.* 2007, 3:135, *Pharmacol. Ther.* 2004, 102:155),

mood disorders (*Trends Pharmacol. Sci.* 2009, 30:563), ischemic or traumatic brain injury (*Steroids* 2011, 76:845), and the like. Further, without wishing to be bound by theory, evidence indicates NMDA receptors play an important role in lasting changes in synaptic transmission and synaptic plasticity, including an essential role in the induction of two forms of synaptic plasticity, such as long term potentiation (LTP) and long term depression (LTD) (*Cell* 1994, 78:535).

[0007] The identification of non-selective competitive antagonists and NMDA receptor channel blockers has greatly increased the understanding of the roles played by these receptors and their corresponding relation to disease. However, the widespread clinical use of these agents is limited by adverse side effects relating to motor and cognitive functions (*Curr. Opin. Pharmacol.* 2006, 6:53).

[0008] Selective noncompetitive allosteric modulators are compounds that do not directly act on receptors by themselves, but binding of these compounds modulates, positively or negatively, the response of the receptor to glutamate, glycine, or other orthosteric agonists by modulating the affinity of an orthosteric agonist at the orthosteric binding site, or by modifying other conformational states of the receptor affecting channel function. Selective noncompetitive allosteric modulators are thus an attractive mechanism for regulating appropriate physiological receptor activation (*Curr. Opin. Pharmacol.* 2007, 7:39, *Mol. Pharm* 2011, 80:782, *J. Pharmacol. Exp. Ther.* 2010, 335:614, *J. Med. Chem.* 2010, 53:5476).

[0009] Unfortunately, there remains a need for therapeutic agents that act on the NMDA GluN2 receptors, but which have minimal adverse effects. Therefore, there remains a need for methods and compositions that provide efficacious and selective antagonists of the NMDA receptor. These needs and other needs are met by the present invention

SUMMARY

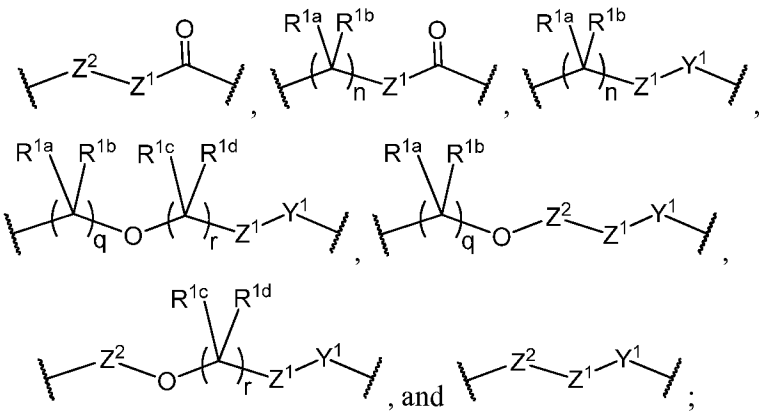
[0010] In accordance with the purpose(s) of the invention, as embodied and broadly described herein, the invention, in one aspect, relates to compounds useful as modulators (*i.e.*, inhibitors) of the NMDA receptor, methods of making same, pharmaceutical compositions comprising same, and methods of treating neurological and psychiatric disorders associated with glutamate dysfunction using same.

[0011] Disclosed are compounds having a structure represented by a formula::

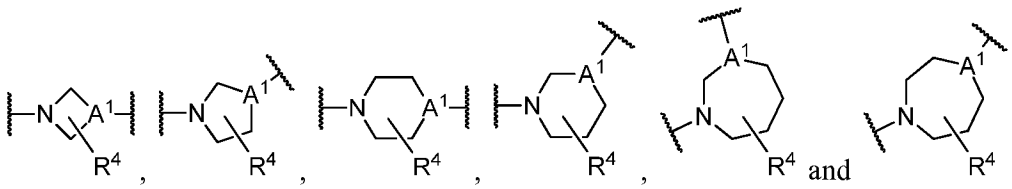
$$Ar^1—L—Ar^2,$$

wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-

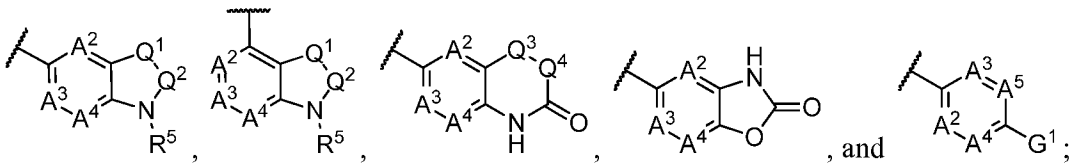
C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein L is selected from:



wherein each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein m is an integer from 1-3; wherein n is an integer from 1-4; wherein q is an integer from 0-1; wherein r is an integer from 0-1; wherein Y^1, when present, is selected from —O— and —$CR^{2a}R^{2b}$—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1, when present, is a 4- to 7-membered hetercycloalkyl selected from:



wherein A^1 is N or CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein Ar^2 is selected from:



wherein A^2 is selected from N and CR^{6a}; wherein A^3, when present, is selected from N and CR^{6b}; and wherein A^4, when present, is selected from N and CR^{6c}; and wherein A^5, when

present, is selected from N and CR^{6d}; wherein each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein Q^1, when present, is selected from $—CR^{7a}=$, $—CR^{7a}R^{7b}—$, —O—, —S—, —N=, $—NR^{8a}—$, and (C=O); wherein Q^2, when present, is selected from =N—, $=CR^{7c}—$, $—NR^{8b}—$, (C=NH), (S=O), (SO_2), (C=S), and (C=O); provided that Q^1 and Q^2 are not simultaneously (C=O); wherein Q^3, when present, is selected from $—CR^{7a}=$, $—CR^{7a}R^{7b}—$, —O—, —S—, —N=, $—NR^{8a}—$, and $—NR^{8a}—$; wherein Q^4, when present, is selected from $=CR^{7c}—$, $—CR^{7c}R^{7d}—$, —O—, —S—, $—NR^{8b}—$, and (C=O); provided that Q^3 and Q^4 are not simultaneously $—NR^{8a}—$ and $—NR^{8b}—$, respectively, or that or Q^3 and Q^4 are not simultaneously —O— or —S—; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{8a} and R^{8b}, when present is independently selected from hydrogen and C1-C8 alkyl; wherein G^1, when present, is selected from —OH, $—NHR^9$, $—NH(C1\text{-}C6\ alkyl)NR^{10a}R^{10b}$, $—OR^9$, $—NH(C=O)R^9$; $—NH(C=O)OR^9$; and $—NH(C=O)NR^{10a}R^{10b}$; wherein each of R^9, when present, is selected from C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl; wherein each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl; or a pharmaceutically acceptable salt, solvate, or polymorph thereof.

[0012] Also disclosed are pharmaceutical compositions comprising an effective amount of at least one disclosed compound, a product of a disclosed method of making, or pharmaceutically acceptable salt, solvate, or polymorph thereof, and a pharmaceutically acceptable carrier.

[0013] Also disclosed are methods for manufacturing a medicament comprising combining at least one disclosed compound, or a product of a disclosed method of making, with a pharmaceutically acceptable carrier or diluent. Additionally, the invention relates to a compound as defined herein, or pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, for use as a medicament, and to a compound as defined herein for use in the treatment or in the prevention of neurological and psychiatric disorders and diseases.

[0014] Also disclosed are methods for the treatment of a neurological and/or psychiatric disorder associated with NMDA receptor function in a mammal comprising the step of administering to the mammal an effective amount of at least one disclosed compound, a

product of a disclosed method of making, or pharmaceutically acceptable salt, solvate, or polymorph thereof

[0015] Also disclosed are methods for inhibition of NMDA receptor activity in a mammal comprising the step of administering to the mammal an effective amount of at least one disclosed compound, a product of a disclosed method of making, or pharmaceutically acceptable salt, solvate, or polymorph thereof.

[0016] Also disclosed are methods for inhibition of NMDA receptor activity in at least one cell comprising the step of contacting the cell with an effective amount of at least one disclosed compound, a product of a disclosed method of making, or pharmaceutically acceptable salt, solvate, or polymorph thereof.

[0017] Also disclosed are methods for modulating NMDA activity in a mammal comprising the step of administering to the mammal an effective amount of at least one disclosed compound or pharmaceutically acceptable salt, solvate, or polymorph thereof.

[0018] Also disclosed are kits of at least one disclosed compound, a product of a disclosed method of making, or a pharmaceutically acceptable salt, hydrate, solvate or polymorph thereof, and one or more of: (a) at least one agent known to increase NMDA receptor activity; (b) at least one agent known to decrease NMDA receptor activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; (d) instructions for treating a disorder associated with NMDA receptor activity; or (e) instructions for administering the compound in connection with treating a neurological and/or psychiatric disorder.

[0019] Additionally, the invention also relates to a product comprising a compound as described herein and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of neurological and psychiatric disorders and diseases.

[0020] Also disclosed are uses of a disclosed compound, a disclosed product of a disclosed method of making, or pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal.

[0021] While aspects of the present invention can be described and claimed in a particular statutory class, such as the system statutory class, this is for convenience only and one of skill in the art will understand that each aspect of the present invention can be described and claimed in any statutory class. Unless otherwise expressly stated, it is in no way intended that any method or aspect set forth herein be construed as requiring that its

steps be performed in a specific order. Accordingly, where a method claim does not specifically state in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, or the number or type of aspects described in the specification.

[0022] Additional advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or can be learned by practice of the invention. The advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DESCRIPTION

[0023] The present invention can be understood more readily by reference to the following detailed description of the invention and the Examples included therein.

[0024] Before the present compounds, compositions, articles, systems, devices, and/or methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

[0025] All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

A. DEFINITIONS

[0026] As used herein, nomenclature for compounds, including organic compounds, can be given using common names, IUPAC, IUBMB, or CAS recommendations for nomenclature. When one or more stereochemical features are present, Cahn-Ingold-Prelog

rules for stereochemistry can be employed to designate stereochemical priority, *E*/*Z* specification, and the like. One of skill in the art can readily ascertain the structure of a compound if given a name, either by systemic reduction of the compound structure using naming conventions, or by commercially available software, such as CHEMDRAW™ (Cambridgesoft Corporation, U.S.A.).

[0027] As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a functional group," "an alkyl," or "a residue" includes mixtures of two or more such functional groups, alkyls, or residues, and the like.

[0028] Ranges can be expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. It is also understood that there are a number of values disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0029] References in the specification and concluding claims to parts by weight of a particular element or component in a composition denotes the weight relationship between the element or component and any other elements or components in the composition or article for which a part by weight is expressed. Thus, in a compound containing 2 parts by weight of component X and 5 parts by weight component Y, X and Y are present at a weight ratio of 2:5, and are present in such ratio regardless of whether additional components are contained in the compound.

[0030] A weight percent (wt. %) of a component, unless specifically stated to the contrary, is based on the total weight of the formulation or composition in which the component is included.

[0031] As used herein, the terms "optional" or "optionally" means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

[0032] As used herein, the term "allosteric site" refers to a ligand binding site that is topographically distinct from the orthosteric binding site.

[0033] As used herein, the term "modulator" refers to a molecular entity (e.g., but not limited to, a ligand and a disclosed compound) that modulates the activity of the target receptor protein.

[0034] As used herein, the term "ligand" refers to a natural or synthetic molecular entity that is capable of associating or binding to a receptor to form a complex and mediate, prevent or modify a biological effect. Thus, the term "ligand" encompasses allosteric modulators, inhibitors, activators, agonists, antagonists, natural substrates and analogs of natural substrates.

[0035] As used herein, the terms "natural ligand" and "endogenous ligand" are used interchangeably, and refer to a naturally occurring ligand, found in nature, which binds to a receptor.

[0036] As used herein, the terms "GluN2B", "NR2B", "NR2B-containing NMDA receptor", "2B" and "NMDA receptor subunit GluN2B", are used interchangeably, and refer to the presence of a specific NMDA receptor subunit subtype within a tetrameric NMDA complex (e.g. GluN1/GluN2B/GluN2/GluN2B). Thus, the terms "GluN2B", "NR2B", "NR2B-containing NMDA receptor", "2B", and "NMDA receptor subunit GluN2B" describe a tetrameric NMDA complex comprising GluN1 and GluN2B, unless stated otherwise. In this context, GluN2A can be used interchangeably with NR2A, GluN2D with NR2D, GluN2C with NR2C, GluN3A with NR3A, GluN3B with NR3B, and GluN1 with NR1.

[0037] As used herein, the term "orthosteric site" refers to the primary binding site on a receptor that is recognized by the endogenous ligand or agonist for that receptor. For example, the orthosteric site in the NMDA GluN2 receptor is the site that glutamate binds.

[0038] As used herein, the term "NMDA receptor antagonist" refers to any exogenously administered compound or agent that is capable of partially or completely inhibiting, or reversing, the effect of an agonist (e.g. glutamate and/or glycine) on the NMDA receptor. The term is inclusive of compounds or agents characterized or described as antagonists, noncompetitive antagonists, uncompetitive antagonists, partial antagonists, and negative allosteric modulators. For example, NMDA receptor antagonists can mediate their effects by binding to the orthosteric site or to allosteric sites on receptors, or they may interact at unique binding sites not normally involved in the biological regulation of the receptor's activity. Thus, a NMDA receptor antagonist directly or indirectly inhibits the activity of the NMDA receptor in the presence or in the absence of glutamate, glycine or another agonist, in an

animal, in particular a mammal, for example a human. It is understood that a NMDA receptor antagonist is a type of compound or agent that does not provoke a biological response itself upon binding to the NMDA receptor, but blocks or dampens agonist-mediated responses. Thus, NMDA receptor antagonists have affinity but no efficacy for their cognate receptors, and binding of a NMDA receptor antagonist will disrupt the interaction of the endogenous ligand, an agonist or inverse agonist with NMDA receptors, and thus, inhibit their response to such activators. In various aspects, a NMDA receptor antagonist decreases the activity of the NMDA receptor in a cell in the presence of extracellular glutamate. The cell can be a Xenopus oocyte injected with cRNA for human NMDA receptor, e.g., GluN1 and/or GluN2. The cell can be a Xenopus oocyte injected with cRNA for rat NMDA receptor, e.g., GluN1 and/or GluN2. The cell can be a Xenopus oocyte injected with cRNA for mammalian NMDA receptor, e.g., GluN1 and/or GluN2. The compound that is a "NMDA receptor antagonist" includes a compound that is a "NMDA receptor competitive antagonist," a "NMDA receptor noncompetitive antagonist," a "NMDA receptor partial antagonist," a "NMDA receptor uncompetitive antagonist," and a "NMDA receptor negative allosteric modulator."

[0039] As used herein, the term "NMDA receptor competitive antagonist" refers to any exogenously administered compound or agent that is capable of binding to the orthosteric site of NMDA receptors without activating the receptor. Thus, a competitive antagonist can interact with a NMDA receptor and compete with an endogenous ligand, glutamate and/or glycine, for binding to the receptor and decrease the ability of the receptor to conduct ions and/or transduce an intracellular signal in response to endogenous ligand binding.

[0040] As used herein, the term "NMDA receptor non-competitive antagonist" refers to any exogenously administered compound or agent that binds to site that is not the orthosteric binding site of NMDA receptors, and is capable of partially or completely inhibiting, or reversing, the effect of an agonist (e.g. glutamate and/or glycine) on the NMDA receptor. Thus, a non-competitive antagonist can interact with a NMDA receptor and decrease the binding of an endogenous ligand, e.g. glutamate and/or glycine, to the receptor and/or decrease the ability of the receptor to conduct ions and/or transduce an intracellular signal in response to endogenous ligand binding.

[0041] As used herein, the term "NMDA partial antagonist" refers to any exogenously administered compound or agent that can bind to an orthosteric or an allosteric site, but the effect of binding is to only partially block effect of NMDA receptor response to an agonist, e.g. glutamate and/ or glycine. Thus, a non-competitive antagonist can interact with a

NMDA receptor, but is not capable of fully inhibiting the response of the NMDA receptor to an agonist, e.g. glutamate and/ or glycine.

[0042] As used herein, the term "NMDA negative allosteric modulator" refers to any exogenously administered compound or agent that directly or indirectly inhibits the activity of the NMDA receptor in the presence of glutamate and/or glycine, or another agonist, in an animal, in particular a mammal, for example a human. For example, while not intended to be limiting towards the present invention, a selective NMDA negative allosteric modulator can preferentially bind to the NMDA receptor GluN1 subunit, the GluN2 subunit, or both, and decrease NMDA receptor activity in the presence of glutamate by acting as a non-competitive antagonist. The cell can be a Xenopus oocyte injected with cRNA for human NMDA receptor, e.g., GluN1 and/or GluN2. The cell can be a Xenopus oocyte injected with cRNA for rat NMDA receptor, e.g., GluN1 and/or GluN2. The cell can be a Xenopus oocyte injected with cRNA for mammalian NMDA receptor, e.g., GluN1 and/or GluN2.

[0043] As used herein, the term "subject" can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. Thus, the subject of the herein disclosed methods can be a human, non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig or rodent. The term does not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. In one aspect, the subject is a mammal. A patient refers to a subject afflicted with a disease or disorder. The term "patient" includes human and veterinary subjects. In some aspects of the disclosed methods, the subject has been diagnosed with a need for treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for inhibition of NMDA receptor activity prior to the administering step. In some aspects of the disclosed method, the subject has been diagnosed with a need for partial inhibition of NMDA receptor activity prior to the administering step.

[0044] As used herein, the term "treatment" refers to the medical management of a patient with the intent to cure, ameliorate, stabilize, or prevent a disease, pathological condition, or disorder. This term includes active treatment, that is, treatment directed specifically toward the improvement of a disease, pathological condition, or disorder, and also includes causal treatment, that is, treatment directed toward removal of the cause of the associated disease, pathological condition, or disorder. In addition, this term includes palliative treatment, that is, treatment designed for the relief of symptoms rather than the curing of the disease, pathological condition, or disorder; preventative treatment, that is,

treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder; and supportive treatment, that is, treatment employed to supplement another specific therapy directed toward the improvement of the associated disease, pathological condition, or disorder. In various aspects, the term covers any treatment of a subject, including a mammal (e.g., a human), and includes: (i) preventing the disease from occurring in a subject that can be predisposed to the disease but has not yet been diagnosed as having it; (ii) inhibiting the disease, i.e., arresting its development; or (iii) relieving the disease, i.e., causing regression of the disease. In one aspect, the subject is a mammal such as a primate, and, in a further aspect, the subject is a human. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.).

[0045] As used herein, the term "prevent" or "preventing" refers to precluding, averting, obviating, forestalling, stopping, or hindering something from happening, especially by advance action. It is understood that where reduce, inhibit or prevent are used herein, unless specifically indicated otherwise, the use of the other two words is also expressly disclosed.

[0046] As used herein, the term "diagnosed" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by the compounds, compositions, or methods disclosed herein. For example, "diagnosed with a disorder treatable by modulation of NMDA" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by a compound or composition that can modulate NMDA. As a further example, "diagnosed with a need for modulation of NMDA" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition characterized by NMDA activity. Such a diagnosis can be in reference to a disorder, such as a neurodegenerative disease, and the like, as discussed herein. For example, the term "diagnosed with a need for inhibition of NMDA receptor activity" refers to having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by inhibition of NMDA receptor activity. For example, "diagnosed with a need for partial or uncompetative antagonism of NMDA receptor activity" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have a condition that can be diagnosed or treated by partial or uncompetative antagonism of NMDA receptor activity. For example, "diagnosed with a need for treatment of one or

more neurological and/or psychiatric disorders associated with glutamate dysfunction" means having been subjected to a physical examination by a person of skill, for example, a physician, and found to have one or more neurological and/or psychiatric disorder associated with glutamate dysfunction.

[0047] As used herein, the phrase "identified to be in need of treatment for a disorder," or the like, refers to selection of a subject based upon need for treatment of the disorder. For example, a subject can be identified as having a need for treatment of a disorder (e.g., a disorder related to NMDA receptor activity) based upon an earlier diagnosis by a person of skill and thereafter subjected to treatment for the disorder. It is contemplated that the identification can, in one aspect, be performed by a person different from the person making the diagnosis. It is also contemplated, in a further aspect, that the administration can be performed by one who subsequently performed the administration.

[0048] As used herein, the terms "administering" and "administration" refer to any method of providing a pharmaceutical preparation to a subject. Such methods are well known to those skilled in the art and include, but are not limited to, oral administration, transdermal administration, administration by inhalation, nasal administration, topical administration, intravaginal administration, ophthalmic administration, intraaural administration, intracerebral administration, rectal administration, sublingual administration, buccal administration, and parenteral administration, including injectable such as intravenous administration, intra-arterial administration, intramuscular administration, and subcutaneous administration. Administration can be continuous or intermittent. In various aspects, a preparation can be administered therapeutically; that is, administered to treat an existing disease or condition. In further various aspects, a preparation can be administered prophylactically; that is, administered for prevention of a disease or condition.

[0049] The term "contacting" as used herein refers to bringing a disclosed compound and a cell, target NMDA glutamate receptor, or other biological entity together in such a manner that the compound can affect the activity of the target (e.g., spliceosome, cell, etc.), either directly; i.e., by interacting with the target itself, or indirectly; i.e., by interacting with another molecule, co-factor, factor, or protein on which the activity of the target is dependent.

[0050] As used herein, the terms "effective amount" and "amount effective" refer to an amount that is sufficient to achieve the desired result or to have an effect on an undesired condition. For example, a "therapeutically effective amount" refers to an amount that is sufficient to achieve the desired therapeutic result or to have an effect on undesired symptoms, but is generally insufficient to cause adverse side effects. The specific

therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the route of administration; the rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of a compound at levels lower than those required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved. If desired, the effective daily dose can be divided into multiple doses for purposes of administration. Consequently, single dose compositions can contain such amounts or submultiples thereof to make up the daily dose. The dosage can be adjusted by the individual physician in the event of any contraindications. Dosage can vary, and can be administered in one or more dose administrations daily, for one or several days. Guidance can be found in the literature for appropriate dosages for given classes of pharmaceutical products. In further various aspects, a preparation can be administered in a "prophylactically effective amount"; that is, an amount effective for prevention of a disease or condition.

[0051] As used herein, "kit" means a collection of at least two components constituting the kit. Together, the components constitute a functional unit for a given purpose. Individual member components may be physically packaged together or separately. For example, a kit comprising an instruction for using the kit may or may not physically include the instruction with other individual member components. Instead, the instruction can be supplied as a separate member component, either in a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as a recorded presentation.

[0052] As used herein, "instruction(s)" means documents describing relevant materials or methodologies pertaining to a kit. These materials may include any combination of the following: background information, list of components and their availability information (purchase information, etc.), brief or detailed protocols for using the kit, trouble-shooting, references, technical support, and any other related documents. Instructions can be supplied with the kit or as a separate member component, either as a paper form or an electronic form which may be supplied on computer readable memory device or downloaded from an internet website, or as a recorded presentation. Instructions can comprise one or multiple documents, and are meant to include future updates.

[0053] As used herein, the terms "therapeutic agent" includes any synthetic or naturally occurring biologically active compound or composition of matter which, when administered to an organism (human or nonhuman animal), induces a desired pharmacologic, immunogenic, and/or physiologic effect by local and/or systemic action. The term therefore encompasses those compounds or chemicals traditionally regarded as drugs, vaccines, and biopharmaceuticals including molecules such as proteins, peptides, hormones, nucleic acids, gene constructs and the like. Examples of therapeutic agents are described in well-known literature references such as the Merck Index (14^{th} edition), the Physicians' Desk Reference (64^{th} edition), and The Pharmacological Basis of Therapeutics (12^{th} edition) , and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances that affect the structure or function of the body, or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. For example, the term "therapeutic agent" includes compounds or compositions for use in all of the major therapeutic areas including, but not limited to, adjuvants; anti-infectives such as antibiotics and antiviral agents; analgesics and analgesic combinations, anorexics, anti-inflammatory agents, anti-epileptics, local and general anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergics, antiarrhythmics, antihypertensive agents, hormones, and nutrients, antiarthritics, antiasthmatic agents, anticonvulsants, antihistamines, antinauseants, antineoplastics, antipruritics, antipyretics; antispasmodics, cardiovascular preparations (including calcium channel blockers, beta-blockers, beta-agonists and antiarrythmics), antihypertensives, diuretics, vasodilators; central nervous system stimulants; cough and cold preparations; decongestants; diagnostics; hormones; bone growth stimulants and bone resorption inhibitors; immunosuppressives; muscle relaxants; psychostimulants; sedatives; tranquilizers; proteins, peptides, and fragments thereof (whether naturally occurring, chemically synthesized or recombinantly produced); and nucleic acid molecules (polymeric forms of two or more nucleotides, either ribonucleotides (RNA) or deoxyribonucleotides (DNA) including both double- and single-stranded molecules, gene constructs, expression vectors, antisense molecules and the like), small molecules (e.g., doxorubicin) and other biologically active macromolecules such as, for example, proteins and enzymes. The agent may be a biologically active agent used in medical, including veterinary, applications and in agriculture, such as with plants, as well as other areas. The term therapeutic agent also

includes without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of disease or illness; or substances which affect the structure or function of the body; or pro- drugs, which become biologically active or more active after they have been placed in a predetermined physiological environment.

[0054] As used herein, "EC_{50}," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% activation or enhancement of a biological process, or component of a process. For example, EC_{50} can refer to the concentration of agonist that provokes a response halfway between the baseline and maximum response in an *in vitro* assay. For example, an EC_{50} for NMDA receptor can be determined in an *in vitro* or cell-based assay system. Such *in vitro* assay systems frequently utilize a cell line that either expresses endogenously a target of interest, or has been transfected with a suitable expression vector that directs expression of a recombinant form of the target such as NMDA receptor, e.g., GluN1 or GluN2. For example, the EC_{50} for GluN1 or GluN2 can be determined using Xenopus oocytes injected with a cRNA for human NMDA receptor, e.g., GluN1 and/or GluN2. Alternatively, the EC_{50} for GluN1 or GluN2 can be determined using Xenopus oocytes injected with cRNA for rat NMDA receptor, e.g., GluN1 and/or GluN2. In another example, the EC_{50} for GluN1 or GluN2 can be determined using Xenopus oocytes injected with cRNA for mammalian NMDA receptor, e.g., GluN1 and/or GluN2.

[0055] As used herein, "IC_{50}," is intended to refer to the concentration of a substance (e.g., a compound or a drug) that is required for 50% inhibition of a biological process, or component of a process. For example, IC_{50} refers to the half maximal (50%) inhibitory concentration (IC) of a substance as determined in a suitable assay. For example, an IC_{50} for NMDA receptor can be determined in an *in vitro* or cell-based assay system. Frequently, receptor assays, including suitable assays for NMDA, make use of a suitable cell-line, e.g. a cell line that either expresses endogenously a target of interest, or has been transfected with a suitable expression vector that directs expression of a recombinant form of the target such as NMDA receptor, e.g., GluN1 or GluN2. For example, the IC_{50} for GluN1 or GluN2 can be determined using Xenopus oocytes injected with a cRNA for human NMDA receptor, e.g., GluN1 and/or GluN2. Alternatively, the IC_{50} for GluN1 or GluN2 can be determined using Xenopus oocytes injected with a cRNA for rat NMDA receptor, e.g., GluN1 and/or GluN2. In another example, the IC_{50} for GluN1 or GluN2 can be determined using Xenopus oocytes injected with a cRNA for mammalian NMDA receptor, e.g., GluN1 and/or GluN2.

[0056] The term "pharmaceutically acceptable" describes a material that is not biologically or otherwise undesirable, i.e., without causing an unacceptable level of undesirable biological effects or interacting in a deleterious manner.

[0057] As used herein, the term "derivative" refers to a compound having a structure derived from the structure of a parent compound (e.g., a compound disclosed herein) and whose structure is sufficiently similar to those disclosed herein and based upon that similarity, would be expected by one skilled in the art to exhibit the same or similar activities and utilities as the claimed compounds, or to induce, as a precursor, the same or similar activities and utilities as the claimed compounds. Exemplary derivatives include salts, esters, amides, salts of esters or amides, and N-oxides of a parent compound.

[0058] As used herein, the term "pharmaceutically acceptable carrier" refers to sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. These compositions can also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms can be ensured by the inclusion of various antibacterial and antifungal agents such as paraben, chlorobutanol, phenol, sorbic acid and the like. It can also be desirable to include isotonic agents such as sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the inclusion of agents, such as aluminum monostearate and gelatin, which delay absorption. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide, poly(orthoesters) and poly(anhydrides). Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable media just prior to use. Suitable inert carriers can include sugars such

as lactose. Desirably, at least 95% by weight of the particles of the active ingredient have an effective particle size in the range of 0.01 to 10 micrometers.

[0059] A residue of a chemical species, as used in the specification and concluding claims, refers to the moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ units in the polyester, regardless of whether ethylene glycol was used to prepare the polyester. Similarly, a sebacic acid residue in a polyester refers to one or more $-CO(CH_2)_8CO-$ moieties in the polyester, regardless of whether the residue is obtained by reacting sebacic acid or an ester thereof to obtain the polyester.

[0060] 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, and aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described below. 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, can have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This disclosure is not intended to be limited in any manner by the permissible substituents of organic compounds. Also, the terms "substitution" or "substituted with" include 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, *e.g.*, a compound that does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. It is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[0061] In defining various terms, "A^1," "A^2," "A^3," and "A^4" are used herein as generic symbols to represent various specific substituents. These symbols can be any substituent, not limited to those disclosed herein, and when they are defined to be certain substituents in one instance, they can, in another instance, be defined as some other substituents.

[0062] The term " aliphatic" or "aliphatic group," as used herein, denotes a hydrocarbon moiety that may be straight-chain (i.e., unbranched), branched, or cyclic (including fused, bridging, and spirofused polycyclic) and may be completely saturated or may contain one or

more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic groups contain 1-20 carbon atoms. Aliphatic groups include, but are not limited to, linear or branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0063] The term "alkyl" as used herein is a branched or unbranched saturated hydrocarbon group of 1 to 24 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *s*-butyl, *t*-butyl, *n*-pentyl, isopentyl, *s*-pentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, tetradecyl, hexadecyl, eicosyl, tetracosyl, and the like. It is understand that the alkyl group is acyclic. The alkyl group can be branched or unbranched. The alkyl group can also be substituted or unsubstituted. For example, the alkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol, as described herein. A "lower alkyl" group is an alkyl group containing from one to six (e.g., from one to four) carbon atoms. The term alkyl group can also be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like up to and including a C1-C24 alkyl.

[0064] Throughout the specification "alkyl" is generally used to refer to both unsubstituted alkyl groups and substituted alkyl groups; however, substituted alkyl groups are also specifically referred to herein by identifying the specific substituent(s) on the alkyl group. For example, the term "halogenated alkyl" or "haloalkyl" specifically refers to an alkyl group that is substituted with one or more halide, *e.g.*, fluorine, chlorine, bromine, or iodine. Alternatively, the term "monohaloalkyl" specifically refers to an alkyl group that is substituted with a single halide, *e.g.* fluorine, chlorine, bromine, or iodine. The term "polyhaloalkyl" specifically refers to an alkyl group that is independently substituted with two or more halides, *i.e.* each halide substituent need not be the same halide as another halide substituent, nor do the multiple instances of a halide substituent need to be on the same carbon. The term "alkoxyalkyl" specifically refers to an alkyl group that is substituted with one or more alkoxy groups, as described below. The term "aminoalkyl" specifically refers to an alkyl group that is substituted with one or more amino groups. The term "hydroxyalkyl" specifically refers to an alkyl group that is substituted with one or more hydroxy groups. When "alkyl" is used in one instance and a specific term such as "hydroxyalkyl" is used in another, it is not meant to imply that the term "alkyl" does not also refer to specific terms such as "hydroxyalkyl" and the like.

[0065] This practice is also used for other groups described herein. That is, while a term such as "cycloalkyl" refers to both unsubstituted and substituted cycloalkyl moieties, the substituted moieties can, in addition, be specifically identified herein; for example, a particular substituted cycloalkyl can be referred to as, *e.g.*, an "alkylcycloalkyl." Similarly, a substituted alkoxy can be specifically referred to as, *e.g.*, a "halogenated alkoxy," a particular substituted alkenyl can be, *e.g.*, an "alkenylalcohol," and the like. Again, the practice of using a general term, such as "cycloalkyl," and a specific term, such as "alkylcycloalkyl," is not meant to imply that the general term does not also include the specific term.

[0066] The term "cycloalkyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. The cycloalkyl group can be substituted or unsubstituted. The cycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0067] The term "polyalkylene group" as used herein is a group having two or more CH_2 groups linked to one another. The polyalkylene group can be represented by the formula —$(CH_2)_a$—, where "a" is an integer of from 2 to 500.

[0068] The terms "alkoxy" and "alkoxyl" as used herein to refer to an alkyl or cycloalkyl group bonded through an ether linkage; that is, an "alkoxy" group can be defined as —OA^1 where A^1 is alkyl or cycloalkyl as defined above. "Alkoxy" also includes polymers of alkoxy groups as just described; that is, an alkoxy can be a polyether such as —OA^1—OA^2 or —OA^1—$(OA^2)_a$—OA^3, where "a" is an integer of from 1 to 200 and A^1, A^2, and A^3 are alkyl and/or cycloalkyl groups.

[0069] The term "alkenyl" as used herein is a hydrocarbon group of from 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon double bond. Asymmetric structures such as $(A^1A^2)C=C(A^3A^4)$ are intended to include both the *E* and *Z* isomers. This can be presumed in structural formulae herein wherein an asymmetric alkene is present, or it can be explicitly indicated by the bond symbol C=C. The alkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0070] The term "cycloalkenyl" as used herein is a non-aromatic carbon-based ring composed of at least three carbon atoms and containing at least one carbon-carbon double

bound, *i.e.*, C=C. Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, norbornenyl, and the like. The cycloalkenyl group can be substituted or unsubstituted. The cycloalkenyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0071] The term "alkynyl" as used herein is a hydrocarbon group of 2 to 24 carbon atoms with a structural formula containing at least one carbon-carbon triple bond. The alkynyl group can be unsubstituted or substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol, as described herein.

[0072] The term "cycloalkynyl" as used herein is a non-aromatic carbon-based ring composed of at least seven carbon atoms and containing at least one carbon-carbon triple bound. Examples of cycloalkynyl groups include, but are not limited to, cycloheptynyl, cyclooctynyl, cyclononynyl, and the like. The cycloalkynyl group can be substituted or unsubstituted. The cycloalkynyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, amino, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0073] The term "aromatic group" as used herein refers to a ring structure having cyclic clouds of delocalized π electrons above and below the plane of the molecule, where the π clouds contain $(4n+2)$ π electrons. A further discussion of aromaticity is found in Morrison and Boyd, Organic Chemistry , (5th Ed., 1987), Chapter 13, entitled " Aromaticity," pages 477-497, incorporated herein by reference. The term "aromatic group" is inclusive of both aryl and heteroaryl groups.

[0074] The term "aryl" as used herein is a group that contains any carbon-based aromatic group including, but not limited to, benzene, naphthalene, phenyl, biphenyl, anthracene, and the like. The aryl group can be substituted or unsubstituted. The aryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, heteroaryl, aldehyde, $-NH_2$, carboxylic acid, ester, ether, halide, hydroxy, ketone, azide, nitro, silyl, sulfo-oxo, or thiol as described herein. The term "biaryl" is a specific type of aryl group and is included in the definition of "aryl." In

addition, the aryl group can be a single ring structure or comprise multiple ring structures that are either fused ring structures or attached via one or more bridging groups such as a carbon-carbon bond. For example, biaryl refers to two aryl groups that are bound together via a fused ring structure, as in naphthalene, or are attached via one or more carbon-carbon bonds, as in biphenyl.

[0075] The term "aldehyde" as used herein is represented by the formula —C(O)H. Throughout this specification "C(O)" is a short hand notation for a carbonyl group, *i.e.*, C=O.

[0076] The terms "amine" or "amino" as used herein are represented by the formula —NA^1A^2, where A^1 and A^2 can be, independently, hydrogen or alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. A specific example of amino is —NH_2.

[0077] The term "alkylamino" as used herein is represented by the formulas —NH(—alkyl) and —N(—alkyl)$_2$, and where alkyl is as described herein. The alkyl group can be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like, up to and including a C1-C24 alkyl. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, and N-ethyl-N-propylamino group. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group, and the like.

[0078] The term "monoalkylamino" as used herein is represented by the formula —NH(—alkyl), where alkyl is as described herein. The alkyl group can be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like, up to and including a C1-C24 alkyl. Representative examples include, but are not limited to, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, (sec-butyl)amino group, (tert-butyl)amino group, pentylamino group, isopentylamino group, (tert-pentyl)amino group, hexylamino group, and the like.

[0079] The term "dialkylamino" as used herein is represented by the formula —N(—alkyl)$_2$, where alkyl is as described herein. The alkyl group can be a C1 alkyl, C1-C2 alkyl, C1-C3 alkyl, C1-C4 alkyl, C1-C5 alkyl, C1-C6 alkyl, C1-C7 alkyl, C1-C8 alkyl, C1-C9 alkyl, C1-C10 alkyl, and the like, up to and including a C1-C24 alkyl. It is understood that each alkyl group can be independently varied, e.g. as in the representative compounds such as N-ethyl-N-methylamino group, N-methyl-N-propylamino group, and N-ethyl-N-propylamino group. Representative examples include, but are not limited to, dimethylamino group, diethylamino group, dipropylamino group, diisopropylamino group, dibutylamino group, diisobutylamino group, di(sec-butyl)amino group, di(tert-butyl)amino group, dipentylamino group, diisopentylamino group, di(tert-pentyl)amino group, dihexylamino group, N-ethyl-N-methylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group, and the like.

[0080] The term "carboxylic acid" as used herein is represented by the formula —C(O)OH.

[0081] The term "ester" as used herein is represented by the formula —OC(O)A^1 or —C(O)OA^1, where A^1 can be alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "polyester" as used herein is represented by the formula —(A^{1}O(O)C-A^2-C(O)O)$_a$— or —(A^{1}O(O)C-A^2-OC(O))$_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer from 1 to 500. "Polyester" is as the term used to describe a group that is produced by the reaction between a compound having at least two carboxylic acid groups with a compound having at least two hydroxyl groups.

[0082] The term "ether" as used herein is represented by the formula A^{1}OA^2, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein. The term "polyether" as used herein is represented by the formula —(A^{1}O-A^{2}O)$_a$—, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group described herein and "a" is an integer of from 1 to 500. Examples of polyether groups include polyethylene oxide, polypropylene oxide, and polybutylene oxide.

[0083] The terms "halo," "halogen," or "halide," as used herein can be used interchangeably and refer to F, Cl, Br, or I.

[0084] The terms "pseudohalide," "pseudohalogen" or "pseudohalo," as used herein can be used interchangeably and refer to functional groups that behave substantially similar to

halides. Such functional groups include, by way of example, cyano, thiocyanato, azido, trifluoromethyl, trifluoromethoxy, perfluoroalkyl, and perfluoroalkoxy groups.

[0085] The term "heteroalkyl," as used herein refers to an alkyl group containing at least one heteroatom. Suitable heteroatoms include, but are not limited to, O, N, Si, P and S, wherein the nitrogen, phosphorous and sulfur atoms are optionally oxidized, and the nitrogen heteroatom is optionally quaternized. Heteroalkyls can be substituted as defined above for alkyl groups.

[0086] The term "heteroaryl," as used herein refers to an aromatic group that has at least one heteroatom incorporated within the ring of the aromatic group. Examples of heteroatoms include, but are not limited to, nitrogen, oxygen, sulfur, and phosphorus, where N-oxides, sulfur oxides, and dioxides are permissible heteroatom substitutions. The heteroaryl group can be substituted or unsubstituted, and the heteroaryl group can be monocyclic, bicyclic or multicyclic aromatic ring. The heteroaryl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein. . It is understood that a heteroaryl group may be bound either through a heteroatom in the ring, where chemically possible, or one of carbons comprising the heteroaryl ring.

[0087] A variety of heteroaryl groups are known in the art and include, without limitation, oxygen-containing rings, nitrogen-containing rings, sulfur-containing rings, mixed heteroatom-containing rings, fused heteroatom containing rings, and combinations thereof. Non-limiting examples of heteroaryl rings include furyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl, triazinyl, thienyl, oxazolyl, thiazolyl, oxadiazolyl, oxatriazolyl, oxepinyl, thiepinyl, diazepinyl, benzofuranyl, thionapthene, indolyl, benzazolyl, pyranopyrrolyl, isoindazolyl, indoxazinyl, benzoxazolyl, quinolinyl, isoquinolinyl, benzodiazonyl, naphthyridinyl, benzothienyl, pyridopyridinyl, acridinyl, carbazolyl and purinyl rings.

[0088] The term "monocyclic heteroaryl," as used herein, refers to a monocyclic ring system which is aromatic and in which at least one of the ring atoms is a heteroatom. Monocyclic heteroaryl groups include, but are not limited, to the following exemplary groups: pyridine, pyrimidine, furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, oxadiazole, including, 1,2,3-oxadiazole, 1,2,5-oxadiazole and 1,3,4- thiadiazole, including, 1,2,3-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole, triazole, including, 1,2,3-triazole, 1,3,4-triazole, tetrazole, including 1,2,3,4-tetrazole and 1,2,4,5-tetrazole, pyridazine, pyrazine, triazine, including 1,2,4-triazine and 1,3,5-triazine,

tetrazine, including 1,2,4,5-tetrazine, and the like. Monocyclic heteroaryl groups are numbered according to standard chemical nomenclature.

[0089] The term "bicyclic heteroaryl," as used herein, refers to a ring system comprising a bicyclic ring system in which at least one of the two rings is aromatic and at least one of the two rings contains a heteroatom. Bicyclic heteroaryl encompasses ring systems wherein an aromatic ring is fused with another aromatic ring, or wherein an aromatic ring is fused with a non-aromatic ring. Bicyclic heteroaryl encompasses ring systems wherein a benzene ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms or wherein a pyridine ring is fused to a 5- or a 6-membered ring containing 1, 2 or 3 ring heteroatoms. Examples of bicyclic heteroaryl groups include without limitation indolyl, isoindolyl, indolyl, indolinyl, indolizinyl, quinolinyl, isoquinolinyl, benzofuryl, bexothiophenyl, indazolyl, benzimidazolyl, benzothiazinyl, benzothiazolyl, purinyl, quinolizyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolizinyl, quinoxalyl, naphthyridinyl, and pteridyl. Bicyclic heteroaryls are numbered according to standard chemical nomenclature..

[0090] The term "heterocycloalkyl" as used herein refers to an aliphatic, partially unsaturated or fully saturated, 3- to 14-membered ring system, including single rings of 3 to 8 atoms and bi- and tricyclic ring systems where at least one of the carbon atoms of the ring is replaced with a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus. A heterocycloalkyl can include one to four heteroatoms independently selected from oxygen, nitrogen, and sulfur, wherein a nitrogen and sulfur heteroatom optionally can be oxidized and a nitrogen heteroatom optionally can be substituted. Representative heterocycloalkyl groups include, but are not limited, to the following exemplary groups: pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl. The term heterocycloalkyl group can also be a C2 heterocycloalkyl, C2-C3 heterocycloalkyl, C2-C4 heterocycloalkyl, C2-C5 heterocycloalkyl, C2-C6 heterocycloalkyl, C2-C7 heterocycloalkyl, C2-C8 heterocycloalkyl, C2-C9 heterocycloalkyl, C2-C10 heterocycloalkyl, C2-C11 heterocycloalkyl, and the like up to and including a C2-C14 heterocycloalkyl. For example, a C2 heterocycloalkyl comprises a group which has two carbon atoms and at least one heteroatom, including, but not limited to, aziridinyl, diazetidinyl, oxiranyl, thiiranyl, and the like. Alternatively, for example, a C5 heterocycloalkyl comprises a group which has five carbon atoms and at least one heteroatom, including, but not limited to, piperidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, diazepanyl, and the like. It is understood that a heterocycloalkyl group may be bound either

through a heteroatom in the ring, where chemically possible, or one of carbons comprising the heterocycloalkyl ring. The heterocycloalkyl group can be substituted or unsubstituted. The heterocycloalkyl group can be substituted with one or more groups including, but not limited to, alkyl, cycloalkyl, alkoxy, amino, ether, halide, hydroxy, nitro, silyl, sulfo-oxo, or thiol as described herein.

[0091] The term "hydroxyl" or "hydroxy" as used herein is represented by the formula —OH.

[0092] The term "ketone" as used herein is represented by the formula $A^1C(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0093] The term "azide" or "azido" as used herein is represented by the formula $—N_3$.

[0094] The term "nitro" as used herein is represented by the formula $—NO_2$.

[0095] The term "nitrile" or "cyano" as used herein is represented by the formula —CN.

[0096] The term "silyl" as used herein is represented by the formula $—SiA^1A^2A^3$, where A^1, A^2, and A^3 can be, independently, hydrogen or an alkyl, cycloalkyl, alkoxy, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0097] The term "sulfo-oxo" as used herein is represented by the formulas $—S(O)A^1$, $—S(O)_2A^1$, $—OS(O)_2A^1$, or $—OS(O)_2OA^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. Throughout this specification "S(O)" is a short hand notation for S=O. The term "sulfonyl" is used herein to refer to the sulfo-oxo group represented by the formula $—S(O)_2A^1$, where A^1 can be hydrogen or an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfone" as used herein is represented by the formula $A^1S(O)_2A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein. The term "sulfoxide" as used herein is represented by the formula $A^1S(O)A^2$, where A^1 and A^2 can be, independently, an alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, aryl, or heteroaryl group as described herein.

[0098] The term "thiol" as used herein is represented by the formula —SH.

[0099] "R^1," "R^2," "R^3," "R^n," where n is an integer, as used herein can, independently, possess one or more of the groups listed above. For example, if R^1 is a straight chain alkyl group, one of the hydrogen atoms of the alkyl group can optionally be substituted with a hydroxyl group, an alkoxy group, an alkyl group, a halide, and the like. Depending upon the groups that are selected, a first group can be incorporated within second group or,

alternatively, the first group can be pendant (*i.e.*, attached) to the second group. For example, with the phrase "an alkyl group comprising an amino group," the amino group can be incorporated within the backbone of the alkyl group. Alternatively, the amino group can be attached to the backbone of the alkyl group. The nature of the group(s) that is (are) selected will determine if the first group is embedded or attached to the second group.

[00100] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. In is also contemplated that, in certain aspects, unless expressly indicated to the contrary, individual substituents can be further optionally substituted (i.e., further substituted or unsubstituted).

[00101] The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain aspects, their recovery, purification, and use for one or more of the purposes disclosed herein.

[00102] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or

branched alkylene)O–N(R°)$_2$; or –(C_{1-4} straight or branched alkylene)C(O)O–N(R°)$_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, –CH_2Ph, –O(CH_2)$_{0-1}$Ph, -CH_2-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[00103] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, –(CH_2)$_{0-2}$R$^\bullet$, –(haloR$^\bullet$), –(CH_2)$_{0-2}$OH, –(CH_2)$_{0-2}$OR$^\bullet$, –(CH_2)$_{0-2}$CH(OR$^\bullet$)$_2$; -O(haloR$^\bullet$), –CN, –N_3, –(CH_2)$_{0-2}$C(O)R$^\bullet$, –(CH_2)$_{0-2}$C(O)OH, –(CH_2)$_{0-2}$C(O)OR$^\bullet$, –(CH_2)$_{0-2}$SR$^\bullet$, –(CH_2)$_{0-2}$SH, –(CH_2)$_{0-2}$$NH_2$, –($CH_2$)$_{0-2}NHR^\bullet$, –($CH_2$)$_{0-2}NR^\bullet_2$, –$NO_2$, –SiR$^\bullet_3$, –OSiR$^\bullet_3$, -C(O)SR$^\bullet$, –($C_{1-4}$ straight or branched alkylene)C(O)OR$^\bullet$, or –SSR$^\bullet$ wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, –CH_2Ph, –O(CH_2)$_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[00104] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, =NNR$^*_2$, =NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)$_2$R*, =NR*, =NOR*, –O(C(R$^*_2$))$_{2-3}$O–, or –S(C(R$^*_2$))$_{2-3}$S–, wherein each independent occurrence of R* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: –O(CR$^*_2$)$_{2-3}$O–, wherein each independent occurrence of R* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00105] Suitable substituents on the aliphatic group of R^* include halogen, –$R^\bullet$, -(halo$R^\bullet$), -OH, –$OR^\bullet$, –O(halo$R^\bullet$), –CN, –C(O)OH, –C(O)$OR^\bullet$, –NH_2, –$NHR^\bullet$, –$NR^\bullet_2$, or –NO_2, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00106] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include –$R^\dagger$, –$NR^\dagger_2$, –C(O)$R^\dagger$, –C(O)$OR^\dagger$, –C(O)C(O)$R^\dagger$, –C(O)CH_2C(O)$R^\dagger$, –$S(O)_2R^\dagger$, -$S(O)_2NR^\dagger_2$, –C(S)$NR^\dagger_2$, –C(NH)$NR^\dagger_2$, or –N($R^\dagger$)$S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[00107] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, –$R^\bullet$, -(halo$R^\bullet$), –OH, –$OR^\bullet$, –O(halo$R^\bullet$), –CN, –C(O)OH, –C(O)$OR^\bullet$, –NH_2, –$NHR^\bullet$, –$NR^\bullet_2$, or -NO_2, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, –CH_2Ph, –$O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

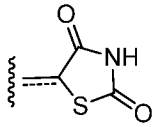
[00108] The term "leaving group" refers to an atom (or a group of atoms) with electron withdrawing ability that can be displaced as a stable species, taking with it the bonding electrons. Examples of suitable leaving groups include halides and sulfonate esters, including, but not limited to, triflate, mesylate, tosylate, and brosylate.

[00109] The terms "hydrolysable group" and "hydrolysable moiety" refer to a functional group capable of undergoing hydrolysis, e.g., under basic or acidic conditions. Examples of hydrolysable residues include, without limitation, acid halides, activated carboxylic acids, and various protecting groups known in the art (see, for example, "Protective Groups in Organic Synthesis," T. W. Greene, P. G. M. Wuts, Wiley-Interscience, 1999).

[00110] The term "organic residue" defines a carbon containing residue, i.e., a residue comprising at least one carbon atom, and includes but is not limited to the carbon-containing groups, residues, or radicals defined hereinabove. Organic residues can contain various

heteroatoms, or be bonded to another molecule through a heteroatom, including oxygen, nitrogen, sulfur, phosphorus, or the like. Examples of organic residues include but are not limited alkyl or substituted alkyls, alkoxy or substituted alkoxy, mono or di-substituted amino, amide groups, etc. Organic residues can preferably comprise 1 to 18 carbon atoms, 1 to 15, carbon atoms, 1 to 12 carbon atoms, 1 to 8 carbon atoms, 1 to 6 carbon atoms, or 1 to 4 carbon atoms. In a further aspect, an organic residue can comprise 2 to 18 carbon atoms, 2 to 15, carbon atoms, 2 to 12 carbon atoms, 2 to 8 carbon atoms, 2 to 4 carbon atoms, or 2 to 4 carbon atoms.

[00111] A very close synonym of the term "residue" is the term "radical," which as used in the specification and concluding claims, refers to a fragment, group, or substructure of a molecule described herein, regardless of how the molecule is prepared. For example, a 2,4-thiazolidinedione radical in a particular compound has the structure



regardless of whether thiazolidinedione is used to prepare the compound. In some embodiments the radical (for example an alkyl) can be further modified (i.e., substituted alkyl) by having bonded thereto one or more "substituent radicals." The number of atoms in a given radical is not critical to the present invention unless it is indicated to the contrary elsewhere herein.

[00112] "Organic radicals," as the term is defined and used herein, contain one or more carbon atoms. An organic radical can have, for example, 1-26 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 1-8 carbon atoms, 1-6 carbon atoms, or 1-4 carbon atoms. In a further aspect, an organic radical can have 2-26 carbon atoms, 2-18 carbon atoms, 2-12 carbon atoms, 2-8 carbon atoms, 2-6 carbon atoms, or 2-4 carbon atoms. Organic radicals often have hydrogen bound to at least some of the carbon atoms of the organic radical. One example, of an organic radical that comprises no inorganic atoms is a 5, 6, 7, 8-tetrahydro-2-naphthyl radical. In some embodiments, an organic radical can contain 1-10 inorganic heteroatoms bound thereto or therein, including halogens, oxygen, sulfur, nitrogen, phosphorus, and the like. Examples of organic radicals include but are not limited to an alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, mono-substituted amino, di-substituted amino, acyloxy, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy, haloalkyl, haloalkoxy, aryl,

substituted aryl, heteroaryl, heterocyclic, or substituted heterocyclic radicals, wherein the terms are defined elsewhere herein. A few non-limiting examples of organic radicals that include heteroatoms include alkoxy radicals, trifluoromethoxy radicals, acetoxy radicals, dimethylamino radicals and the like.

[00113] "Inorganic radicals," as the term is defined and used herein, contain no carbon atoms and therefore comprise only atoms other than carbon. Inorganic radicals comprise bonded combinations of atoms selected from hydrogen, nitrogen, oxygen, silicon, phosphorus, sulfur, selenium, and halogens such as fluorine, chlorine, bromine, and iodine, which can be present individually or bonded together in their chemically stable combinations. Inorganic radicals have 10 or fewer, or preferably one to six or one to four inorganic atoms as listed above bonded together. Examples of inorganic radicals include, but not limited to, amino, hydroxy, halogens, nitro, thiol, sulfate, phosphate, and like commonly known inorganic radicals. The inorganic radicals do not have bonded therein the metallic elements of the periodic table (such as the alkali metals, alkaline earth metals, transition metals, lanthanide metals, or actinide metals), although such metal ions can sometimes serve as a pharmaceutically acceptable cation for anionic inorganic radicals such as a sulfate, phosphate, or like anionic inorganic radical. Inorganic radicals do not comprise metalloids elements such as boron, aluminum, gallium, germanium, arsenic, tin, lead, or tellurium, or the noble gas elements, unless otherwise specifically indicated elsewhere herein.

[00114] Compounds described herein can contain one or more double bonds and, thus, potentially give rise to cis/trans (E/Z) isomers, as well as other conformational isomers. Unless stated to the contrary, the invention includes all such possible isomers, as well as mixtures of such isomers.

[00115] Unless stated to the contrary, a formula with chemical bonds shown only as solid lines and not as wedges or dashed lines contemplates each possible isomer, *e.g.*, each enantiomer and diastereomer, and a mixture of isomers, such as a racemic or scalemic mixture. Compounds described herein can contain one or more asymmetric centers and, thus, potentially give rise to diastereomers and optical isomers. Unless stated to the contrary, the present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. Mixtures of stereoisomers, as well as isolated specific stereoisomers, are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[00116] Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound. For example, a compound prefixed with (-) or l meaning that the compound is levorotatory or a compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the disclosed formulas, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Inglod-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

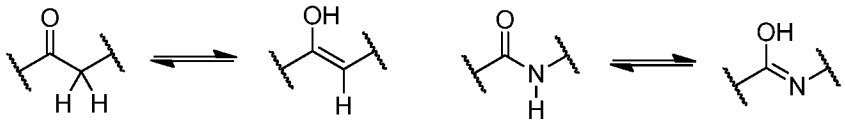
[00117] Compounds described herein comprise atoms in both their natural isotopic abundance and in non-natural abundance. The disclosed compounds can be isotopically-labeled or isotopically-substituted compounds identical to those described, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds further comprise prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and

detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of the present invention and prodrugs thereof can generally be prepared by carrying out the procedures below, by substituting a readily available isotopically labeled reagent for a non- isotopically labeled reagent.

[00118] The compounds described in the invention can be present as a solvate. In some cases, the solvent used to prepare the solvate is an aqueous solution, and the solvate is then often referred to as a hydrate. The compounds can be present as a hydrate, which can be obtained, for example, by crystallization from a solvent or from aqueous solution. In this connection, one, two, three or any arbitrary number of solvent or water molecules can combine with the compounds according to the invention to form solvates and hydrates. Unless stated to the contrary, the invention includes all such possible solvates.

[00119] The term "co-crystal" means a physical association of two or more molecules which owe their stability through non-covalent interaction. One or more components of this molecular complex provide a stable framework in the crystalline lattice. In certain instances, the guest molecules are incorporated in the crystalline lattice as anhydrates or solvates, see e.g. "Crystal Engineering of the Composition of Pharmaceutical Phases. Do Pharmaceutical Co-crystals Represent a New Path to Improved Medicines?" Almarasson, O., et. al., The Royal Society of Chemistry, 1889-1896, 2004. Examples of co-crystals include p-toluenesulfonic acid and benzenesulfonic acid.

[00120] It is also appreciated that certain compounds described herein can be present as an equilibrium of tautomers. For example, ketones with an α-hydrogen can exist in an equilibrium of the keto form and the enol form.



keto form enol form amide form imidic acid form

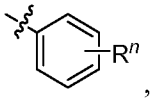
[00121] Likewise, amides with an N-hydrogen can exist in an equilibrium of the amide form and the imidic acid form. As another example, pyridinones can exist in two tautomeric forms, as shown below.



[00122] Unless stated to the contrary, the invention includes all such possible tautomers.

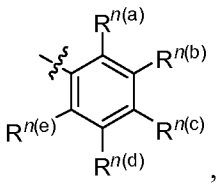
[00123] It is known that chemical substances form solids which are present in different states of order which are termed polymorphic forms or modifications. The different modifications of a polymorphic substance can differ greatly in their physical properties. The compounds according to the invention can be present in different polymorphic forms, with it being possible for particular modifications to be metastable. Unless stated to the contrary, the invention includes all such possible polymorphic forms.

[00124] In some aspects, a structure of a compound can be represented by a formula:



,

which is understood to be equivalent to a formula:



,

wherein n is typically an integer. That is, R^n is understood to represent five independent substituents, $R^{n(a)}$, $R^{n(b)}$, $R^{n(c)}$, $R^{n(d)}$, and $R^{n(e)}$. By "independent substituents," it is meant that each R substituent can be independently defined. For example, if in one instance $R^{n(a)}$ is halogen, then $R^{n(b)}$ is not necessarily halogen in that instance.

[00125] Certain materials, compounds, compositions, and components disclosed herein can be obtained commercially or readily synthesized using techniques generally known to those of skill in the art. For example, the starting materials and reagents used in preparing the disclosed compounds and compositions are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wis.), Acros Organics (Morris Plains, N.J.), Fisher Scientific (Pittsburgh, Pa.), or Sigma (St. Louis, Mo.) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplemental volumes (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991); March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition); and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

[00126] The following abbreviations are used herein. "ACN" means acetonitrile, "EtOAc" means ethyl acetate, "DCE" means 1,2-dichloroethane "DCM" means dichloromethane,

"DIPE" means diisopropylether, "DMF" means *N*,*N*-dimethylformamide, "EtOH" means ethanol, "HATU" means 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, "HPLC" means high-performance liquid chromatography, "LCMS" means liquid chromatography/mass spectrometry, "MeOH" means methanol, "Ms" means methylsulfonyl, ""CDI" means 1,1'-carbonyldiimidazole, "TFAA" means trifluoroacetic anhydride, "DMSO" means dimethyl sulfoxide, "t-BuLi" means tert-butyllithium, "Boc" means tert-butyloxycarbonyl, "Et_3N" means triethylamine, "DBU" means 1,8-diazabicyclo[5.4.0]undec-7-ene, "DMAP" means 4-dimethylaminopyridine, "TMSOTf" means trimethylsilyl chloride, "iPrOH" means anhydrous isopropanol", "NMR" means nuclear magnetic resonance, "RP" means reverse phase, "RT" means room temperature, "TEA" means triethylamine, and "THF" means tetrahydrofuran.

[00127] Unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including: matters of logic with respect to arrangement of steps or operational flow; plain meaning derived from grammatical organization or punctuation; and the number or type of embodiments described in the specification.

[00128] Disclosed are the components to be used to prepare the compositions of the invention as well as the compositions themselves to be used within the methods disclosed herein. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc. of these materials are disclosed that while specific reference of each various individual and collective combinations and permutation of these compounds cannot be explicitly disclosed, each is specifically contemplated and described herein. For example, if a particular compound is disclosed and discussed and a number of modifications that can be made to a number of molecules including the compounds are discussed, specifically contemplated is each and every combination and permutation of the compound and the modifications that are possible unless specifically indicated to the contrary. Thus, if a class of molecules A, B, and C are disclosed as well as a class of molecules D, E, and F and an example of a combination molecule, A-D is disclosed, then even if each is not individually recited each is individually and collectively contemplated meaning combinations, A-E, A-F, B-D, B-E, B-F, C-D, C-E, and C-F are

considered disclosed. Likewise, any subset or combination of these is also disclosed. Thus, for example, the sub-group of A-E, B-F, and C-E would be considered disclosed. This concept applies to all aspects of this application including, but not limited to, steps in methods of making and using the compositions of the invention. Thus, if there are a variety of additional steps that can be performed it is understood that each of these additional steps can be performed with any specific embodiment or combination of embodiments of the methods of the invention.

[00129] It is understood that the compositions disclosed herein have certain functions. Disclosed herein are certain structural requirements for performing the disclosed functions, and it is understood that there are a variety of structures that can perform the same function that are related to the disclosed structures, and that these structures will typically achieve the same result.

B. COMPOUNDS

[00130] In one aspect, the invention relates to compounds useful as modulators of the NMDA receptor, such as an inhibitor of NMDA receptor activity. More specifically, in one aspect, the present invention relates to compounds that are antagonists of the NMDA receptor. The compounds can, in one aspect, exhibit subtype selectivity.

[00131] In one aspect, the compounds of the invention are useful in the treatment of neurological and/or psychiatric disorders associated with glutamate dysfunction and other diseases in which NMDA receptors are involved, as further described herein.

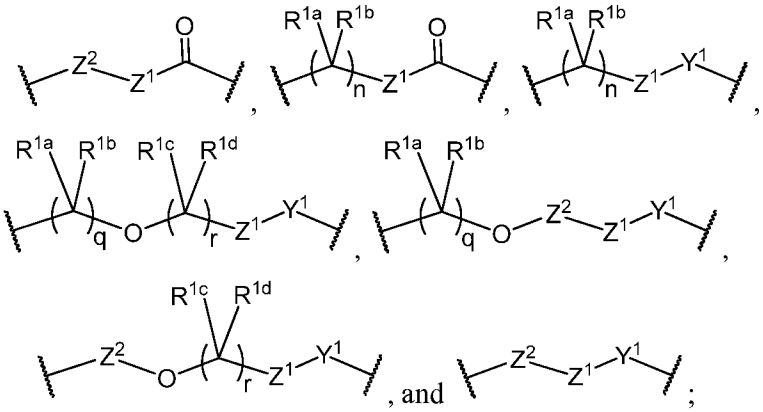
[00132] It is contemplated that each disclosed derivative can be optionally further substituted. It is also contemplated that any one or more derivative can be optionally omitted from the invention. It is understood that a disclosed compound can be provided by the disclosed methods. It is also understood that the disclosed compounds can be employed in the disclosed methods of using.

1. STRUCTURE

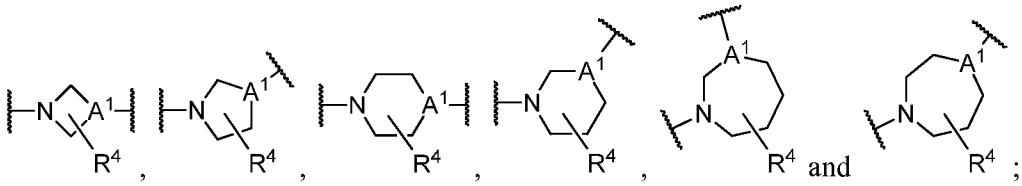
[00133] In one aspects, the invention relates to a compound having a structure represented by a formula:

$$Ar^1—L—Ar^2,$$

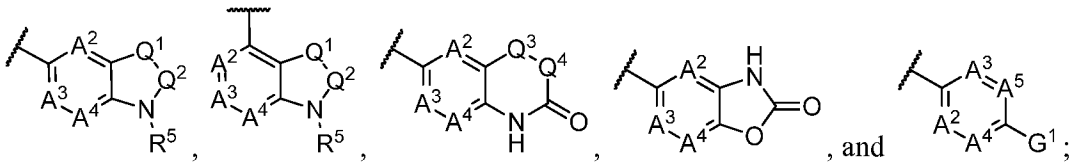
wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein L is selected from:



wherein each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein m is an integer from 1-3; wherein n is an integer from 1-4; wherein q is an integer from 0-1; wherein r is an integer from 0-1; wherein Y^1, when present, is selected from —O— and —$CR^{2a}R^{2b}$—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1, when present, is a 4- to 7-membered hetercycloalkyl selected from:



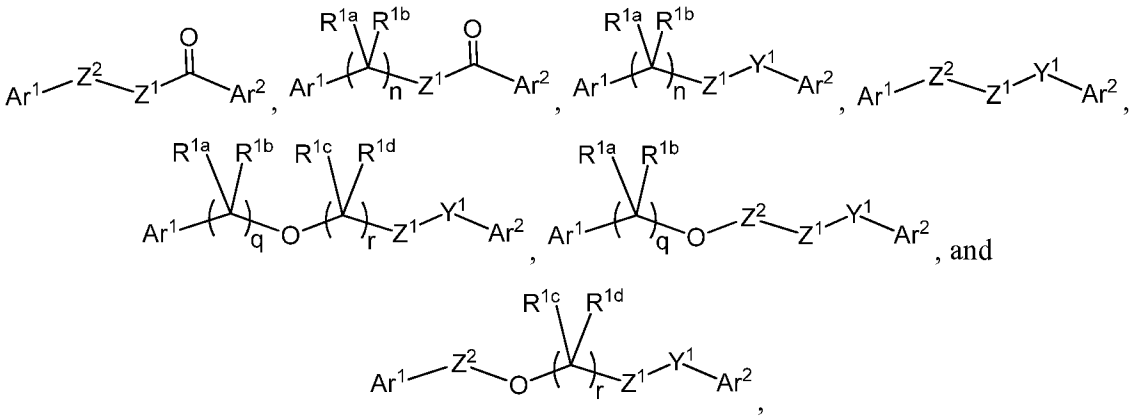
wherein A^1 is N or CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein Ar^2 is selected from:



wherein A^2 is selected from N and CR^{6a}; wherein A^3, when present, is selected from N and CR^{6b}; and wherein A^4, when present, is selected from N and CR^{6c}; and wherein A^5, when present, is selected from N and CR^{6d}; wherein each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl,

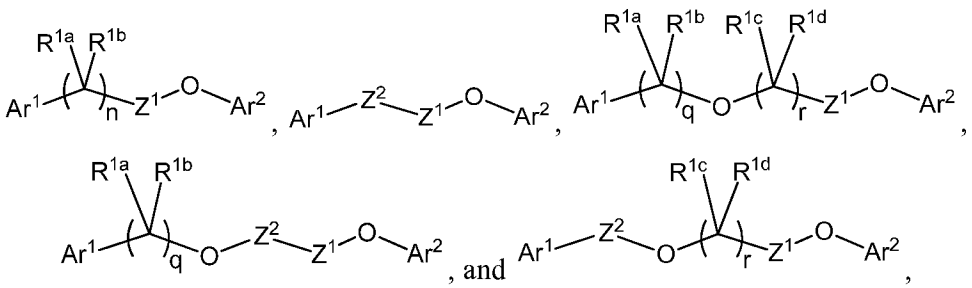
C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —N=, —NR^{8a}—, and (C=O); wherein Q^2, when present, is selected from =N—, =CR^{7c}—, —NR^{8b}—, (C=NH), (S=O), (SO_2), (C=S), and (C=O); provided that Q^1 and Q^2 are not simultaneously (C=O); wherein Q^3, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —N=, —NR^{8a}—, and —NR^{8a}—; wherein Q^4, when present, is selected from =CR^{7c}—, —$CR^{7c}R^{7d}$—, —O—, —S—, —NR^{8b}—, and (C=O); provided that Q^3 and Q^4 are not simultaneously —NR^{8a}— and —NR^{8b}—, respectively, or that or Q^3 and Q^4 are not simultaneously —O— or —S—; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{8a} and R^{8b}, when present is independently selected from hydrogen and C1-C8 alkyl; wherein G^1, when present, is selected from —OH, —NHR^9, —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$, —OR^9, —NH(C=O)R^9; —NH(C=O)OR^9; and —NH(C=O)$NR^{10a}R^{10b}$; wherein each of R^9, when present, is selected from C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl; wherein each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl; or a pharmaceutically acceptable salt, solvate, or polymorph thereof.

[00134] In various aspects, the invention relates to a compound having a structure selected from:



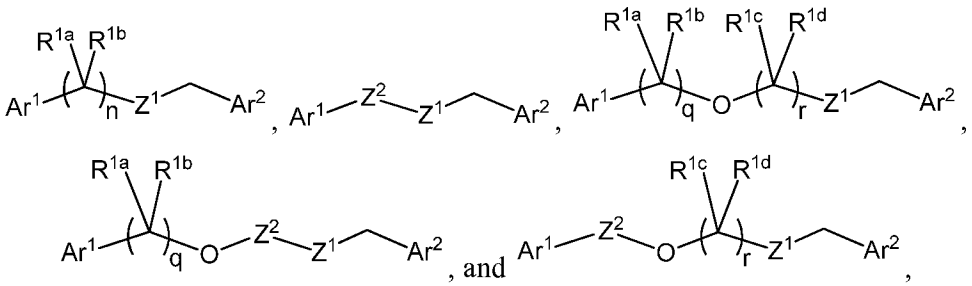
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00135] In various aspects, the invention relates to a compound having a structure selected from:



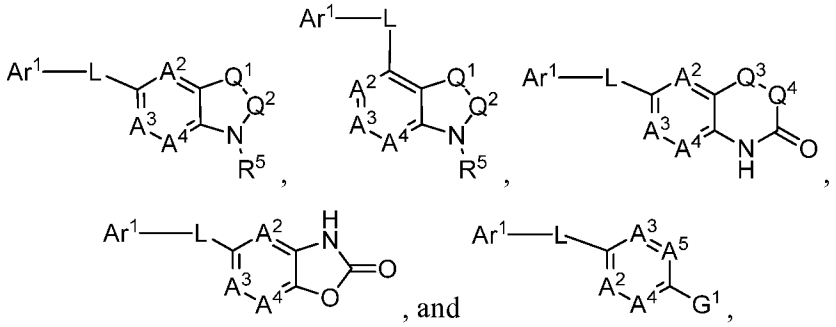
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00136] In various aspects, the invention relates to a compound having a structure selected from:



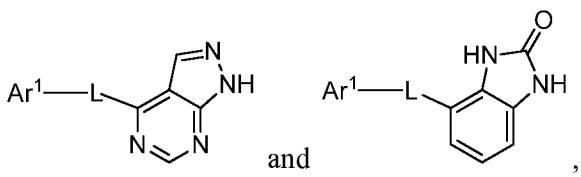
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00137] In various aspects, the invention relates to a compound having a structure selected from:



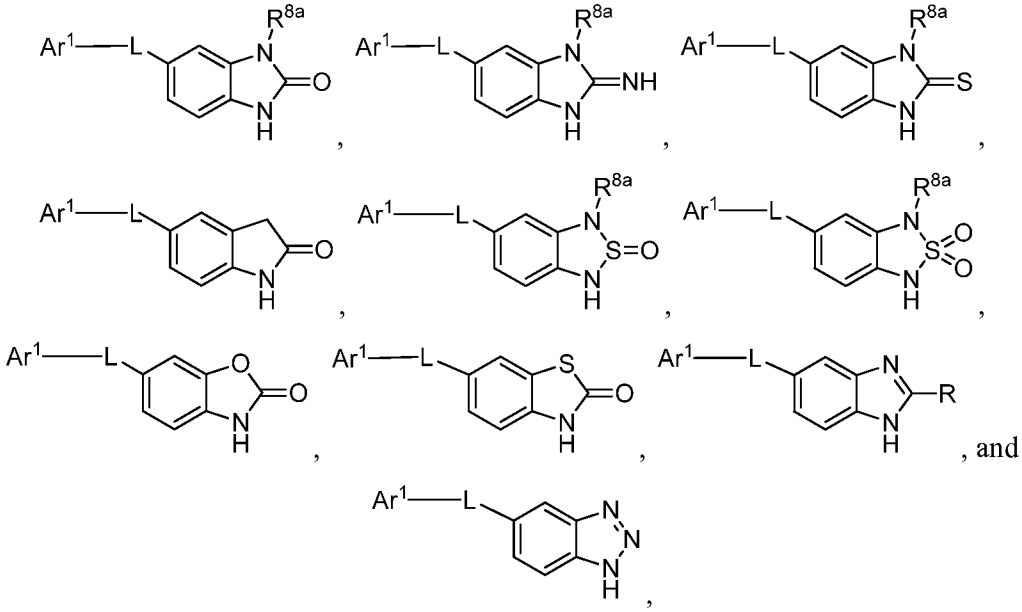
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00138] In various aspects, the invention relates to a compound having a structure selected from:



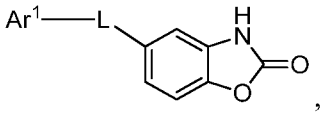
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00139] In various aspects, the invention relates to a compound having a structure selected from:



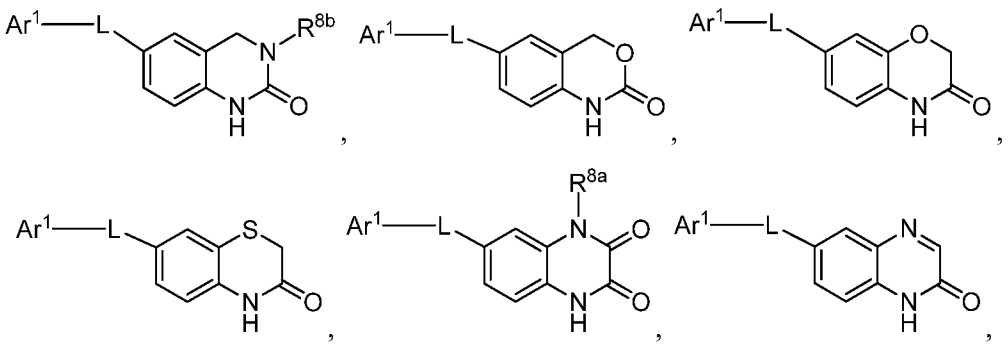
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

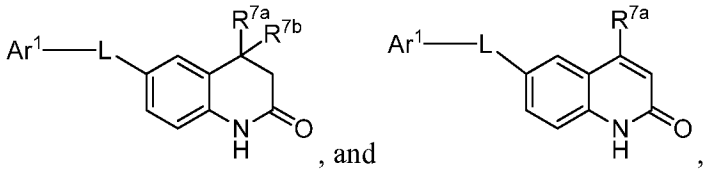
[00140] In various aspects, the invention relates to a compound having a structure represented by a formula:



wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

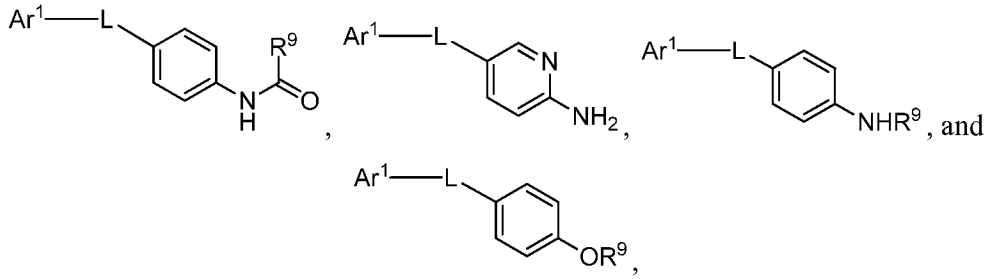
[00141] In various aspects, the invention relates to a compound having a structure selected from:





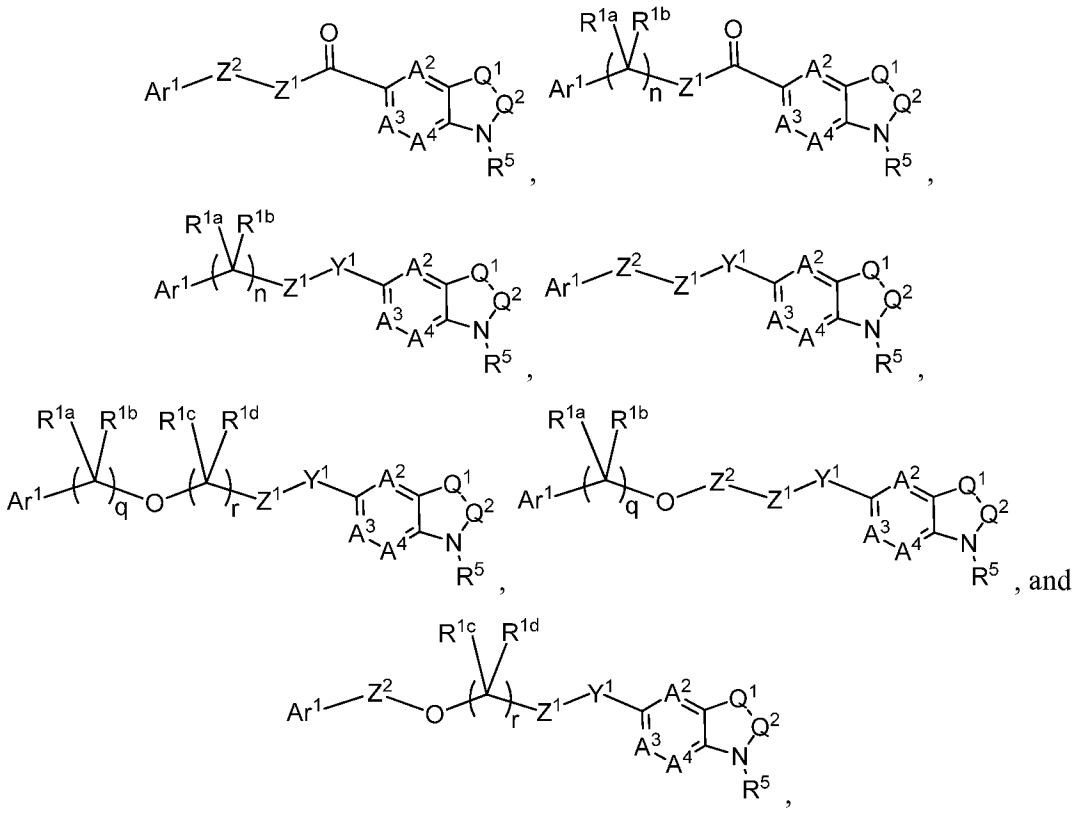
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00142] In various aspects, the invention relates to a compound having a structure selected from:



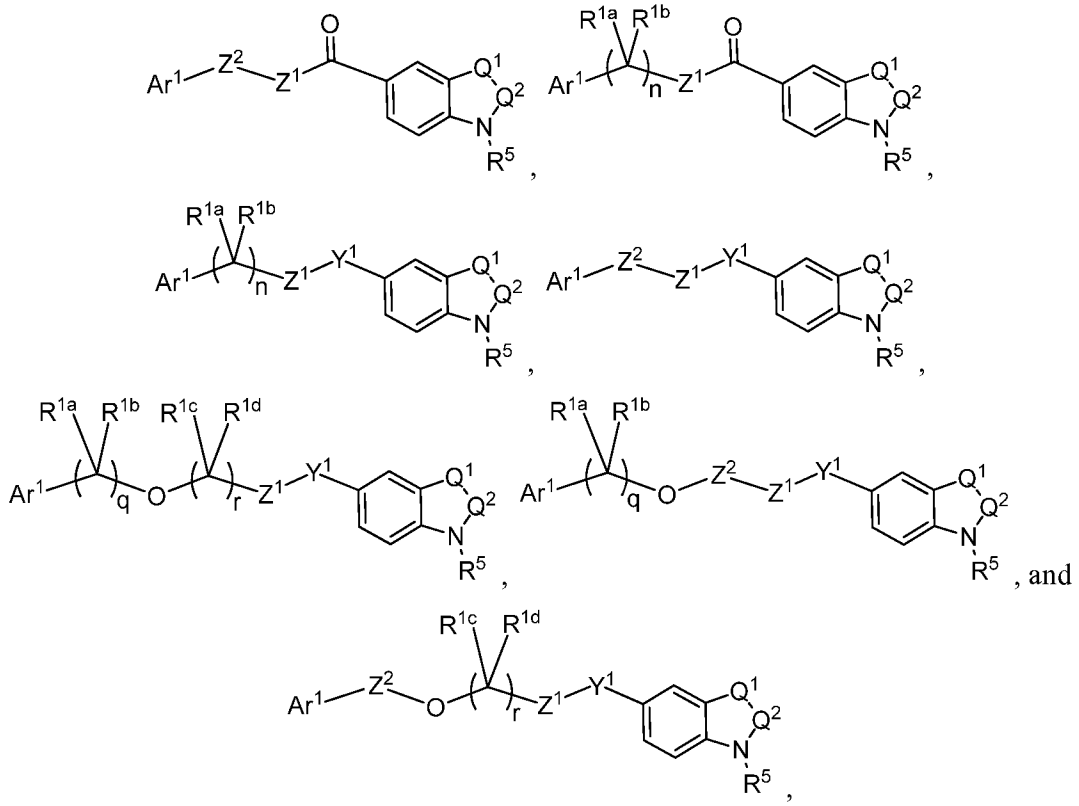
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00143] In various aspects, the invention relates to a compound having a structure selected from:



wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

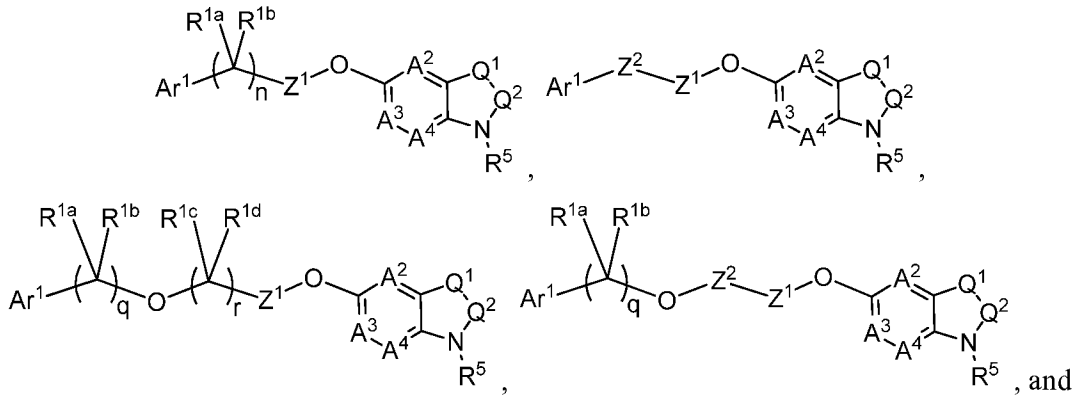
[00144] In various aspects, the invention relates to a compound having a structure selected from:



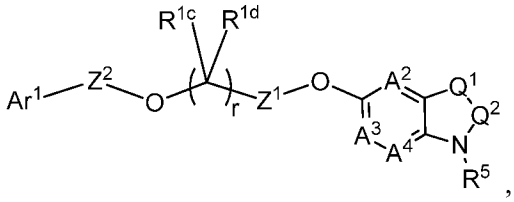
, and

wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00145] In various aspects, the invention relates to a compound having a structure selected from:

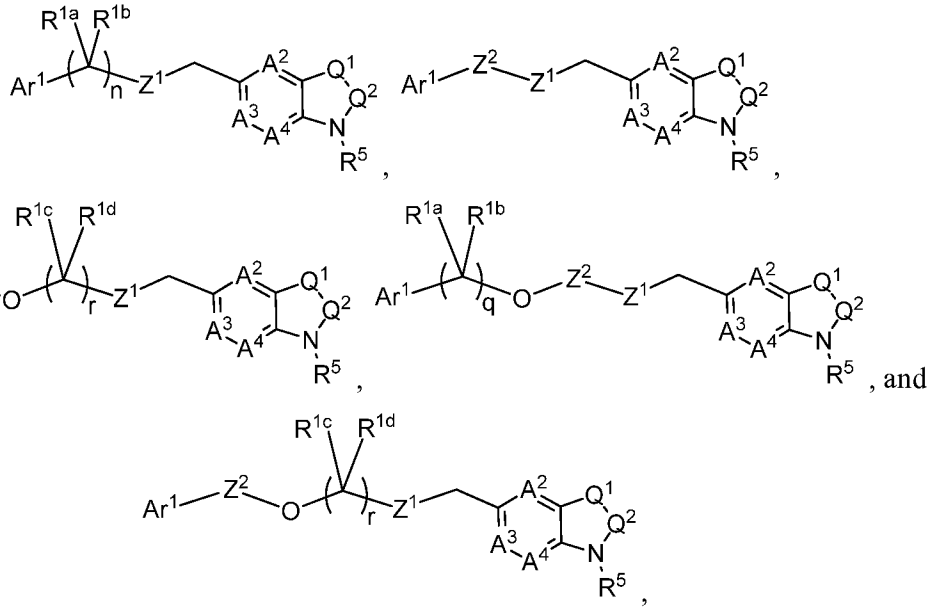


, and



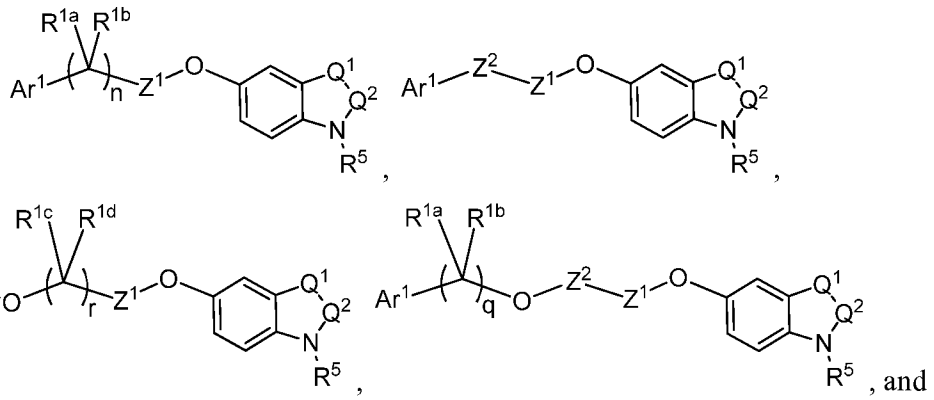
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

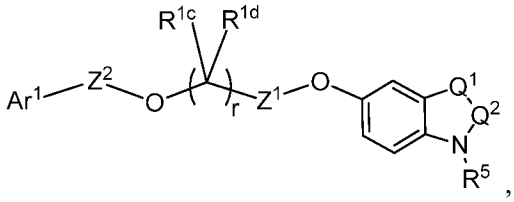
[00146] In various aspects, the invention relates to a compound having a structure selected from:



wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

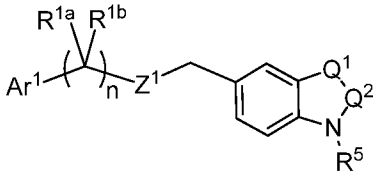
[00147] In various aspects, the invention relates to a compound having a structure selected from:

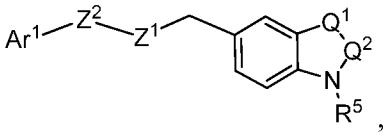


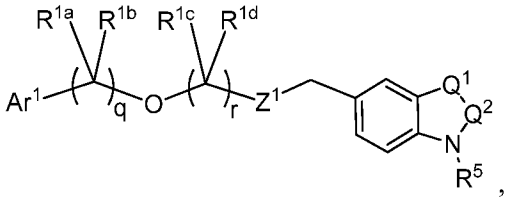


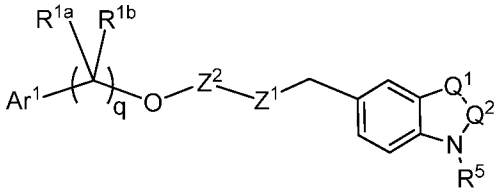
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00148] In various aspects, the invention relates to a compound having a structure selected from:

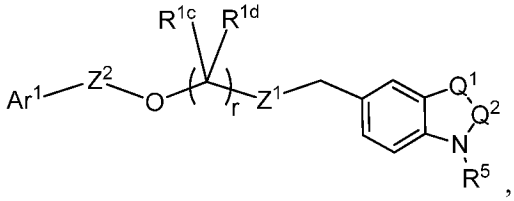






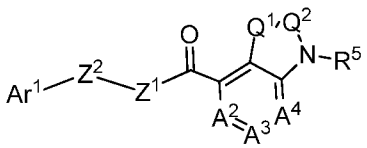


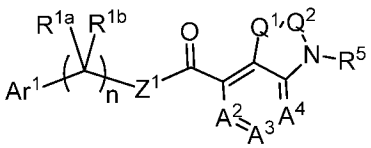
, and

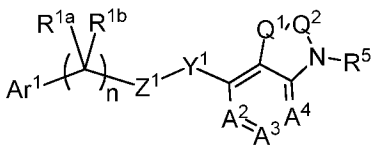


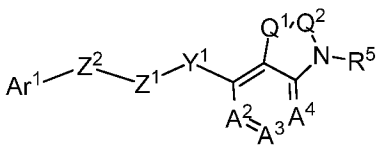
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

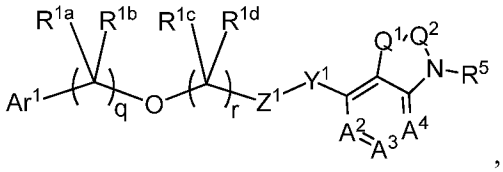
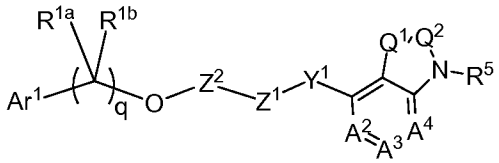
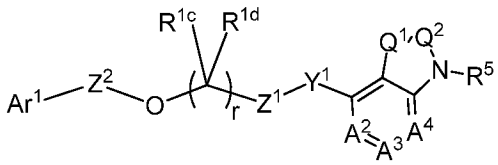
[00149] In various aspects, the invention relates to a compound having a structure represented by a formula:





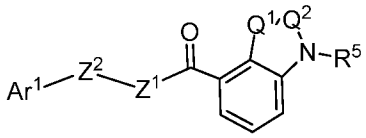
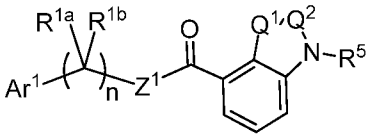
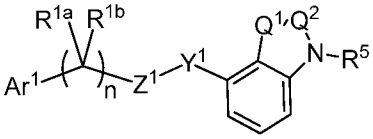
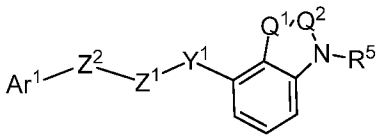
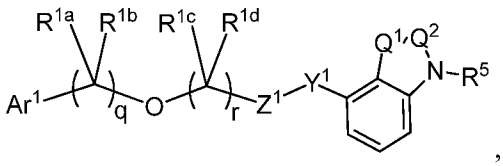
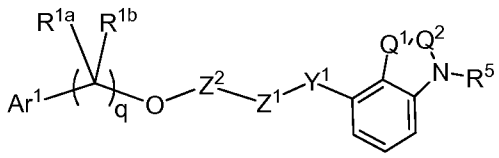
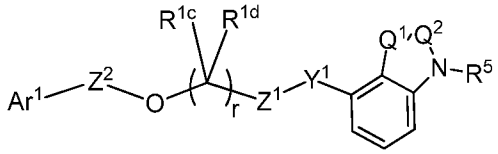





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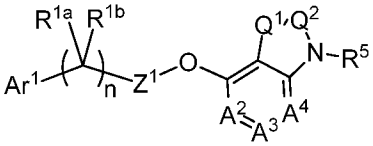
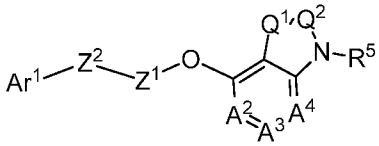
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

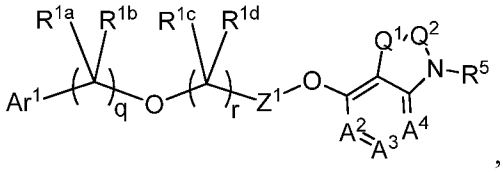
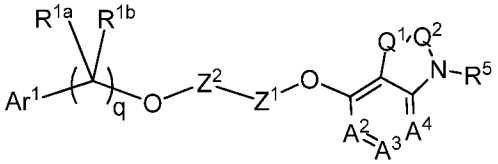
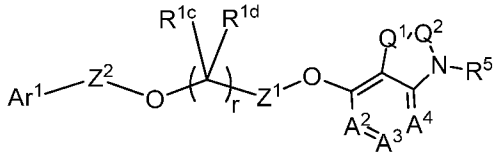
[00150] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

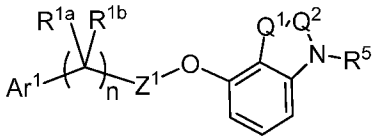
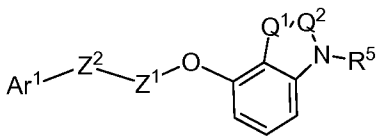
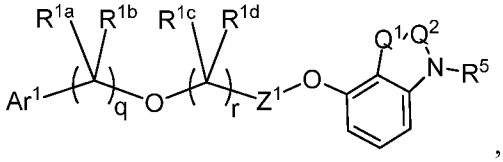
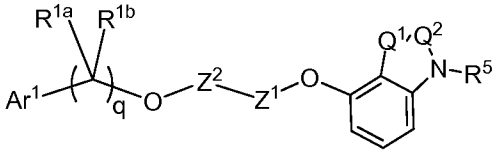
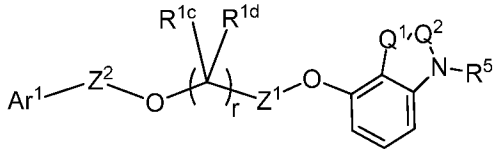
[00151] In various aspects, the invention relates to a compound having a structure represented by a formula:


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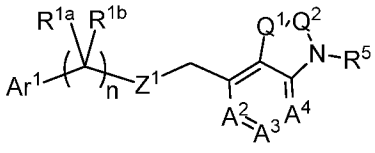
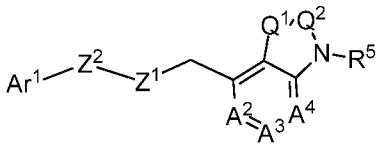
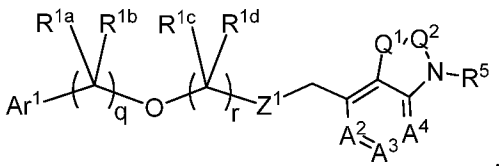
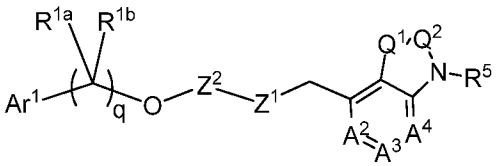
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

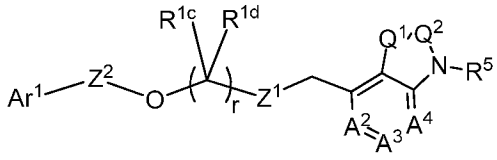
[00152] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

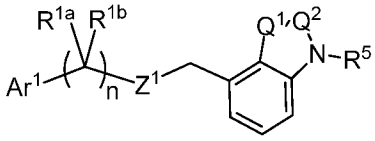
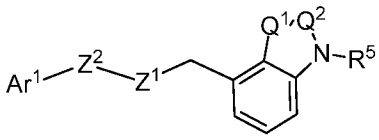
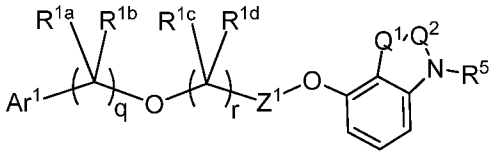
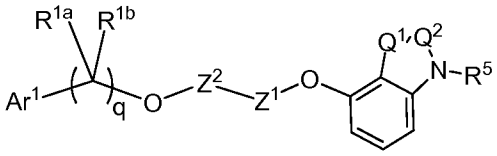
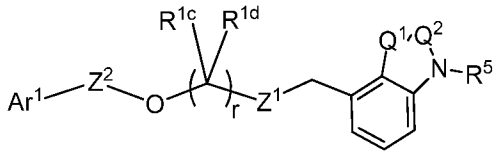
[00153] In various aspects, the invention relates to a compound having a structure represented by a formula:


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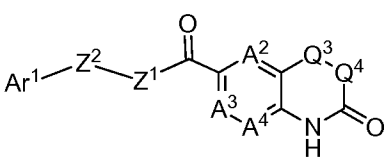
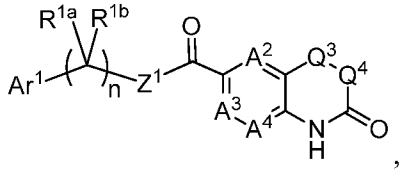
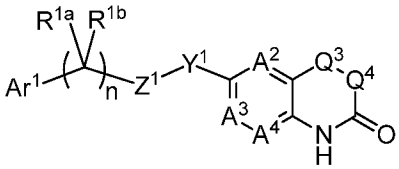
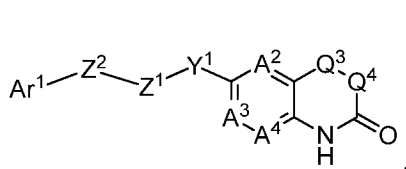
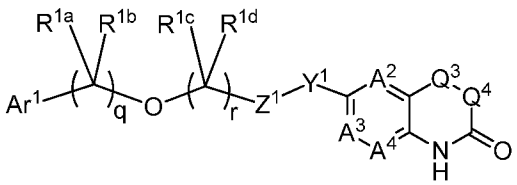
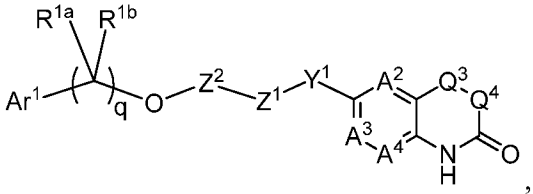
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

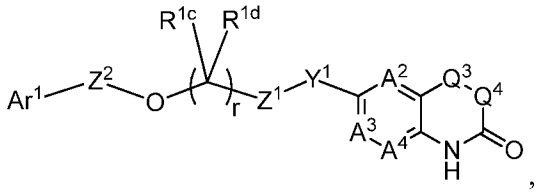
[00154] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

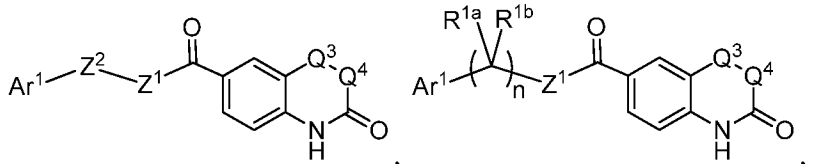
[00155] In various aspects, the invention relates to a compound having a structure represented by a formula:

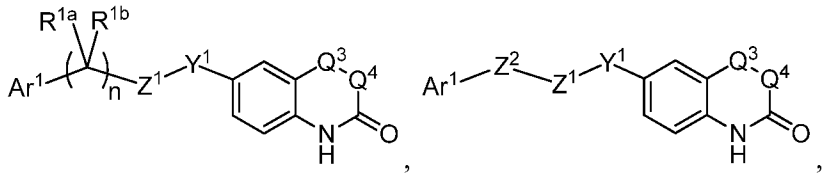

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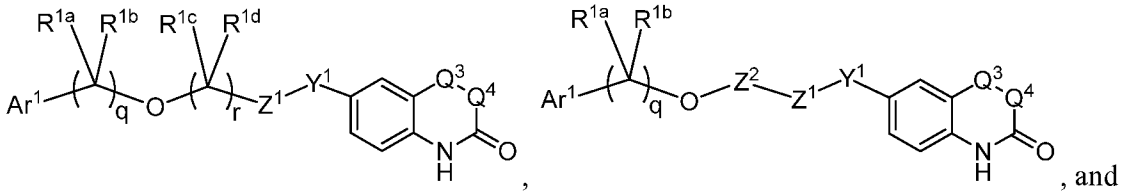


wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

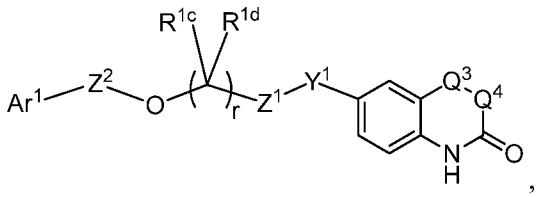
[00156] In various aspects, the invention relates to a compound having a structure represented by a formula:





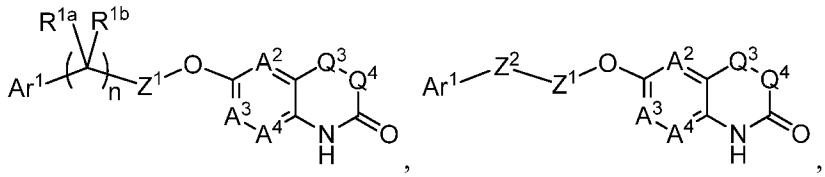


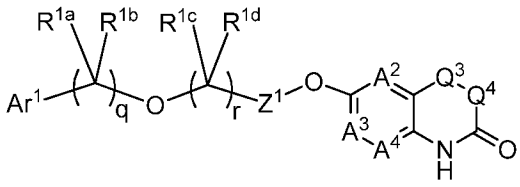
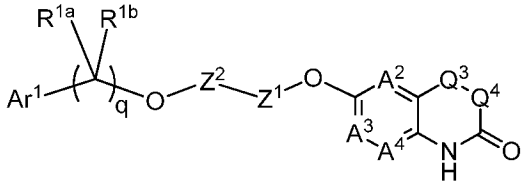
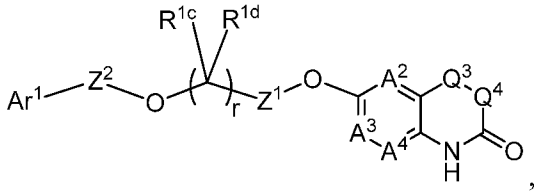
, and



wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

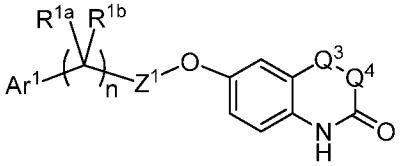
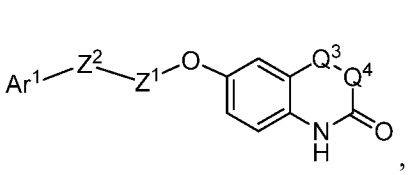
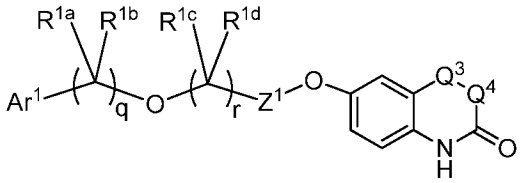
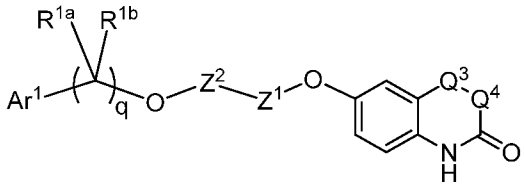
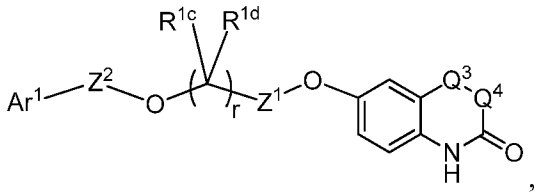
[00157] In various aspects, the invention relates to a compound having a structure represented by a formula:




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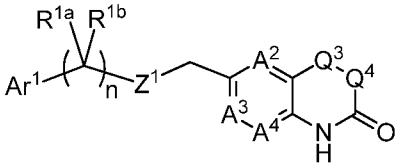
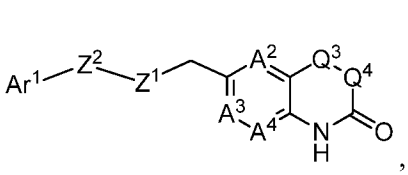
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

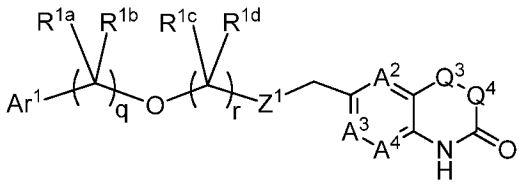
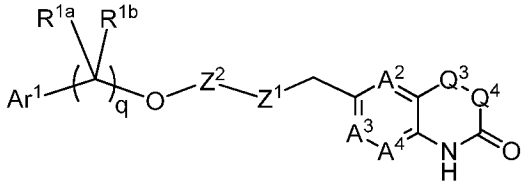
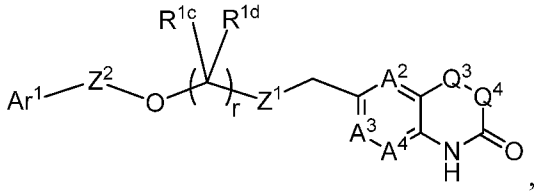
[00158] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

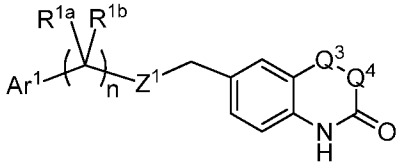
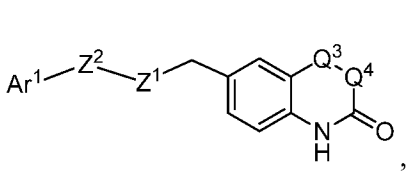
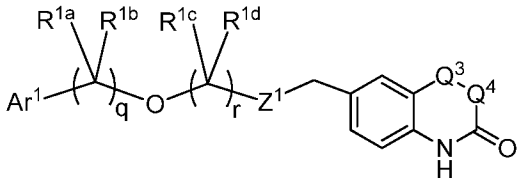
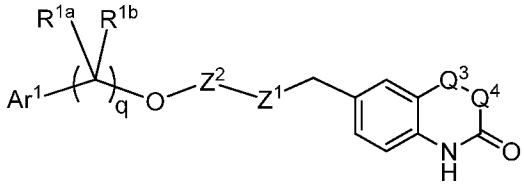
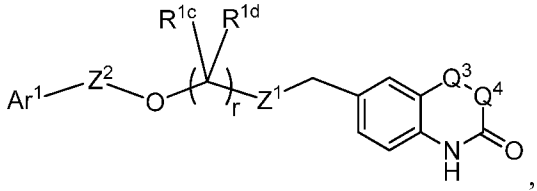
[00159] In various aspects, the invention relates to a compound having a structure represented by a formula:


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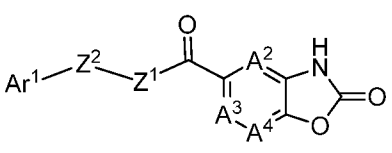
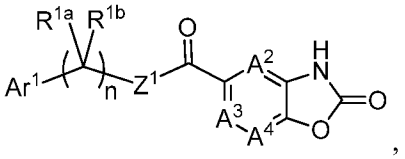
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

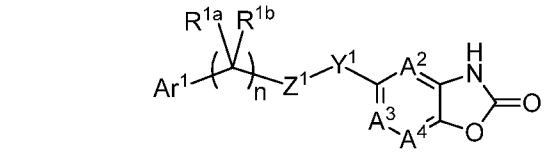
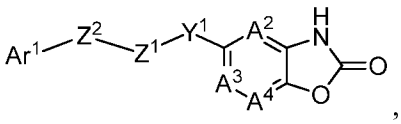
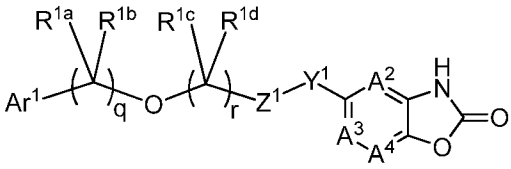
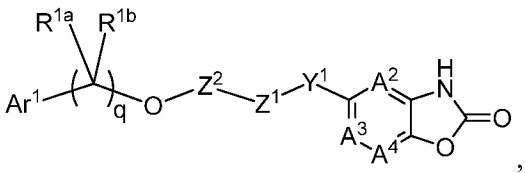
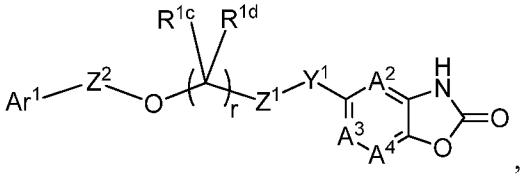
[00160] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

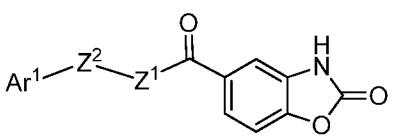
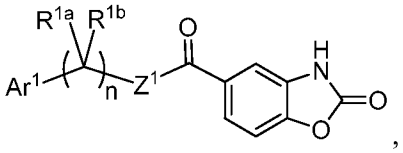
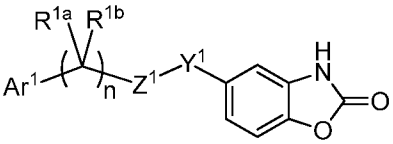
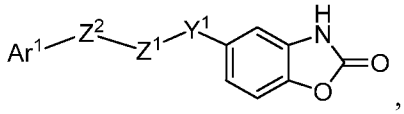
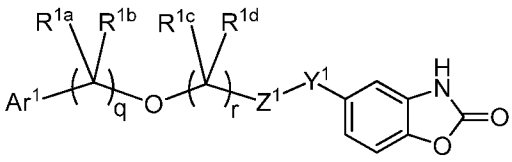
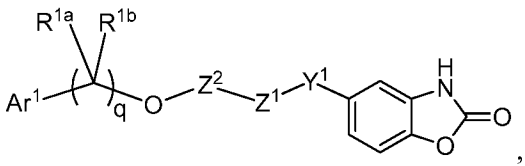
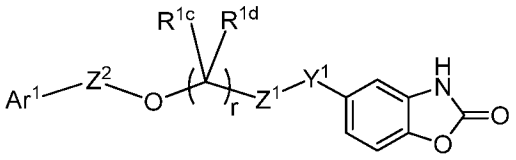
[00161] In various aspects, the invention relates to a compound having a structure represented by a formula:


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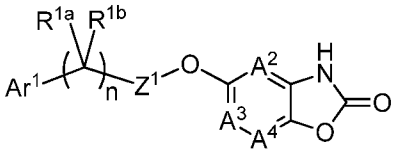
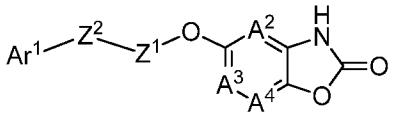
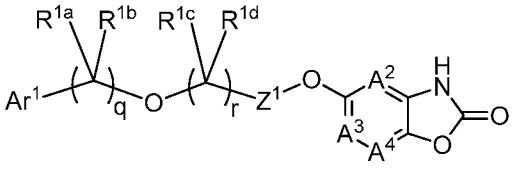
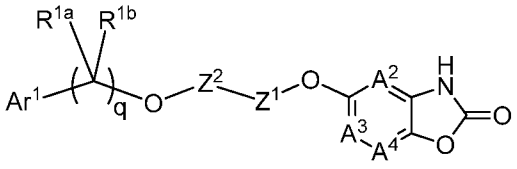
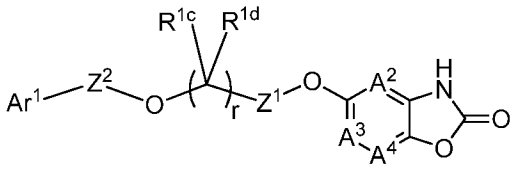
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00162] In various aspects, the invention relates to a compound having a structure represented by a formula:


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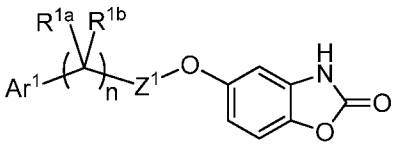
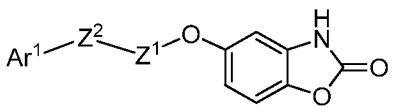
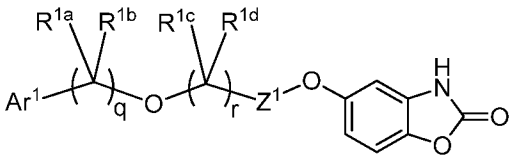
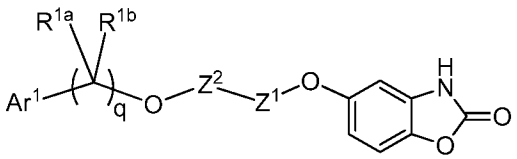
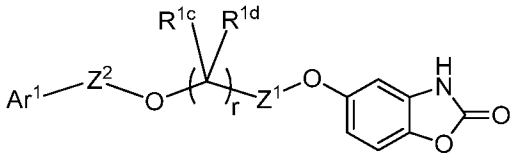
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00163] In various aspects, the invention relates to a compound having a structure represented by a formula:


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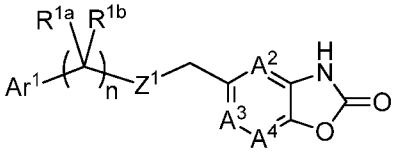
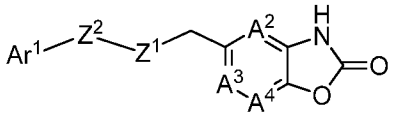
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

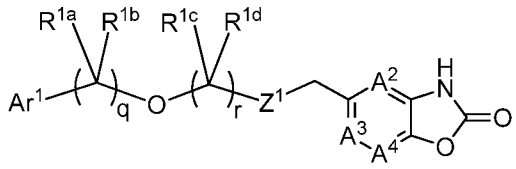
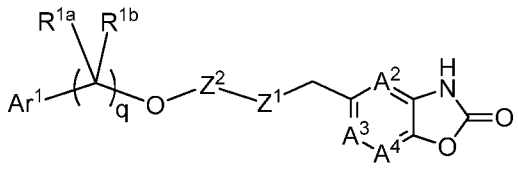
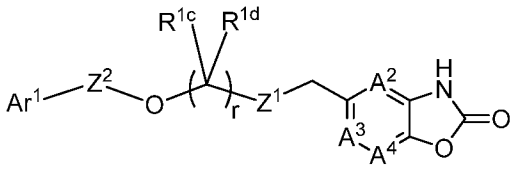
[00164] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

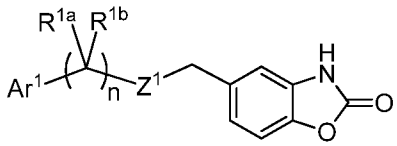
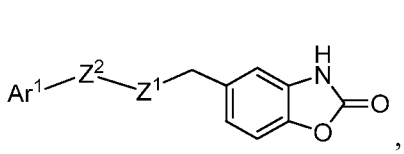
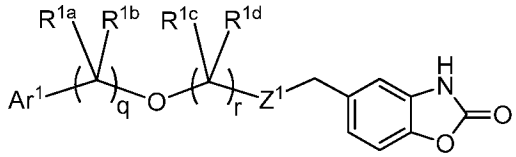
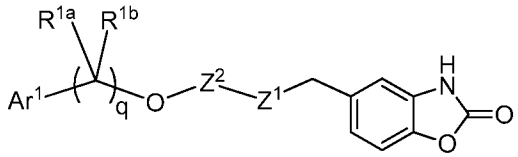
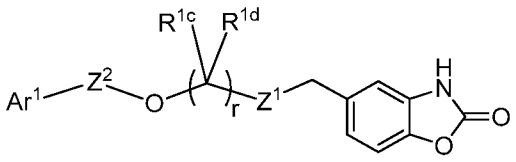
[00165] In various aspects, the invention relates to a compound having a structure represented by a formula:


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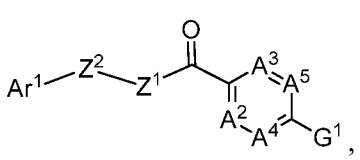
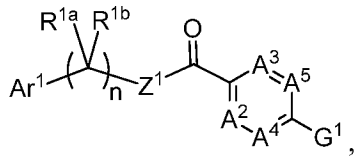
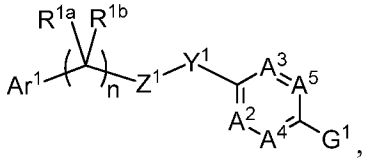
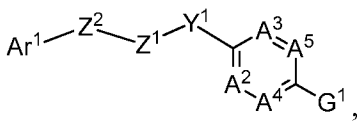
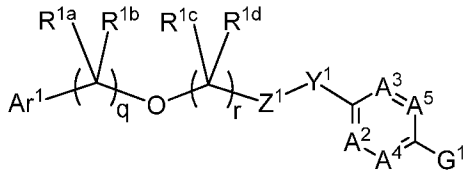
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

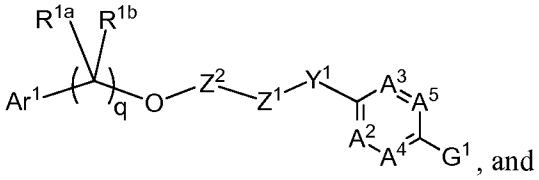
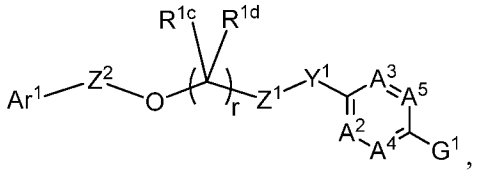
[00166] In various aspects, the invention relates to a compound having a structure represented by a formula:


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wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

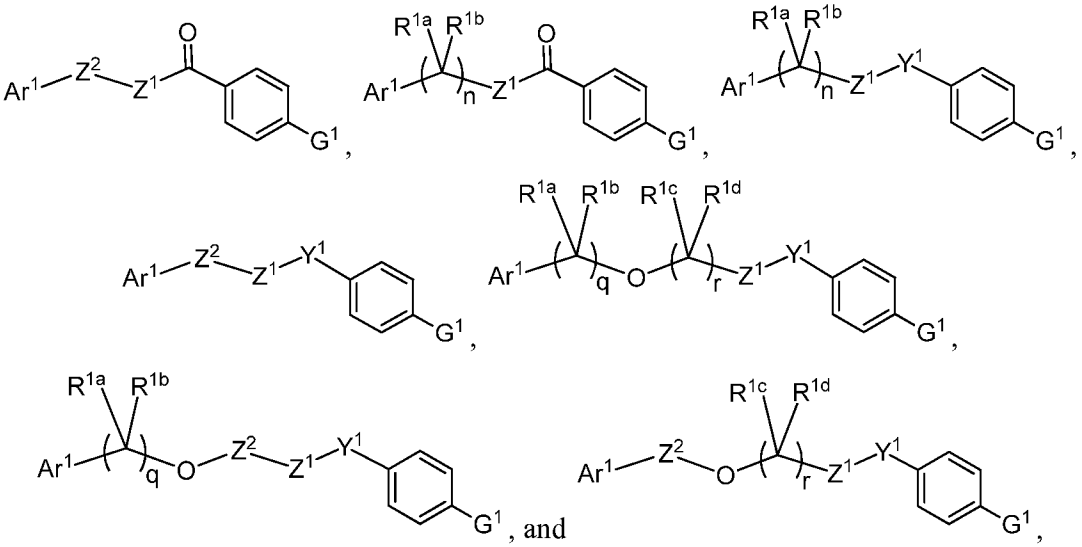
[00167] In various aspects, the invention relates to a compound having a structure represented by a formula:


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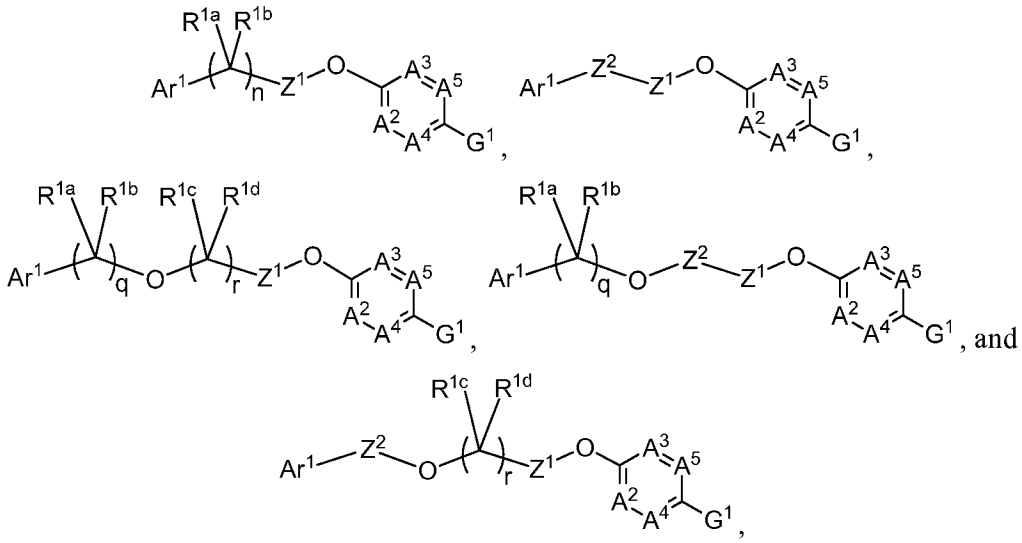
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00168] In various aspects, the invention relates to a compound having a structure represented by a formula:



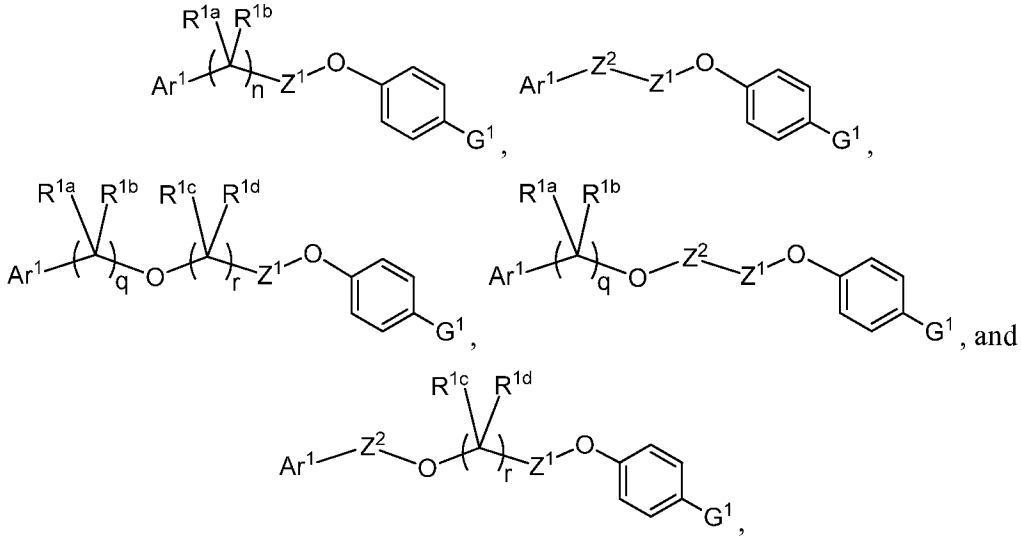
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00169] In various aspects, the invention relates to a compound having a structure represented by a formula:



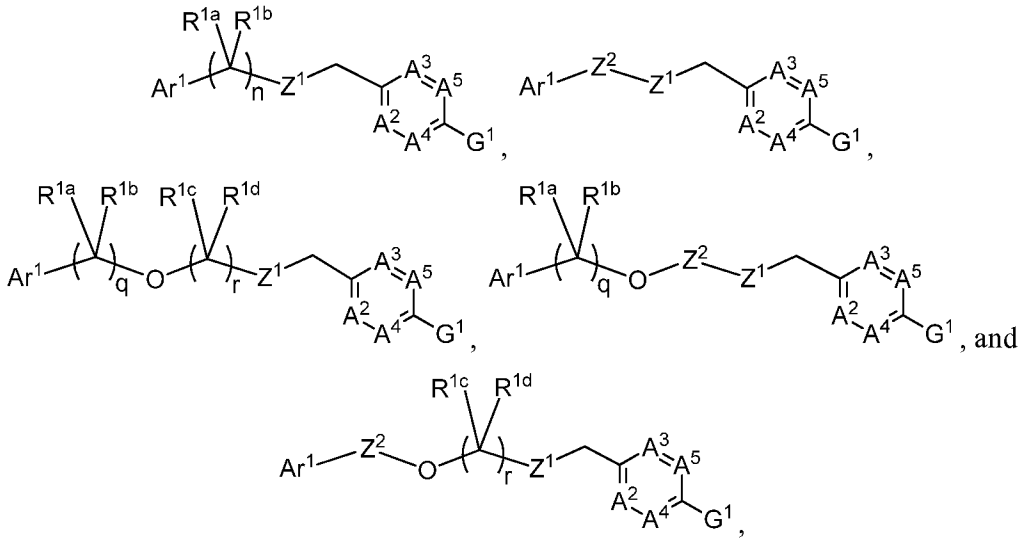
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00170] In various aspects, the invention relates to a compound having a structure represented by a formula:



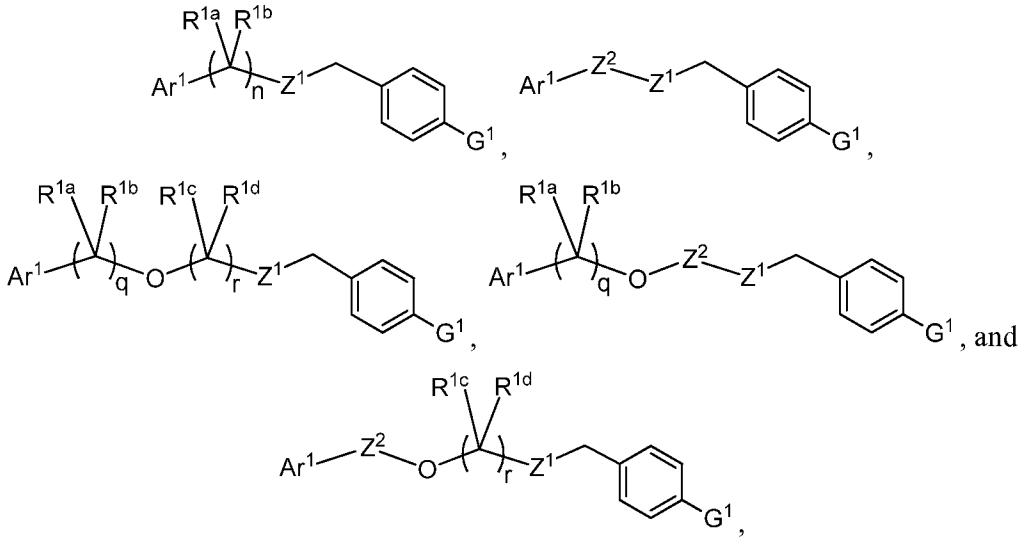
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00171] In various aspects, the invention relates to a compound having a structure represented by a formula:



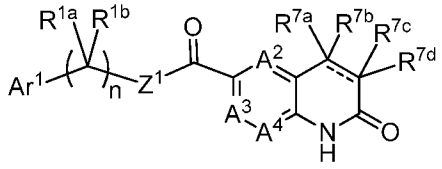
wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00172] In various aspects, the invention relates to a compound having a structure represented by a formula:

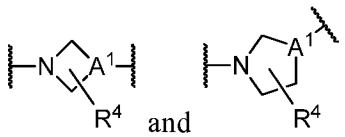


wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00173] In various aspects, the invention relates to a compound having a structure represented by a formula:



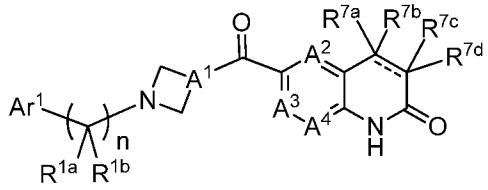
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Z^1 is a 4- or 5-membered hetercycloalkyl selected from:



wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c};

wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

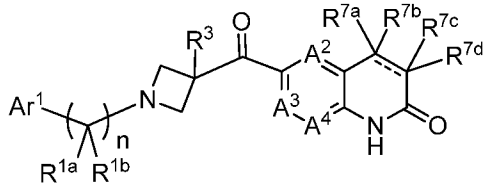
[00174] In a further aspect, the invention relates to a compound having a structure represented by the formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

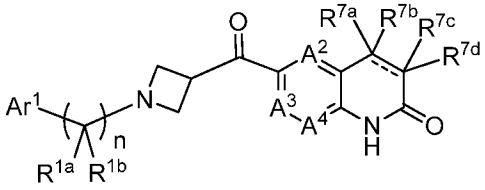
[00175] In a further aspect, the invention relates to a compound having a structure represented by the formula:



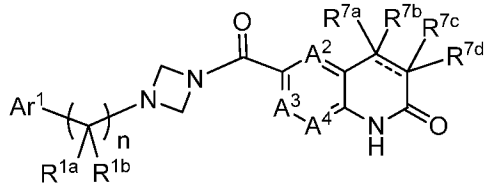
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00176] In a further aspect, the invention relates to a compound having a structure selected from:



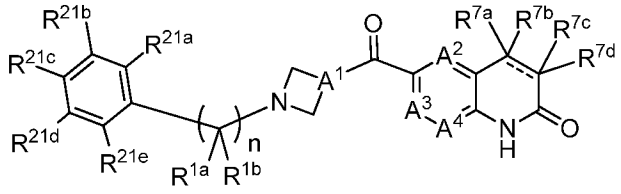
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

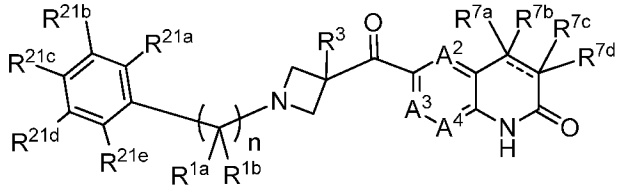
[00177] In a further aspect, the invention relates to a compound having a structure selected from:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

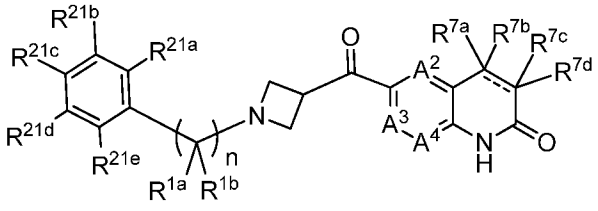
[00178] In a further aspect, the invention relates to a compound having a structure selected from:



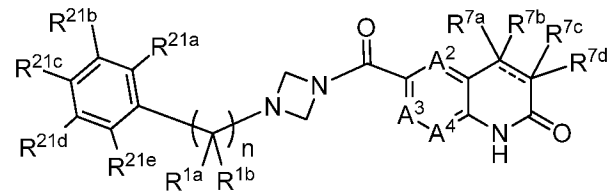
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00179] In a further aspect, the invention relates to a compound having a structure selected from:



and

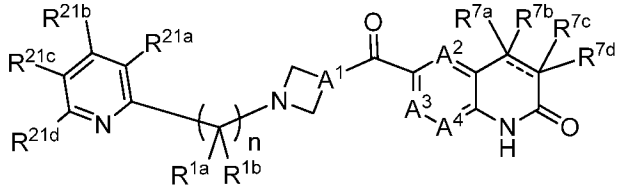


;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and

C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

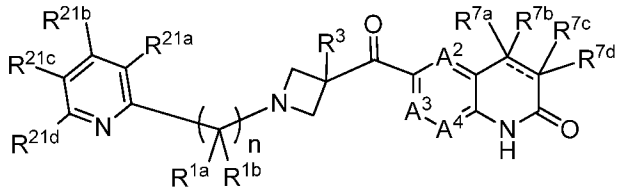
[00180] In a further aspect, the invention relates to a compound having a structure represented by the formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

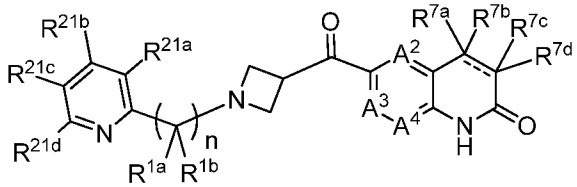
[00181] In a further aspect, the invention relates to a compound having a structure represented by the formula:



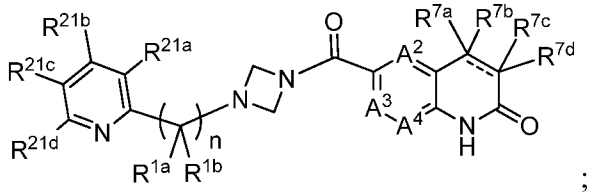
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00182] In a further aspect, the invention relates to a compound having a structure selected from:



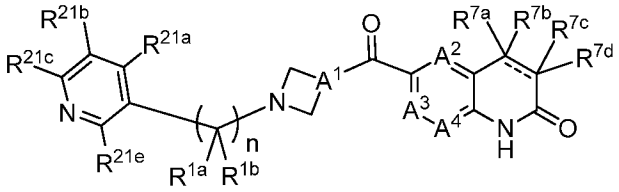
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

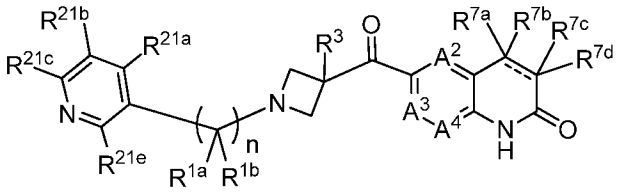
[00183] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

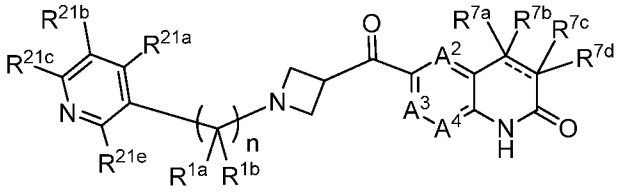
[00184] In a further aspect, the invention relates to a compound having a structure represented by a formula:



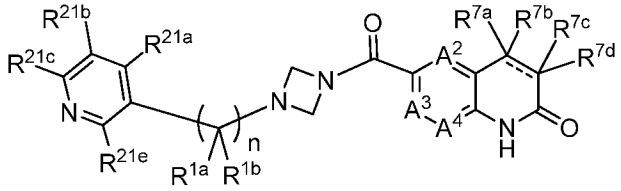
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00185] In a further aspect, the invention relates to a compound having a structure selected from:



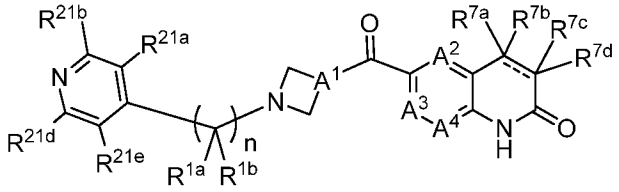
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

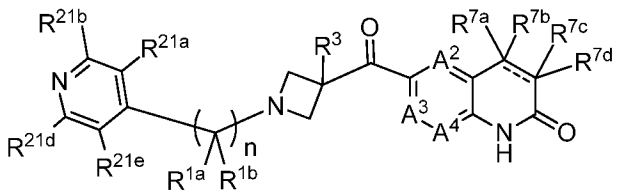
[00186] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00187] In a further aspect, the invention relates to a compound having a structure represented by a formula:

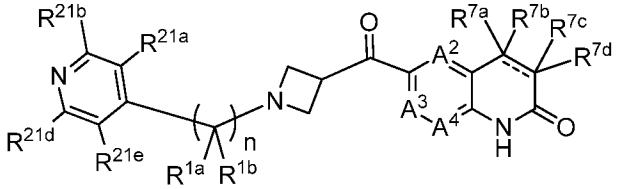


,

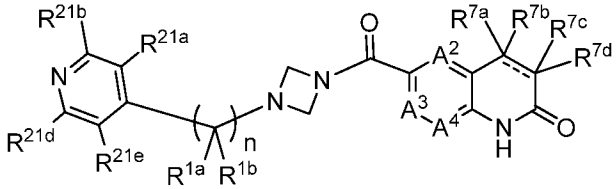
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00188] In a further aspect, the invention relates to a compound having a structure selected from:



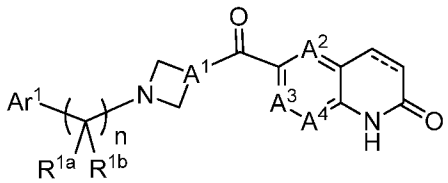
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

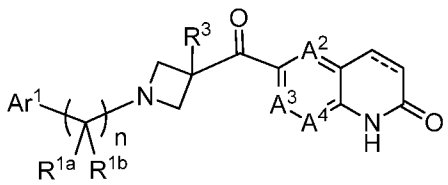
[00189] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

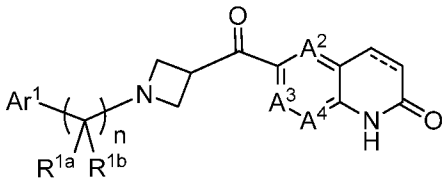
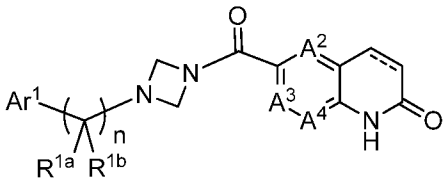
[00190] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

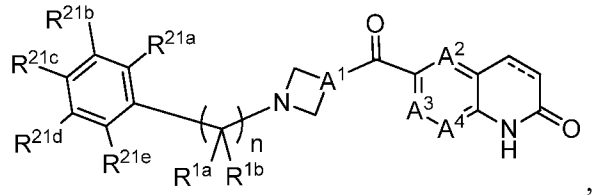
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00191] In a further aspect, the invention relates to a compound having a structure selected from:


and

;

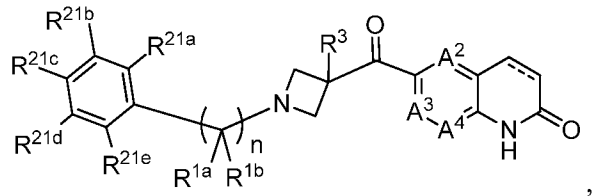
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00192] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

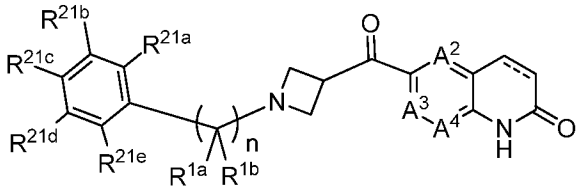
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00193] In a further aspect, the invention relates to a compound having a structure represented by a formula:

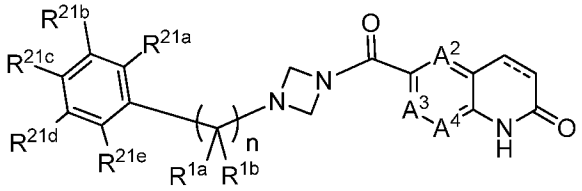

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00194] In a further aspect, the invention relates to a compound having a structure selected from:



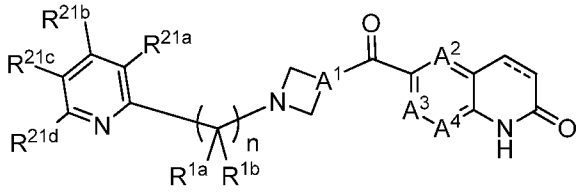
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

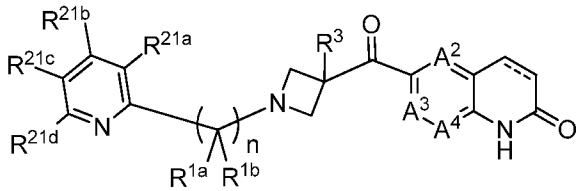
[00195] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00196] In a further aspect, the invention relates to a compound having a structure represented by a formula:

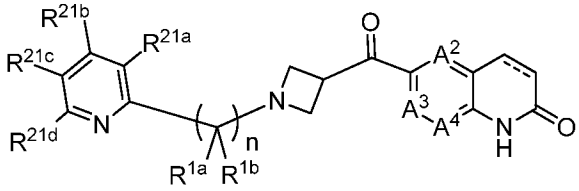


,

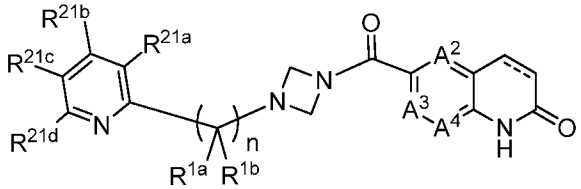
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00197] In a further aspect, the invention relates to a compound having a structure selected from:

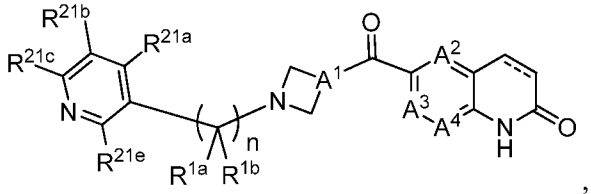


and



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

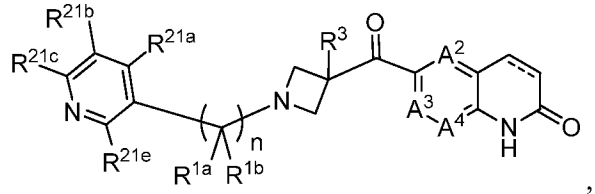
[00198] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

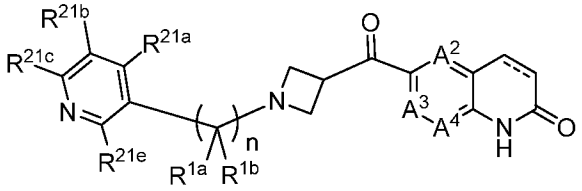
[00199] In a further aspect, the invention relates to a compound having a structure represented by a formula:



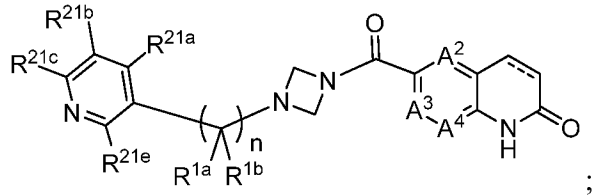
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00200] In a further aspect, the invention relates to a compound having a structure selected from:



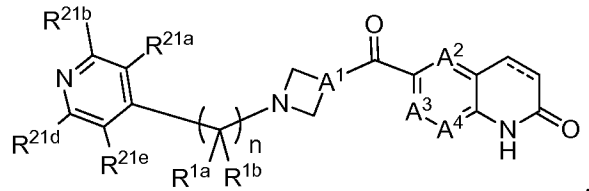
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00201] In a further aspect, the invention relates to a compound having a structure represented by a formula:

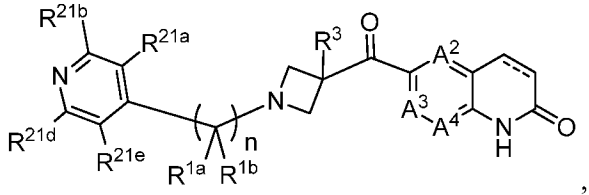


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

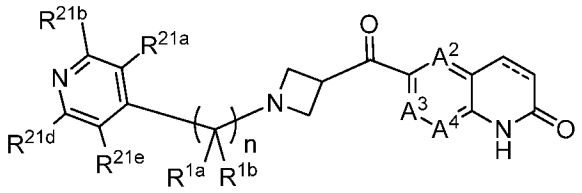
[00202] In a further aspect, the invention relates to a compound having a structure represented by a formula:



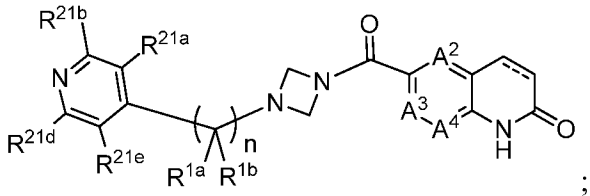
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00203] In a further aspect, the invention relates to a compound having a structure selected from:



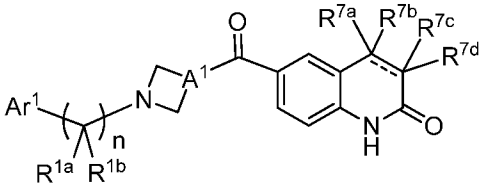
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

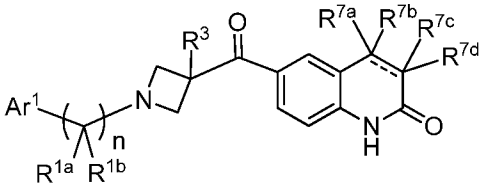
[00204] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

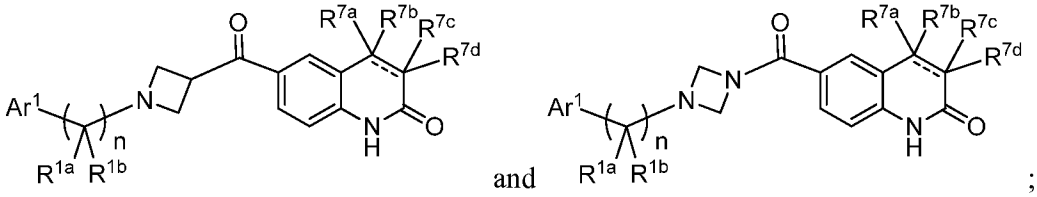
[00205] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00206] In a further aspect, the invention relates to a compound having a structure selected from:

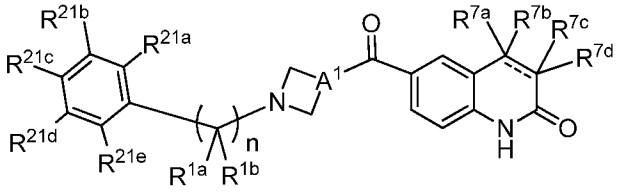


and

;

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

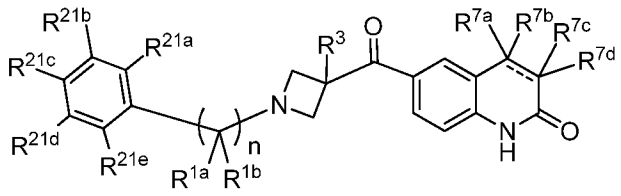
[00207] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

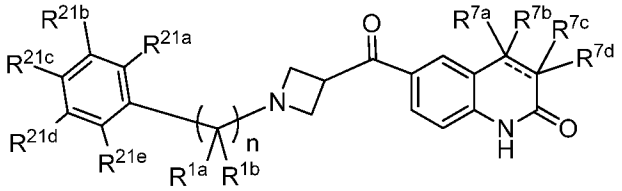
[00208] In a further aspect, the invention relates to a compound having a structure represented by a formula:



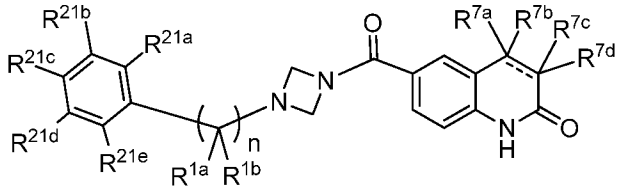
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00209] In a further aspect, the invention relates to a compound having a structure selected from:



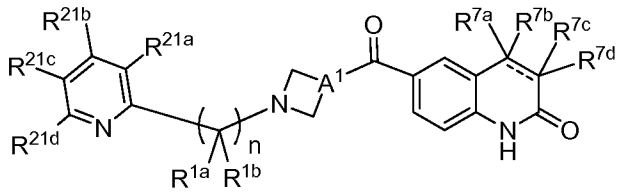
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00210] In a further aspect, the invention relates to a compound having a structure represented by a formula:

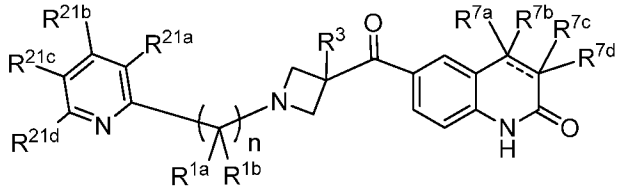


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

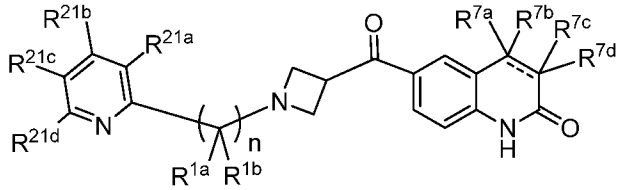
[00211] In a further aspect, the invention relates to a compound having a structure represented by a formula:



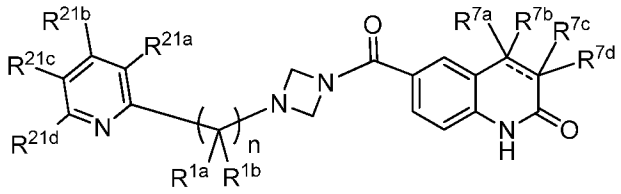
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00212] In a further aspect, the invention relates to a compound having a structure selected from:



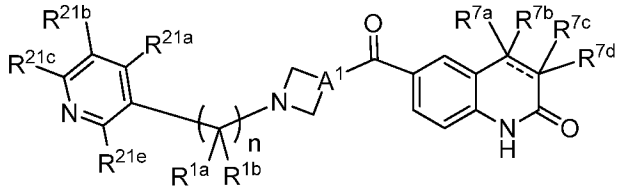
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

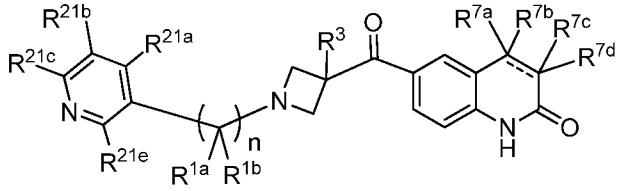
[00213] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

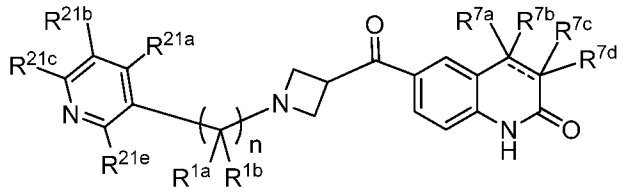
[00214] In a further aspect, the invention relates to a compound having a structure represented by a formula:



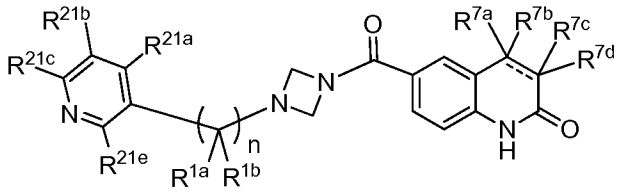
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00215] In a further aspect, the invention relates to a compound having a structure selected from:



and

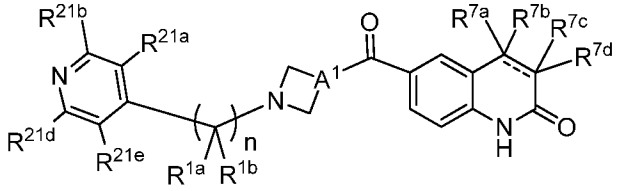


;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

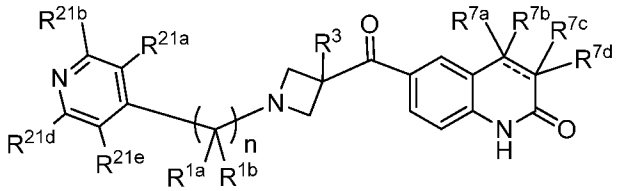
[00216] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

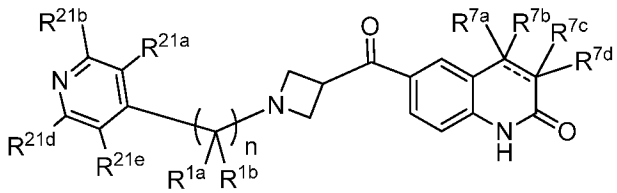
[00217] In a further aspect, the invention relates to a compound having a structure represented by a formula:



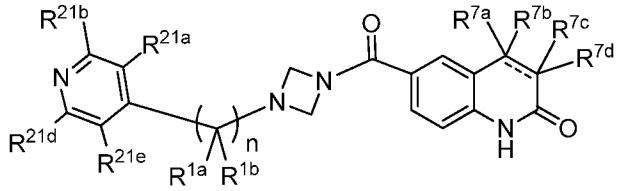
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00218] In a further aspect, the invention relates to a compound having a structure selected from:



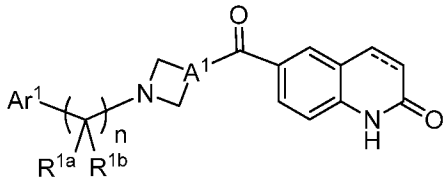
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

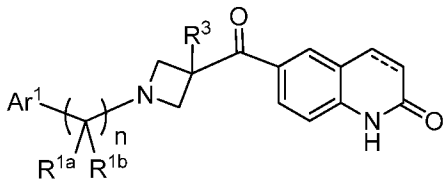
[00219] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

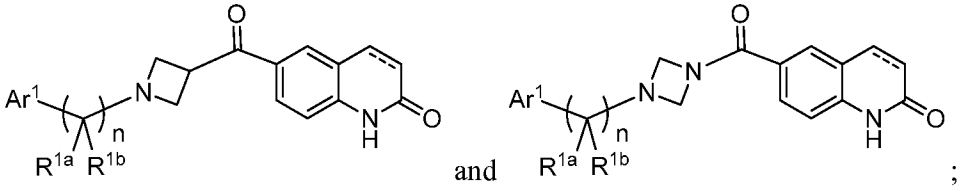
[00220] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00221] In a further aspect, the invention relates to a compound having a structure selected from:

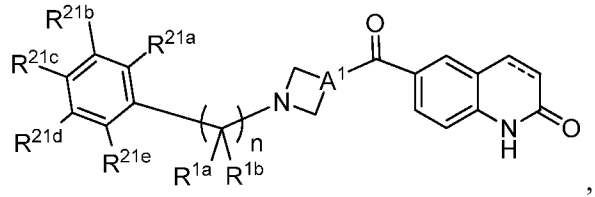


;

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00222] In a further aspect, the invention relates to a compound having a structure

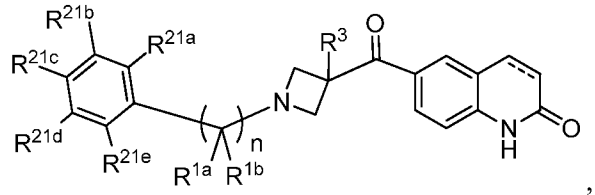
represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

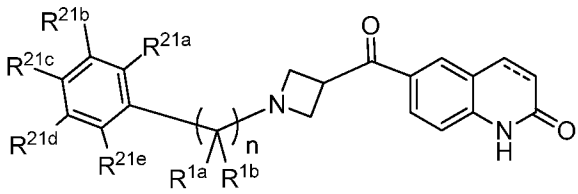
[00223] In a further aspect, the invention relates to a compound having a structure represented by a formula:



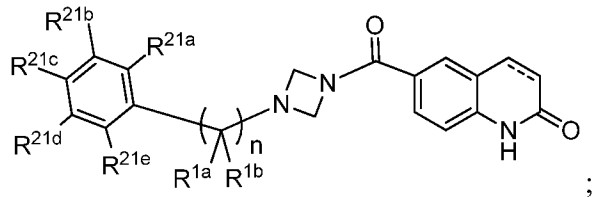
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00224] In a further aspect, the invention relates to a compound having a structure selected from:



and

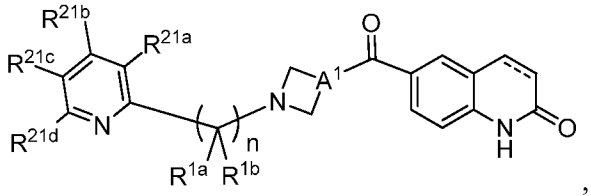


;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4

alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

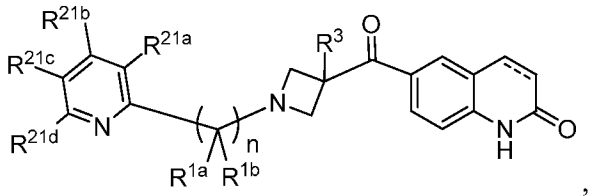
[00225] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

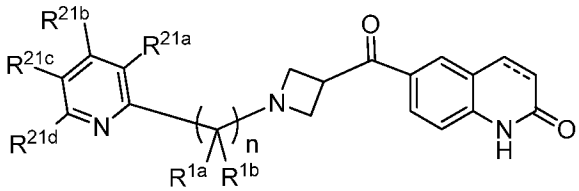
[00226] In a further aspect, the invention relates to a compound having a structure represented by a formula:



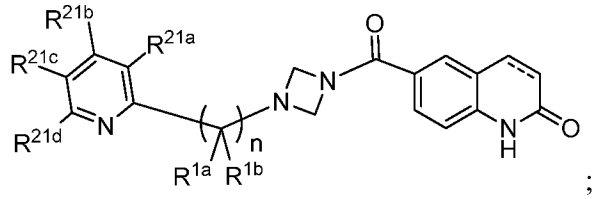
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00227] In a further aspect, the invention relates to a compound having a structure selected from:



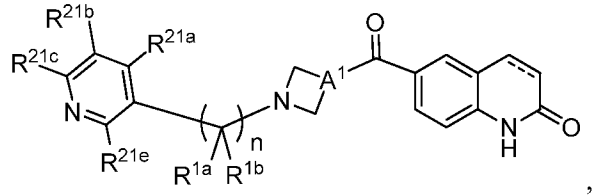
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

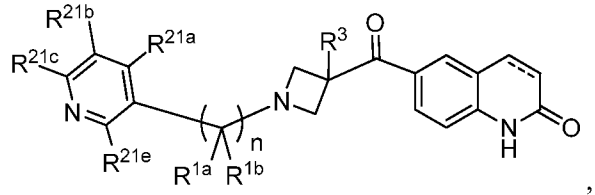
[00228] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

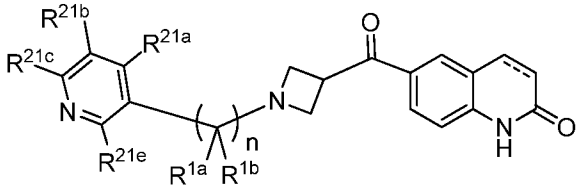
[00229] In a further aspect, the invention relates to a compound having a structure represented by a formula:



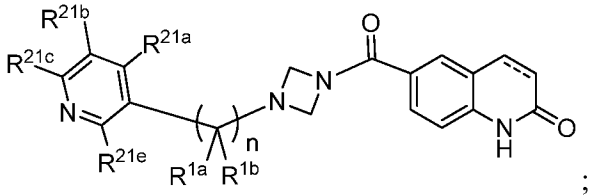
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00230] In a further aspect, the invention relates to a compound having a structure selected from:



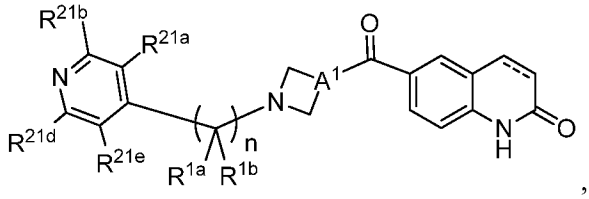
and



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

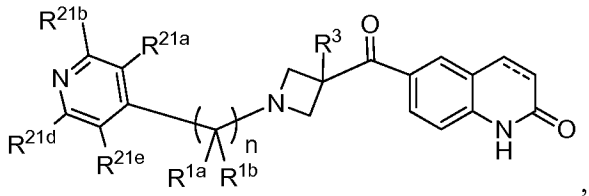
[00231] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00232] In a further aspect, the invention relates to a compound having a structure represented by a formula:

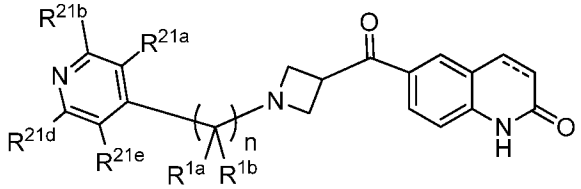


,

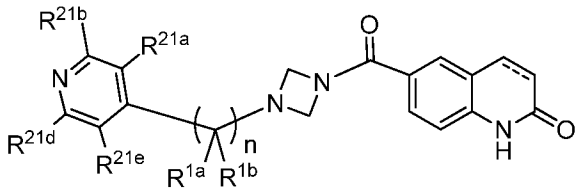
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00233] In a further aspect, the invention relates to a compound having a structure represented by a formula:



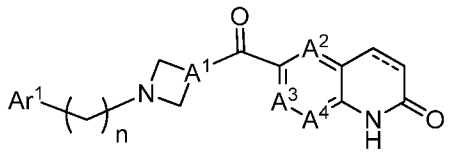
or



;

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

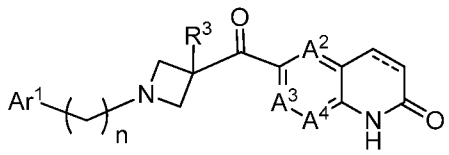
[00234] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

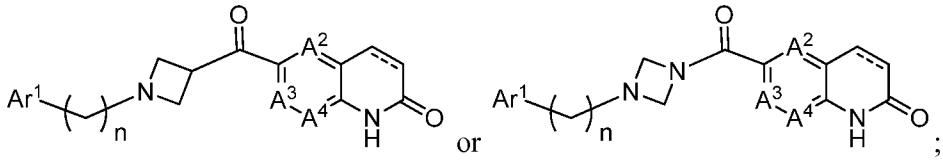
[00235] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

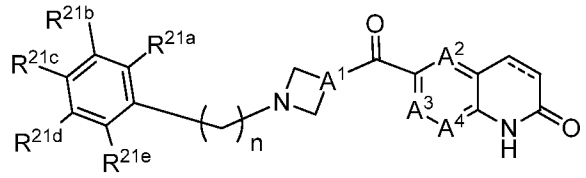
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00236] In a further aspect, the invention relates to a compound having a structure represented by a formula:



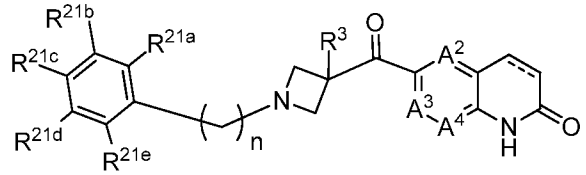
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00237] In a further aspect, the invention relates to a compound having a structure represented by a formula:



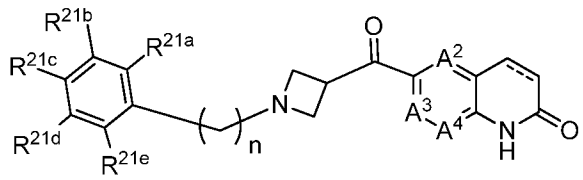
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00238] In a further aspect, the invention relates to a compound having a structure represented by a formula:

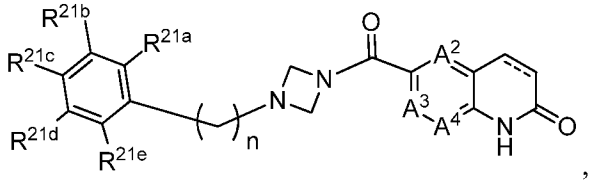


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00239] In a further aspect, the invention relates to a compound having a structure represented by a formula:

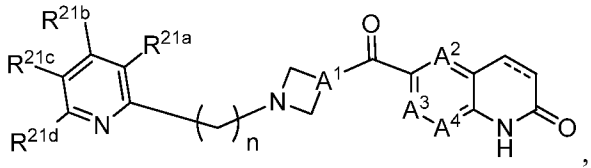


or



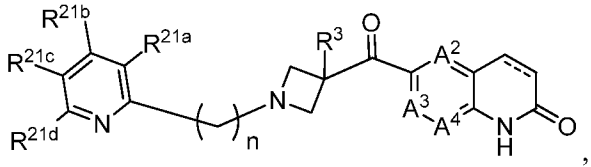
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00240] In a further aspect, the invention relates to a compound having a structure represented by a formula:



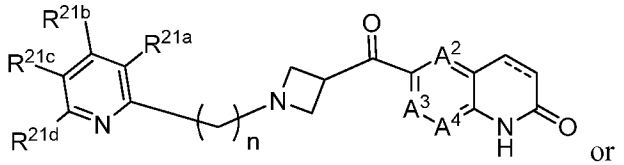
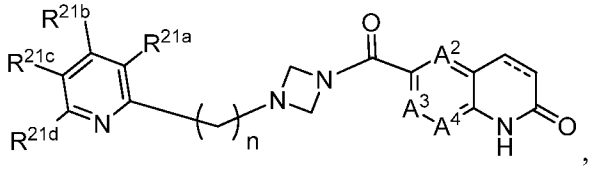
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00241] In a further aspect, the invention relates to a compound having a structure represented by a formula:



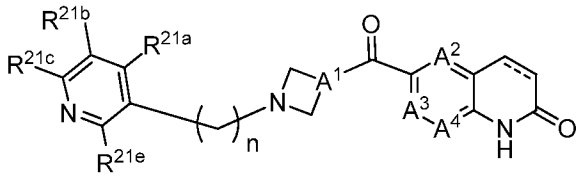
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00242] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

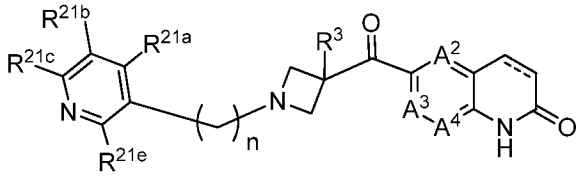
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00243] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

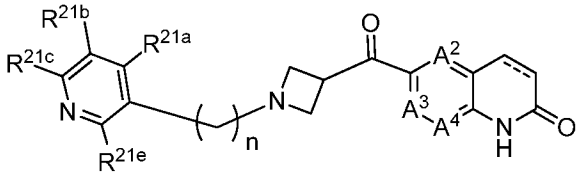
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00244] In a further aspect, the invention relates to a compound having a structure represented by a formula:

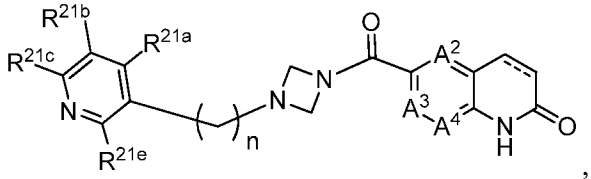

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00245] In a further aspect, the invention relates to a compound having a structure represented by a formula:



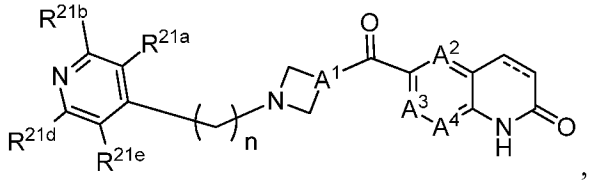
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

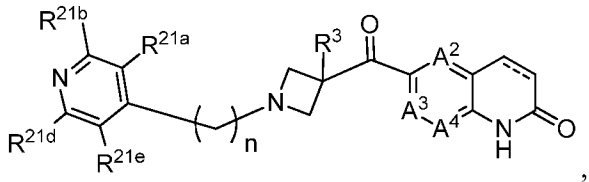
[00246] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00247] In a further aspect, the invention relates to a compound having a structure represented by a formula:

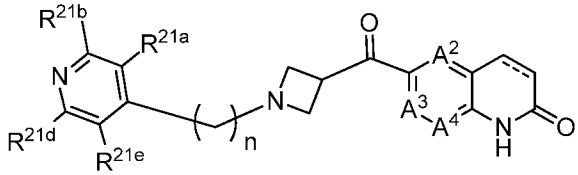


,

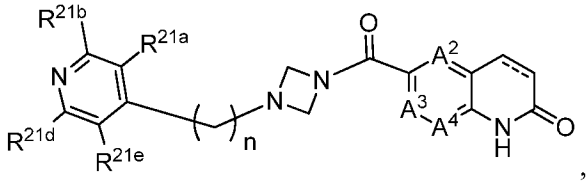
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00248] In a further aspect, the invention relates to a compound having a structure represented by a formula:



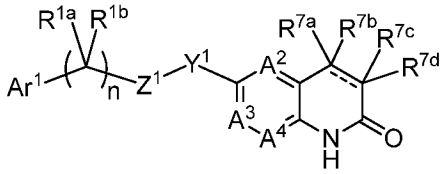
or



,

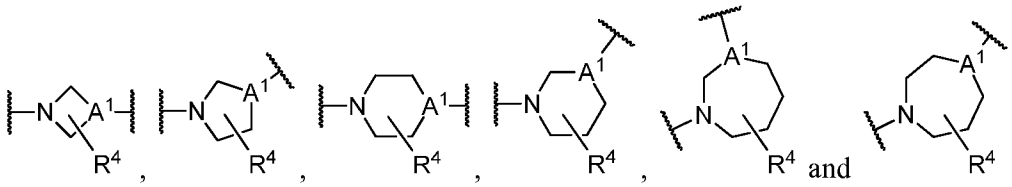
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00249] In various aspects, the invention relates to a compound having a structure represented by a formula:



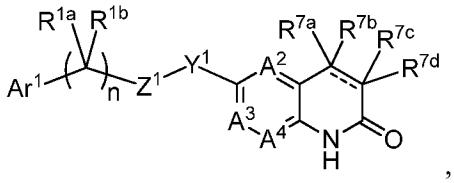
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Y^1 is selected from —O— and —CR^2R^{2b}—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is a 4- to 7-membered hetercycloalkyl selected from:

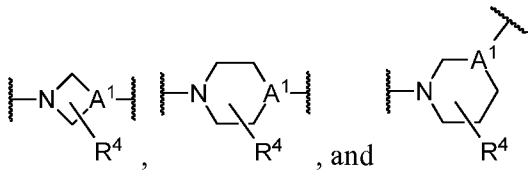


wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00250] In various aspects, the invention relates to a compound having a structure represented by a formula:

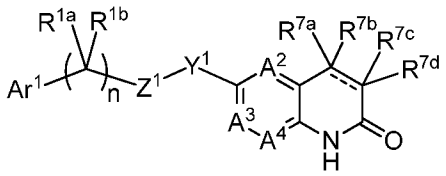


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein $Y^1$is selected from —O— and —CR^2R^{2b}—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is a 4- or 6-membered hetercycloalkyl selected from:

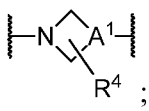


wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00251] In various aspects, the invention relates to a compound having a structure represented by a formula:



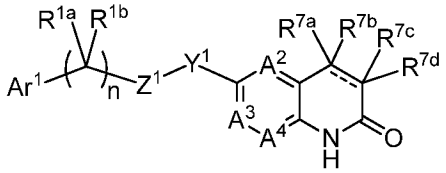
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Y^1 is selected from —O— and —CR^2R^{2b}—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is:



wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from

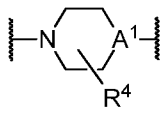
hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00252] In various aspects, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Y^1 is selected from —O— and —CR^2R^{2b}—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is:

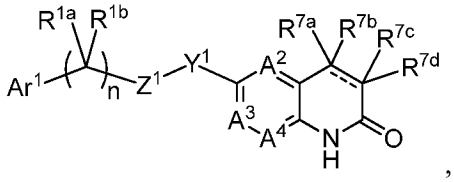


;

wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl,

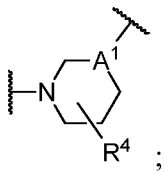
C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00253] In various aspects, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Y^1 is selected from —O— and —CR^2R^{2b}—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is:

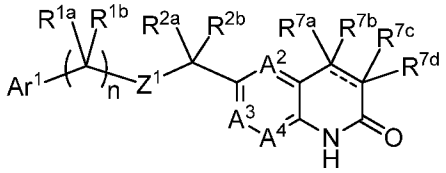


;

wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt,

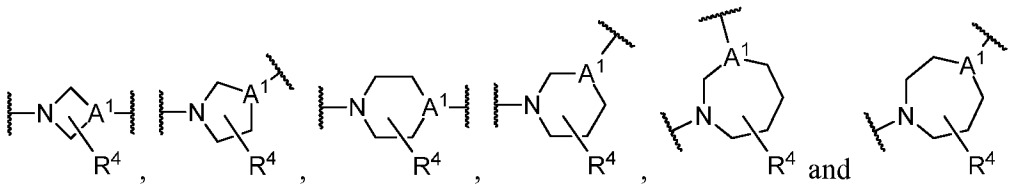
hydrate, solvate, or polymorph thereof.

[00254] In various aspects, the invention relates to a compound having a structure represented by a formula:



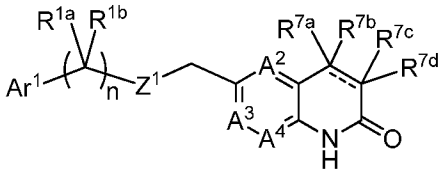
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Z^1 is a 4- to 7-membered hetercycloalkyl selected from:



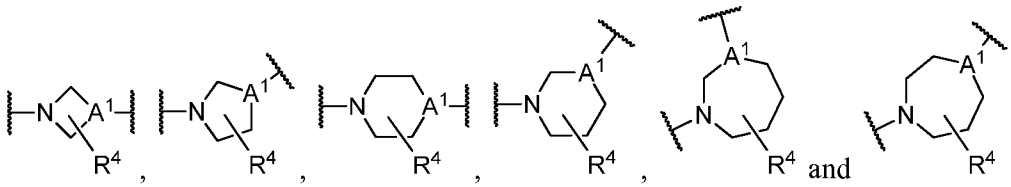
; wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00255] In various aspects, the invention relates to a compound having a structure represented by a formula:



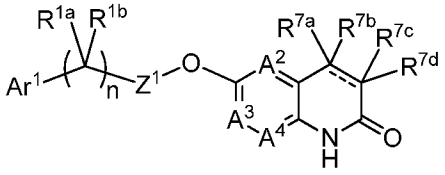
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Z^1 is a 4- to 7-membered hetercycloalkyl selected from:



wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

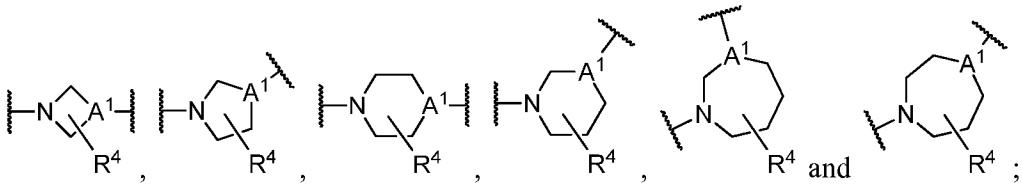
[00256] In various aspects, the invention relates to a compound having a structure represented by a formula:



,

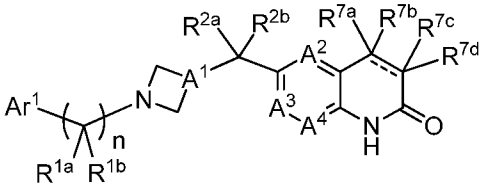
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is

selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Z^1 is a 4- to 7-membered hetercycloalkyl selected from:



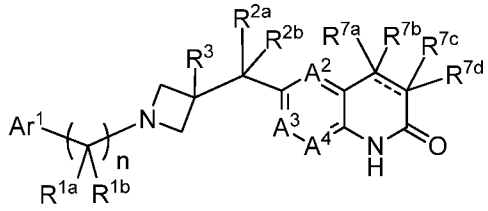
wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00257] In a further aspect, the invention relates to a compound having a structure represented by a formula:



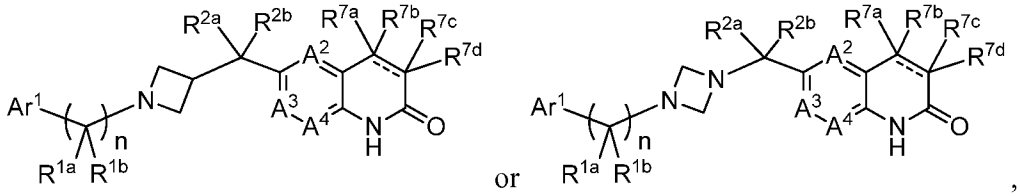
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00258] In a further aspect, the invention relates to a compound having a structure represented by a formula:



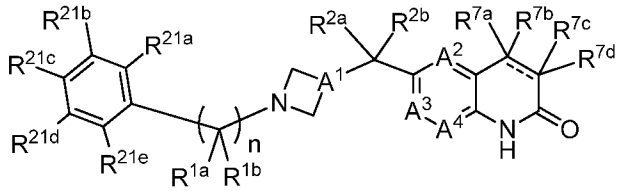
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00259] In a further aspect, the invention relates to a compound having a structure represented by a formula:



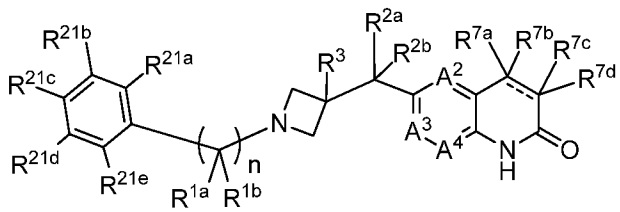
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00260] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

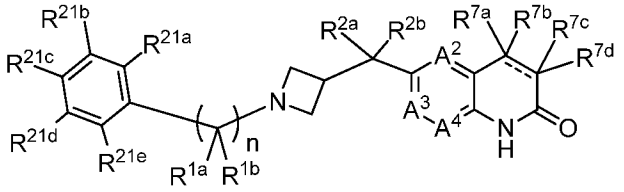
[00261] In a further aspect, the invention relates to a compound having a structure represented by a formula:



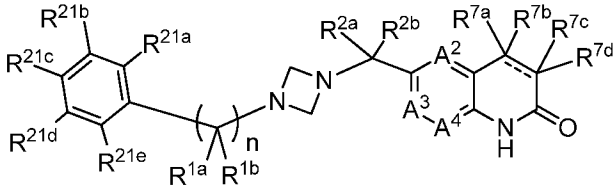
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4

alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00262] In a further aspect, the invention relates to a compound having a structure represented by a formula:



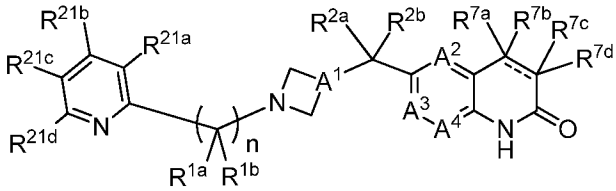
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

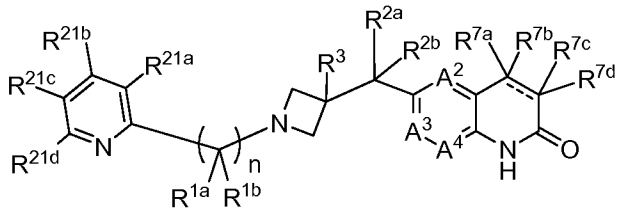
[00263] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

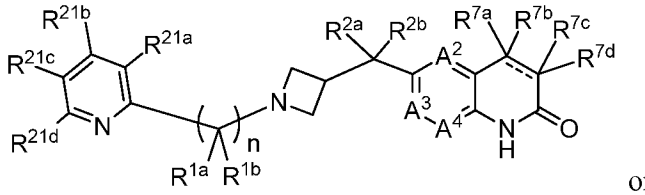
[00264] In a further aspect, the invention relates to a compound having a structure represented by a formula:



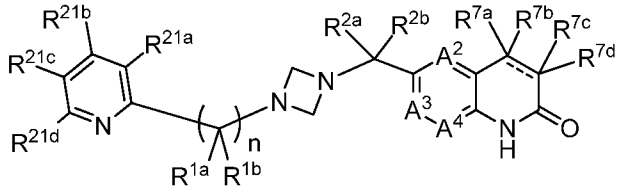
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00265] In a further aspect, the invention relates to a compound having a structure represented by a formula:



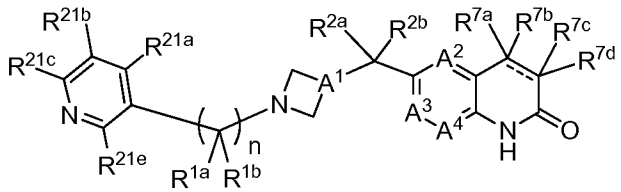
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00266] In a further aspect, the invention relates to a compound having a structure represented by a formula:

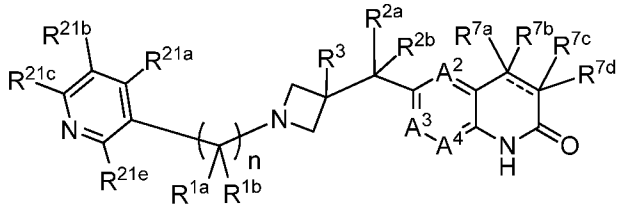


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

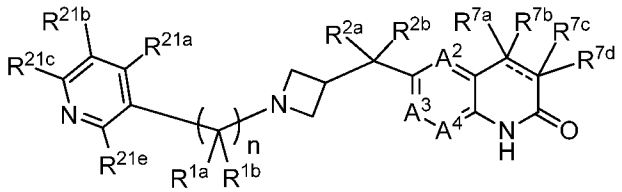
[00267] In a further aspect, the invention relates to a compound having a structure represented by a formula:



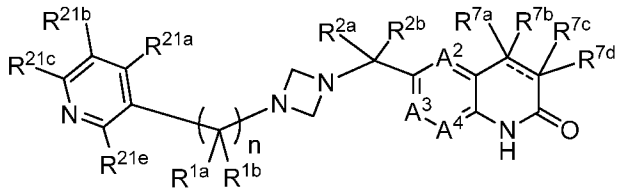
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00268] In a further aspect, the invention relates to a compound having a structure represented by a formula:



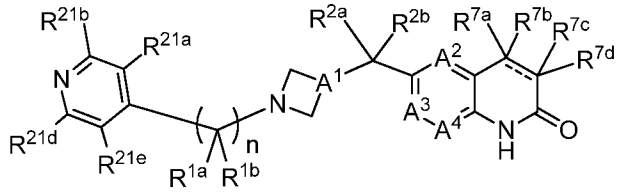
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

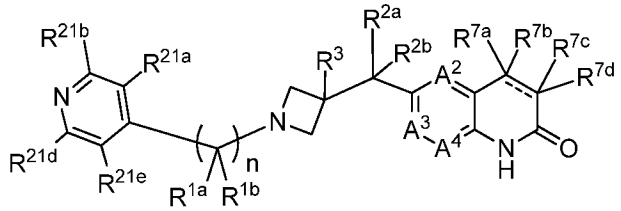
[00269] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

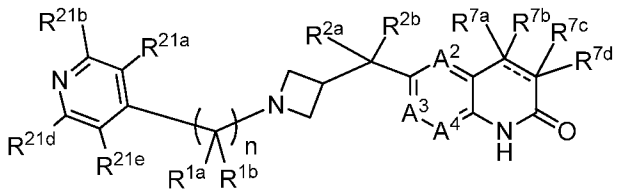
[00270] In a further aspect, the invention relates to a compound having a structure represented by a formula:



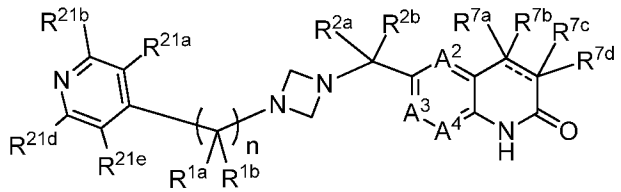
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00271] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

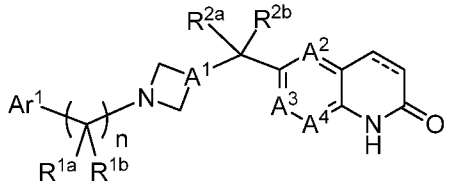


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

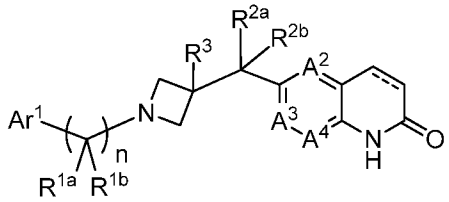
[00272] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

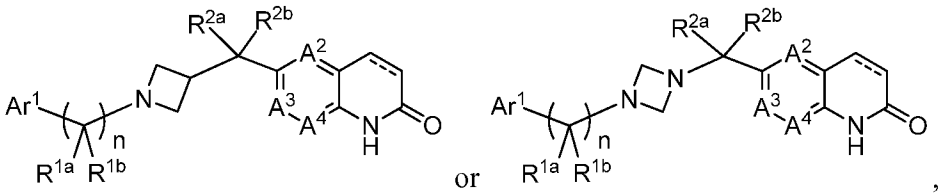
[00273] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

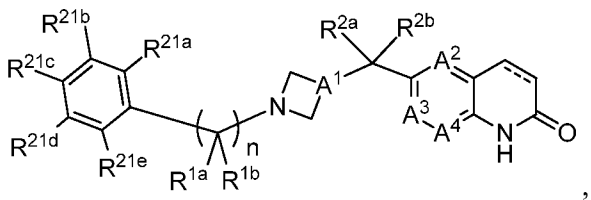
[00274] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00275] In a further aspect, the invention relates to a compound having a structure represented by a formula:

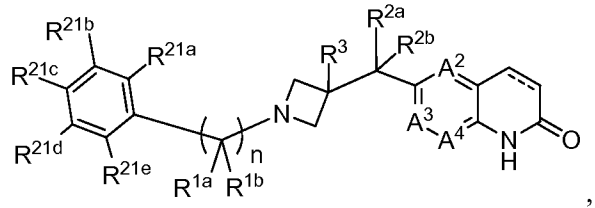


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

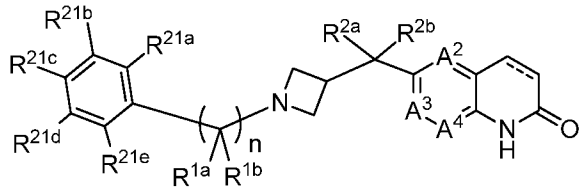
[00276] In a further aspect, the invention relates to a compound having a structure represented by a formula:



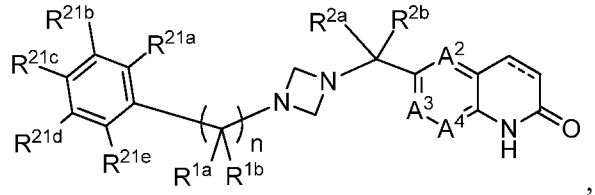
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00277] In a further aspect, the invention relates to a compound having a structure represented by a formula:



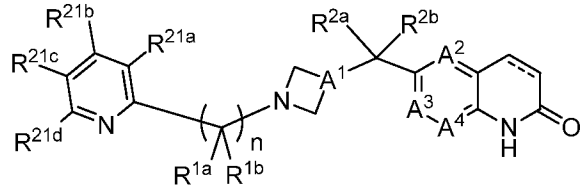
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

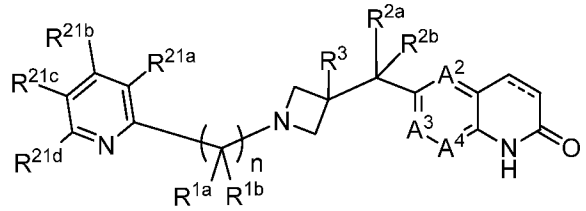
[00278] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

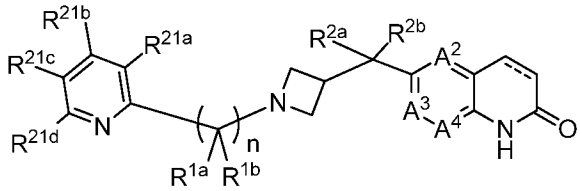
[00279] In a further aspect, the invention relates to a compound having a structure represented by a formula:



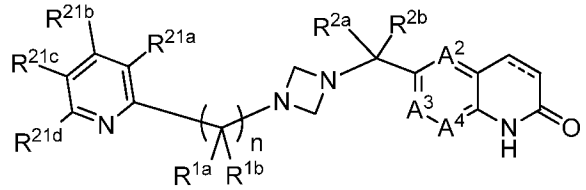
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00280] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

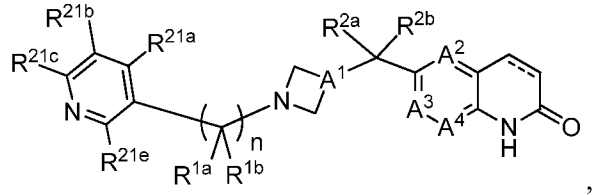


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

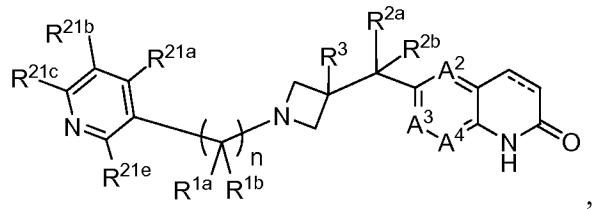
[00281] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

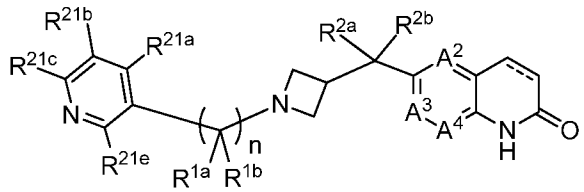
[00282] In a further aspect, the invention relates to a compound having a structure represented by a formula:



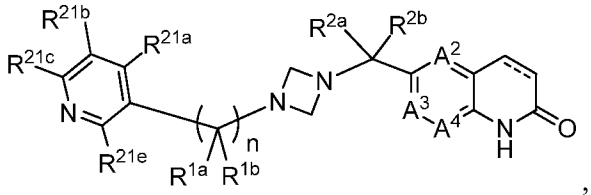
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00283] In a further aspect, the invention relates to a compound having a structure represented by a formula:



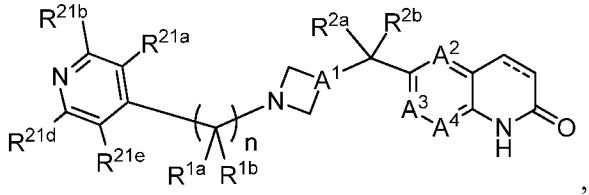
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

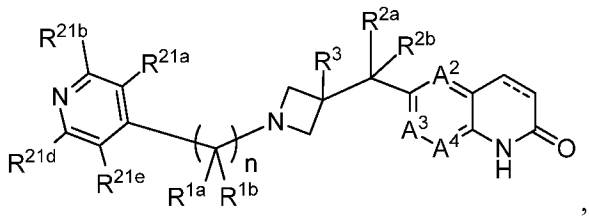
[00284] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

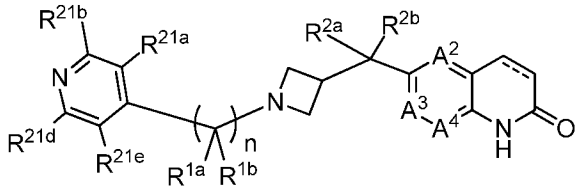
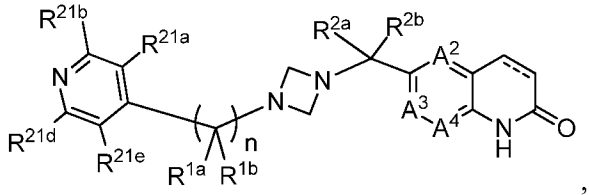
[00285] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

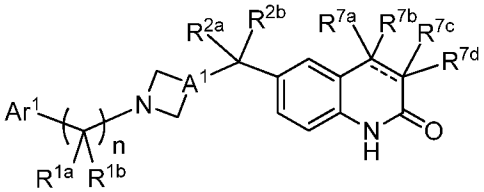
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00286] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

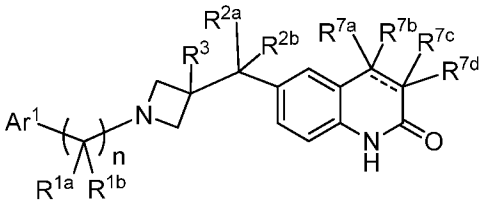
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00287] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

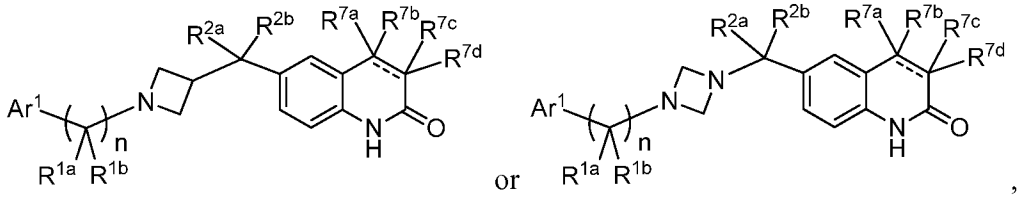
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00288] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

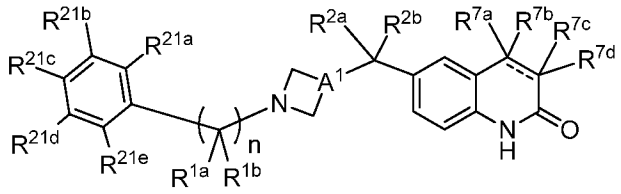
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00289] In a further aspect, the invention relates to a compound having a structure represented by a formula:



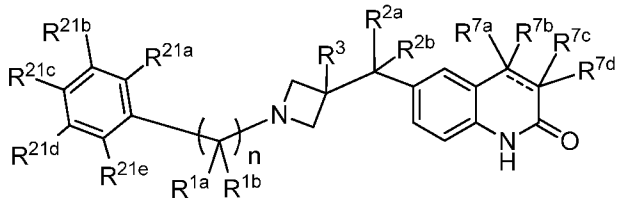
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00290] In a further aspect, the invention relates to a compound having a structure represented by a formula:



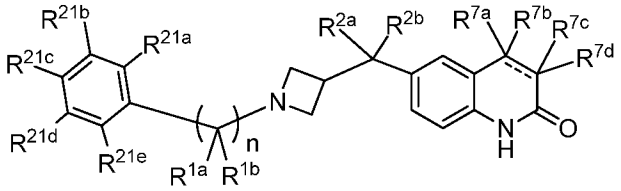
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00291] In a further aspect, the invention relates to a compound having a structure represented by a formula:

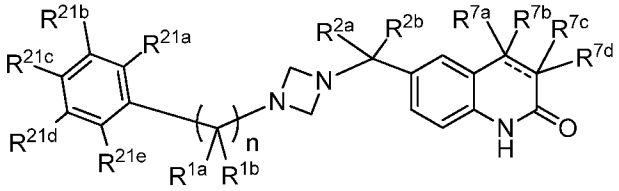


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00292] In a further aspect, the invention relates to a compound having a structure represented by a formula:



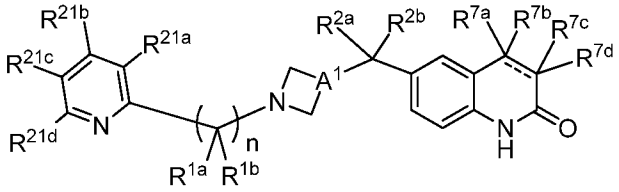
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

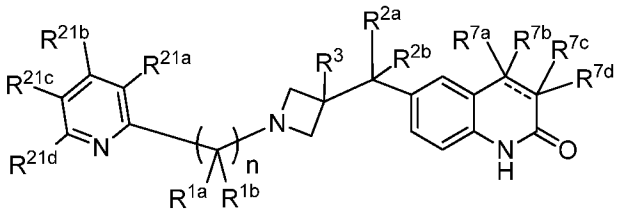
[00293] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00294] In a further aspect, the invention relates to a compound having a structure represented by a formula:

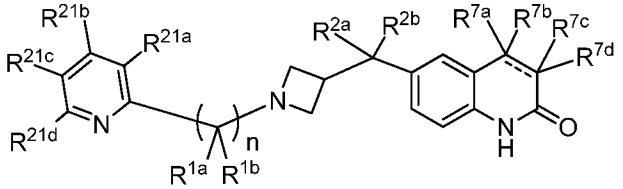


,

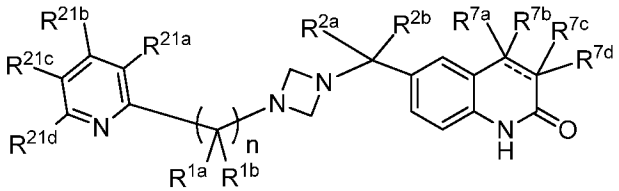
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00295] In a further aspect, the invention relates to a compound having a structure represented by a formula:



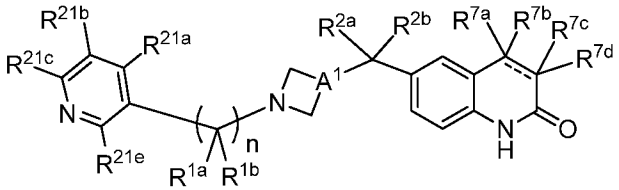
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

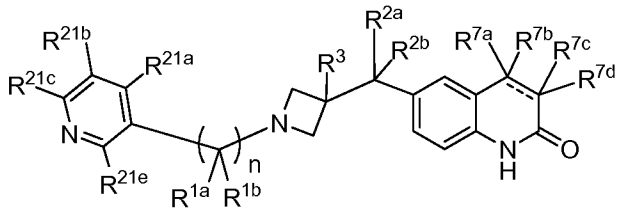
[00296] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

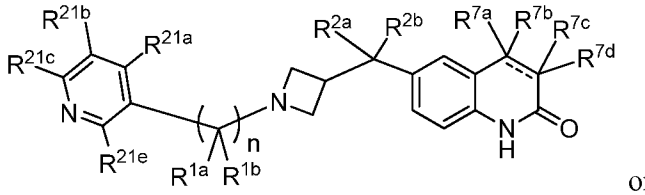
[00297] In a further aspect, the invention relates to a compound having a structure represented by a formula:



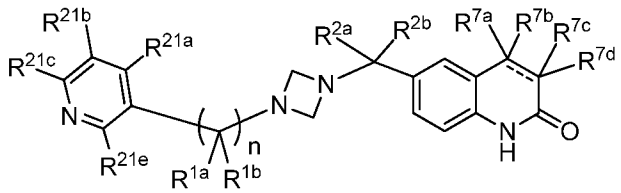
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00298] In a further aspect, the invention relates to a compound having a structure represented by a formula:



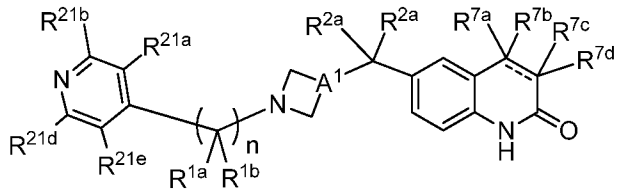
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00299] In a further aspect, the invention relates to a compound having a structure represented by a formula:

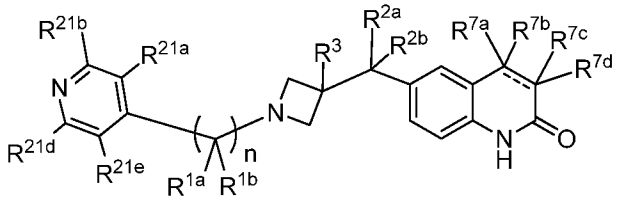


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

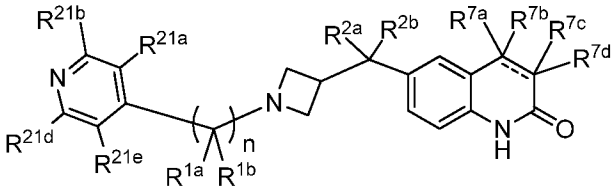
[00300] In a further aspect, the invention relates to a compound having a structure represented by a formula:



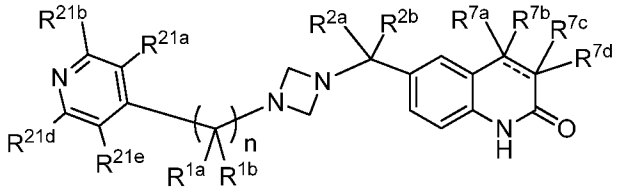
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00301] In a further aspect, the invention relates to a compound having a structure represented by a formula:



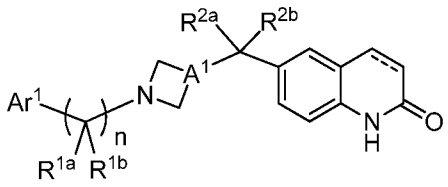
or



,

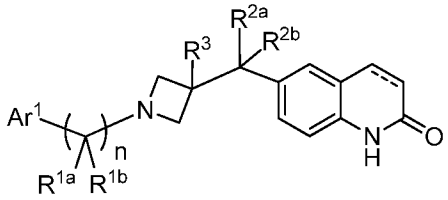
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00302] In a further aspect, the invention relates to a compound having a structure represented by a formula:



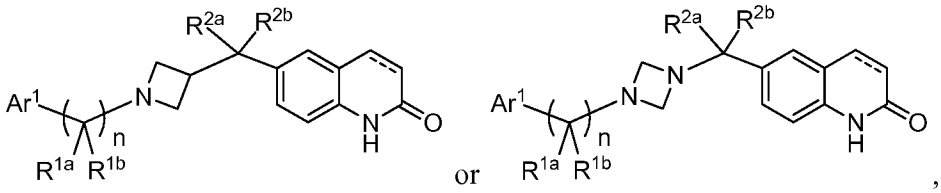
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00303] In a further aspect, the invention relates to a compound having a structure represented by a formula:



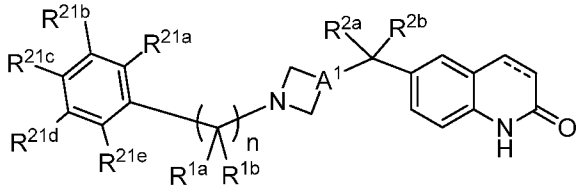
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00304] In a further aspect, the invention relates to a compound having a structure represented by a formula:



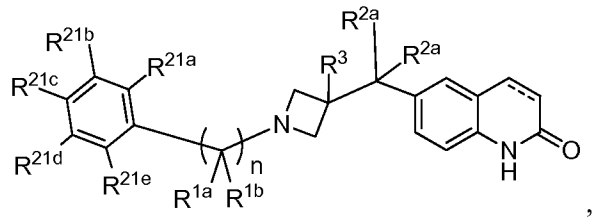
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00305] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

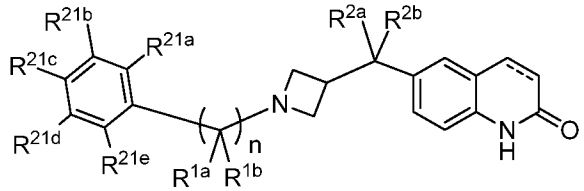
[00306] In a further aspect, the invention relates to a compound having a structure represented by a formula:



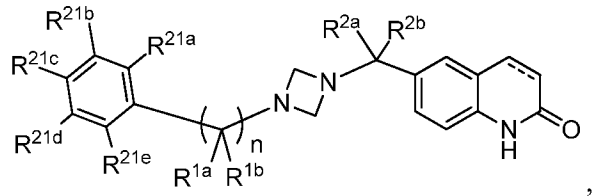
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00307] In a further aspect, the invention relates to a compound having a structure represented by a formula:



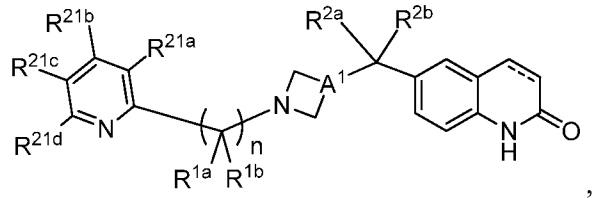
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00308] In a further aspect, the invention relates to a compound having a structure represented by a formula:

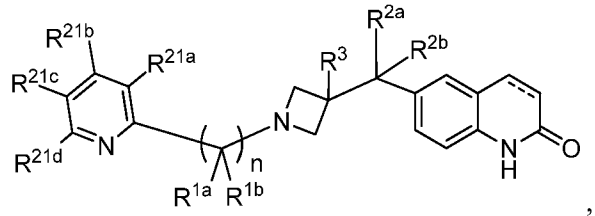


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

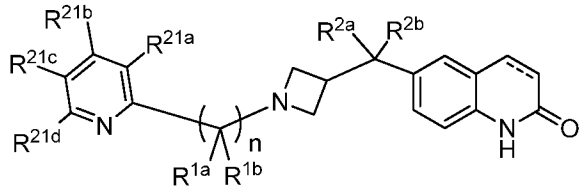
[00309] In a further aspect, the invention relates to a compound having a structure represented by a formula:



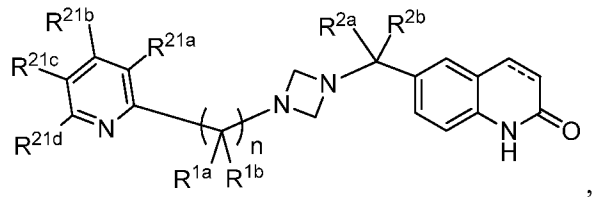
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00310] In a further aspect, the invention relates to a compound having a structure represented by a formula:



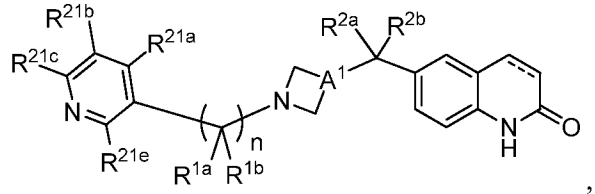
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

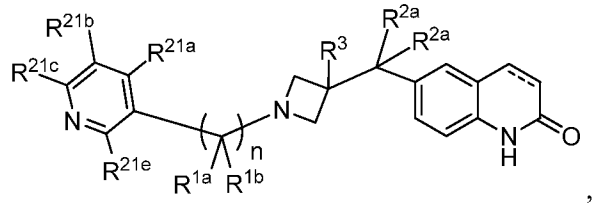
[00311] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

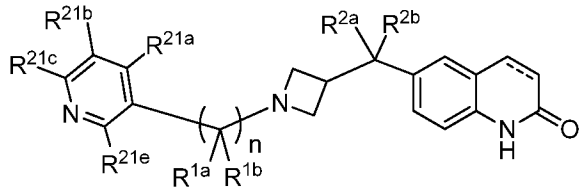
[00312] In a further aspect, the invention relates to a compound having a structure represented by a formula:



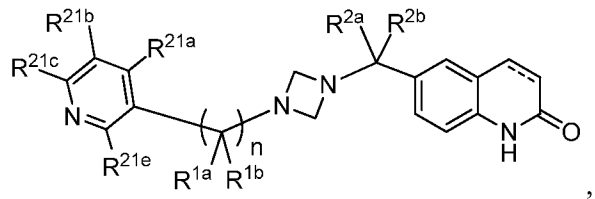
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00313] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

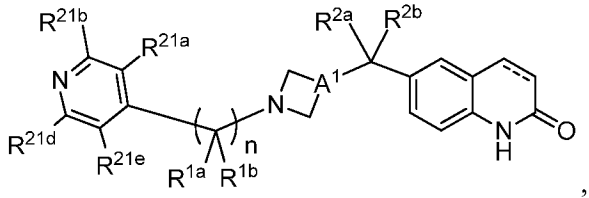


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

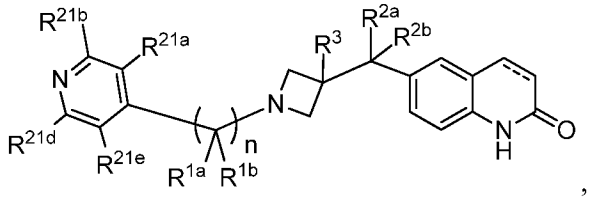
[00314] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

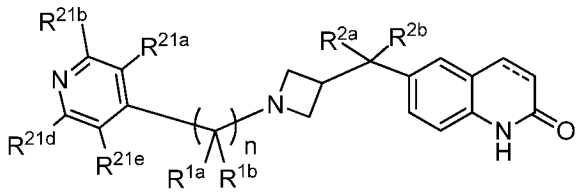
[00315] In a further aspect, the invention relates to a compound having a structure represented by a formula:



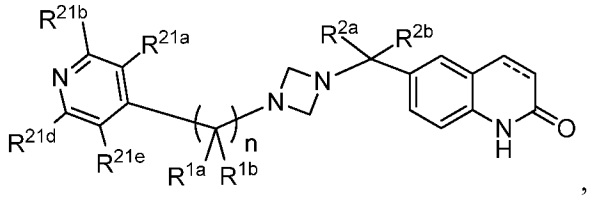
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00316] In a further aspect, the invention relates to a compound having a structure represented by a formula:

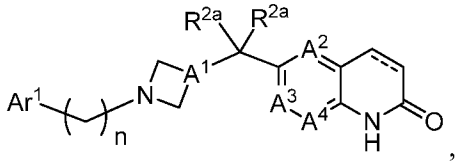


or



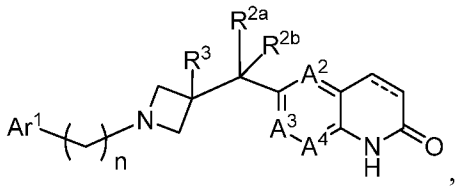
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00317] In a further aspect, the invention relates to a compound having a structure represented by a formula:



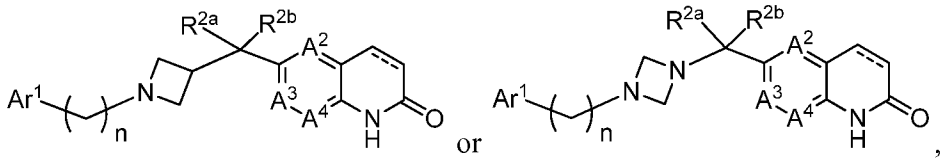
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00318] In a further aspect, the invention relates to a compound having a structure represented by a formula:



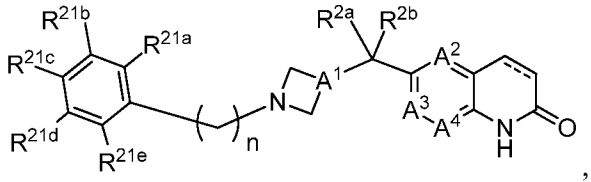
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00319] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

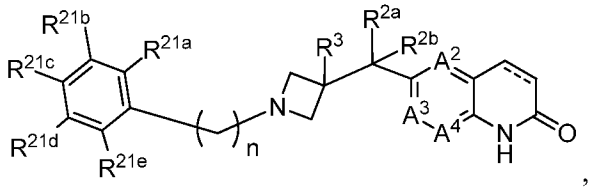
[00320] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

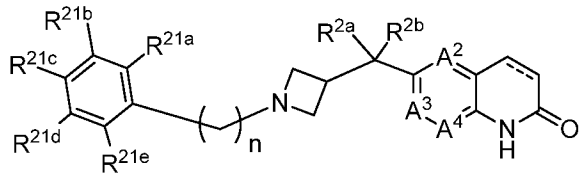
[00321] In a further aspect, the invention relates to a compound having a structure represented by a formula:



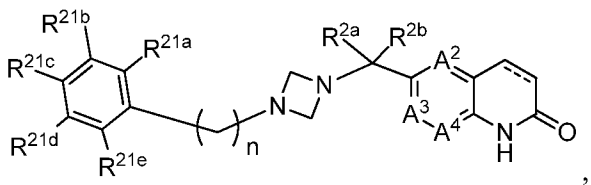
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00322] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

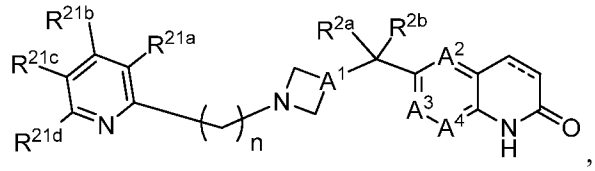


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all

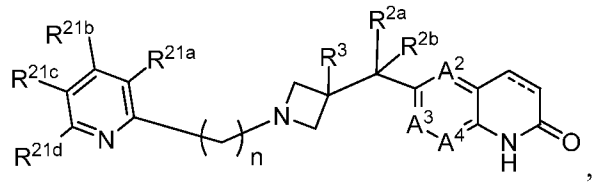
other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00323] In a further aspect, the invention relates to a compound having a structure represented by a formula:



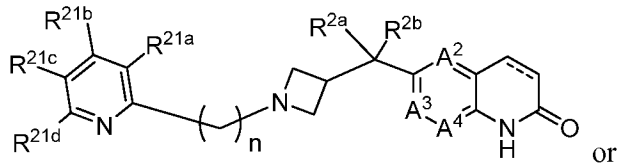
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00324] In a further aspect, the invention relates to a compound having a structure represented by a formula:

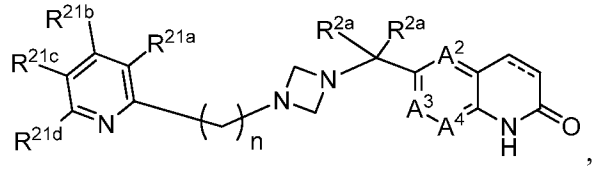


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00325] In a further aspect, the invention relates to a compound having a structure represented by a formula:



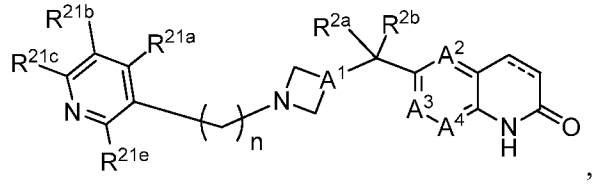
or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

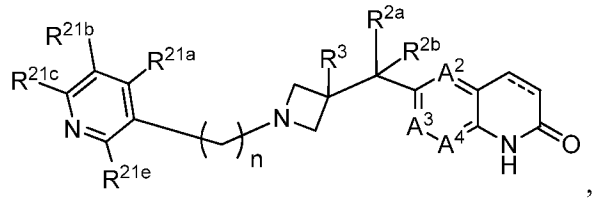
[00326] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

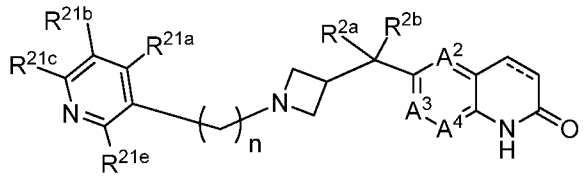
[00327] In a further aspect, the invention relates to a compound having a structure represented by a formula:



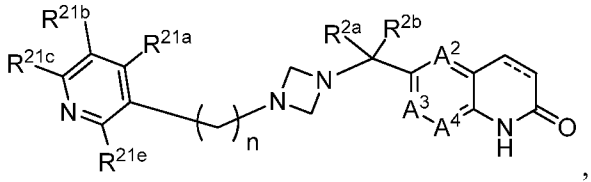
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00328] In a further aspect, the invention relates to a compound having a structure represented by a formula:



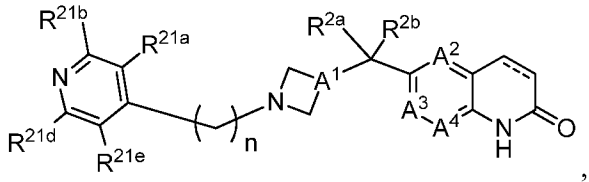
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

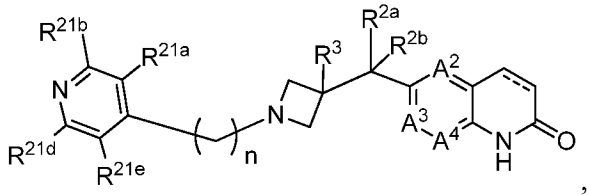
[00329] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

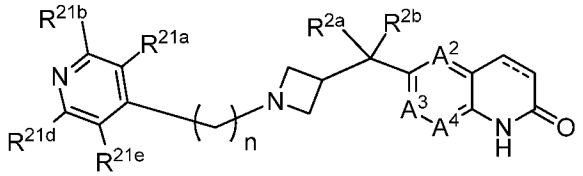
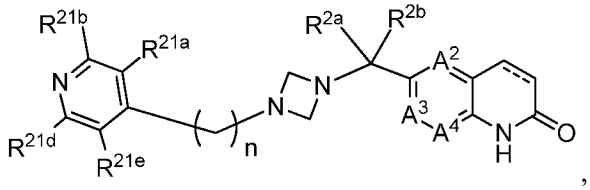
[00330] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

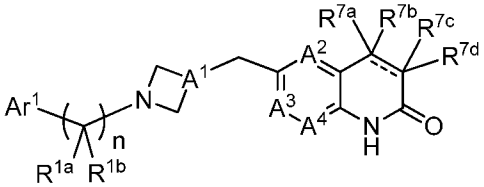
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00331] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

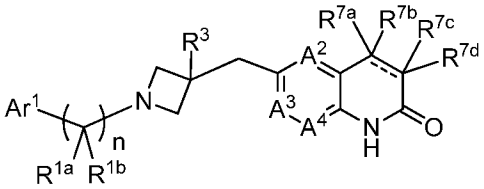
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00332] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

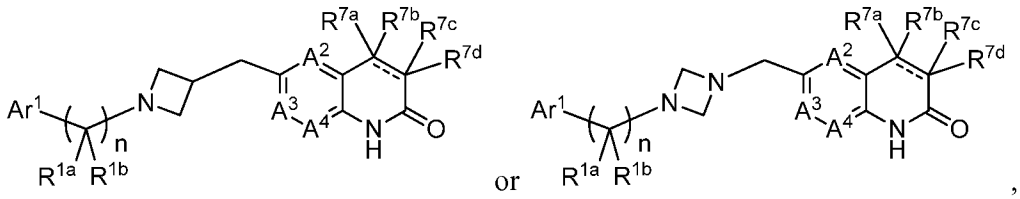
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00333] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

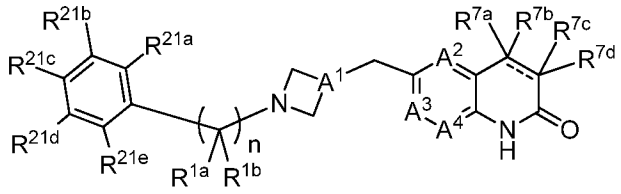
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00334] In a further aspect, the invention relates to a compound having a structure represented by a formula:



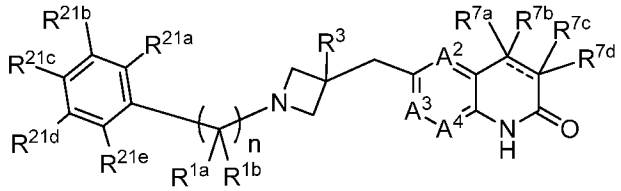
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00335] In a further aspect, the invention relates to a compound having a structure represented by a formula:



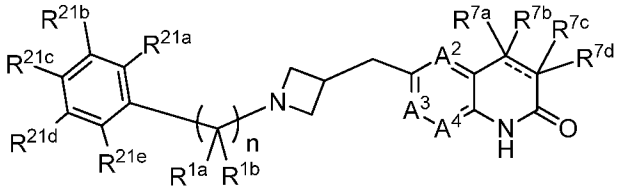
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00336] In a further aspect, the invention relates to a compound having a structure represented by a formula:

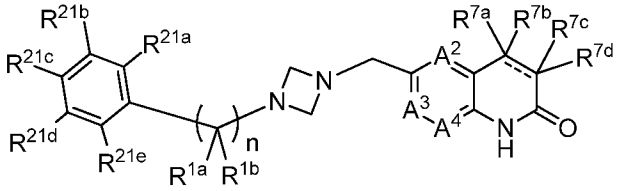


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00337] In a further aspect, the invention relates to a compound having a structure represented by a formula:



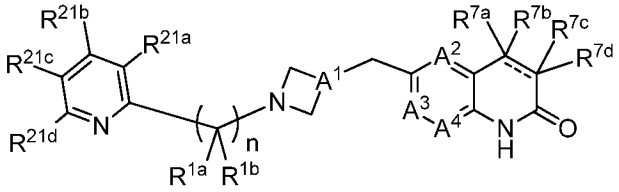
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

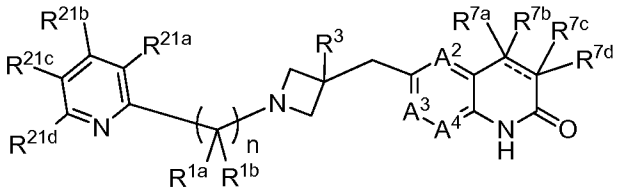
[00338] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00339] In a further aspect, the invention relates to a compound having a structure represented by a formula:

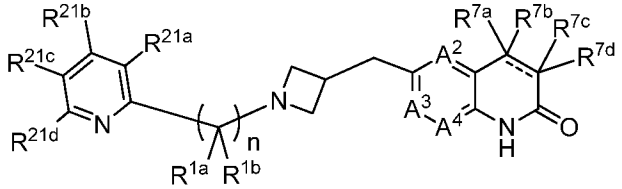


,

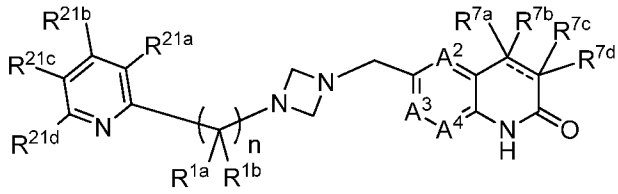
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00340] In a further aspect, the invention relates to a compound having a structure represented by a formula:



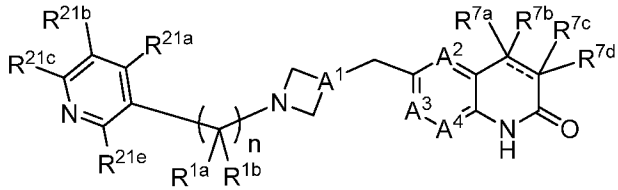
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

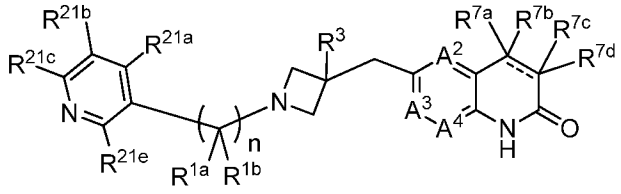
[00341] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

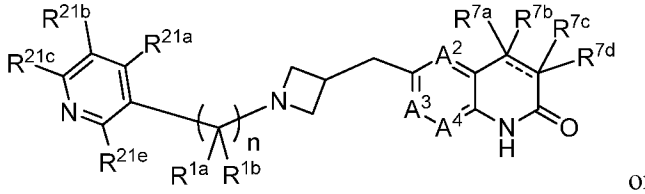
[00342] In a further aspect, the invention relates to a compound having a structure represented by a formula:



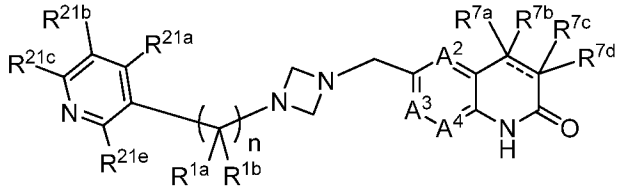
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00343] In a further aspect, the invention relates to a compound having a structure represented by a formula:



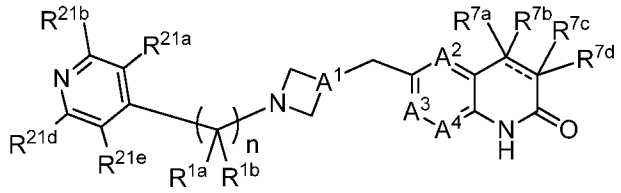
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00344] In a further aspect, the invention relates to a compound having a structure represented by a formula:

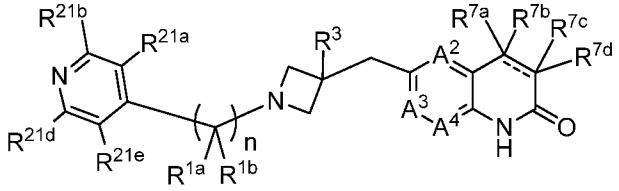


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

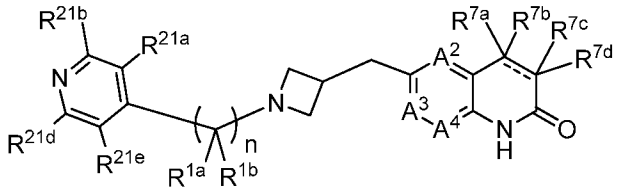
[00345] In a further aspect, the invention relates to a compound having a structure represented by a formula:



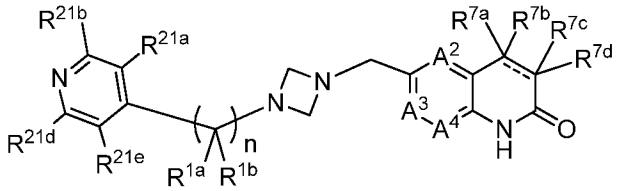
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00346] In a further aspect, the invention relates to a compound having a structure represented by a formula:



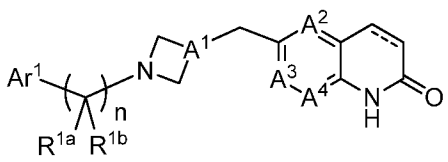
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

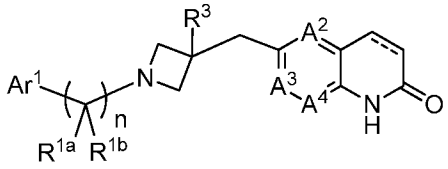
[00347] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

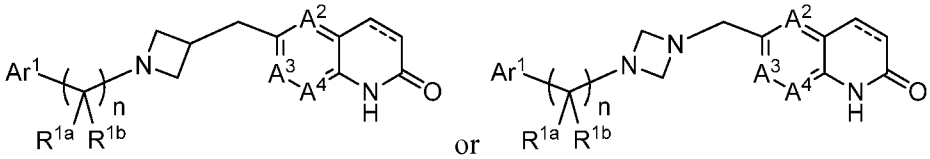
[00348] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00349] In a further aspect, the invention relates to a compound having a structure represented by a formula:

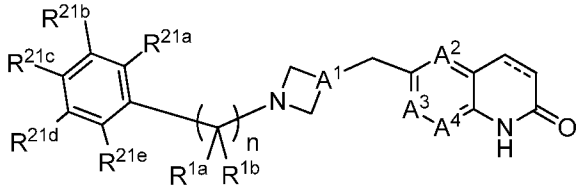


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

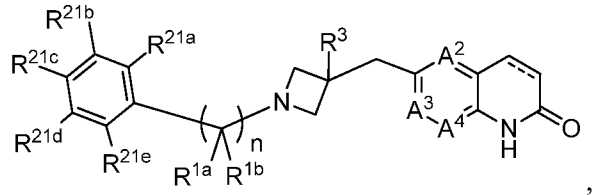
[00350] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

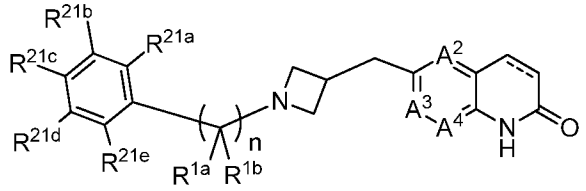
[00351] In a further aspect, the invention relates to a compound having a structure represented by a formula:



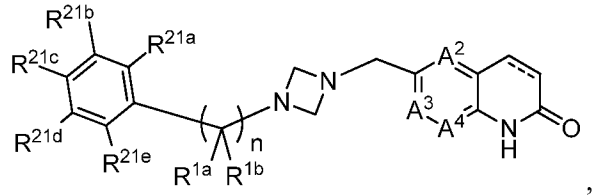
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00352] In a further aspect, the invention relates to a compound having a structure represented by a formula:



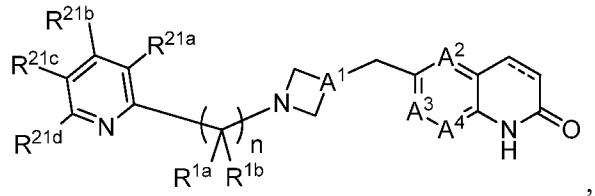
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00353] In a further aspect, the invention relates to a compound having a structure represented by a formula:

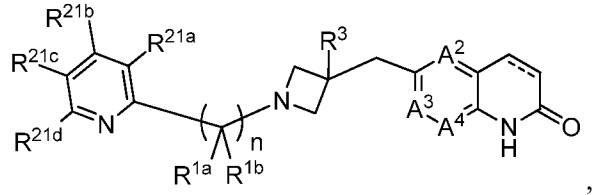


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

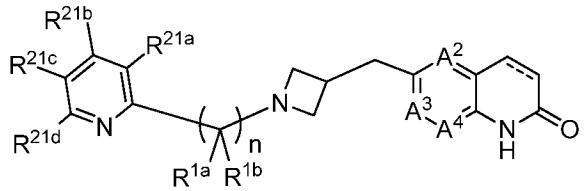
[00354] In a further aspect, the invention relates to a compound having a structure represented by a formula:



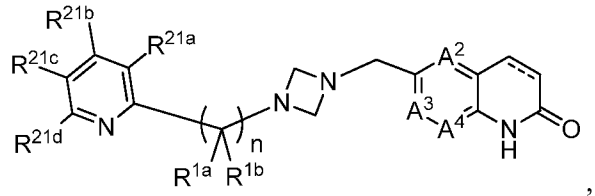
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00355] In a further aspect, the invention relates to a compound having a structure represented by a formula:



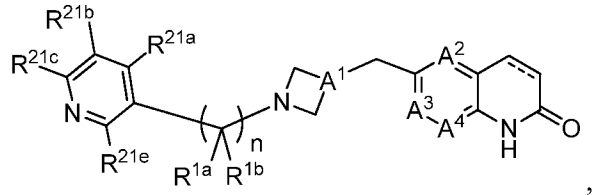
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

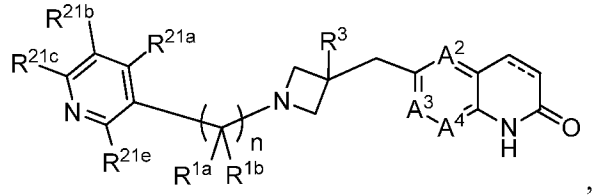
[00356] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

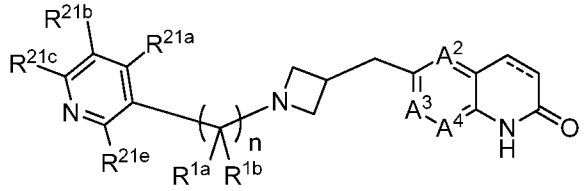
[00357] In a further aspect, the invention relates to a compound having a structure represented by a formula:



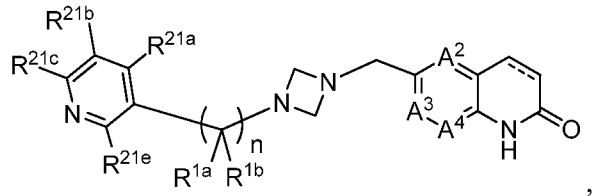
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00358] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

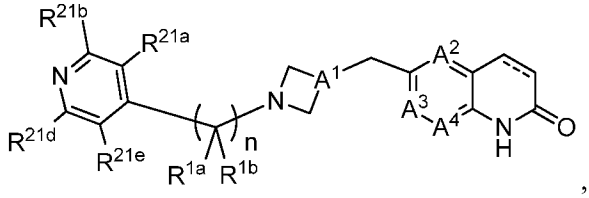


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

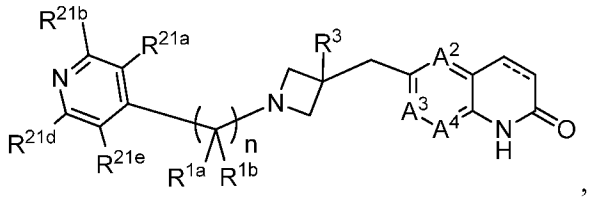
[00359] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

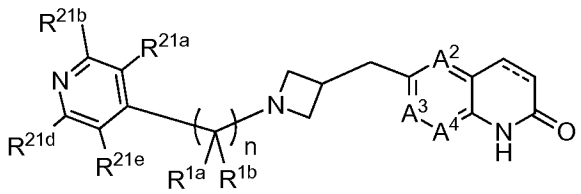
[00360] In a further aspect, the invention relates to a compound having a structure represented by a formula:



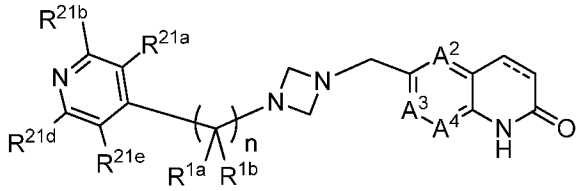
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00361] In a further aspect, the invention relates to a compound having a structure represented by a formula:



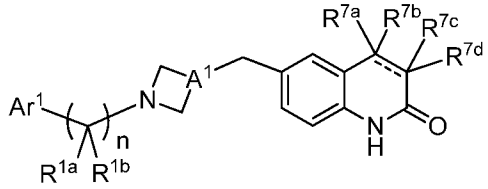
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

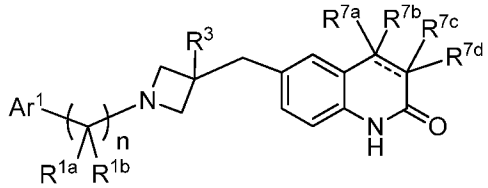
[00362] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

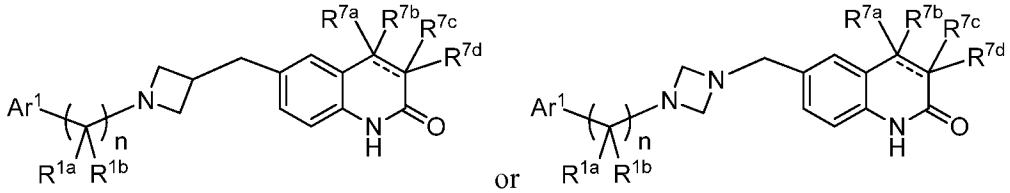
[00363] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

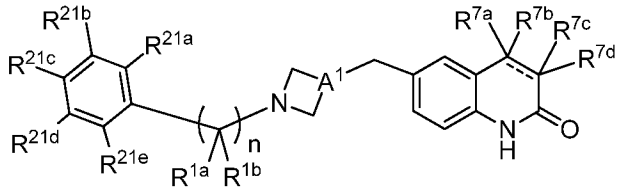
[00364] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

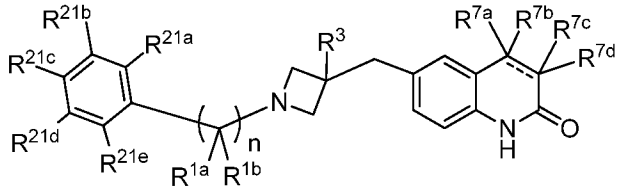
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00365] In a further aspect, the invention relates to a compound having a structure represented by a formula:



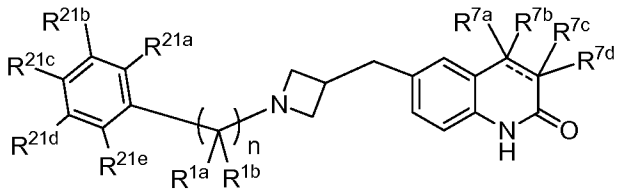
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00366] In a further aspect, the invention relates to a compound having a structure represented by a formula:

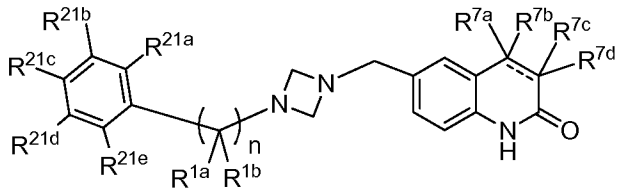


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00367] In a further aspect, the invention relates to a compound having a structure represented by a formula:



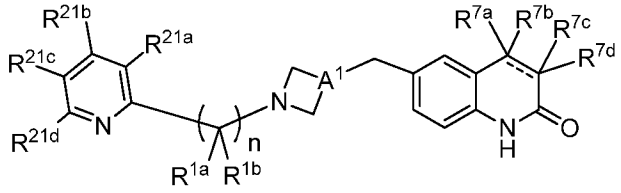
or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

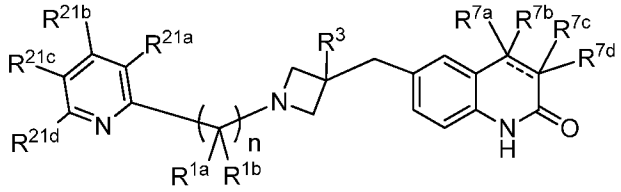
[00368] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

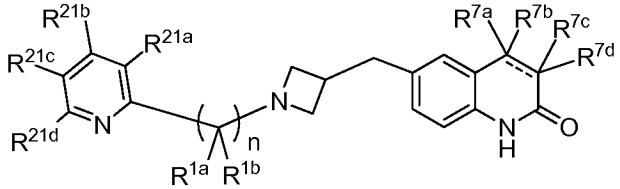
[00369] In a further aspect, the invention relates to a compound having a structure represented by a formula:



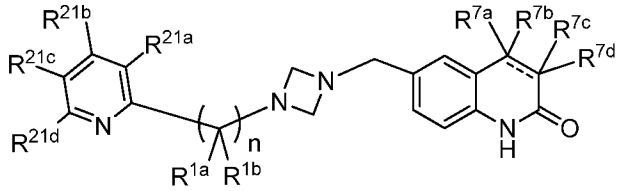
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00370] In a further aspect, the invention relates to a compound having a structure represented by a formula:



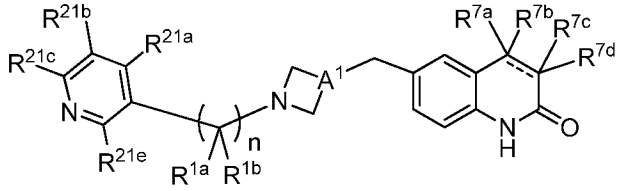
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

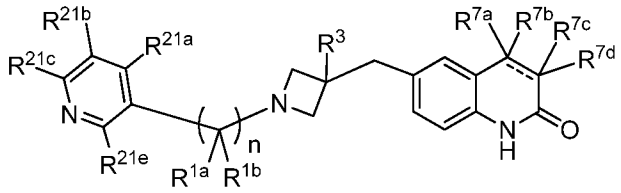
[00371] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

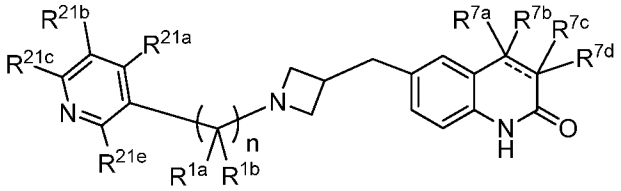
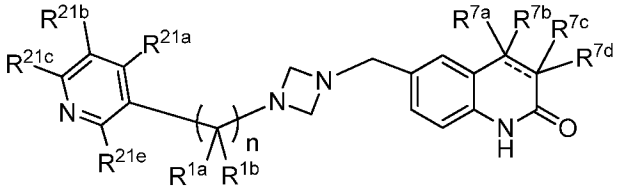
[00372] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

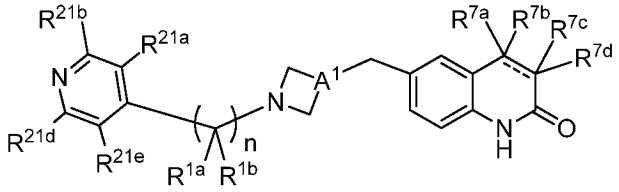
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00373] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

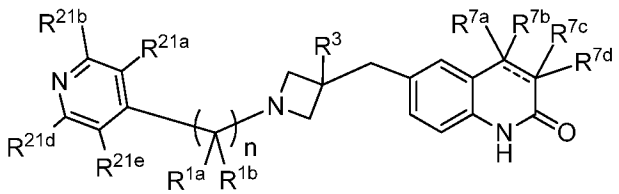
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00374] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

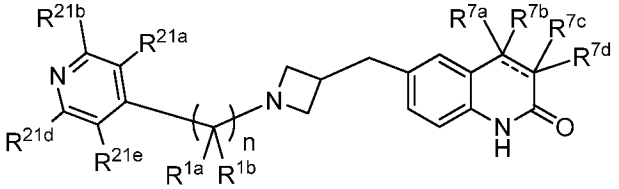
[00375] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

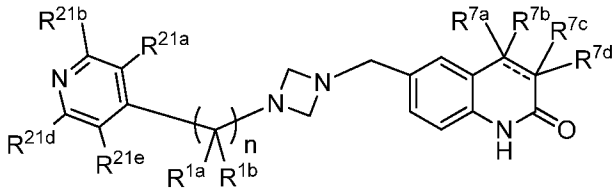
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00376] In a further aspect, the invention relates to a compound having a structure represented by a formula:



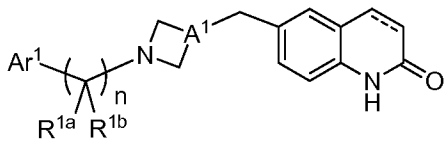
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

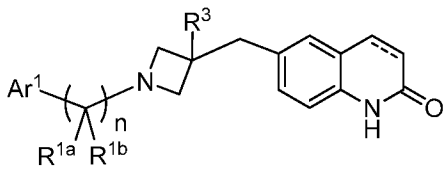
[00377] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

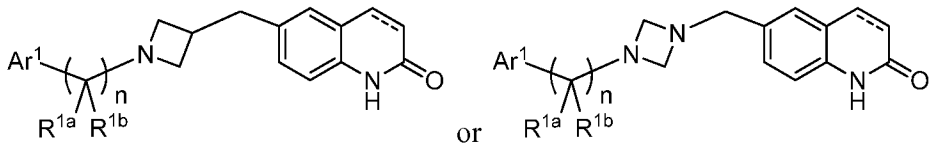
[00378] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

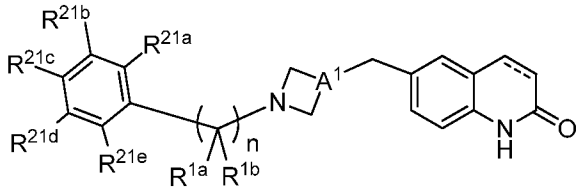
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00379] In a further aspect, the invention relates to a compound having a structure represented by a formula:



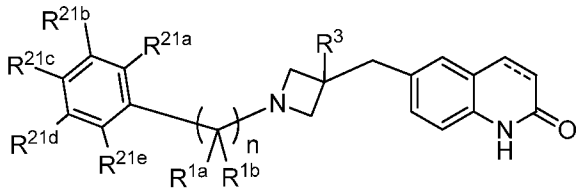
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00380] In a further aspect, the invention relates to a compound having a structure represented by a formula:



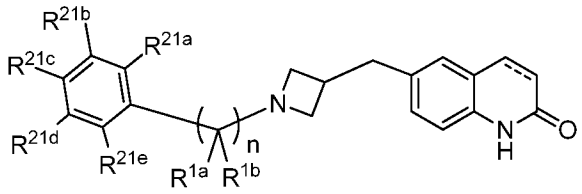
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

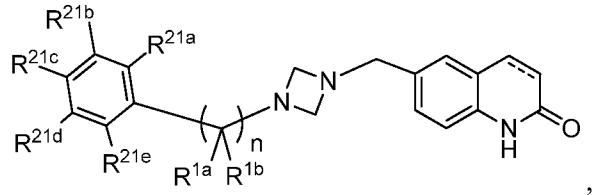
[00381] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

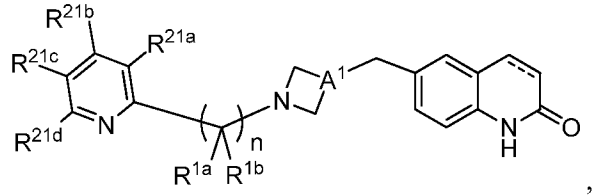
[00382] In a further aspect, the invention relates to a compound having a structure represented by a formula:





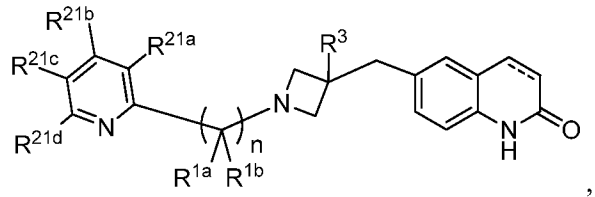
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00383] In a further aspect, the invention relates to a compound having a structure represented by a formula:



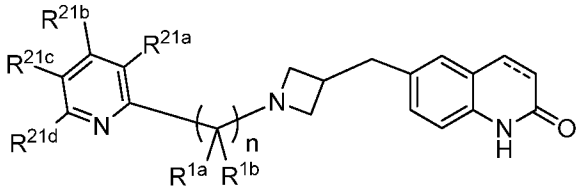
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00384] In a further aspect, the invention relates to a compound having a structure represented by a formula:

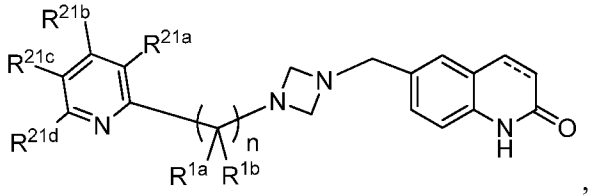


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00385] In a further aspect, the invention relates to a compound having a structure represented by a formula:



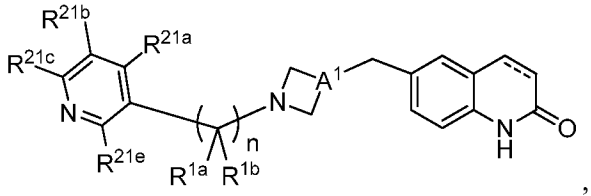
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

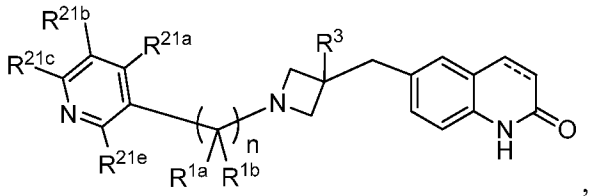
[00386] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00387] In a further aspect, the invention relates to a compound having a structure represented by a formula:

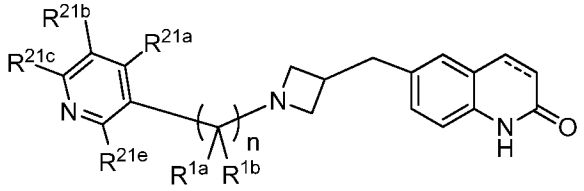


,

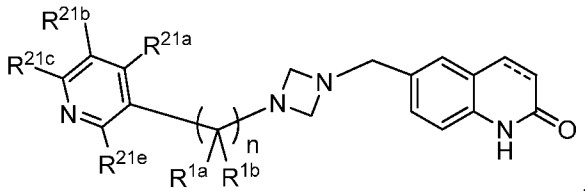
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00388] In a further aspect, the invention relates to a compound having a structure represented by a formula:



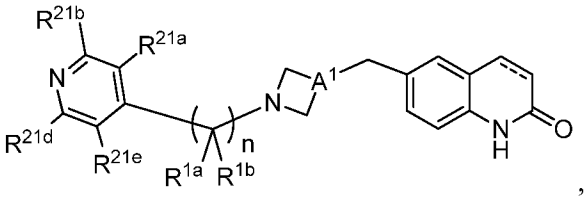
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

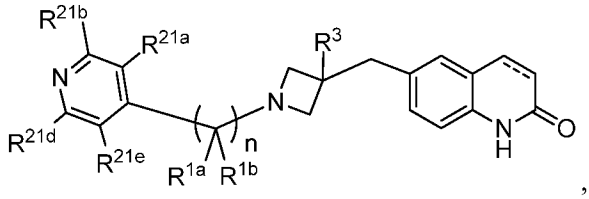
[00389] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

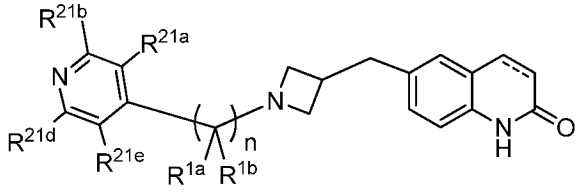
[00390] In a further aspect, the invention relates to a compound having a structure represented by a formula:



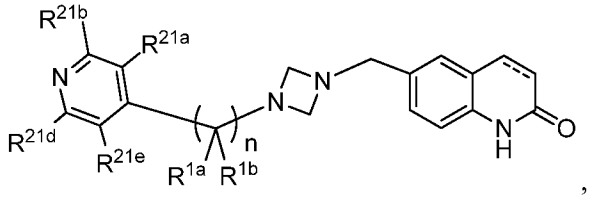
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00391] In a further aspect, the invention relates to a compound having a structure represented by a formula:



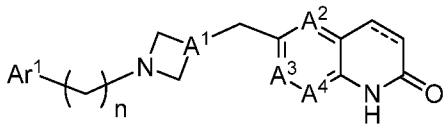
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

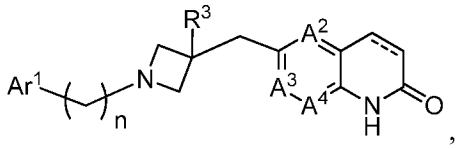
[00392] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

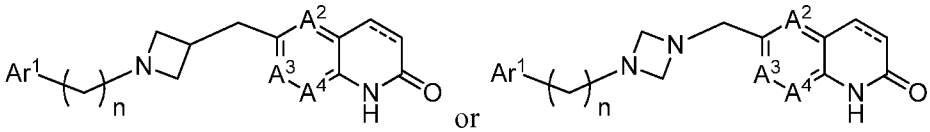
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00393] In a further aspect, the invention relates to a compound having a structure represented by a formula:



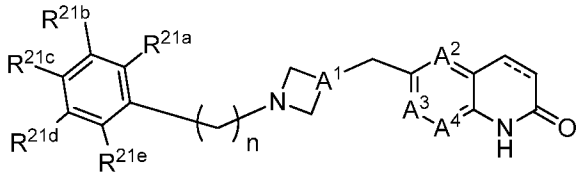
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00394] In a further aspect, the invention relates to a compound having a structure represented by a formula:



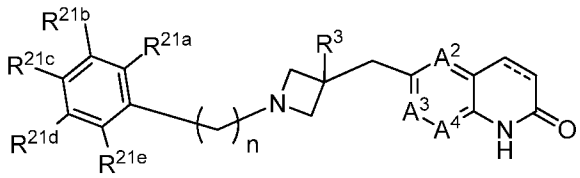
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00395] In a further aspect, the invention relates to a compound having a structure represented by a formula:



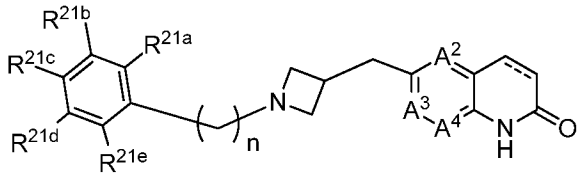
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00396] In a further aspect, the invention relates to a compound having a structure represented by a formula:

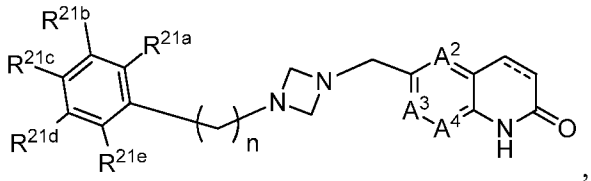


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00397] In a further aspect, the invention relates to a compound having a structure represented by a formula:



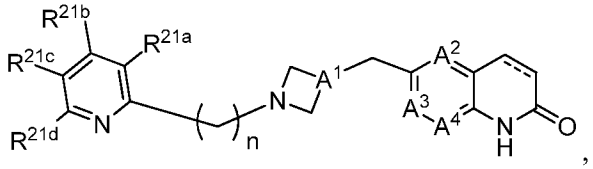
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

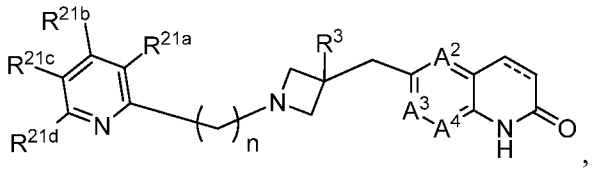
[00398] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00399] In a further aspect, the invention relates to a compound having a structure represented by a formula:

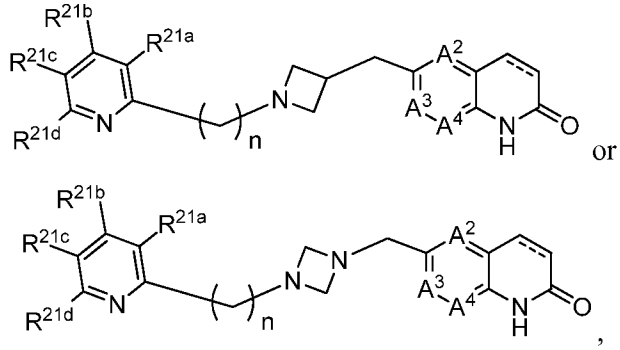


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00400] In a further aspect, the invention relates to a compound having a structure represented by a formula:

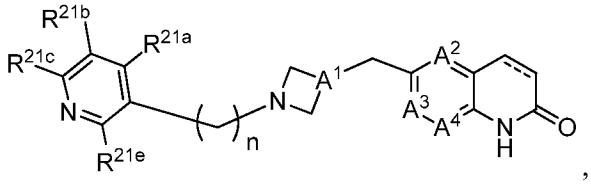


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

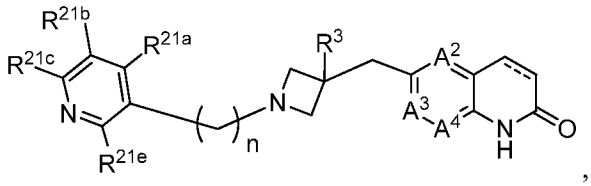
[00401] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00402] In a further aspect, the invention relates to a compound having a structure represented by a formula:

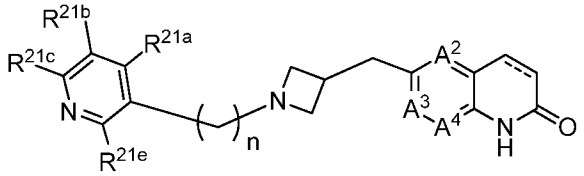


,

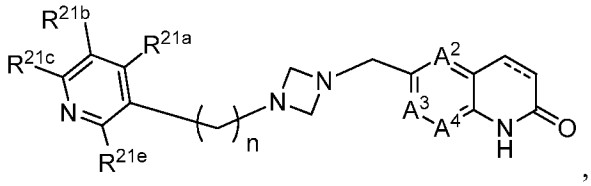
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00403] In a further aspect, the invention relates to a compound having a structure represented by a formula:



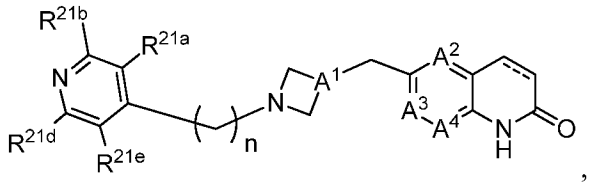
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

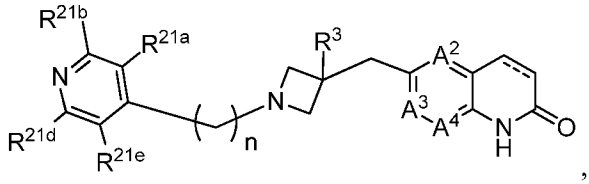
[00404] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

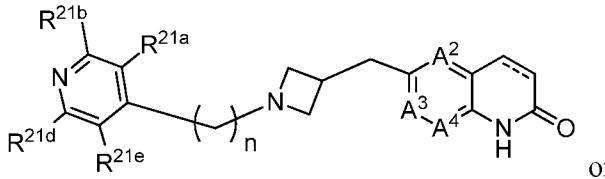
[00405] In a further aspect, the invention relates to a compound having a structure represented by a formula:



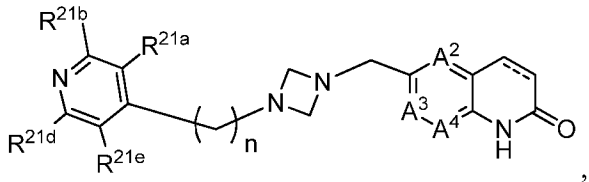
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00406] In a further aspect, the invention relates to a compound having a structure represented by a formula:



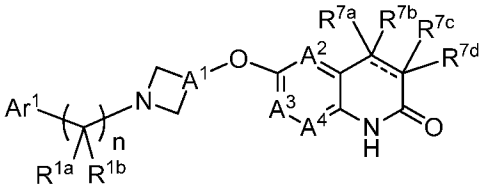
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

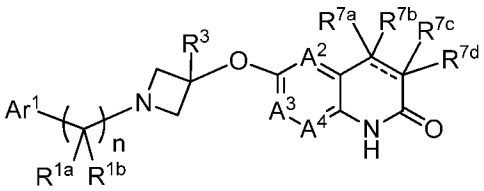
[00407] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

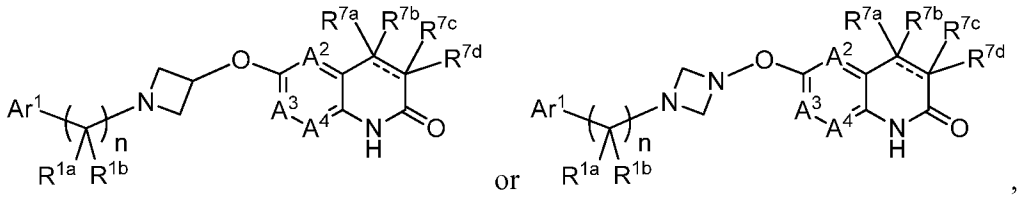
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00408] In a further aspect, the invention relates to a compound having a structure represented by a formula:



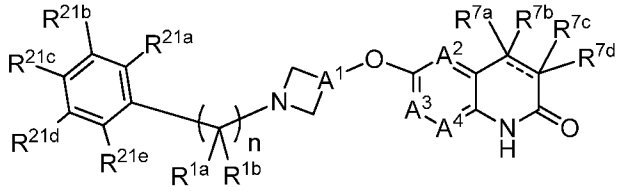
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00409] In a further aspect, the invention relates to a compound having a structure represented by a formula:



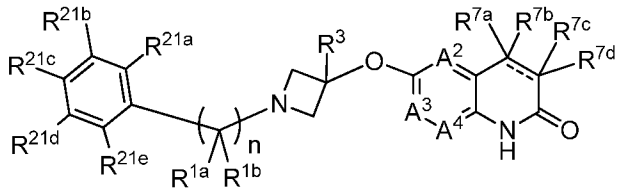
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00410] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

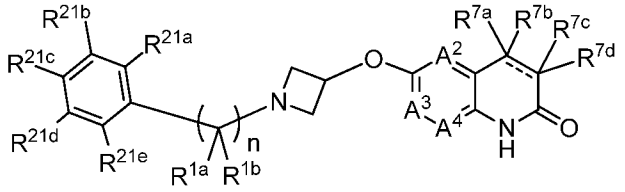
[00411] In a further aspect, the invention relates to a compound having a structure represented by a formula:



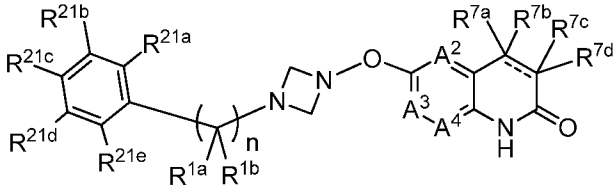
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4

alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00412] In a further aspect, the invention relates to a compound having a structure represented by a formula:



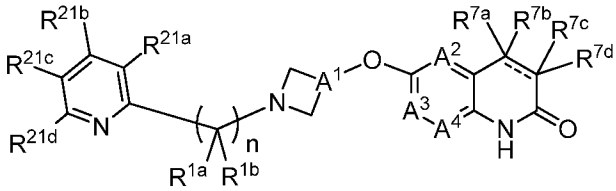
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

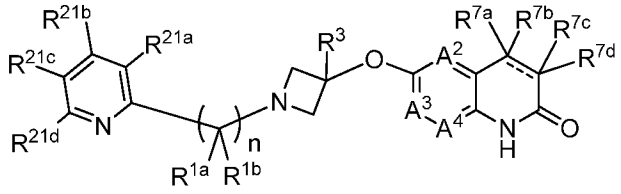
[00413] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

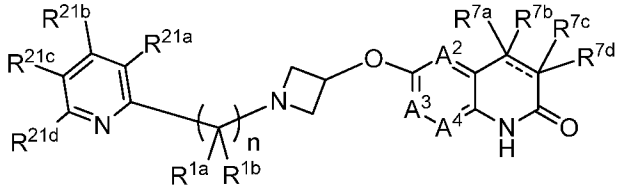
[00414] In a further aspect, the invention relates to a compound having a structure represented by a formula:



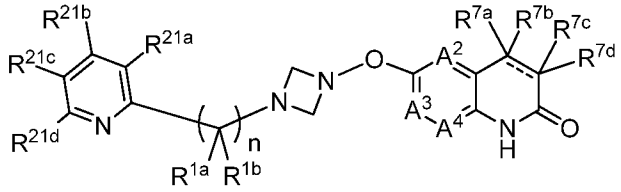
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00415] In a further aspect, the invention relates to a compound having a structure represented by a formula:



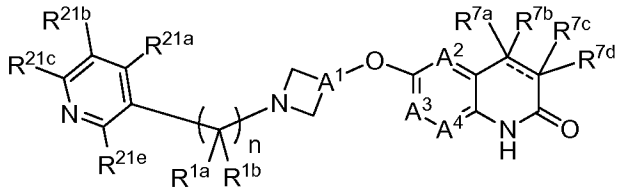
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00416] In a further aspect, the invention relates to a compound having a structure represented by a formula:

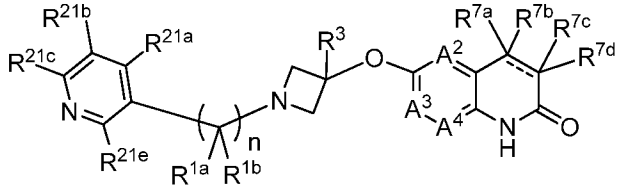


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

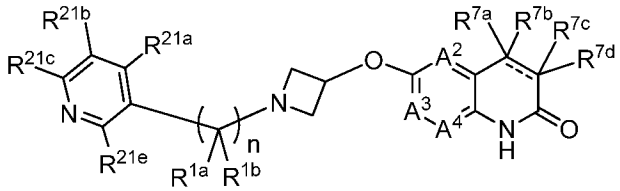
[00417] In a further aspect, the invention relates to a compound having a structure represented by a formula:



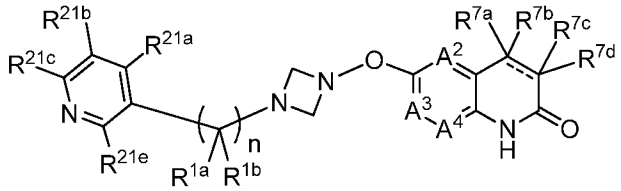
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00418] In a further aspect, the invention relates to a compound having a structure represented by a formula:



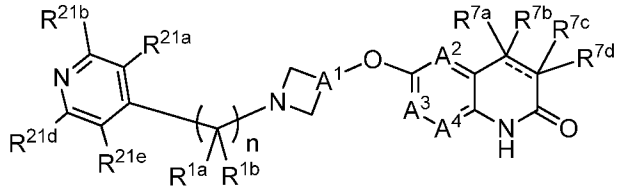
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

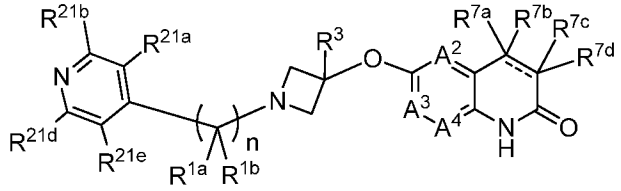
[00419] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

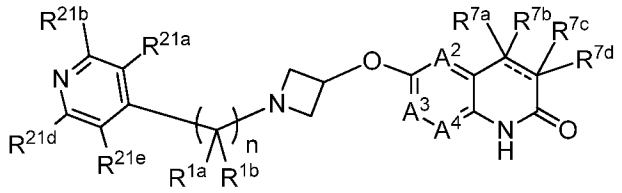
[00420] In a further aspect, the invention relates to a compound having a structure represented by a formula:



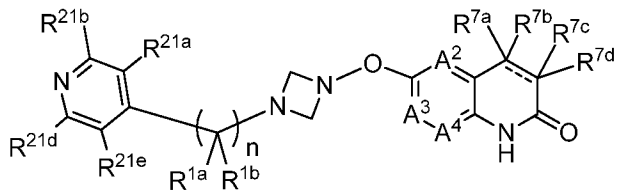
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00421] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

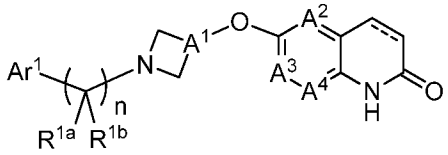


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

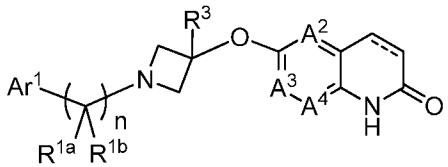
[00422] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

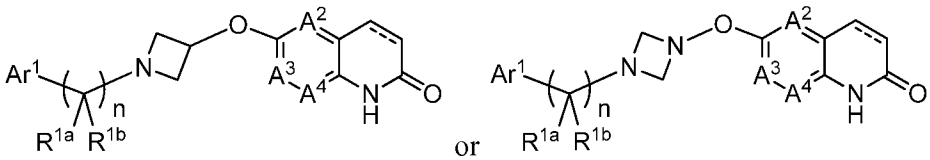
[00423] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

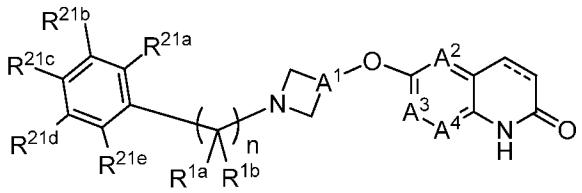
[00424] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00425] In a further aspect, the invention relates to a compound having a structure represented by a formula:

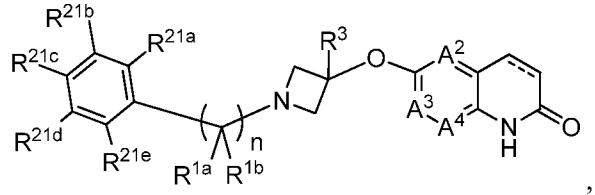


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and

C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

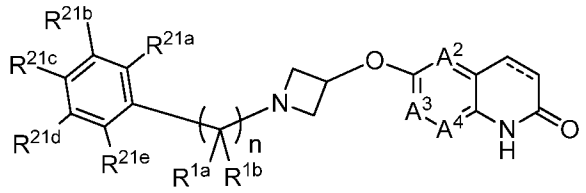
[00426] In a further aspect, the invention relates to a compound having a structure represented by a formula:



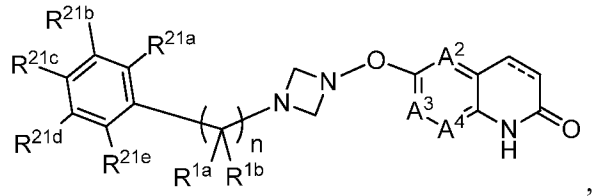
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00427] In a further aspect, the invention relates to a compound having a structure represented by a formula:



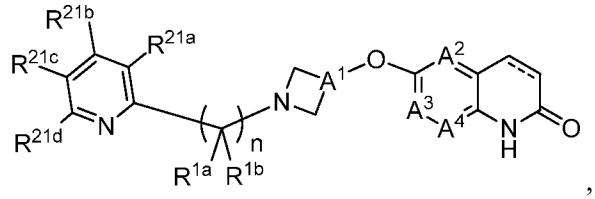
or



,

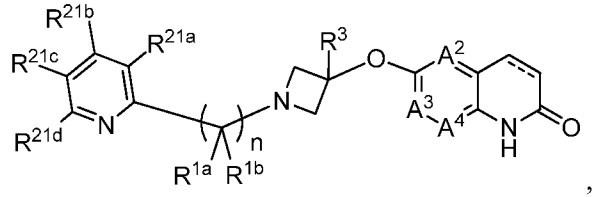
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00428] In a further aspect, the invention relates to a compound having a structure represented by a formula:



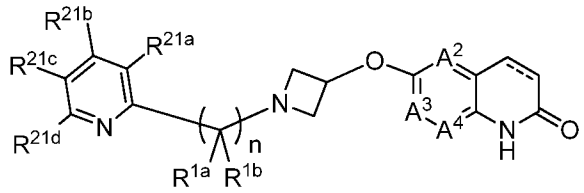
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00429] In a further aspect, the invention relates to a compound having a structure represented by a formula:

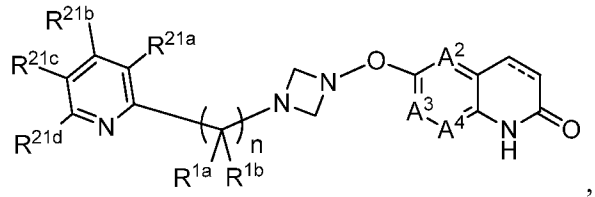


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00430] In a further aspect, the invention relates to a compound having a structure represented by a formula:



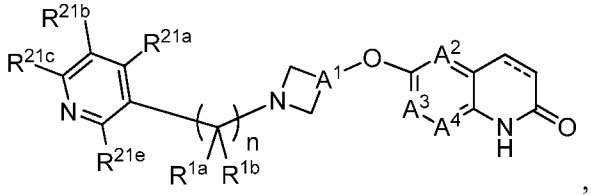
or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

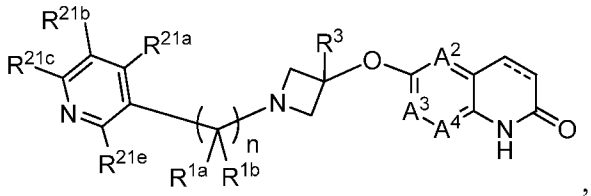
[00431] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

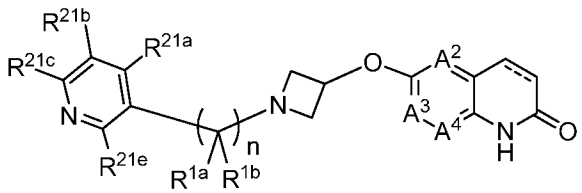
[00432] In a further aspect, the invention relates to a compound having a structure represented by a formula:



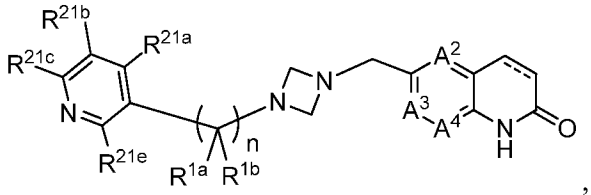
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00433] In a further aspect, the invention relates to a compound having a structure represented by a formula:



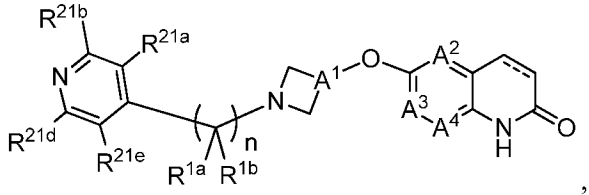
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

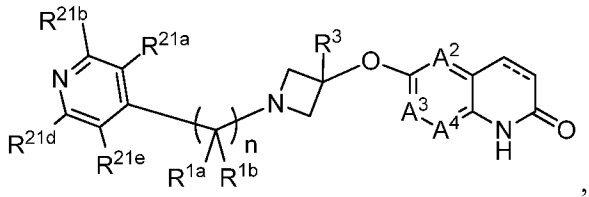
[00434] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

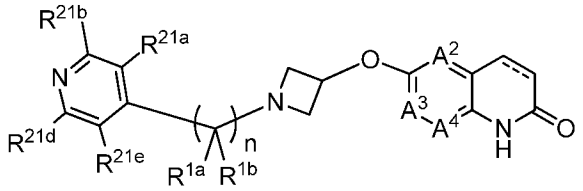
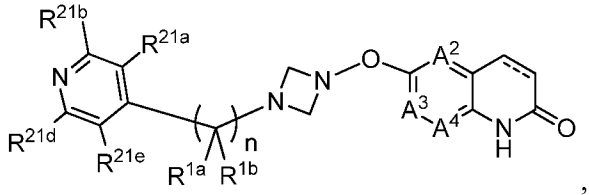
[00435] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

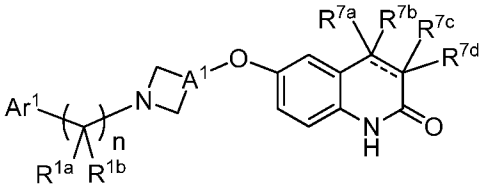
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00436] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

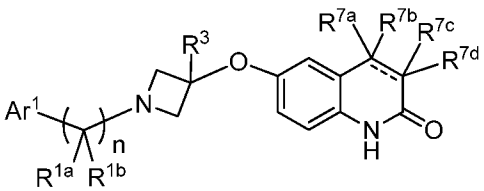
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00437] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

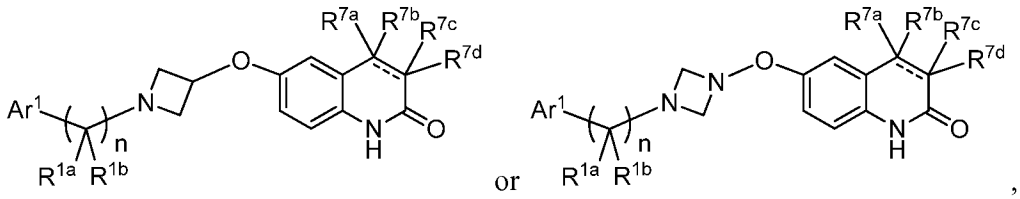
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00438] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

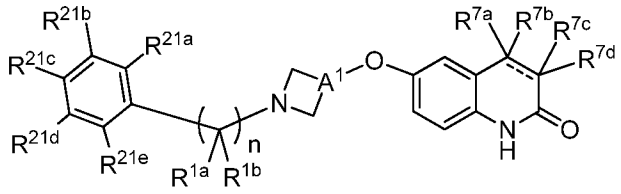
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00439] In a further aspect, the invention relates to a compound having a structure represented by a formula:



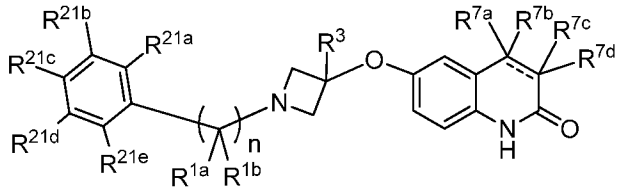
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00440] In a further aspect, the invention relates to a compound having a structure represented by a formula:



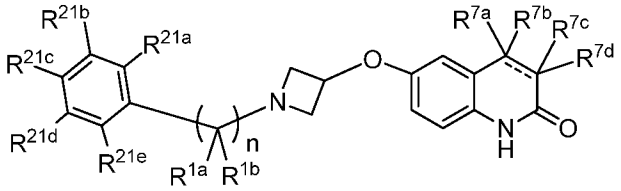
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00441] In a further aspect, the invention relates to a compound having a structure represented by a formula:

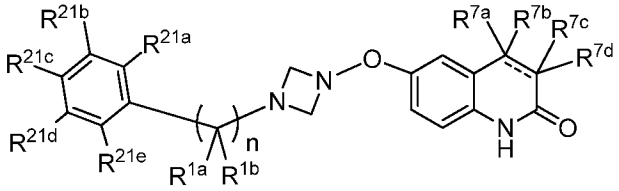


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00442] In a further aspect, the invention relates to a compound having a structure represented by a formula:



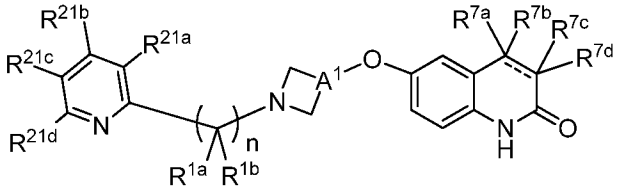
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

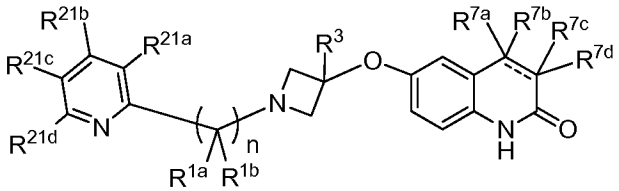
[00443] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00444] In a further aspect, the invention relates to a compound having a structure represented by a formula:

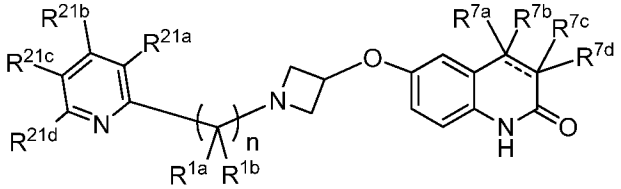


,

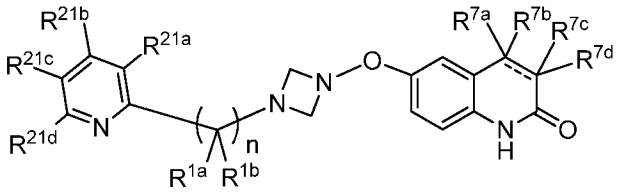
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00445] In a further aspect, the invention relates to a compound having a structure represented by a formula:



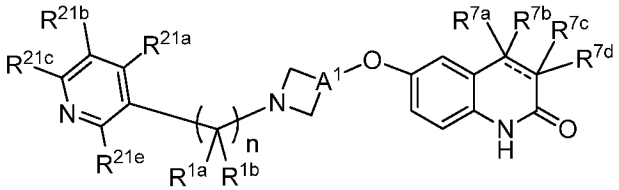
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

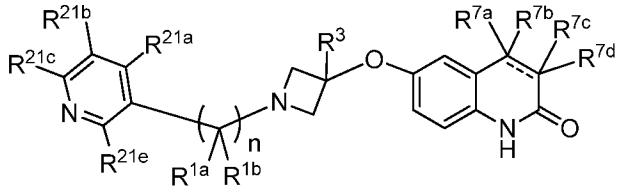
[00446] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

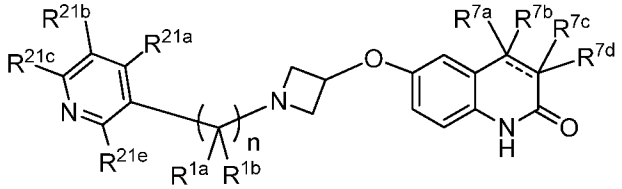
[00447] In a further aspect, the invention relates to a compound having a structure represented by a formula:



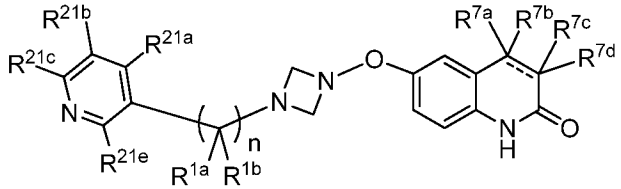
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00448] In a further aspect, the invention relates to a compound having a structure represented by a formula:



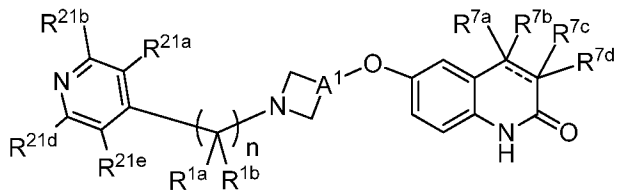
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00449] In a further aspect, the invention relates to a compound having a structure represented by a formula:

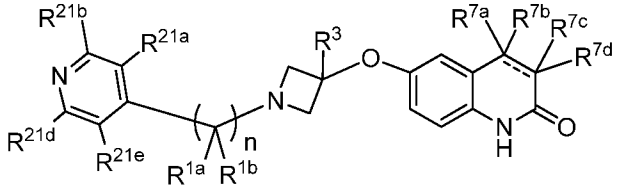


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

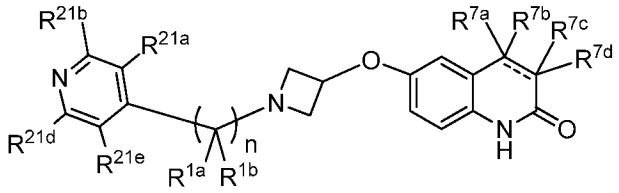
[00450] In a further aspect, the invention relates to a compound having a structure represented by a formula:



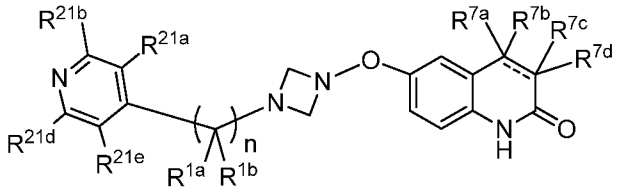
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00451] In a further aspect, the invention relates to a compound having a structure represented by a formula:



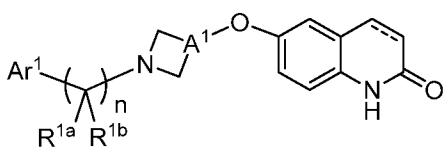
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

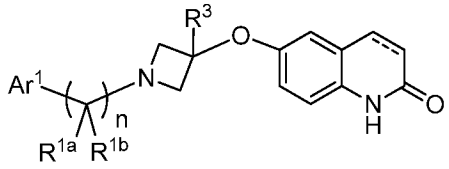
[00452] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

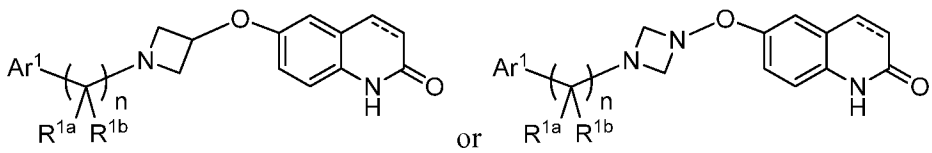
[00453] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00454] In a further aspect, the invention relates to a compound having a structure represented by a formula:

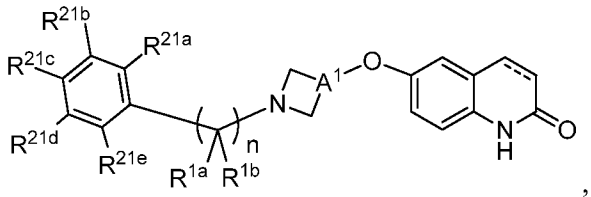


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

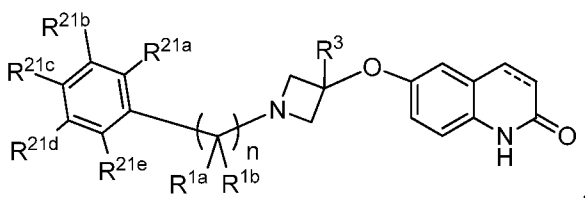
[00455] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

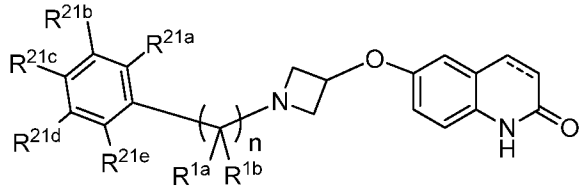
[00456] In a further aspect, the invention relates to a compound having a structure represented by a formula:



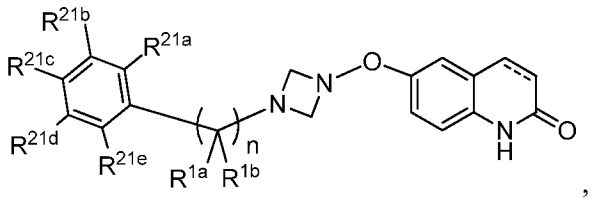
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00457] In a further aspect, the invention relates to a compound having a structure represented by a formula:



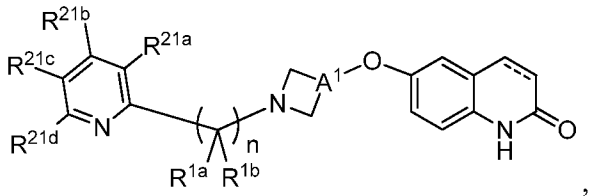
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

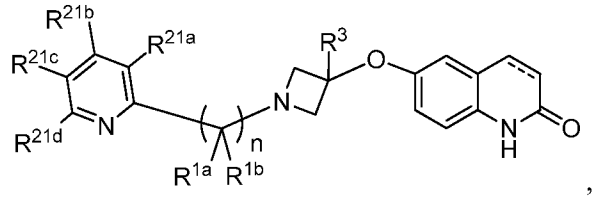
[00458] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

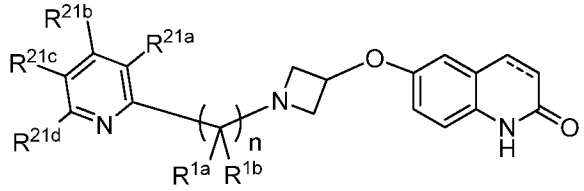
[00459] In a further aspect, the invention relates to a compound having a structure represented by a formula:



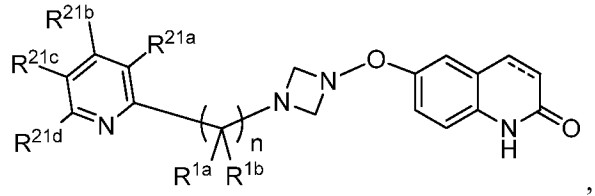
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00460] In a further aspect, the invention relates to a compound having a structure represented by a formula:



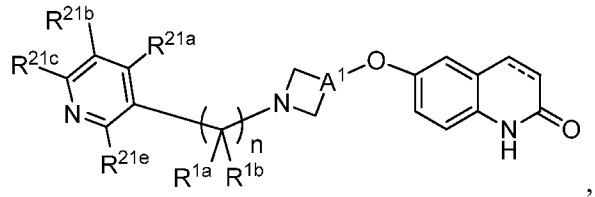
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00461] In a further aspect, the invention relates to a compound having a structure represented by a formula:

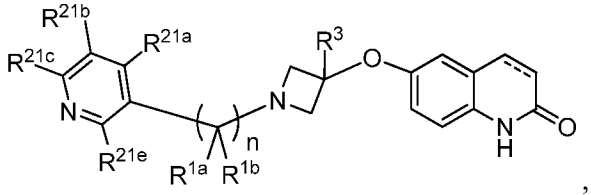


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

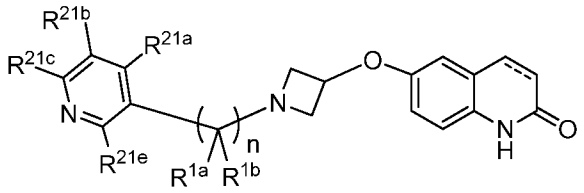
[00462] In a further aspect, the invention relates to a compound having a structure represented by a formula:



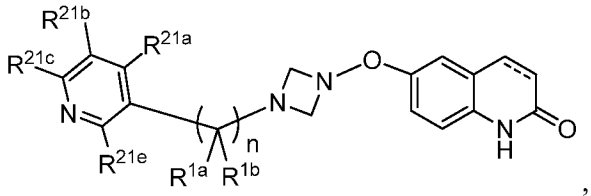
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00463] In a further aspect, the invention relates to a compound having a structure represented by a formula:



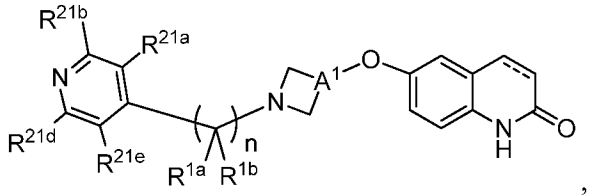
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

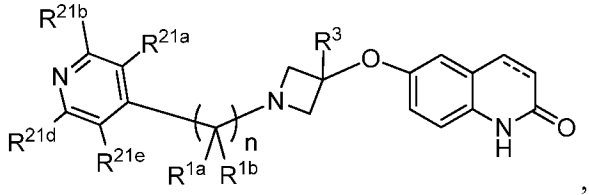
[00464] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

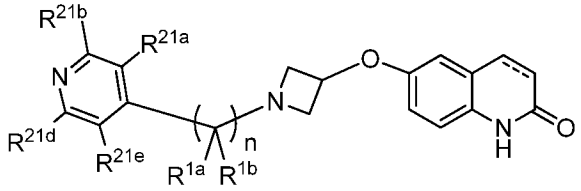
[00465] In a further aspect, the invention relates to a compound having a structure represented by a formula:



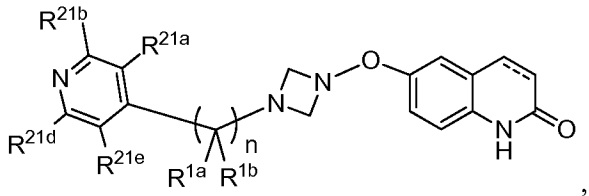
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00466] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

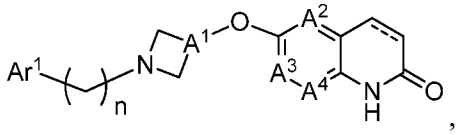


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

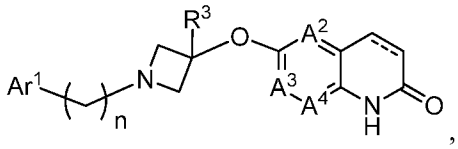
dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00467] In a further aspect, the invention relates to a compound having a structure represented by a formula:



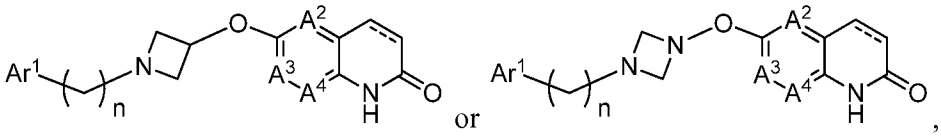
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00468] In a further aspect, the invention relates to a compound having a structure represented by a formula:



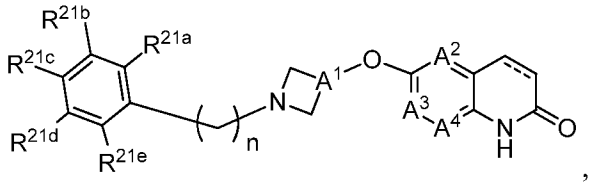
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00469] In a further aspect, the invention relates to a compound having a structure represented by a formula:



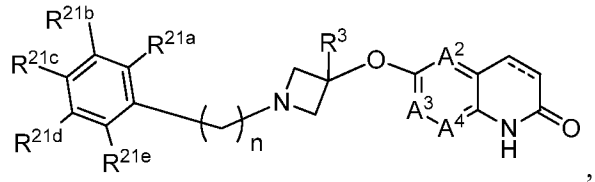
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00470] In a further aspect, the invention relates to a compound having a structure represented by a formula:



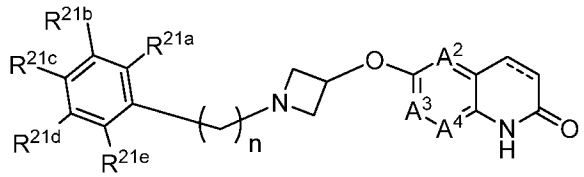
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00471] In a further aspect, the invention relates to a compound having a structure represented by a formula:

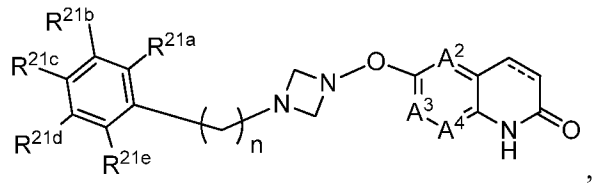


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00472] In a further aspect, the invention relates to a compound having a structure represented by a formula:

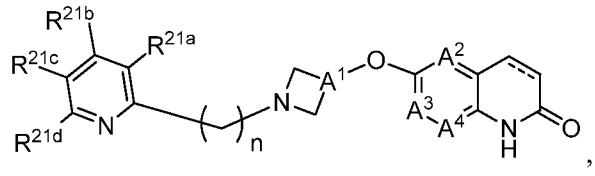


or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

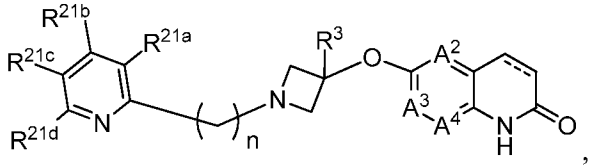
[00473] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

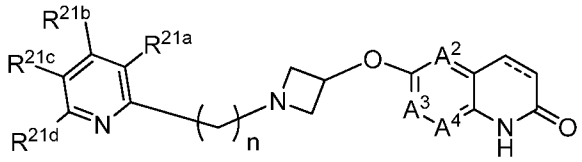
[00474] In a further aspect, the invention relates to a compound having a structure represented by a formula:



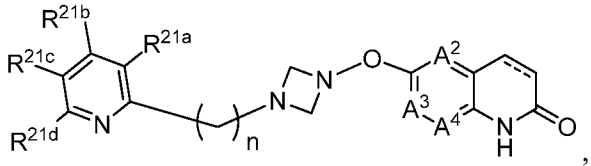
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00475] In a further aspect, the invention relates to a compound having a structure represented by a formula:



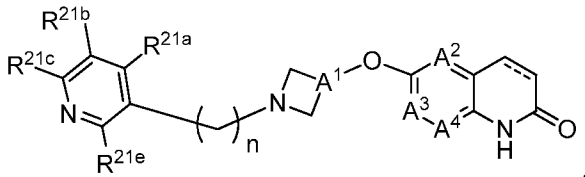
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00476] In a further aspect, the invention relates to a compound having a structure represented by a formula:

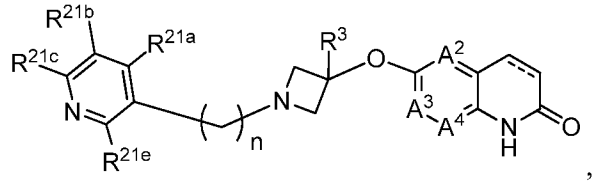


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

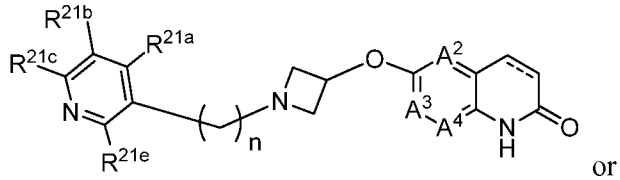
[00477] In a further aspect, the invention relates to a compound having a structure represented by a formula:



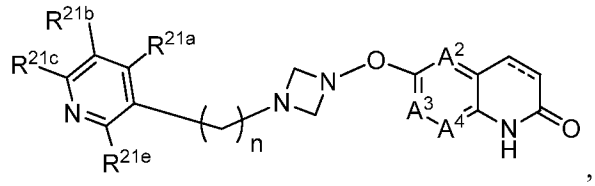
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00478] In a further aspect, the invention relates to a compound having a structure represented by a formula:



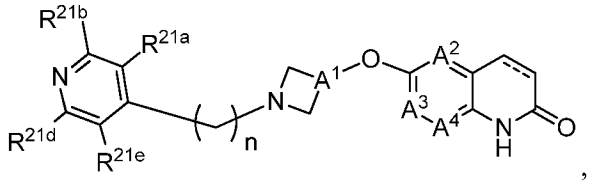
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

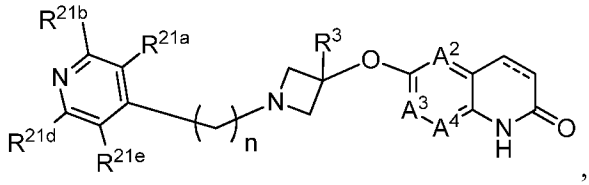
[00479] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

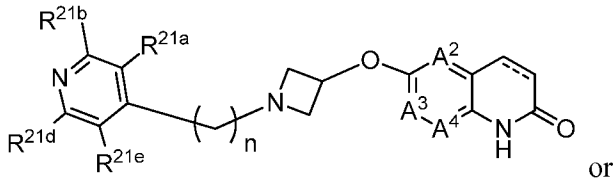
[00480] In a further aspect, the invention relates to a compound having a structure represented by a formula:



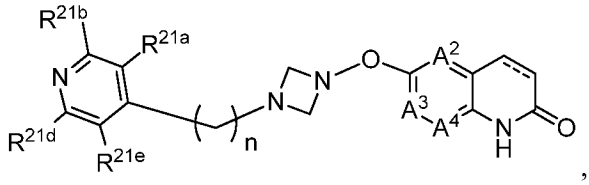
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00481] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

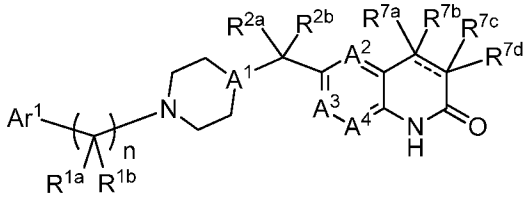


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein

all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

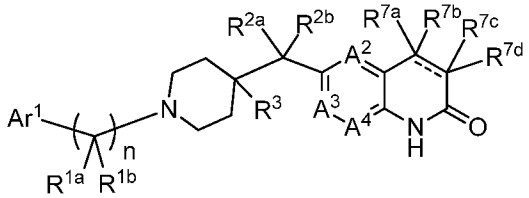
[00482] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

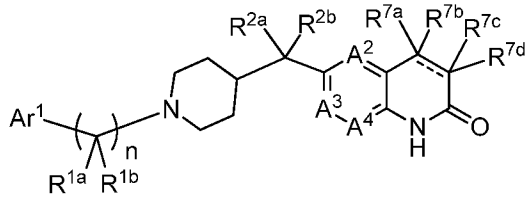
[00483] In a further aspect, the invention relates to a compound having a structure represented by a formula:



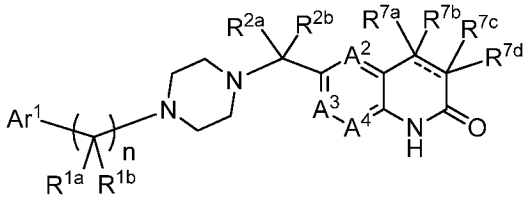
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00484] In a further aspect, the invention relates to a compound having a structure represented by a formula:



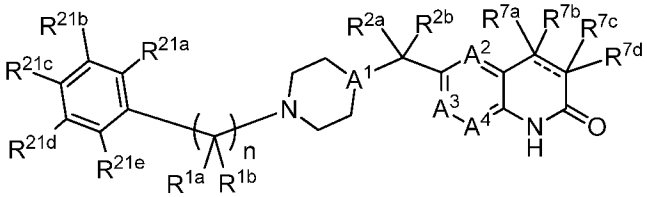
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00485] In a further aspect, the invention relates to a compound having a structure represented by a formula:

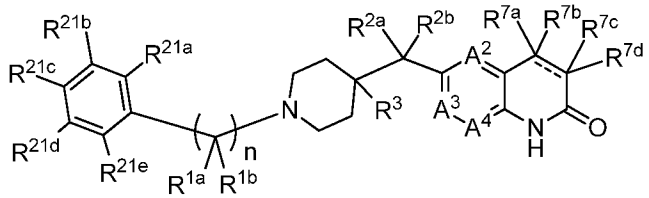


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

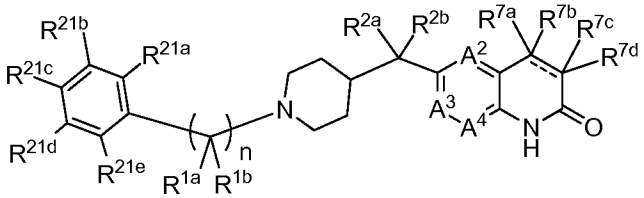
[00486] In a further aspect, the invention relates to a compound having a structure represented by a formula:



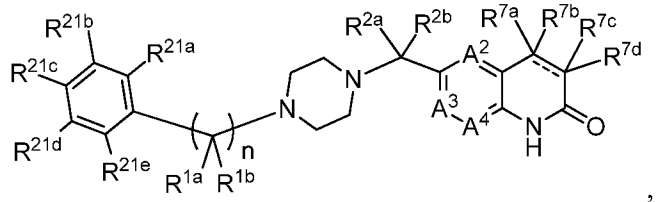
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00487] In a further aspect, the invention relates to a compound having a structure represented by a formula:



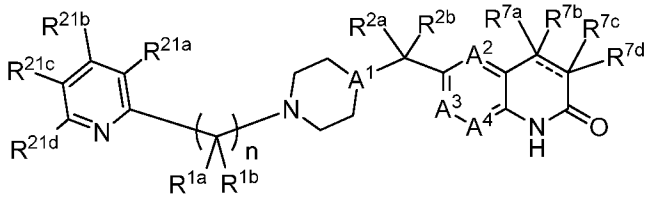
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

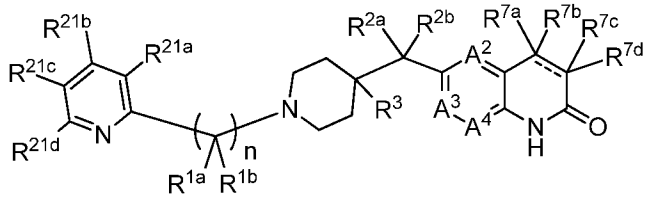
[00488] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

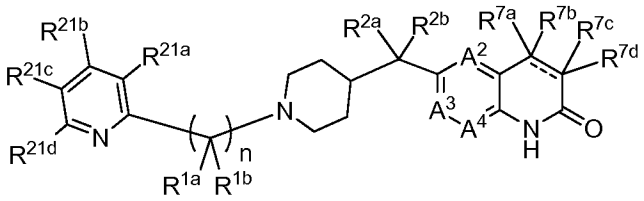
[00489] In a further aspect, the invention relates to a compound having a structure represented by a formula:



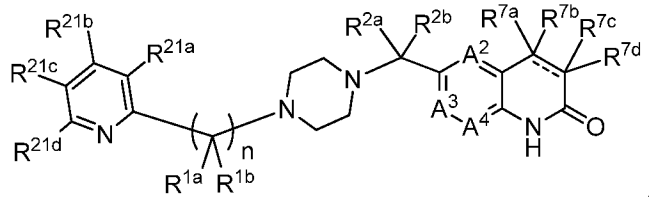
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00490] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

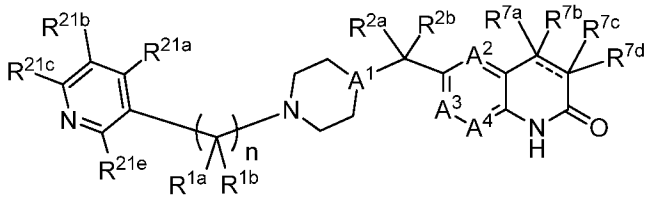


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

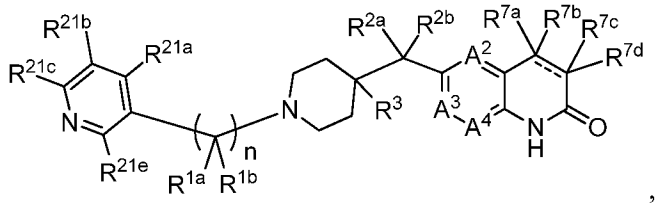
[00491] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

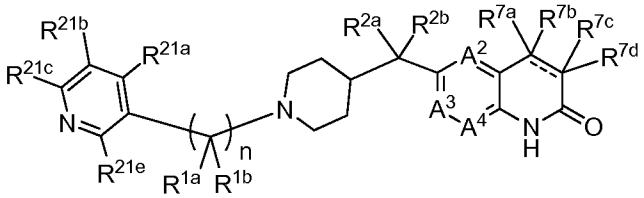
[00492] In a further aspect, the invention relates to a compound having a structure represented by a formula:



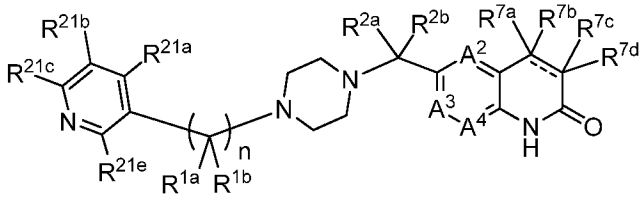
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00493] In a further aspect, the invention relates to a compound having a structure represented by a formula:



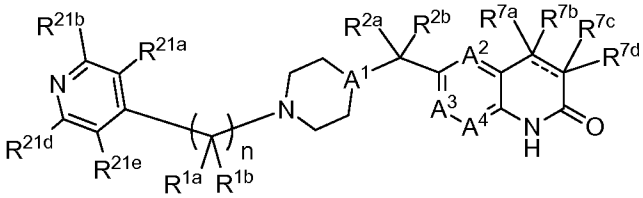
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

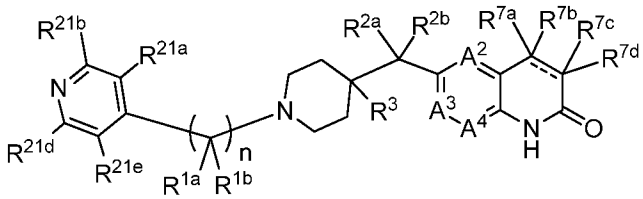
[00494] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

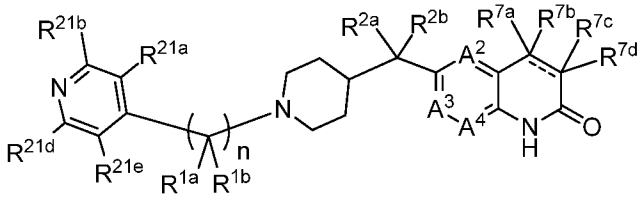
[00495] In a further aspect, the invention relates to a compound having a structure represented by a formula:



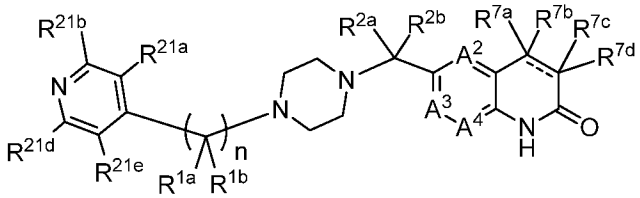
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00496] In a further aspect, the invention relates to a compound having a structure represented by a formula:



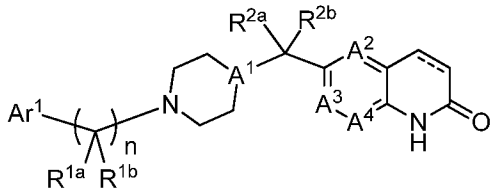
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

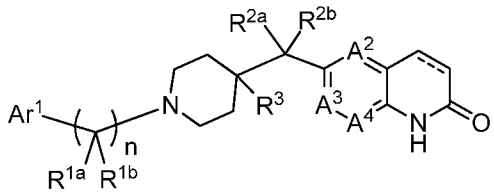
[00497] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

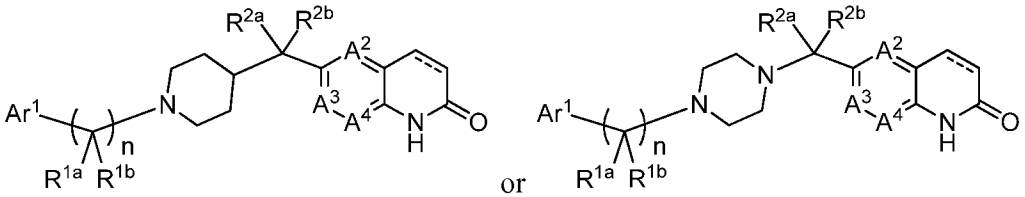
[00498] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

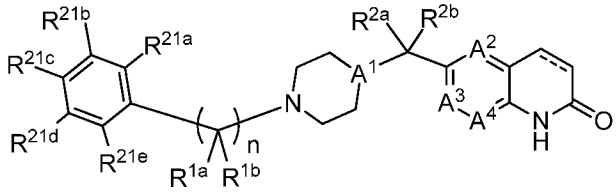
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00499] In a further aspect, the invention relates to a compound having a structure represented by a formula:



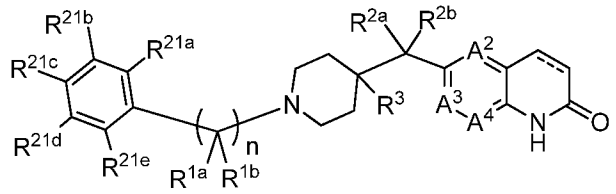
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00500] In a further aspect, the invention relates to a compound having a structure represented by a formula:



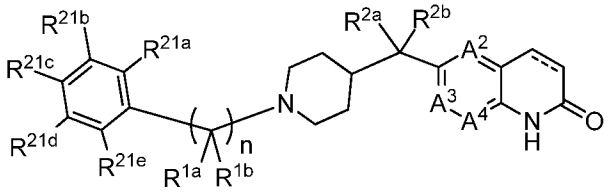
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00501] In a further aspect, the invention relates to a compound having a structure represented by a formula:

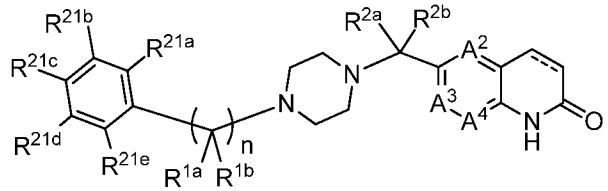


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00502] In a further aspect, the invention relates to a compound having a structure represented by a formula:



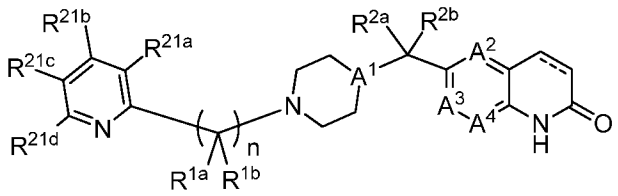
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

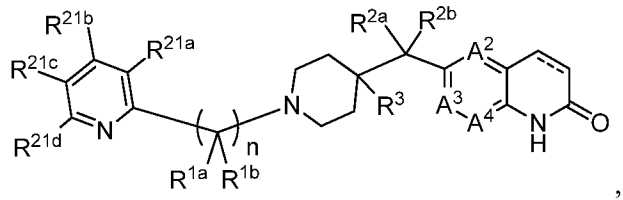
[00503] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00504] In a further aspect, the invention relates to a compound having a structure represented by a formula:

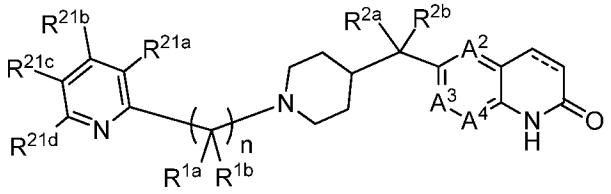


,

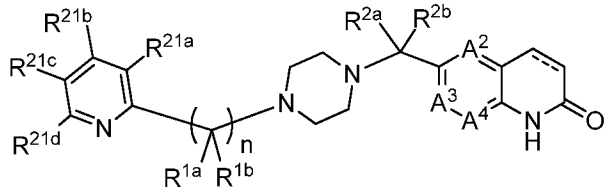
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00505] In a further aspect, the invention relates to a compound having a structure represented by a formula:



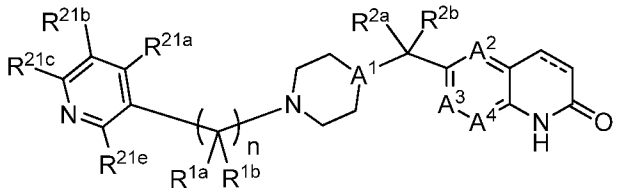
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

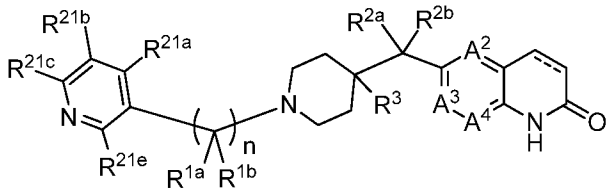
[00506] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

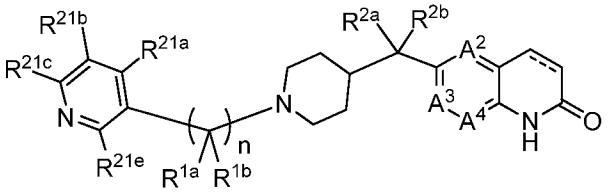
[00507] In a further aspect, the invention relates to a compound having a structure represented by a formula:



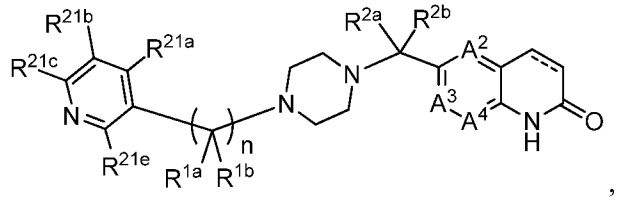
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00508] In a further aspect, the invention relates to a compound having a structure represented by a formula:



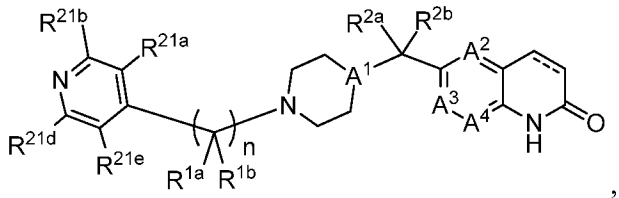
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00509] In a further aspect, the invention relates to a compound having a structure represented by a formula:

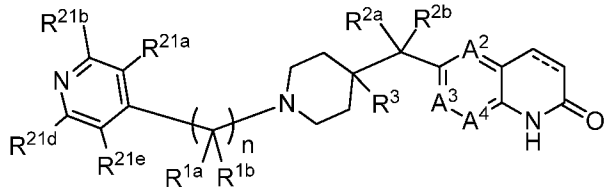


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

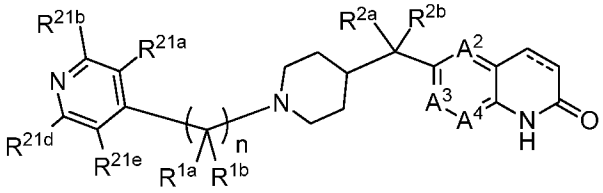
[00510] In a further aspect, the invention relates to a compound having a structure represented by a formula:



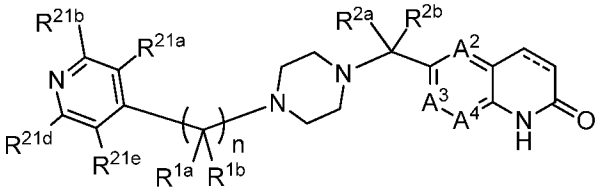
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00511] In a further aspect, the invention relates to a compound having a structure represented by a formula:



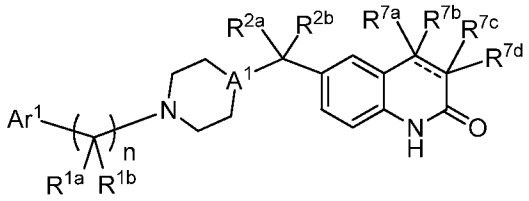
or



,

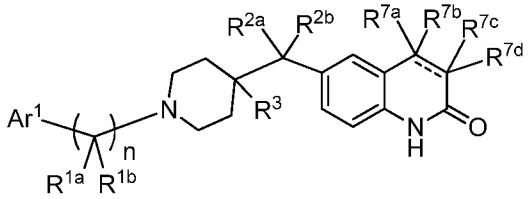
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00512] In a further aspect, the invention relates to a compound having a structure represented by a formula:



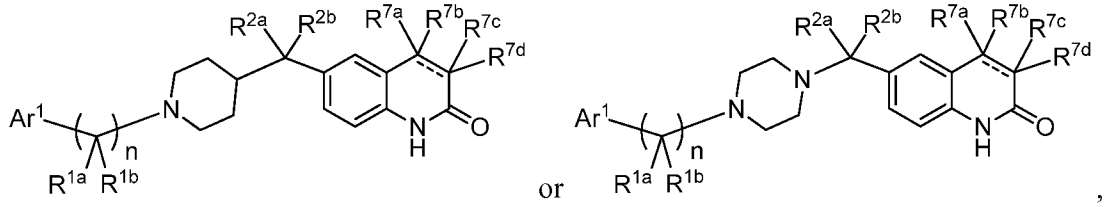
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00513] In a further aspect, the invention relates to a compound having a structure represented by a formula:



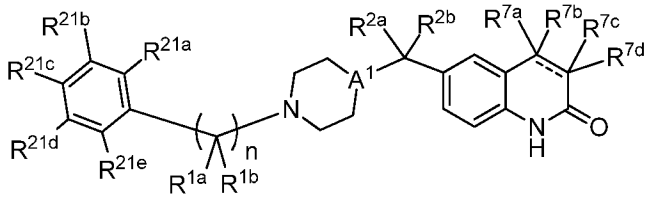
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00514] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

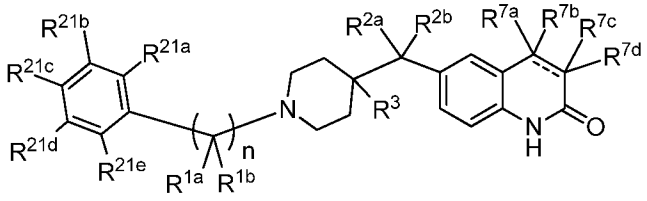
[00515] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all

other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

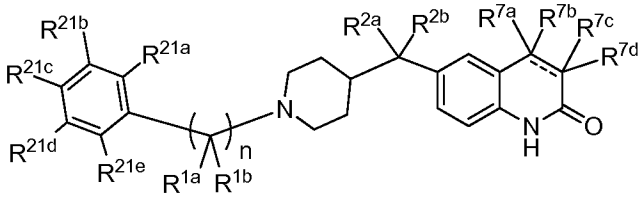
[00516] In a further aspect, the invention relates to a compound having a structure represented by a formula:



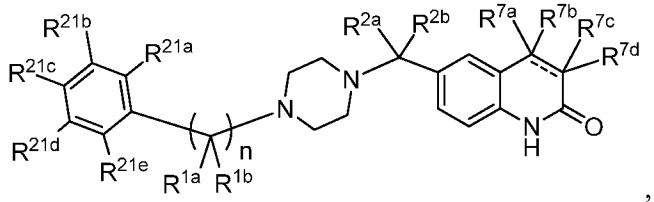
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00517] In a further aspect, the invention relates to a compound having a structure represented by a formula:



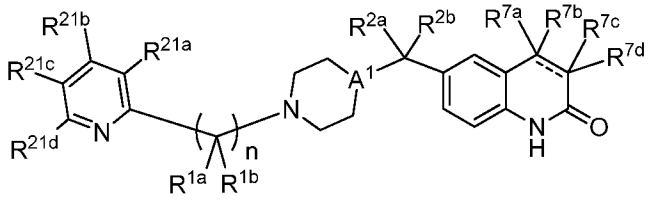
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

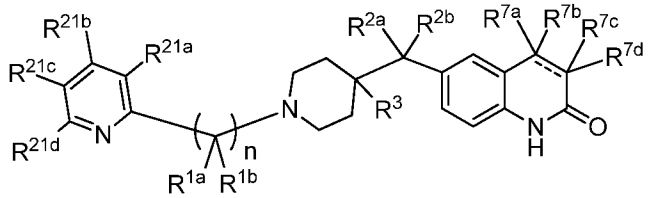
[00518] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

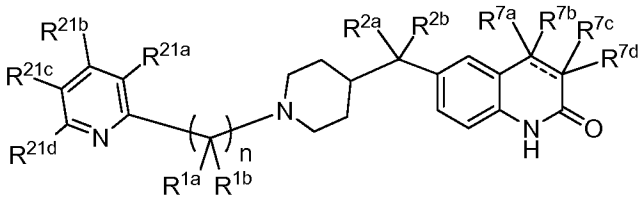
[00519] In a further aspect, the invention relates to a compound having a structure represented by a formula:



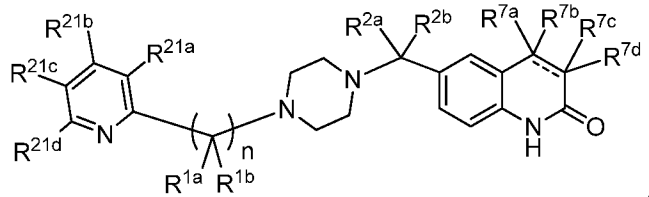
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00520] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

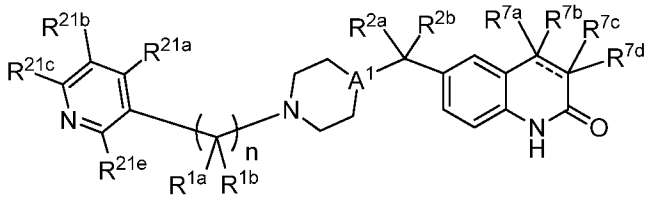


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

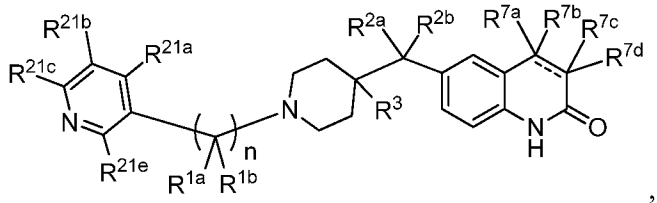
[00521] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

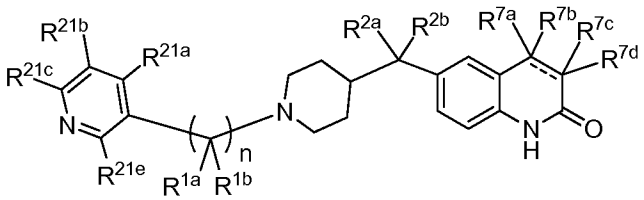
[00522] In a further aspect, the invention relates to a compound having a structure represented by a formula:



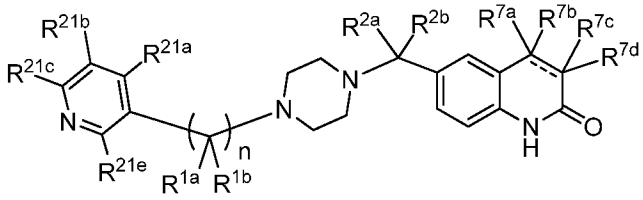
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00523] In a further aspect, the invention relates to a compound having a structure represented by a formula:



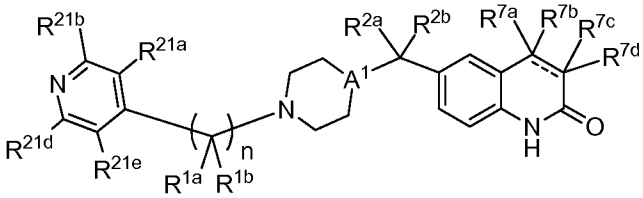
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

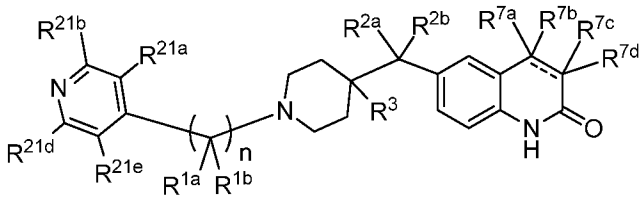
[00524] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

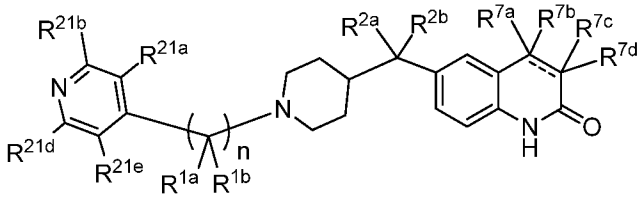
[00525] In a further aspect, the invention relates to a compound having a structure represented by a formula:



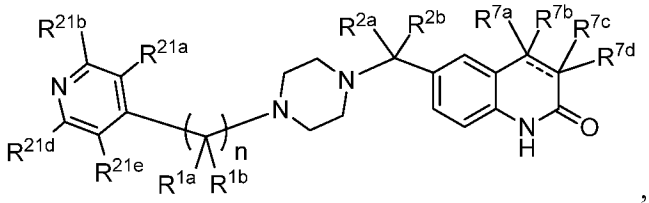
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00526] In a further aspect, the invention relates to a compound having a structure represented by a formula:



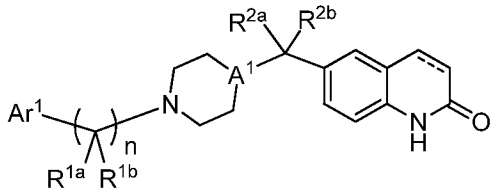
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

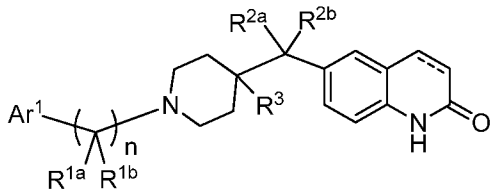
[00527] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

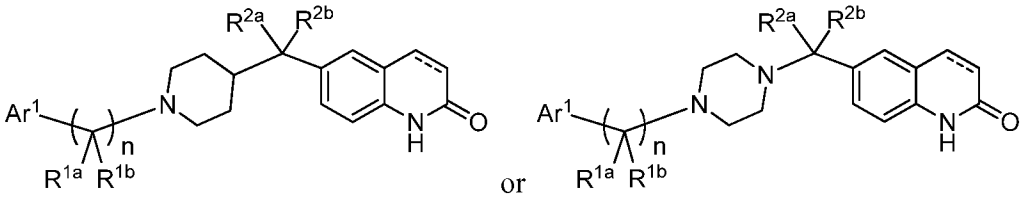
[00528] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

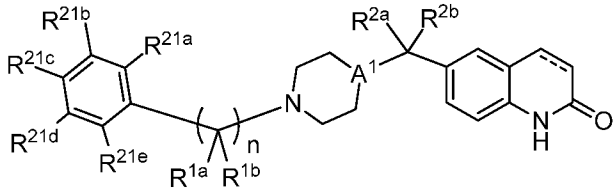
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00529] In a further aspect, the invention relates to a compound having a structure represented by a formula:



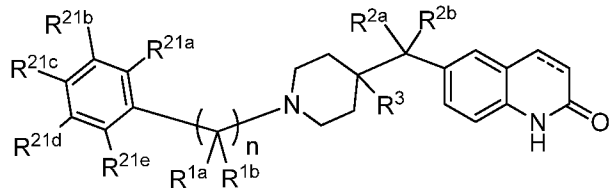
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00530] In a further aspect, the invention relates to a compound having a structure represented by a formula:



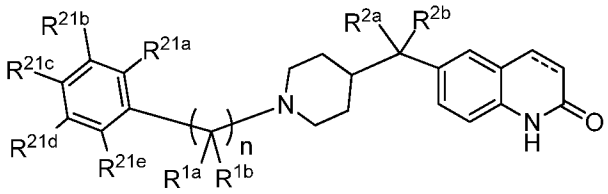
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00531] In a further aspect, the invention relates to a compound having a structure represented by a formula:

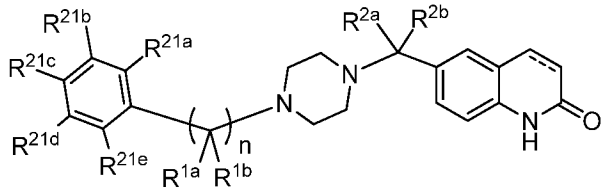


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00532] In a further aspect, the invention relates to a compound having a structure represented by a formula:



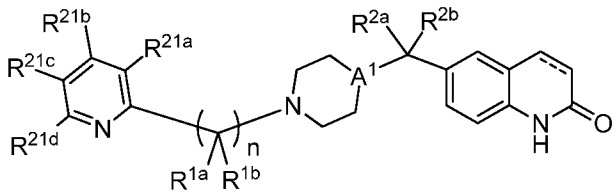
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

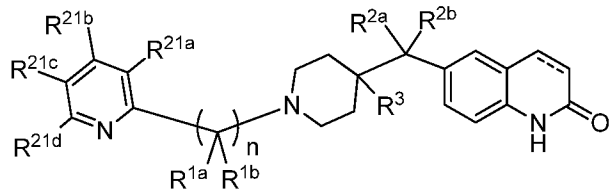
[00533] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00534] In a further aspect, the invention relates to a compound having a structure represented by a formula:

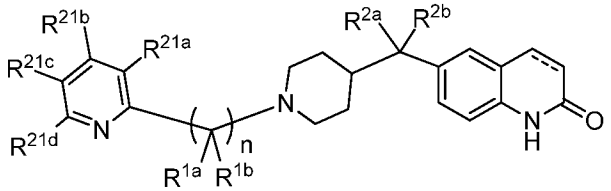


,

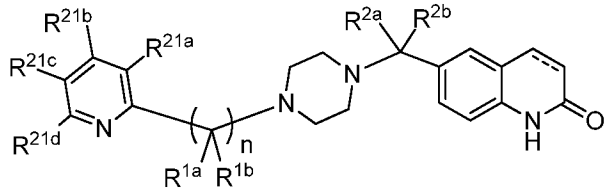
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00535] In a further aspect, the invention relates to a compound having a structure represented by a formula:



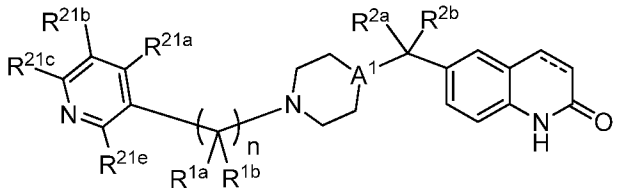
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

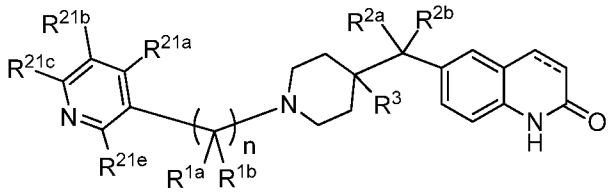
[00536] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

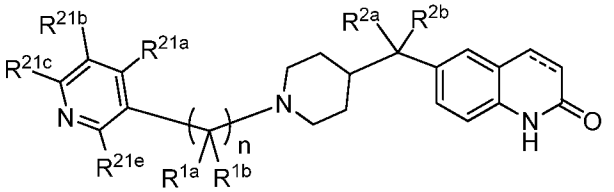
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00537] In a further aspect, the invention relates to a compound having a structure represented by a formula:

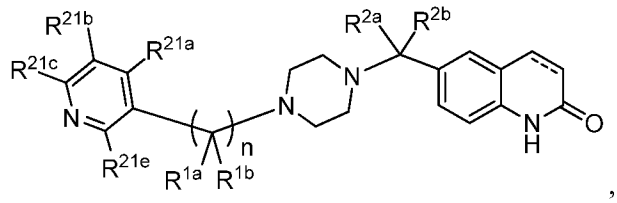


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00538] In a further aspect, the invention relates to a compound having a structure represented by a formula:

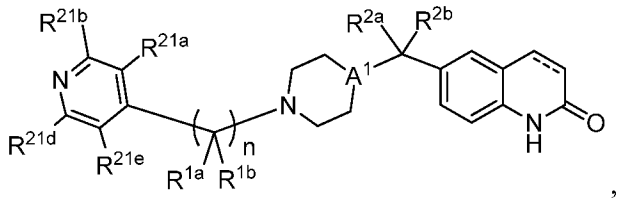


or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

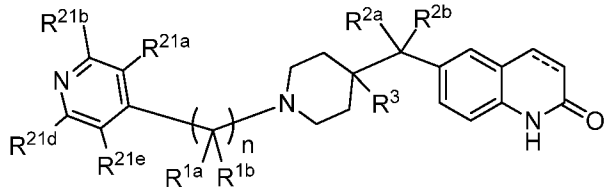
[00539] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

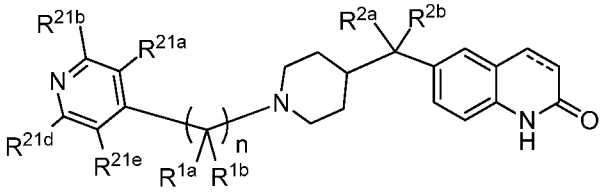
[00540] In a further aspect, the invention relates to a compound having a structure represented by a formula:



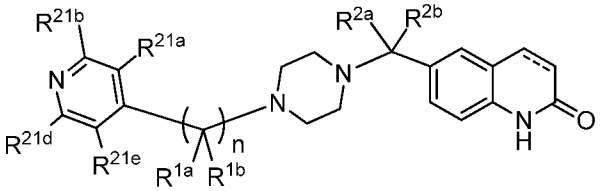
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00541] In a further aspect, the invention relates to a compound having a structure represented by a formula:



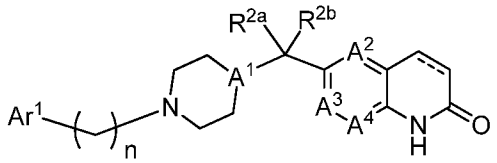
or



,

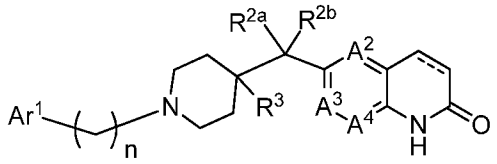
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00542] In a further aspect, the invention relates to a compound having a structure represented by a formula:



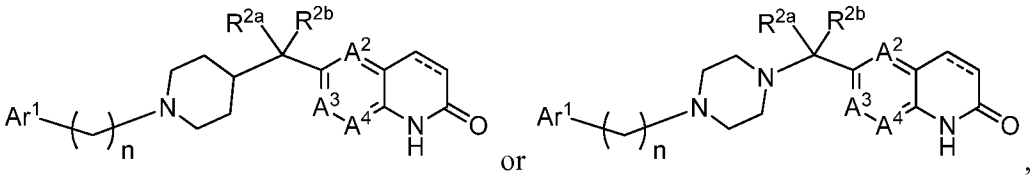
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00543] In a further aspect, the invention relates to a compound having a structure represented by a formula:



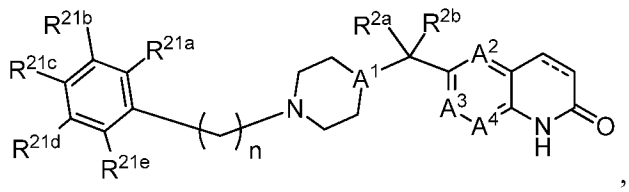
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00544] In a further aspect, the invention relates to a compound having a structure represented by a formula:



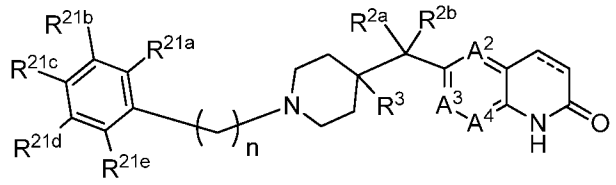
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00545] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

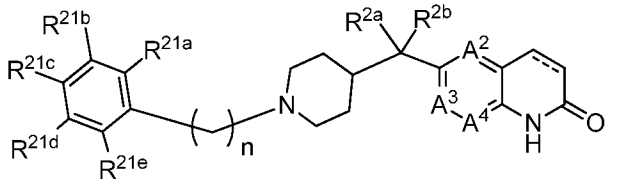
[00546] In a further aspect, the invention relates to a compound having a structure represented by a formula:



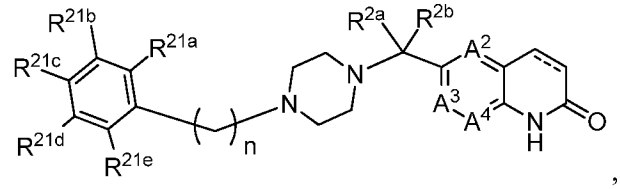
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00547] In a further aspect, the invention relates to a compound having a structure represented by a formula:



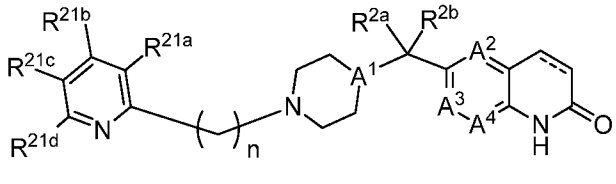
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00548] In a further aspect, the invention relates to a compound having a structure represented by a formula:

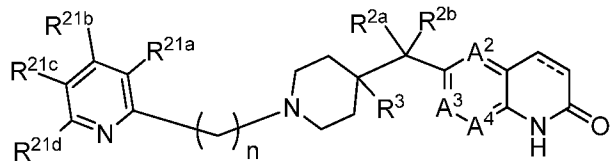


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other

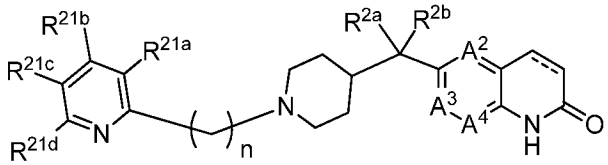
variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00549] In a further aspect, the invention relates to a compound having a structure represented by a formula:

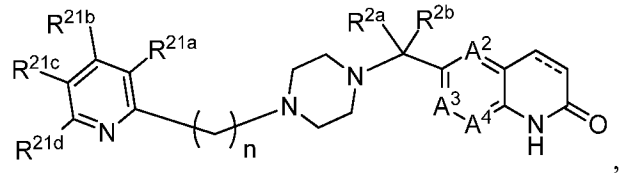


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00550] In a further aspect, the invention relates to a compound having a structure represented by a formula:

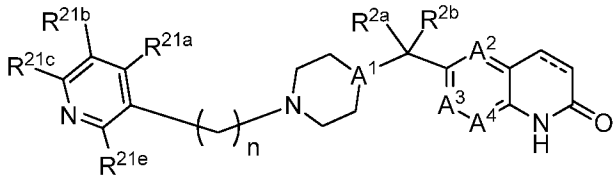


or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

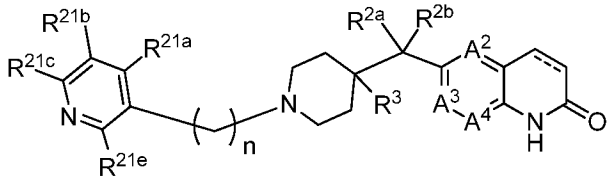
[00551] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

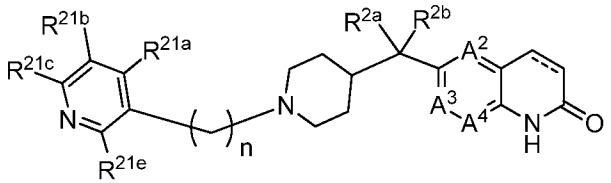
[00552] In a further aspect, the invention relates to a compound having a structure represented by a formula:



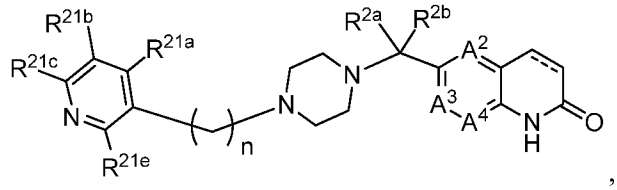
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00553] In a further aspect, the invention relates to a compound having a structure represented by a formula:



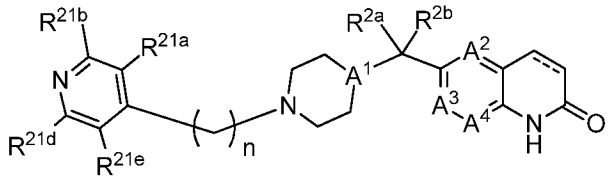
or



,

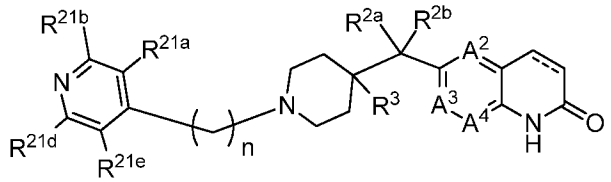
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00554] In a further aspect, the invention relates to a compound having a structure represented by a formula:



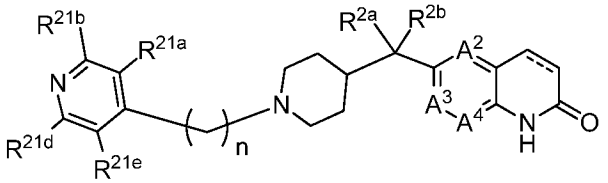
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00555] In a further aspect, the invention relates to a compound having a structure represented by a formula:

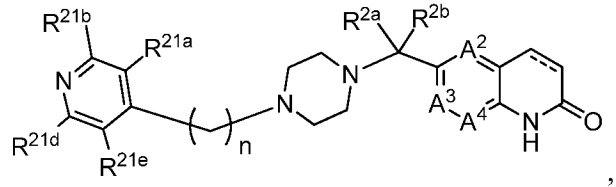


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00556] In a further aspect, the invention relates to a compound having a structure represented by a formula:



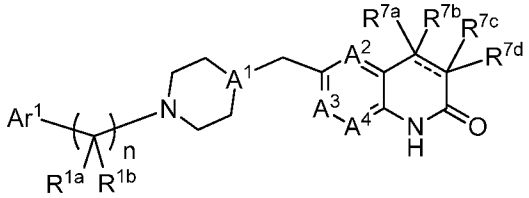
or



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein

all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

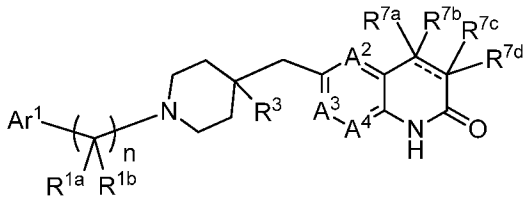
[00557] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

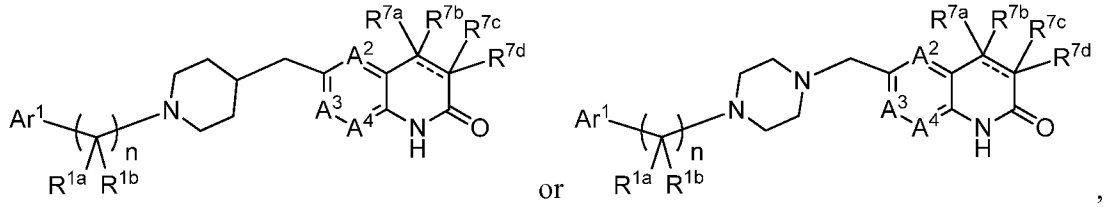
[00558] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

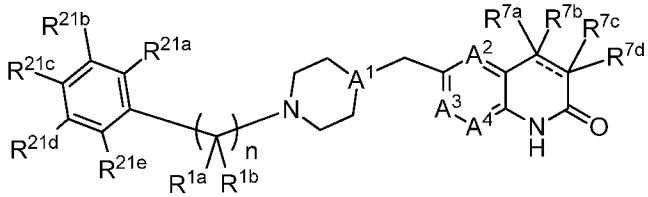
[00559] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00560] In a further aspect, the invention relates to a compound having a structure represented by a formula:

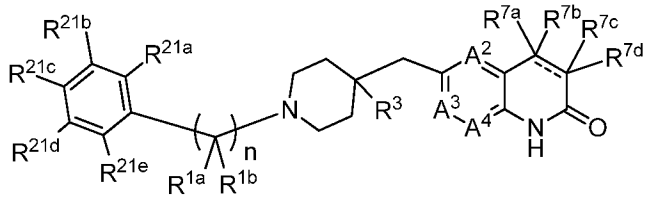


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

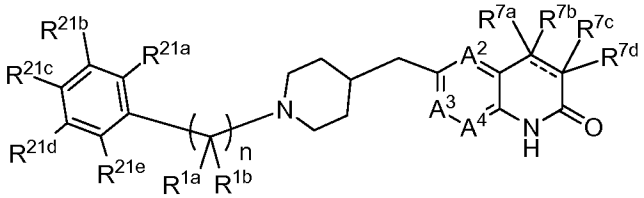
[00561] In a further aspect, the invention relates to a compound having a structure represented by a formula:



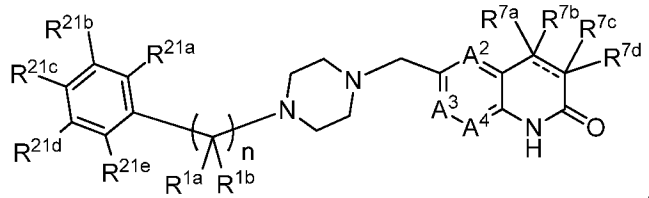
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00562] In a further aspect, the invention relates to a compound having a structure represented by a formula:



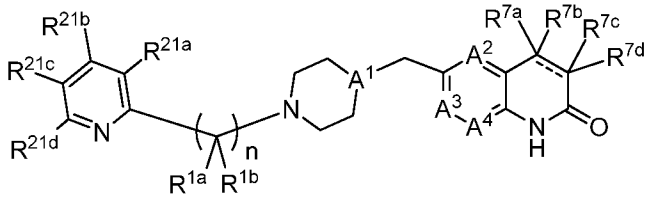
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

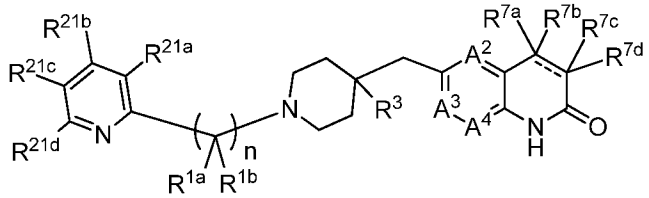
[00563] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

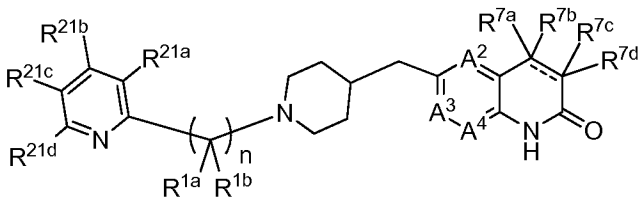
[00564] In a further aspect, the invention relates to a compound having a structure represented by a formula:



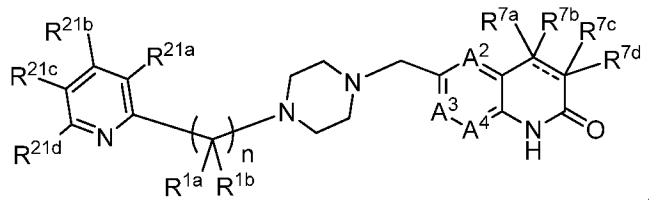
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00565] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

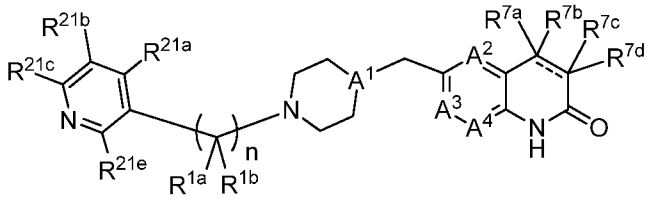


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

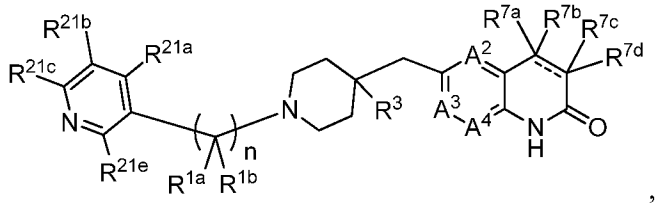
[00566] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

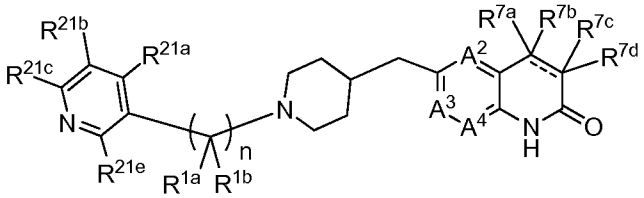
[00567] In a further aspect, the invention relates to a compound having a structure represented by a formula:



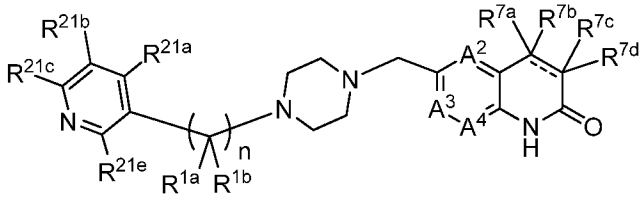
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00568] In a further aspect, the invention relates to a compound having a structure represented by a formula:



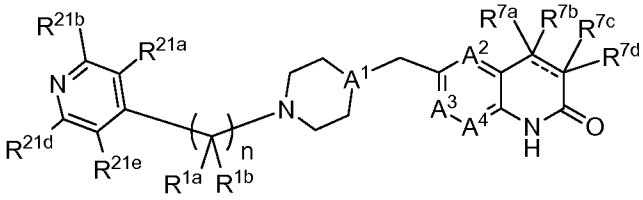
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

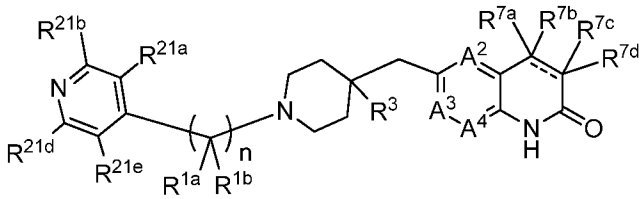
[00569] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

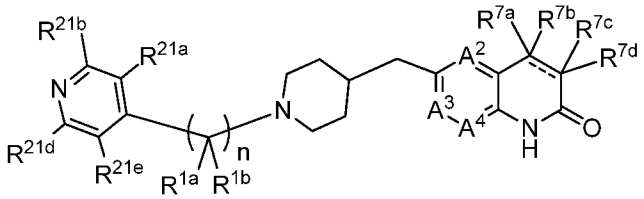
[00570] In a further aspect, the invention relates to a compound having a structure represented by a formula:



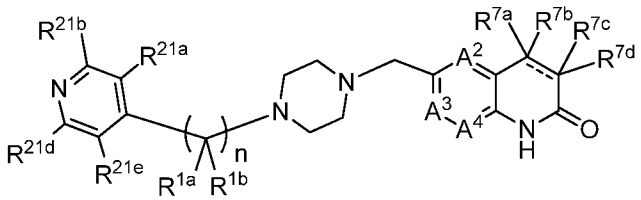
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00571] In a further aspect, the invention relates to a compound having a structure represented by a formula:



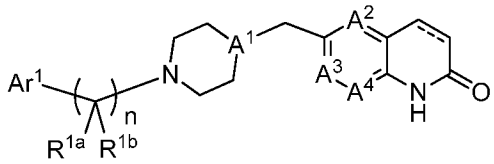
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

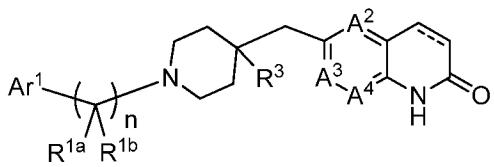
[00572] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

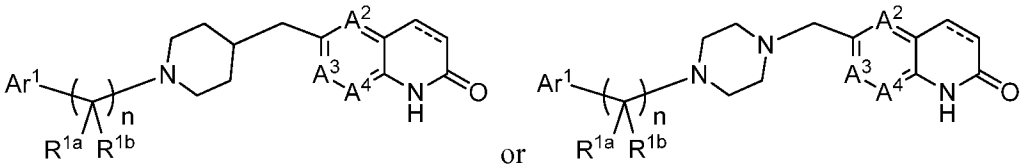
[00573] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

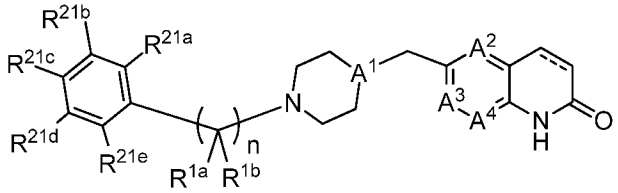
[00574] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

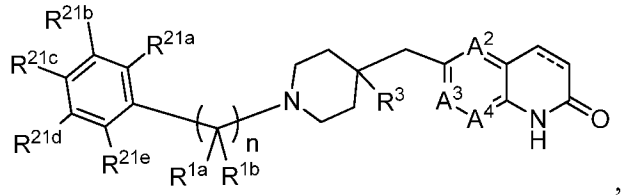
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00575] In a further aspect, the invention relates to a compound having a structure represented by a formula:



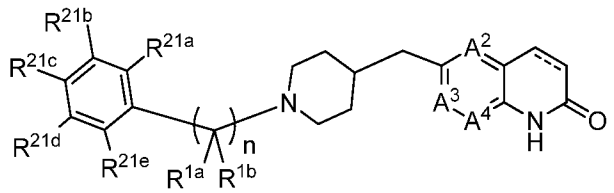
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00576] In a further aspect, the invention relates to a compound having a structure represented by a formula:

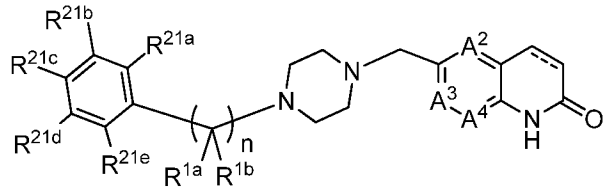


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00577] In a further aspect, the invention relates to a compound having a structure represented by a formula:



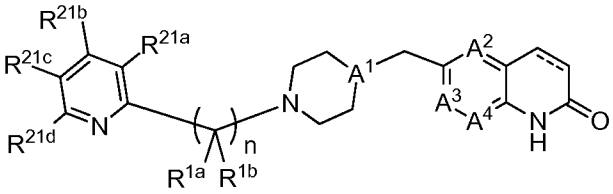
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

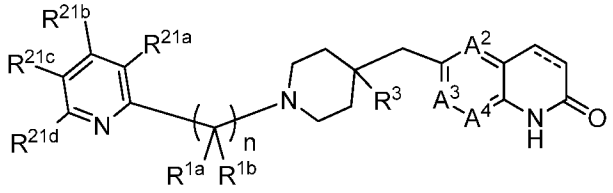
[00578] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

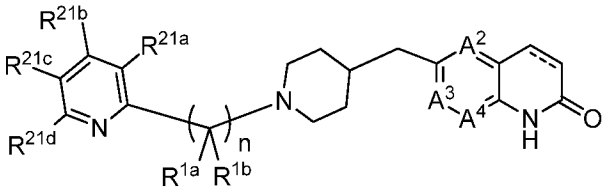
[00579] In a further aspect, the invention relates to a compound having a structure represented by a formula:



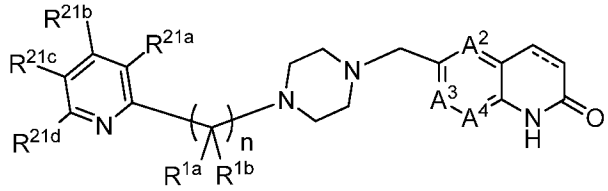
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00580] In a further aspect, the invention relates to a compound having a structure represented by a formula:



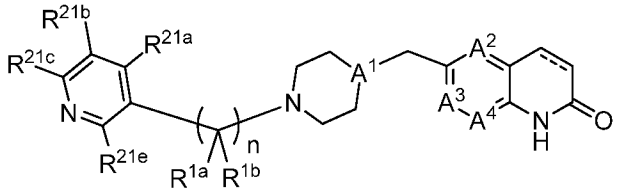
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

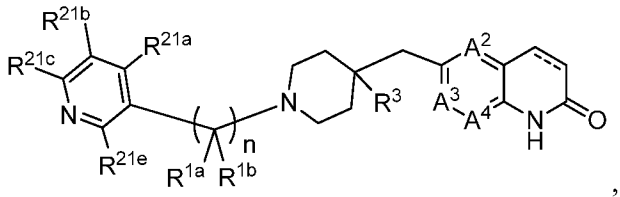
[00581] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00582] In a further aspect, the invention relates to a compound having a structure represented by a formula:

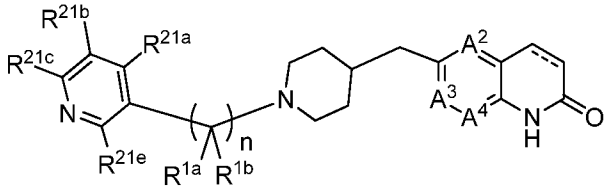


,

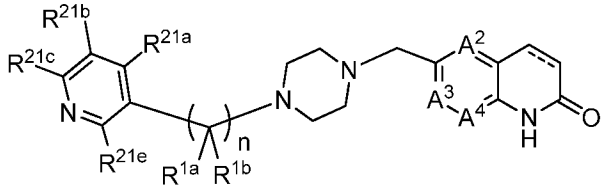
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00583] In a further aspect, the invention relates to a compound having a structure represented by a formula:



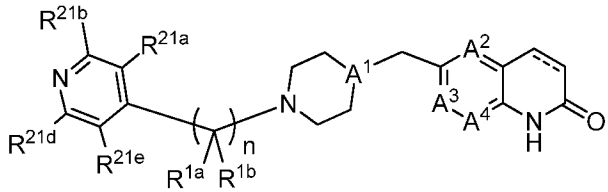
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

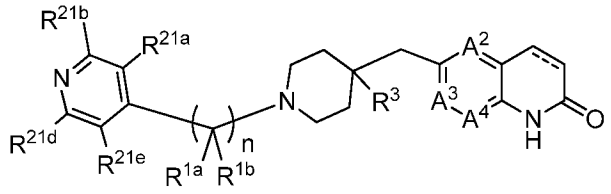
[00584] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

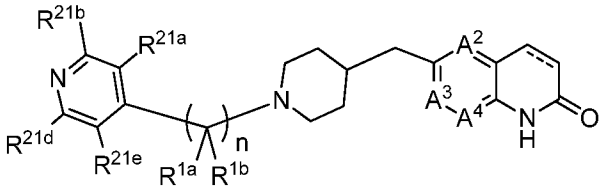
[00585] In a further aspect, the invention relates to a compound having a structure represented by a formula:



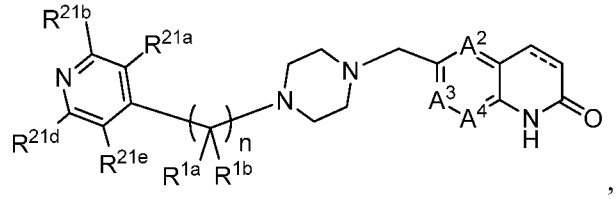
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00586] In a further aspect, the invention relates to a compound having a structure represented by a formula:



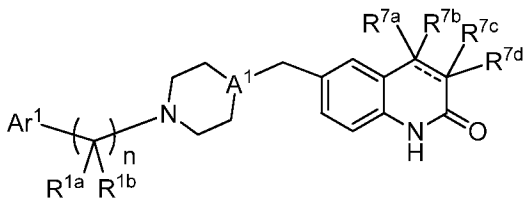
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00587] In a further aspect, the invention relates to a compound having a structure represented by a formula:

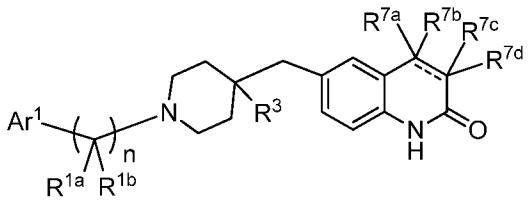


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00588] In a further aspect, the invention relates to a compound having a structure

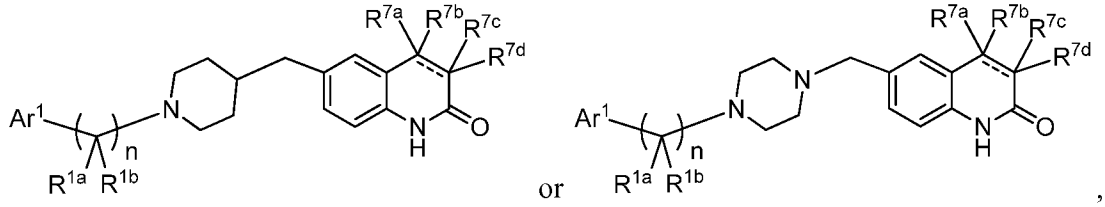
represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00589] In a further aspect, the invention relates to a compound having a structure represented by a formula:

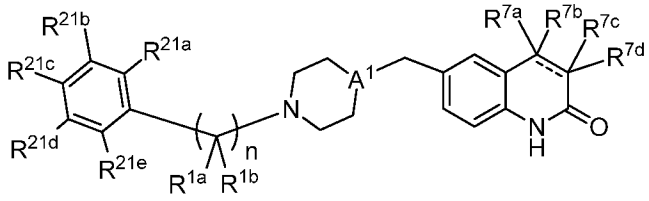


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

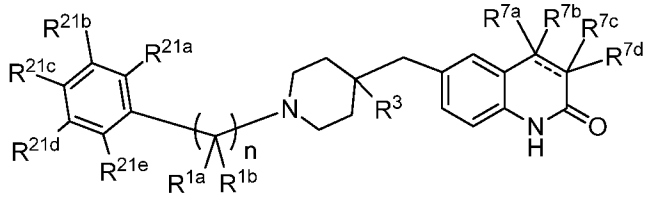
[00590] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

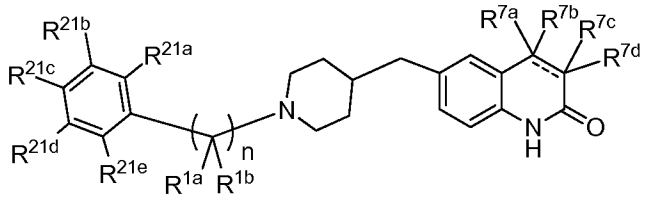
[00591] In a further aspect, the invention relates to a compound having a structure represented by a formula:



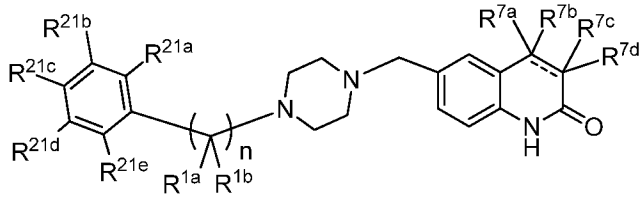
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00592] In a further aspect, the invention relates to a compound having a structure represented by a formula:



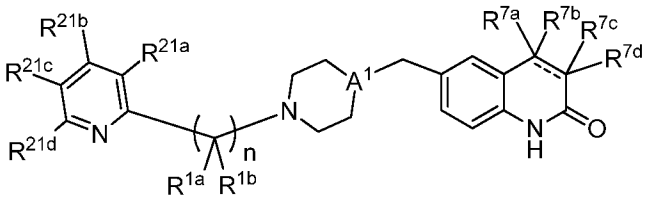
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

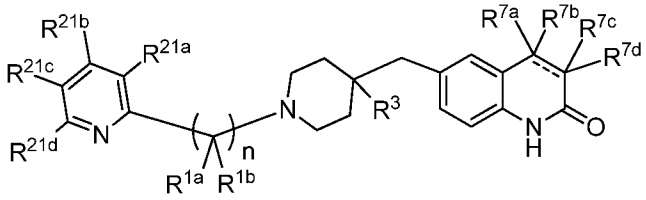
[00593] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

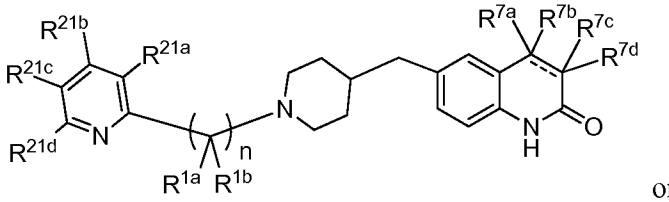
[00594] In a further aspect, the invention relates to a compound having a structure represented by a formula:



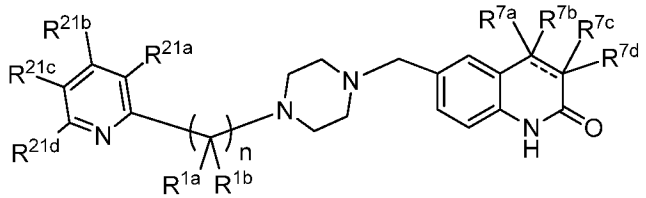
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00595] In a further aspect, the invention relates to a compound having a structure represented by a formula:



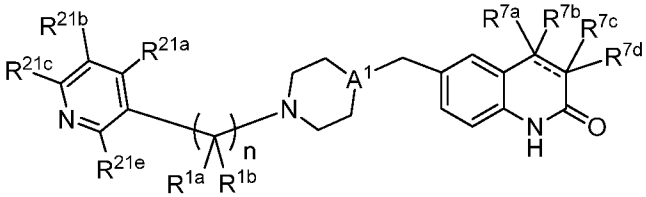
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00596] In a further aspect, the invention relates to a compound having a structure represented by a formula:

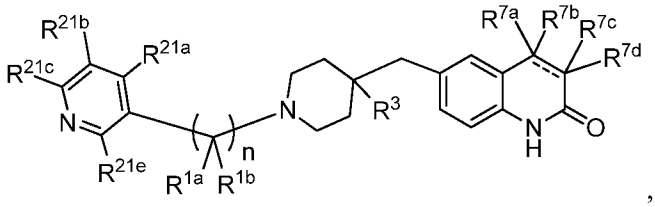


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

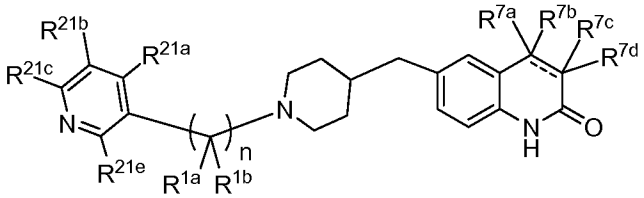
[00597] In a further aspect, the invention relates to a compound having a structure represented by a formula:



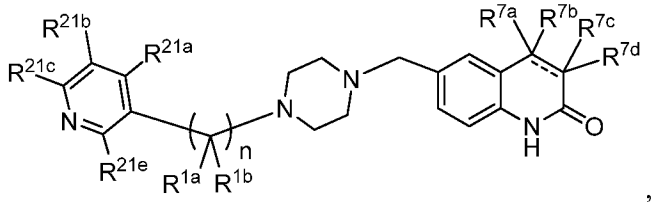
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00598] In a further aspect, the invention relates to a compound having a structure represented by a formula:



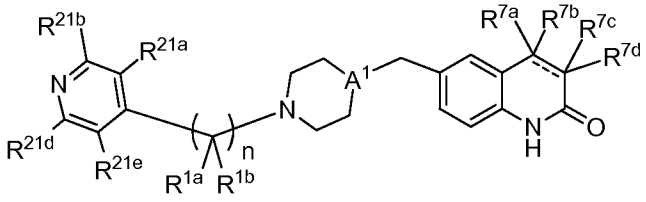
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

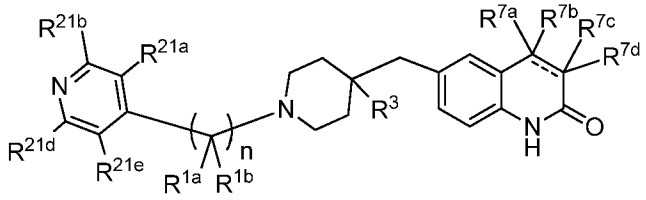
[00599] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

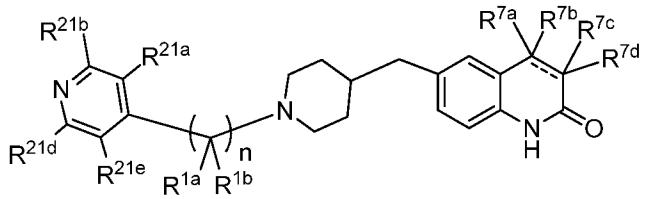
[00600] In a further aspect, the invention relates to a compound having a structure represented by a formula:



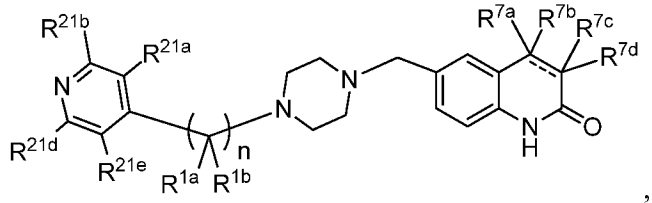
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00601] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

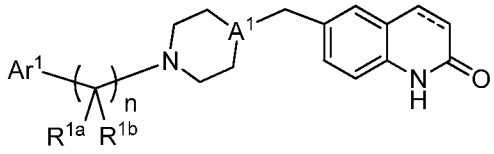


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

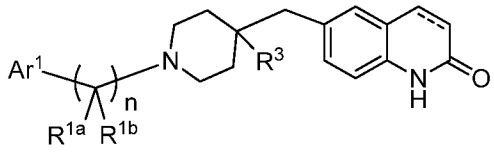
[00602] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

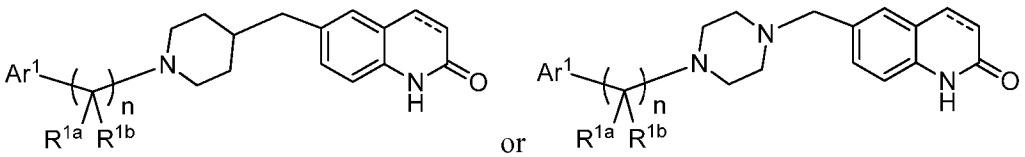
[00603] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

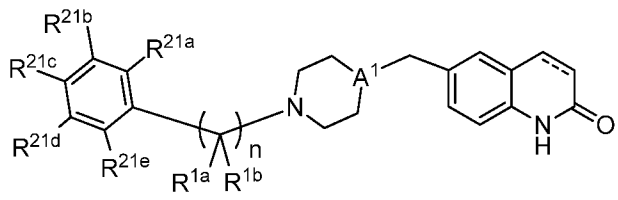
[00604] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00605] In a further aspect, the invention relates to a compound having a structure represented by a formula:

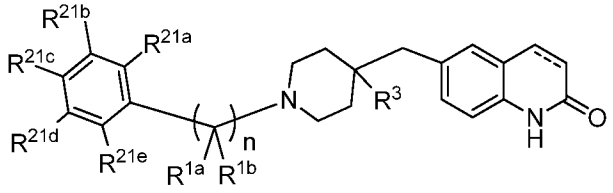


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4

alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

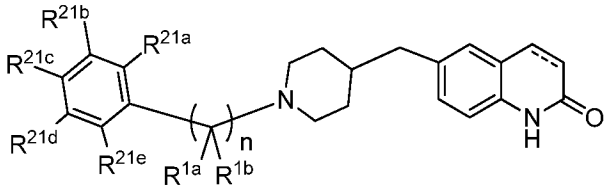
[00606] In a further aspect, the invention relates to a compound having a structure represented by a formula:



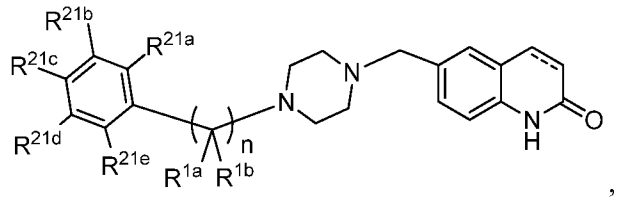
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00607] In a further aspect, the invention relates to a compound having a structure represented by a formula:



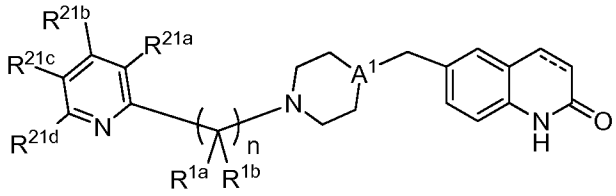
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

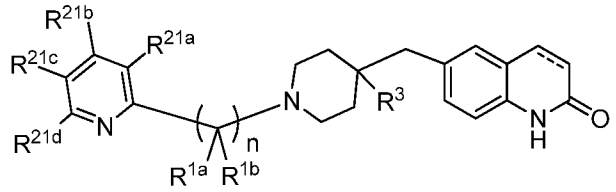
[00608] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

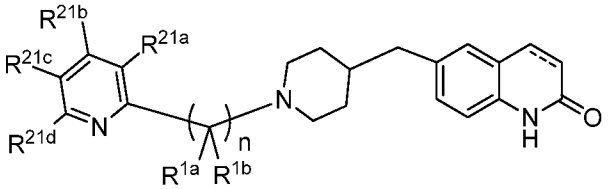
[00609] In a further aspect, the invention relates to a compound having a structure represented by a formula:



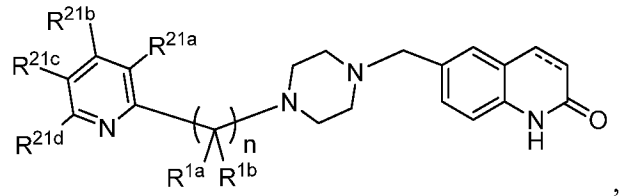
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00610] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

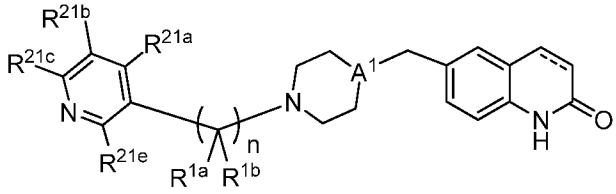


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

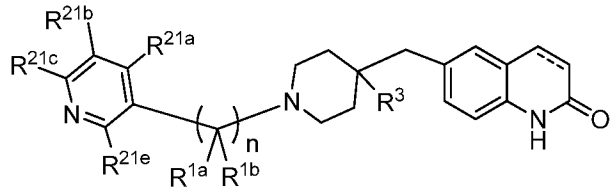
[00611] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

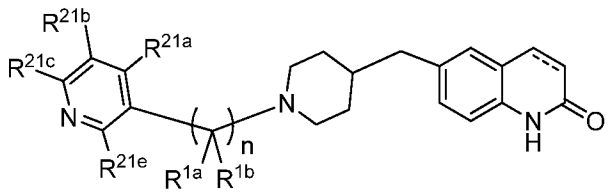
[00612] In a further aspect, the invention relates to a compound having a structure represented by a formula:



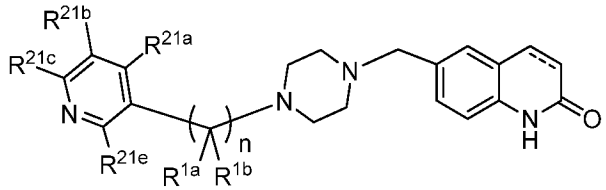
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00613] In a further aspect, the invention relates to a compound having a structure represented by a formula:



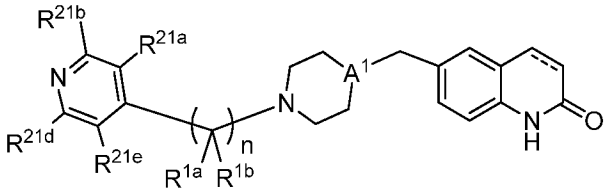
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

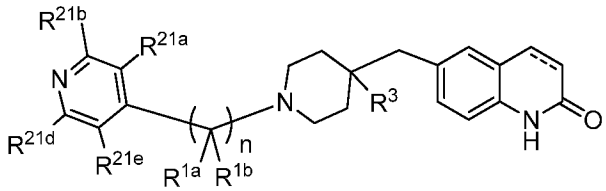
[00614] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

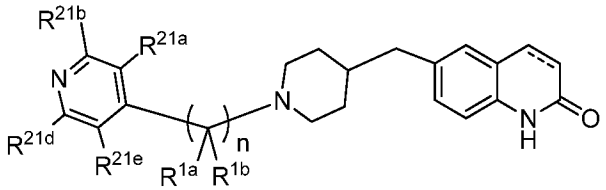
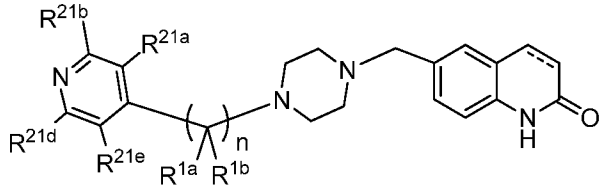
[00615] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

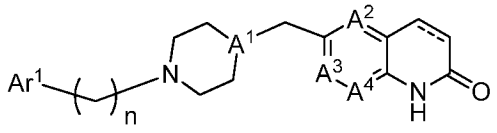
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00616] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

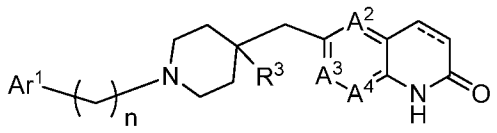
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00617] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

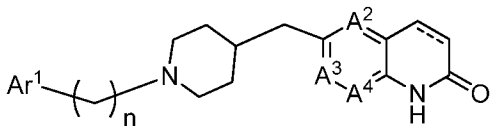
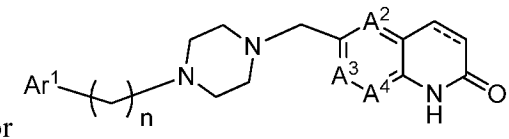
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00618] In a further aspect, the invention relates to a compound having a structure represented by a formula:


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

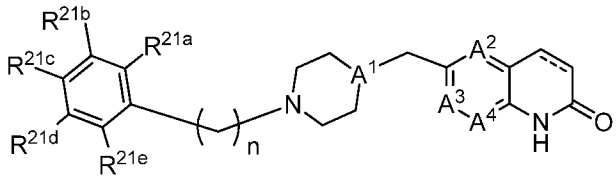
[00619] In a further aspect, the invention relates to a compound having a structure represented by a formula:


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other

variables are as defined herein; or a pharmaceutically acceptable salt thereof.

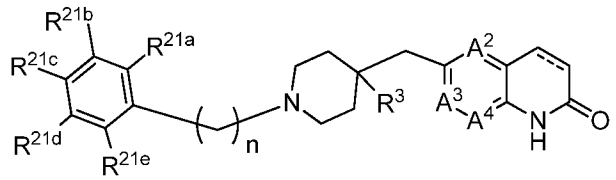
[00620] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

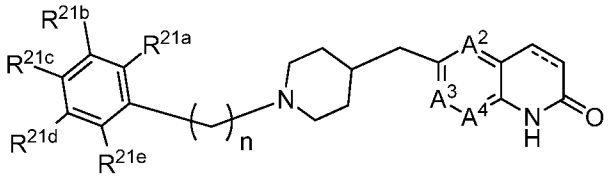
[00621] In a further aspect, the invention relates to a compound having a structure represented by a formula:



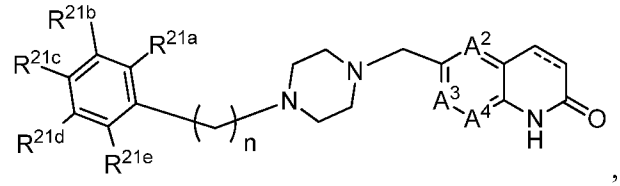
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00622] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

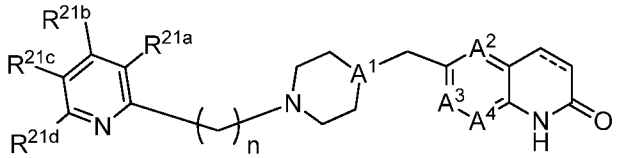


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

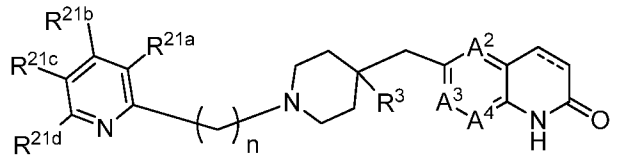
[00623] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

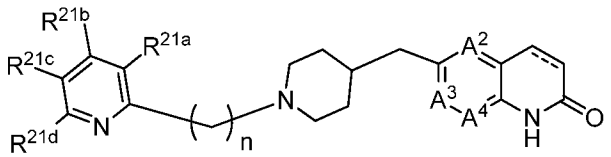
[00624] In a further aspect, the invention relates to a compound having a structure represented by a formula:



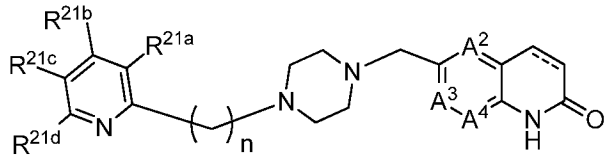
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00625] In a further aspect, the invention relates to a compound having a structure represented by a formula:



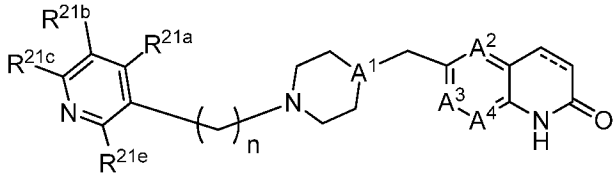
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

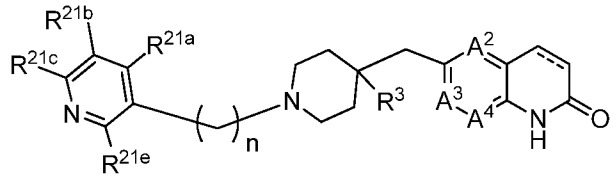
[00626] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

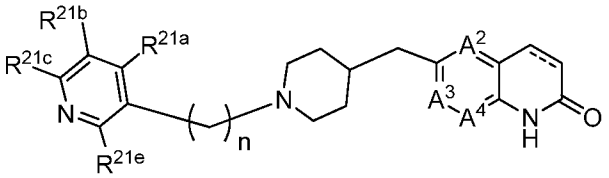
[00627] In a further aspect, the invention relates to a compound having a structure represented by a formula:



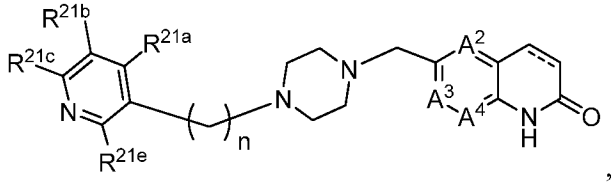
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00628] In a further aspect, the invention relates to a compound having a structure represented by a formula:



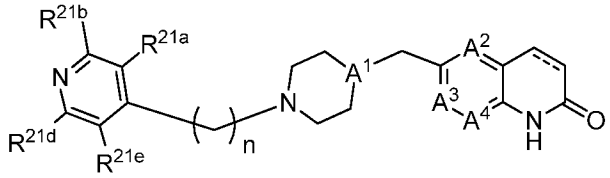
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

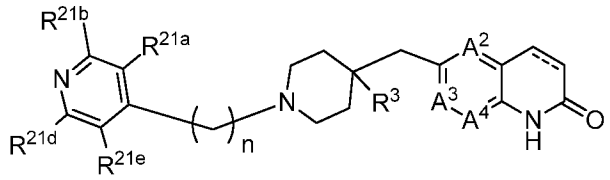
[00629] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00630] In a further aspect, the invention relates to a compound having a structure represented by a formula:

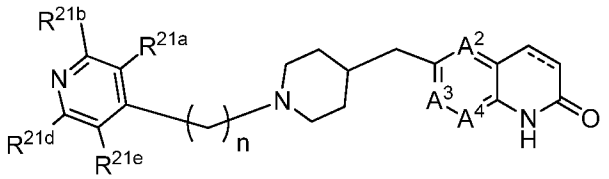


,

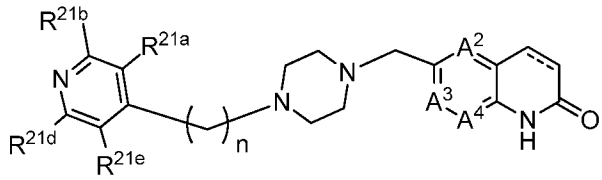
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein

all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00631] In a further aspect, the invention relates to a compound having a structure represented by a formula:



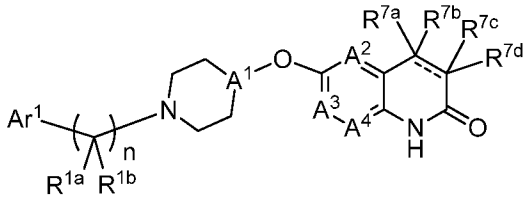
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

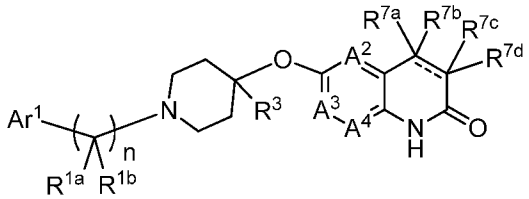
[00632] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00633] In a further aspect, the invention relates to a compound having a structure represented by a formula:

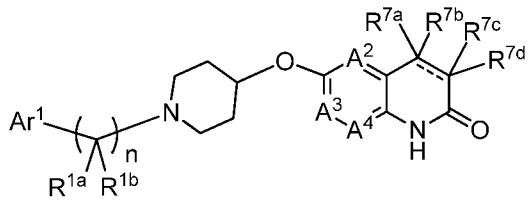


,

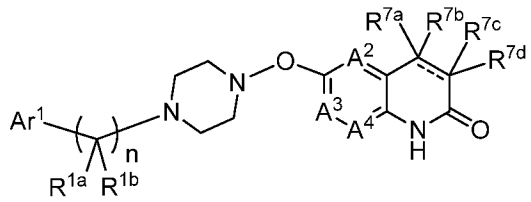
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00634] In a further aspect, the invention relates to a compound having a structure

represented by a formula:



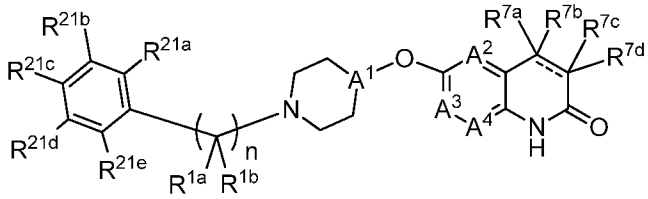
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

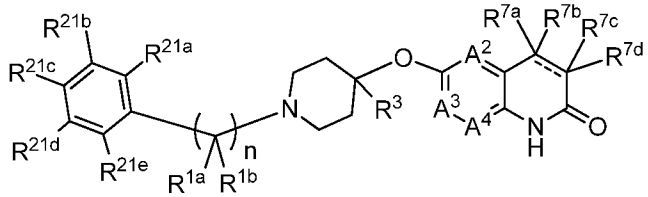
[00635] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

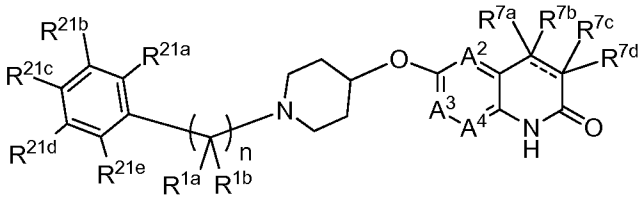
[00636] In a further aspect, the invention relates to a compound having a structure represented by a formula:



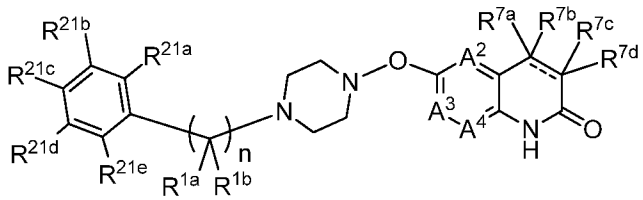
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00637] In a further aspect, the invention relates to a compound having a structure represented by a formula:



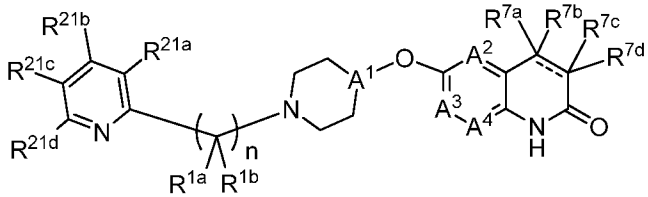
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

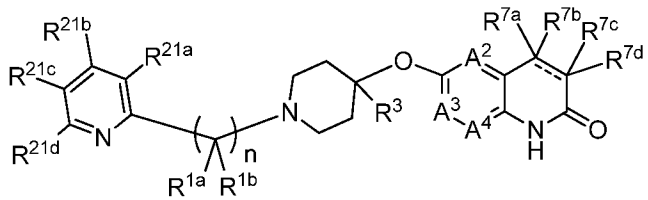
[00638] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00639] In a further aspect, the invention relates to a compound having a structure represented by a formula:

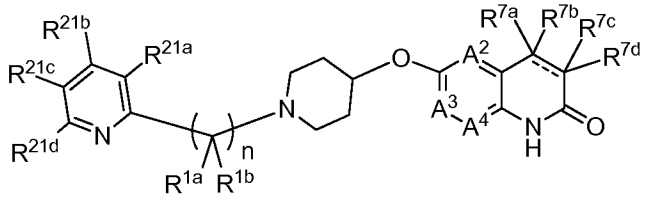


,

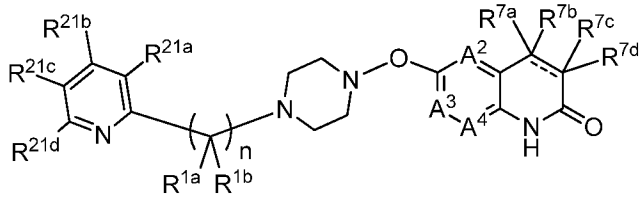
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00640] In a further aspect, the invention relates to a compound having a structure represented by a formula:



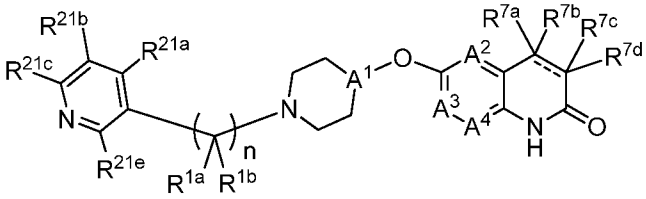
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

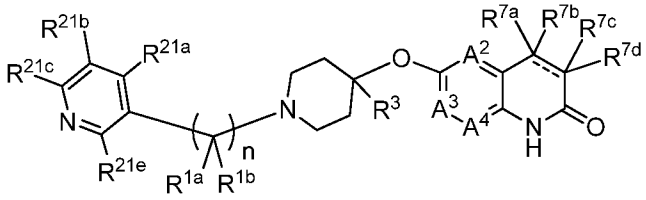
[00641] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

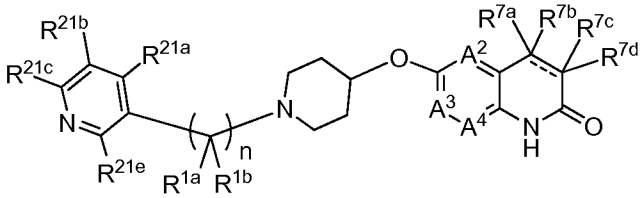
[00642] In a further aspect, the invention relates to a compound having a structure represented by a formula:



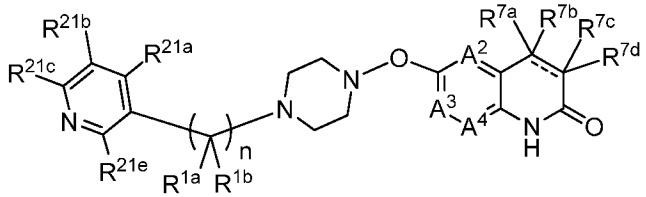
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00643] In a further aspect, the invention relates to a compound having a structure represented by a formula:



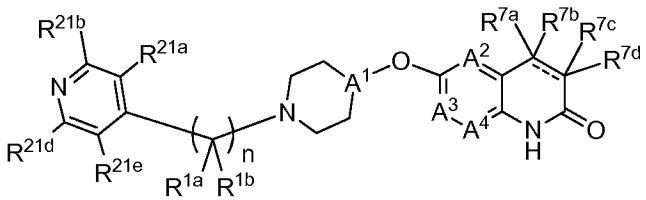
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00644] In a further aspect, the invention relates to a compound having a structure represented by a formula:

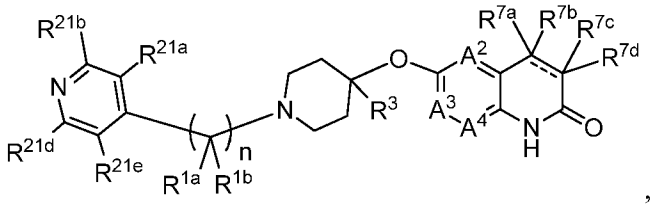


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

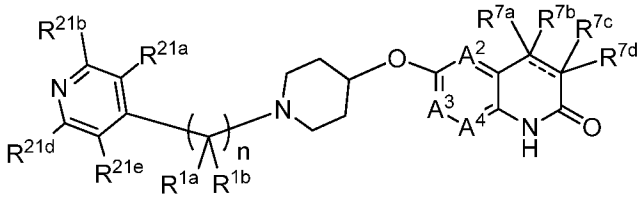
[00645] In a further aspect, the invention relates to a compound having a structure represented by a formula:



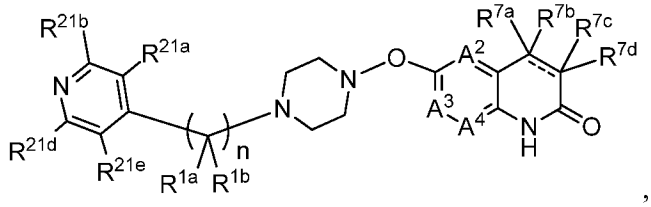
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00646] In a further aspect, the invention relates to a compound having a structure represented by a formula:



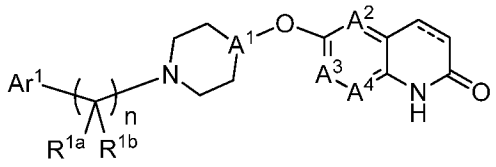
or



,

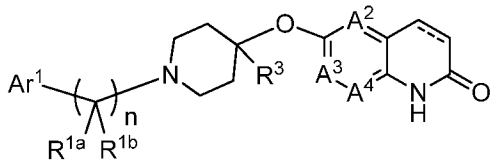
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00647] In a further aspect, the invention relates to a compound having a structure represented by a formula:



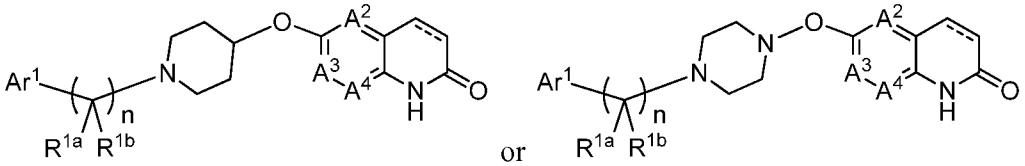
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00648] In a further aspect, the invention relates to a compound having a structure represented by a formula:



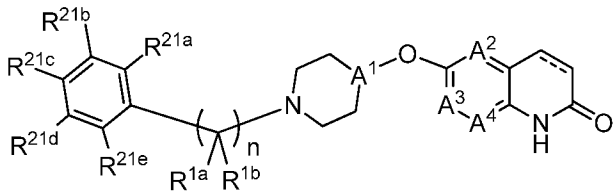
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00649] In a further aspect, the invention relates to a compound having a structure represented by a formula:



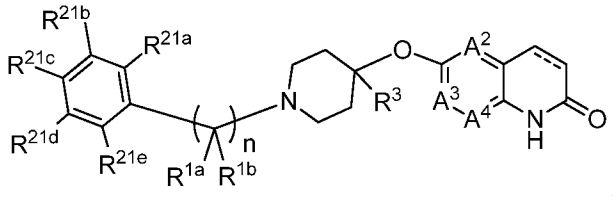
wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00650] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

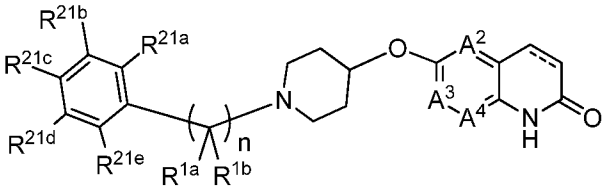
[00651] In a further aspect, the invention relates to a compound having a structure represented by a formula:



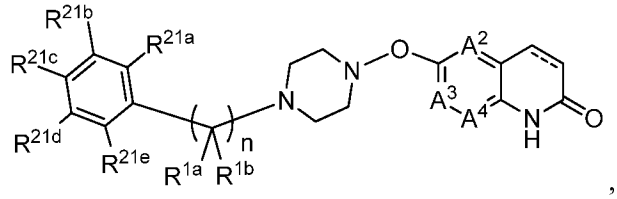
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00652] In a further aspect, the invention relates to a compound having a structure represented by a formula:



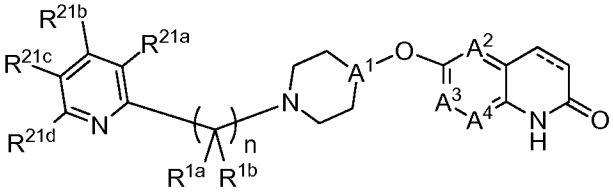
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00653] In a further aspect, the invention relates to a compound having a structure represented by a formula:

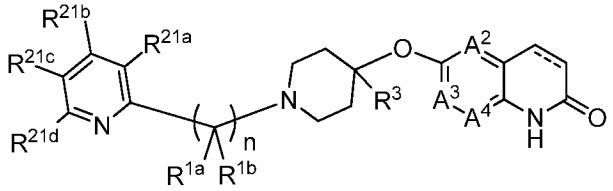


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

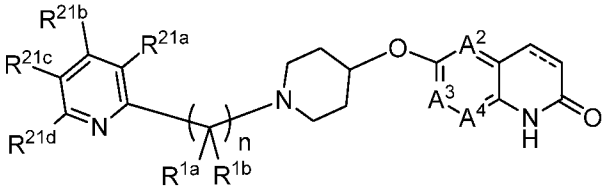
[00654] In a further aspect, the invention relates to a compound having a structure represented by a formula:



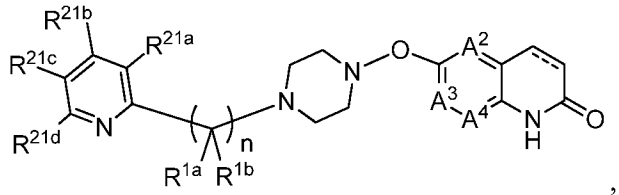
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00655] In a further aspect, the invention relates to a compound having a structure represented by a formula:



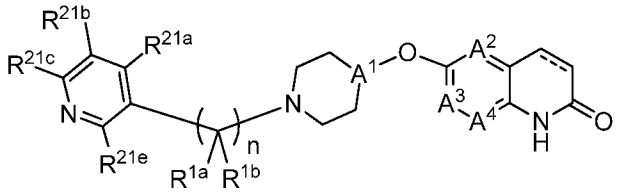
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

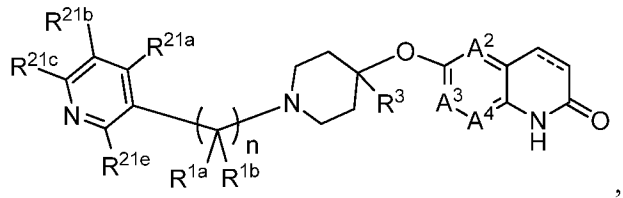
[00656] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

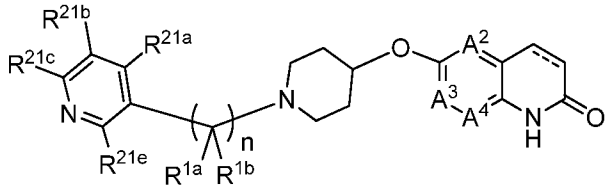
[00657] In a further aspect, the invention relates to a compound having a structure represented by a formula:



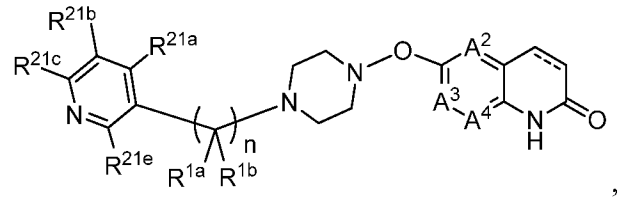
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00658] In a further aspect, the invention relates to a compound having a structure represented by a formula:



or

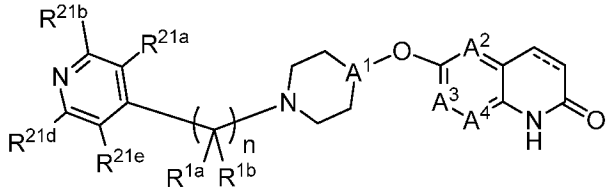


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

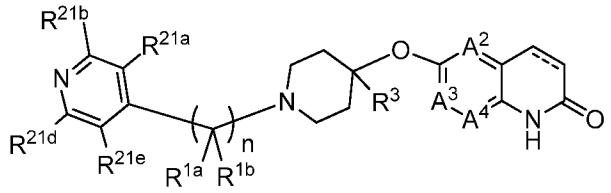
[00659] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

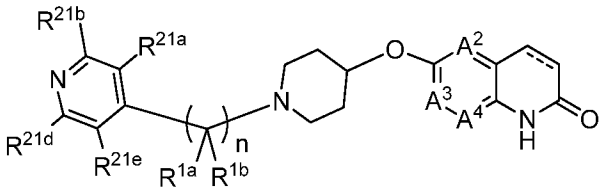
[00660] In a further aspect, the invention relates to a compound having a structure represented by a formula:



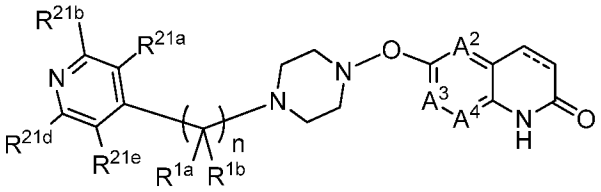
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00661] In a further aspect, the invention relates to a compound having a structure represented by a formula:



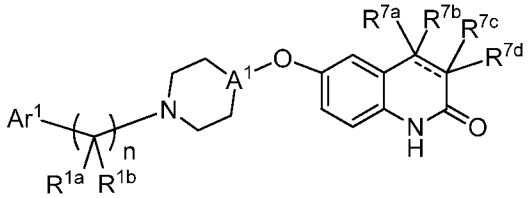
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

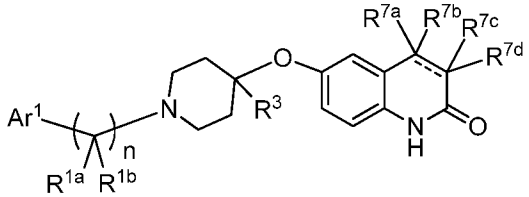
[00662] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

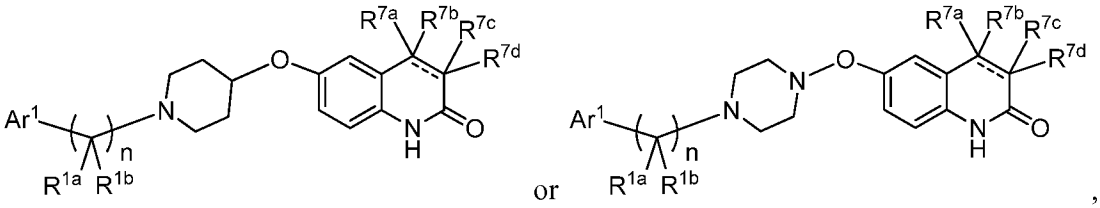
[00663] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

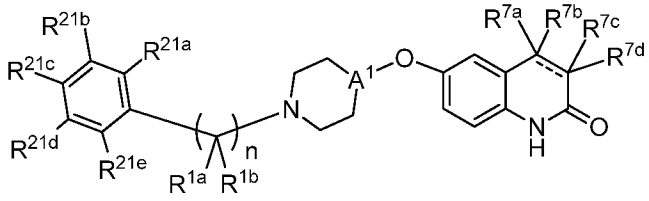
[00664] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

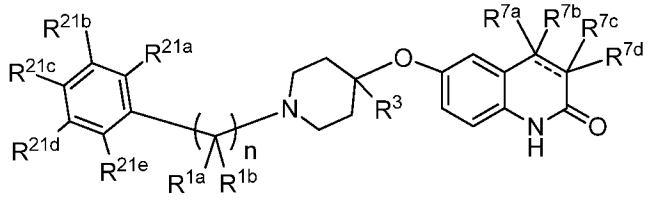
[00665] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

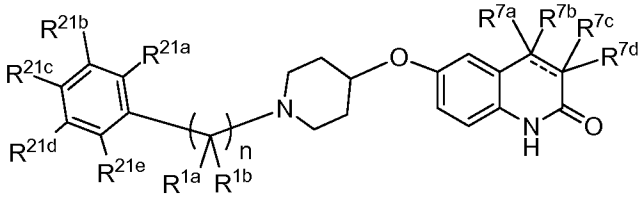
[00666] In a further aspect, the invention relates to a compound having a structure represented by a formula:



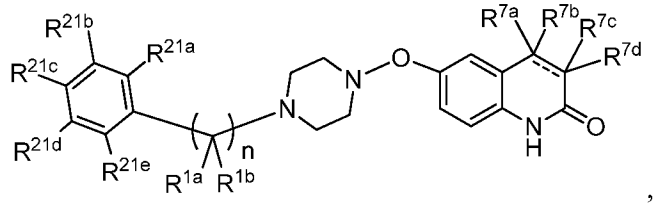
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00667] In a further aspect, the invention relates to a compound having a structure represented by a formula:



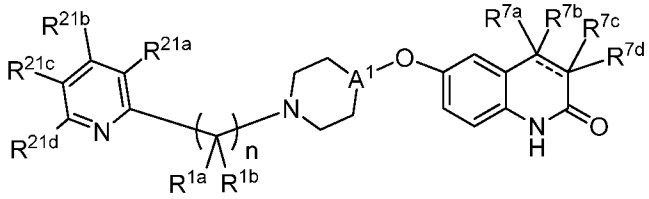
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

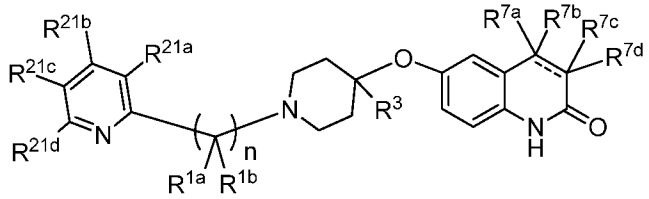
[00668] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

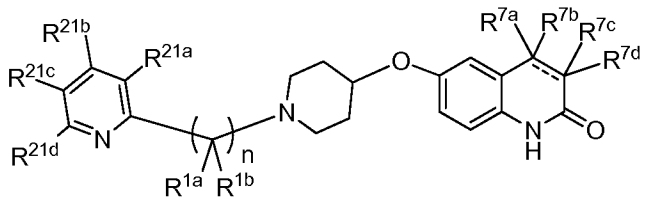
[00669] In a further aspect, the invention relates to a compound having a structure represented by a formula:



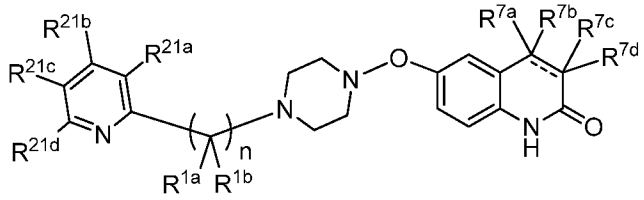
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00670] In a further aspect, the invention relates to a compound having a structure represented by a formula:



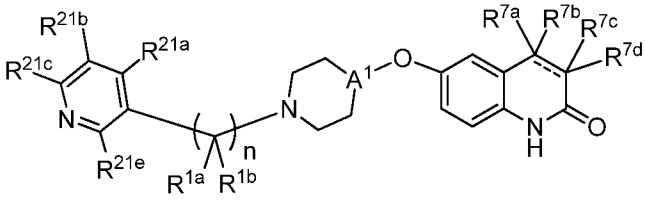
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

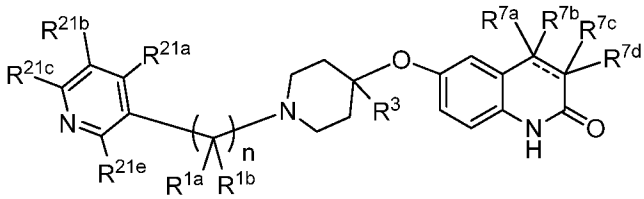
[00671] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

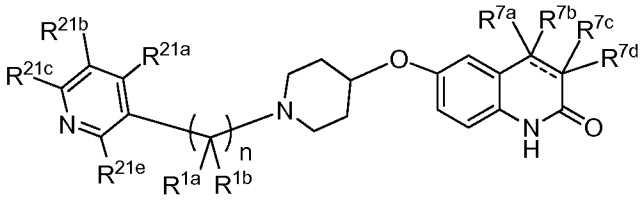
[00672] In a further aspect, the invention relates to a compound having a structure represented by a formula:



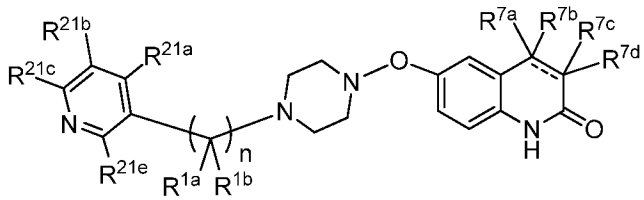
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00673] In a further aspect, the invention relates to a compound having a structure represented by a formula:



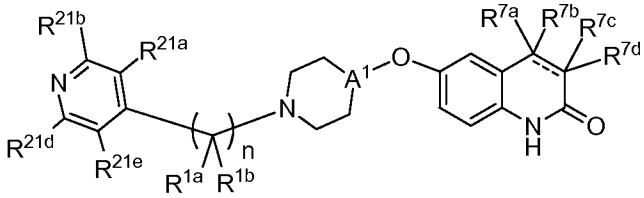
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

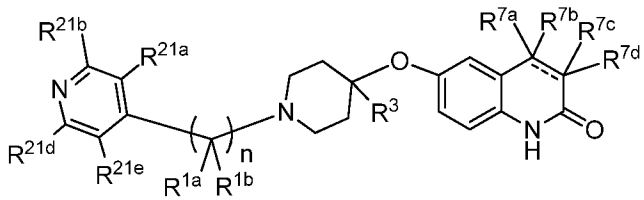
[00674] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00675] In a further aspect, the invention relates to a compound having a structure represented by a formula:

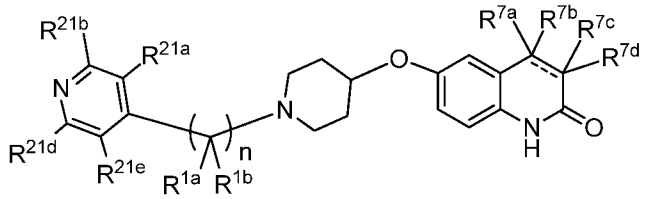


,

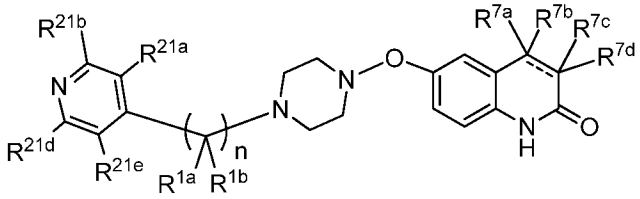
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00676] In a further aspect, the invention relates to a compound having a structure represented by a formula:



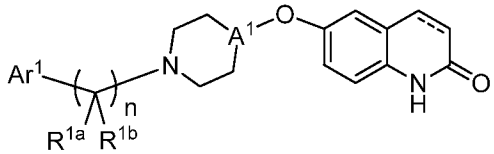
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

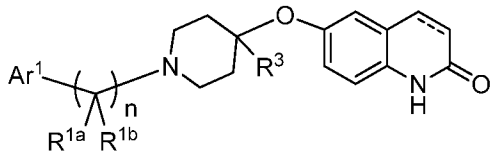
[00677] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

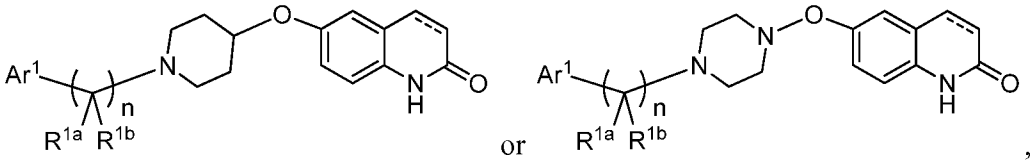
[00678] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00679] In a further aspect, the invention relates to a compound having a structure represented by a formula:

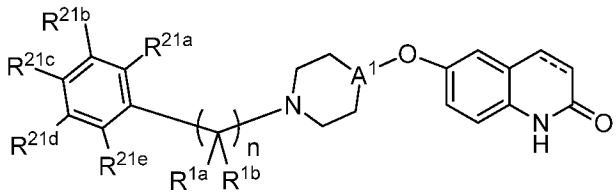


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

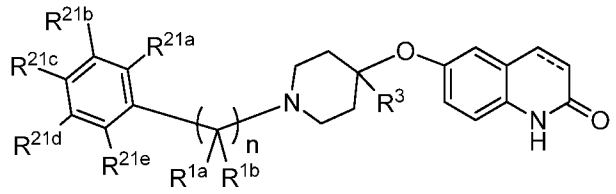
[00680] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

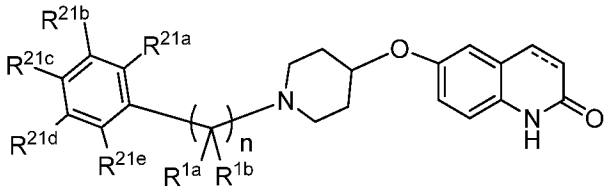
[00681] In a further aspect, the invention relates to a compound having a structure represented by a formula:



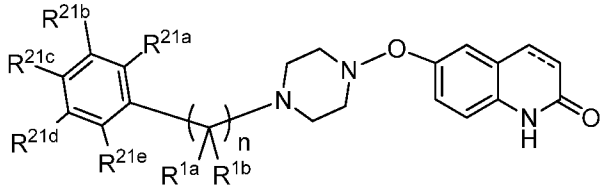
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00682] In a further aspect, the invention relates to a compound having a structure represented by a formula:



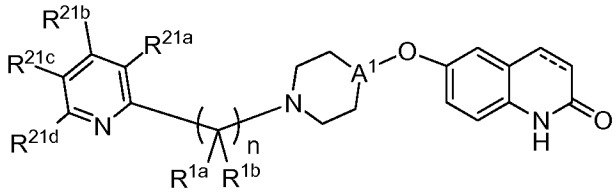
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

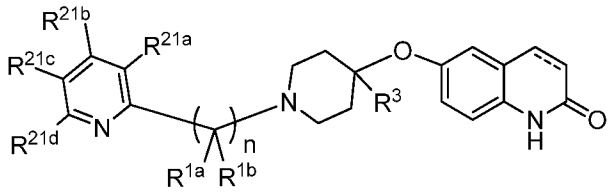
[00683] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00684] In a further aspect, the invention relates to a compound having a structure represented by a formula:

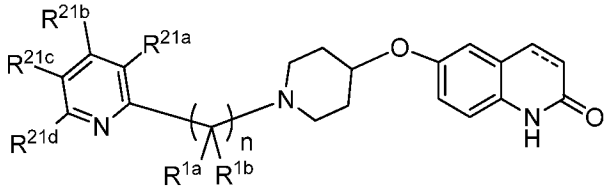


,

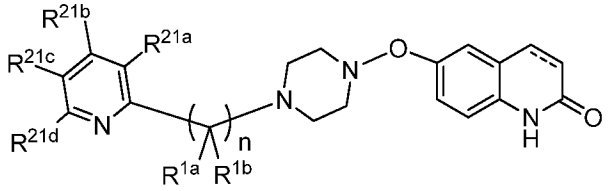
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00685] In a further aspect, the invention relates to a compound having a structure represented by a formula:



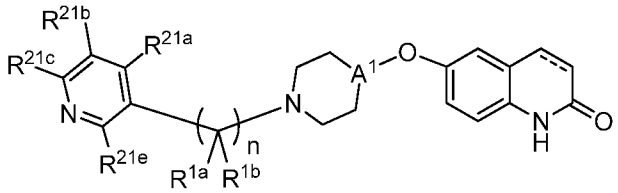
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

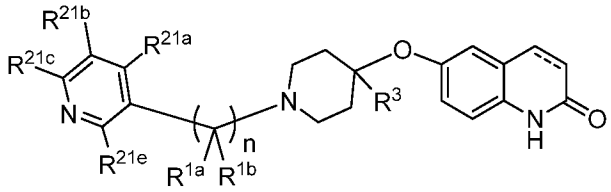
[00686] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

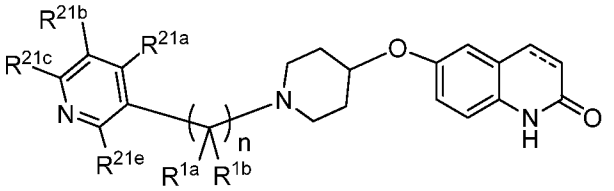
[00687] In a further aspect, the invention relates to a compound having a structure represented by a formula:



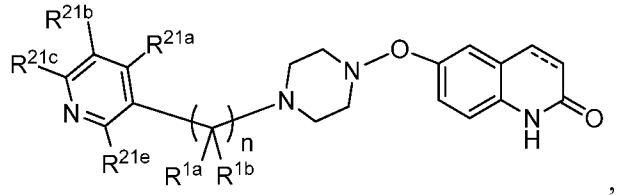
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00688] In a further aspect, the invention relates to a compound having a structure represented by a formula:



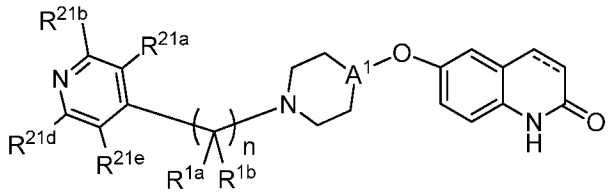
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00689] In a further aspect, the invention relates to a compound having a structure represented by a formula:

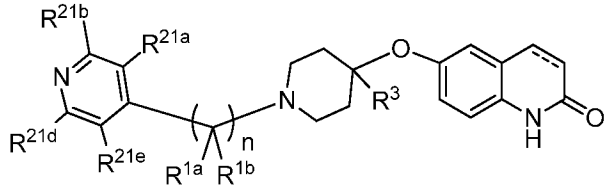


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4

dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

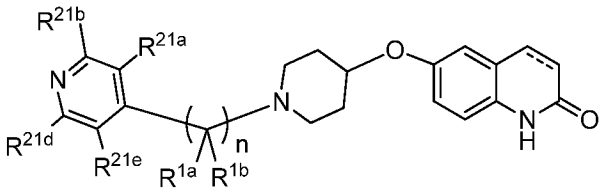
[00690] In a further aspect, the invention relates to a compound having a structure represented by a formula:



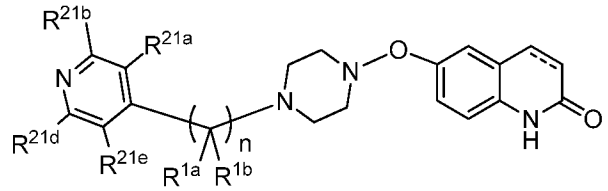
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00691] In a further aspect, the invention relates to a compound having a structure represented by a formula:



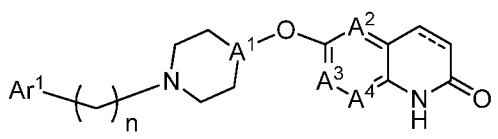
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

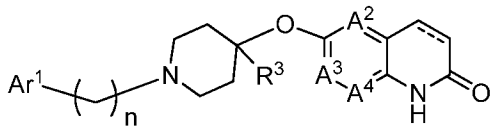
[00692] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

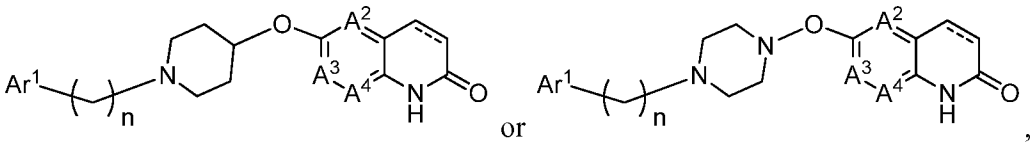
[00693] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00694] In a further aspect, the invention relates to a compound having a structure represented by a formula:

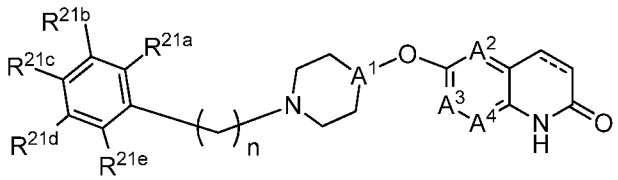


or

,

wherein ----- is an optional covalent bond, wherein valence is satisfied; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

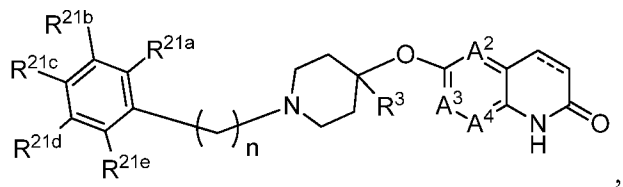
[00695] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00696] In a further aspect, the invention relates to a compound having a structure represented by a formula:

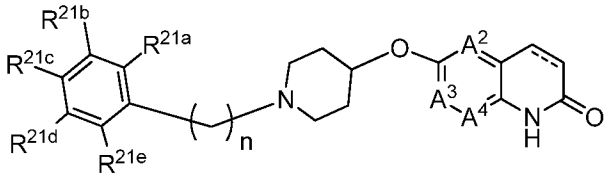


,

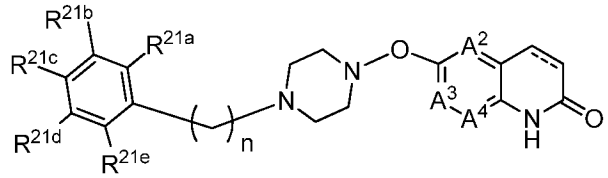
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a},

R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00697] In a further aspect, the invention relates to a compound having a structure represented by a formula:



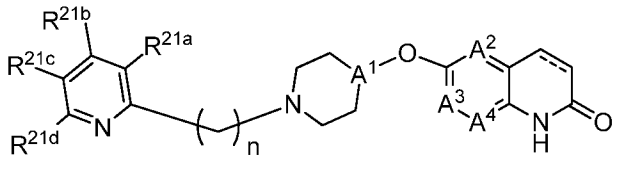
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least three of R^{21a}-R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

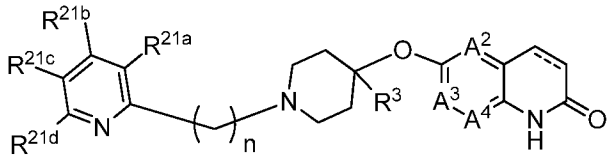
[00698] In a further aspect, the invention relates to a compound having a structure represented by a formula:



,

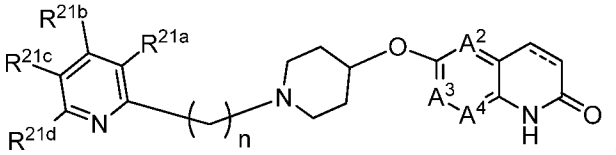
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00699] In a further aspect, the invention relates to a compound having a structure represented by a formula:

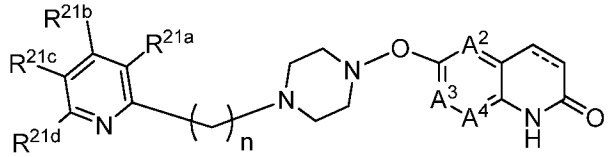


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00700] In a further aspect, the invention relates to a compound having a structure represented by a formula:

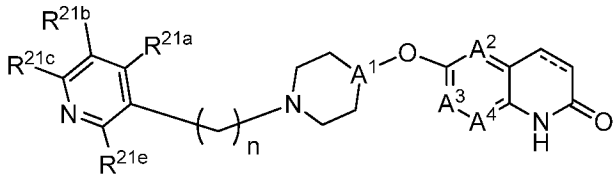


or



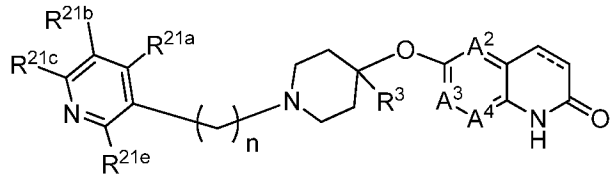
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21d} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}-R^{21d} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00701] In a further aspect, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

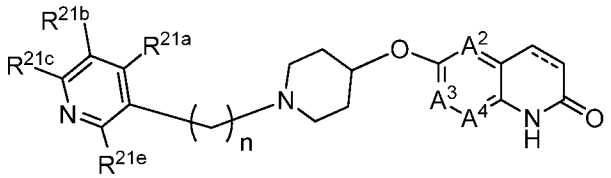
[00702] In a further aspect, the invention relates to a compound having a structure represented by a formula:



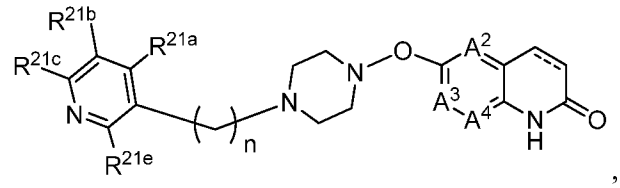
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00703] In a further aspect, the invention relates to a compound having a structure represented by a formula:



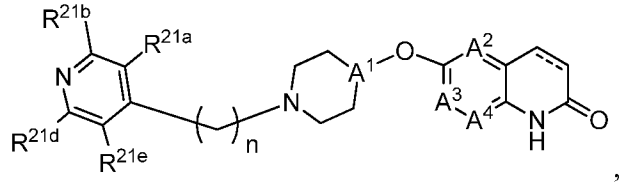
or



,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21c}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00704] In a further aspect, the invention relates to a compound having a structure represented by a formula:

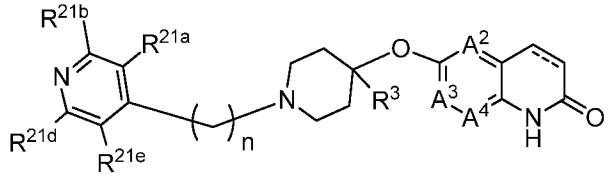


,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl,

C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

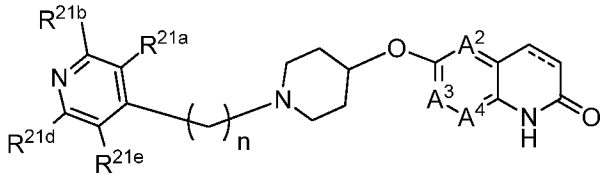
[00705] In a further aspect, the invention relates to a compound having a structure represented by a formula:



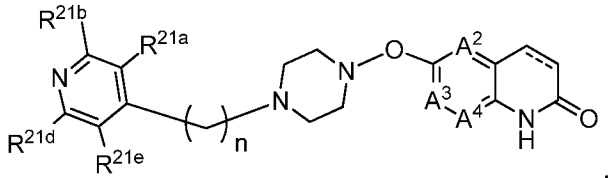
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00706] In a further aspect, the invention relates to a compound having a structure represented by a formula:



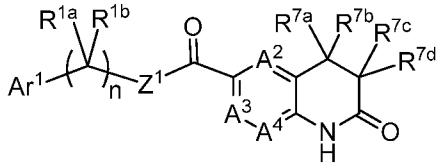
or



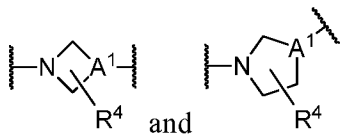
,

wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein each of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that at least two of R^{21a}, R^{21b}, R^{21d}, and R^{21e} is hydrogen; and wherein all other variables are as defined herein; or a pharmaceutically acceptable salt thereof.

[00707] In various aspects, the invention relates to a compound having a structure represented by a formula:

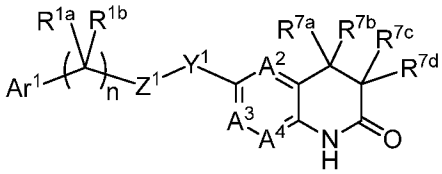


wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Z^1 is a 4- or 5-membered hetercycloalkyl selected from:



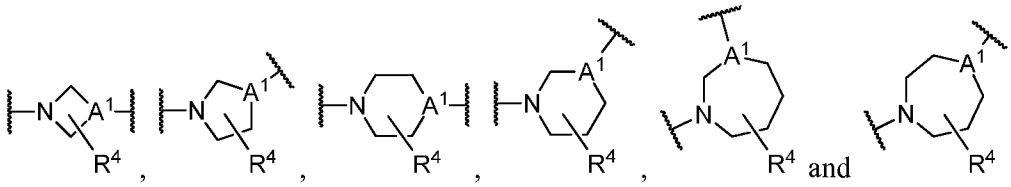
wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00708] In various aspects, the invention relates to a compound having a structure represented by a formula:



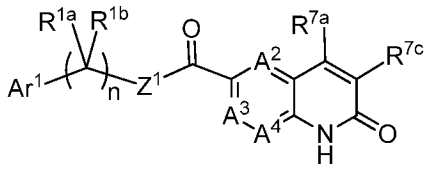
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups

independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Y^1 is selected from —O— and —CR^2R^{2b}—; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is a 4- to 7-membered hetercycloalkyl selected from:



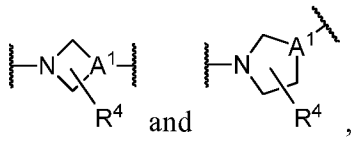
wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00709] In various aspects, the invention relates to a compound having a structure represented by a formula:



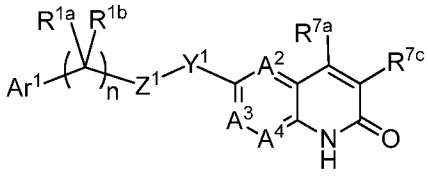
wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, —NH_2, —OH,

—CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Z^1 is a 4- or 5-membered hetercycloalkyl selected from:

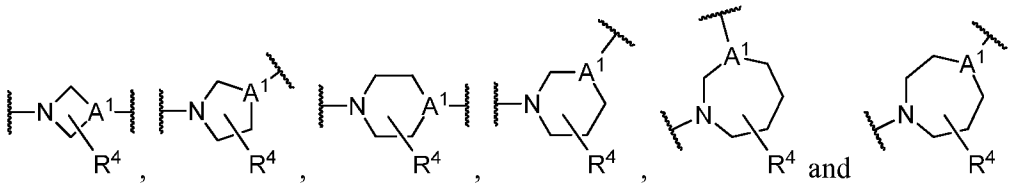


wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

[00710] In various aspects, the invention relates to a compound having a structure represented by a formula:



wherein ----- is an optional covalent bond, wherein valence is satisfied; wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, $—NH_2$, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each occurrence of R^{1a} and R^{1b} is independently selected from hydrogen, halogen, $—NH_2$, —OH, —CN, and C1-C3 alkyl; wherein n is an integer from 1-4; wherein Y^1 is selected from —O— and $—CR^2R^{2b}—$; wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, $—NH_2$, —OH, —CN, and C1-C3 alkyl; wherein Z^1 is a 4- to 7-membered hetercycloalkyl selected from:



wherein A^1 is selected from N and CR^3; wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl; wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino; wherein A^2 is selected from N and CR^{6a}; wherein A^3 is selected from N and CR^{6b}; and wherein A^4 is selected from N and CR^{6c}; wherein each of R^{6a}, R^{6b}, and R^{6c}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof.

a. AR^1 GROUPS

[00711] In one aspect, Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a further aspect, Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is unsubstituted.

[00712] In a further aspect, Ar^1 is phenyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is

phenyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is phenyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is phenyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is phenyl and is unsubstituted.

[00713] In a further aspect, Ar^1 is heterocyclyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is heterocyclyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is heterocyclyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is heterocyclyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is heterocyclyl and is unsubstituted.

[00714] In a further aspect, Ar^1 is pyridinyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is pyridinyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is pyridinyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyridinyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyridinyl and is unsubstituted.

[00715] In a further aspect, Ar^1 is pyrimidinyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is pyrimidinyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4

alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is pyrimidinyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyrimidinyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyrimidinyl and is unsubstituted.

[00716] In a further aspect, Ar^1 is pyridazinyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is pyridazinyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is pyridazinyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyridazinyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyridazinyl and is unsubstituted.

[00717] In a further aspect, Ar^1 is imidazolyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is imidazolyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a yet further aspect, Ar^1 is imidazolyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is imidazolyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is imidazolyl and is unsubstituted.

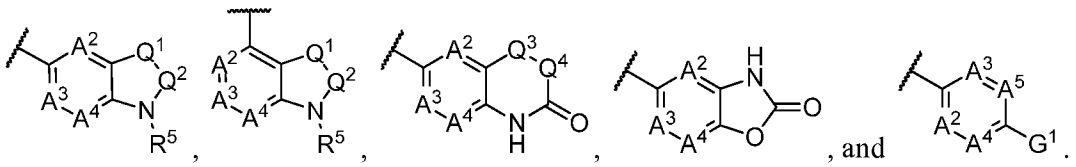
[00718] In a further aspect, Ar^1 is pyrazolyl substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Ar^1 is pyrazolyl substituted with 1-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and

C1-C4 dialkylamino. In a yet further aspect, Ar^1 is pyrazolyl substituted with two groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyrazolyl monosubstituted with a group selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Ar^1 is pyrazolyl and is unsubstituted.

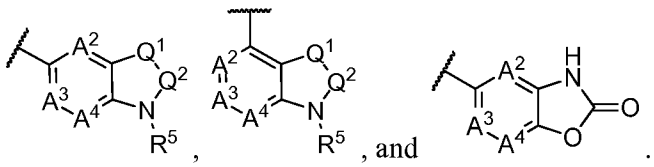
[00719] In a further aspect, Ar^1 is substituted with 0-2 groups independently selected from —F, —Cl, —CN, methyl, ethyl, propyl, $—CH_2F$, $—CH_2Cl$, $—CH_2CH_2F$, $—CH_2CH_2Cl$, $—CHF_2$, $—CF_3$, $—CHCl_2$, $—CCl_3$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—N(CH_3)_2$, and $—N(CH_3)CH_2CH_3$. In a further aspect, Ar^1 is substituted with 0-2 groups independently selected from —F, —Cl, —CN, methyl, ethyl, propyl, $—CH_2F$, $—CH_2Cl$, $—CH_2CH_2F$, $—CH_2CH_2Cl$, $—CHF_2$, $—CF_3$, $—CHCl_2$, $—CCl_3$, $—CH_2CHF_2$, $—CH_2CF_3$, $—CH_2CHCl_2$, $—CH_2CCl_3$, $—OCH_3$, $—OCH_2CH_3$, $—NHCH_3$, $—NHCH_2CH_3$, $—N(CH_3)_2$, and $—N(CH_3)CH_2CH_3$.

b. AR^2 GROUPS

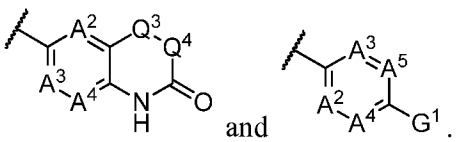
[00720] In one aspect, Ar^2 is selected from:



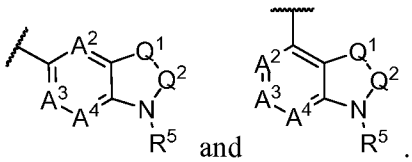
[00721] In a further aspect, Ar^2 is selected from:



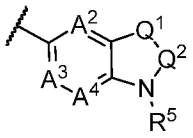
[00722] In a further aspect, Ar^2 is selected from:



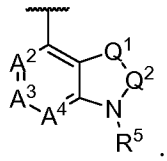
[00723] In a further aspect, Ar^2 is selected from:



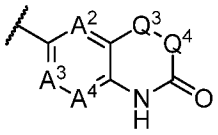
[00724] In a further aspect, Ar^2 is:



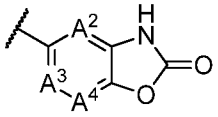
[00725] In a further aspect, Ar^2 is:



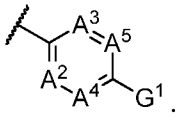
[00726] In a further aspect, Ar^2 is:



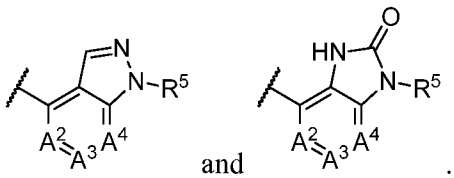
[00727] In a further aspect, Ar^2 is:



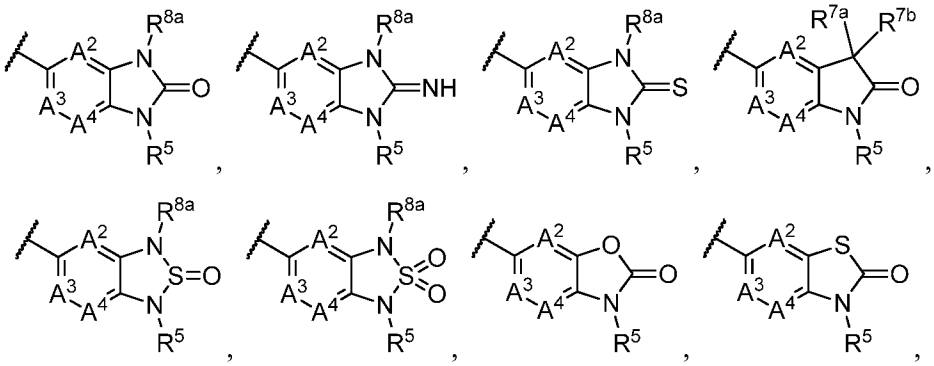
[00728] In a further aspect, Ar^2 is:

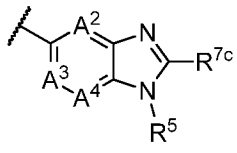
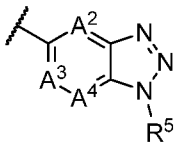


[00729] In a further aspect, Ar^2 is selected from:

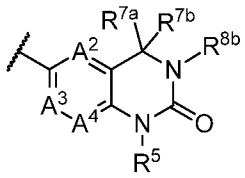
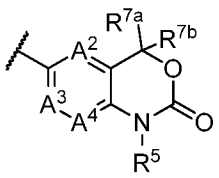
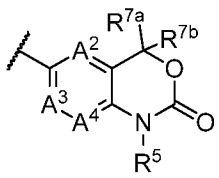
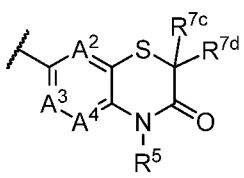
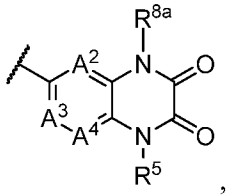
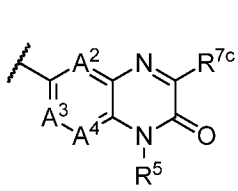
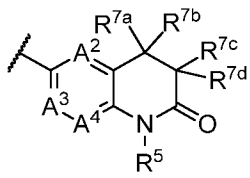
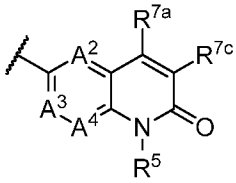


[00730] In a further aspect, Ar^2 is selected from:

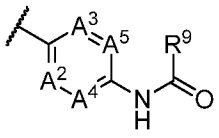
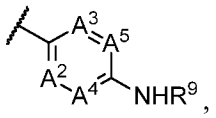
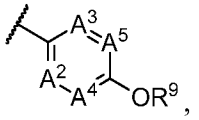
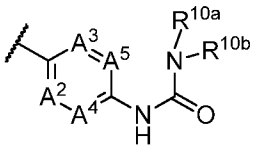
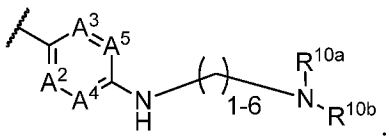



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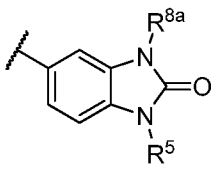
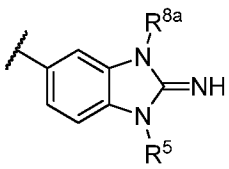
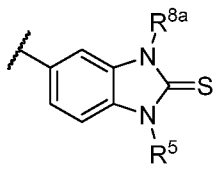
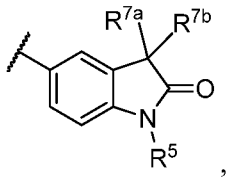
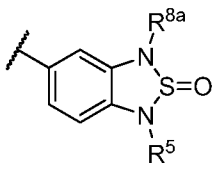
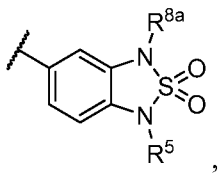
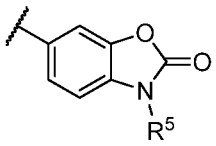
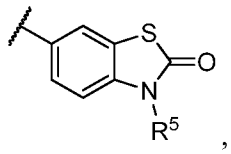
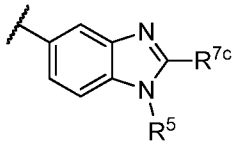
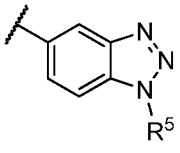
[00731] In a further aspect, Ar^2 is selected from:


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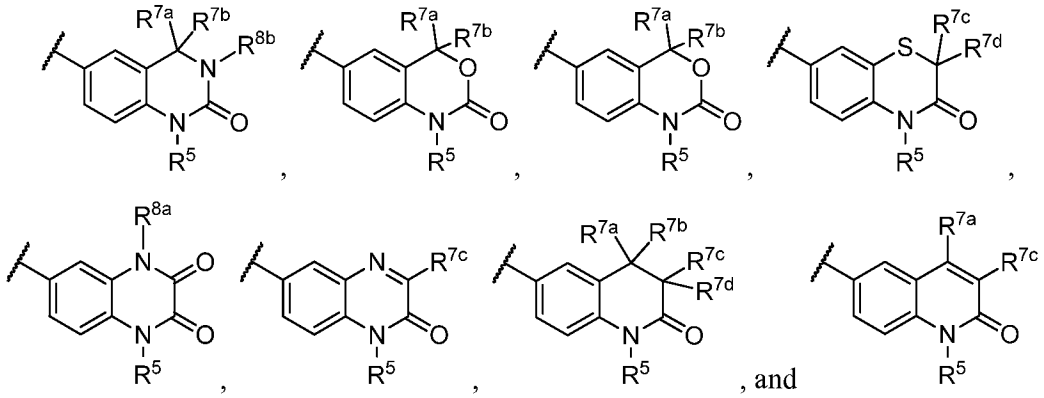
[00732] In a further aspect, Ar^2 is selected from:


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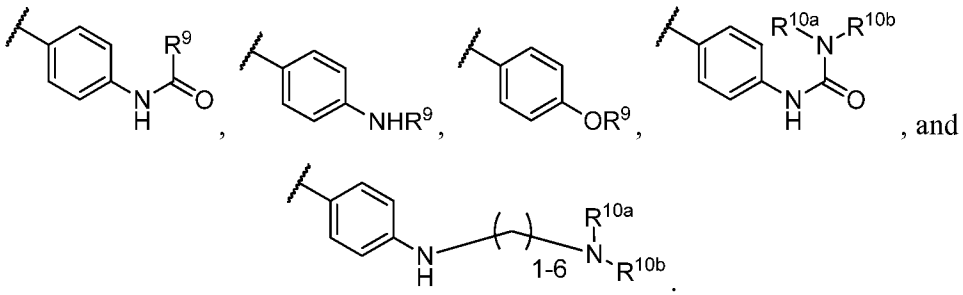
[00733] In a further aspect, Ar^2 is selected from:


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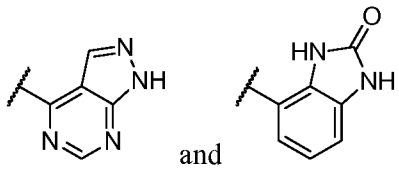
[00734] In a further aspect, Ar^2 is selected from:



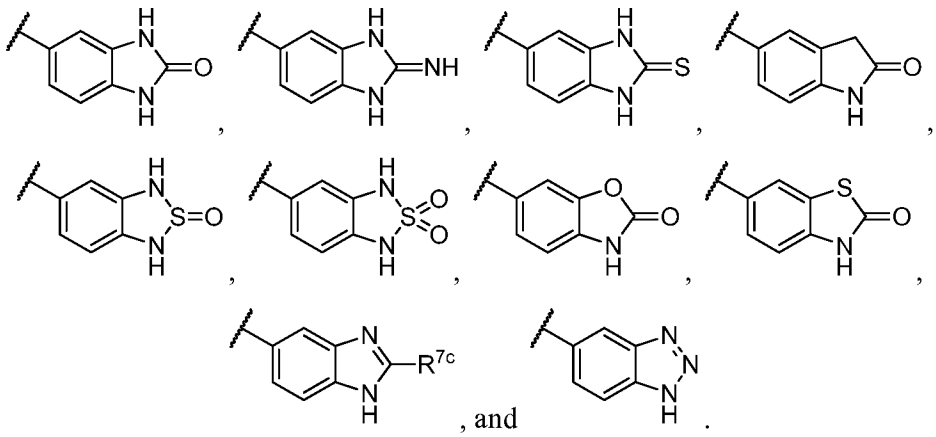
[00735] In a further aspect, Ar^2 is selected from:



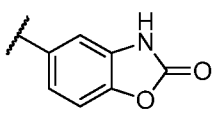
[00736] In a further aspect, Ar^2 is selected from:



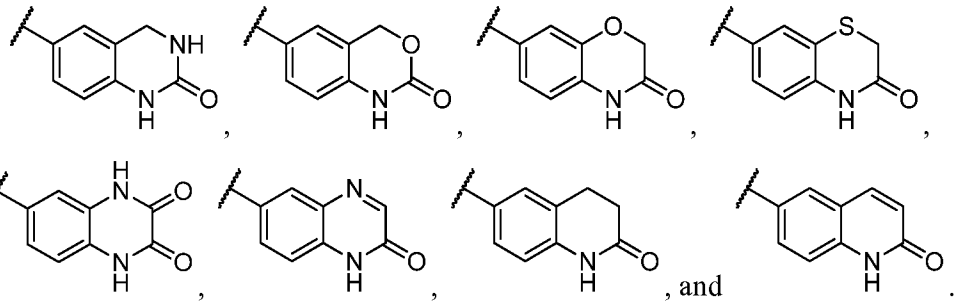
[00737] In a further aspect, Ar^2 is selected from:



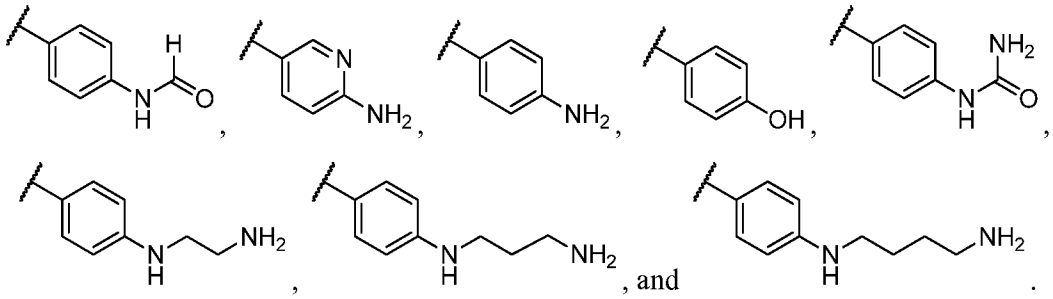
[00738] In a further aspect, Ar^2 is:



[00739] In a further aspect, Ar^2 is selected from:

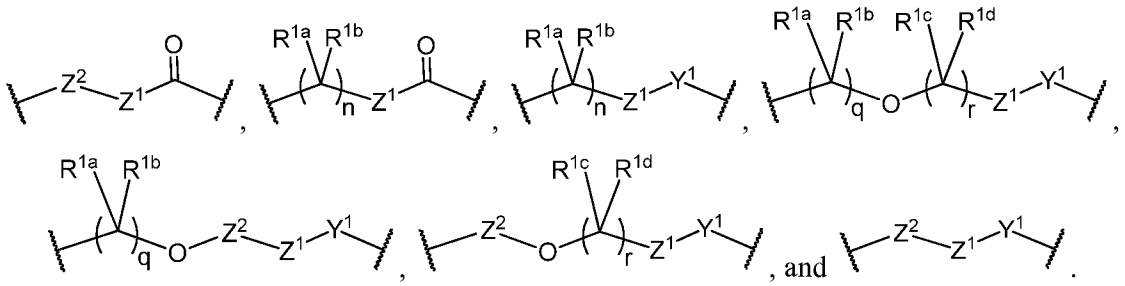


[00740] In a further aspect, Ar^2 is selected from:

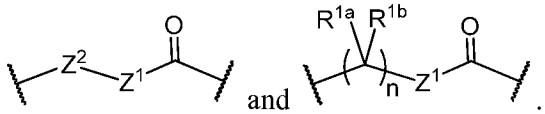


c. L GROUPS

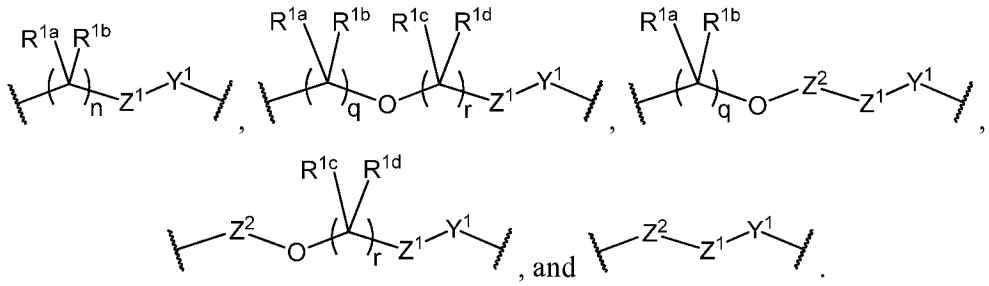
[00741] In one aspect, L is selected from:



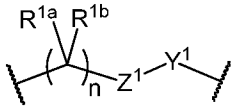
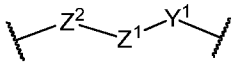
[00742] In one aspect, L is selected from:



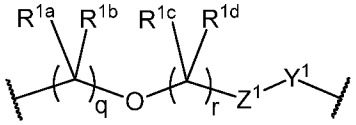
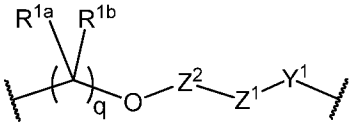
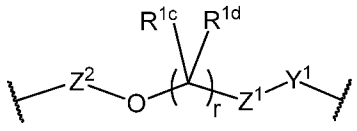
[00743] In one aspect, L is selected from:



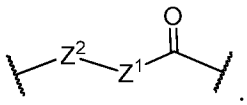
[00744] In one aspect, L is selected from:


and

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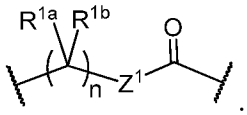
[00745] In one aspect, L is selected from:


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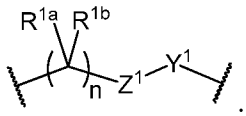
[00746] In one aspect, L is:


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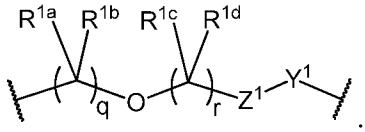
[00747] In one aspect, L is:


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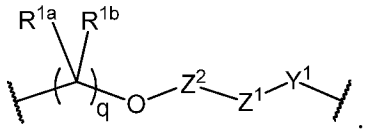
[00748] In one aspect, L is:


.

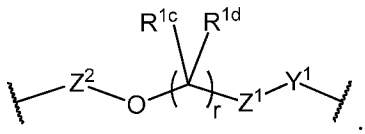
[00749] In one aspect, L is:


.

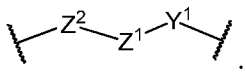
[00750] In one aspect, L is:


.

[00751] In one aspect, L is:


.

[00752] In one aspect, L is:

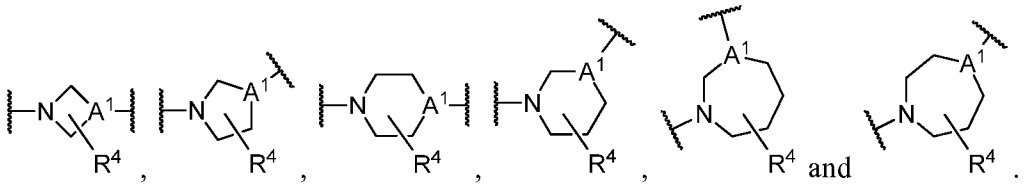

.

d. Y^1 GROUPS

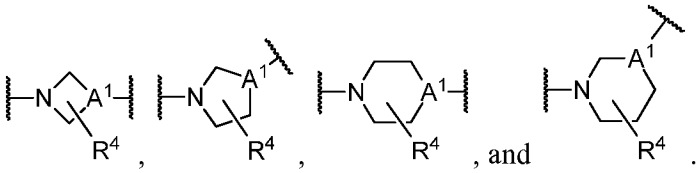
[00753] In one aspect, Y^1, when present, is selected from —O— and —$CR^{2a}R^{2b}$—. In a further aspect, Y^1, when present, is —O—. In a still further aspect, Y^1, when present, is —$CR^{2a}R^{2b}$—.

e. Z^1 GROUPS

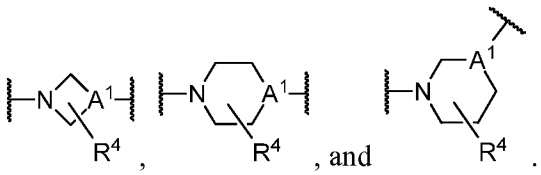
[00754] In one aspect, Z^1, when present, is a 4- to 7-membered hetercycloalkyl selected from:



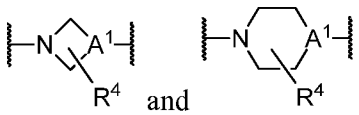
[00755] In one aspect, Z^1, when present, is selected from:



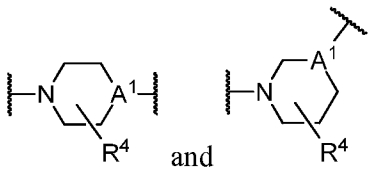
[00756] In one aspect, Z^1, when present, is selected from:



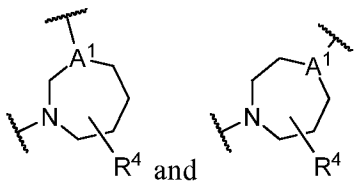
[00757] In one aspect, Z^1, when present, is selected from:



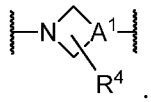
[00758] In one aspect, Z^1, when present, is selected from:



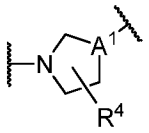
[00759] In one aspect, Z^1, when present, is selected from:



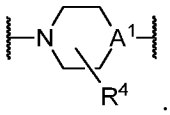
[00760] In one aspect, Z^1, when present, is:



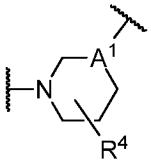
[00761] In one aspect, Z^1, when present, is:



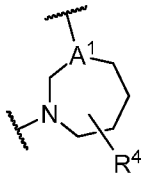
[00762] In one aspect, Z^1, when present, is:



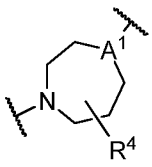
[00763] In one aspect, Z^1, when present, is:



[00764] In one aspect, Z^1, when present, is:



[00765] In one aspect, Z^1, when present, is:



f. Z^2 GROUPS

[00766] In one aspect, Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a further aspect, Z^2, when present, is a 3- to 6-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In a still further aspect, Z^2, when present, is a 4- or 6-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH,

—CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In an even further aspect, Z^2, when present, is an unsubstituted 3- to 7-membered cycloalkyl.

[00767] In a further aspect, Z^2, when present, is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In one aspect, Z^2, when present, is selected from cyclobutyl, and cyclohexyl.

[00768] In a further aspect, Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from —F, —Cl, —NH_2, —OH, —CN, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, methoxy, —$NHCH_3$, and —$N(CH_3)_2$. In a still further aspect, Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 1-2 groups independently selected from —F, —Cl, —NH_2, —OH, —CN, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, methoxy, —$NHCH_3$, and —$N(CH_3)_2$. In a yet further aspect, Z^2, when present, is a 3- to 7-membered cycloalkyl monosubstituted with a group selected from —F, —Cl, —NH_2, —OH, —CN, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, methoxy, —$NHCH_3$, and —$N(CH_3)_2$.

g. A^1 GROUPS

[00769] In one aspect, A^1 is N or CR^3. In a further aspect, A^1 is N. In a still further aspect, A^1 is CR^3.

h. A^2, A^3, A^4, AND A^5 GROUPS

[00770] In one aspect, A^2 is selected from N and CR^{6a}; A^3, when present, is selected from N and CR^{6b}; A^4, when present, is selected from N and CR^{6c}; and A^5, when present, is selected from N and CR^{6d}.

[00771] In a further aspect, A^2 is CR^{6a}; A^3, when present, is CR^{6b}; A^4, when present, is CR^{6c}; and A^5, when present, is CR^{6d}.

[00772] In a further aspect, A^2 is selected from N and CR^{6a}; A^3, when present, is CR^{6b}; A^4, when present, is CR^{6c}; and A^5, when present, is CR^{6d}. In a still further aspect, A^2 is CR^{6a}; A^3, when present, is selected from N and CR^{6b}; A^4, when present, is CR^{6c}; and A^5, when present, is CR^{6d}. In a yet further aspect, A^2 is CR^{6a}; A^3, when present, is CR^{6b}; A^4, when present, is selected from N and CR^{6c}; and A^5, when present, is CR^{6d}. In an even further aspect, A^2 is CR^{6a}; A^3, when present, is CR^{6b}; A^4, when present, is CR^{6c}; and A^5, when present, is selected from N and CR^{6d}.

[00773] In a further aspect, A^2 is N; A^3, when present, is CR^{6b}; A^4, when present, is CR^{6c}; and A^5, when present, is CR^{6d}. In a still further aspect, A^2 is CR^{6a}; A^3, when present, is N; A^4, when present, is CR^{6c}; and A^5, when present, is CR^{6d}. In a yet further aspect, A^2 is CR^{6a};

A^3, when present, is CR^{6b}; A^4, when present, is N; and A^5, when present, is CR^{6d}. In an even further aspect, A^2 is CR^{6a}; A^3, when present, is CR^{6b}; A^4, when present, is CR^{6c}; and A^5, when present, is N.

[00774] In a further aspect, A^2 is N; A^3, when present, is N; and A^4, when present, is CR^{6c}. In a still further aspect, A^2 is N; A^3, when present, is CR^{6b}; and A^4, when present, is N. In a yet further aspect, A^2 is CR^{6a}; A^3, when present, is N; and A^4, when present, is N.

[00775] In a further aspect, A^2 is N; A^3, when present, is N; and A^4, when present, is CR^{6c}; and A^5, when present, is CR^{6d}. In a still further aspect, A^2 is N; A^3, when present, is CR^{6b}; and A^4, when present, is N; and A^5, when present, is CR^{6d}. In a yet further aspect, A^2 is N; A^3, when present, is CR^{6b}; and A^4, when present, is CR^{6c}; and A^5, when present, is N.

[00776] In a yet further aspect, A^2 is CR^{6a}; A^3, when present, is N; and A^4, when present, is N; and A^5, when present, is CR^{6d}. In a still further aspect, A^2 is CR^{6a}; A^3, when present, is N; and A^4, when present, is CR^{6c}; and A^5, when present, is N. In a yet further aspect, A^2 is CR^{6a}; A^3, when present, is CR^{6b}; and A^4, when present, is N; and A^5, when present, is N.

i. G^1 GROUPS

[00777] In one aspect, G^1, when present, is selected from —OH, —NHR^9, —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$, —OR^9, —NH(C=O)R^9; —NH(C=O)OR^9; and —NH(C=O)$NR^{10a}R^{10b}$.

[00778] In a further aspect, G^1, when present, is selected from —OH and —OR^9. In a still further aspect, G^1, when present, is selected from —OH, —OR^9, and —NHR^9. In a yet further aspect, G^1, when present, is selected from —OR^9 and —NHR^9.

[00779] In a further aspect, G^1, when present, is selected from —NHR^9 and —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$.

[00780] In a further aspect, G^1, when present, is selected from —NH(C=O)R^9; —NH(C=O)OR^9; and —NH(C=O)$NR^{10a}R^{10b}$.

[00781] In a further aspect, G^1, when present, is —OH. In a still further aspect, G^1, when present, is —NHR^9. In a yet further aspect, G^1, when present, is —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$. In an even further aspect, G^1, when present, is —OR^9. In a still further aspect, G^1, when present, is —NH(C=O)R^9. In a yet further aspect, G^1, when present, is —NH(C=O)OR^9. In an even further aspect, G^1, when present, is and —NH(C=O)$NR^{10a}R^{10b}$. In a still further aspect, G^1, when present, is —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$.

[00782] In a further aspect, G^1, when present, is selected from —$NH(CH_2)NR^{10a}R^{10b}$, —$NH(CH_2)_2NR^{10a}R^{10b}$, —$NH(CH_2)_3NR^{10a}R^{10b}$, —$NH(CH_2)_4NR^{10a}R^{10b}$, —$NH(CH_2)_5NR^{10a}R^{10b}$, and —$NH(CH_2)_6NR^{10a}R^{10b}$. In a still further aspect, G^1, when present, is selected from —$NH(CH_2)NR^{10a}R^{10b}$, —$NH(CH_2)_2NR^{10a}R^{10b}$, and —$NH(CH_2)_3NR^{10a}R^{10b}$. In a yet further

aspect, G^1, when present, is selected from —$NH(CH_2)NR^{10a}R^{10b}$, —$NH(CH_2)_2NR^{10a}R^{10b}$, —$NH(CH_2)_3NR^{10a}R^{10b}$, and —$NH(CH_2)_4NR^{10a}R^{10b}$. In an even further aspect, G^1, when present, is selected from —$NH(CH_2)NR^{10a}R^{10b}$, —$NH(CH_2)_2NR^{10a}R^{10b}$, —$NH(CH_2)_3NR^{10a}R^{10b}$, —$NH(CH_2)_4NR^{10a}R^{10b}$, and —$NH(CH_2)_5NR^{10a}R^{10b}$. In a still further aspect, G^1, when present, is selected from —$NH(CH_2)_2NR^{10a}R^{10b}$ and —$NH(CH_2)_3NR^{10a}R^{10b}$. In a yet further aspect, G^1, when present, is selected from —$NH(CH_2)NR^{10a}R^{10b}$ and —$NH(CH_2)_2NR^{10a}R^{10b}$. In an even further aspect, G^1, when present, is —$NH(CH_2)NR^{10a}R^{10b}$. In a still further aspect, G^1, when present, is —$NH(CH_2)_2NR^{10a}R^{10b}$. In a yet further aspect, G^1, when present, is —$NH(CH_2)_3NR^{10a}R^{10b}$. In an even further aspect, G^1, when present, is —$NH(CH_2)_4NR^{10a}R^{10b}$. In a still further aspect, G^1, when present, is —$NH(CH_2)_5NR^{10a}R^{10b}$. In a yet further aspect, G^1, when present, is —$NH(CH_2)_6NR^{10a}R^{10b}$.

j. Q^1 GROUP

[00783] In one aspect, Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —NR^{8a}—, and (C=O). In a further aspect, Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, and (C=O). In a still further aspect, Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —NR^{8a}—, and (C=O). In a yet further aspect, Q^1, when present, is selected from —O—, —S—, and (C=O).

[00784] In a further aspect, Q^1, when present, is selected from —CR^{7a}= and —$CR^{7a}R^{7b}$—. In a still further aspect, Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, and —NR^{8a}—. In a yet further aspect, Q^1, when present, is selected from —O— and —S—.

[00785] In a further aspect, Q^1, when present, is —CR^{7a}=. In a still further aspect, Q^1, when present, is —$CR^{7a}R^{7b}$—. In a yet further aspect, Q^1, when present, is —O—. In an even further aspect, Q^1, when present, is —S—. In a still further aspect, Q^1, when present, is —NR^{8a}—. In a yet further aspect, Q^1, when present, is (C=O).

k. Q^2 GROUP

[00786] In one aspect, Q^2, when present, is selected from =N—, =CR^{7c}—, —NR^{8b}—, (C=NH), (S=O), (SO_2), (C=S), and (C=O). In a further aspect, Q^2, when present, is selected from =N—, —NR^{8b}—, and (C=O). In a still further aspect, Q^2, when present, is selected from (C=NH), (S=O), (SO_2), (C=S), and (C=O). In a yet further aspect, Q^2, when present, is selected from =N—, =CR^{7c}—, —NR^{8b}—, and (C=O).

[00787] In a further aspect, Q^2, when present, is selected from =N— and —NR^{8b}—. In a still further aspect, Q^2, when present, is selected from (C=NH), (S=O), (SO_2), and (C=S). In a yet further aspect, Q^2, when present, is selected from =N—, =CR^{7c}—, and —NR^{8b}—. In an even further aspect, Q^2, when present, is selected from (S=O), (SO_2), and (C=S). In a still

further aspect, Q^2, when present, is selected from (C=NH), (S=O), (C=S), and (C=O). In a yet further aspect, Q^2, when present, is selected from (S=O), (C=S), and (C=O).

[00788] In a further aspect, Q^2, when present, is =N—. In a still further aspect, Q^2, when present, is $=CR^{7c}$—. In a yet further aspect, Q^2, when present, is $—NR^{8b}$—. In an even further aspect, Q^2, when present, is (C=NH). In a still further aspect, Q^2, when present, is (S=O). In a yet further aspect, Q^2, when present, is (SO_2). In an even further aspect, Q^2, when present, is (C=S). In a still further aspect, Q^2, when present, is (C=O).

l. Q^3 GROUP

[00789] In one aspect, Q^3, when present, is selected from $—CR^{7a}=$, $—CR^{7a}R^{7b}$—, —O—, —S—, —N=, and $—NR^{8a}$—. In a further aspect, Q^3, when present, is selected from $—CR^{7a}=$ and $—CR^{7a}R^{7b}$—. In a still further aspect, Q^3, when present, is selected from —O— and —S—. In a yet further aspect, Q^3, when present, is selected from —N= and $—NR^{8a}$—. In an even further aspect, Q^3, when present, is selected from $—CR^{7a}=$, $—CR^{7a}R^{7b}$—, —N=, and $—NR^{8a}$—.

[00790] In a further aspect, Q^3, when present, is $—CR^{7a}=$. In a still further aspect, Q^3, when present, is $—CR^{7a}R^{7b}$—. In a yet further aspect, Q^3, when present, is —O—. In an even further aspect, Q^3, when present, is —S—. In a still further aspect, Q^3, when present, is —N=. In a yet further aspect, Q^3, when present, is $—NR^{8a}$—.

m. Q^4 GROUP

[00791] In one aspect, Q^4, when present, is selected from $=CR^{7c}$—, $—CR^{7c}R^{7d}$—, —O—, —S—, $—NR^{8b}$—, and (C=O); provided that Q^3 and Q^4 are not simultaneously $—NR^{8a}$— and $—NR^{8b}$—, respectively, or that Q^3 and Q^4 are not simultaneously —O— or —S—. In a further aspect, Q^4, when present, is selected from —O—, —S—, and (C=O); provided that Q^3 and Q^4 are not simultaneously —O— or —S—. In a still further aspect, Q^4, when present, is selected from $=CR^{7c}$—, $—CR^{7c}R^{7d}$—, $—NR^{8b}$—, and (C=O); provided that Q^3 and Q^4 are not simultaneously $—NR^{8a}$— and $—NR^{8b}$—, respectively. In an even further aspect, Q^4, when present, is selected from $=CR^{7c}$—, $—CR^{7c}R^{7d}$ — and (C=O).

[00792] In a further aspect, Q^4, when present, is selected from —O— and —S—; provided that Q^3 and Q^4 are not simultaneously —O— or —S—. In a still further aspect, Q^4, when present, is selected from $=CR^{7c}$—, $—CR^{7c}R^{7d}$—, and $—NR^{8b}$—; provided that Q^3 and Q^4 are not simultaneously $—NR^{8a}$— and $—NR^{8b}$—, respectively. In an even further aspect, Q^4, when present, is selected from $=CR^{7c}$— and $—CR^{7c}R^{7d}$ —.

[00793] In a further aspect, Q^4, when present, is $=CR^{7c}$—. In a still further aspect, Q^4, when present, is $—CR^{7c}R^{7d}$—. In a yet further aspect, Q^4, when present, is —O—, provided that Q^3 and Q^4 are not simultaneously —O— or —S—. In an even further aspect, Q^4, when

present, is —S—, provided that Q^3 and Q^4 are not simultaneously —O— or —S—. In a still further aspect, Q^4, when present, is —NR^{8b}—, provided that Q^3 and Q^4 are not simultaneously —NR^{8a}— and —NR^{8b}—, respectively. In a yet further aspect, Q^4, when present, is (C=O).

n. R^{1A}, $R1^B$, R^{1C}, AND R^{1D} GROUPS

[00794] In one aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl. In a further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is hydrogen.

[00795] In a further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl, and ethyl. In a still further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, and —CN. In a yet further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —Cl, methyl, and ethyl. In a still further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, methyl and ethyl. In a yet further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —CN, methyl and ethyl. In an even further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —Cl, —OH, —CN, methyl and ethyl.

[00796] In a further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —NH_2, —OH, —CN, methyl, and ethyl. In a still further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —NH_2, —OH, and —CN. In a yet further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, methyl, and ethyl. In an even further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, methyl, and ethyl. In a still further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —NH_2, —OH, methyl and ethyl. In a yet further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —NH_2, —CN, methyl and ethyl. In an even further aspect, each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, —F, —OH, —CN, methyl and ethyl.

o. R^{2A} AND R^{2B} GROUPS

[00797] In one aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl. In a further aspect, each of R^{2a} and R^{2b} is hydrogen.

[00798] In a further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl and ethyl. In a still further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, and —CN. In a yet further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, methyl and ethyl. In an even further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —Cl, methyl and ethyl. In a still further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, methyl and ethyl. In a yet further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —Cl, —NH_2, —CN, methyl and ethyl. In an even further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —Cl, —OH, —CN, methyl and ethyl.

[00799] In a further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —NH_2, —OH, —CN, methyl and ethyl. In a still further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —NH_2, —OH, and —CN. In a yet further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, methyl and ethyl. In an even further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, methyl and ethyl. In a still further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —NH_2, —OH, methyl and ethyl. In a yet further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —NH_2, —CN, methyl and ethyl. In an even further aspect, each of R^{2a} and R^{2b} is independently selected from hydrogen, —F, —OH, —CN, methyl and ethyl.

p. R^3 GROUPS

[00800] In one aspect, R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl. In a further aspect, R^3 is hydrogen. In a still further aspect, R^3 is —F. In a yet further aspect, R^3 is methyl.

[00801] In a further aspect, R^3 is selected from hydrogen, —F, —Cl, —OH, methyl, and ethyl. In a still further aspect, R^3 is selected from hydrogen, methyl, and ethyl. In a yet further aspect, R^3 is selected from hydrogen, —F, —Cl, and —OH. In an even further aspect, R^3 is selected from —F, —Cl, and —OH.

q. R^4 GROUPS

[00802] In one aspect, each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino. In one aspect, each occurrence of R^4 is hydrogen.

[00803] In a further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl, ethyl, propyl, —CH_2F, —CH_2Cl, —CH_2CH_2F, —CH_2CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, —CH_2CHF_2, —CH_2CF_3, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —$O(CH_2)_2CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, and —$N(CH_3)CH_2CH_3$. In a still further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl, ethyl, —CH_2F, —CH_2CH_2F, —CHF_2, —CF_3, —CH_2CHF_2, —CH_2CF_3, —OCH_3, —OCH_2CH_3, —$O(CH_2)_2CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, and —$N(CH_3)CH_2CH_3$. In a yet further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl, —CH_2F, —CHF_2, —CF_3, —OCH_3, —OCH_2CH_3, —$NHCH_3$, and —$N(CH_3)_2$.

[00804] In a further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, and —CN. In a still further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, and —Cl. In a yet further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, —NH_2, —OH, and —CN.

[00805] In a further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, —Cl, methyl, ethyl, propyl, —CH_2F, —CH_2Cl, —CH_2CH_2F, —CH_2CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, —CH_2CHF_2, —CH_2CF_3, —CH_2CHCl_2, and —CH_2CCl_3. In a still further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, methyl, ethyl, —CH_2F, —CH_2CH_2F, —CHF_2, —CF_3, —CH_2CHF_2, and —CH_2CF_3. In a yet further aspect, each occurrence of R^4 is independently selected from hydrogen, —F, methyl, —CH_2F, —CHF_2, and —CF_3.

[00806] In a further aspect, each occurrence of R^4 is independently selected from hydrogen, —OCH_3, —OCH_2CH_3, —$O(CH_2)_2CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, and —$N(CH_3)CH_2CH_3$. In a still further aspect, each occurrence of R^4 is independently selected from hydrogen, —OCH_3, —OCH_2CH_3, —$O(CH_2)_2CH_3$, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, and —$N(CH_3)CH_2CH_3$. In a yet further aspect, each occurrence of R^4 is independently selected from hydrogen, —OCH_3, —OCH_2CH_3, —$NHCH_3$, and —$N(CH_3)_2$.

r. R^5 GROUPS

[00807] In one aspect, R^5, when present, is selected from hydrogen, C1-C2 monohaloalkyl, C1-C2 polyhaloalkyl, and C1-C2 alkyl. In a further aspect, R^5, when present, is hydrogen. In a still further aspect, R^5, when present, is methyl. In a yet further aspect, R^5, when present, is ethyl. In an even further aspect, R^5, when present, is $-CF_3$.

[00808] In a further aspect, R^5, when present, is selected from hydrogen, methyl, $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $-CF_3$, $-CHCl_2$, and $-CCl_3$. In a still further aspect, R^5, when present, is selected from hydrogen, methyl, $-CH_2F$, $-CHF_2$, and $-CF_3$. In a yet further aspect, R^5, when present, is selected from hydrogen, methyl, and ethyl. In an even further aspect, R^5, when present, is selected from hydrogen and methyl.

s. $R6^A$, $R6^B$, R^{6C}, AND $R6^D$ GROUPS

[00809] In one aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino. In one aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is hydrogen.

[00810] In a further aspect, hydrogen, —F, —Cl, —CN, methyl, ethyl, $-CH_2F$, $-CH_2Cl$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CHF_2$, $-CF_3$, $-CHCl_2$, $-CCl_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CHCl_2$, $-CH_2CCl_3$, $-OCH_3$, $-OCH_2CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, and $-N(CH_3)CH_2CH_3$. In a still further aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, —F, —Cl, —CN, methyl, $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $-CF_3$, $-CHCl_2$, $-CCl_3$, $-OCH_3$, $-NHCH_3$, and $-N(CH_3)_2$. In a yet further aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, —F, and —Cl. In an even further aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, methyl, $-CH_2F$, $-CH_2Cl$, $-CHF_2$, $-CF_3$, $-CHCl_2$, and $-CCl_3$. In a still further aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, methyl, $-CH_2F$, $-CHF_2$, and $-CF_3$. In a yet further aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, methyl, ethyl $-CH_2F$, $-CHF_2$, and $-CF_3$. In an even further aspect, each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, $-OCH_3$, $-NHCH_3$, and $-N(CH_3)_2$.

t. R^{7A}, R^{7B}, R^{7C}, AND R^{7D} GROUPS

[00811] In one aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino. In a further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is hydrogen.

[00812] In a further aspect, hydrogen, —F, —Cl, —CN, methyl, ethyl, —CH_2F, —CH_2Cl, —CH_2CH_2F, —CH_2CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, —CH_2CHF_2, —CH_2CF_3, —CH_2CHCl_2, —CH_2CCl_3, —OCH_3, —OCH_2CH_3, —$NHCH_3$, —$NHCH_2CH_3$, —$N(CH_3)_2$, and —$N(CH_3)CH_2CH_3$. In a still further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, —F, —Cl, —CN, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, —OCH_3, —$NHCH_3$, and —$N(CH_3)_2$. In a yet further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, —F, and —Cl. In an even further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, and —CCl_3. In a still further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, methyl, —CH_2F, —CHF_2, and —CF_3. In a yet further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, methyl, ethyl —CH_2F, —CHF_2, and —CF_3. In an even further aspect, each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, —OCH_3, —$NHCH_3$, and —$N(CH_3)_2$.

u. R^{8A} AND R^{8B} GROUPS

[00813] In one aspect, each of R^{8a} and R^{8b}, when present, is independently selected from hydrogen and C1-C8 alkyl. In a further aspect, each of R^{8a} and R^{8b}, when present, is hydrogen.

[00814] In a further aspect, each of R^{8a} and R^{8b}, when present, is selected from methyl, ethyl, propyl, isopropyl, *tert*-butyl, *sec*-butyl, isobutyl, neopentyl, isopentyl, *sec*-pentyl, *tert*-pentyl, 3,3-dimethylbutan-2-yl, 2,3-dimethylbutan-2-yl. In a still further aspect, each of R^{8a} and R^{8b}, when present, is selected from methyl, ethyl, propyl, isopropyl, *tert*-butyl, *sec*-butyl, isobutyl, and *tert*-butyl. In a yet further aspect, each of R^{8a} and R^{8b}, when present, is selected from methyl, ethyl, propyl, and isopropyl. In an even further aspect, each of R^{8a} and R^{8b}, when present, is methyl.

[00815] In a further aspect, R^{8a}, when present, is hydrogen and R^{8b}, when present, is selected from methyl, ethyl, propyl, isopropyl, *tert*-butyl, *sec*-butyl, isobutyl, neopentyl, isopentyl, *sec*-pentyl, *tert*-pentyl, 3,3-dimethylbutan-2-yl, 2,3-dimethylbutan-2-yl. In a still further aspect, R^{8a}, when present, is hydrogen and R^{8b}, when present, is selected from methyl, ethyl, propyl, isopropyl, *tert*-butyl, *sec*-butyl, isobutyl, and *tert*-butyl. In a yet further aspect, R^{8a}, when present, is hydrogen and R^{8b}, when present, is selected from methyl, ethyl, propyl, and isopropyl. In an even further aspect, R^{8a}, when present, is hydrogen and R^{8b}, when present, is methyl.

v. R^9 GROUPS

[00816] In one aspect, R^9, when present, is selected from C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl. In a further aspect, R^9, when present, is selected from methyl, ethyl, —CH_2F, —CH_2Cl, —CH_2CH_2F, —CH_2CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, , —CH_2CHF_2, —CH_2CF_3, —CH_2CHCl_2, and —CH_2CCl_3. In a still further aspect, R^9, when present, is selected from methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, and —CCl_3. In a yet further aspect, R^9, when present, is selected from methyl, —CH_2F, —CHF_2, and —CF_3. In an even further aspect, R^9, when present, is methyl. In a still further aspect, R^9, when present, is ethyl. In a yet further aspect, R^9, when present, is propyl. In an even further aspect, R^9, when present, is —CF_3. In a still further aspect, R^9, when present, is —CH_2CF_3.

w. R^{10A} AND R^{10B} GROUPS

[00817] In one aspect, each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl. In a further aspect, each of R^{10a} and R^{10b}, when present, is hydrogen.

[00818] In a further aspect, each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, methyl, ethyl, —CH_2F, —CH_2Cl, —CH_2CH_2F, —CH_2CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, , —CH_2CHF_2, —CH_2CF_3, —CH_2CHCl_2, and —CH_2CCl_3. In a still further aspect, each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, and —CCl_3. In a yet further aspect, each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, methyl, —CH_2F, —CHF_2, and —CF_3.

x. R^{21A}, R^{21B}, R^{21C}, R^{21D}, AND R^{21E} GROUPS

[00819] In one aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that no more than two of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen. In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino, provided that no more than one of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen. In a yet further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is hydrogen.

[00820] In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, methoxy, —$NHCH_3$, and —$N(CH_3)_2$, provided that

no more than two of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen. In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, methyl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, methoxy, —$NHCH_3$, and —$N(CH_3)_2$, provided that no more than one of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen.

[00821] In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, and —CN, provided that no more than two of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen. In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —F, —Cl, —NH_2, —OH, —CN, provided that no more than one of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen.

[00822] In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —F, and —Cl, provided that no more than two of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} are not hydrogen. In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —F, and —Cl, and —$N(CH_3)_2$, provided that no more than one of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen.

[00823] In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen and —Cl, provided that no more than two of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} are not hydrogen. In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen and —Cl, provided that no more than one of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen.

[00824] In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —Cl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, provided that no more than two of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen. In a further aspect, each of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e}, when present, is independently selected from hydrogen, —Cl, —CH_2F, —CH_2Cl, —CHF_2, —CF_3, —$CHCl_2$, —CCl_3, provided that no more than one of R^{21a}, R^{21b}, R^{21c}, R^{21d}, and R^{21e} is not hydrogen.

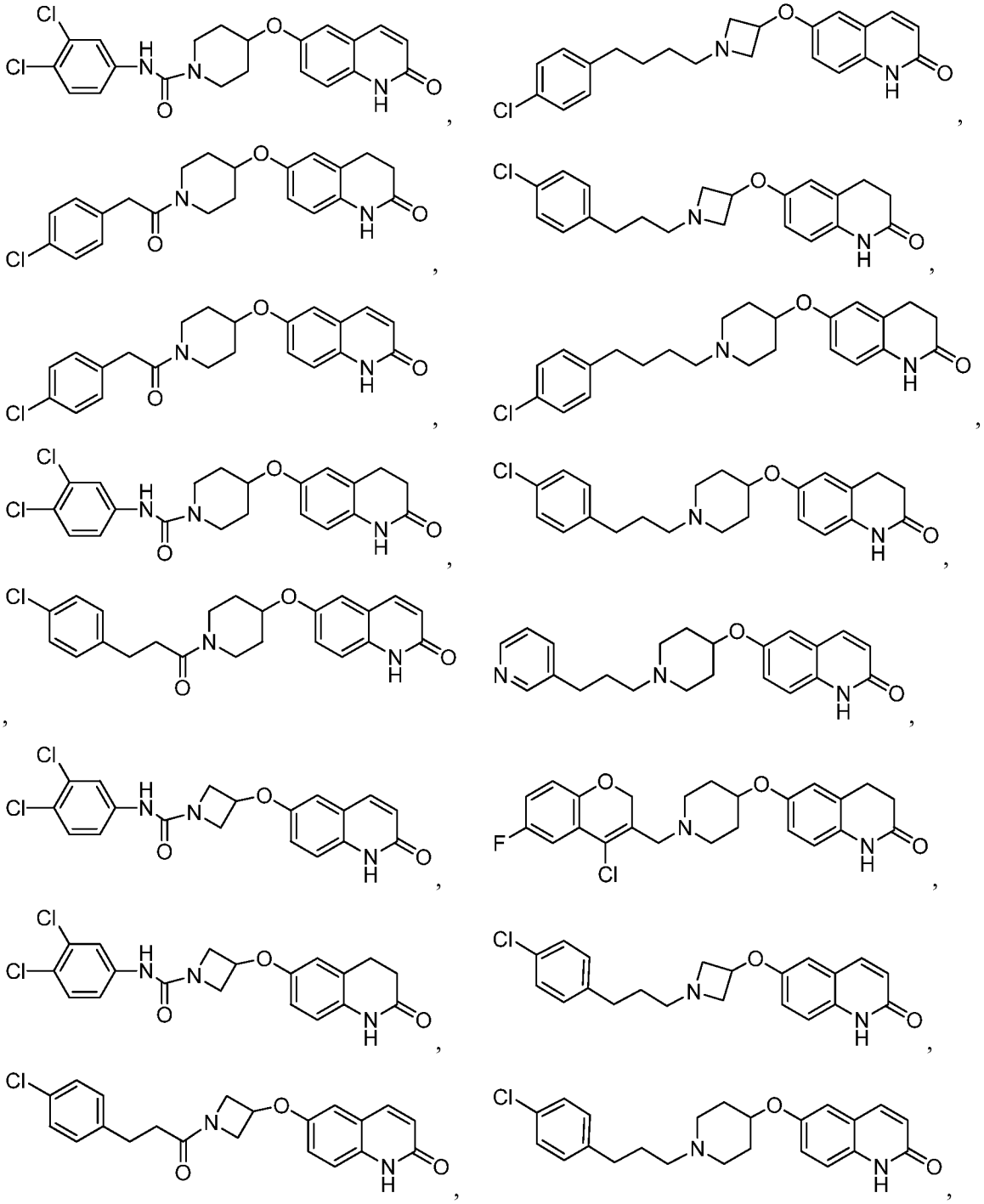
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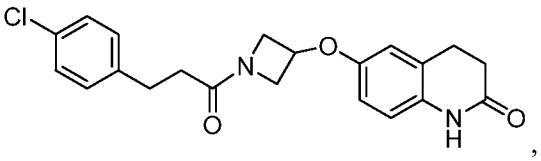
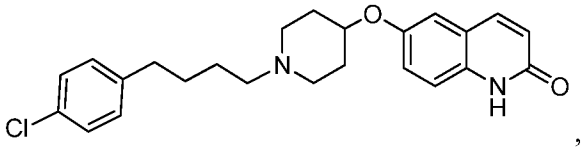
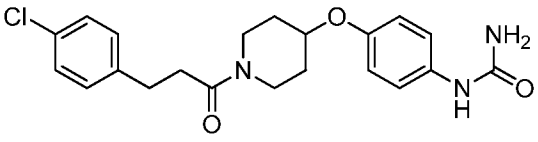
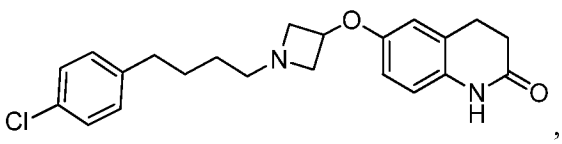
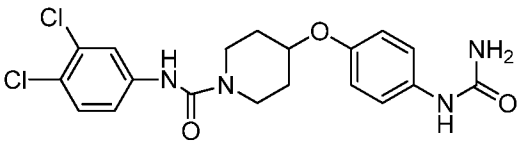
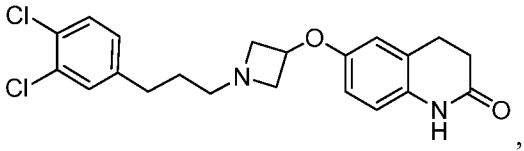
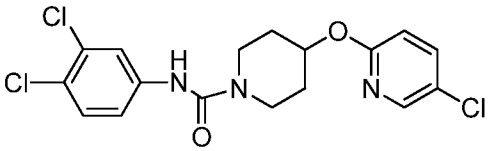
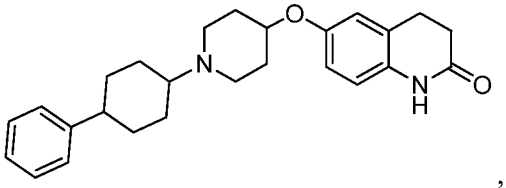
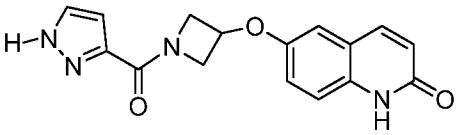
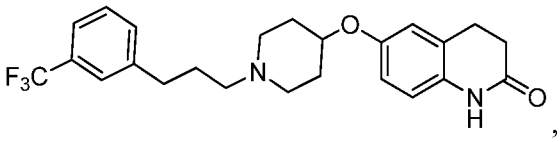
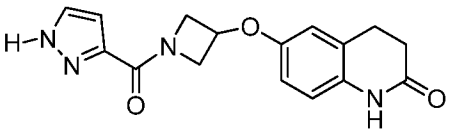
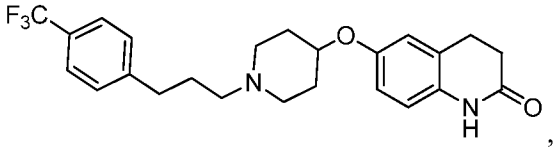
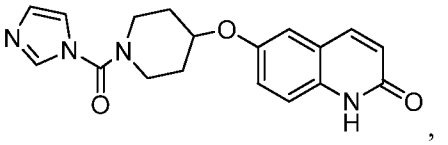
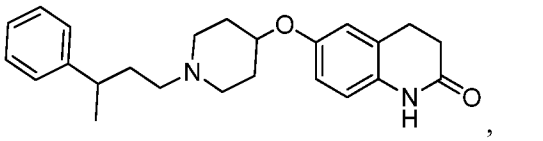
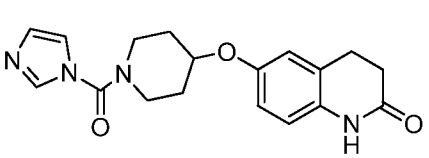
[00825] In one aspect, halogen is fluoro, chloro, bromo or iodo. In a further aspect, halogen is fluoro, chloro, or bromo. In a yet further aspect, halogen is fluoro or chloro. In a further aspect, halogen is chloro or bromo. In a further aspect, halogen is fluoro. In an even further aspect, halogen is chloro. In a yet further aspect, halogen is iodo. In a still further aspect, halogen is bromo.

[00826] It is also contemplated that pseudohalogens (e.g. triflate, mesylate, brosylate, etc.) can be used as leaving groups in place of halogens in certain aspects.

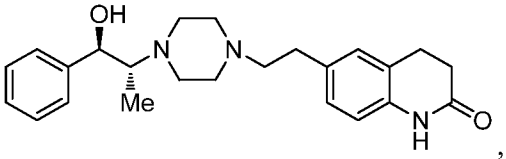
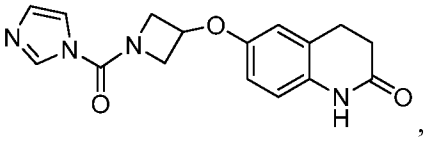
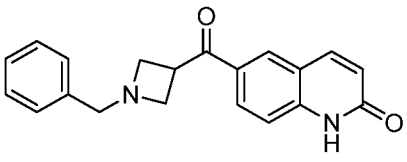
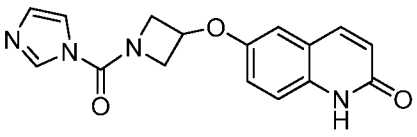
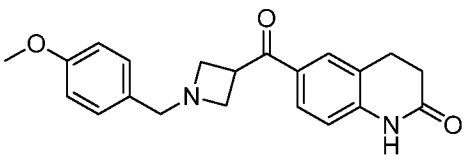
2. EXAMPLE COMPOUNDS

[00827] In one aspect, a compound can be present as:



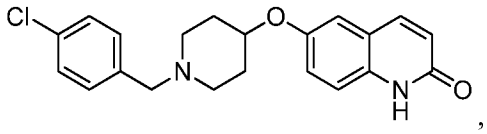
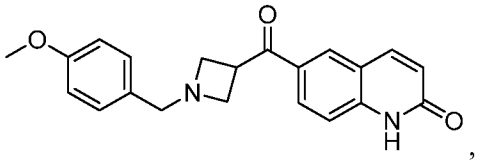
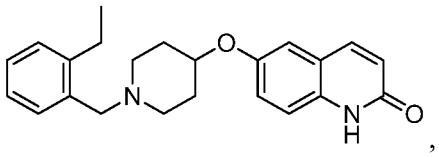
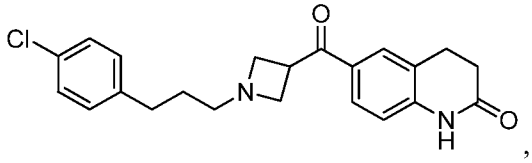
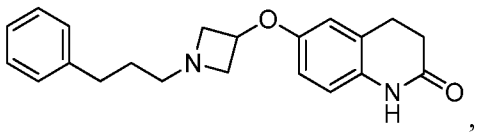
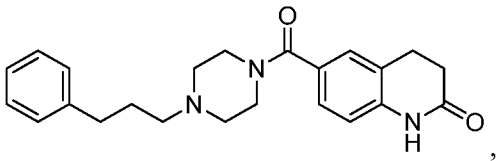
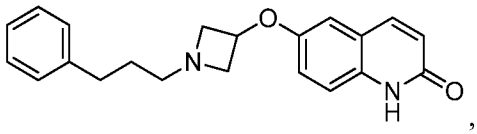
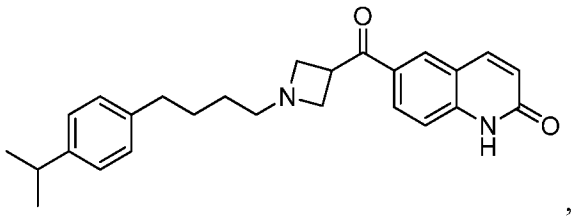
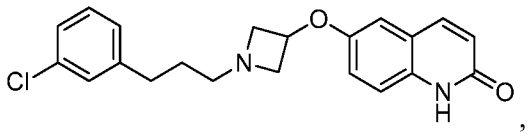
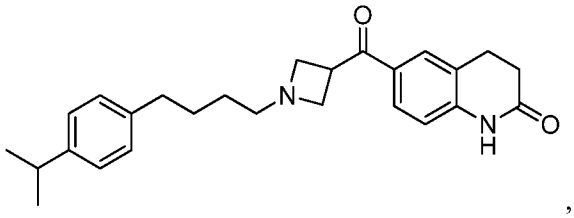
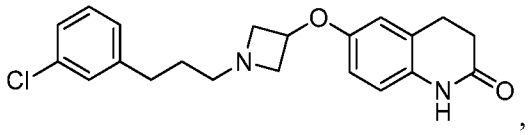
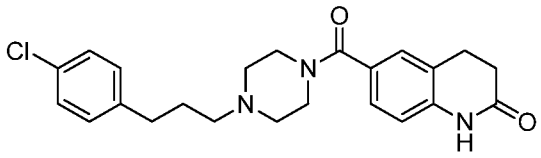
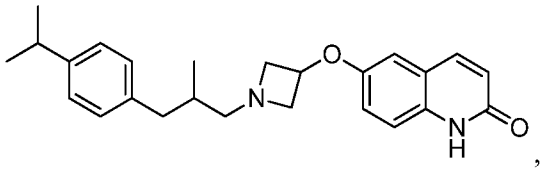
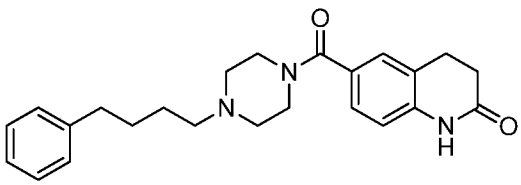
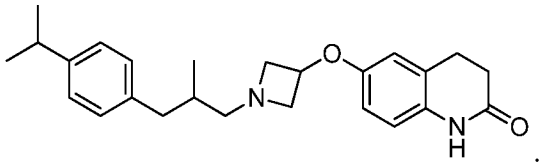

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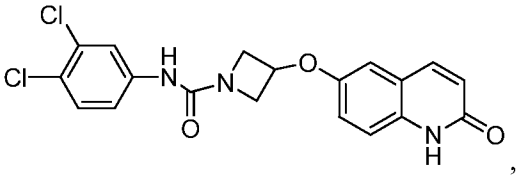
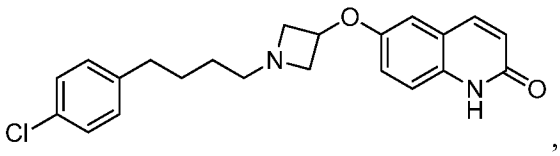
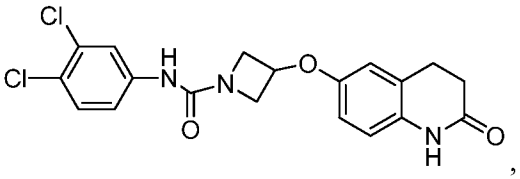
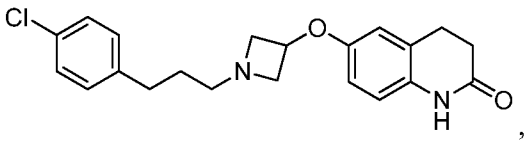
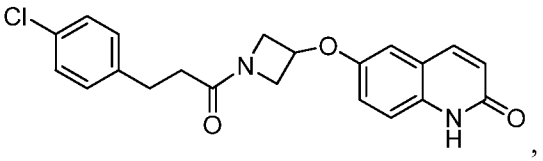
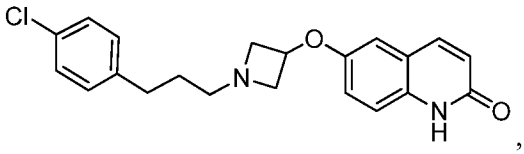
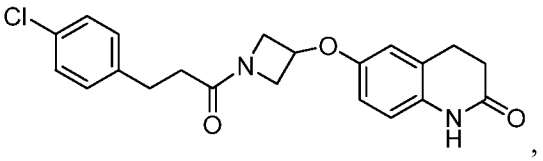
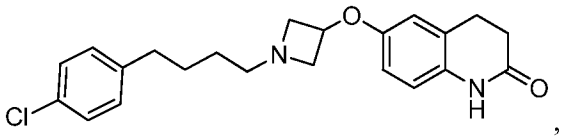
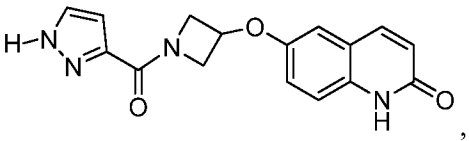
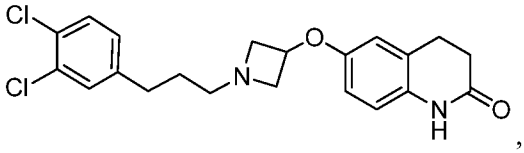
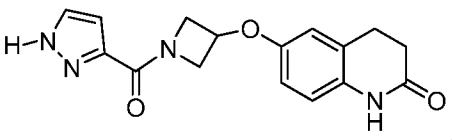
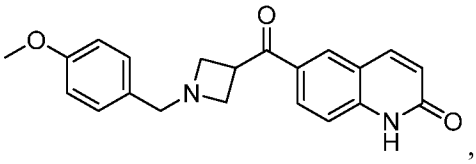
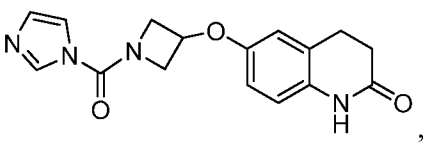
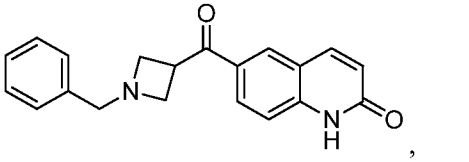
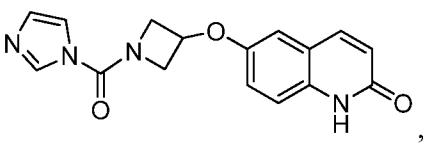
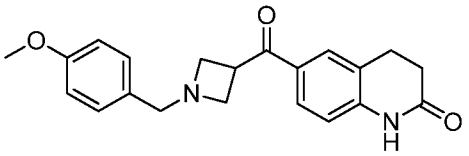
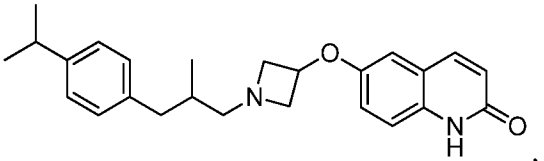
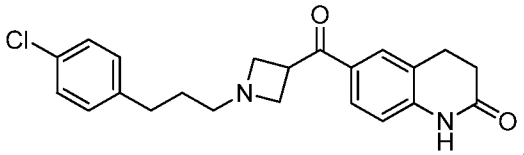
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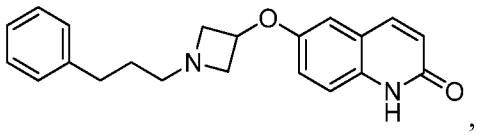
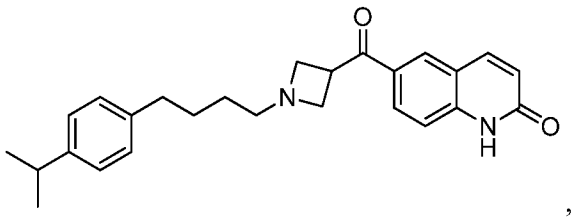
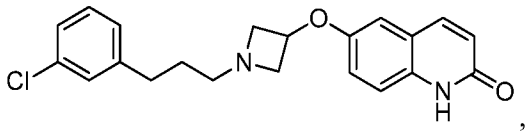
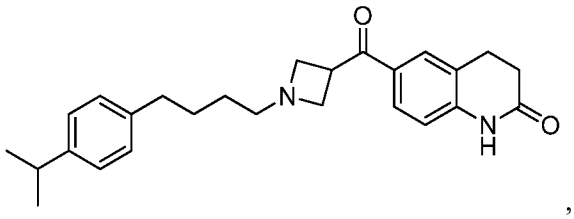
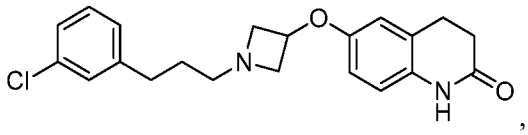
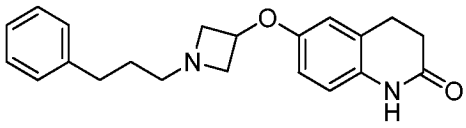
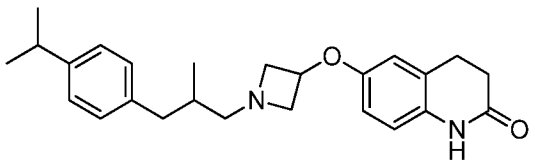
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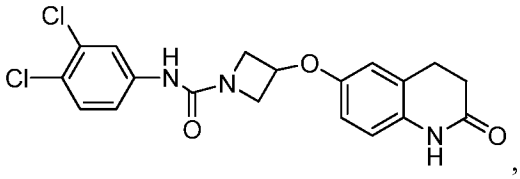
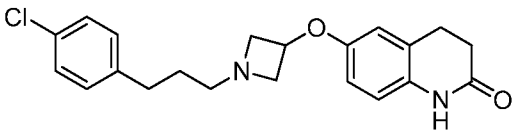
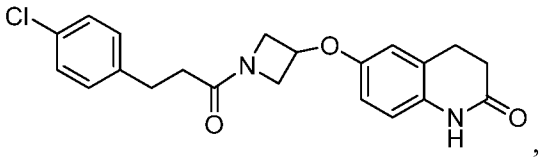
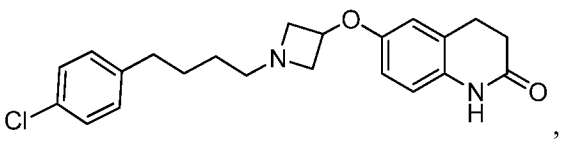
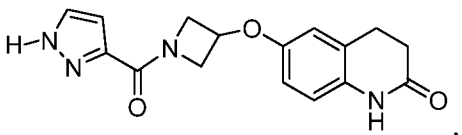
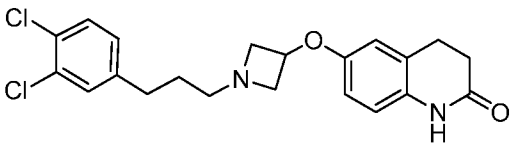
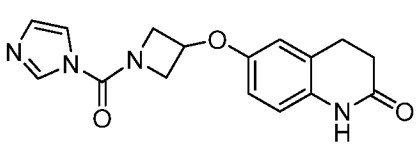
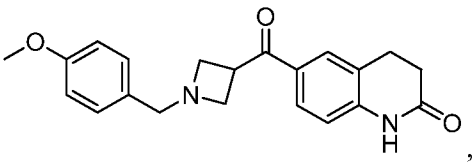

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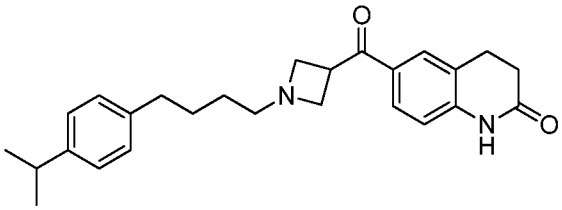
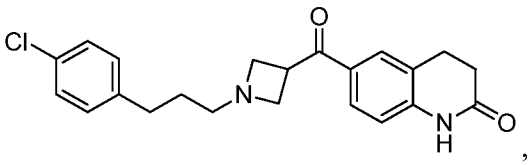
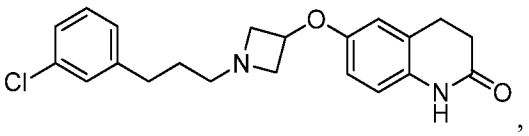
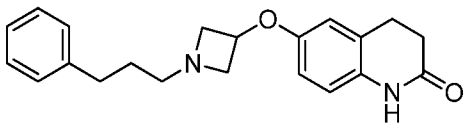
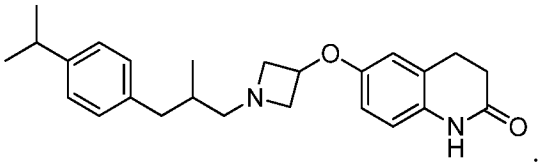
[00828] In one aspect, a compound can be present as:


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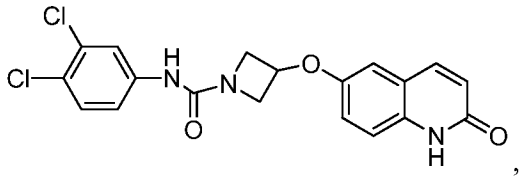
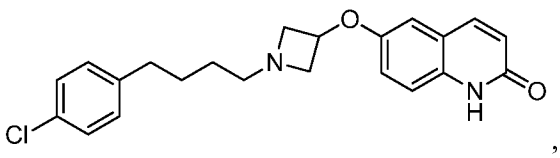
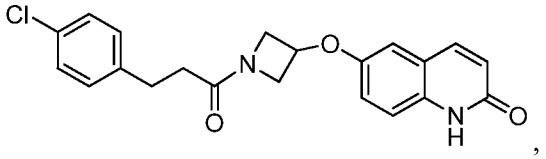
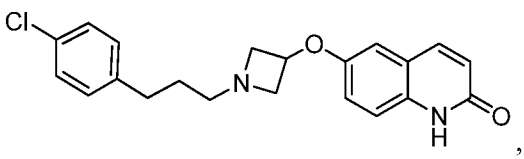
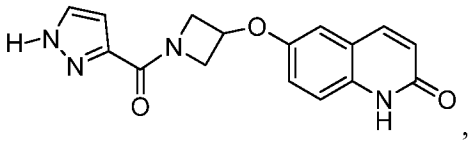
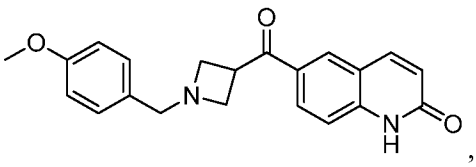
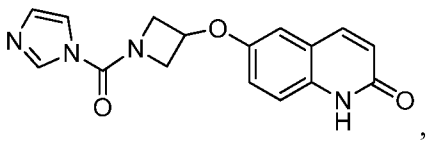
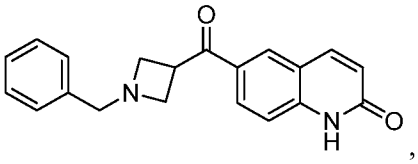
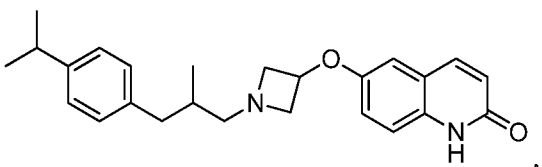
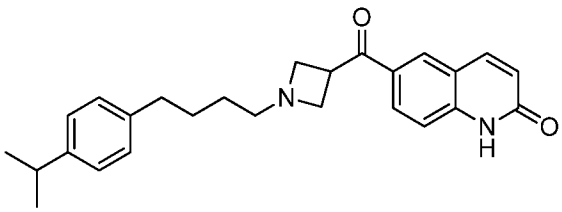

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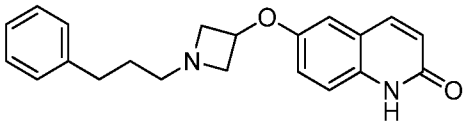
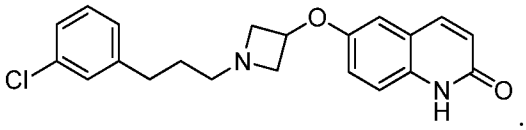
[00829] In one aspect, a compound can be present as:


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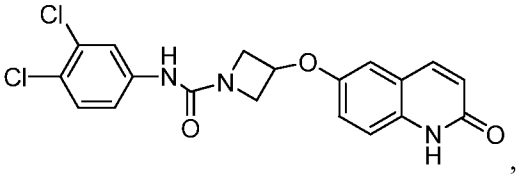
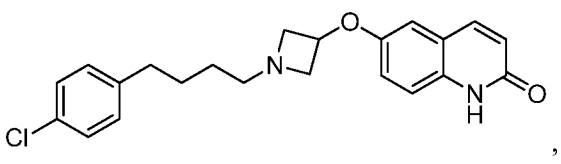

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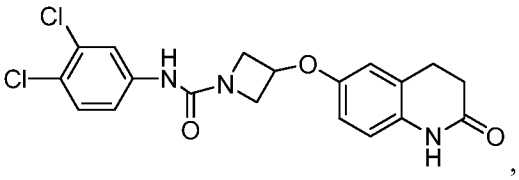
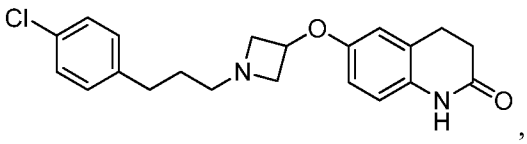
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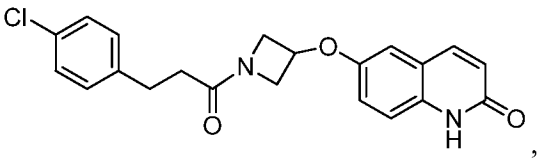
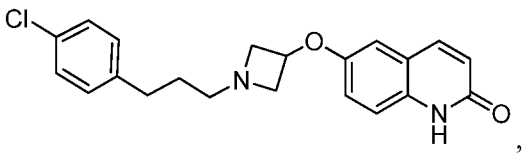

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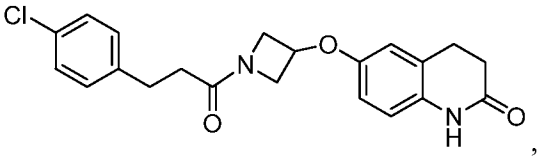
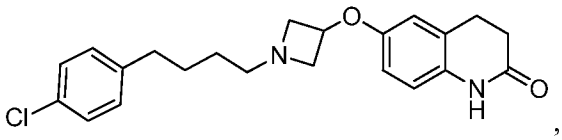
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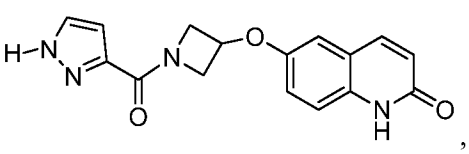
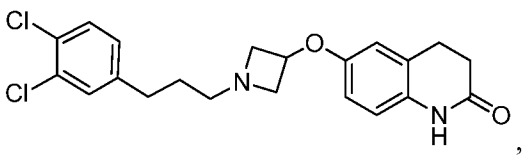
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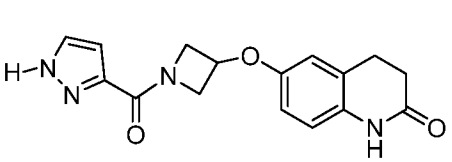
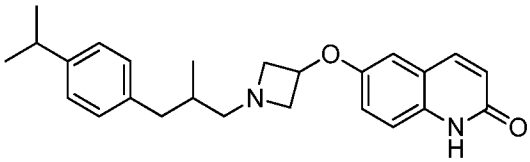
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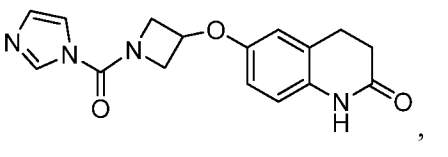
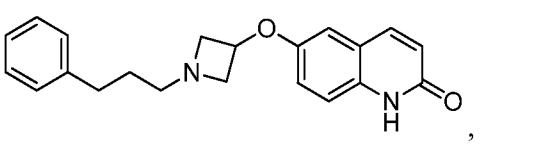
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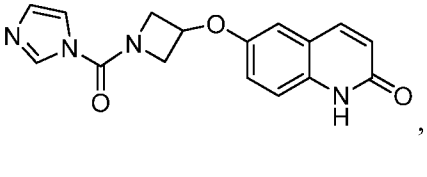
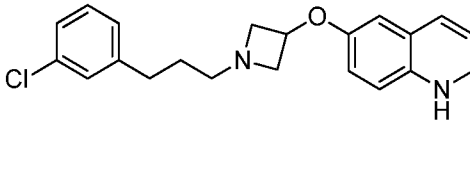
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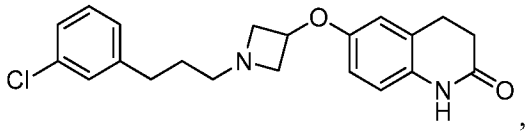
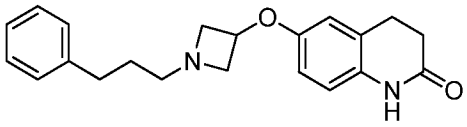
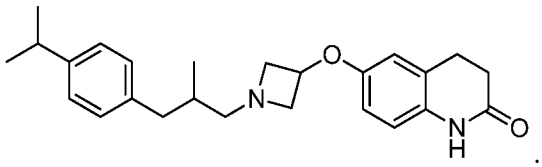
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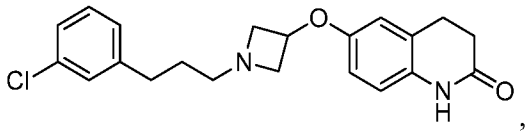
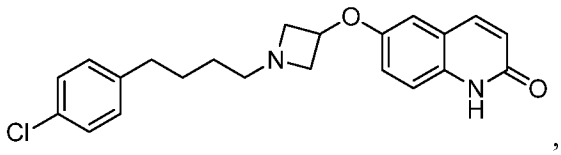
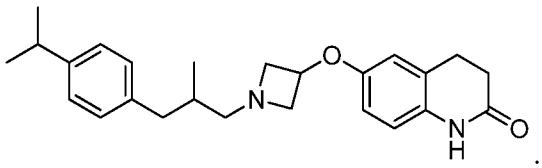
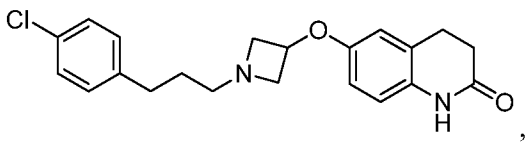
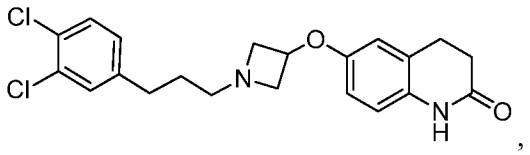
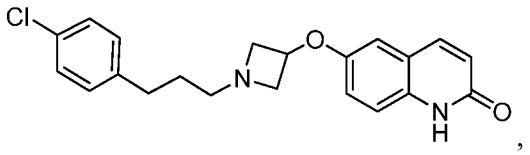
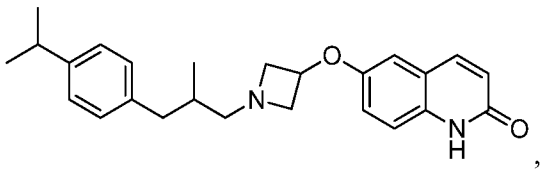
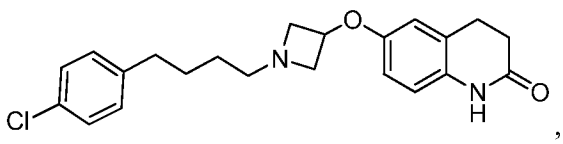
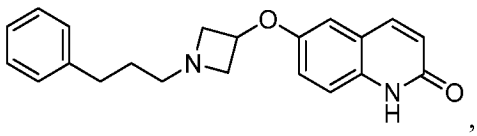
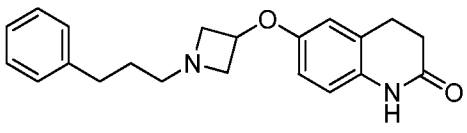
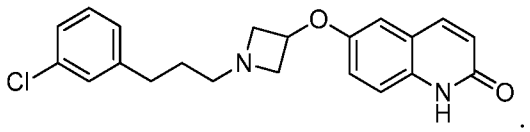
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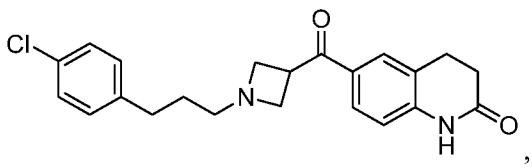
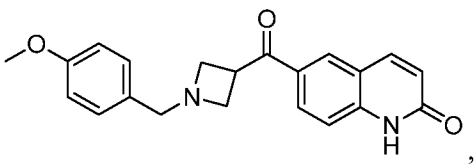
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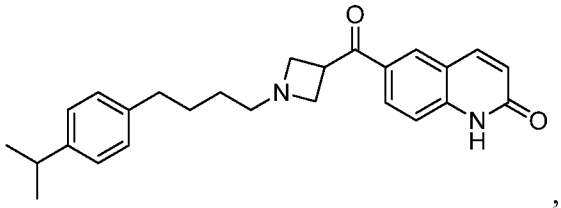
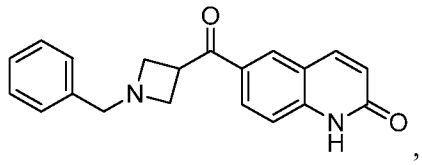
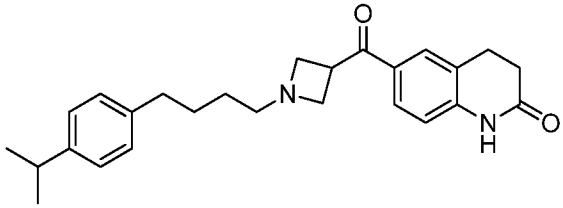
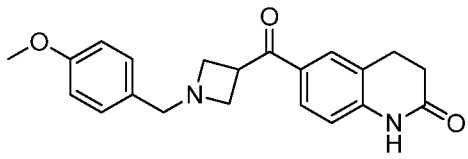

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[00832] In one aspect, a compound can be present as:

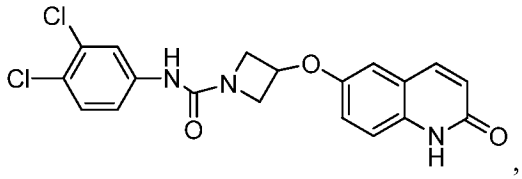
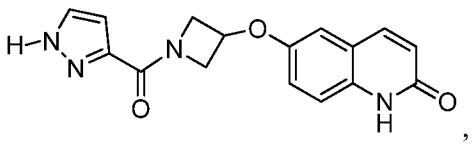
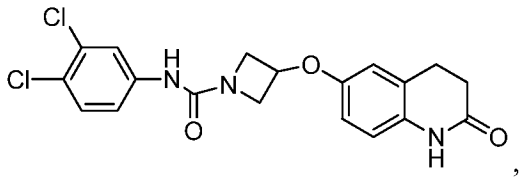
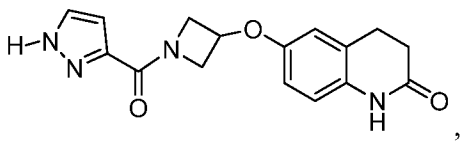
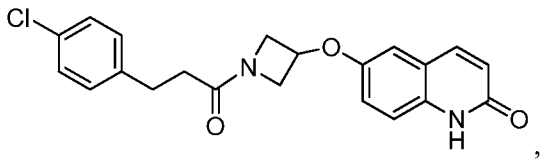
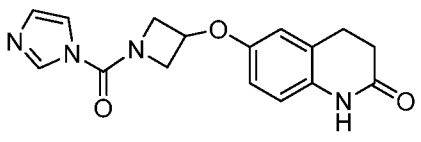
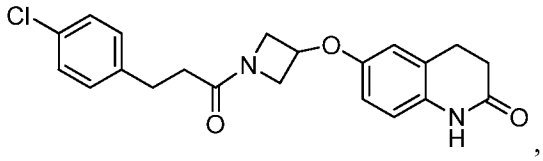
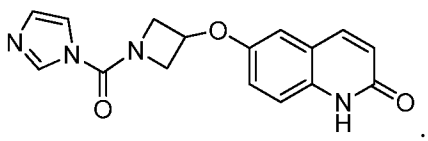

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[00833] In one aspect, a compound can be present as:

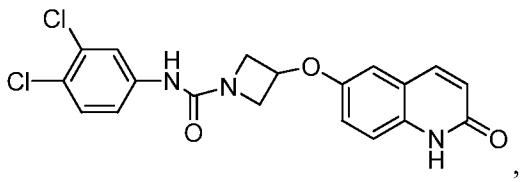
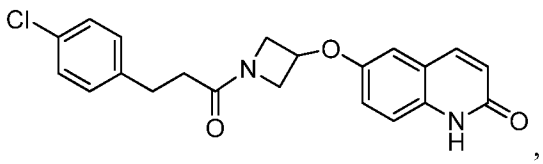

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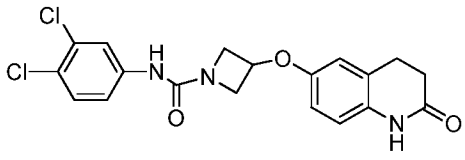
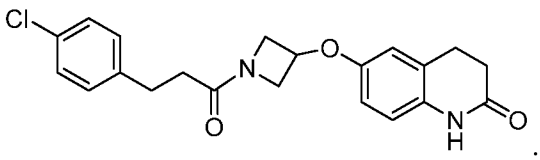

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or .

[00834] In one aspect, a compound can be present as:

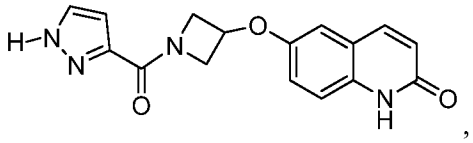
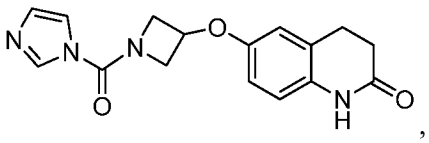

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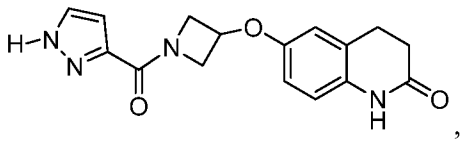
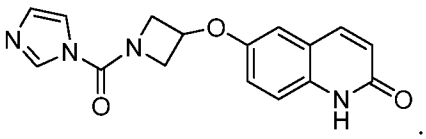
[00835] In one aspect, a compound can be present as:


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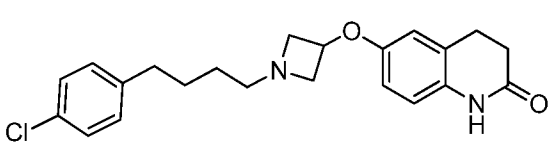
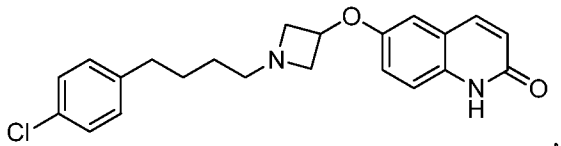

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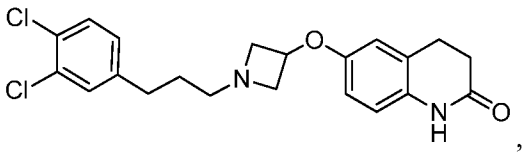
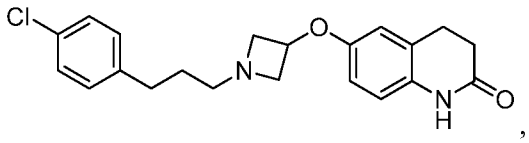
[00836] In one aspect, a compound can be present as:

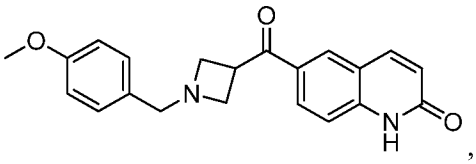
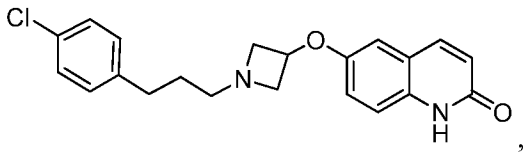

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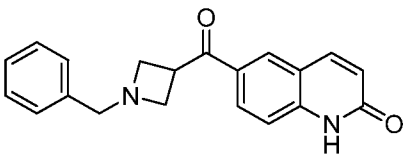
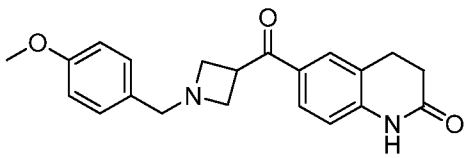

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or

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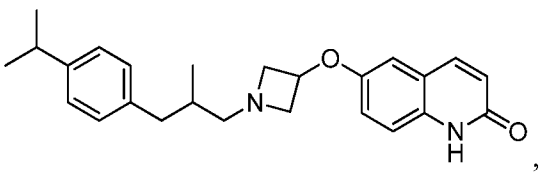
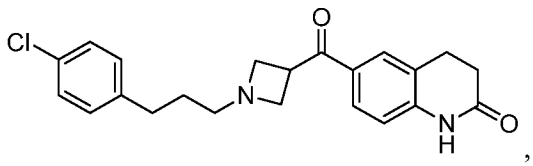
[00837] In one aspect, a compound can be present as:

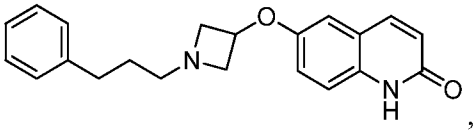
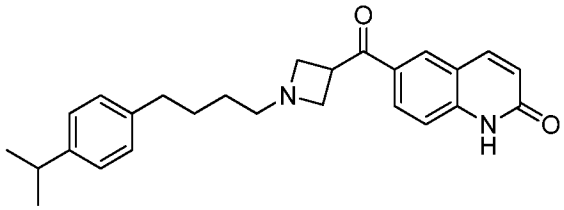
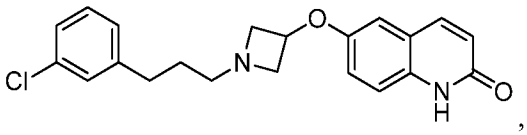
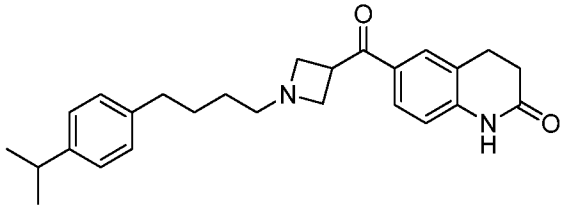
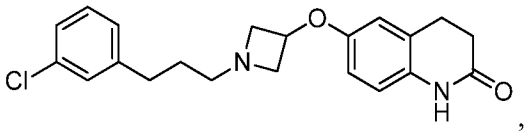
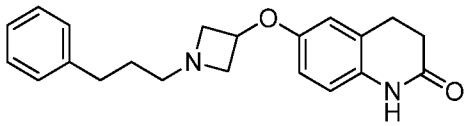
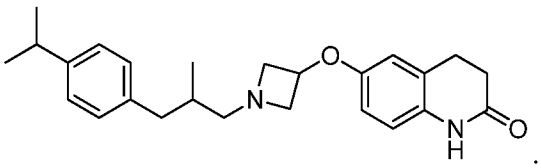

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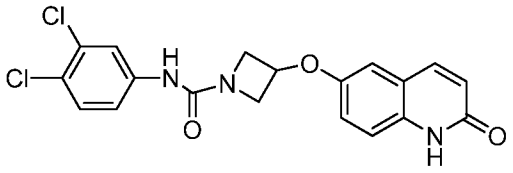
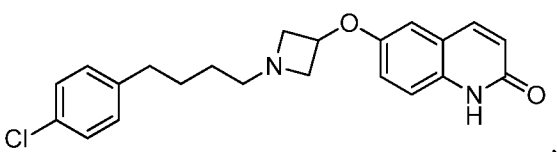
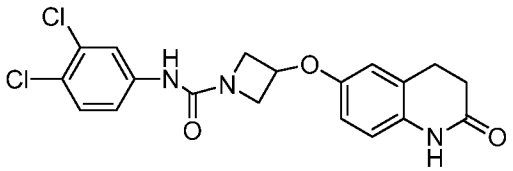
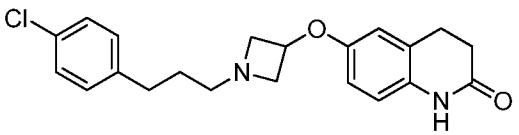
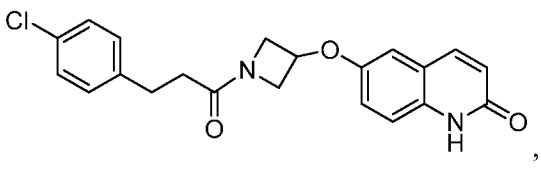
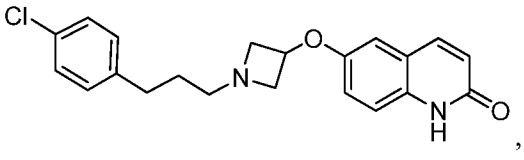
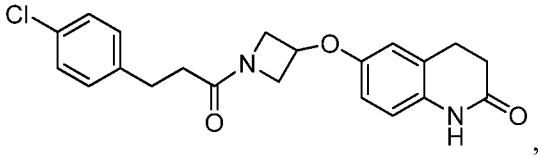
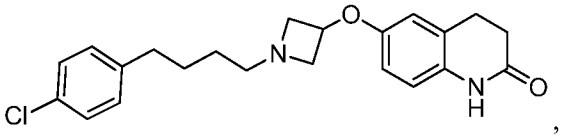

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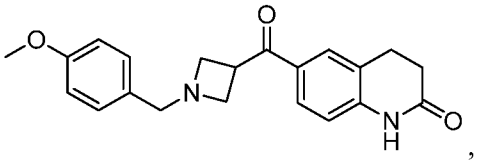
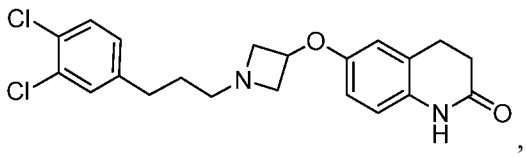
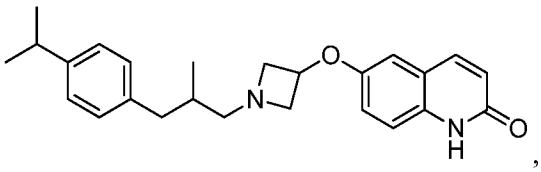
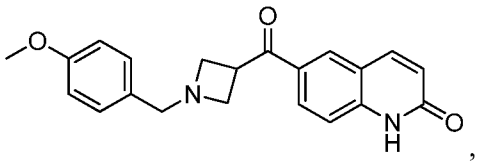
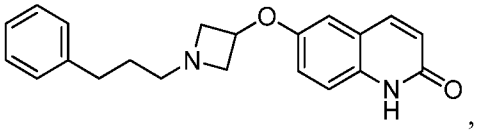
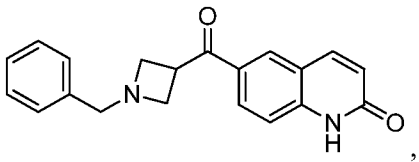
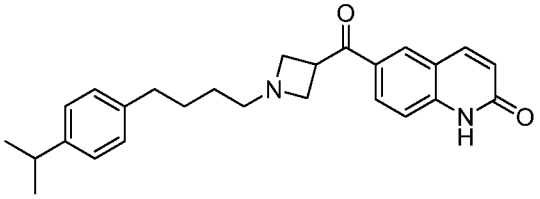
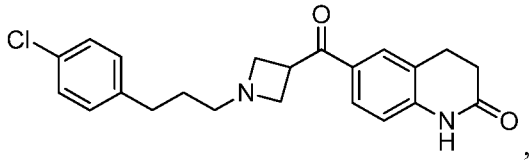
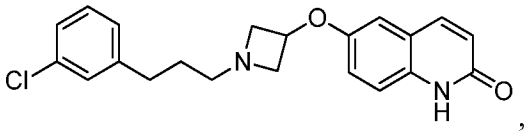
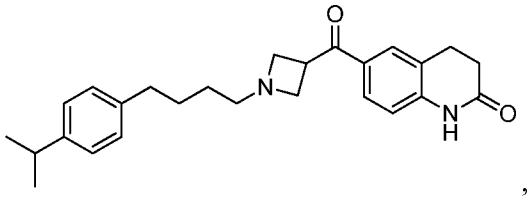
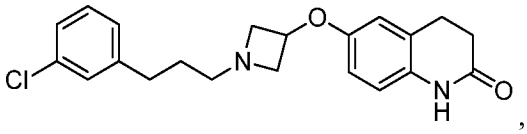
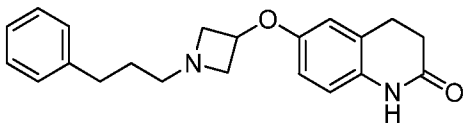
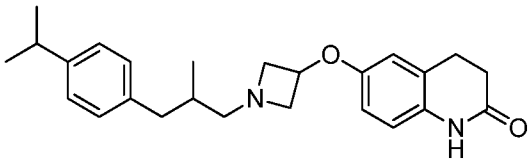

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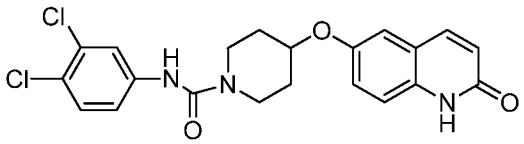
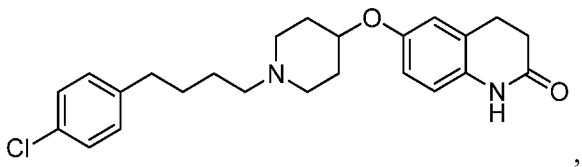

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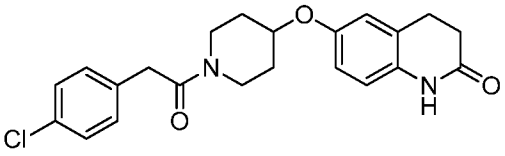
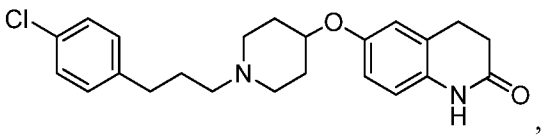
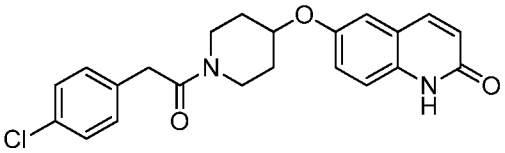
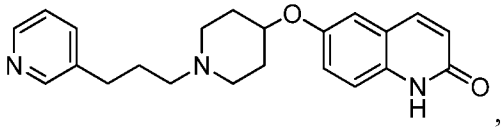
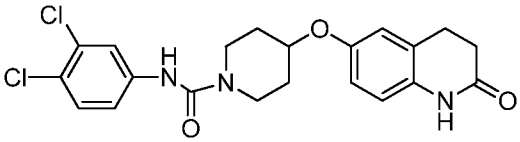
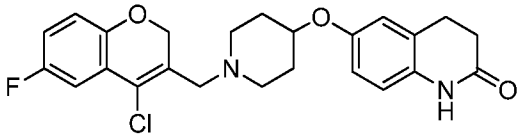
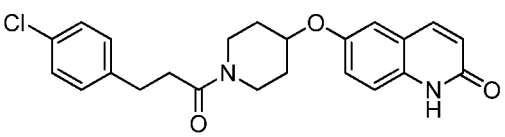
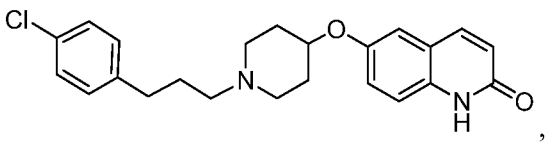
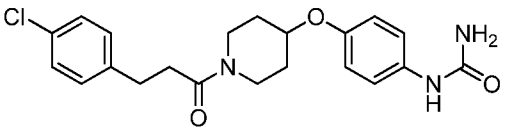
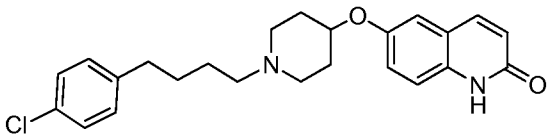
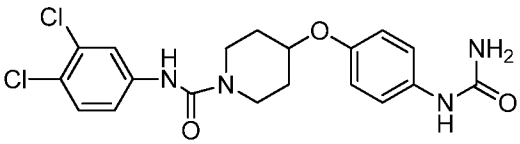
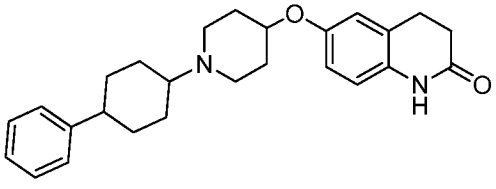
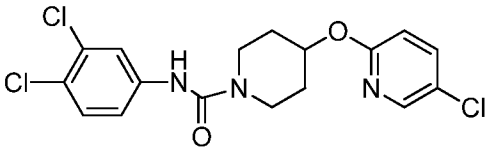
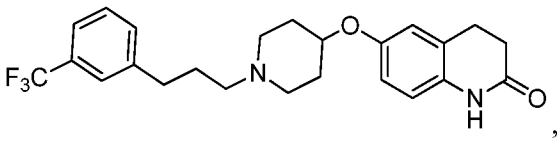
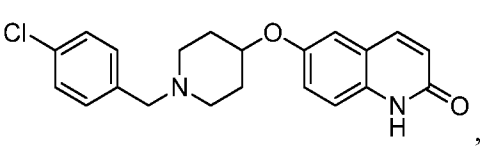
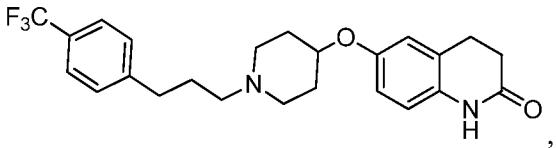
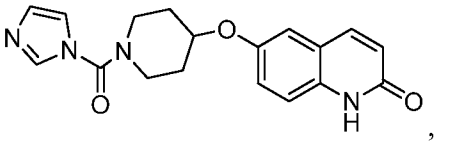
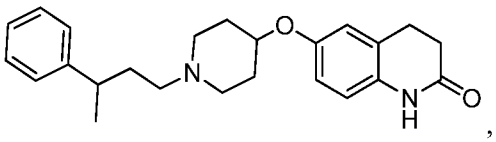
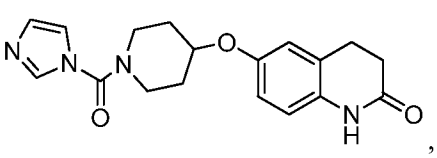
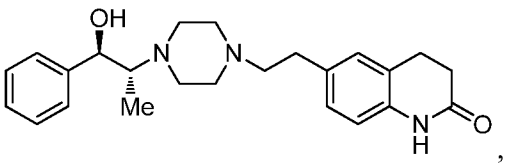
[00838] In one aspect, a compound can be present as:

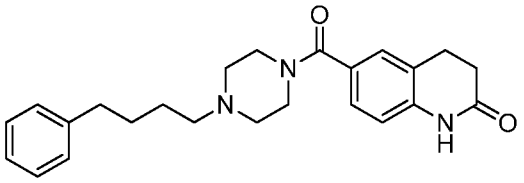
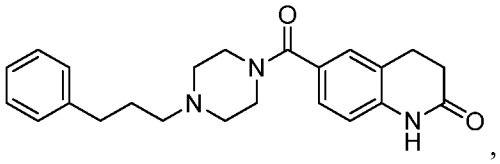
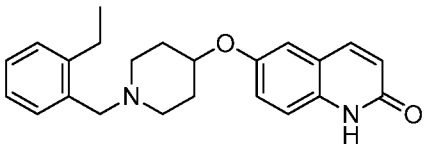
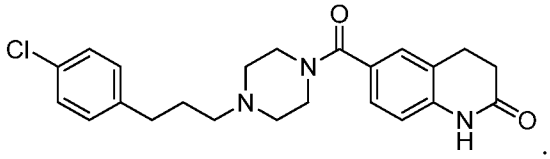

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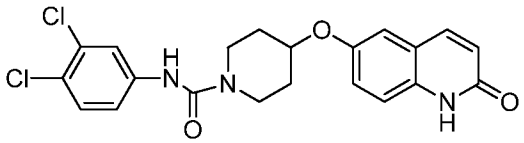
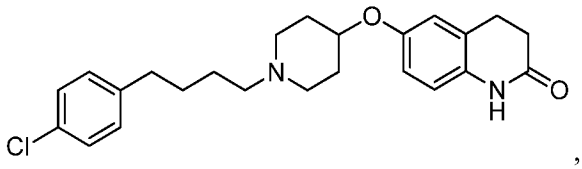
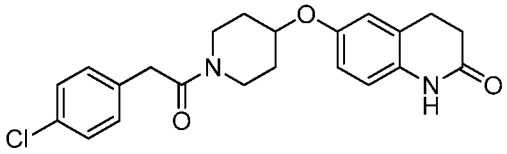
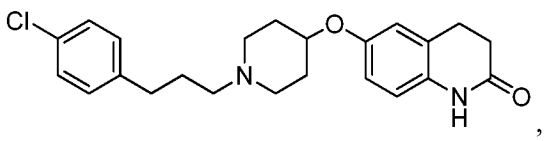
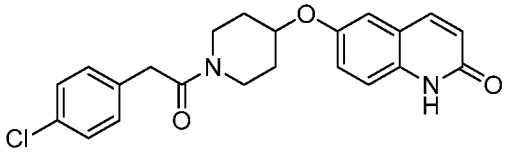
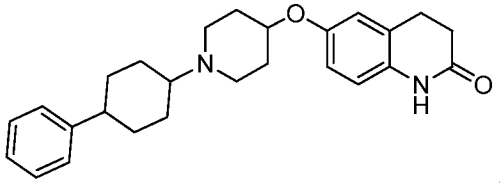
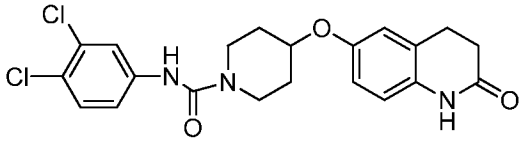
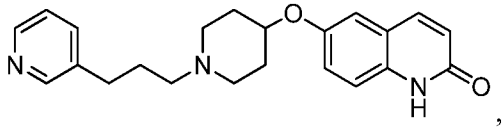
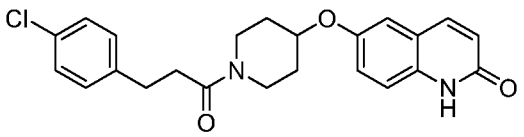
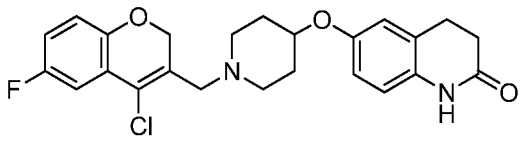
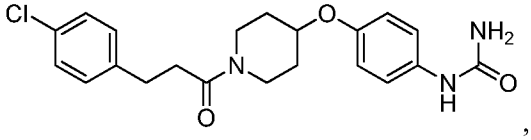
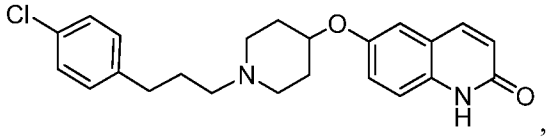
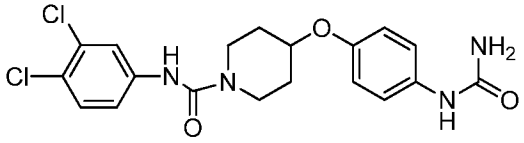
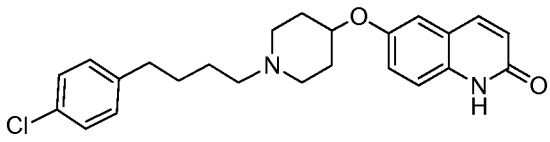
[00839] In one aspect, a compound can be present as:

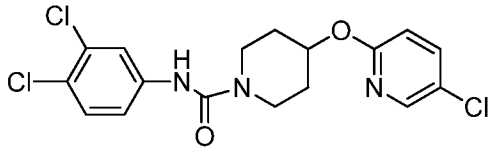
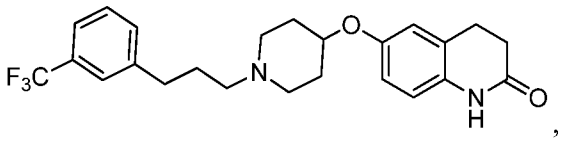
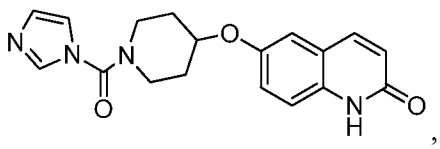
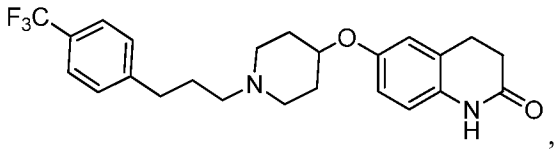
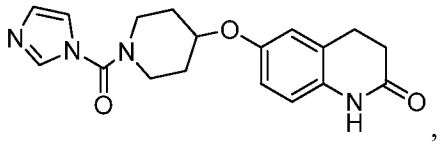
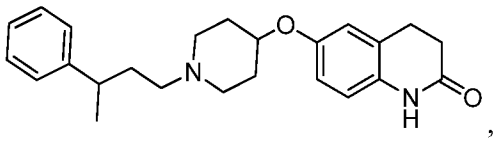
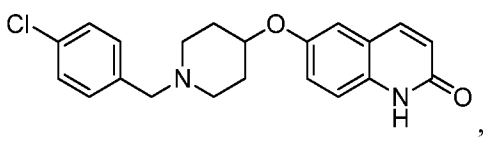
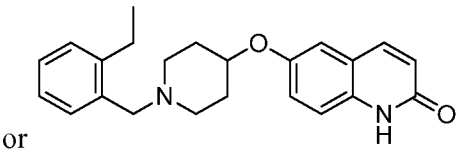

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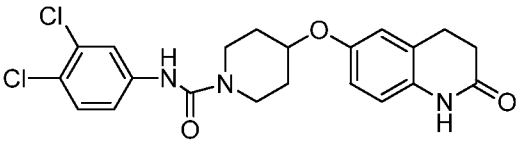
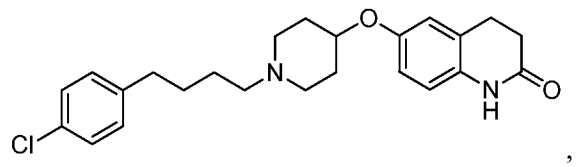
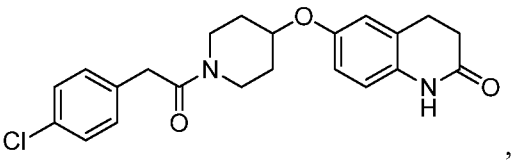
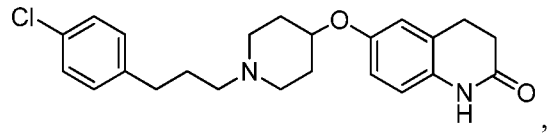
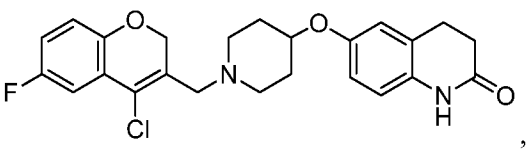
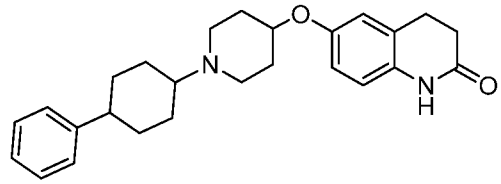
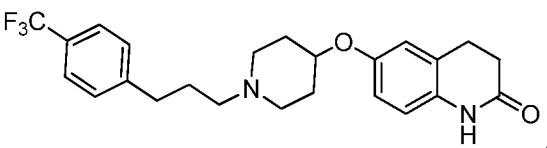
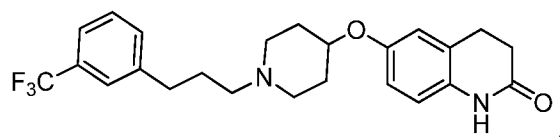
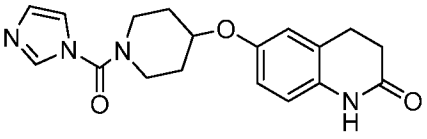
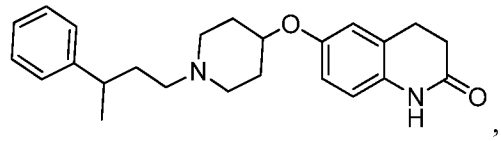

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[00840] In one aspect, a compound can be present as:

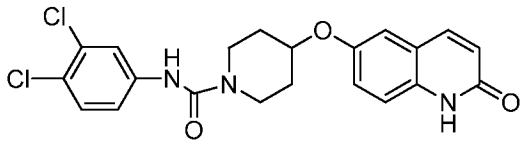
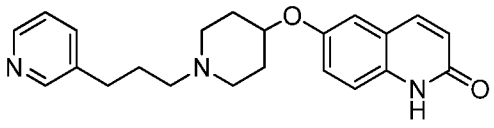
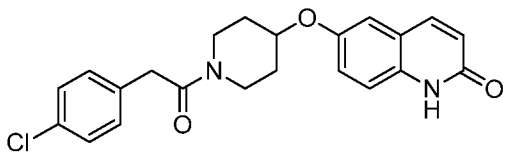
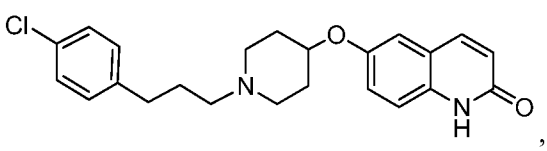
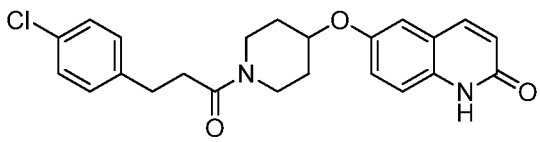
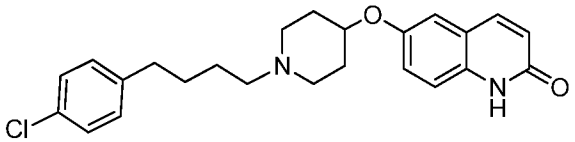
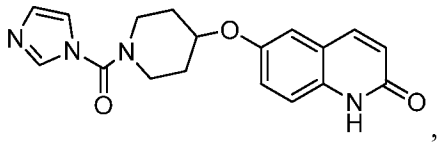
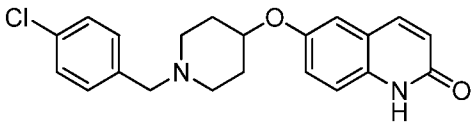
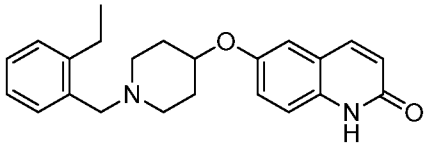

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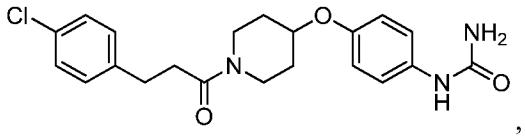
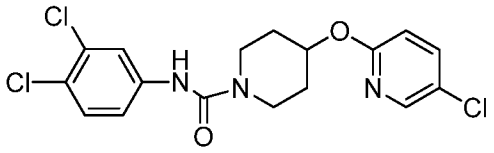
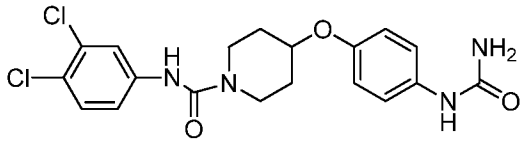
[00841] In one aspect, a compound can be present as:


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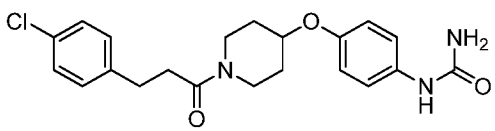
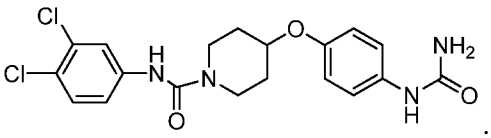
[00842] In one aspect, a compound can be present as:


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or

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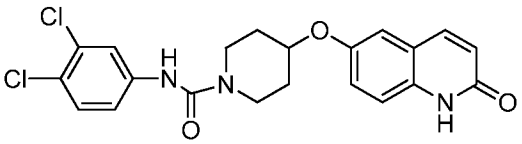
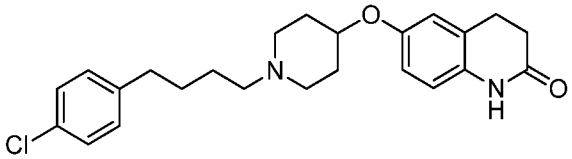
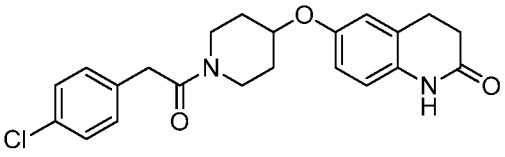
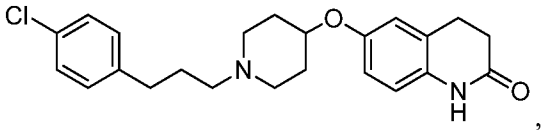
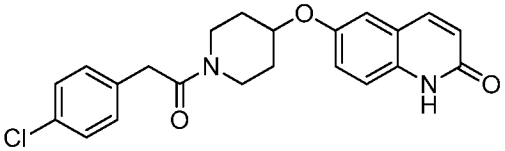
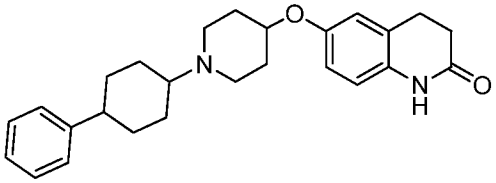
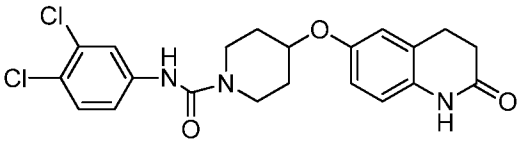
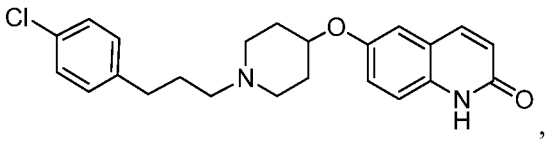
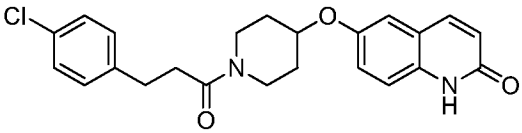
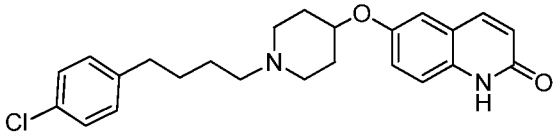
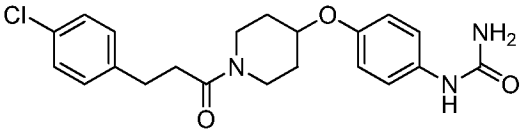
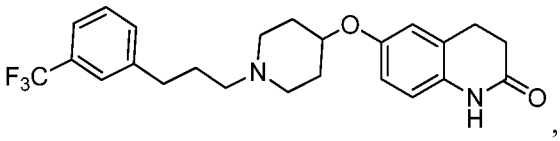
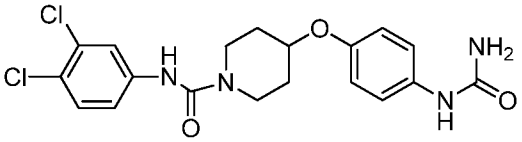
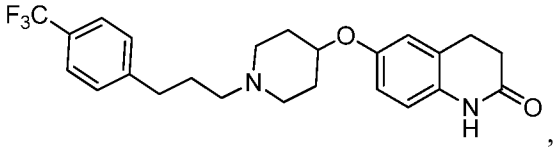
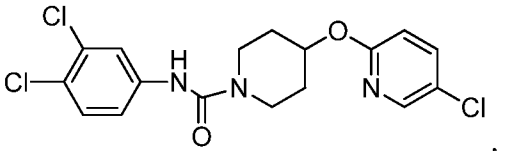
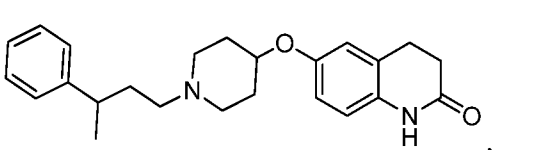
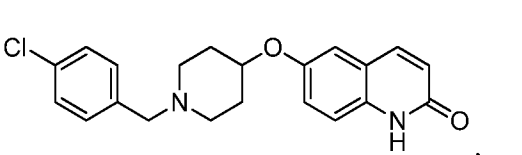
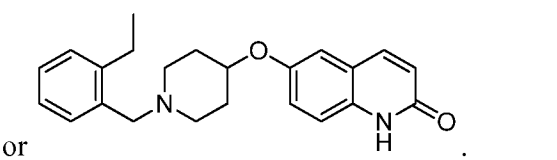
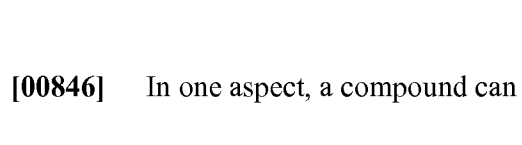
[00843] In one aspect, a compound can be present as:


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[00844] In one aspect, a compound can be present as:


or

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[00845] In one aspect, a compound can be present as:

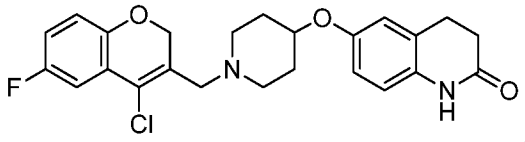
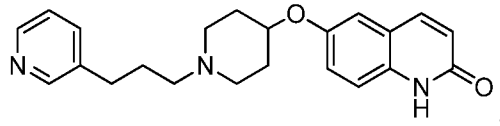

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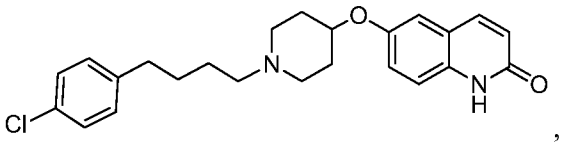
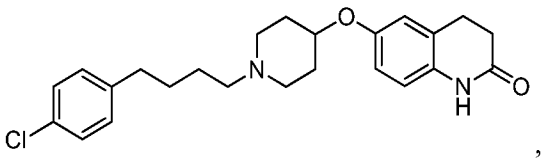
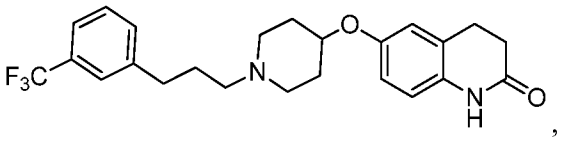
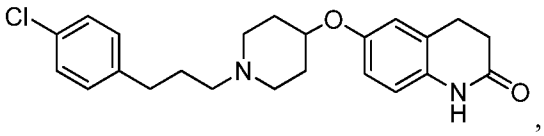
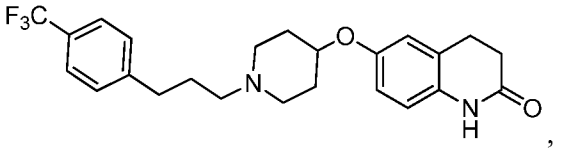
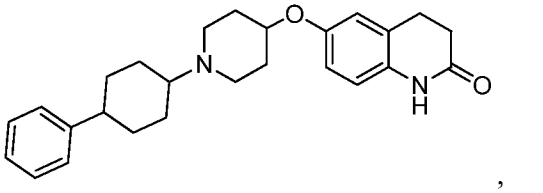
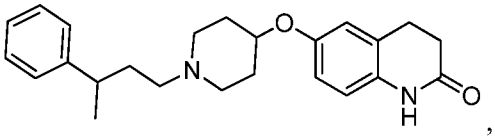
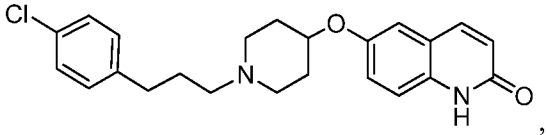
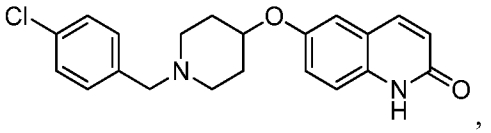
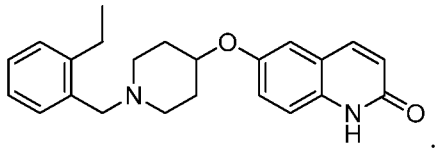
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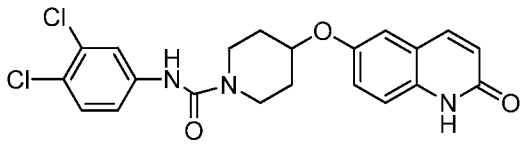
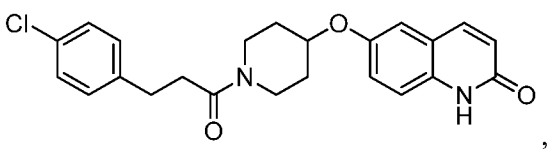
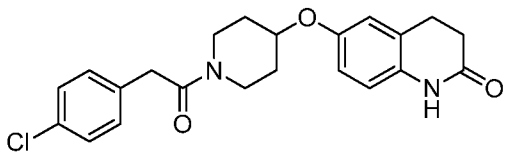
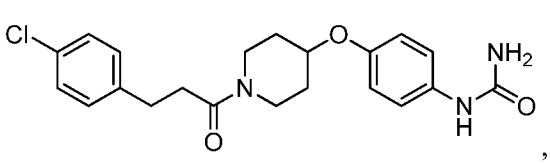
[00846] In one aspect, a compound can be present as:

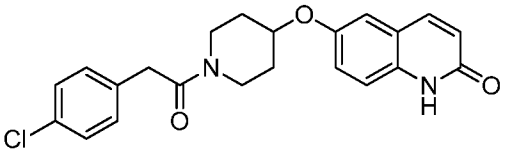
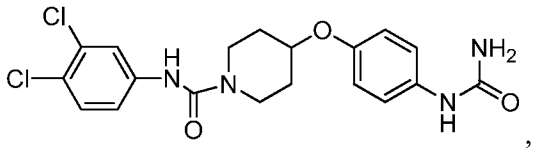
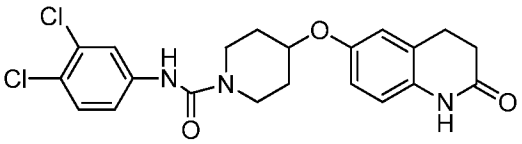
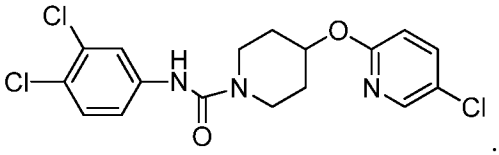

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[00847] In one aspect, a compound can be present as:

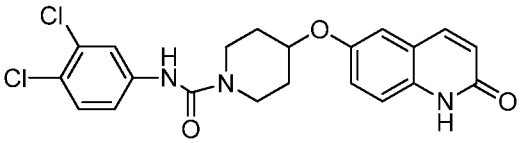
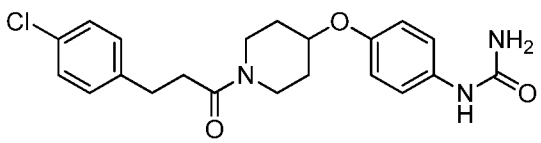
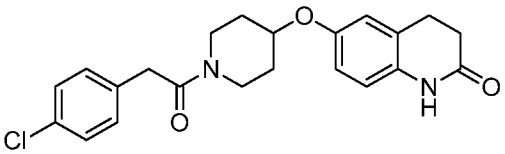
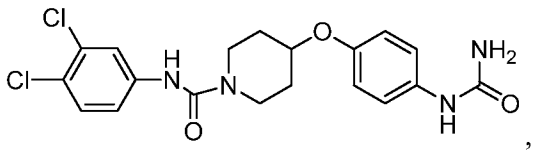
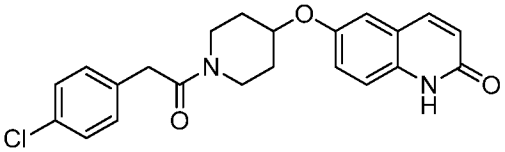
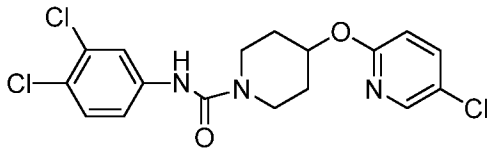
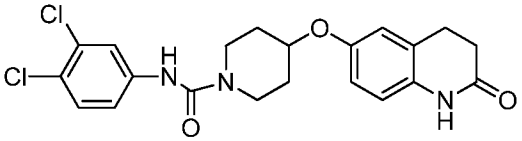
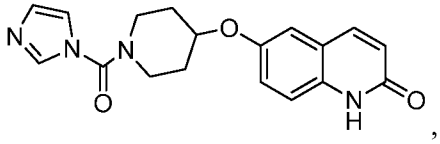
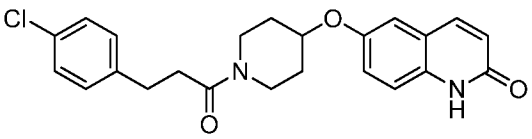
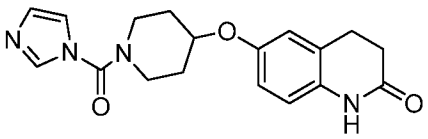

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[00848] In one aspect, a compound can be present as:

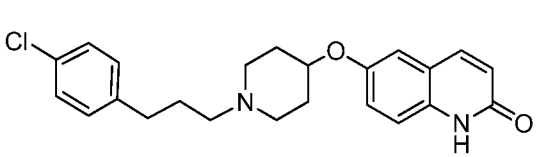
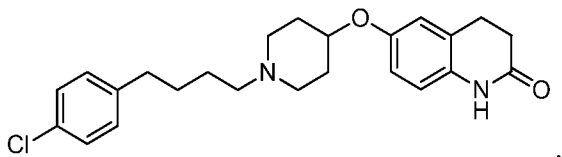

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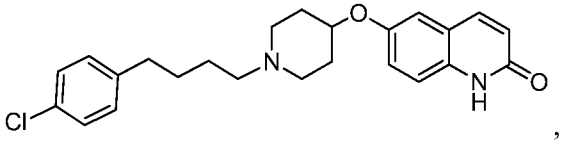
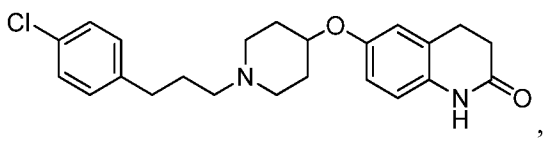
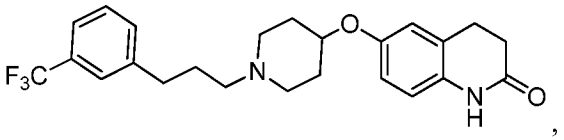
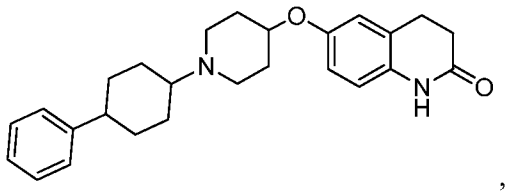
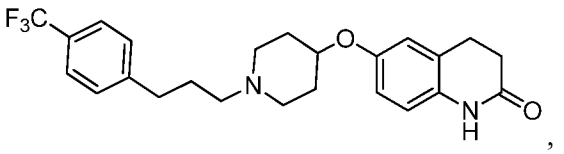
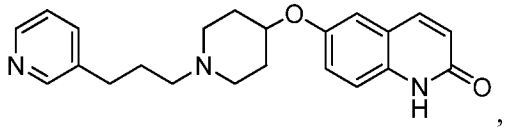
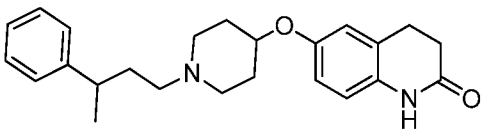
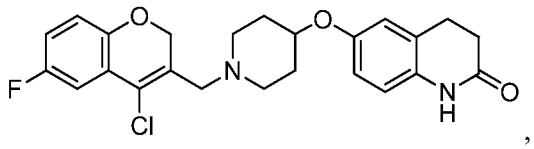
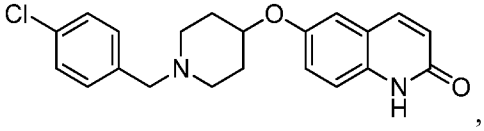
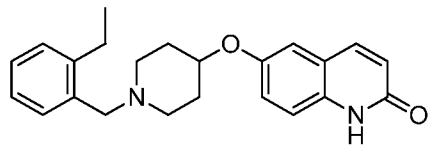

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or

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[00849] In one aspect, a compound can be present as:

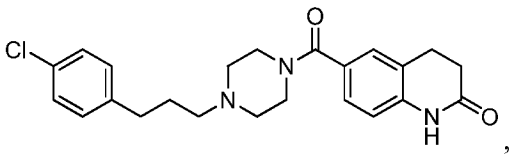
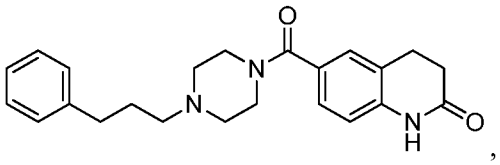
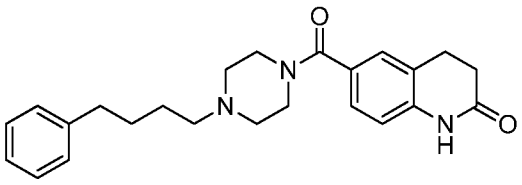
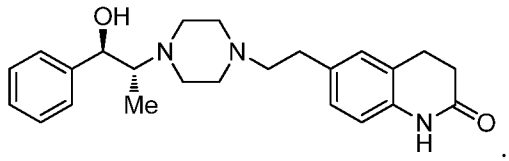

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[00850] In one aspect, a compound can be present as:

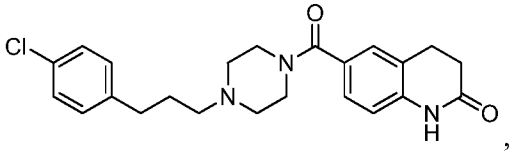
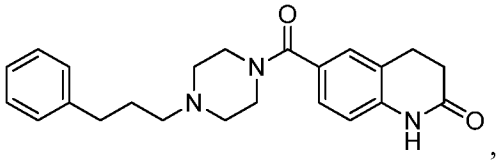

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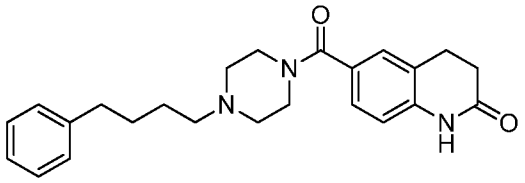

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[00851] In one aspect, a compound can be present as:


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or

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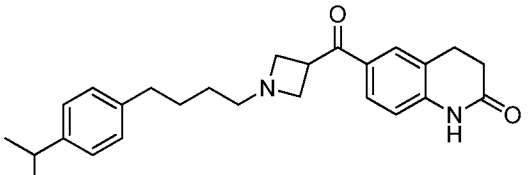
[00852] In one aspect, a compound can be present as:


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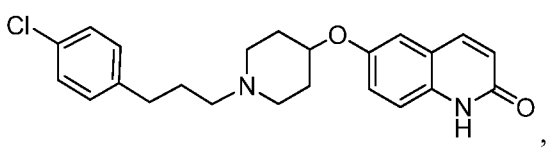


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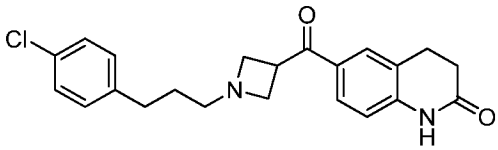
[00853] In one aspect, a compound can be present as:



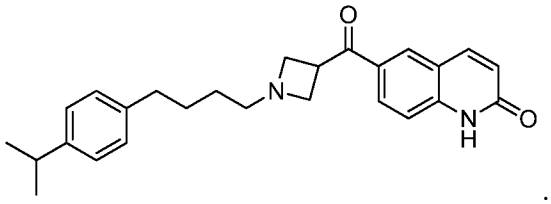
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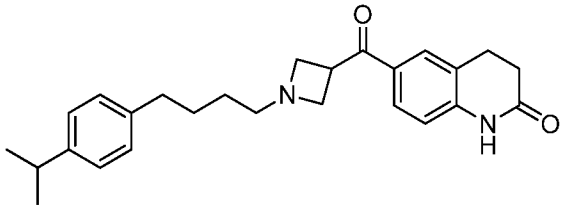


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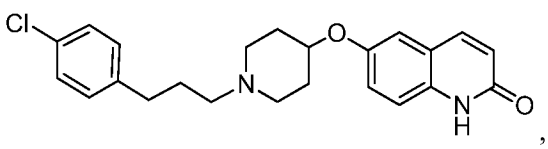


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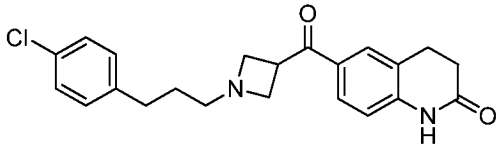
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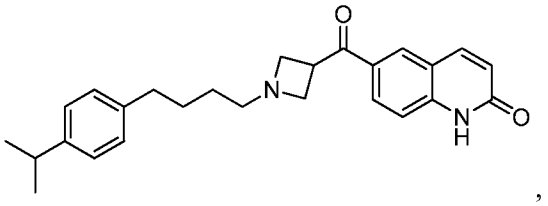
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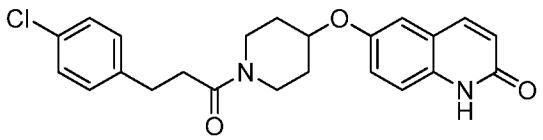
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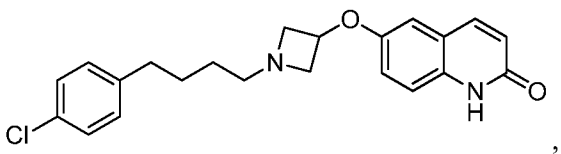
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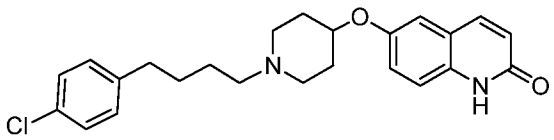
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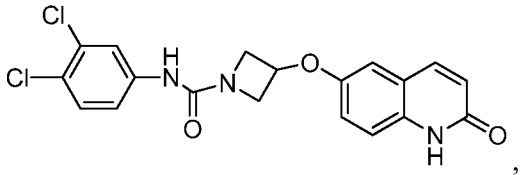
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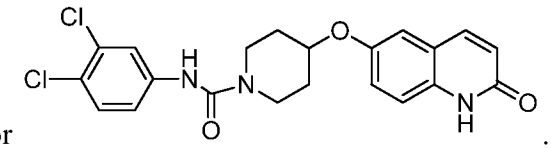
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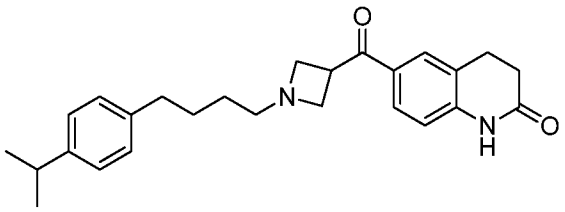
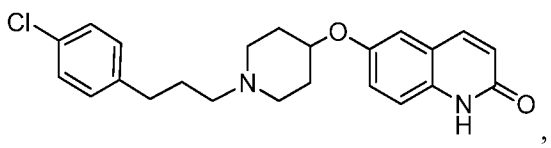
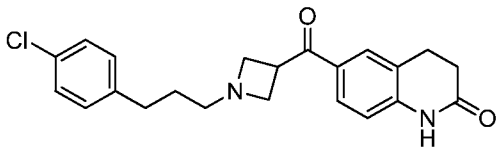
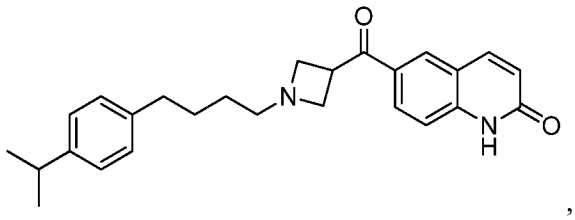
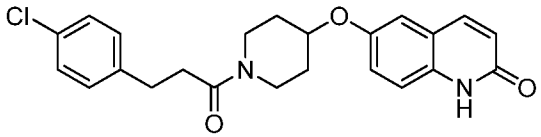
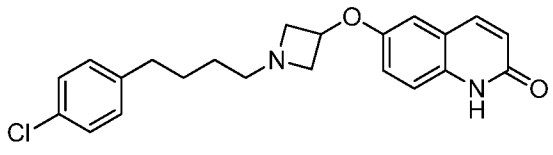
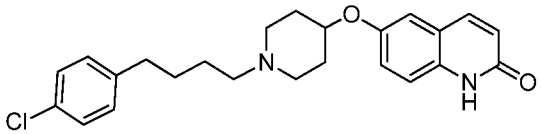
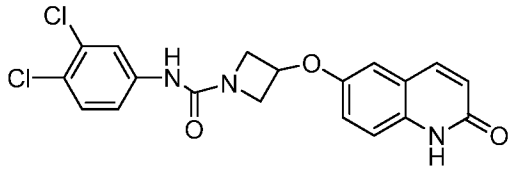
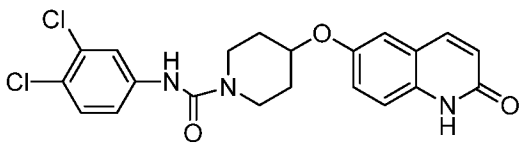
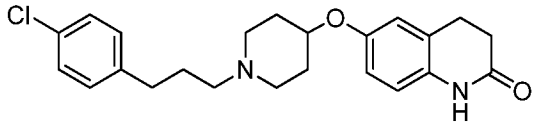
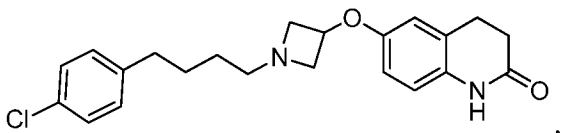
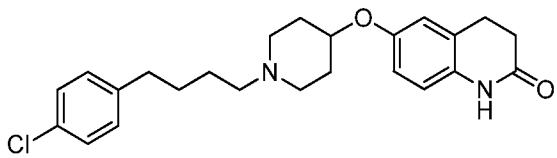
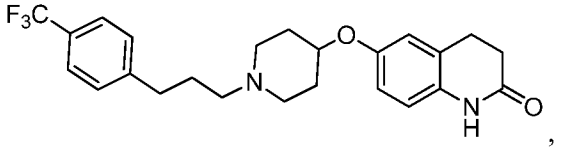
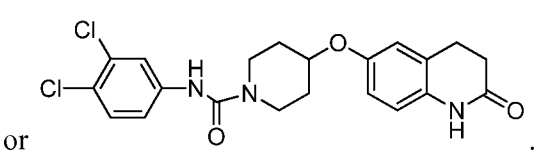
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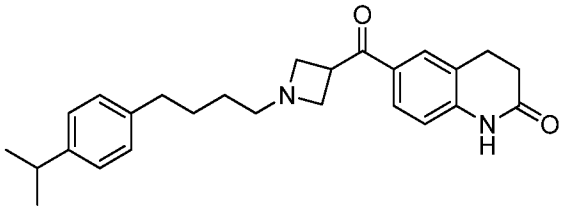
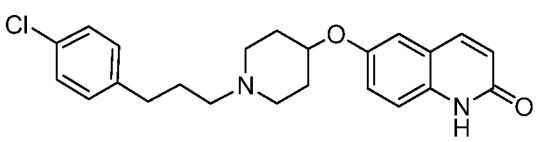
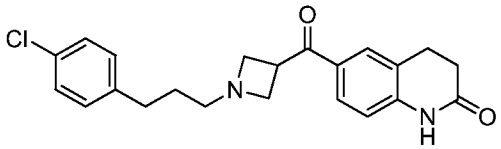
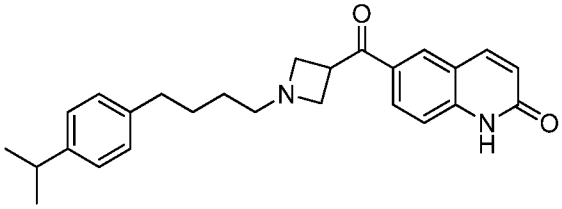
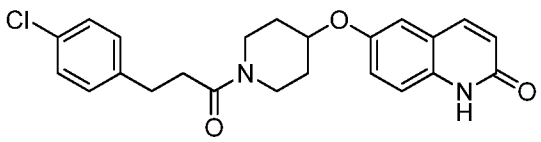
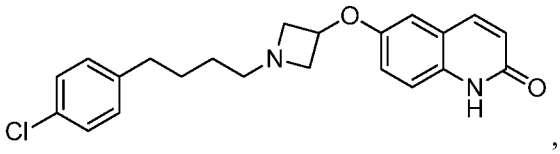
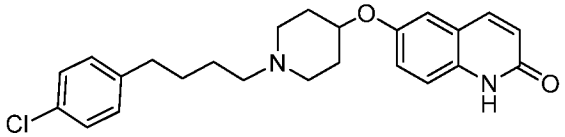
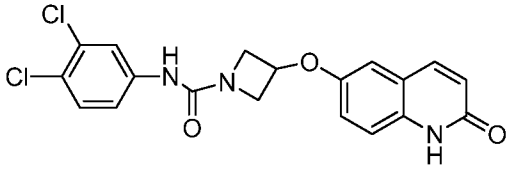
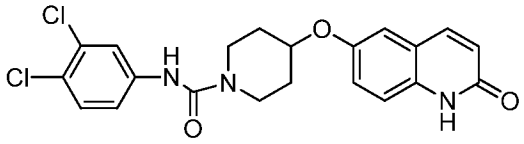
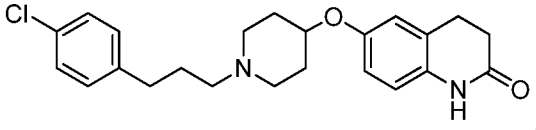
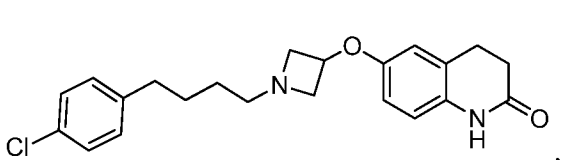
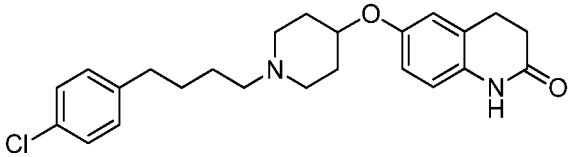
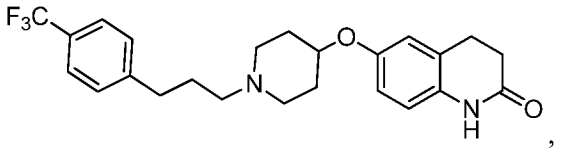
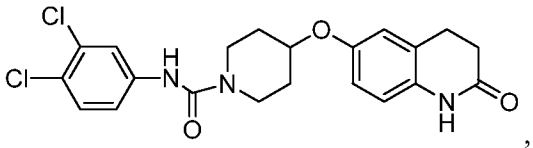
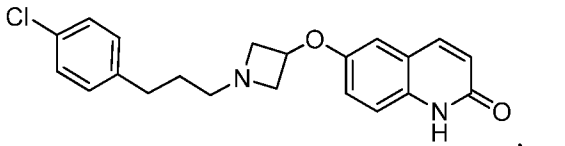
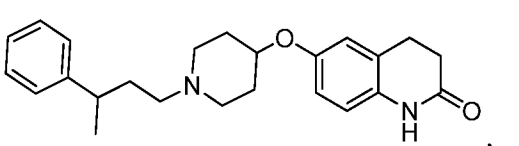
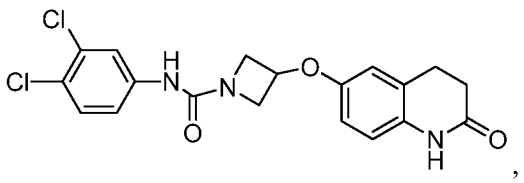
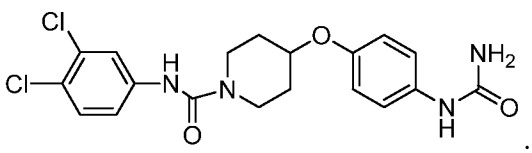
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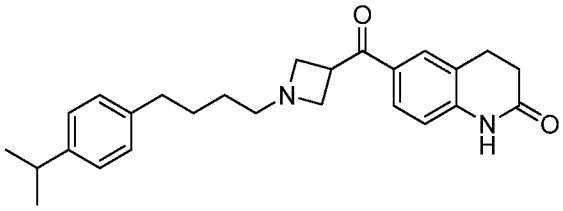
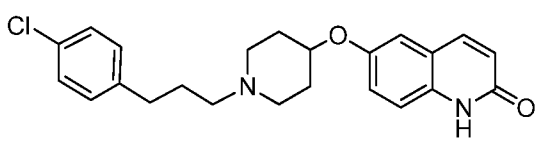
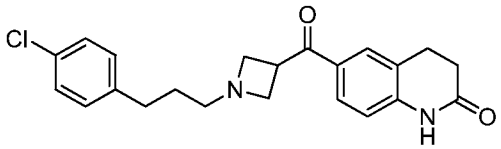
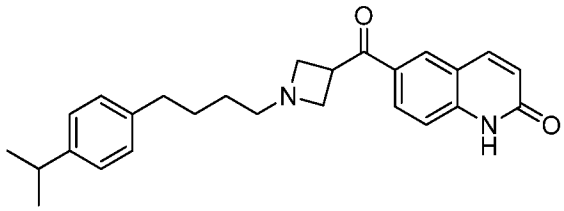
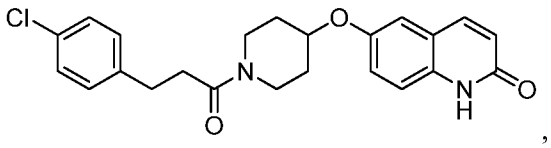
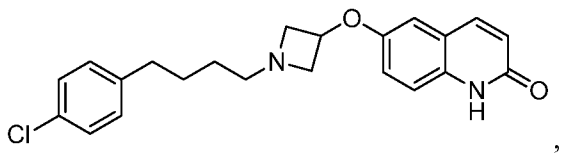
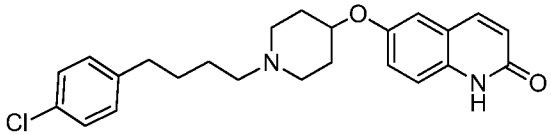
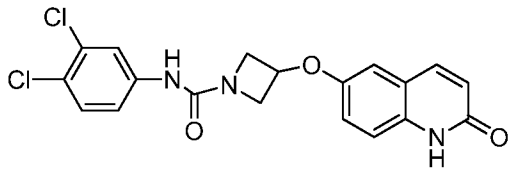
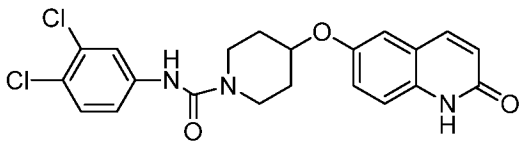
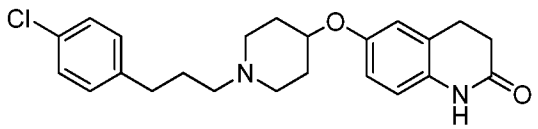
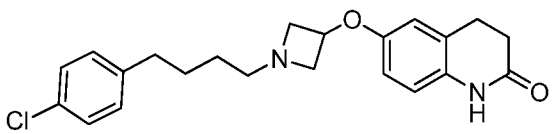
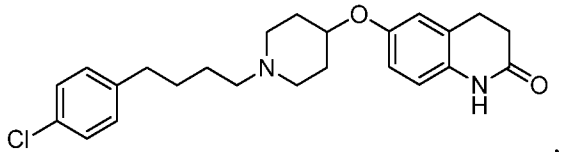
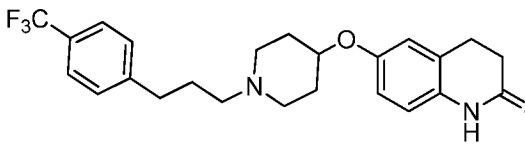
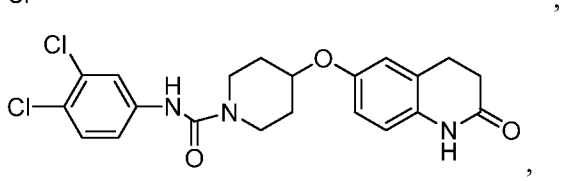
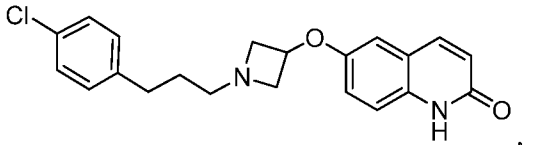
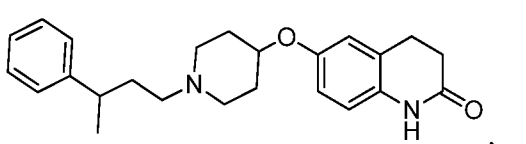
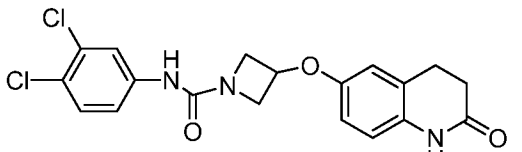
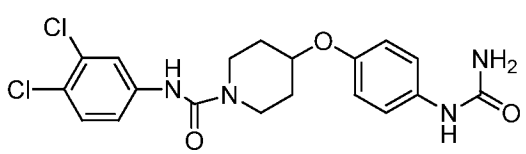
[00855] In one aspect, a compound can be present as:

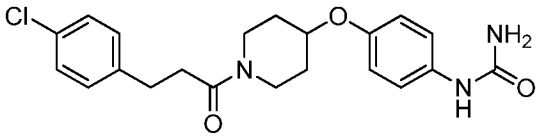
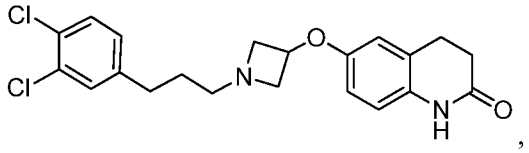
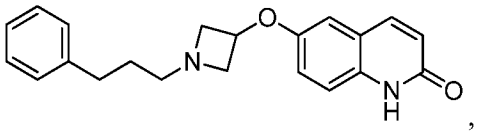
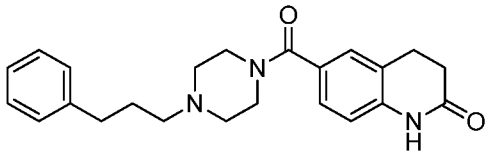
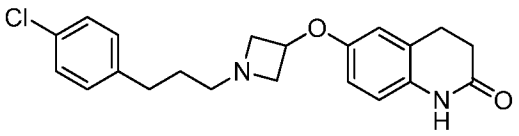
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[00856] In one aspect, a compound can be present as:

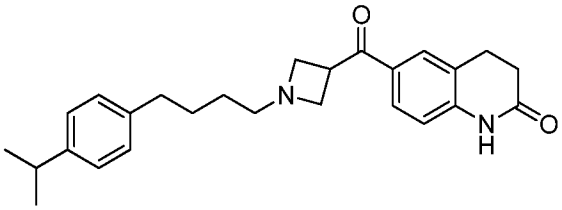
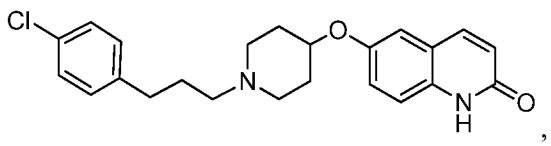
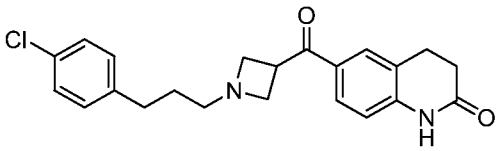
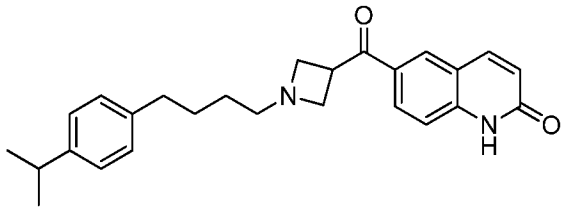
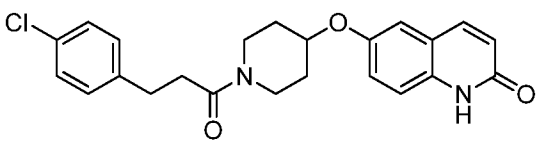
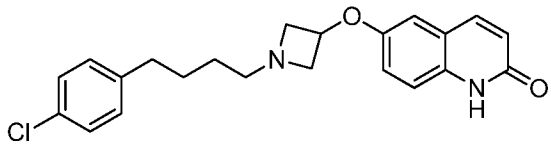
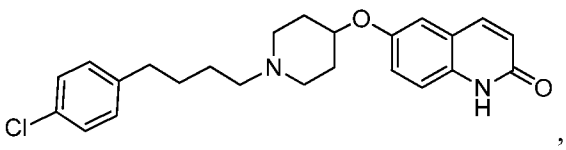
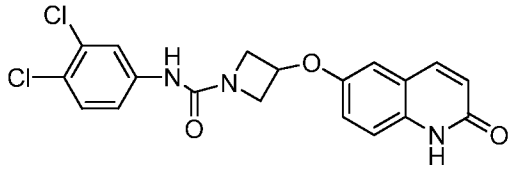
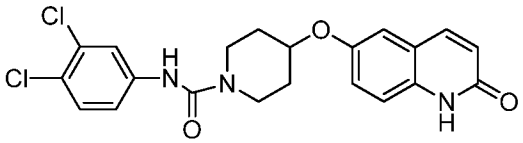
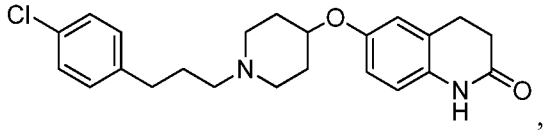
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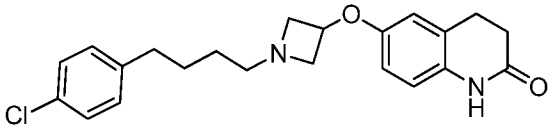
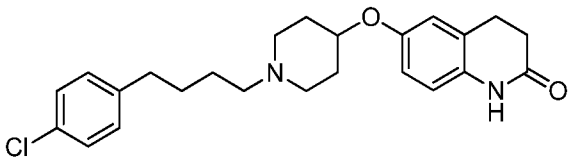
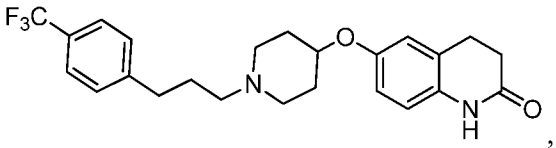
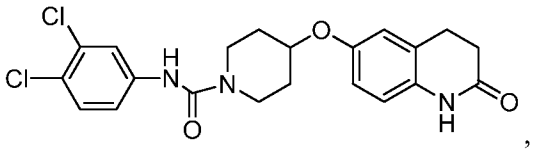
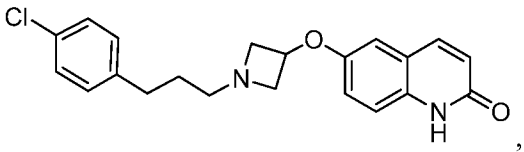
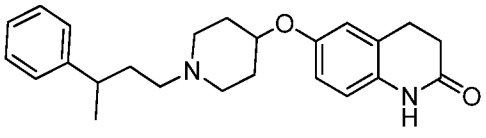
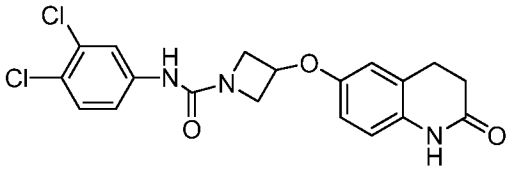
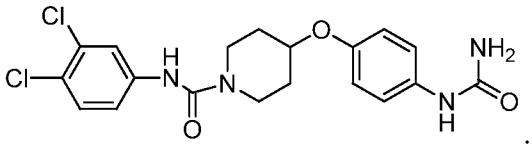
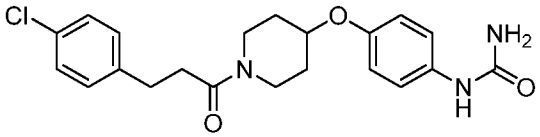
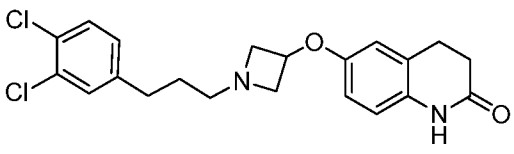
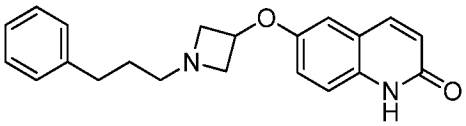
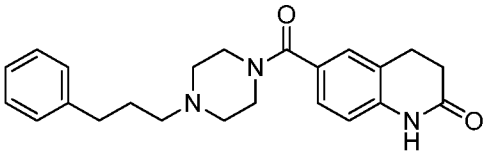
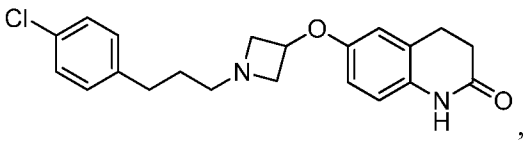
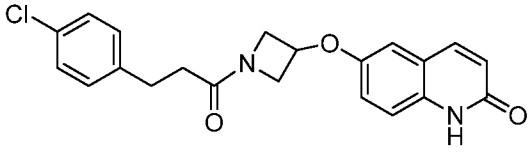
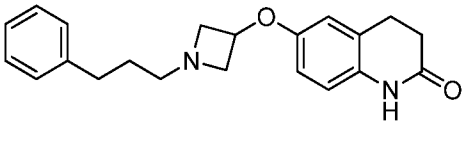
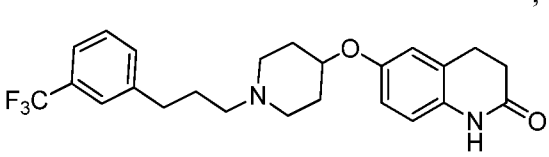
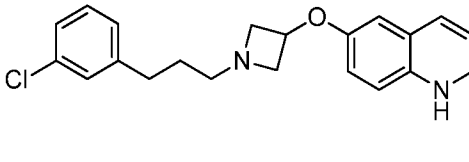
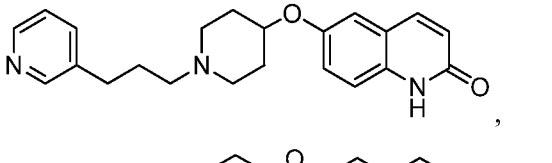
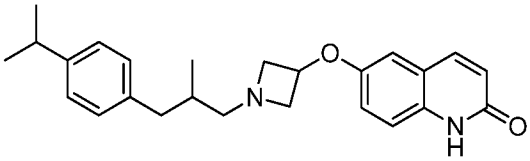
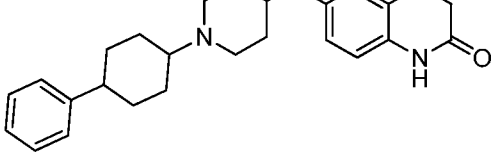
[00857] In one aspect, a compound can be present as:

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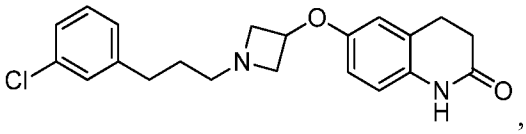
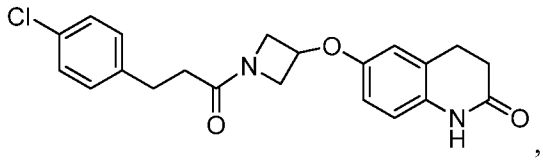
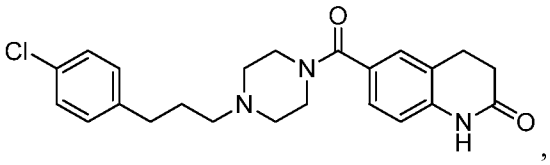
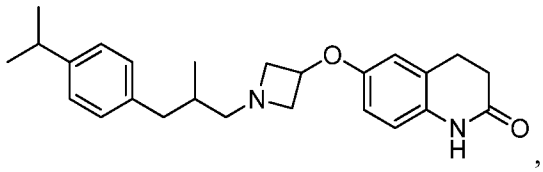
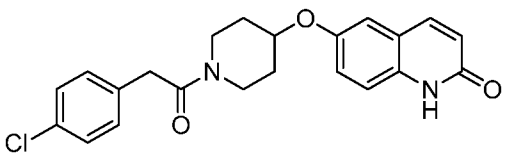
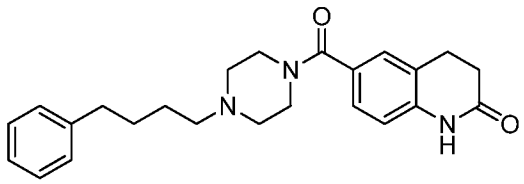
[00858] In one aspect, a compound can be present as:


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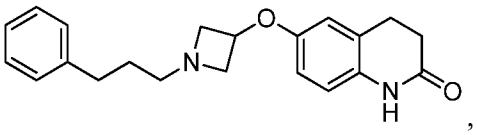
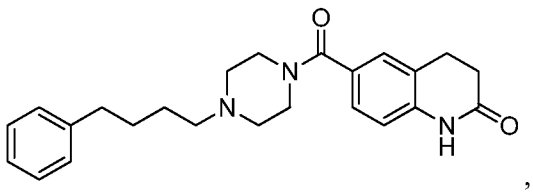
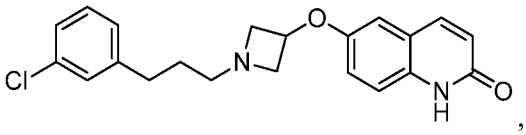
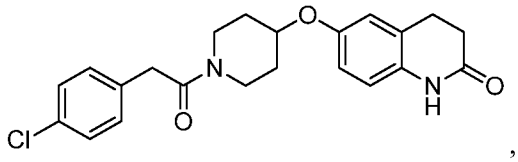
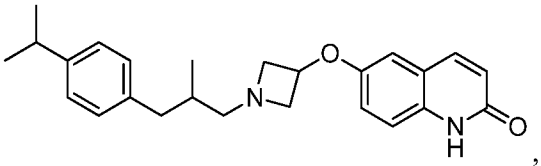
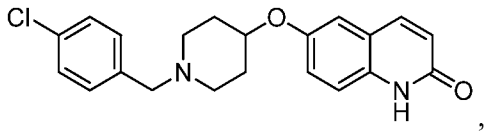
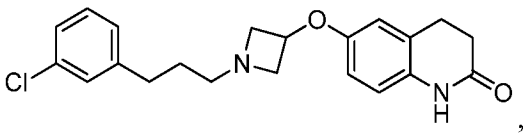
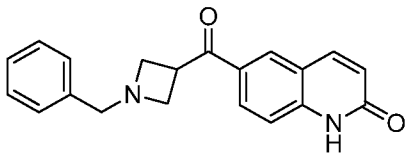
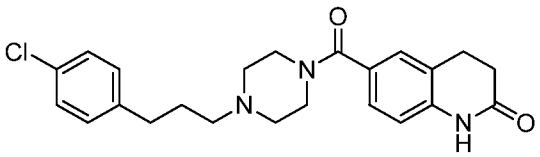
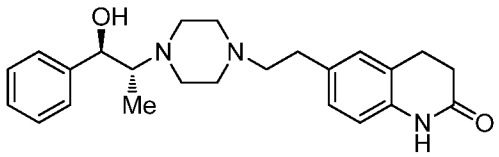

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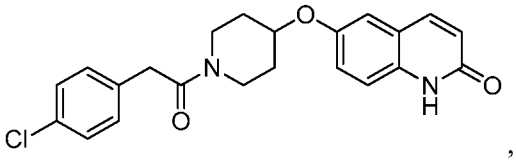
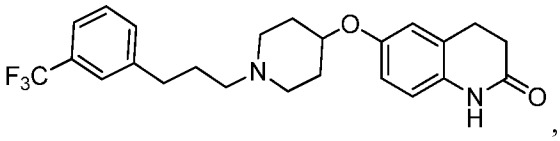
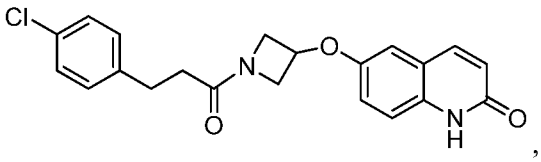
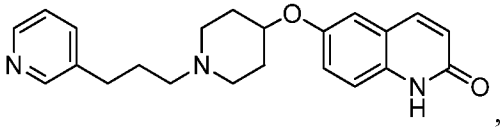
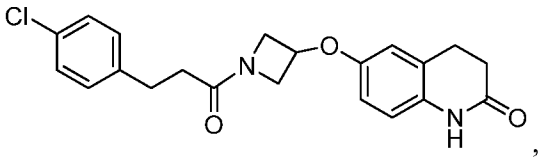
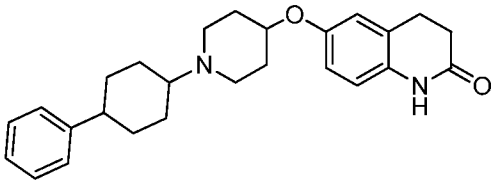
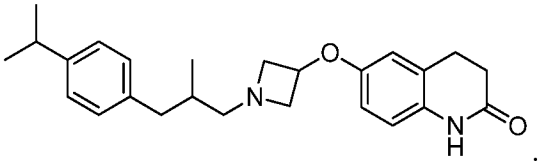
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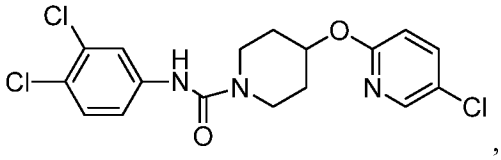
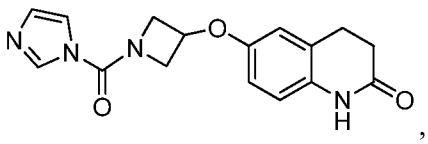
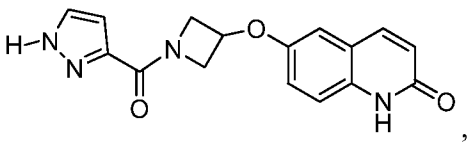
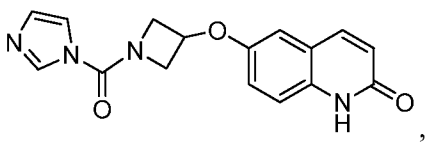
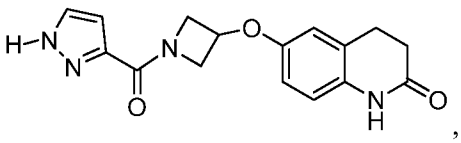
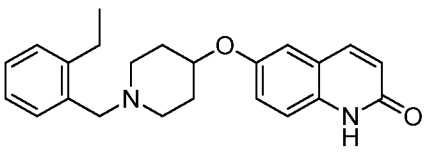
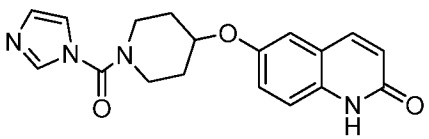
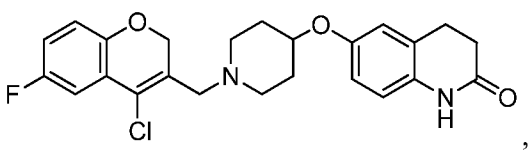
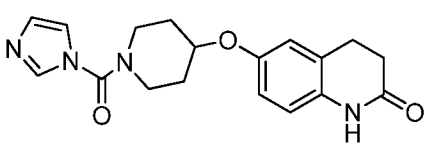
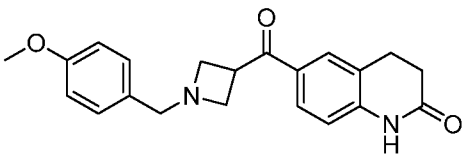

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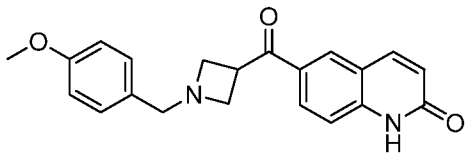
[00859] In one aspect, a compound can be present as:


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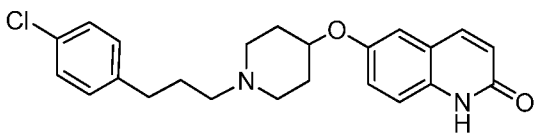
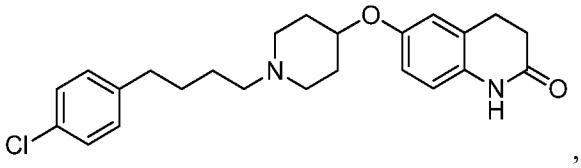
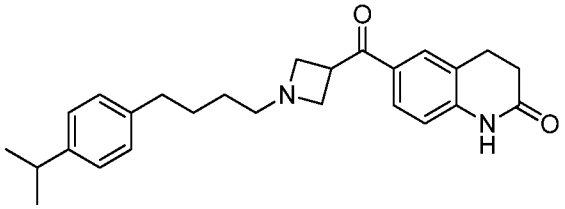
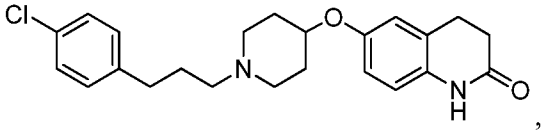
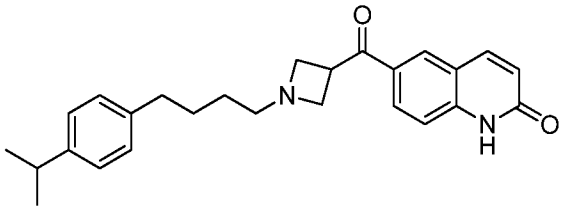
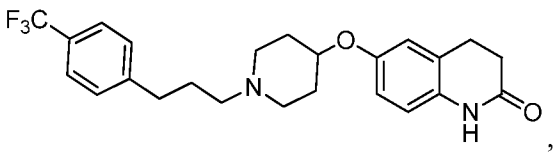
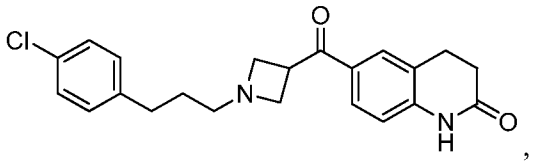
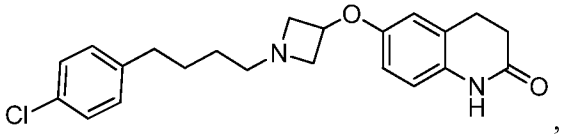
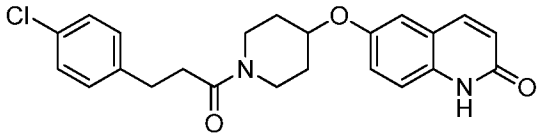
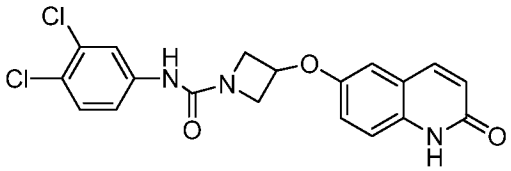
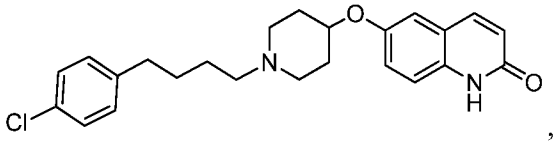
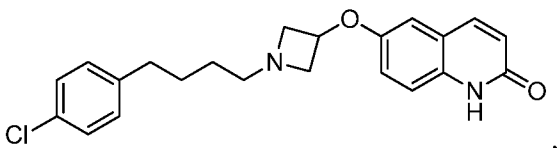
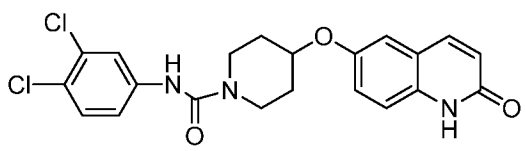
[00860] In one aspect, a compound can be present as:


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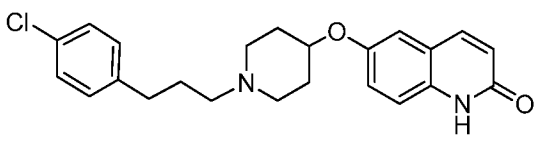
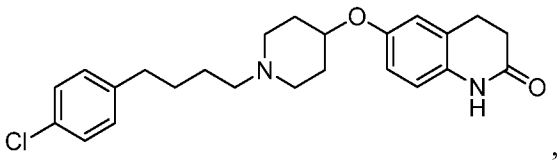
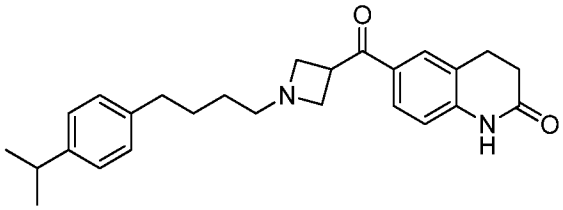
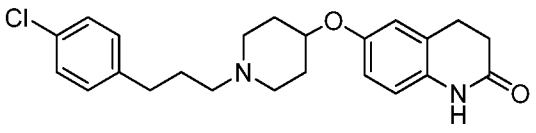
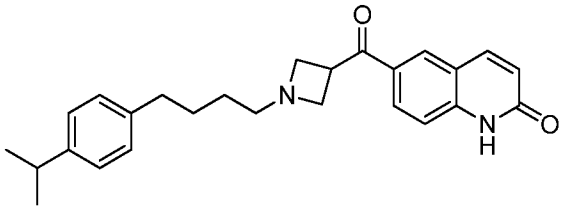
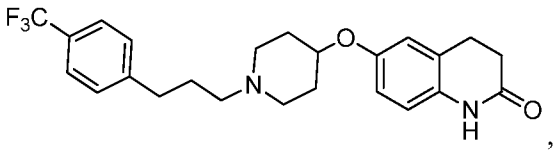
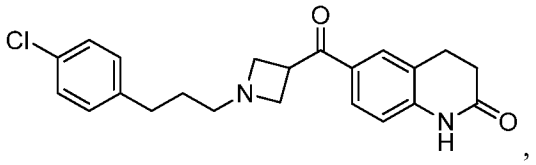
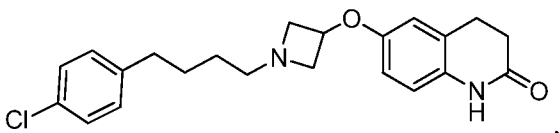
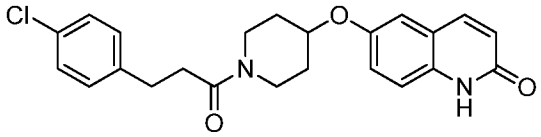
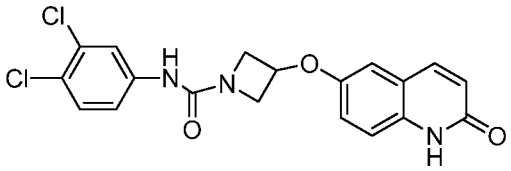
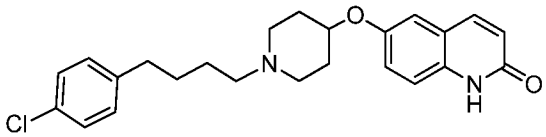
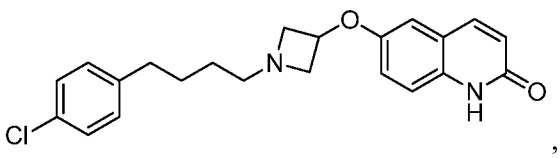
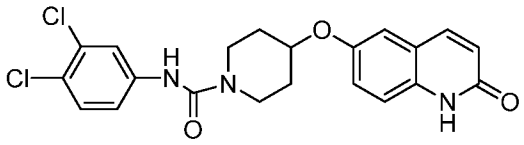
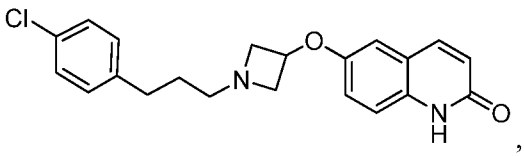
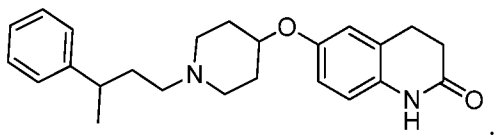
or .

[00861] In one aspect, a compound can be present as:

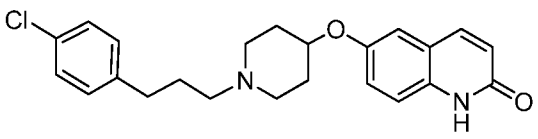
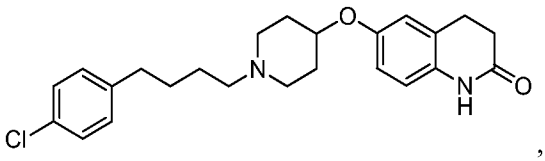
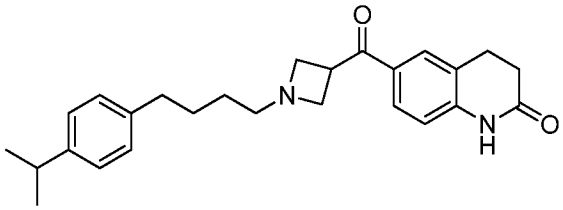
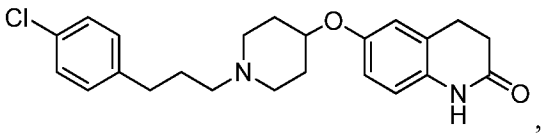
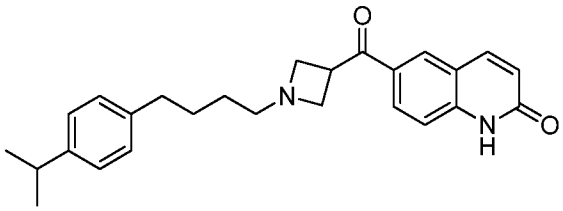
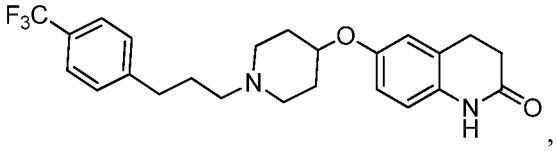
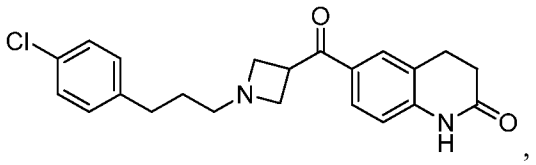
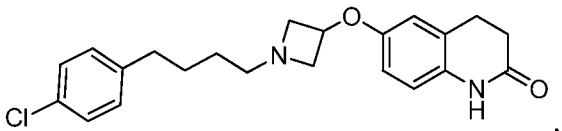
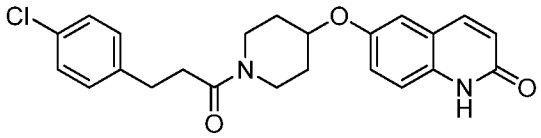
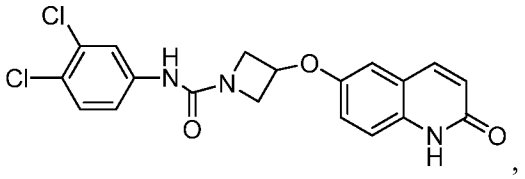
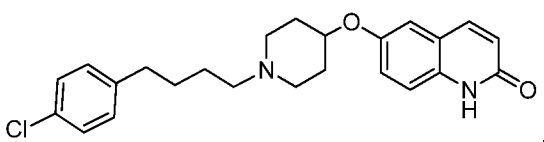
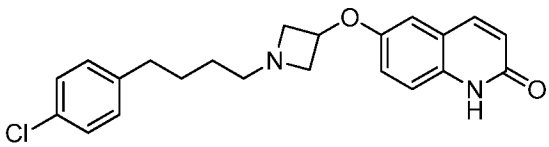
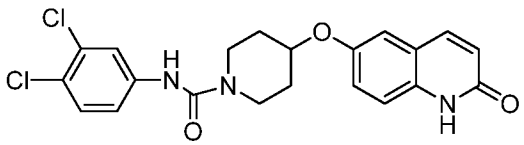
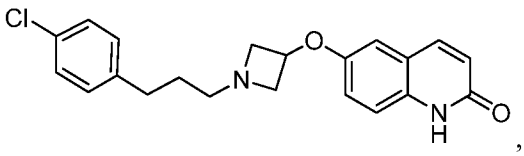
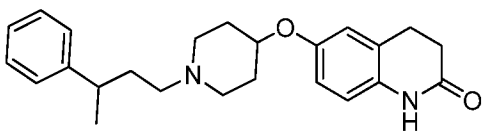
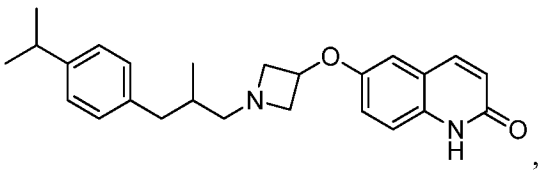
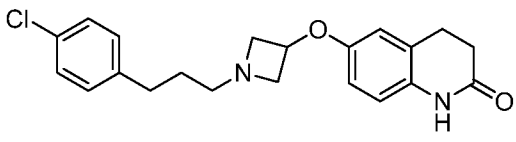
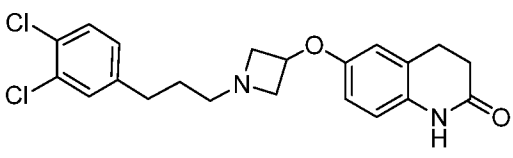
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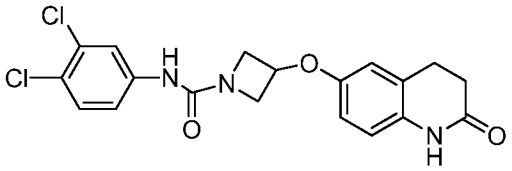
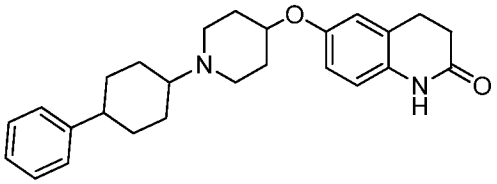
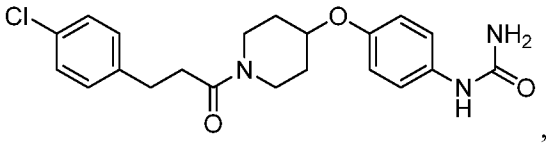
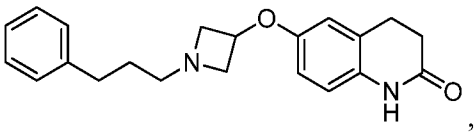
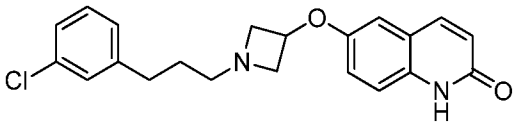
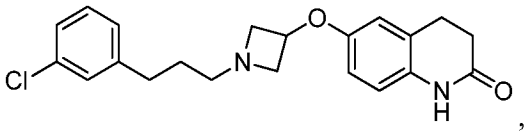
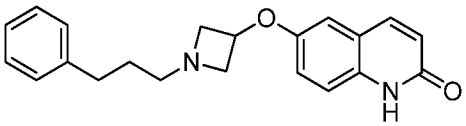
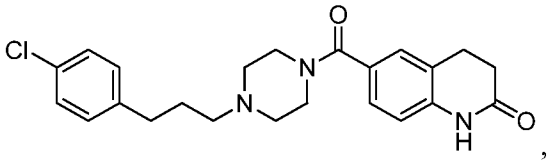
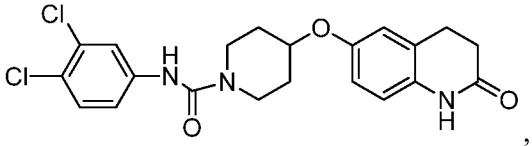
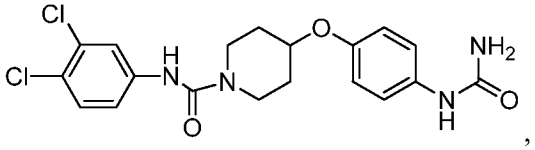
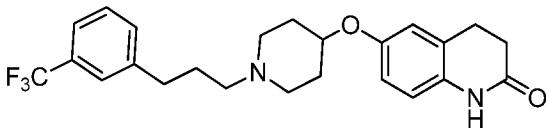
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[00862] In one aspect, a compound can be present as:

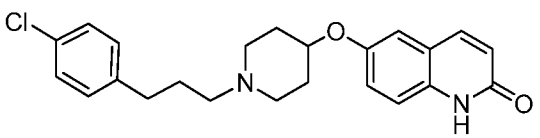
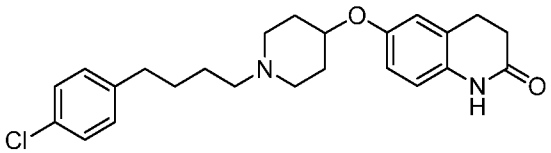
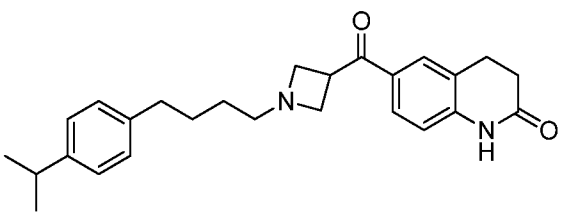
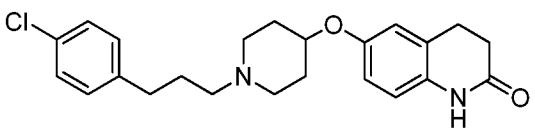

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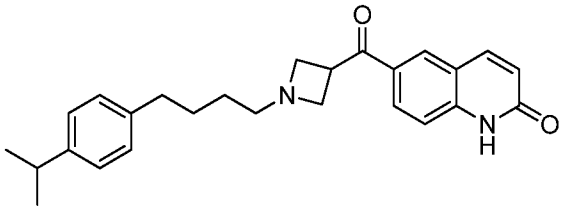
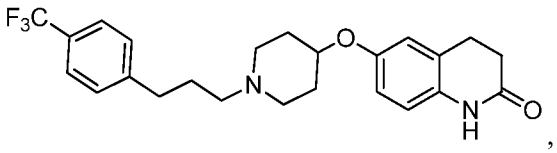
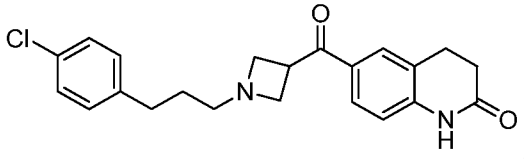
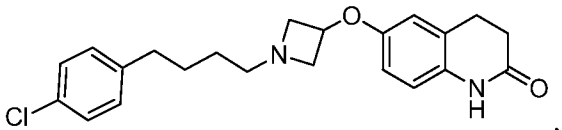
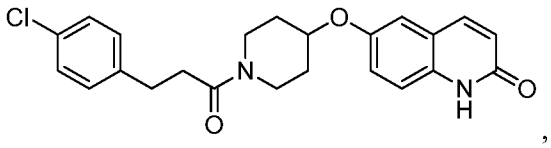
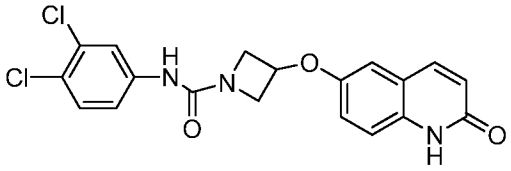
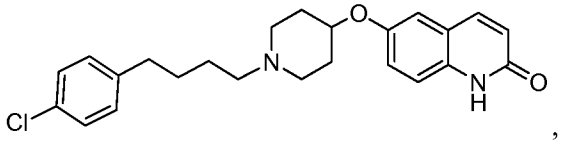
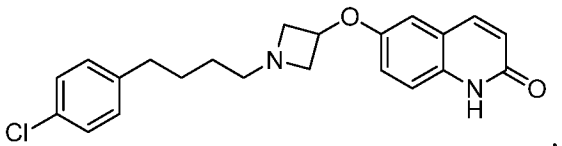
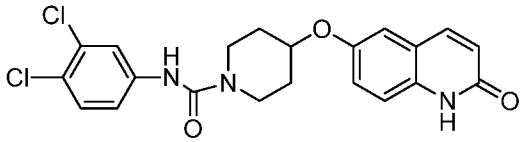
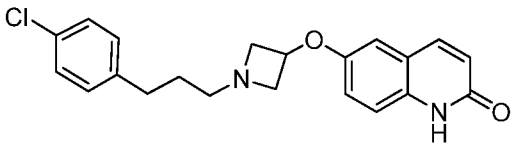
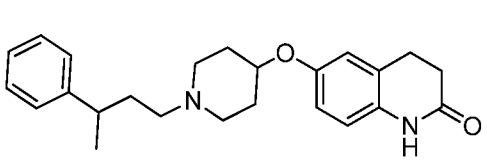
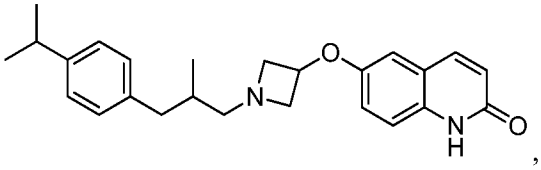
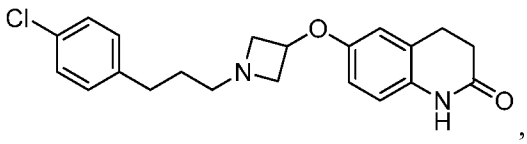
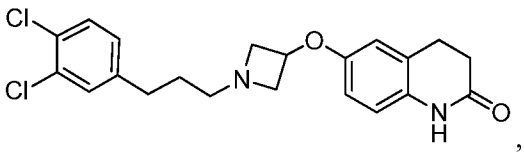
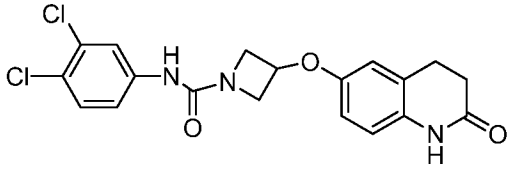
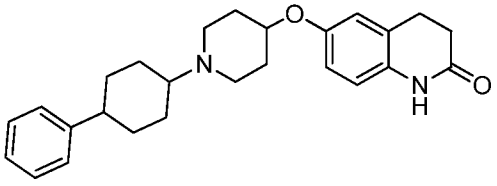
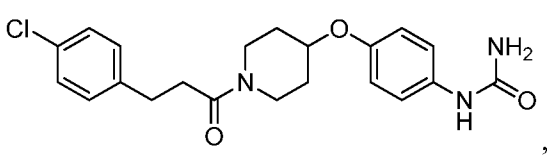
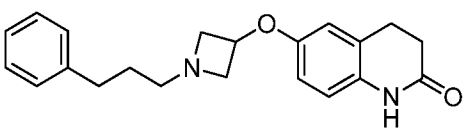
[00863] In one aspect, a compound can be present as:

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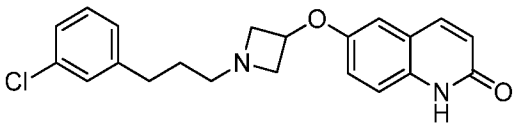
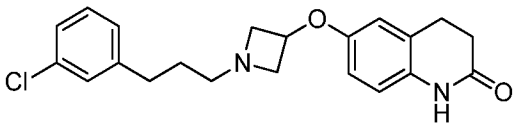
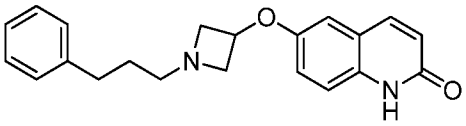
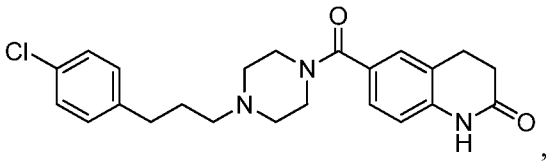
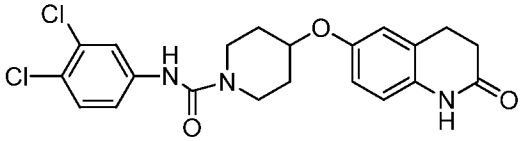
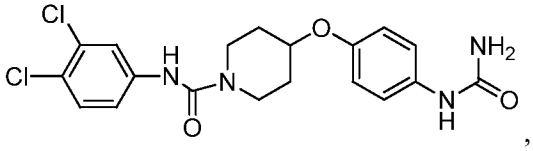
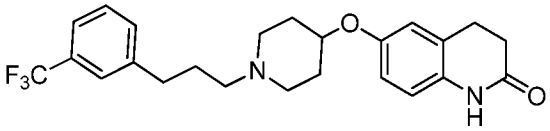
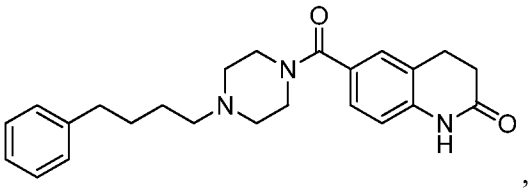
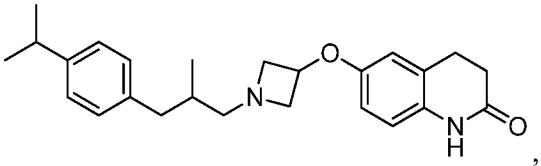
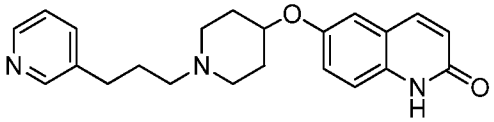
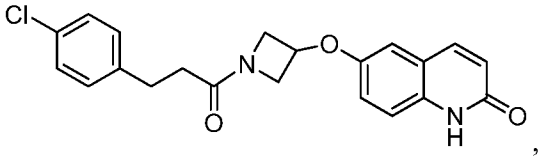
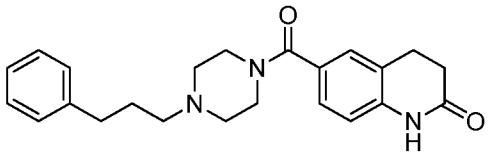
[00864] In one aspect, a compound can be present as:


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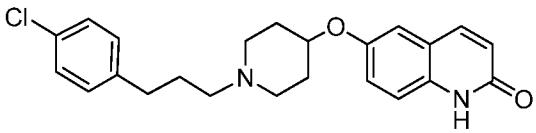
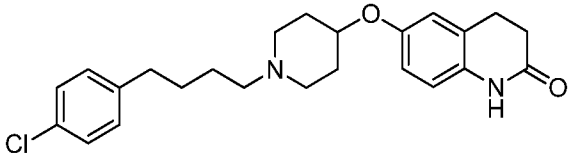
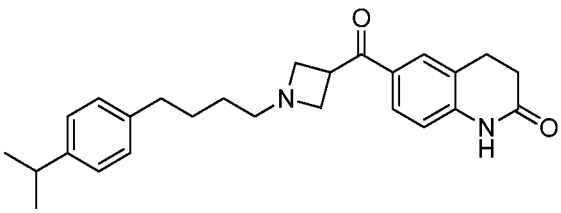
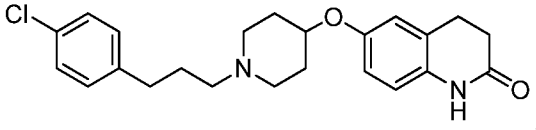

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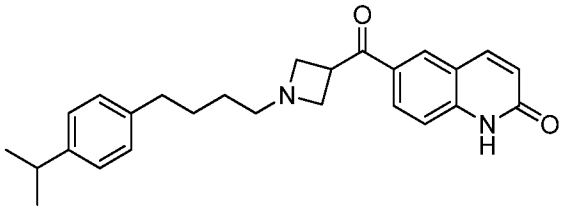
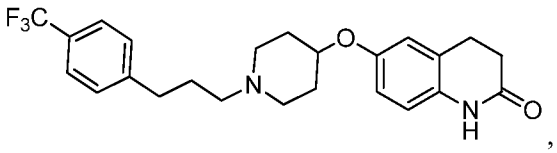
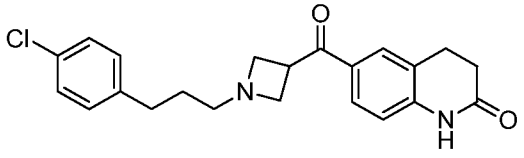
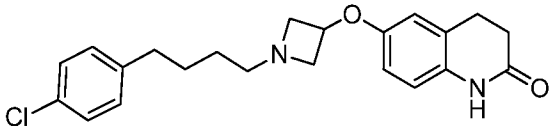
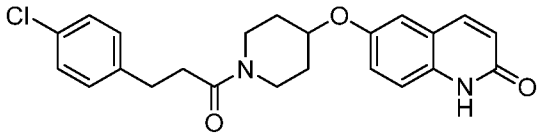
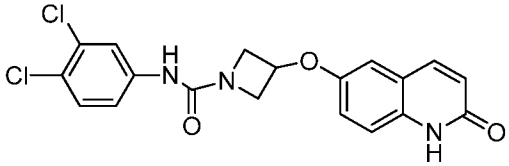
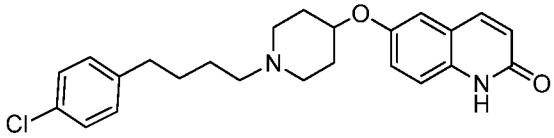
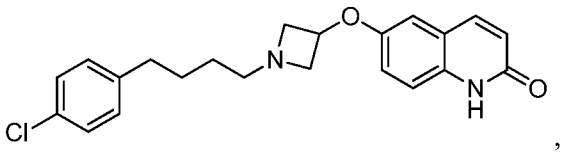
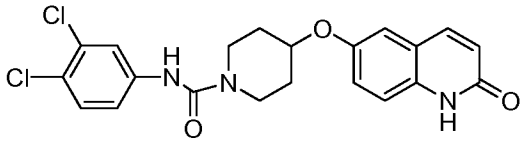
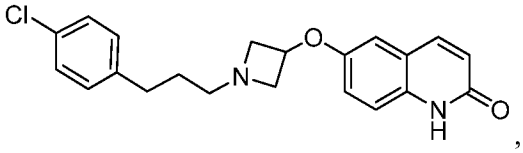
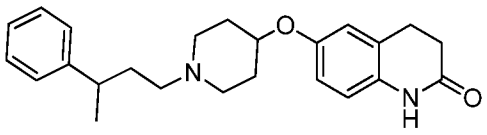
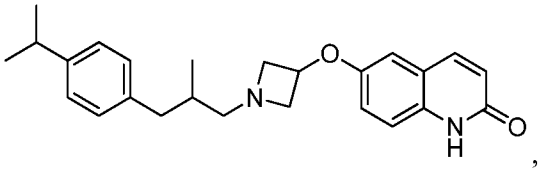
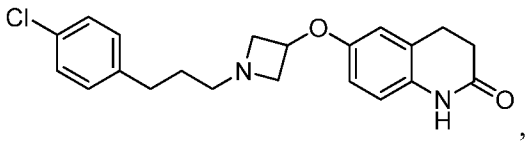
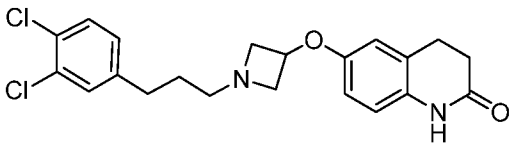
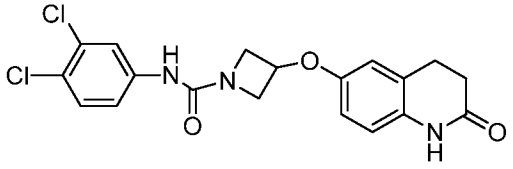
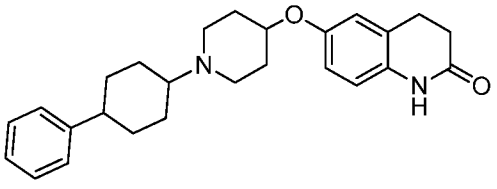
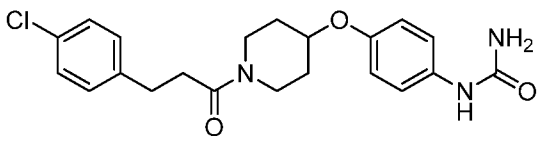
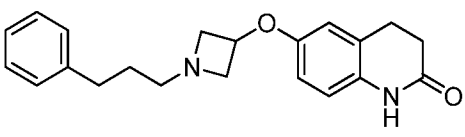
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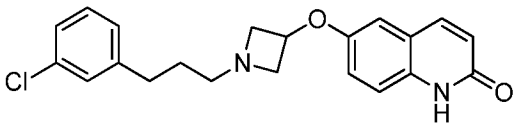
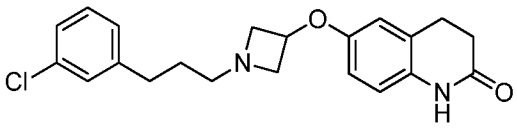
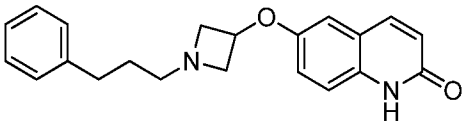
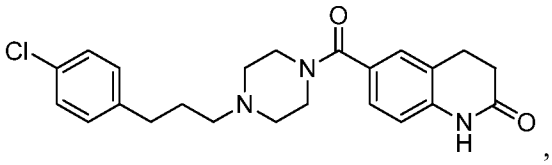
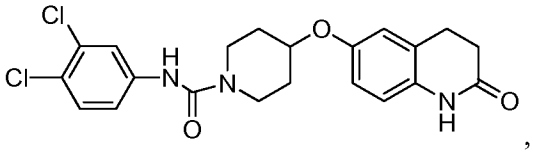
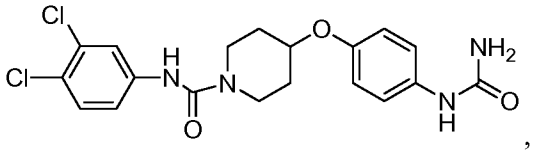
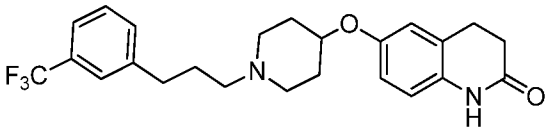
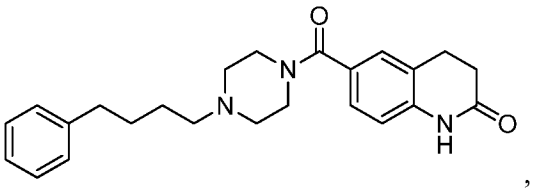
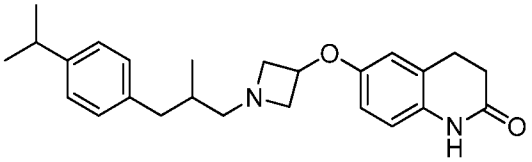
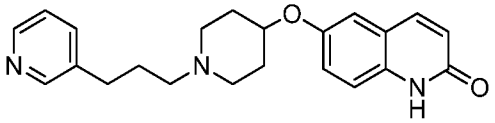
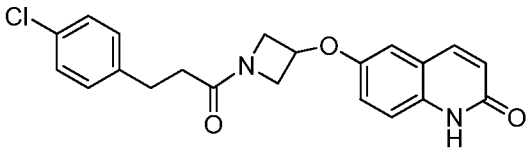
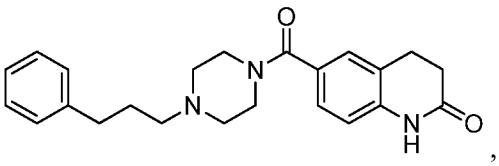
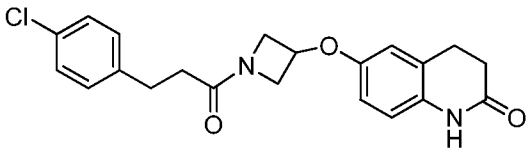
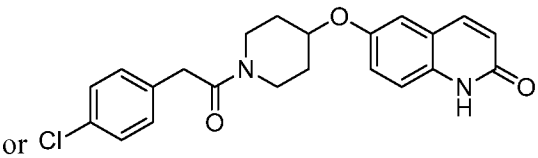
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[00865] In one aspect, a compound can be present as:

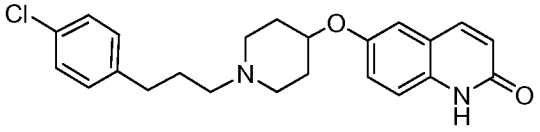
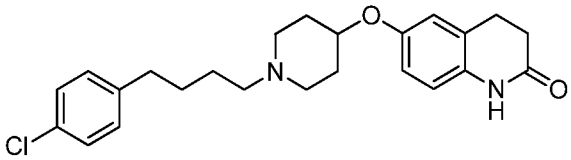
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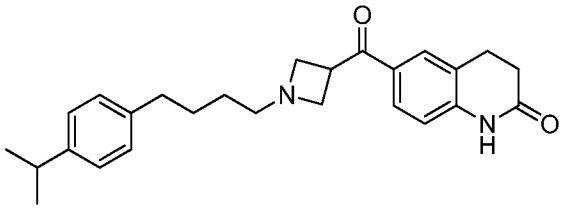
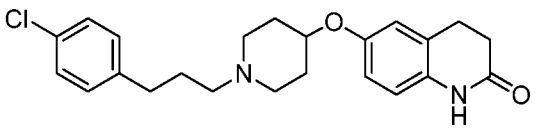
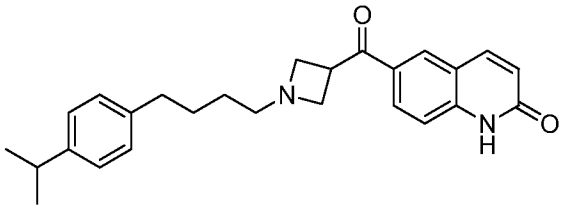
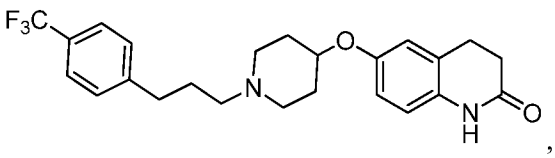
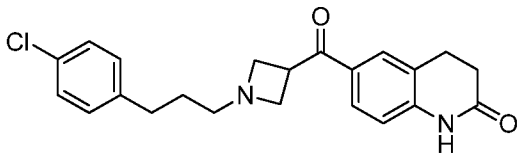
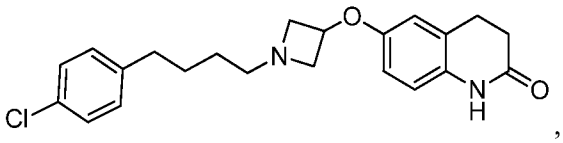
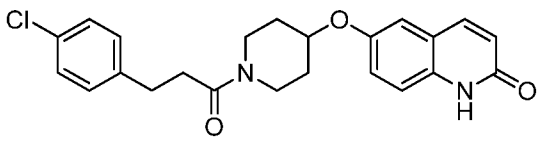
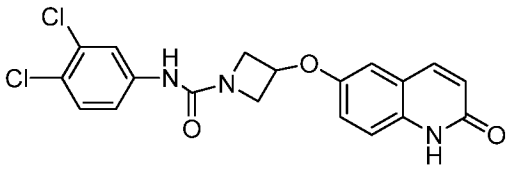
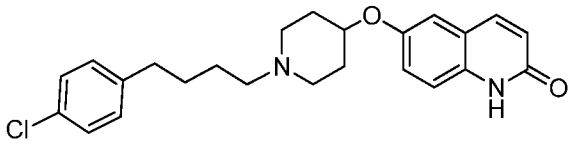
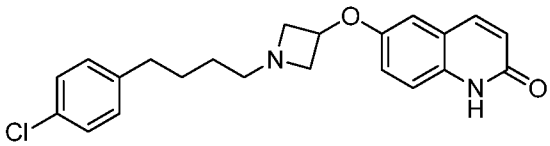
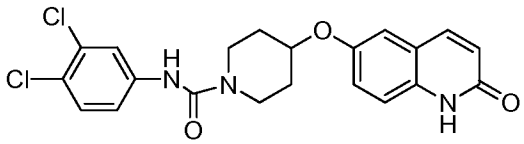
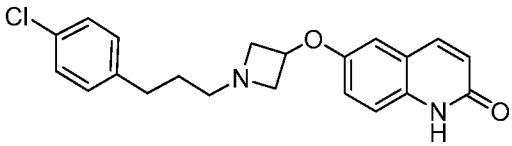
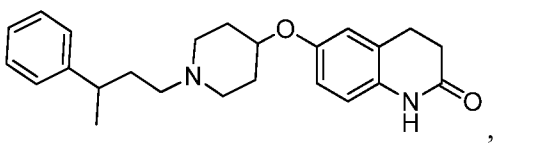
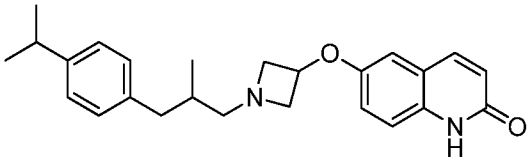
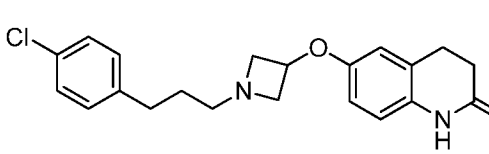
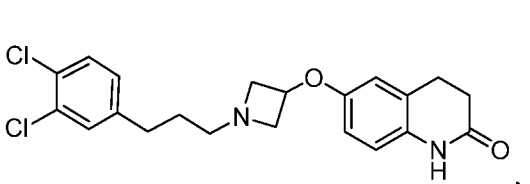

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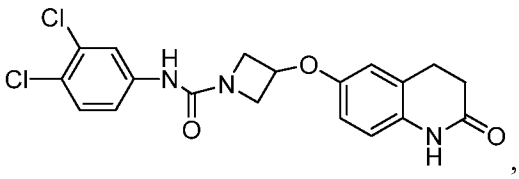
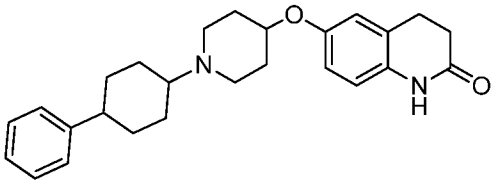
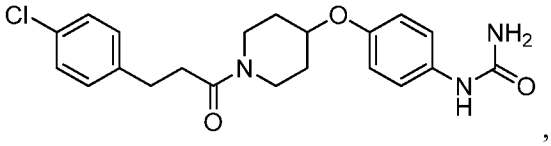
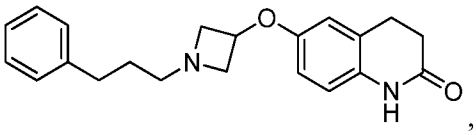
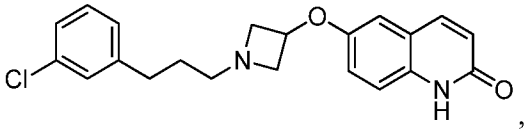
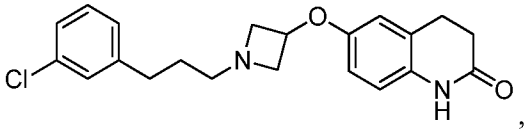
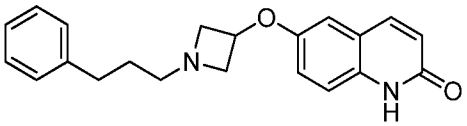
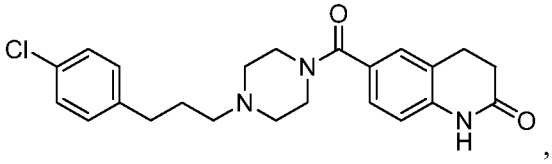
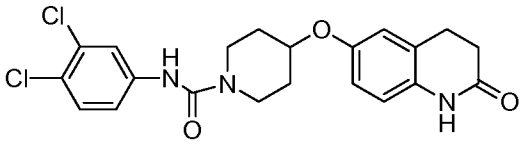
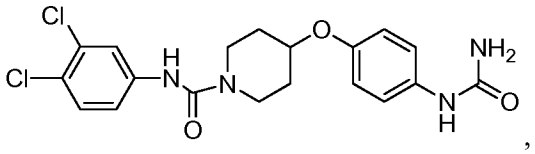
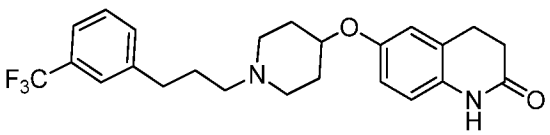
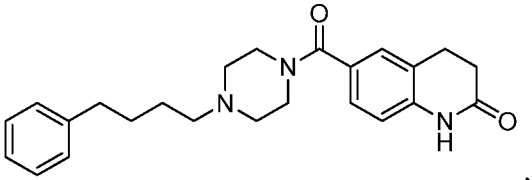
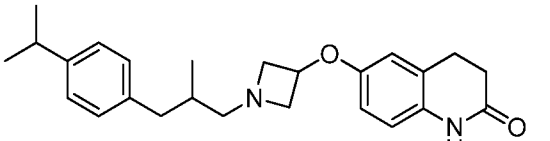
[00866] In one aspect, a compound can be present as:


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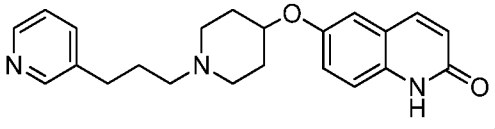
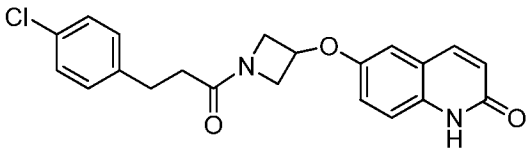
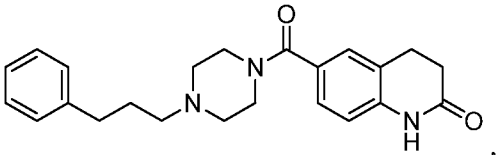
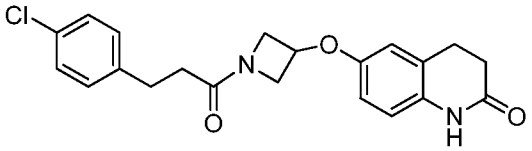
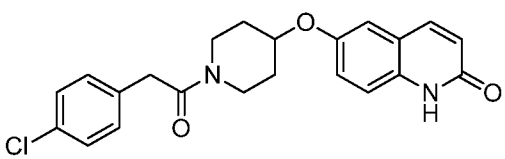

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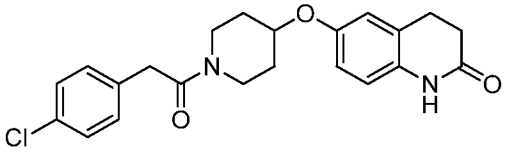
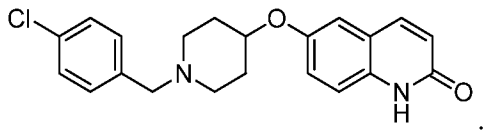

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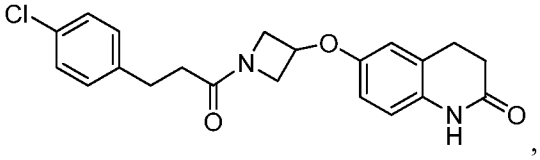
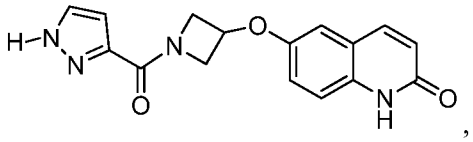
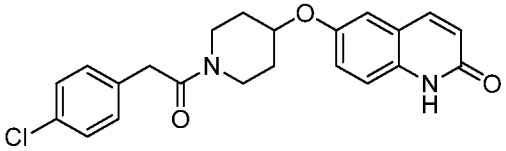
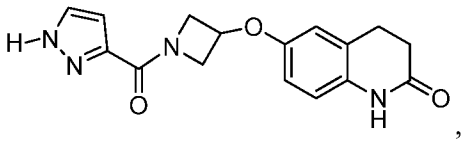
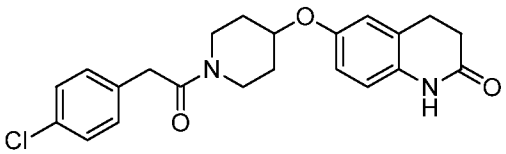
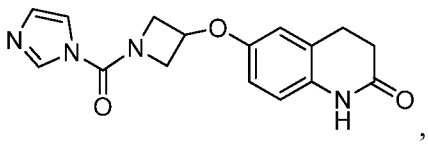
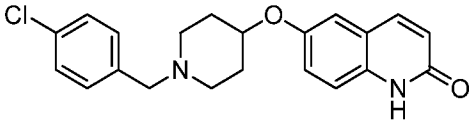
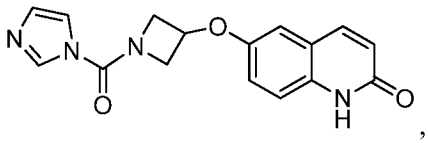
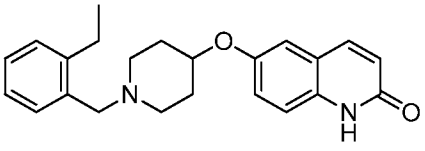
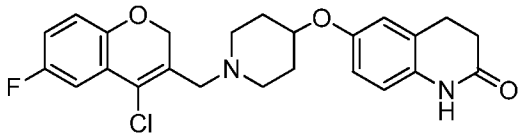
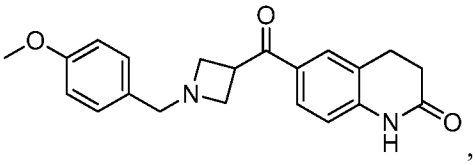
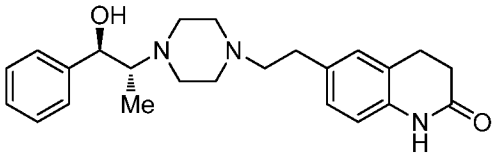
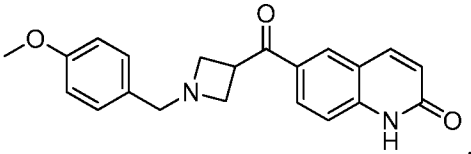
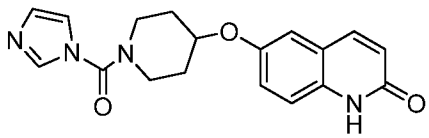
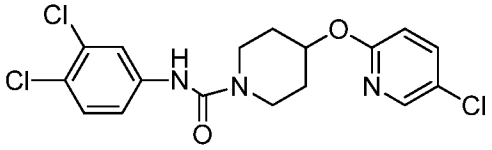
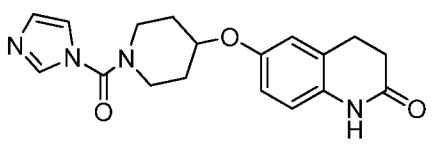
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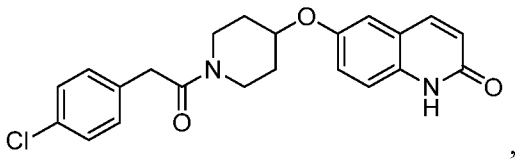
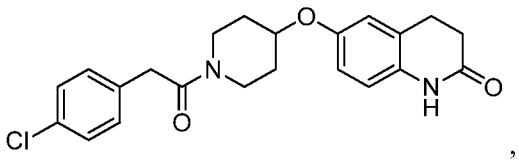
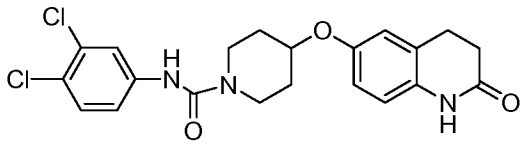
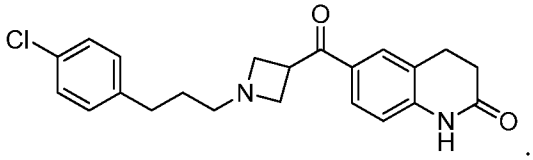
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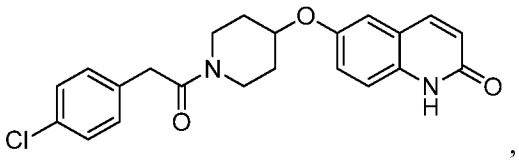
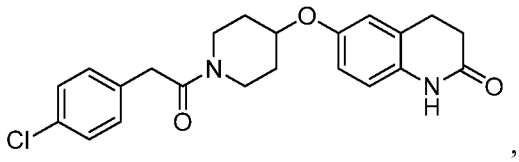
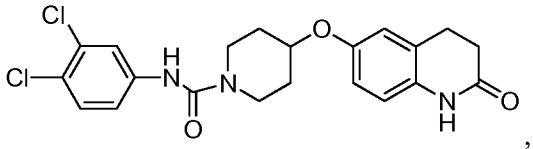
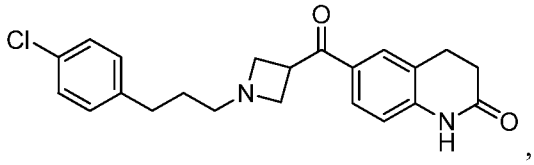
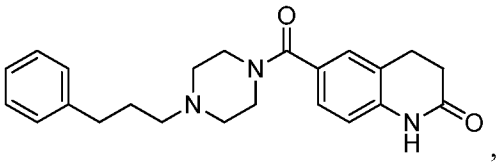
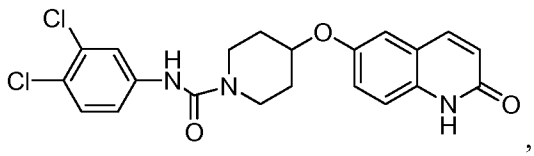
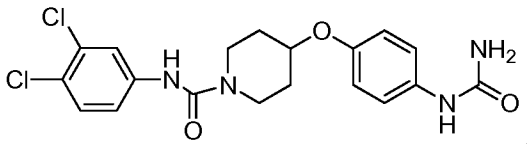
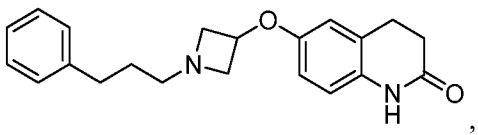
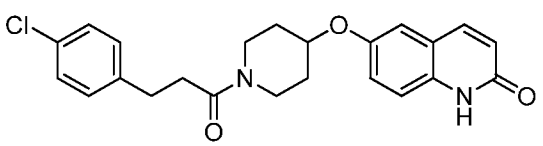
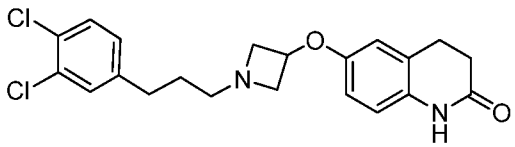
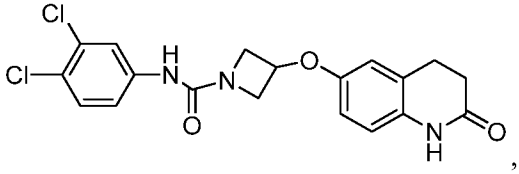
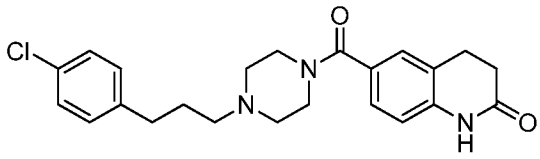
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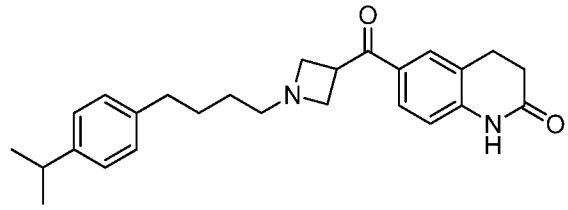
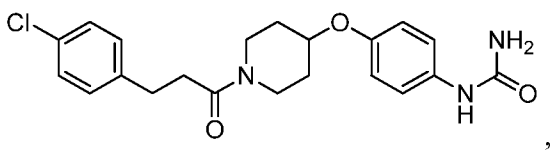
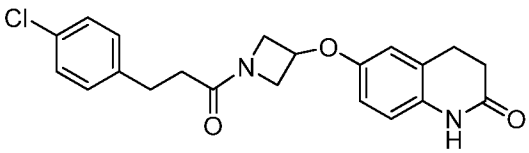
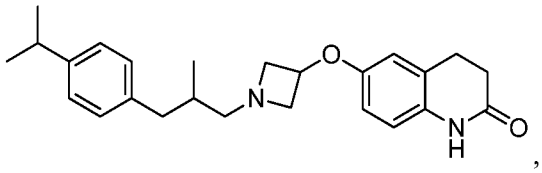
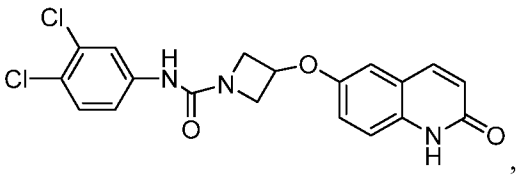
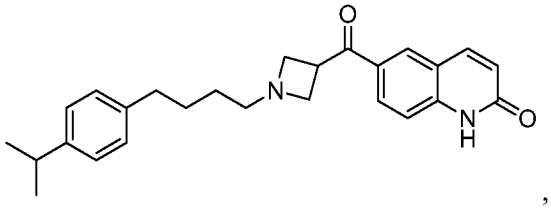
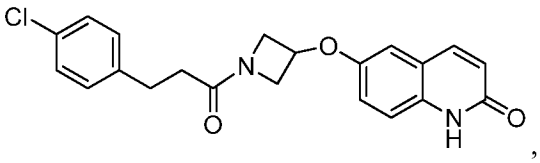
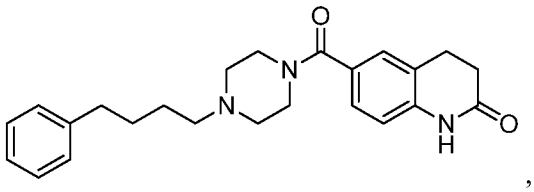
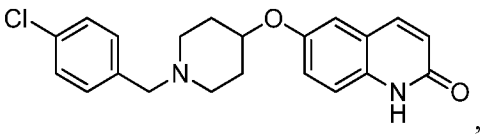
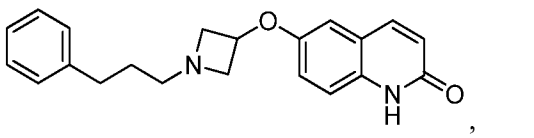
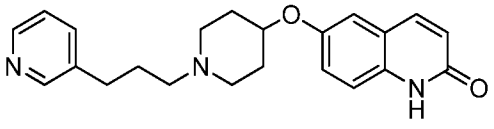
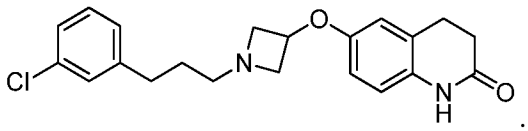

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[00868] In one aspect, a compound can be present as:

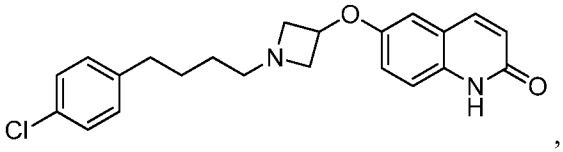
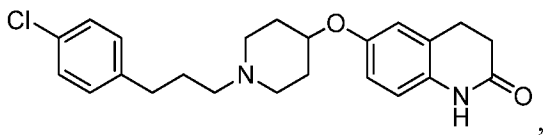
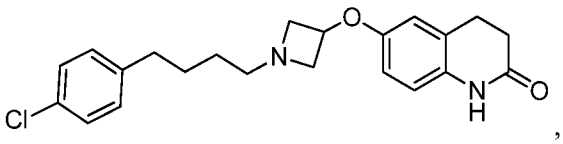
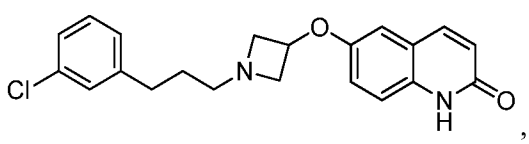

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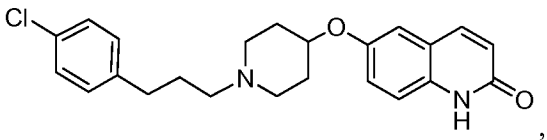
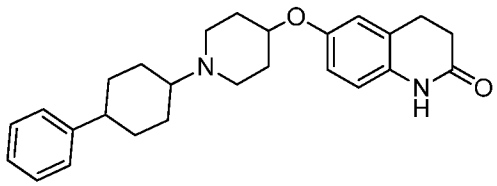
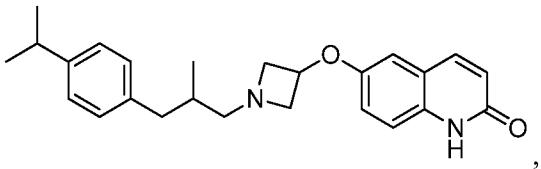
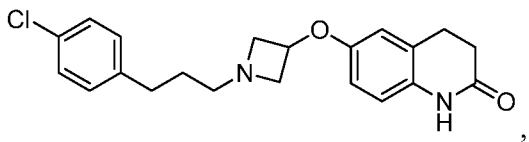
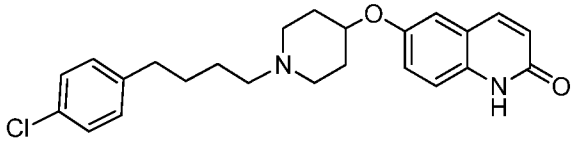
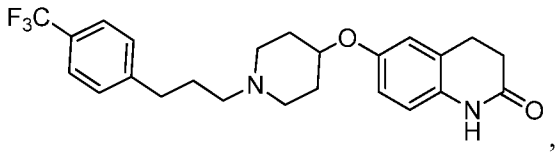
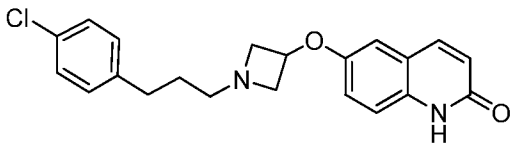
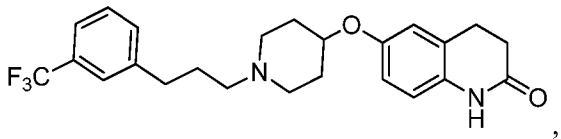
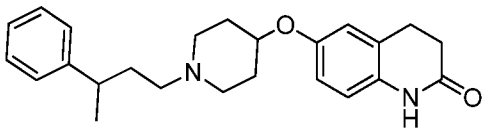
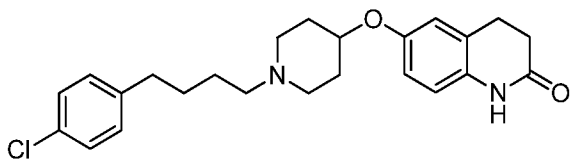
[00869] In one aspect, a compound can be present as:


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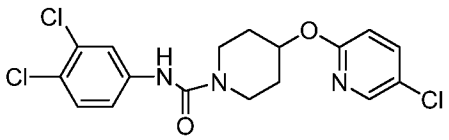
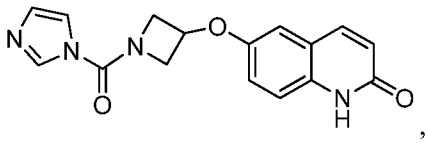
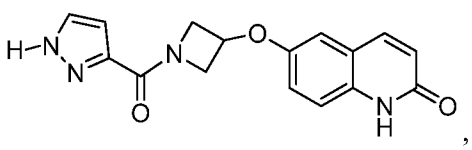
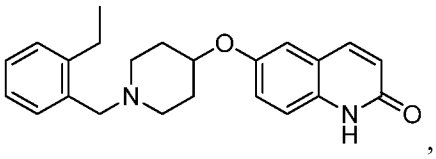
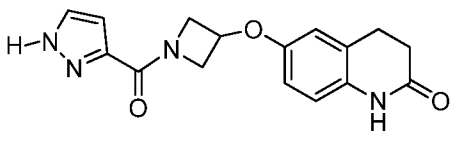
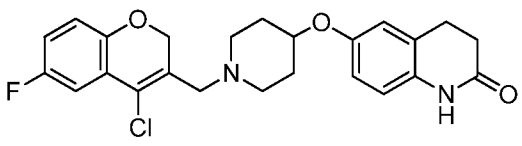
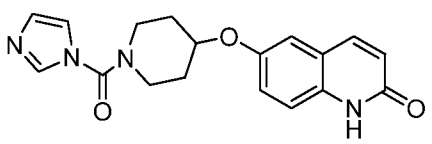
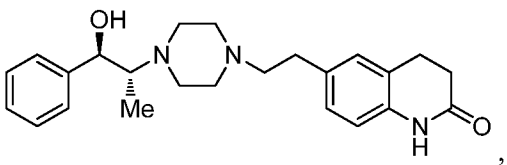

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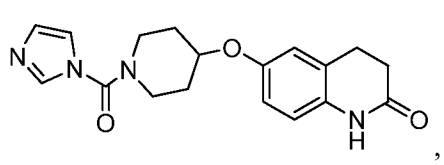
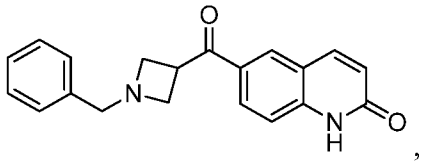
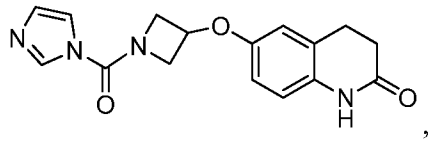
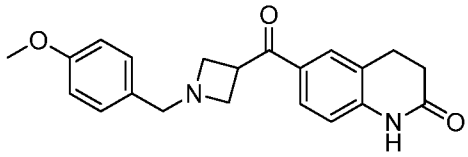
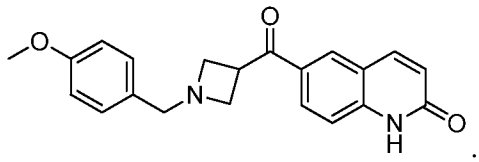
[00870] In one aspect, a compound can be present as:


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[00871] In one aspect, a compound can be present as:


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[00872] Compounds are shown above are depicted having a basic group or acidic group and named as the free base acid. Depending on the reaction and purification conditions, various compounds having a basic group were isolated in either the free base form, or as a salt (e.g. HCl salt), or in both free base and salt forms.

[00873] It is contemplated that one or more compounds can optionally be omitted from the disclosed invention.

3. MODULATION OF NMDA RECEPTOR RESPONSE

[00874] Generally, the disclosed compounds exhibit inhibition of NMDA receptor response to an agonist (e.g., glutamate and/or glycine). The inhibition of NMDA receptor activity can be observed as a decrease in response the presence of glutamate and/or glycine in Xenopus oocytes injected with a cRNA for human or rat NMDA receptor, e.g., GluN1, GluN2 and/or GluN3 receptor subunit, in the presence of the compound, compared to the response to glutamate and/or glycine in the absence of the compound. For example, a compound can exhibit inhibition of NMDA receptor activity with an IC_{50} of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. In a further aspect, the NMDA is rat NMDA. In a still further aspect, the NMDA is human NMDA. In a yet further aspect, a compound can exhibit inhibition of GluN1 receptor subunit activity with an IC50 of less than about 10,000 nM, of less than about 5,000 nM. of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. In a still further aspect, the GluN1 is rat GluN1. In an even further aspect, the GluN1 is human GluN1. In a yet further aspect, a compound can exhibit inhibition of GluN2 receptor subunit activity with an IC50 of less than about 10,000 nM, of

less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. In a still further aspect, the GluN2 is rat GluN2. In an even further aspect, the GluN2 is human GluN2. In a yet further aspect, a compound can exhibit inhibition of GluN3 receptor subunit activity with an IC50 of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM. In a still further aspect, the GluN3 is rat GluN3. In an even further aspect, the GluN3 is human GluN3.

[00875] It is to be understood that "transfected with NMDA" or "transfected with GluN2" (e.g. human GluN2) refers to transfection of the indicated cells with an appropriate expression construct comprising the nucleic acid sequence coding for the indicated NMDA receptor or NMDA receptor subunit. The nucleic acid sequence for a NMDA receptor or NMDA receptor subunit can be a cDNA sequence which is full-length or alternatively a partial cDNA sequence of a subset of the full-length cDNA sequence. Appropriate expression constructs are available to one skilled in the art, as are methods for manipulation of the desired cDNA sequence.

[00876] In one aspect, the disclosed compounds exhibit inhibition of NMDA receptor response to an agonist (e.g., glutamate and/or glycine) can be observed as a decrease in response to maximal concentrations of glutamate and/or glycine in Xenopus oocytes injected with a cRNA for human or rat NMDA receptor, e.g., GluN1, GluN2 and/or GluN3 receptor subunit, in the presence of the compound, compared to the response to glutamate and/or glycine in the absence of the compound. In a further aspect, the disclosed compounds exhibit inhibition of NMDA receptor response to an agonist (e.g., glutamate and/or glycine) can be observed as a decrease in response to non-maximal concentrations of glutamate and/or glycine in Xenopus oocytes injected with a cRNA for human or rat NMDA receptor, e.g., GluN1, GluN2 and/or GluN3 receptor subunit, in the presence of the compound, compared to the response to glutamate and/or glycine in the absence of the compound.

C. NMDA RECEPTOR ACTIVITY INHIBITION

[00877] The human NMDA subtype of glutamate-gated ion channels comprise heterotetrametric assemblies composed of three subunits subtypes, GluN1, GluN2 (A, B, C, and/or D), and GluN3 (A and B), which are critical in determining biological and pharmacological properties of the NMDA receptor. Moreover, a functional channel requires the co-expression of at least one GluN1 subunit and one or more GluN2 subunits. Generally, this results in a NMDA receptor comprising a tetramer with two GluN1 and two identical or different GluN2 subunits. In rare cases, cells express the GluN3 subunit, which co-assembles

with GluN1 or GluN1 and GluN2 to form GluN1–GluN3 or GluN1–GluN2–GluN3 tetrameric complexes. While GluN1 subunits are expressed virtually uniformally in all neurons and at all developmental stages, the GluN2 subunits exhibit different regional distribution and developmental expression, and can provide a more selective therapeutic target.

[00878] NMDA receptor subunits share a common modular design, each representing a functional unit, including: the extracellular area containing two large bi-lobed domains, the amino terminal domain (ATD) and the ligand binding domain (LBD, which binds glycine in GluN1 and GluN3, and glutamate in GluN2), the membrane domain comprising three transmembrane segments and a re-entrant loop that forms the ion channel, and the C-terminal cytoplasmic domain. As a result, the NMDA receptor has multiple binding and regulatory sites in addition to an ion channel, which also contains several internal binding sites. To function, the NMDA receptor requires co-activation by the binding of a co-agonist, glycine, at GluN1 subunits, in addition to glutamate binding on GluN2 subunits. At resting membrane potentials, NMDA receptors are largely inactive due to a voltage-dependent block of the channel pore by magnesium ions. Depolarization releases this channel block and permits passage of calcium and monovalent ions such as sodium ions. Additionally, the highly modular organization of the extracellular domains is believed to provide additional potential regulatory sites at various protein-protein interfaces that can modulate NMDA receptor activity.

The utility of the disclosed compounds and products of disclosed methods of making, in accordance with the present invention as modulators of NMDA receptor activity, in particular GluN2B activity, can be demonstrated by methodology known in the art. For example, Xenopus oocytes injected with a cRNA for human or rat GluN1 and GluN2B were plated in a dual-voltage track Plexiglas recording chamber for use in an electrophysiological NMDA receptor activity assay. The oocytes were perfused with a solution comprising 90 mM NaCl, 1 mM KCl, 10 mM HEPES, 10 mM EDTA and 0.5 mM $BaCl_2$. The pH was adjusted by addition of 1-3 M NaOH of HCl, and the final concentrations of glutamate and glycine in the solutions were 50 μM and 30 μM, respectively. The baseline leak current at -40mV was measured before and after application of the compounds of the present invention. Response of the oocytes was measured by applying, in successive fashion, maximal glutamate/glycine followed by glutamate/glycine plus variable concentrations of compounds. Dose response curves consisting of 4 to 8 concentrations were obtained in this manner. The level of

inhibition by the compounds of the present inventions was quantified as a percent of the initial glutamate response, and averaged together across oocytes from multiple experiments. Results were pooled, and the average percent responses at antagonist concentrations were fit by the equation, Percent Response = (100 - minimum) / (1 + ([conc] / IC_{50})^{nH}) + minimum, where minimum is the residual percent response in saturating concentration of the disclosed compounds, IC_{50} is the concentration of antagonist that causes half of the achievable inhibition, and nH is a slope factor describing steepness of the inhibition curve.

[00879] In an alternative assay, Xenopus oocytes were injected with a cRNA for either human or rat GluN2A, GluN2C or GluN2D NMDA receptor subtype. In this assay, a concentration of the antagonist was perfused with 100 μM glutamate and 30 μM glycine onto the oocyte for two minutes. The remaining current in the presence of the antagonist was measured and compared to the maximal current obtained with 100 μM glutamate and 30 μM glycine alone (defined as 100%). Thus, a value less than 100% is an indication of the degree of NMDA inhibition at the given concentration of the present compound for that NMDA receptor subunit.

[00880] In one aspect, the disclosed compounds inhibit the effect of an agonist response (e.g., glutamine and glycine) of NMDA. Without wishing to be bound by a particular theory, the compounds of the present invention can inhibit NMDA activity by acting as antagonists. In various aspects, the compounds can inhibit NMDA activity by acting as partial inhibitors. In various further aspects, the compounds can inhibit NMDA activity by acting as negative allosteric modulators.

[00881] In one aspect, the disclosed compounds can exhibit a diminution, inhibition or abolishment of the NMDA response to glutamate and/or glycine and such diminution, inhibition or abolishment of the NMDA response can be determined from a decrease in current in GluN1/GluN2B injected Xenopus oocytes in the presence of the compound, compared to the NMDA receptor response in the absence of the compound. For example, a disclosed compound can have an IC_{50} of less than about 10 μM, of less than about 5 μM, of less than about 1 μM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM. In a further aspect, the GluN1/GluN2B injected Xenopus oocytes are injected with cRNA encoding human GluN1 and GluN2B. In a still further aspect, the Xenopus oocytes are injected with cRNA encoding rat GluN1 and GluN2B.

[00882] In one aspect, the disclosed compounds can exhibit a decrease in the NMDA response to glutamate and/or glycine in Xenopus oocytes injected with a cRNA for

mammalian NMDA receptor, e.g., GluN1 and GluN2B, in the presence of the compound, compared to the response to glutamate and/or glycine in the absence of the compound. For example, Xenopus oocytes can be injected with cRNA encoding human NMDA receptor, e.g., GluN1 and GluN2B. Alternatively, for example, Xenopus oocytes can be injected with cRNA encoding rat GluN1 and GluN2B. For example, a compound can exhibit antagonism of GluN1 and GluN2B with an IC_{50} of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, or of less than about 100 nM when determined in Xenopus oocytes injected with cRNA encoding rat GluN1 and GluN2B. Alternatively, the disclosed compounds exhibit a decrease in the GluN1 and GluN2B receptor response to glutamate and glycine in Xenopus oocytes injected with a cRNA encoding human GluN1 and GluN2B, in the presence of the compound, compared to the response to glutamate and/or glycine in the absence of the compound. For example, a compound can exhibit antagonism of NMDA receptor, e.g., GluN1 and GluN2B with an IC_{50} of less than about 10,000 nM, of less than about 5,000 nM, of less than about 1,000 nM, of less than about 500 nM, of less than about 100 nM, or of less than about 50 nM when determined in Xenopus oocytes injected with cRNA encoding human GluN1 and GluN2B.

[00883] In one aspect, a disclosed compound can exhibit antagonism of the NMDA receptor, e.g., GluN1 and GluN2B, response to glutamate and/or glycine. In a further aspect, a disclosed compound exhibits antagonism of the GluN1 and GluN2B response to glutamate and/or glycine with an IC_{50} of less than about 10,000 nM. In a still further aspect, a disclosed compound exhibits antagonism of the GluN1 and GluN2B response to glutamate and/or glycine with an IC_{50} of less than about 5,000 nM. In a yet further aspect, a disclosed compound exhibits antagonism of the GluN1 and GluN2B response to glutamate and/or glycine with an IC_{50} of less than about 1,000 nM. In an even further aspect, a disclosed compound exhibits antagonism of the GluN1 and GluN2B response to glutamate and/or glycine with an IC_{50} of less than about 500 nM. In a still further aspect, a disclosed compound exhibits antagonism of the GluN1 and GluN2B response to glutamate and/or glycine with an IC_{50} of less than about 100 nM. In a yet further aspect, a disclosed compound exhibits antagonism of the GluN1 and GluN2B response to glutamate and/or glycine with an IC_{50} of less than about 50 nM.

[00884] In various further aspects, a disclosed compound can exhibit a diminution, inhibition or abolishment of the GluN1 and GluN2B response in GluN1 and GluN2B injected Xenopus oocytes with an IC_{50} less than the IC_{50} for GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D response in GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D injected

Xenopus oocytes. That is, a disclosed compound can have selectivity for the GluN2B receptor vis-à-vis one or more of the GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D receptors. For example, in one aspect, a disclosed compound can diminish, abolish or inhibit the GluN2B response with an IC_{50} of about 5-fold less than that for GluN1/GluN2A, of about 10-fold less than that for GluN1/GluN2A, of about 20-fold less than that for GluN1/GluN2A, of about 30-fold less than that for GluN1/GluN2A, of about 50-fold less than that for GluN1/GluN2A, of about 100-fold less than that for GluN1/GluN2A, or of >100-fold less than that of that for GluN1/GluN2A. In a further aspect, a disclosed compound can diminish, abolish or inhibit the GluN2B response with an IC_{50} of about 5-fold less than that for GluN1/GluN2C, of about 10-fold less than that for GluN1/GluN2C, of about 20-fold less than that for GluN1/GluN2C, of about 30-fold less than that for GluN1/GluN2C, of about 50-fold less than that for GluN1/GluN2C, of about 100-fold less than that for GluN1/GluN2C, or of >100-fold less than that of that for GluN1/GluN2C. In a still further aspect, a disclosed compound can diminish, abolish or inhibit the GluN2B response with an IC_{50} of about 5-fold less than that for GluN1/GluN2D, of about 10-fold less than that for GluN1/GluN2D, of about 20-fold less than that for GluN1/GluN2D, of about 30-fold less than that for GluN1/GluN2D, of about 50-fold less than that for GluN1/GluN2D, of about 100-fold less than that for GluN1/GluN2D, or of >100-fold less than that of that for GluN1/GluN2D. In a further aspect, a disclosed compound can diminish, abolish or inhibit the GluN2B response with an IC_{50} of about 5-fold less than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors, of about 10-fold less than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors, of about 20-fold less than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors, of about 30-fold less than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors, of about 50-fold less than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors, of about 100-fold less than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors, or of >100-fold than that for the GluN1/GluN2A, GluN1/GluN2C or GluN1/GluN2D receptors. In various further aspects, a disclosed compound can diminish, abolish or inhibit the GluN2B response in GluN2B injected Xenopus oocytes and is inactive for one or more of GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D response in GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D injected Xenopus oocytes .

[00885] In vivo efficacy for disclosed compounds and products of disclosed methods of making can be measured in a number of preclinical rat or mouse behavioral model known as the forced swim test, or in a preclinical rat or mouse model of cerebral ischemia or stroke,

known as the middle cerebral artery occlusion model. For example, disclosed compounds can reverse amphetamine-induced hyperlocomotion in male Sprague-Dawley rats at doses ranging from 1 to 100 mg/kg p.o.

[00886] For example, rodents, such as mice or rats, can be tested in a Forced Swim Test. Here, the animal is taken from their home cage and administered a drug or vehicle control solution. At a defined period of time post administration the mouse or rat will be placed into a chamber of water of defined diameter appropriate for the species and deep enough to prevent the animal from touching the bottom. The water is kept at 25 °C. The swimming behavior can be observed directly or videotaped for later viewing. The animal is allowed to swim for 6 minutes and the immobility time is counted and recorded. Immobility refers to the time that the animal spends floating or engaged in minimal activity to keep afloat. The total immobility times for each animal will be recorded and can be used as an endpoint measured for effects of drug in the experiment. Compounds that inhibit NMDA receptors including those that are selective for GluN2B receptors can decrease the total immobility time (*Eur J Pharm* 1999, 375: 31; *Pharm Bioch Behav* 1995, 52: 621; *Biol Psych* 2008, 63: 349; *Science* 2010, 329: 959).

D. METHODS OF MAKING THE COMPOUNDS

[00887] In one aspect, the invention relates to methods of making compounds useful as modulators of NMDA receptors, which can be useful in the treatment of neurological and psychiatric disorders associated with NMDA receptor activation and other diseases in which NMDA receptors are involved.

[00888] The compounds of this invention can be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature, exemplified in the experimental sections or clear to one skilled in the art. For clarity, examples having a single substituent are shown where multiple substituents are allowed under the definitions disclosed herein.

[00889] Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in the following Reaction Schemes, in addition to other standard manipulations known in the literature or to one skilled in the art. The following examples are provided so that the invention might be more fully understood, are illustrative only, and should not be construed as limiting.

[00890] In one aspect, the disclosed compounds comprise the products of the synthetic methods described herein. In a further aspect, the disclosed compounds comprise a compound produced by a synthetic method described herein. In a still further aspect, the

invention comprises a pharmaceutical composition comprising a therapeutically effective amount of the product of the disclosed methods and a pharmaceutically acceptable carrier. In a still further aspect, the invention comprises a method for manufacturing a medicament comprising combining at least one compound of any of disclosed compounds or at least one product of the disclosed methods with a pharmaceutically acceptable carrier or diluent.

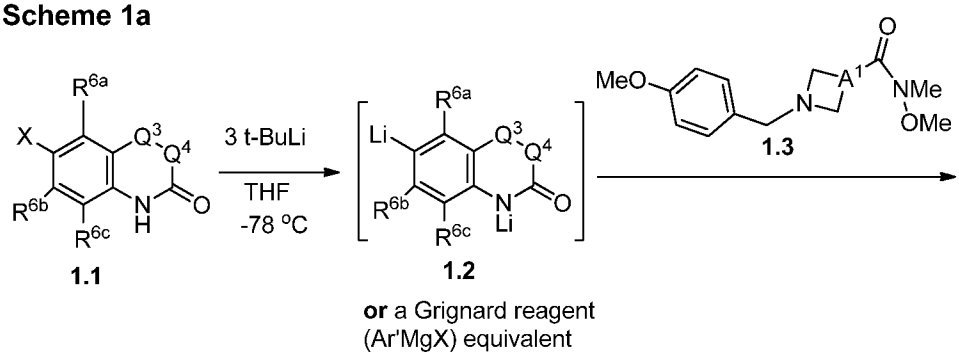
[00891] The compounds according to the invention can generally be prepared by a succession of steps, each of which is known to the skilled person. In particular, the compounds can be prepared according to the following synthesis methods. It is also contemplated that pseudohalogens (e.g. triflate, mesylate, brosylate, etc.) can be used as leaving groups in place of halogens in certain aspects.

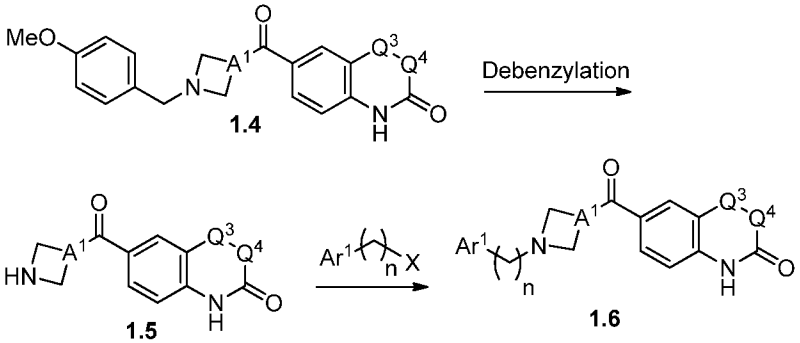
[00892] The disclosed compounds may be synthesized in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of disclosed compounds may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of disclosed compounds involves liquid chromatography using a chiral stationary phase. In a further aspect, pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

1. ROUTE I

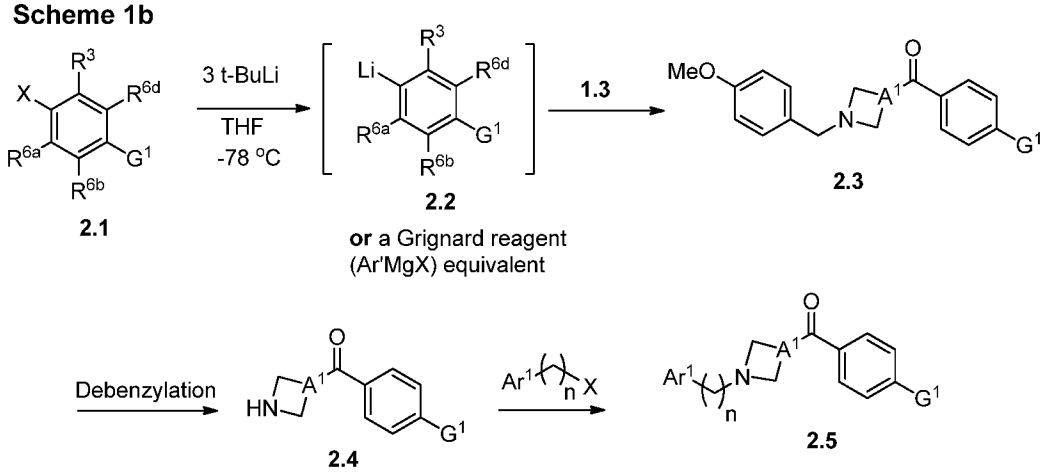
[00893] In one aspect, compounds of the present invention can be prepared as shown below.

Scheme 1a

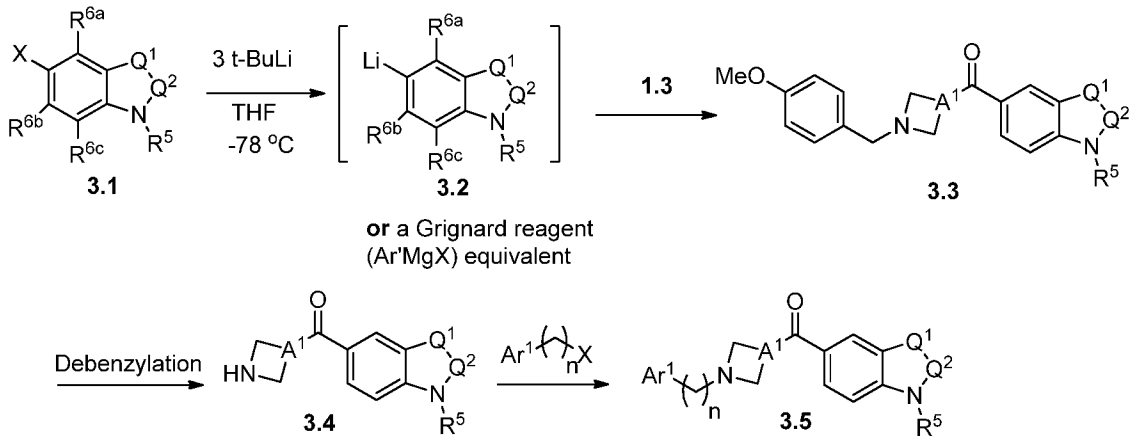




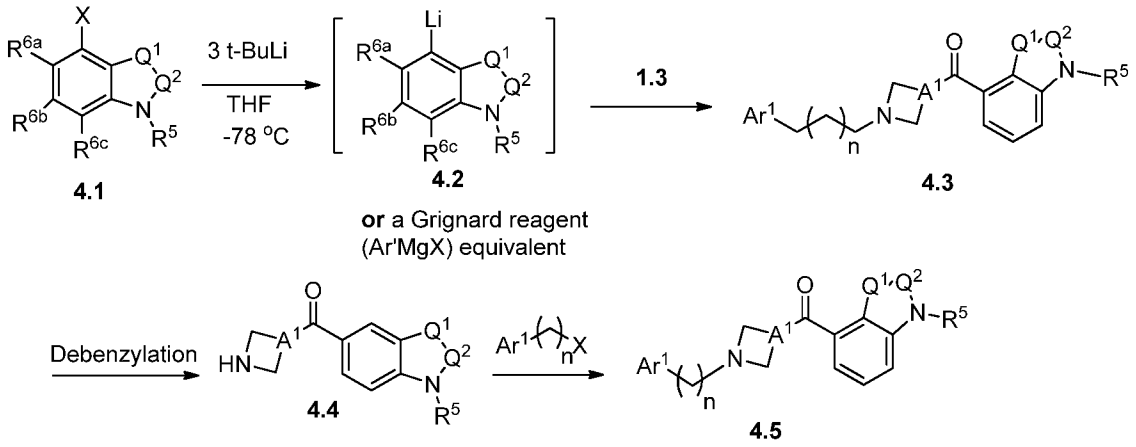
Scheme 1b



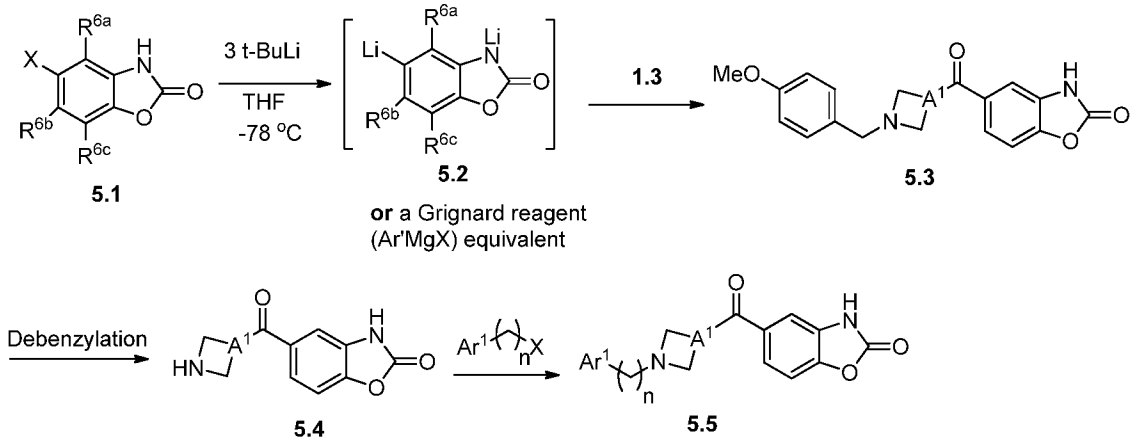
Scheme 1c



Scheme 1d

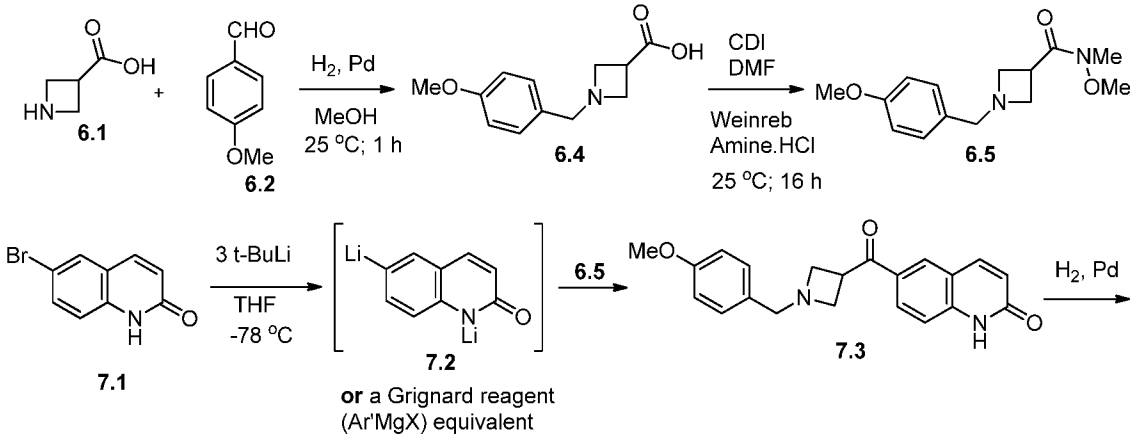


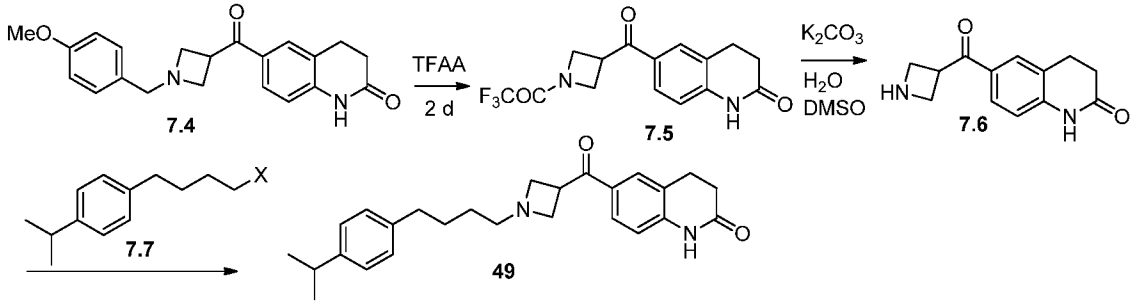
Scheme 1e



[00894] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

Scheme 1.



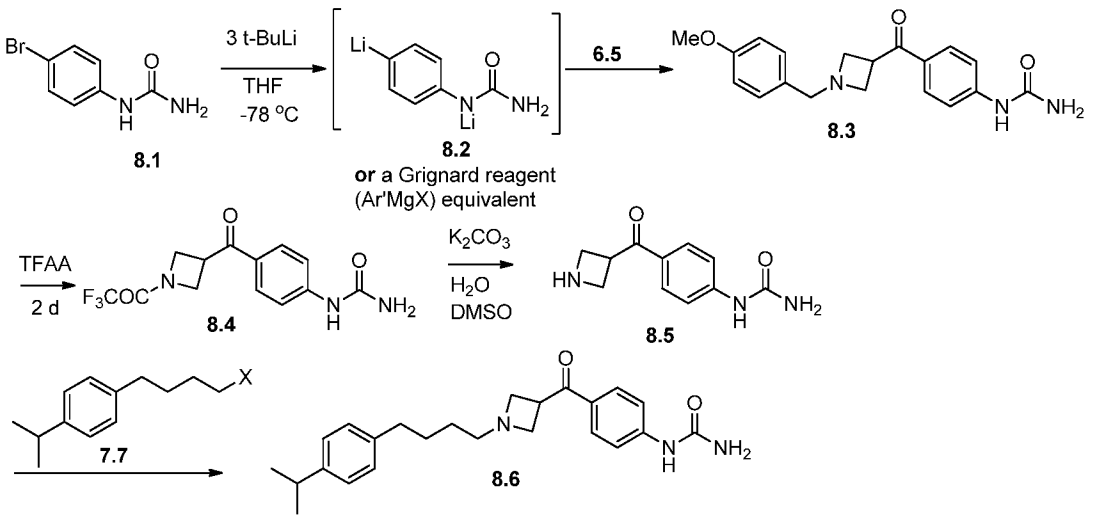


[00895] Thus, in one aspect, an intermediate of type **1.3** can be prepared with a suitable substituted azetidine-3-carboxylic acid (**6.1**). Suitable azetidine carboxylic acids are commercially available or can be readily prepared by one skilled in the art. The azetidine-3-carboxylic acid (**6.1**) is reacted with 4-methoxybenzaldehyde (**6.2**), under hydrogen, in the presence of a suitable catalyst, such as palladium on activated carbon, in a suitable inert solvent, such as methanol, under suitable reaction conditions such as at a convenient temperature, typically ranging between 0 °C and 40 °C, for a period of time to ensure the completion of the reaction, e.g. about 1 hour. Upon completion, the residue obtained is dissolved in tetrahydrofuran (THF) and evaporated, further triturated with ethyl acetate, and dried under vacuum. The reaction product, 1-(4-methoxybenzyl)azetidine-3-carboxylic acid (**6.4**) is then dissolved in dimethylformamide (DMF), and 1,1'-carbonyldiimidazole (CDI) is added. After 15 minutes, Weinreb amine hydrochloride salt and triethyl amine are added to the reaction mixture and stirred for a time sufficient to complete the reaction, e.g., about 16 hours, to provide compounds of type **1.3** after extraction with a suitable solvent, e.g., dichloromethane, and washing with brine. The organic solution is then dried over $MgSO_4$ and evaporated on a rotary evaporator. The unpurified product, a compound of type **1.3**, can be further isolated by methods known to one skilled in the art [e.g., phase separator (extraction), and concentration under a vacuum; followed by purification, e.g., chromatography]. Alternatively, piperidine analogues of compounds **1.3** can be prepared following the procedure for azetedine compound **1.3** from suitable starting compounds. Without wishing to be bound by theory, both azetidine and piperidine derivatives are believed to exhibit similar reaction trends in compounds of this kind.

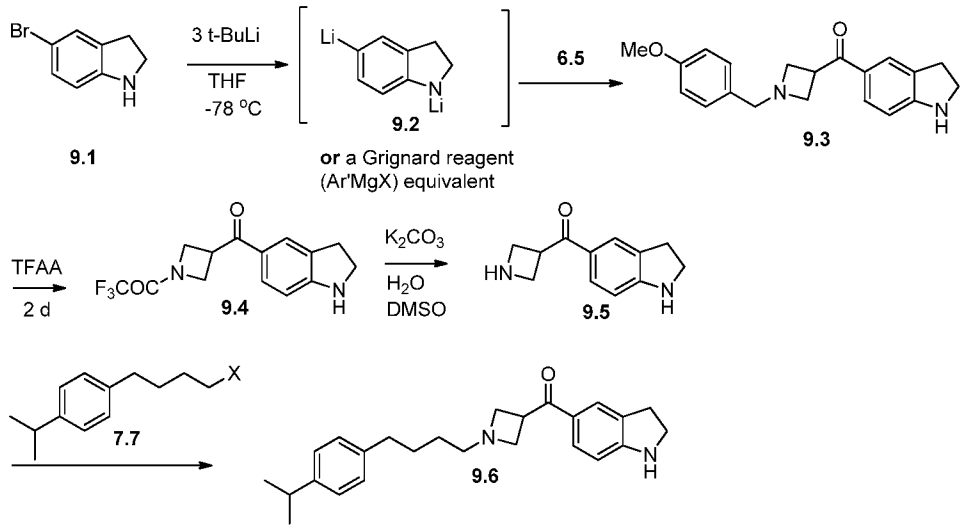
[00896] In various aspects, compounds of type (**49**) can be prepared starting with a compound of type (**7.1**), which is commercially available or prepared by methods known to one skilled in the art. Thus, a compound of type (**7.3**) can be prepared by an acylation reaction with a suitable Weinreb amide, e.g. (**6.5**) as shown above. The reaction is carried out at a suitable temperature, e.g. -78 °C, in a suitable solvent, using a suitable base, e.g. tert-

butyllithium (t-BuLi). A compound of type (**7.4**) can be prepared by reduction of a compound of type (**7.3**). For example, as shown above, such a reduction reaction can be accomplished using a suitable hydrogen source, e.g. hydrogen gas, with a suitable catalyst, e.g. palladium. A compound of type (**7.5**) can be prepared by substitution of a compound of type (**7.4**). For example, as shown above, such a substitution reaction can be accomplished using a suitable electrophile, e.g. trifluoroacetic anhydride, for a period of time sufficient to complete the reaction, e.g. 2 days. A compound of type (**7.6**) can be prepared by deprotection of a compound of type (**7.5**). For example, as shown above, such a deprotection reaction can be accomplished using a suitable base, e.g. potassium carbonate, in a suitable solvent mixture, e.g. water and DMSO. A compound of type (**49**) can be prepared by alkylation of a compound of type (**7.6**). For example, as shown above, such an alkylation reaction can be accomplished using suitable alkyl halides, e.g. (**7.7**), which are commercially available or prepared by methods known to one skilled in the art. More specific examples are set forth below.

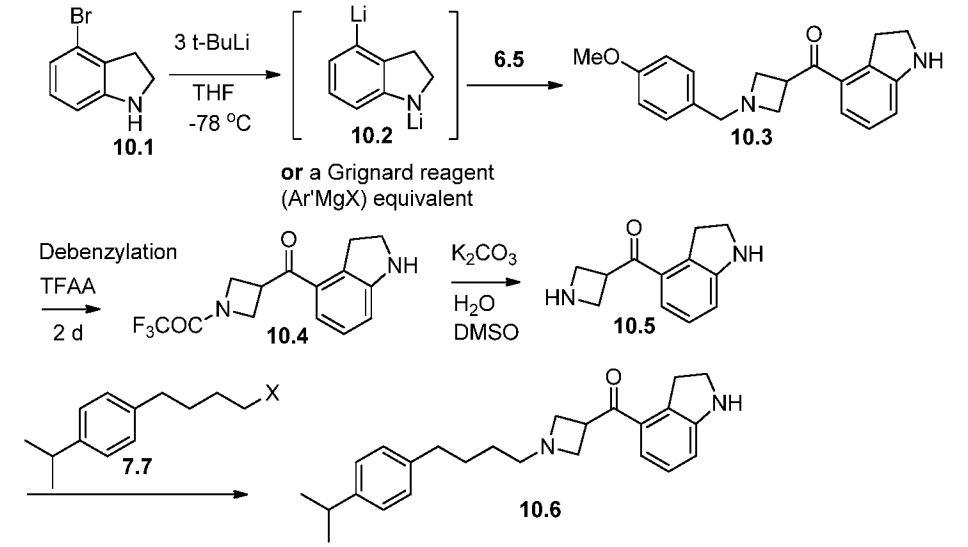
Scheme 2.



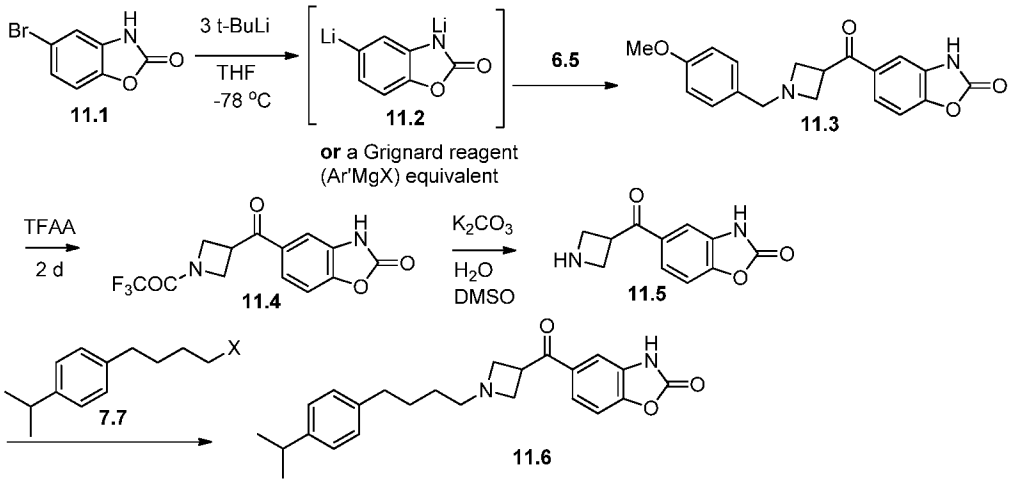
Scheme 3.



Scheme 4.



Scheme 5.

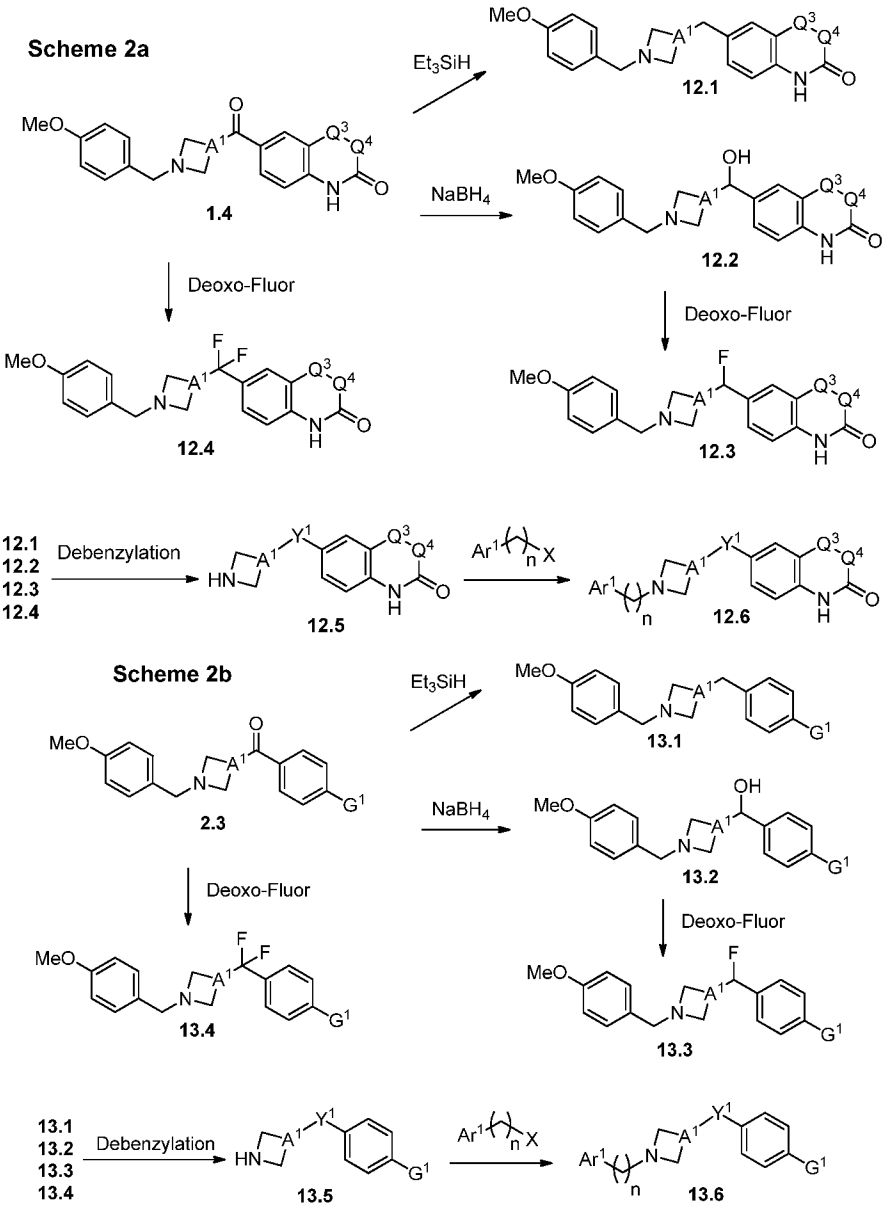


[00897] More specific examples are set forth within the Experimental section.

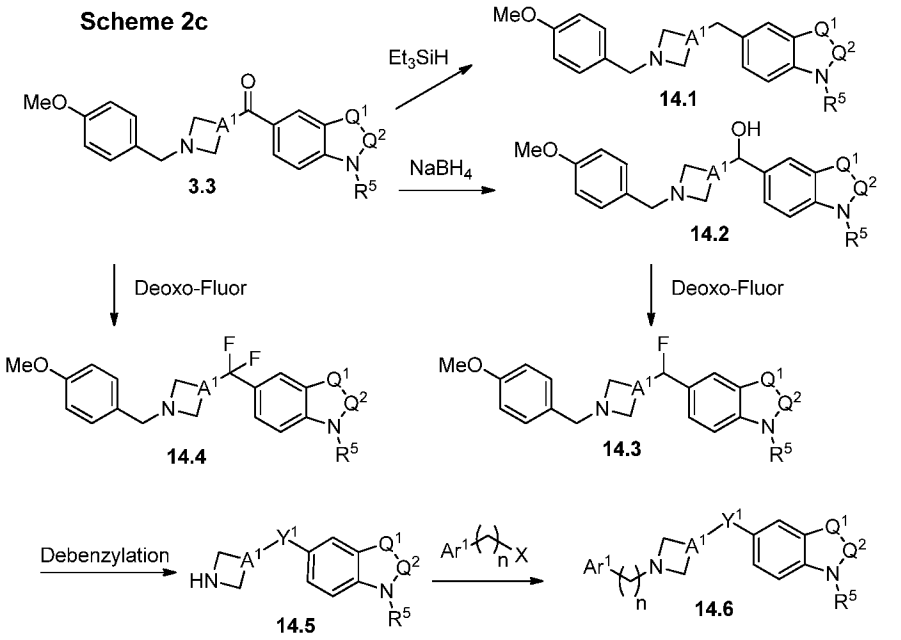
[00898] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed method can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

2. ROUTE II

[00899] In one aspect, compounds of the present invention can be prepared as shown below.

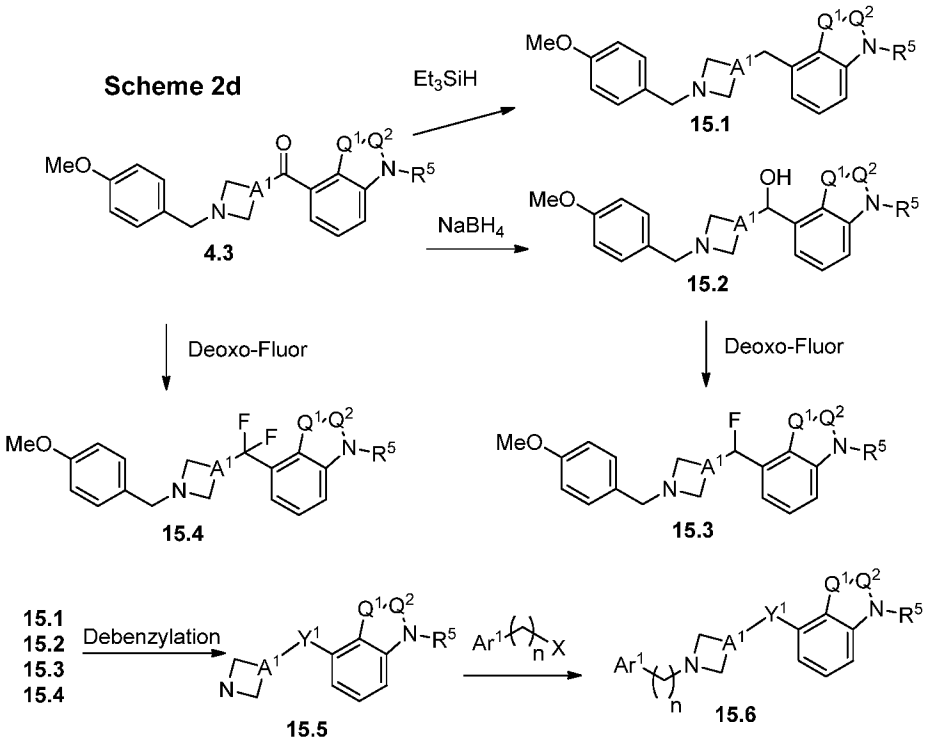


Scheme 2c

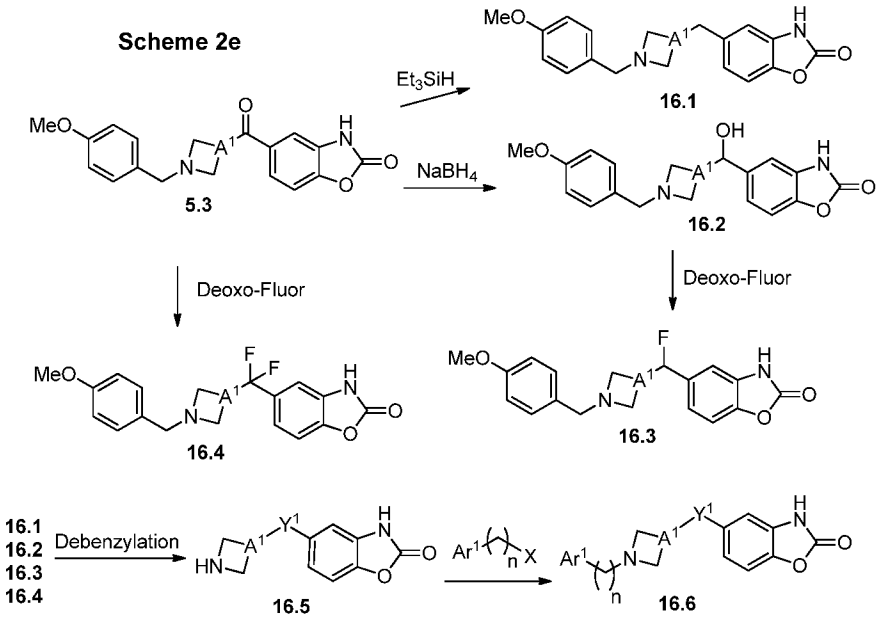


3.3 14.1 14.2 14.4 14.3 14.5 14.6

Scheme 2d

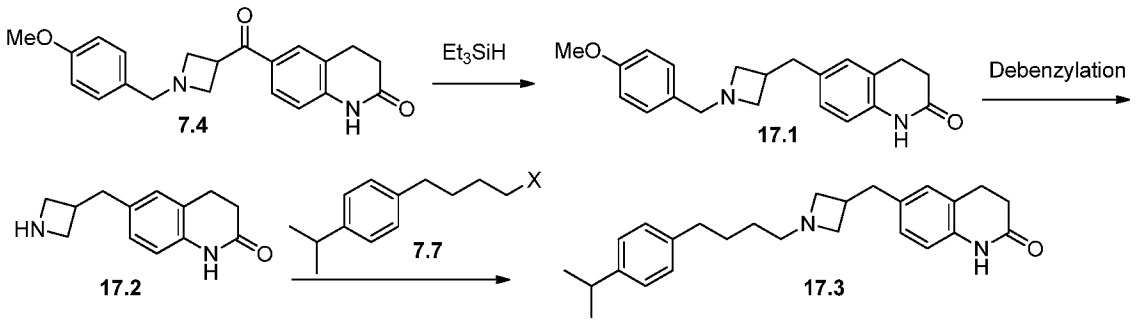


4.3 15.1 15.2 15.4 15.3 15.1 15.2 15.3 15.4 15.5 15.6



[00900] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

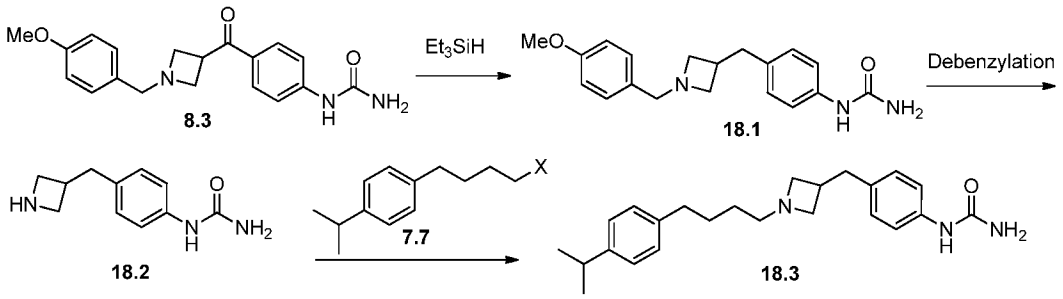
Scheme 6.



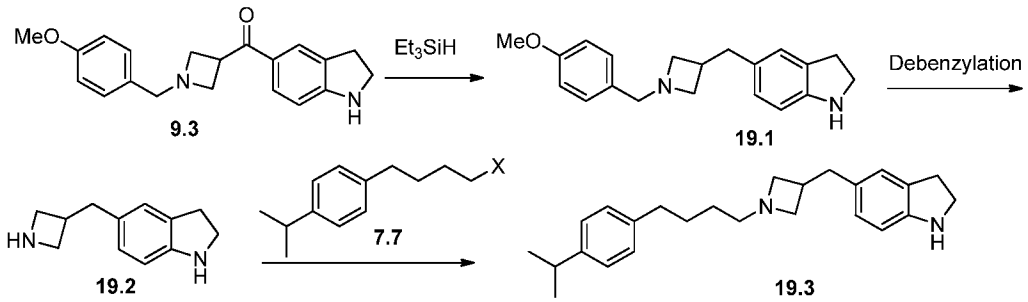
[00901] In various aspects, compounds of type (**17.1**) can be prepared starting with a compound of type (**7.4**), which is commercially available or prepared by methods known to one skilled in the art. Thus, a compound of type (**17.1**) can be prepared by a reduction reaction with a suitable reducing agent, e.g. triethylsilane as shown above. A compound of type (**17.2**) can be prepared by debenzylation of a compound of type (**17.1**). Such a reaction is known to one skilled in the art. A compound of type (**17.3**) can be prepared by alkylation of a compound of type (**17.2**). For example, as shown above, such a reaction can be accomplished using a suitable alkyl halide, e.g. (**7.7**), which is commercially available or prepared by methods known to one skilled in the art.

[00902] More specific examples are set forth below.

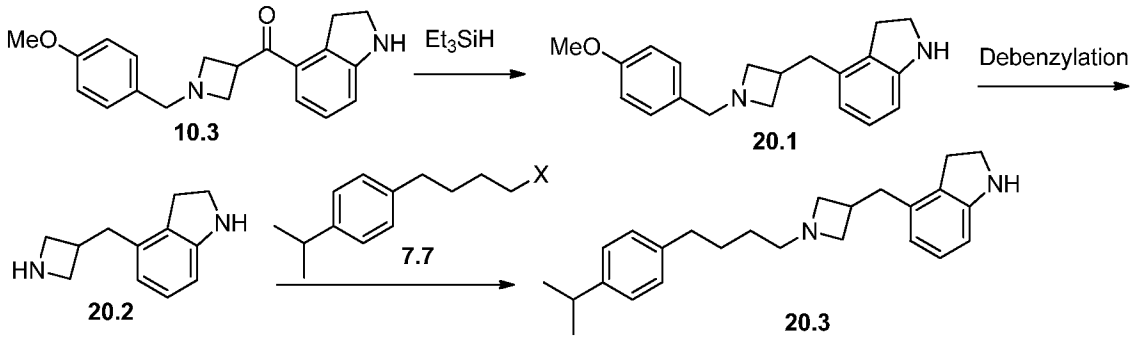
Scheme 7a.



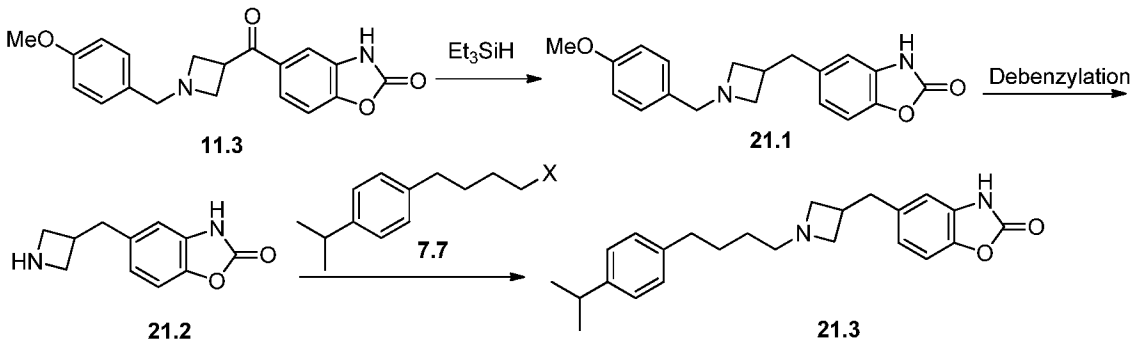
Scheme 7b.



Scheme 8.



Scheme 9.



[00903] More specific examples are set forth within the Experimental section.

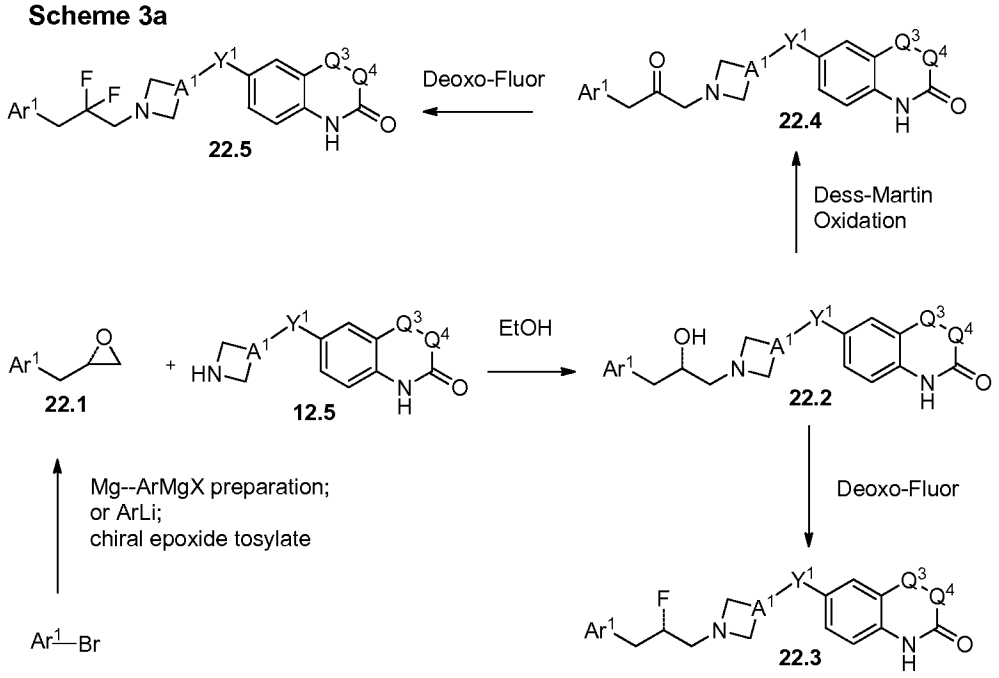
[00904] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is

understood that a disclosed method can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

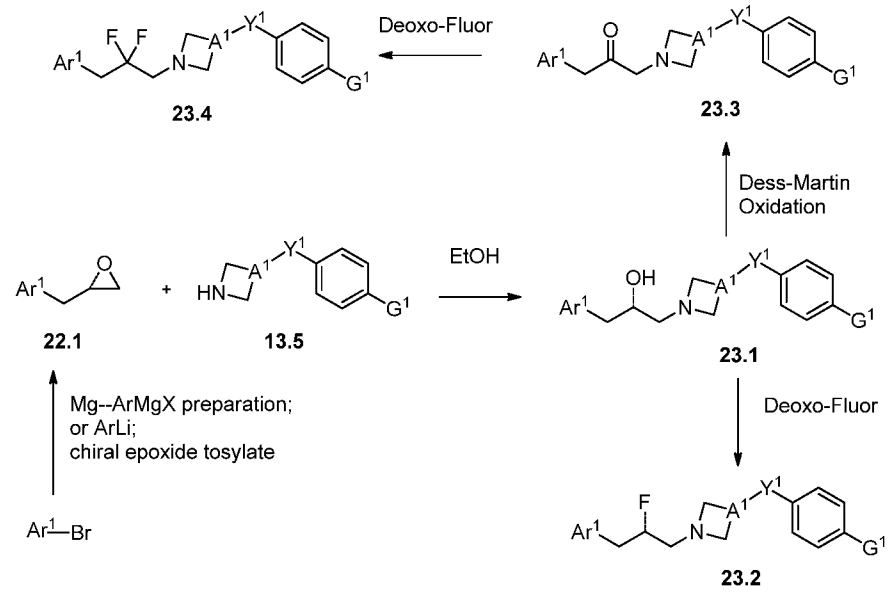
3. ROUTE III

[00905] In one aspect, compounds of the present invention can be prepared as shown below.

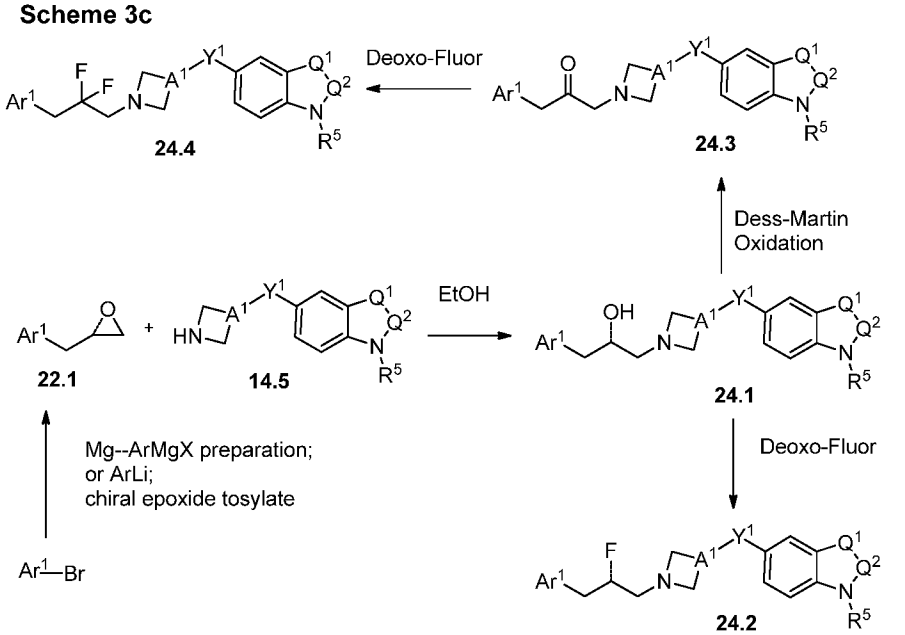
Scheme 3a



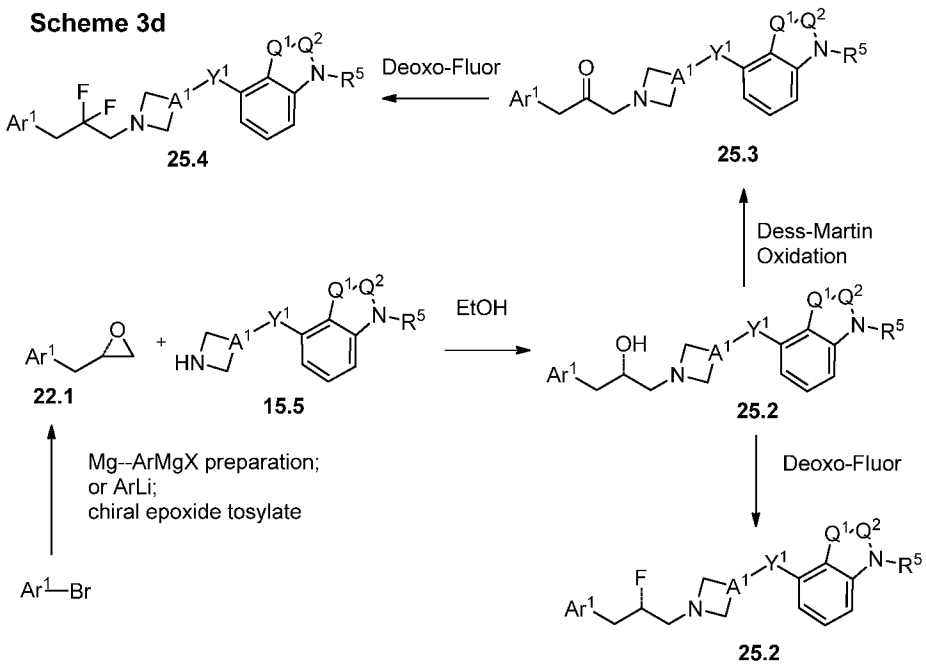
Scheme 3b



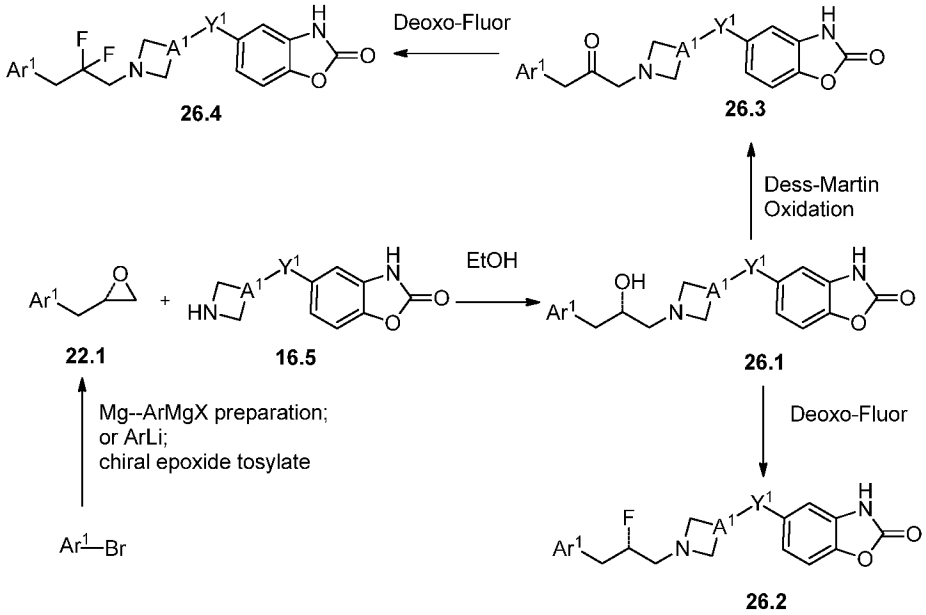
Scheme 3c



Scheme 3d

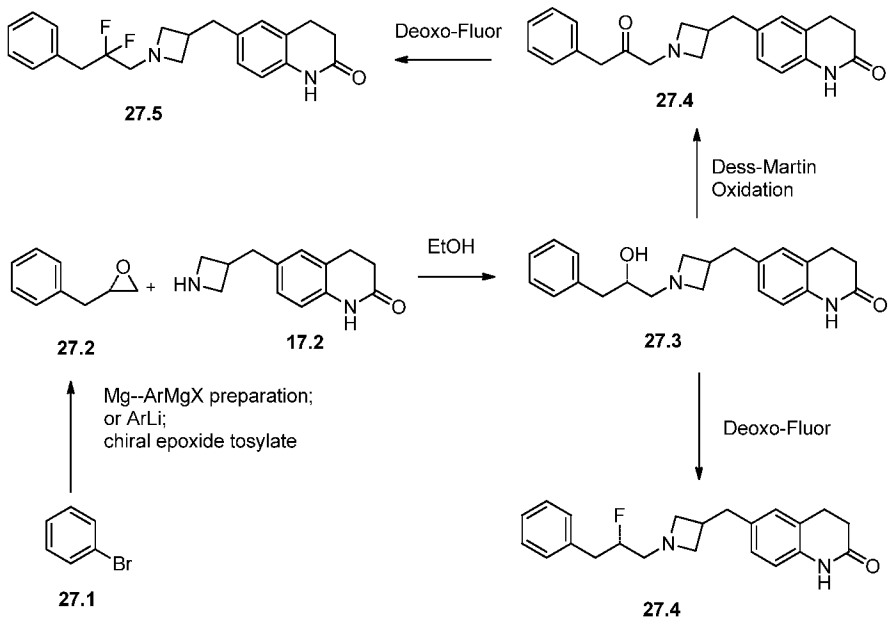


Scheme 3e



[00906] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth below.

Scheme 10.

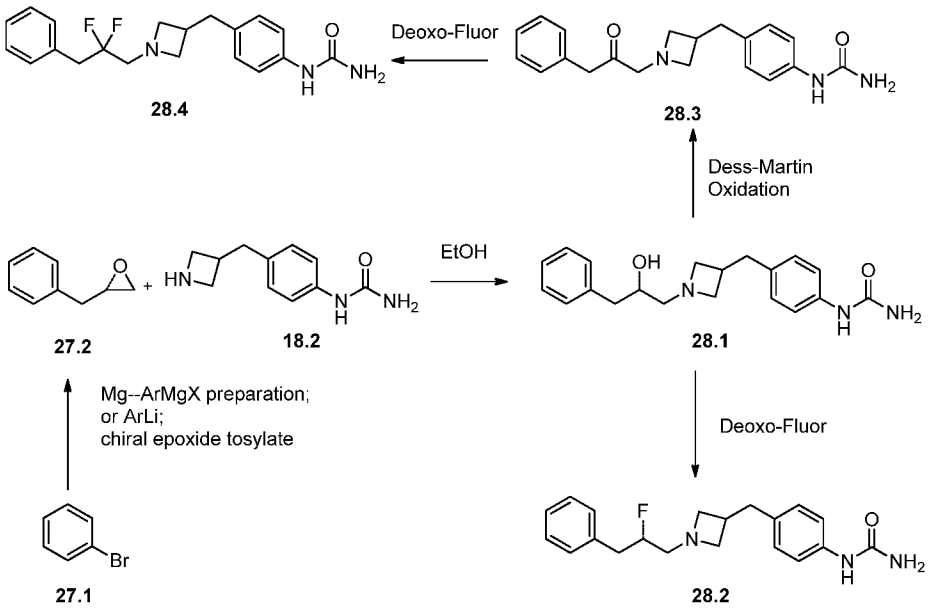


[00907] In various aspects, compounds of type (**27.2**) can be prepared starting with a compound of type (**27.1**), which is commercially available or prepared by methods known to one skilled in the art. Thus, a compound of type (**27.2**) can be prepared by coupling with a suitable coupling agent, e.g. a chiral epoxide tosylate as shown above. Chiral epoxide tosylates are commercially available or prepared by methods known to one skilled in the art.

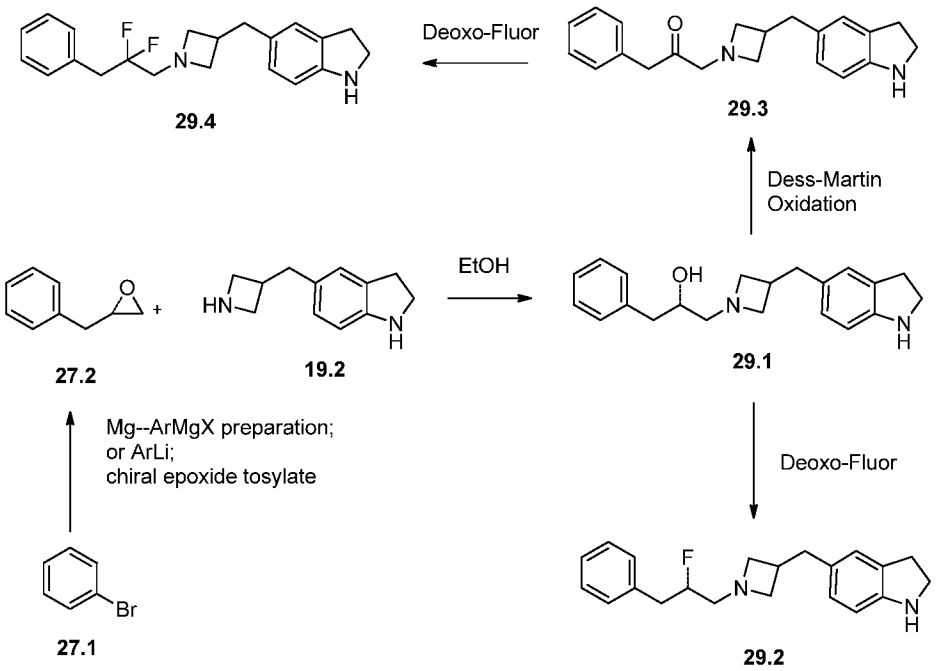
The reaction is carried out with an appropriate aryl lithium or aryl magnesium reagent. A compound of type (**27.3**) can be prepared by alkylation of a compound of type (**17.2**), which can be prepared as described herein, with a compound of type (**27.2**). For example, as shown above, such an alkylation reaction can be performed in a suitable polar protic solvent, e.g. EtOH. A compound of type (**27.4**) can be prepared by fluorination of a compound of type (**27.3**). For example, as shown above, such a fluorination reaction can be accomplished using a suitable fluorinating agent, e.g. Deoxo-Fluor. Alternatively, a compound of type (**27.4**) can be prepared by oxidation of a compound of type (**27.3**). For example, as shown above, such an oxidation reaction can be accomplished using a suitable oxidizing agent, e.g. Dess-Martin reagent. A compound of type (**27.5**) can be prepared by fluorination of a compound of type (**27.4**). For example, as shown above, such a fluorination reaction can be accomplished using a suitable fluorinating agent, e.g. Deoxo-Fluor.

[00908] More specific examples are set forth below.

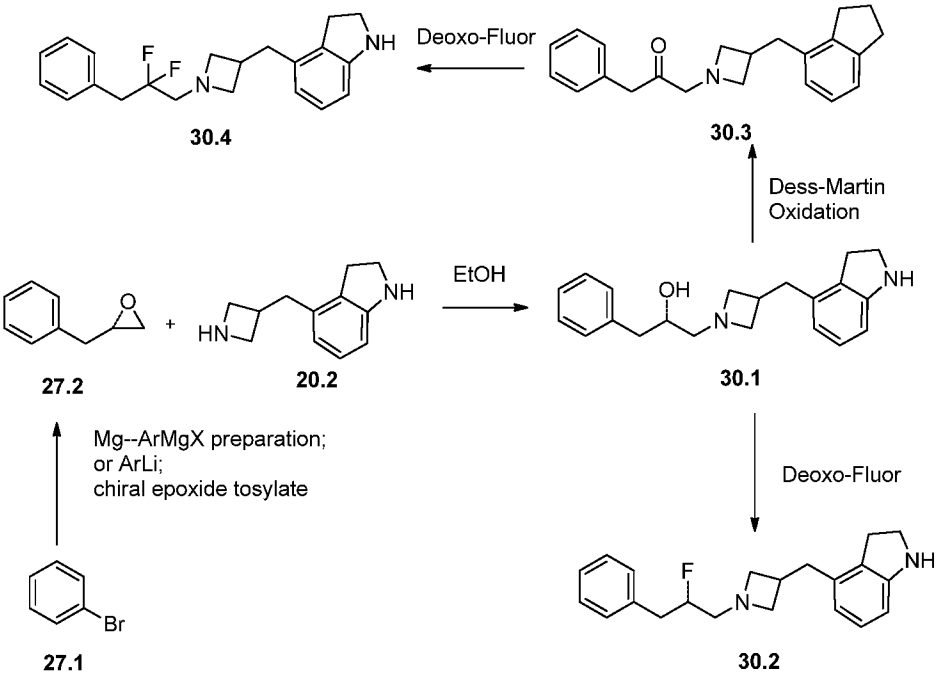
Scheme 11.



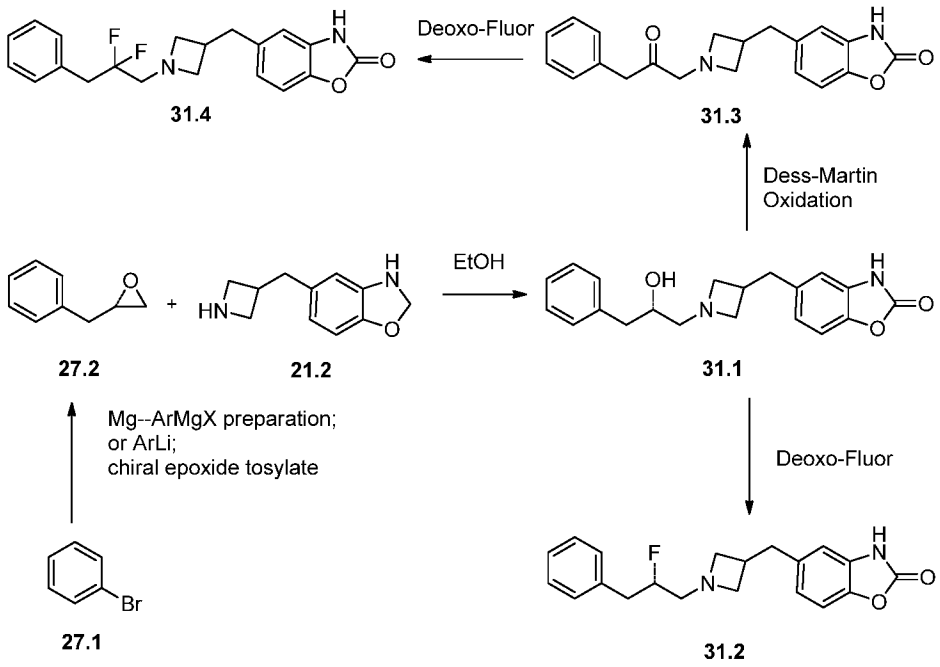
Scheme 12.



Scheme 13.



Scheme 14.



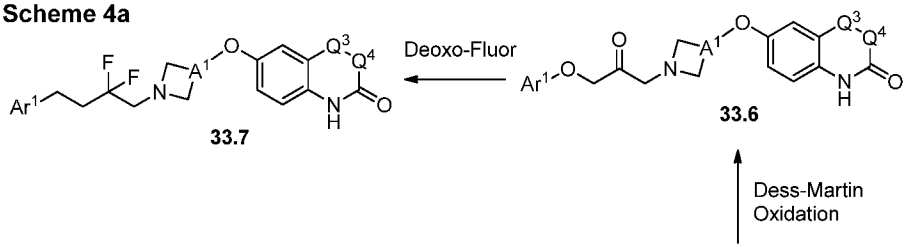
[00909] More specific examples are set forth within the Experimental section.

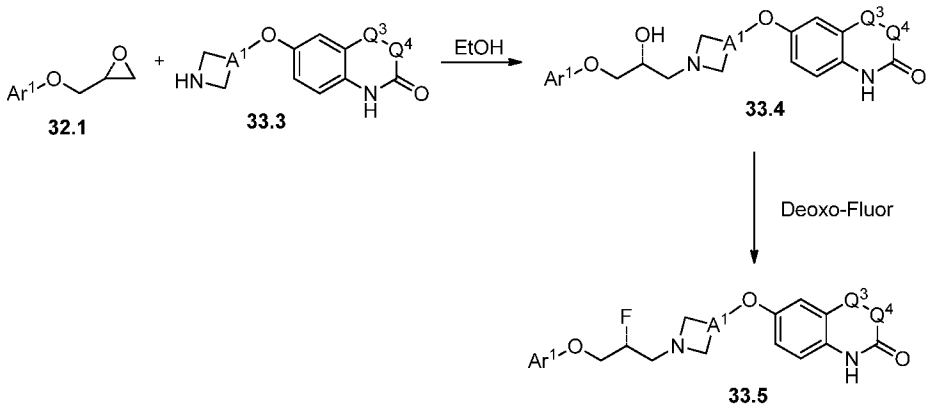
[00910] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed method can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

4. ROUTE IV

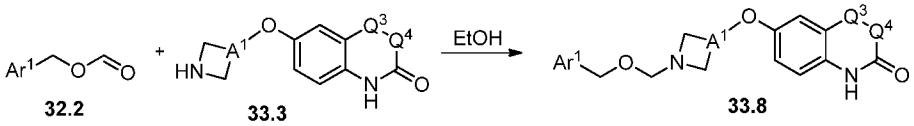
[00911] In one aspect, compounds of the present invention can be prepared as shown below.

Scheme 4a



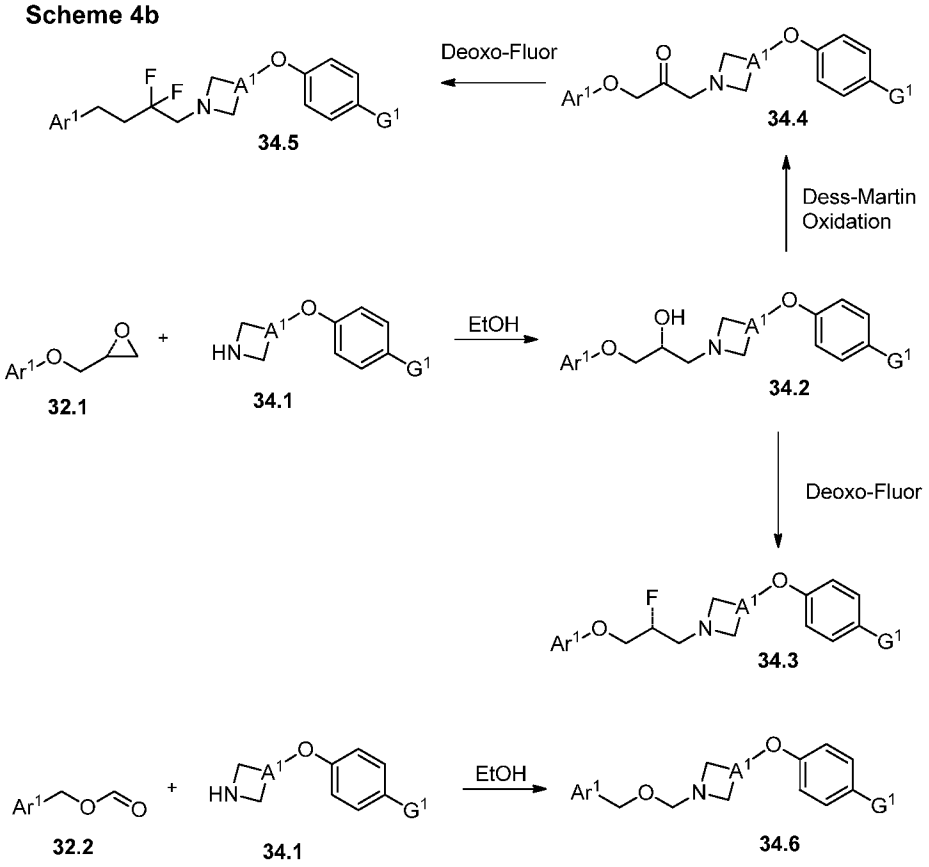


32.1 33.3 33.4 33.5



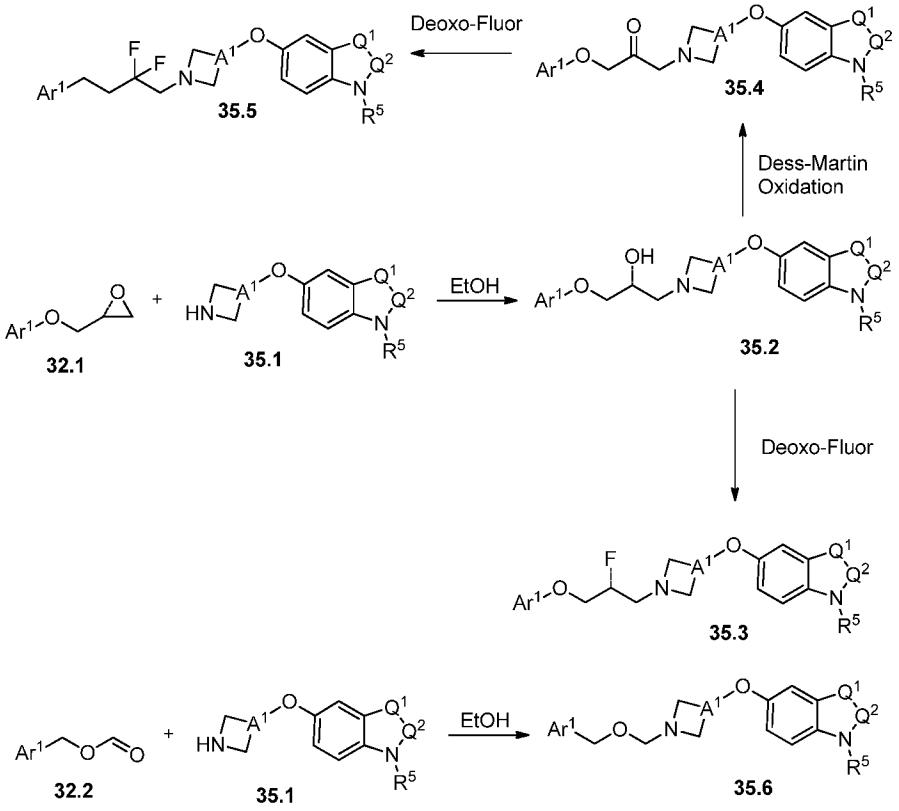
32.2 33.3 33.8

Scheme 4b

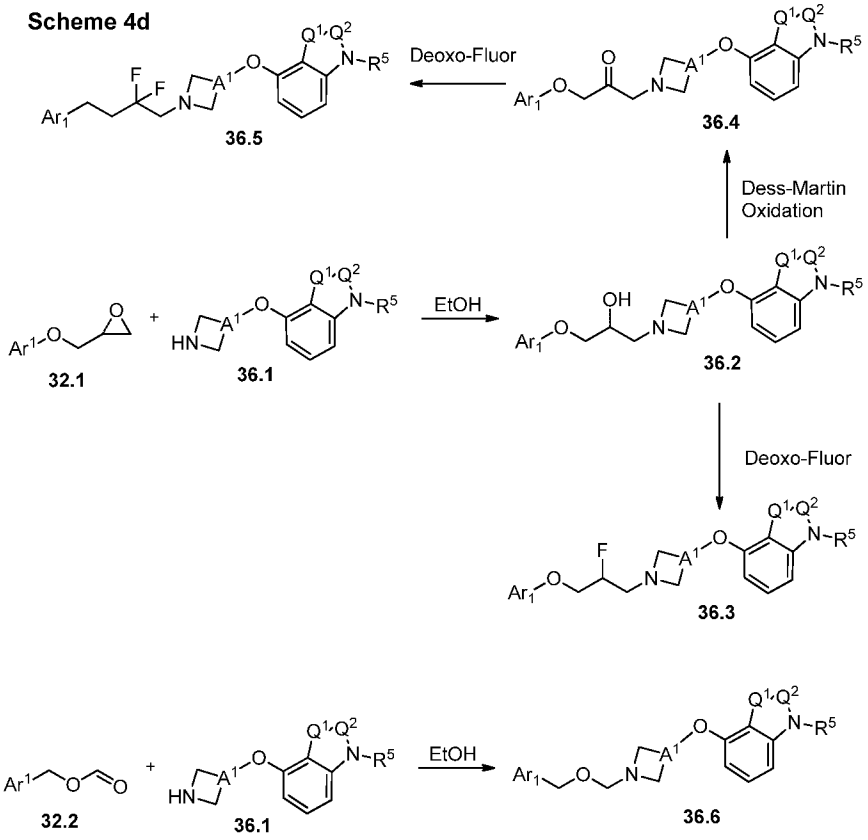


34.5 34.4 32.1 34.1 34.2 34.3 32.2 34.1 34.6

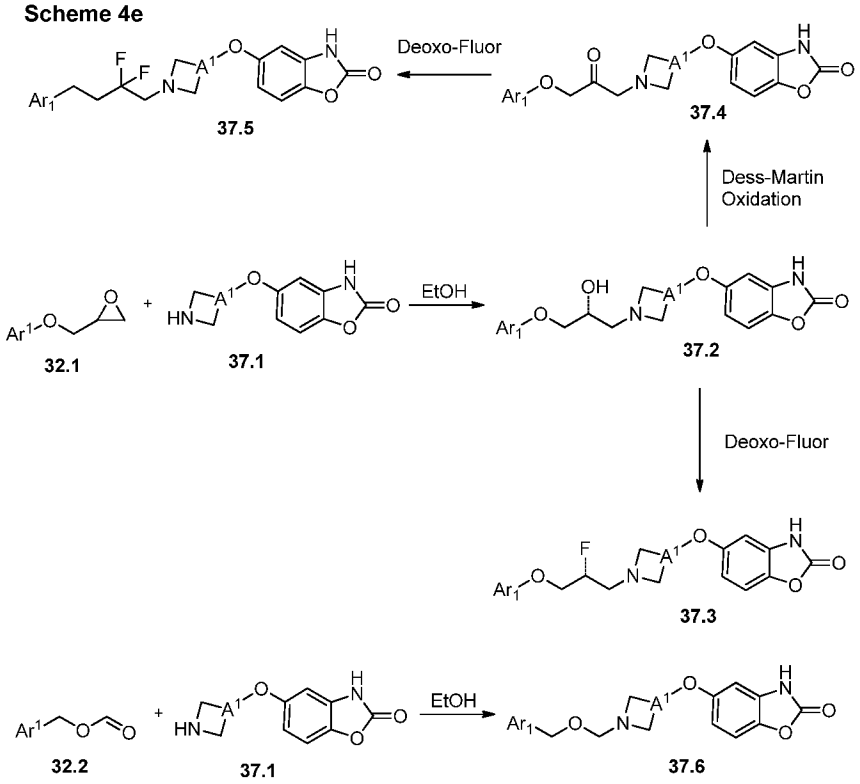
Scheme 4c



Scheme 4d

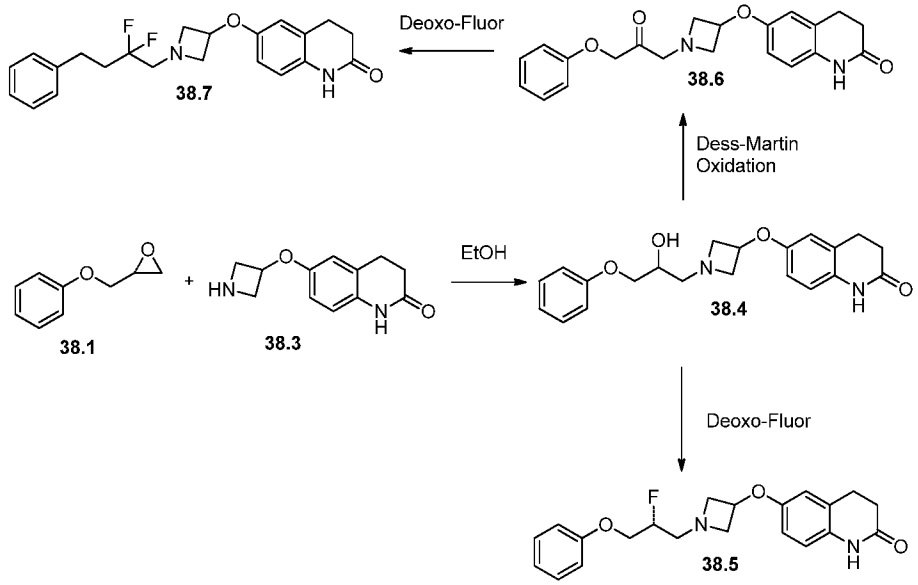


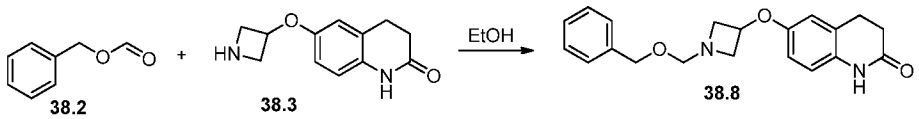
Scheme 4e



[00912] Compounds are represented in generic form, with substituents as noted in compound descriptions elsewhere herein. A more specific example is set forth.

Scheme 15.



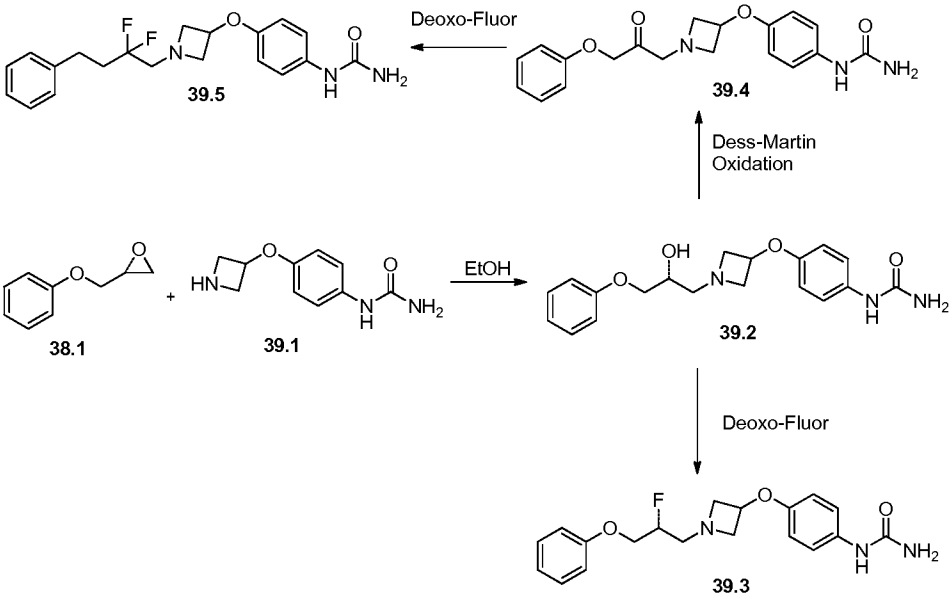


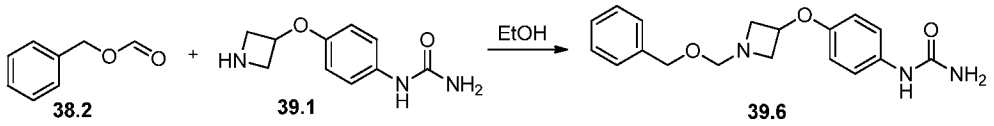
[00913] In various aspects, compounds of type (**38.4**) can be prepared by alkylation of a compound of type (**38.3**) with a compound of type (**38.1**), which can be prepared as described herein. For example, as shown above, such an alkylation reaction can be performed in a suitable polar protic solvent, e.g. EtOH. A compound of type (**38.5**) can be prepared by fluorination of a compound of type (**38.4**). For example, as shown above, such a fluorination reaction can be accomplished using a suitable fluorinating agent, e.g. Deoxo-Fluor. Alternatively, a compound of type (**38.6**) can be prepared by oxidation of a compound of type (**38.4**). For example, as shown above, such an oxidation reaction can be accomplished using a suitable oxidizing agent, e.g. Dess-Martin reagent. A compound of type (**38.7**) can be prepared by fluorination of a compound of type (**38.6**). For example, as shown above, such a fluorination reaction can be accomplished using a suitable fluorinating agent, e.g. Deoxo-Fluor.

[00914] In various aspects, compounds of type (**38.8**) can be prepared reductive amination of a compound of type (**38.3**) with a compound of type (**38.2**), which can be prepared as described herein. For example, as shown above, such a reaction can be performed in a suitable polar protic solvent, e.g. EtOH.

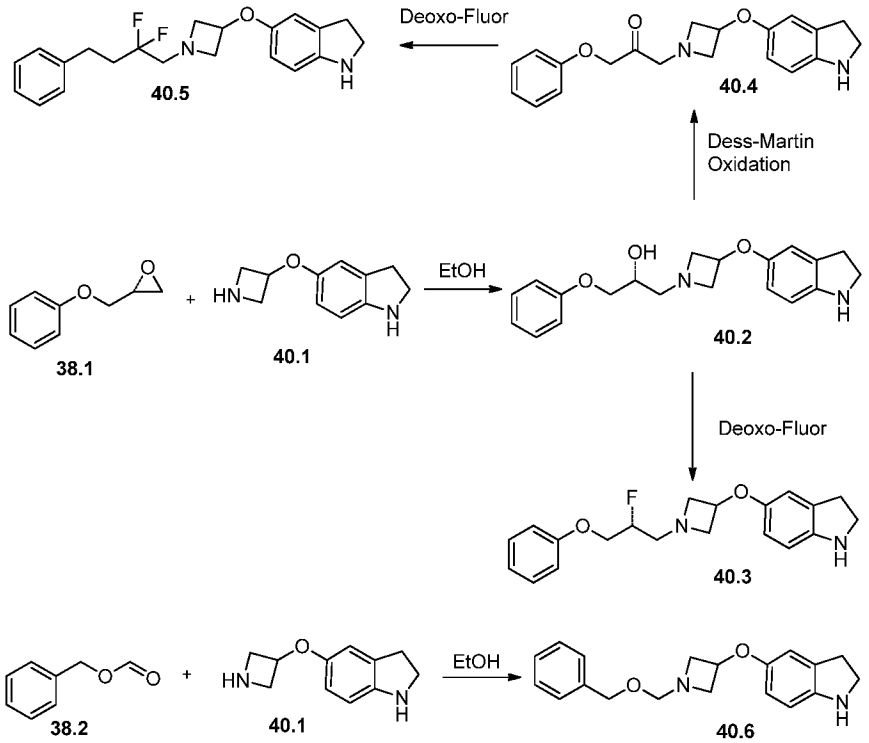
[00915] More specific examples are set forth below.

Scheme 16.

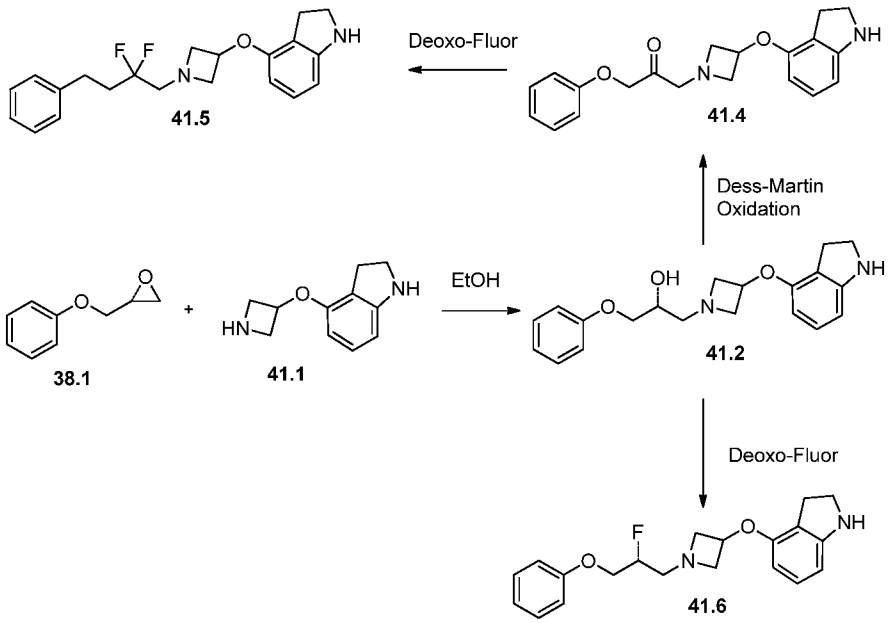


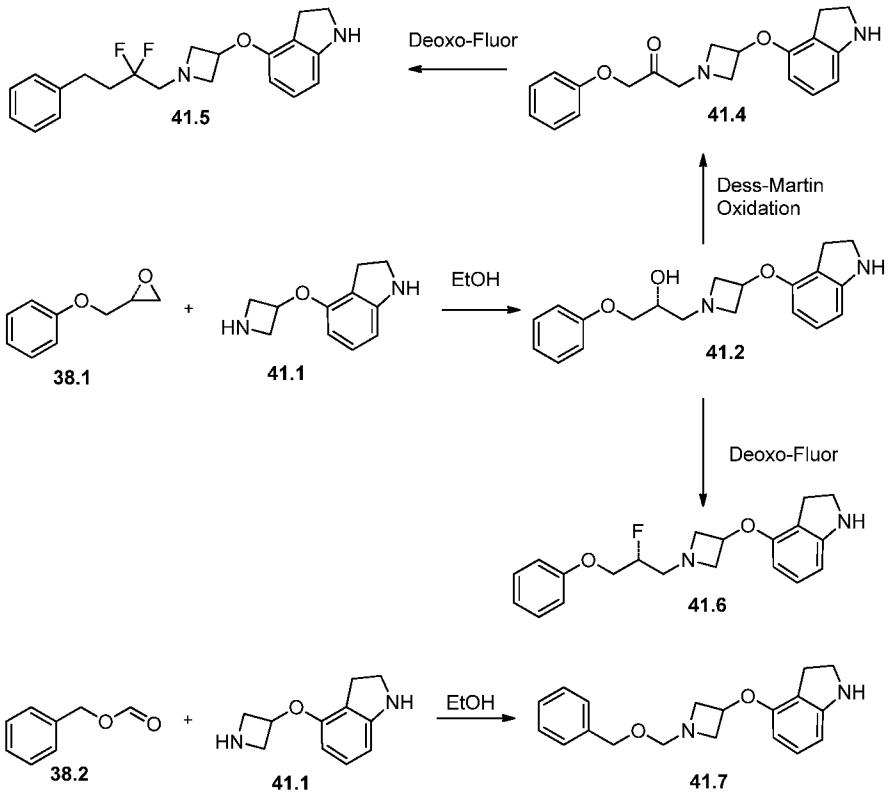


Scheme 17.

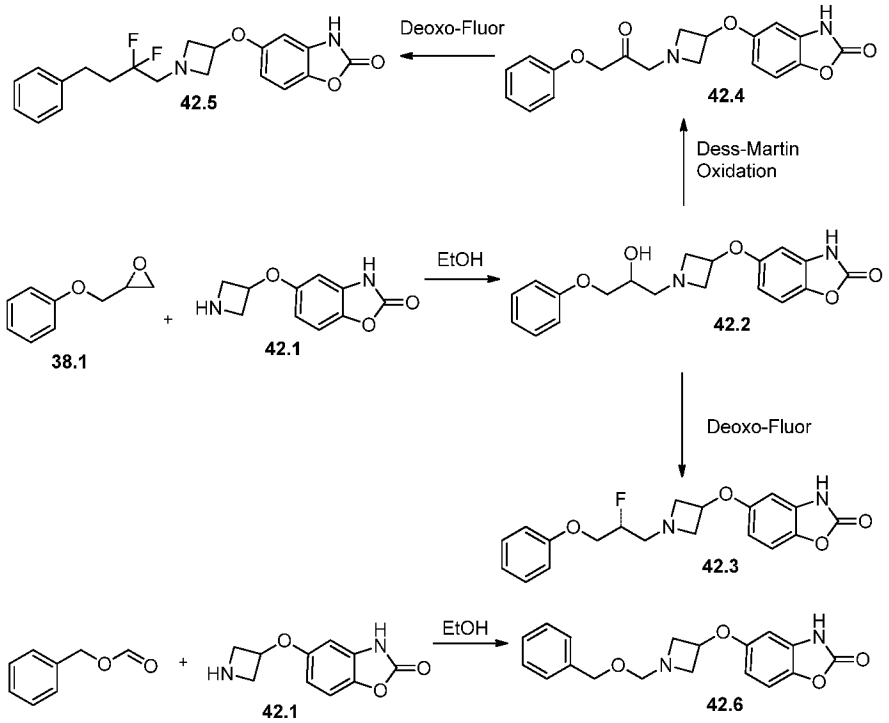


Scheme 18.





Scheme 19.



[00916] More specific examples are set forth within the Experimental section.

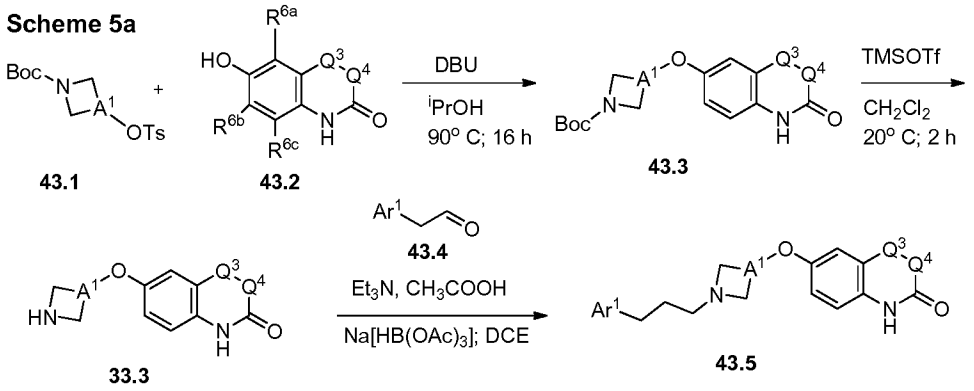
[00917] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step,

manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed method can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

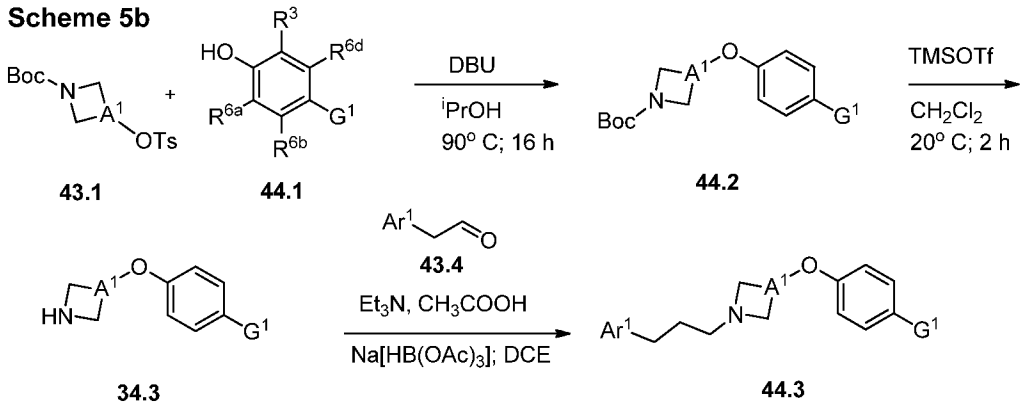
5. ROUTE V

[00918] In one aspect, substituted bicyclic oxazole lactam analogs of the present invention can be prepared as shown below.

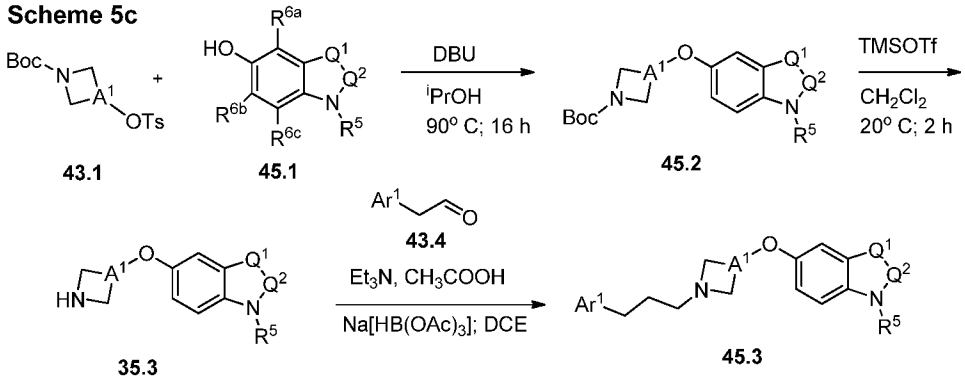
Scheme 5a



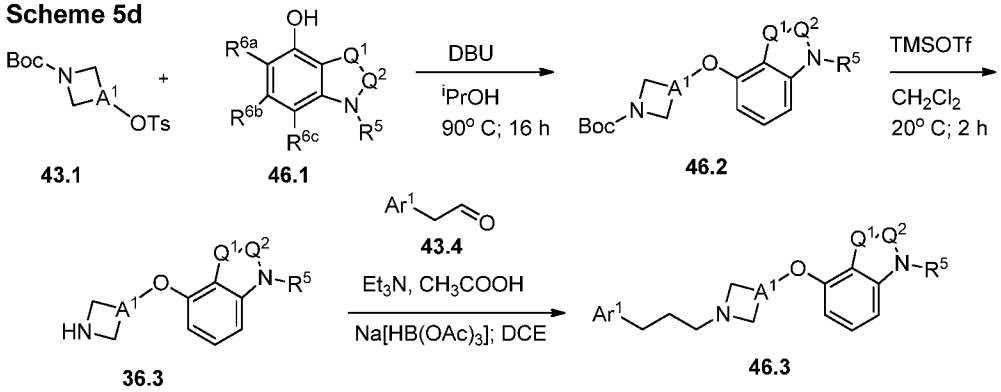
Scheme 5b



Scheme 5c

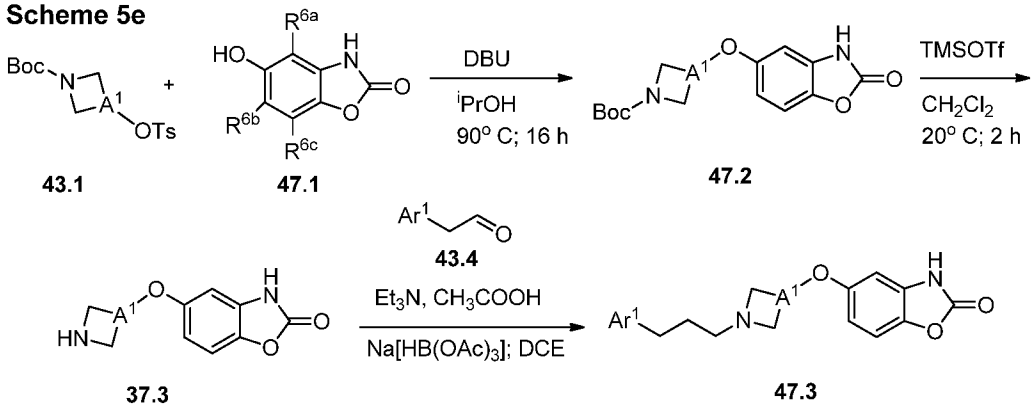


Scheme 5d



43.1 46.1 46.2 43.4 36.3 46.3

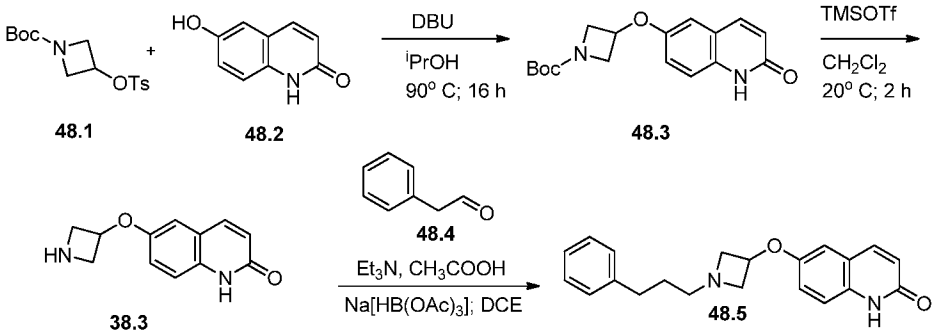
Scheme 5e



43.1 47.1 47.2 43.4 37.3 47.3

[00919] More specific examples are set forth here.

Scheme 20.



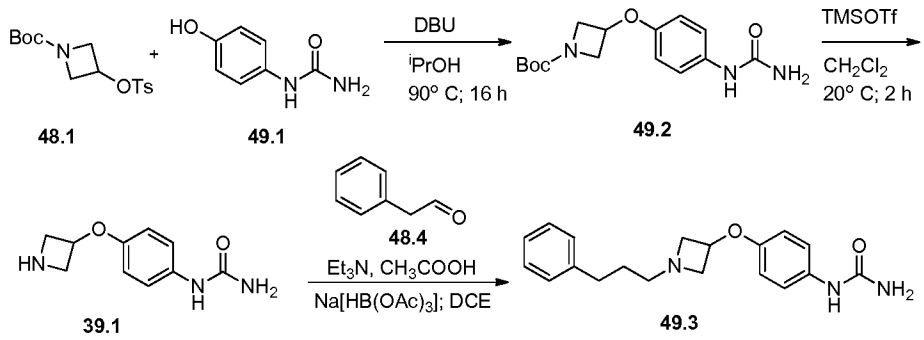
48.1 48.2 48.3 48.4 38.3 48.5

[00920] In various aspects, compounds of type (**48.3**) can be prepared starting with a compound of type (**48.1**), which is commercially available or prepared by methods known to one skilled in the art. Thus, a compound of type (**48.3**) can be prepared by a substitution reaction with a suitable nucleophile, (**48.2**) as shown above. A compound of type (**48.2**) is commercially available or prepared by methods known to one skilled in the art. The reaction is carried out with a suitable base, e.g. DBU, in a suitable solvent, e.g. isopropyl alcohol (*i*-PrOH), at a suitable temperature, e.g. 90 °C, for a period of time sufficient to complete the reaction, e.g. 16 hours. A compound of type (**38.3**) can be prepared by deprotection of a

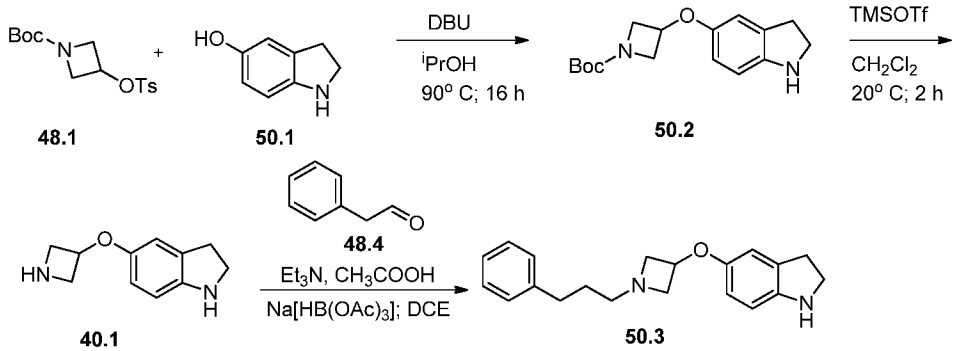
compound of type (**48.3**). For example, as shown above, such a deprotection reaction can be accomplished using a suitable deprotecting agent, e.g. TMSOTF, in a suitable solvent, e.g. dichloromethane, at a suitable temperature, e.g. 20 °C, for a period of time sufficient to complete the reaction, e.g. 2 hours. A compound of type (**48.5**) can be prepared reductive amination of a compound of type (**38.3**). For example, as shown above, such a reaction can be accomplished using a suitable carbonyl, e.g. (**48.4**), which is commercially available or prepared by methods known to one of skill in the art. The reaction is performed using a suitable base, e.g. triethylamine, a suitable catalyst, e.g. acetic acid, a suitable reducing agent, e.g. sodium triacetioxyborohydride, in a suitable solvent, e.g. 1,2-dichloroethane (DCE).

[00921] More specific examples are set forth below.

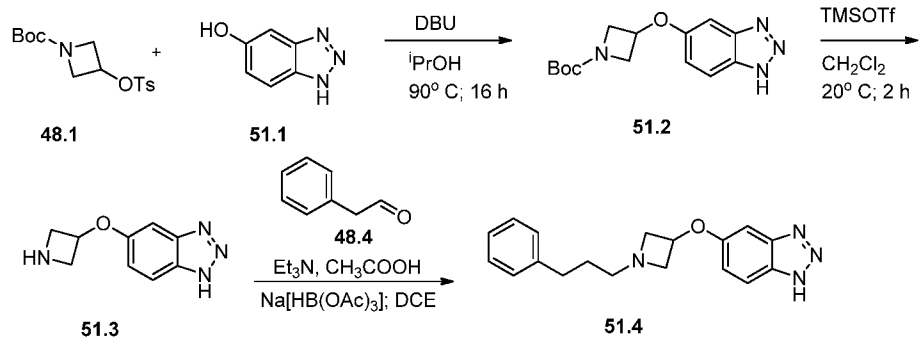
Scheme 21.



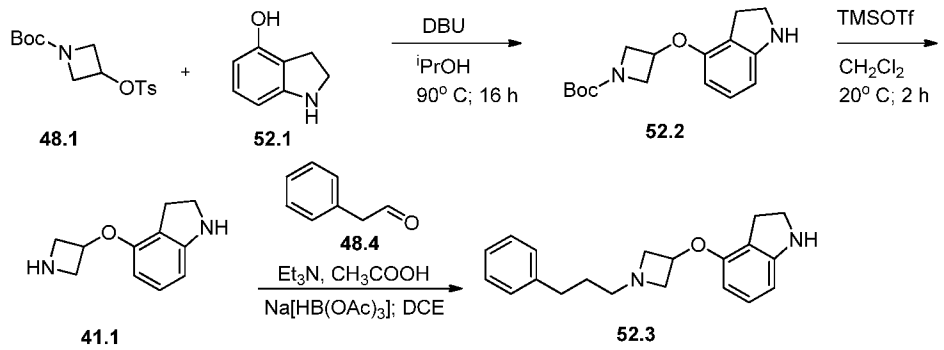
Scheme 22.



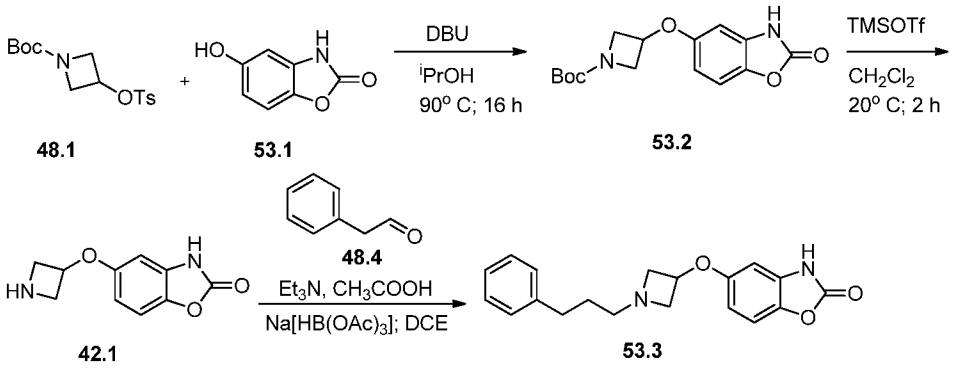
Scheme 23.



Scheme 24.



Scheme 25.



[00922] More specific examples are set forth within the Experimental section.

[00923] It is contemplated that each disclosed method can further comprise additional steps, manipulations, and/or components. It is also contemplated that any one or more step, manipulation, and/or component can be optionally omitted from the invention. It is understood that a disclosed method can be used to provide the disclosed compounds. It is also understood that the products of the disclosed methods can be employed in the disclosed methods of using.

E. PHARMACEUTICAL COMPOSITIONS

[00924] In one aspect, the invention relates to pharmaceutical compositions comprising the disclosed compounds. That is, a pharmaceutical composition can be provided comprising a therapeutically effective amount of at least one disclosed compound or at least one product of a disclosed method and a pharmaceutically acceptable carrier.

[00925] In certain aspects, the disclosed pharmaceutical compositions comprise the disclosed compounds (including pharmaceutically acceptable salt(s) thereof) as an active ingredient, a pharmaceutically acceptable carrier, and, optionally, other therapeutic ingredients or adjuvants. The instant compositions include those suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous)

administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00926] In various aspects, the invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and, as active ingredient, a therapeutically effective amount of a disclosed compound, a product of a disclosed method of making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, or a stereochemically isomeric form thereof. In a further aspect, a disclosed compound, a product of a disclosed method of making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, or a stereochemically isomeric form thereof, or any subgroup or combination thereof may be formulated into various pharmaceutical forms for administration purposes.

[00927] As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (-ic and -ous), ferric, ferrous, lithium, magnesium, manganese (-ic and -ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[00928] As used herein, the term "pharmaceutically acceptable non-toxic acids", includes inorganic acids, organic acids, and salts prepared therefrom, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic,

glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[00929] For therapeutic use, salts of the disclosed compounds are those wherein the counter ion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not, are included within the ambit of the present invention.

[00930] The pharmaceutically acceptable acid and base addition salts as mentioned hereinabove or hereinafter are meant to comprise the therapeutically active non-toxic acid and base addition salt forms which the disclosed compounds are able to form. The pharmaceutically acceptable acid addition salts can conveniently be obtained by treating the base form with such appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids. Conversely said salt forms can be converted by treatment with an appropriate base into the free base form.

[00931] The disclosed compounds containing an acidic proton may also be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-*n*-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline; the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

[00932] In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in 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, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, and/or pharmaceutically acceptable salt(s) thereof, can also be administered by controlled release means and/or delivery devices. The compositions can be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[00933] It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

[00934] Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of the compounds of the invention. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[00935] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup,

peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[00936] In order to enhance the solubility and/or the stability of the compounds of Formula (I) in pharmaceutical compositions, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives, in particular hydroxyalkyl substituted cyclodextrins, e.g. 2-hydroxypropyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin. Also co-solvents such as alcohols may improve the solubility and/or the stability of the compounds according to the invention in pharmaceutical compositions.

[00937] Because of the ease in administration, oral administration is preferred, and tablets and capsules represent the most advantageous oral dosage unit forms in which case solid pharmaceutical carriers are obviously employed. In preparing the compositions for oral dosage form, any convenient pharmaceutical media can be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets can be coated by standard aqueous or nonaqueous techniques

[00938] A tablet containing the composition of this invention can be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets can be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, 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.

[00939] The pharmaceutical compositions of the present invention comprise a compound of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered.

The pharmaceutical compositions can be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[00940] Pharmaceutical compositions of the present invention suitable for parenteral administration can be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[00941] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[00942] Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations.

[00943] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, mouth washes, gargles, and the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations can be prepared, utilizing a compound of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

[00944] In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a

significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

[00945] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories can be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[00946] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, and/or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

[00947] The exact dosage and frequency of administration depends on the particular disclosed compound, a product of a disclosed method of making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, or a stereochemically isomeric form thereof; the particular condition being treated and the severity of the condition being treated; various factors specific to the medical history of the subject to whom the dosage is administered such as the age; weight, sex, extent of disorder and general physical condition of the particular subject, as well as other medication the individual may be taking; as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

[00948] Depending on the mode of administration, the pharmaceutical composition will comprise from 0.05 to 99 % by weight, preferably from 0.1 to 70 % by weight, more preferably from 0.1 to 50 % by weight of the active ingredient, and, from 1 to 99.95 % by weight, preferably from 30 to 99.9 % by weight, more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

[00949] In the treatment conditions which require positive allosteric modulation of metabotropic glutamate receptor activity an appropriate dosage level will generally be about 0.01 to 1000 mg per kg patient body weight per day and can be administered in single or multiple doses. In various aspects, the dosage level will be about 0.1 to about 500 mg/kg per day, about 0.1 to 250 mg/kg per day, or about 0.5 to 100 mg/kg per day. A suitable dosage level can be about 0.01 to 1000 mg/kg per day, about 0.01 to 500 mg/kg per day, about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage can be 0.05 to 0.5, 0.5 to 5.0 or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750, 800, 900 and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage of the patient to be treated. The compound can be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. This dosing regimen can be adjusted to provide the optimal therapeutic response.

[00950] Such unit doses as described hereinabove and hereinafter can be administered more than once a day, for example, 2, 3, 4, 5 or 6 times a day. In various aspects, such unit doses can be administered 1 or 2 times per day, so that the total dosage for a 70 kg adult is in the range of 0.001 to about 15 mg per kg weight of subject per administration. In a further aspect, dosage is 0.01 to about 1.5 mg per kg weight of subject per administration, and such therapy can extend for a number of weeks or months, and in some cases, years. It will be understood, however, that the specific dose level for any particular patient will depend on a variety of factors including the activity of the specific compound employed; the age, body weight, general health, sex and diet of the individual being treated; the time and route of administration; the rate of excretion; other drugs that have previously been administered; and the severity of the particular disease undergoing therapy, as is well understood by those of skill in the area.

[00951] A typical dosage can be one 1 mg to about 100 mg tablet or 1 mg to about 300 mg taken once a day, or, multiple times per day, or one time-release capsule or tablet taken once a day and containing a proportionally higher content of active ingredient. The time-release effect can be obtained by capsule materials that dissolve at different pH values, by capsules that release slowly by osmotic pressure, or by any other known means of controlled release.

[00952] It can be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician

will know how and when to start, interrupt, adjust, or terminate therapy in conjunction with individual patient response.

[00953] The present invention is further directed to a method for the manufacture of a medicament for modulating NMDA receptor activity (*e.g.*, treatment of one or more neurological and/or psychiatric disorders associated with glutamate dysfunction) in mammals (*e.g.*, humans) comprising combining one or more disclosed compounds, products, or compositions with a pharmaceutically acceptable carrier or diluent. Thus, in one aspect, the invention relates to a method for manufacturing a medicament comprising combining at least one disclosed compound or at least one disclosed product with a pharmaceutically acceptable carrier or diluent.

[00954] The disclosed pharmaceutical compositions can further comprise other therapeutically active compounds, which are usually applied in the treatment of the above mentioned pathological conditions.

[00955] It is understood that the disclosed compositions can be prepared from the disclosed compounds. It is also understood that the disclosed compositions can be employed in the disclosed methods of using.

[00956] As already mentioned, the invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound, a product of a disclosed method of making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, and a pharmaceutically acceptable carrier. Additionally, the invention relates to a process for preparing a such pharmaceutical composition, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to the invention.

[00957] As already mentioned, the invention also relates to a pharmaceutical composition comprising a disclosed compound, a product of a disclosed method of making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, and one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for a disclosed compound or the other drugs may have utility as well as to the use of such a composition for the manufacture of a medicament. The present invention also relates to a combination of disclosed compound, a product of a disclosed method of making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, and a NMDA receptor antagonist. The present invention also relates to such a combination for use as a medicine. The present invention also relates to a product comprising (a) disclosed compound, a product of a disclosed method of

making, a pharmaceutically acceptable salt thereof, a hydrate thereof, a solvate thereof, a polymorph thereof, and (b) a NMDA receptor antagonist, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of NMDA receptor modulators, in particular negative NMDA modulators. The different drugs of such a combination or product may be combined in a single preparation together with pharmaceutically acceptable carriers or diluents, or they may each be present in a separate preparation together with pharmaceutically acceptable carriers or diluents.

F. METHODS OF USING THE COMPOUNDS AND COMPOSITIONS

[00958] The ionotropic glutamate receptors, which mediate excitatory synaptic transmission, are: kainite receptors, AMPA receptors and NMDA receptors. In addition to mediating excitatory synaptic transmission between neurons in the central nervous system, the NMDA subtype of glutamate-gated ion channels is involved in a variety of both physiological and pathological processes in the central nervous system. Moreover, NMDA receptors are found in neurons throughout the brain including the cortico-limbic regions, which have been reported to participate in emotional functions, anxiety and depression. To this end, many studies have also reported benefits of NMDA receptor antagonists in a variety of neurological and psychiatric disorders, including, but not limited to, neuropsychiatric disorders, neurodegenerative disorders including Parkinson's Disease and Alzheimer's disease, brain cancer, mood disorders including depressive disorders and bipolar disorders, as well as neurologic disorders including chronic and neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events. Thus, modulation of the NMDA receptor system is an important therapeutic goal. While GluN1 subunits are expressed virtually uniformally in all neurons and at all developmental stages, the GluN2 subunits exhibit different regional distribution and developmental patterns, and can provide a more selective therapeutic target.

[00959] Traumatic brain injuries ("TBI") comprise penetrating head injuries and closed head injuries. Penetrating brain injuries can occur when an object, like shrapnel, enters the brain and causes damage in a specific anatomical region of the brain. Closed head injuries can occur as a result of a blow to the head, which can happen during a fall, car accident, explosive blast injury, sporting event, or any number of different ways. Concussions can be considered a type of TBI.

[00960] The compounds disclosed herein are modulators of NMDA receptors, in particular they are inhibitors of NMDA receptor activity. Without wishing to be bound by a particular theory, the compounds of the present invention can inhibit NMDA activity by acting as antagonists. In various aspects, the compounds can inhibit NMDA activity by acting as partial antagonists. In various further aspects, the compounds can inhibit NMDA activity by acting as negative allosteric modulators.

[00961] Father, without wishing to be bound by a particular theory, the disclosed compound can exhibit a diminution, inhibition or abolishment of the NMDA receptor subunit GluN1/GluN2B response in NMDA-transfected Xenopus oocytes with an IC_{50} less than the IC_{50} for one or more of GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D response in NMDA-transfected Xenopus oocytes. That is, a disclosed compound can have selectivity for the NMDA receptor subunit GluN1/GluN2B vis-à-vis one or more of the GluN1/GluN2A, GluN1/GluN2C and GluN1/GluN2D receptors.

[00962] Hence, the present invention relates to compounds disclosed herein for use as a medicament, as well as to the use of a compound disclosed herein or a pharmaceutical composition according to the invention for the manufacture of a medicament, including, for example, the manufacture of a medicament for treating or preventing, in particular treating, a condition in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of inhibitors of NMDA activity, e.g. NMDA receptor antagonists thereof. The present invention also relates to a compound disclosed herein or a pharmaceutical composition according to the invention for use in the treatment or prevention of a condition in a subject such as a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of inhibitors of NMDA, e.g. NMDA receptor antagonists thereof.

1. TREATMENT METHODS

[00963] The compounds disclosed herein are useful for treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and/or psychiatric disorders, including abnormalities of the nervous system, in a subject such as a mammal, including a human. The present invention also relates to the use of a compound disclosed herein or a pharmaceutical composition according to the invention for the manufacture of a medicament for treating, preventing, ameliorating, controlling or reducing the risk of various neurological and psychiatric disorders associated with glutamate receptor dysfunction in a subject such as a mammal, including a human, the treatment or prevention of which is affected or facilitated by the neuromodulatory effect of modulators of NMDA, e.g. negative modulators thereof.

[00964] In various aspects, the neurological and/or psychiatric disorder may be associated with NMDA receptor activation, and in particular with activation of NMDA receptors comprising a GluN2 subunit, e.g. GluN2B. In a further aspect, disorders that can be treated or for which symptoms can be reduced include neuropsychiatric disorders, neurodegenerative disorders, as well as neurologic disorders including neuropathic pain, stroke, traumatic brain injury, epilepsy, and other neurologic events.

[00965] In various aspects, the disclosed compounds are used for the treatment or prevention of neuropsychiatric disorders. Examples of these disorders include, without limitation, depression, anxiety, schizophrenia, bipolar disorder, obsessive-compulsive disorder, alcohol and substance abuse, and attention-deficit hyperactivity disorder.

[00966] In a further aspect, the disclosed compounds are useful for the treatment or prevention of neurodegenerative disorders. These disorders are typically characterized by gradual and progressive nervous system dysfunction due to loss of neuronal cells and neuronal tissue. Examples of such disorders include, without limitation, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS/Lou Gehrig's disease), Multiple Sclerosis, spinal muscular atrophy, spinal & bulbar muscular atrophy, familial spastic paraparesis, Machado Joseph disease, Friedreich's ataxia and Lewy body disease.

[00967] In a further aspect, the disclosed compounds are useful for the treatment or prevention of neurologic disorders. Examples of these disorders include, without limitation, neuropathic pain, stroke, traumatic brain injury, and epilepsy.

[00968] In one aspect, disclosed are methods for the treatment or prevention of a neurological disorder, such as a neuropsychiatric or neurological disease or disorder or a disorder resulting from injury, trauma, infection or ischemia, comprising administering a disclosed compound, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, to the subject. In a further aspect, the disorder is a neuropsychiatric disorder. In a still further aspect, the disorder is neuropathic pain. In yet a further aspect, the disorder is an injury resulting from an ischemic event or neuropathic injury or injection.

[00969] In various aspects, methods are provided for the treatment or prevention of neurodegeneration in subjects with Parkinson's, Alzheimer's, Huntington's chorea, ALS, and other neurodegenerative conditions.

[00970] In a further aspect, uses of the compounds in the treatment or manufacture of a medicament for such disorders are also provided.

[00971] In one aspect, disclosed are methods for the treatment or prevention of a neurological disorder, such as a neuropsychiatric or neurodegenerative disease or disorder or a disorder resulting from injury, trauma, infection or ischemia, comprising: administering to a subject a disclosed compound of or pharmaceutically acceptable salt, ester or prodrug thereof, either alone or in combination, in which the subject is suffering from a reduced pH in a region of the brain. In further aspect, a disorder has caused a region of the brain with a pH below pH 7.6, or below 7.5, or below 7.4, or below 7.3, or below 7.2, or below 7.1, or below 7, or below 6.9, or below 6.8, or below 6.7, or below 6.6 or below 6.5 or below 6.4. In a further aspect, the reduced pH is due to pathological conditions such as hypoxia resulting from stroke, traumatic brain injury, global ischemia, such as global ischemia that may occur during cardiac surgery, hypoxia, including hypoxia that may occur following cessation of breathing, pre-eclampsia, spinal cord trauma, epilepsy, status epilepticus, neuropathic pain, inflammatory pain, chronic pain, vascular dementia and glioma tumors.

[00972] In further aspect, disclosed are methods for attenuating the progression of an ischemic or excitotoxic cascade, comprising: an effective amount of at least one disclosed compound, a pharmaceutically acceptable salt, solvate, or polymorph thereof. In a yet further aspect, disclosed are methods to decrease infarct volume comprising administering at least one disclosed compound, or pharmaceutically acceptable salt, solvate, or polymorph thereof.

[00973] In a further aspect, disclosed are methods to decrease behavioral deficits associated with an ischemic event comprising administering at least one disclosed compound, or pharmaceutically acceptable salt, solvate, or polymorph thereof. In a yet further aspect, disclosed are methods for the treatment of patients with ischemic injury or hypoxia; prevention or treatment of neuronal toxicity associated with ischemic injury or hypoxia, comprising administering a compound or composition described herein. In a still further aspect, the ischemic injury is stroke. In an even further aspect, the ischemic injury is vasospasm after subarachnoid hemorrhage. In yet further aspect, the ischemic injury is selected from: traumatic brain injury, cognitive deficit after bypass surgery, cognitive deficit after carotid angioplasty; and/or neonatal ischemia following hypothermic circulatory arrest, or a combination thereof.

[00974] In a further aspect, the compounds and methods according to the present inventions can be used prophylactically in a subject to prevent or protect against neurologic diseases, disorders or conditions, such as those described herein. In a yet further aspect, the subject is at risk or has a predisposition for an ischemic event, such as due to genetic predisposition or medical history. In still further aspect, the subject is at risk for or exhibiting

vasospasms that can be treated or for which symptoms can be alleviated with the disclosed methods and compounds. In an even further aspect, the subject to be prophylactically treated is undergoing cardiac bypass surgery.

[00975] In a further aspect, the present invention provides methods for the treatment of neuropathic pain or related disorders comprising administering at least one disclosed compound, or pharmaceutically acceptable salt, solvate, or polymorph thereof. In a yet further aspect, the neuropathic pain or related disorder is selected from: peripheral diabetic neuropathy, postherpetic neuralgia, complex regional pain syndromes, peripheral neuropathies, chemotherapy-induced neuropathic pain, cancer neuropathic pain, neuropathic low back pain, HIV neuropathic pain, trigeminal neuralgia, central post-stroke pain, or a combination thereof. In a still further aspect, the disorder or dysfunction is associated with symptoms selected from: allodynia, hyperalgesia, abnormal sensations, burning, shooting, stabbing, paroxysmal or electrical-sensations, paresthesias, hyperpathia, dysesthesias, or a combination thereof. In an even further aspect, the symptoms are spontaneous, intermittent, transient, chronic, or a combination thereof.

[00976] In a further aspect, the invention relates to compounds and methods for use in the treatment of neuropathic pain associated with peripheral or central nervous system pathologic events. In a yet further aspect, nervous system event associated with the neuropathic pain is selected from: trauma, ischemia, infection; endocrinologic disorders, including, but not limited to, diabetes mellitus, diabetic neurophathy, amyloidosis, amyloid polyneuropathy (primary and familial), neuropathies with monoclonal proteins, vasculitic neuropathy, HIV infection, herpes zoster—shingles, postherpetic neuralgia; neuropathy associated with Guillain-Barre syndrome; neuropathy associated with Fabry's disease; entrapment due to anatomic abnormalities; trigeminal and other CNS neuralgias; malignancies; inflammatory conditions or autoimmune disorders, including, but not limited to, demyelinating inflammatory disorders, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome; and cryptogenic causes, including, but not limited to, idiopathic distal small-fiber neuropathy. In a still further aspect, the neuropathic pain is associated with exposure to toxins or drugs (such as arsenic, thallium, alcohol, vincristine, cisplatinum and dideoxynucleosides), dietary or absorption abnormalities, immuno-globulinemias, hereditary abnormalities and amputations (including mastectomy). Neuropathic pain can also result from compression of nerve fibers, such as radiculopathies and carpal tunnel syndrome. It will be appreciated by those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention.

[00977] In a further aspect, the present invention provides methods for treating patients with neurodegenerative diseases by administering a compound selected according to the methods or processes described herein. These neurodegenerative disorders include, without limitation, Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS/Lou Gehrig's disease), Multiple Sclerosis, spinal muscular atrophy, spinal and bulbar muscular atrophy, familial spastic paraparesis, Machado Joseph disease, Friedreich's ataxia and Lewy body disease. In one embodiment, the neurodegenerative disease can be Parkinson's disease. In another embodiment, the neurodegenerative disease can be Alzheimer's disease. In another embodiment, the neurodegenerative disease can be Huntington's disease and/or ALS.

[00978] In a further aspect, provided are methods for treating patients with brain tumors by administering a compound selected according to the methods or processes described herein. In some embodiments, the compounds are useful in the treatment of tumor growth. In certain embodiments, the compounds reduce tumor mass. In one embodiment, the compounds are useful in the treatment or prophylaxis of a neurologic event involving acidification of brain or spinal cord tissue. In another embodiment, the NMDA receptor antagonists of this invention are useful both in the treatment of stroke and head trauma, and for use as prophylactic agents for at risk patients. The acid generated by ischemic tissue during stroke is harnessed as a switch to activate the neuroprotective agents described herein. In this way side effects are minimized in unaffected tissue since drug at these sites are less active. These compounds may be used to reduce the amount of neuronal death associated with stroke and head trauma. They may be given chronically to individuals with epilepsy or who are at risk for stroke or head trauma, preoperatively in high risk heart/brain surgery, etc., in order to lengthen the window of opportunity for subsequent therapy.

[00979] Also provided are methods for treating the following diseases or neurological conditions, including, but not limited to: chronic nerve injury, chronic pain syndromes, such as, but not limited to diabetic neuropathy, ischemia, ischemia following transient or permanent vessel occlusion, seizures, spreading depression, restless leg syndrome, hypocapnia, hypercapnia, diabetic ketoacidosis, fetal asphyxia, spinal cord injury, traumatic brain injury, status epilepticus, epilepsy, hypoxia, perinatal hypoxia, concussion, migraine, hypocapnia, hyperventilation, lactic acidosis, fetal asphyxia during parturition, brain gliomas, and/or retinopathies by administering a compound selected according to the methods or processes described herein.

[00980] In one aspect, the disclosed compounds have utility in the treatment or prevention of a variety of neuropsychiatric disorders. Generally, these disorders are mental disturbances attributable to diseases of the nervous system. These disorders include depression, anxiety, schizophrenia, bipolar disorder, obsessive-compulsive disorder, alcohol and substance abuse, and attention-deficit hyperactivity disorder. In specific aspects, the disorders are neuropsychiatric mood disorders, non-limiting examples of which include depression, including major depression, bipolar disorders including cyclothymia (a mild form of bipolar disorder), affective disorders such as SAD (seasonal affective disorder) and mania (euphoric, hyperactive, over inflated ego, unrealistic optimism). Neuropsychiatric disorders also include attention deficit disorders such as ADH or ADHD. In certain embodiments, a method of treatment a neuropsychiatric disorder is provided including administering a compound of the invention, alone or in combination to a host diagnosed with the disorder. Uses of the compounds in the treatment or manufacture of a medicament for such disorders are also provided.

[00981] In certain embodiments, the compounds are used for the treatment of depression in a host diagnosed with the disorder. In certain other embodiments, the compounds are used for treatment of a bipolar disorder in a host diagnosed with the disorder. The compounds can also be used to diminish the severity of depressive or manic episodes or prevent future episodes. In certain embodiments, methods of treating seasonal disorders is provided including administering the compound to a host at risk of suffering from a SAD. In particular, the compounds can be provided on a seasonal basis. In some embodiments, the host has been diagnosed as suffering from or is at risk for SAD or depression. In certain embodiments, the host is at risk of suffering from a mania. The mania can be characterized by euphoria, hyperactivity, over-inflated ego, or unrealistic optimism. In certain embodiments, the host is suffering from an attention deficit disorders such as ADH or ADHD.

[00982] Depression, formally called major depression, major depressive disorder or clinical depression, is a medical illness that involves the mind and body. Most health professionals today consider depression a chronic illness that requires long-term treatment, much like diabetes or high blood pressure. Although some people experience only one episode of depression, most have repeated episodes of depression symptoms throughout their life. Depression is also a common feature of mental illness, whatever its nature and origin. In some instances, the host or patient has a history of a major psychiatric disorder, such as schizophrenia. In other instances, the host does not have a history of a major psychiatric

disorder but has been diagnosed with suffering from at least one depressive episode. In other instances, the host has been diagnosed with bipolar disorder. The host may also have been diagnosed as suffering from panic attacks or anxiety.

[00983] In some instances, the host is not suffering from a chronic disorder but is at risk of a depressive episode, anxiety or a panic attack due to environmental circumstances. The compounds may be given prophylactically to prevent onset of such an episode. For instance, in certain instances the compounds can be provided to a host before a plane trip, a public speech, or other potential stressful even that could lead to an episode. In some embodiments, therefore, a method of prevention of a neuropsychiatric episode is provided, including administering a compound of the invention to a host at risk of suffering from such an episode. In some instances, the compounds are useful for treatment or prophylaxis of disorders such as depression or bipolar disorder associated with an injury or with aging. The compounds may also be useful in the treatment or prophylaxis of schizophrenia.

[00984] In one aspect, the disclosed compounds block GluN2B-containing NMDA receptors, have varying activity against receptors containing GluN2A or GluN2D, and may be selective for other members of the NMDA receptor family (GluN2C, GluN3A and GluN3B). In a further aspect, the compounds are selective NMDA receptor blockers. General blocking of NMDA receptors throughout the brain causes adverse effects such as ataxia, memory deficits, hallucinations and other neurological problems. In one embodiment, the compounds are NMDA receptor antagonists selective for GluN2B, GluN2A, GluN2C, GluN2D, GluN3A, and/or GluN3B that do not interact with other receptors or ion channels at therapeutic concentrations. In one embodiment, the compound is a selective GluN1/GluN2A NMDA receptor and/or a GluN1/GluN2B NMDA receptor antagonist. In one particular embodiment, the compounds can bind to the GluN2B subunit of the NMDA receptor. In another particular embodiment, the compounds are selective for the GluN2B subunit of the NMDA receptor. In one embodiment, the compound is not an NMDA receptor glutamate site antagonist. In another embodiment, the compound is not an NMDA receptor glycine site antagonist.

[00985] GluN2B-containing NMDA receptors may also be referred to as NR2B-containing NMDA receptors. Similarly, GluN2A is used interchangeably with NR2A, GluN2D with NR2D, GluN2C with NR2C, GluN3A with NR3A, and GluN3B with NR3B.

[00986] In certain embodiments, the compounds are administered to a host suffering from or at risk of suffering from age-related depression. The compounds can be administered

prophylactically to a host over the age of 60, or over the age of 70, or over the age of 80 to prevent or reduce the severity of depressive episodes.

[00987] In certain embodiments, compounds of the present invention can be used to inhibit mTOR or mTOR signaling. In one embodiment, the compounds can be used to modulate mTOR activity in the brain, for example in the prefrontal cortex. Compounds which modulate or inhibit mTOR may be useful in the treatment or prophylaxis of depression and other neuropsychiatric disorders.

[00988] In a particular embodiment, compounds of the present invention may be used to treat traumatic brain injury caused by a blast or a blast injury.

[00989] Examples of disorders associated with glutamate dysfunction include: autism, acute and chronic neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, dementia (including AIDS-induced dementia), Alzheimer's disease, Huntington's Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson's disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, addictive behavior, including addiction to substances (including opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), obesity, psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

Epilepsy can be treated or prevented by the compositions disclosed herein, including absence epilepsy. In various aspects, the compositions disclosed herein can have a protective role for spike and wave discharges associated with absence seizures. Anxiety disorders that can be treated or prevented by the compositions disclosed herein include generalized anxiety disorder, panic disorder, and obsessive compulsive disorder. Addictive behaviors include addiction to substances (including opiates, nicotine, tobacco products, alcohol,

benzodiazepines, cocaine, sedatives, hypnotics, etc.), withdrawal from such addictive substances (including substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.) and substance tolerance.

[00990] Thus, in some aspects of the disclosed method, the disorder is dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression.

[00991] Also provided is a method for treating or preventing anxiety, comprising: administering to a subject at least one disclosed compound; at least one disclosed pharmaceutical composition; and/or at least one disclosed product in a dosage and amount effective to treat the disorder in the subject . At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified.

[00992] In various aspects, the condition or disease is a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

[00993] In a further aspect, the central nervous system disorder is an anxiety disorder, selected from the group of agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, posttraumatic stress disorder (PTSD), social phobia and other phobias.

[00994] In a further aspect, the central nervous system disorder is a personality disorder selected from the group of obsessive-compulsive personality disorder and schizoid, schizotypal disorder.

[00995] In a further aspect, the central nervous system disorder is a substance-related disorder selected from the group of alcohol abuse, alcohol dependence, alcohol withdrawal, alcohol withdrawal delirium, alcohol-induced psychotic disorder, amphetamine dependence, amphetamine withdrawal, cocaine dependence, cocaine withdrawal, nicotine dependence, nicotine withdrawal, opioid dependence and opioid withdrawal.

[00996] In a further aspect, the central nervous system disorder is an eating disorder selected from the group of anorexia nervosa and bulimia nervosa.

[00997] In a further aspect, the central nervous system disorder is a mood disorder selected from the group of bipolar disorders (I & II), cyclothymic disorder, depression, dysthymic disorder, major depressive disorder and substance-induced mood disorder.

[00998] In a further aspect, the central nervous system disorder is migraine.

[00999] In a further aspect, the central nervous system disorder is epilepsy or a convulsive disorder selected from the group of generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with or without impairment of consciousness, infantile spasms, epilepsy partialis continua, and other forms of epilepsy.

[001000] In a further aspect, the central nervous system disorder is attention-deficit/hyperactivity disorder.

[001001] In a further aspect, the central nervous system disorder is a cognitive disorder selected from the group of delirium, substance-induced persisting delirium, dementia, dementia due to HIV disease, dementia due to Huntington's disease, dementia due to Parkinson's disease, dementia of the Alzheimer's type, substance-induced persisting dementia and mild cognitive impairment.

[001002] In a further aspect, the central nervous system disorder is ischemia.

[001003] At present, the fourth edition of the Diagnostic & Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association provides a diagnostic tool for the identification of the disorders described herein. The person skilled in the art will recognize that alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders described herein exist, and that these evolve with medical and scientific progresses.

[001004] Therefore, the invention also relates to a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrates, solvates, polymorphs, or stereoisomeric forms thereof, for use in the treatment of any one of the diseases mentioned hereinbefore.

[001005] In a further aspect, the invention also relates to a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, for the treatment or prevention, in particular treatment, of any one of the diseases mentioned hereinbefore.

[001006] In a further aspect, the invention relates to relates to a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, for the manufacture of a medicament for the treatment or prevention of any one of the disease conditions mentioned hereinbefore.

[001007] In a further aspect, the invention also relates to the use of relates to a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, for the manufacture of a medicament for the treatment of any one of the disease conditions mentioned hereinbefore.

[001008] In a further aspect, the invention relates to a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, administered to mammals, e.g. humans, for the treatment or prevention of any one of the diseases mentioned hereinbefore.

[001009] In a further aspect, relates to a method of treating warm-blooded animals, such as mammals including humans, suffering from any one of the diseases mentioned hereinbefore, and a method of preventing in warm-blooded animals, such as mammals including humans, any one of the diseases mentioned hereinbefore by administering a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof. Said methods comprise the administration, i.e. the systemic or topical administration, preferably oral administration, of a therapeutically effective amount of a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, to warm-blooded animals, such as mammals including humans.

[001010] In various aspects, the invention also relates to a method for the prevention and/or treatment of any one of the diseases mentioned hereinbefore comprising administering a therapeutically effective amount of a disclosed compound, or a pharmaceutically acceptable

salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, to a patient in need thereof.

[001011] The compounds of the present invention may be utilized in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which a disclosed compound, or a pharmaceutically acceptable salt, including pharmaceutically acceptable acid or base addition salts, hydrate, solvate, polymorphy, or stereoisomeric form thereof, or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone.

[001012] The disclosed compounds can be used as single agents or in combination with one or more other drugs in the treatment, prevention, control, amelioration or reduction of risk of the aforementioned diseases, disorders and conditions for which compounds of formula I or the other drugs have utility, where the combination of drugs together are safer or more effective than either drug alone. The other drug(s) can be administered by a route and in an amount commonly used therefore, contemporaneously or sequentially with a disclosed compound. When a disclosed compound is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such drugs and the disclosed compound is preferred. However, the combination therapy can also be administered on overlapping schedules. It is also envisioned that the combination of one or more active ingredients and a disclosed compound will be more efficacious than either as a single agent.

[001013] In one aspect, the subject compounds can be coadministered with anti-Alzheimer's agents, beta-secretase inhibitors, gamma-secretase inhibitors, muscarinic agonists, muscarinic potentiators HMG-CoA reductase inhibitors, NSAIDs and anti-amyloid antibodies.

[001014] In another aspect, the subject compounds can be administered in combination with sedatives, hypnotics, anxiolytics, antipsychotics, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), 5-HT2 antagonists, GlyT1 inhibitors and the like such as, but not limited to: risperidone, clozapine, haloperidol, fluoxetine, prazepam, xanomeline, lithium, phenobarbitol, and salts thereof and combinations thereof.

[001015] In another aspect, the subject compound can be used in combination with levodopa (with or without a selective extracerebral decarboxylase inhibitor), anticholinergics such as biperiden, COMT inhibitors such as entacapone, A2a adenosine antagonists, cholinergic agonists, NMDA receptor antagonists and dopamine agonists.

[001016] The pharmaceutical compositions and methods of the present invention can further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

a. TREATMENT OF A NEUROLOGICAL AND/OR PSYCHIATRIC DISORDER ASSOCIATED WITH NMDA RECEPTOR ACTIVITY

[001017] In one aspect, the invention relates to a method for the treatment of a neurological and/or psychiatric disorder associated with NMDA receptor activity in a mammal comprising the step of administering to the mammal an effective amount of at least one compound; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof; wherein the compound is a disclosed compound or a product of a disclosed method of making a compound.

[001018] In one aspect, the invention relates to a method for the treatment of a disorder associated with NMDA receptor activity in a mammal comprising the step of administering to the mammal at least one disclosed compound or at least one disclosed product in a dosage and amount effective to treat the disorder in the mammal.

[001019] In a further aspect, an effective amount is a therapeutically effective amount. In a still further aspect, an effective amount is a prophylactically effective amount. In a yet further aspect, treatment is symptom amelioration or prevention, and wherein an effective amount is a prophylactically effective amount.

[001020] In a further aspect, the compound administered exhibits inhibition of NMDA receptor activity with an IC_{50} of less than about 10,000 nM. In a still further aspect, the compound exhibits inhibition of NMDA receptor activity with an IC_{50} of less than about 5,000 nM. In an even further aspect, the compound exhibits inhibition of NMDA receptor activity with an IC_{50} of less than about 1,000 nM. In a further aspect, the compound exhibits inhibition of NMDA receptor activity with an IC_{50} of less than about 500 nM. In a yet further aspect, the compound exhibits inhibition of NMDA receptor activity with an IC_{50} of less than about 100 nM.

[001021] In one aspect, the mammal that the compound is administered to is a human. In a further aspect, the mammal has been diagnosed with a need for treatment of the disorder prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of treatment of the disorder.

[001022] In a further aspect, the disorder is a neurological and/or psychiatric disorder associated with NMDA receptor activity. In a further aspect, the disorder is selected from autism, panic disorder with or without agoraphobia, agoraphobia without history of panic

disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, stroke, ischemia, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in Alzheimer's disease, and mild cognitive impairment.

b. INHIBITION OF NMDA RECEPTOR ACTIVITY

[001023] In one aspect, the invention relates to a method for inhibition of NMDA receptor activity in a mammal comprising the step of administering to the mammal at least one compound; or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof; wherein the compound is a disclosed compound or a product of a disclosed method of making a compound.

[001024] In various aspects, the invention relates to a method for inhibition of NMDA receptor activity in a mammal comprising the step of administering to the mammal at least one disclosed compound or at least one disclosed product in a dosage and amount effective to decrease NMDA receptor activity in the mammal either in the presence or absence of the endogenous ligand.

[001025] In a further aspect, inhibition of NMDA receptor activity is inhibition of GluNN2 activity. In a still further aspect, inhibition of NMDA receptor activity decreases NMDA receptor activity. In a yet further aspect, inhibition of NMDA receptor activity is partial antagonism of the NMDA receptor. In an even further aspect, inhibition of NMDA receptor activity is negative allosteric modulation of the NMDA receptor.

[001026] In a further aspect, the mammal is a human. In a still further aspect, an effective amount is a therapeutically effective amount. In a yet further aspect, an effective amount is a prophylactically effective amount. In an even further aspect, treatment is symptom amelioration or prevention, and wherein an effective amount is a prophylactically effective amount.

[001027] In a further aspect, the mammal has been diagnosed with a need for inhibition of NMDA receptor activity prior to the administering step. In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to NMDA receptor activity prior to the administering step. In a further aspect, the method further comprises the step of identifying a mammal in need of inhibiting of NMDA receptor activity.

[001028] In a further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 10,000 nM. In a still further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 5,000 nM. In an even further aspect, the compound inhibition of NMDA receptor with an IC_{50} of less than about 1,000 nM. In a further aspect, the compound inhibition of NMDA receptor with an IC_{50} of less than about 500 nM. In a yet further aspect, the compound inhibition of NMDA receptor with an IC_{50} of less than about 100 nM.

[001029] In a further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of between about 10,000 nM to about 1 nM. In a still further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of between about 1,000 nM to about 1 nM. In a yet further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of between about 100 nM to about 1 nM. In an even further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of between about 10 nM to about 1 nM. In a still further aspect, inhibition of NMDA receptor activity is negative allosteric modulation of NMDA activity.

[001030] In a further aspect, the mammal is a human. In a still further aspect, the mammal has been diagnosed with a need for inhibition of NMDA receptor activity prior to the administering step. In a yet further aspect, the method further comprises comprising the step of identifying a mammal in need for inhibition of NMDA receptor activity. In an even further aspect, the NMDA receptor comprises GluNN2 subtype. In a still further aspect, inhibition of NMDA receptor activity treats a disorder associated with NMDA receptor activity in a mammal.

[001031] In a further aspect, inhibition of NMDA receptor activity in a mammal is associated with the treatment of a neurological and/or psychiatric disorder associated with NMDA dysfunction. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, stroke, ischemia, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression. In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, stroke, ischemia, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, panic disorder with or

without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, and substance-induced anxiety disorder. In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in Alzheimer's disease, and mild cognitive impairment.

c. INHIBITING NMDA ACTIVITY IN CELLS

[001032] In one aspect, the invention relates to a method for inhibiting NMDA receptor activity in at least one cell, comprising the step of contacting the at least one cell with an effective amount of at least one compound, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof; wherein the compound is a disclosed compound or a product of a disclosed method of making a compound.

[001033] In one aspect, the invention relates to a method for inhibition of NMDA receptor activity in a mammal by contacting at least one cell in a mammal, comprising the step of contacting the at least one cell with at least one disclosed compound or at least one disclosed product in an amount effective to inhibit GluNN2 activity in the at least one cell.

[001034] In a further aspect, inhibition of NMDA receptor activity is inhibition of GluNN2 activity. In a still further aspect, inhibition of NMDA receptor activity is partial antagonism of the NMDA receptor. In yet further aspect, inhibition of NMDA receptor activity is negative allosteric modulation of the NMDA receptor.

[001035] In a further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 10,000 nM. In a still further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 5,000 nM. In an even further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 1,000 nM. In a further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 500 nM. In a yet further aspect, the compound exhibits inhibition of NMDA receptor with an IC_{50} of less than about 100 nM.

[001036] In one aspect, the cell is mammalian. In a further aspect, the cell is human. In a further aspect, the cell has been isolated from a mammal prior to the contacting step.

[001037] In a further aspect, an effective amount is a therapeutically effective amount. In a yet further aspect, an effective amount is a prophylactically effective amount. In an even further aspect, treatment is symptom amelioration or prevention, and wherein an effective amount is a prophylactically effective amount.

[001038] In a further aspect, contacting is via administration to a mammal. In a further aspect, the mammal has been diagnosed with a need for modulating NMDA activity prior to the administering step. In a further aspect, the mammal has been diagnosed with a need for treatment of a disorder related to NMDA receptor activity prior to the administering step.

[001039] In one aspect, modulating NMDA activity in at least one cell treats a neurological and/or psychiatric disorder. In a further aspect, the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, stroke, ischemia, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression.

In a yet further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, stroke, ischemia, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, and substance-induced anxiety disorder.

In an even further aspect, the disorder is absence epilepsy. In a still further aspect, the disorder is selected from cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in Alzheimer's disease, and mild cognitive impairment.

2. COTHERAPEUTIC METHODS

[001040] The present invention is further directed to administration of a NMDA inhibitor for improving treatment outcomes in the context of cognitive or behavioral therapy. That is, in one aspect, the invention relates to a cotherapeutic method comprising the step of administering to a mammal an effective amount of at least one disclosed compound; at least one product of a disclosed method of making; or a pharmaceutically effective salt, hydrate, solvate, or polymorph thereof.

[001041] In a further aspect, the mammal is a human. In a still further aspect, an effective amount is a therapeutically effective amount. In a yet further aspect, an effective amount is a prophylactically effective amount. In an even further aspect, treatment is symptom

amelioration or prevention, and wherein an effective amount is a prophylactically effective amount.

[001042] In a further aspect, administration improves treatment outcomes in the context of cognitive or behavioral therapy. Administration in connection with cognitive or behavioral therapy can be continuous or intermittent. Administration need not be simultaneous with therapy and can be before, during, and/or after therapy. For example, cognitive or behavioral therapy can be provided within 1, 2, 3, 4, 5, 6, or 7 days before or after administration of the compound. As a further example, cognitive or behavioral therapy can be provided within 1, 2, 3, or 4 weeks before or after administration of the compound. As a still further example, cognitive or behavioral therapy can be provided before or after administration within a period of time of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 half-lives of the administered compound. It is understood that the disclosed cotherapeutic methods can be used in connection with the disclosed compounds, compositions, kits, and uses.

3. MANUFACTURE OF A MEDICAMENT

[001043] In one aspect, the invention relates to a method for the manufacture of a medicament for inhibition of NMDA receptor activity in a mammal comprising combining a therapeutically effective amount of a disclosed compound or product of a disclosed method with a pharmaceutically acceptable carrier or diluent.

[001044] In various aspect, the invention relates methods for the manufacture of a medicament for modulating the activity of NMDA receptor (e.g., treatment of one or more neurological and/or psychiatric disorder associated with glutamate receptor dysfunction) in mammals (e.g., humans) comprising combining one or more disclosed compounds, products, or compositions or a pharmaceutically acceptable salt, solvate, hydrate, or polymorph thereof, with a pharmaceutically acceptable carrier. It is understood that the disclosed methods can be performed with the disclosed compounds, products, and pharmaceutical compositions. It is also understood that the disclosed methods can be employed in connection with the disclosed methods of using.

4. USE OF COMPOUNDS

[001045] In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method of making. In a further aspect, the use relates to the manufacture of a medicament for the treatment of a disorder associated with glutamate receptor dysfunction in a mammal. In a further aspect, the disorder is a neurological and/or psychiatric disorder. In a further aspect, a use relates to treatment of a neurological and/or psychiatric disorder associated with glutamate receptor dysfunction in a mammal.

[001046] In a further aspect, a use relates to inhibition of NMDA receptor activity in a mammal. In a further aspect, a use relates to partial antagonism of NMDA receptor activity in a mammal. In a further aspect, a use relates to enhancing cognition in a mammal. In a further aspect, a use relates to modulating NMDA receptor activity in a mammal. In a further aspect, a use relates to modulating NMDA receptor activity in a cell.

[001047] In one aspect, a use is treatment or prevention of a neurological and/or psychiatric disorder associated with glutamate dysfunction. In a further aspect, the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, stroke, ischemia, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression.

[001048] In one aspect, a use is associated with the treatment or prevention of a disorder associated with uncontrolled cellular proliferation. In a further aspect, the disorder is cancer. In a still further aspect, the cancer is selected from breast cancer, renal cancer, gastric cancer, and colorectal cancer. In a further aspect, the disorder is selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic system cancer, stomach cancer, larynx cancer, lung, pancreatic cancer, breast cancer, and malignant melanoma.

[001049] In one aspect, the invention relates to the use of a disclosed compound or a disclosed product in the manufacture of a medicament for the treatment of a disorder associated with glutamate dysfunction in a mammal. In a further aspect, the disorder is a neurological and/or psychiatric disorder. In a further aspect, the disorder is a disease of uncontrolled cellular proliferation.

[001050] In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, or a pharmaceutical composition for use in treating or preventing a central nervous system disorder selected from the group of disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; neurologic disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; pain and diseases of uncontrolled cellular proliferation.

In a further aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, or a pharmaceutical composition for use wherein the disorders and conditions are selected from the group of; the anxiety disorders are selected from the group of panic disorder; agoraphobia; specific phobia; social phobia; obsessive-compulsive disorder; post-

traumatic stress disorder; acute stress disorder; and generalized anxiety disorder; the movement disorders are selected from the group of epilepsy; Huntington's disease; dyskinesia; Parkinson's disease; restless leg syndrome and essential tremor; Tourette's syndrome and other tic disorders; the substance-related disorders are selected from the group of alcohol abuse; alcohol dependence; alcohol withdrawal; alcohol withdrawal delirium; alcohol-induced psychotic disorder; amphetamine dependence; amphetamine withdrawal; cocaine dependence; cocaine withdrawal; nicotine dependence; nicotine withdrawal; opioid dependence and opioid withdrawal; the mood disorders are selected from depression, mania and bipolar disorder of types I and II; cyclothymic disorder; depression; dysthymic disorder; major depressive disorders and substance-induced mood disorder; the neurodegenerative disorders are selected from the group of Parkinson's disease; Huntington's disease; dementia such as for example Alzheimer's disease; multi-infarct dementia; AIDS-related dementia or frontotemporal dementia; the neurologic disorders are selected from the group of stroke, cerebral ischemia, and brain edema; the disorders or conditions comprising as a symptom a deficiency in attention and/or cognition are selected from the group of dementia, such as Alzheimer's disease; multi-infarct dementia; dementia due to Lewy body disease; alcoholic dementia or substance-induced persisting dementia; dementia associated with intracranial tumors or cerebral trauma; dementia associated with Huntington's disease; dementia associated with Parkinson's disease; AIDS-related dementia; dementia due to Pick's disease; dementia due to Creutzfeldt-Jakob disease; delirium; amnestic disorder; post-traumatic stress disorder; stroke; progressive supranuclear palsy; mental retardation; a learning disorder; attention-deficit/hyperactivity disorder (ADHD); mild cognitive disorder; Asperger's syndrome; and age-related cognitive impairment; pain includes acute and chronic states, severe pain, intractable pain, neuropathic pain and post-traumatic pain, cancer pain, non-cancer pain, pain disorder associated with psychological factors, pain disorder associated with a general medical condition or pain disorder associated with both psychological factors and a general medical condition; the diseases of uncontrolled cellular proliferation are selected from lymphoma, cancers of the brain, genitourinary tract cancer, lymphatic cancer, stomach cancer, larynx cancer, lung cancer, pancreatic cancer, breast cancer, and malignant melanoma.

[001051] In one aspect, the invention relates to the use of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, or a pharmaceutical composition, in combination with an additional pharmaceutical agent for use in the treatment or prevention of a central nervous system

disorder selected from the group of psychotic disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; pain and diseases of uncontrolled cellular proliferation.

[001052] In one aspect, the invention relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of the compound or the product of a disclosed method of making.

[001053] In a further aspect, the invention relates to a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a disclosed compound or a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, or polymorph thereof, for use as a medicament.

5. KITS

[001054] In one aspect, the invention relates to a kit comprising at least one compound, or a pharmaceutically acceptable salt, hydrate, solvate, or polymorph thereof, wherein the compound is a disclosed compound or a product of a disclosed method of making a compound; and one or more of: (a) at least one agent known to increase NMDA receptor activity; (b) at least one agent known to decrease NMDA receptor activity; (c) at least one agent known to treat a neurological and/or psychiatric disorder; (d) instructions for treating a disorder associated with NMDA receptor activity; or (e) instructions for administering the compound in connection with treating a neurological and/or psychiatric disorder.

[001055] In a further aspect, the at least one compound or the at least one product and the at least one agent are co-formulated.

[001056] In a further aspect, the at least one compound or the at least one product and the at least one agent are co-packaged.

[001057] The kits can also comprise compounds and/or products co-packaged, co-formulated, and/or co-delivered with other components. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising a disclosed compound and/or product and another component for delivery to a patient.

[001058] It is contemplated that the disclosed kits can be used in connection with the disclosed methods of making, the disclosed methods of using, and/or the disclosed compositions.

6. NON-MEDICAL USES

[001059] Also provided are the uses of the disclosed compounds and products as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of NMDA related receptor activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of the NMDA receptor. In a further aspect, the invention relates to the use of a disclosed compound or a disclosed product as pharmacological tools in the development and standardization of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of NMDA related receptor activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents of NMDA receptor.

G. EXPERIMENTAL

[001060] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the compounds, compositions, articles, devices and/or methods claimed herein are made and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers (*e.g.*, amounts, temperature, etc.), but some errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, temperature is in °C or is at ambient temperature, and pressure is at or near atmospheric.

[001061] Several methods for preparing the compounds of this invention are illustrated in the following Examples. Starting materials and the requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures or as illustrated herein.

[001062] The following exemplary compounds of the invention were synthesized. The Examples are provided herein to illustrate the invention, and should not be construed as limiting the invention in any way. The Examples are typically depicted in free base form, according to the IUPAC naming convention. However, some of the Examples were obtained or isolated in salt form.

[001063] As indicated, some of the Examples were obtained as racemic mixtures of one or more enantiomers or diastereomers. The compounds may be separated by one skilled in the art to isolate individual enantiomers. Separation can be carried out by the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a

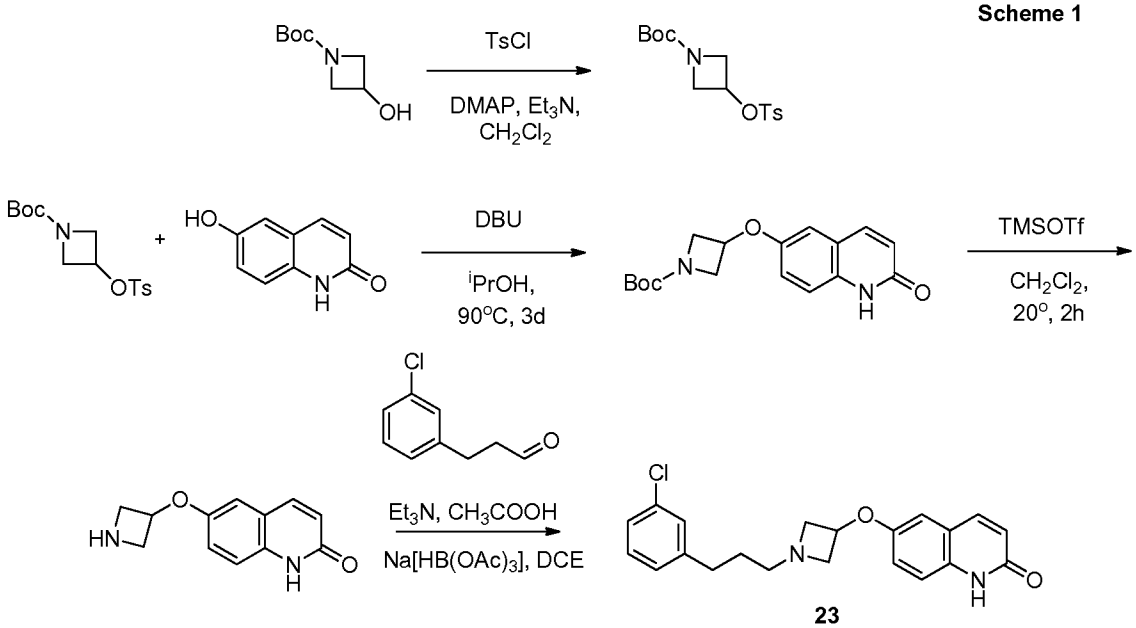
diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. A racemic or diastereomeric mixture of the compounds can also be separated directly by chromatographic methods using chiral stationary phases.

1. General Methods

[001064] All reagents were obtained from commercial suppliers and used without further purification. Unless otherwise specified, all reactions were carried out either in an atmosphere of nitrogen or argon gas. The reaction progress was monitored by thin layer chromatography (TLC) on precoated glass plates (silica gel HL UV254, 0.25 mm thickness) purchased from Sorbent Technologies. Purification was carried out by flash chromatography with high performance silica gel (230-400 mesh) either manually or using Combiflash companion Teledyne Isco instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian or a Bruker 400 MHz spectrometer. The NMR spectra were obtained in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) and referenced to the residual solvent peak; chemical shifts are reported in parts per million and coupling constants in hertz (Hz). Mass spectra were recorded on either a VG 70-S Nier Johnson or JEOL mass spectrometer. Elemental analyses were performed by Atlantic Microlab (Norcross, GA) for C, H, and N.

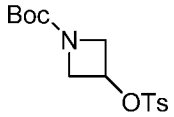
2. Preparation of 6-((1-(3-(3-chlorophenyl)propyl)azetidin-3-yl)oxy)quinolin-2(1H)-one (Compound 23, Scheme 1).

Scheme 1



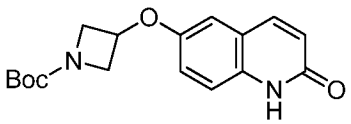
23

a. PREPARATION OF TERT-BUTYL 3-(TOSYLOXY)AZETIDINE-1-CARBOXYLATE (SCHEME 1).



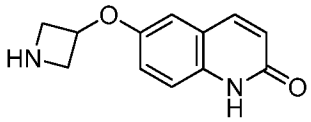
[001065] To a mixture of N-Boc-*3*-hydroxy azetidine (6.23 g, 36 mmol), DMAP (0.44 g, 3.6 mmol), and Et_3N (7.52 mL, 54 mmol) in anhydrous dichloromethane (150 mL) was added *p*-toluenesulfonylchloride (8.23 g, 43 mmol) at 0 °C. The mixture was stirred briskly at 20 °C for 16 h and later diluted with brine (20 mL) and water (20 mL). The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4, and evaporated on a rotary evaporator. The residue obtained was purified by flash column chromatography on silica gel (230-400 mesh; 8 g) using a gradient solvent mixture of hexane:ethylacetate (100:0 to 50:50) to yield the title compound used in the next step. Yield: 12.07 g (quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, 2H), 7.52 (d, 2H), 5.09 (m, 1H), 4.05 (m, 2H), 3.74 (b. m, 2H), 2.45 (s, 3H), 1.29 (s, 9H).

b. PREPARATION OF TERT-BUTYL 3-((2-OXO-1,2-DIHYDROQUINOLIN-6-YL)OXY)AZETIDINE-1-CARBOXYLATE (SCHEME 1).



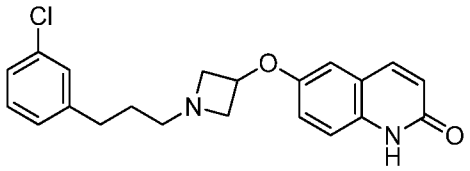
[001066] A mixture of tert-butyl 3-(tosyloxy)azetidine-1-carboxylate (5.4 g, 17 mmol), *6*-hydroxyquinolin-2(1H)-one (2.69 g, 17 mmol), DBU (*1,8*-Diazabicyclo-[5,4,0]undec-*7*-ene, 3.8 mL, 25 mmol) and anhydrous isopropanol (18 mL) was heated at 90 °C for 3 d. An yellowish brown suspension was obtained, which was cooled to rt. The mixture was diluted with ice-cold water to precipitate a pale brown solid, which was collected by filtration and washed successively with water (3 × 10 mL), hexane (2 × 10 mL) and ether (2 × 10 mL). Further purification of the crude precipitate (3.21 g) by flash column chromatography on silica gel (230-400 mesh; 12 g) using a gradient solvent mixture of hexane:ethylacetate (100:0 to 0:100) gave the title product used in the next step. Yield: 2.7 g (51.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.66 (s, 1H), 7.82 (b. s, 1H), 7.25 (b. s, 1H), 7.13 (b. s, 1H), 7.05 (s, 1H), 6.49 (b. s, 1H), 4.98 (s, 1H), 4.33 (s, 2H), 3.80 (s, 2H), 1.39 (s, 9H).

c. PREPARATION OF 6-(AZETIDIN-3-YLOXY)QUINOLIN-2(1H)-ONE (SCHEME 1).



[001067] To a solution of tert-butyl 3-((2-oxo-1,2-dihydroquinolin-6-yl)oxy)azetidine-1-carboxylate (2.4 g, 7.6 mmol) in dichloromethane was added drop wise trimethylsilyltriflate (2.1 mL, 11.3 mmol) at room temperature. A clear colorless solution was obtained, which was stirred for 2 h and later was evaporated on a rotary evaporator under vacuum. The residue was triturated with anhydrous diethyl ether. The resulting white suspension was filtered and washed with ether to isolate the secondary amine salt of triflic acid ($C_{12}H_{12}N_2O_2 \cdot 2CF_3SO_3H$) that was used in the next step. Yield: 3.25 g (82.9 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70 (s, 1H), 9.03 (b. s, 1H), 8.68 (b. s, 1H), 7.84 (d, 1H), 7.28 (d, 1H), 7.13 (m, 1H), 7.10 (s, 1H), 6.53 (d, 1H), 5.07 (m, 1H), 4.46 (m, 2H), 4.02 (m, 2H). ES-MS m/z 217.10 $(C_{12}H_{12}N_2O_2 + 1)^+$.% yield, 60% pure)

d. PREPARATION OF 6-((1-(3-(3-CHLOROPHENYL)PROPYL)AZETIDIN-3-YL)OXY)QUINOLIN-2(1H)-ONE (COMPOUND 23, SCHEME 1).

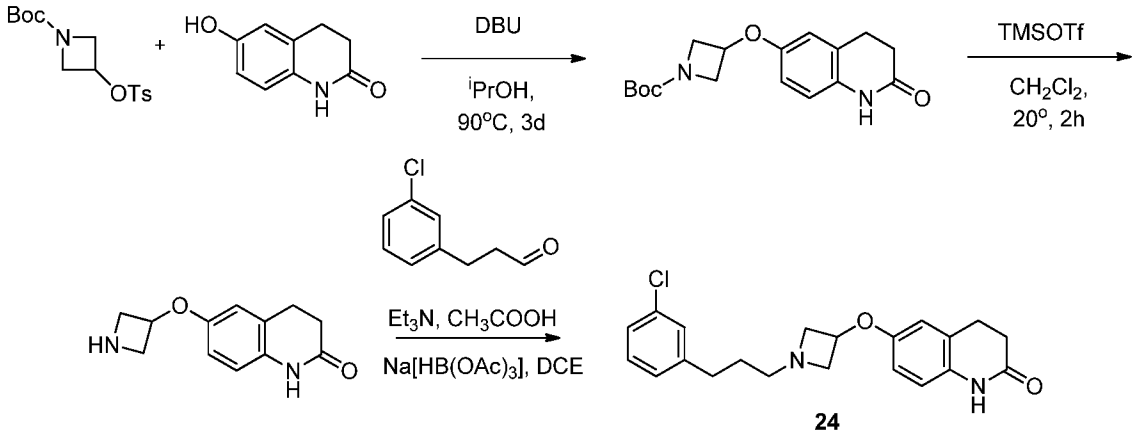


[001068] A suspension of 6-(azetidin-3-yloxy)quinolin-2(1H)-one (0.3 g, 0.58 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.34 mL, 2.4 mmol) was added to the mixture, which was followed by the addition of 3-(3-chlorophenyl)propanal (0.15 mL, 0.98 mmol). Upon stirring, a nearly clear solution was obtained. Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.26 g, 1.22 mmol) were added to the reaction mixture, which was stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate, dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.16 g (74.7 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.63 (s, 1H), 7.83 (d, 1H), 7.24 (m, 4H), 7.20 (d, 1H), 7.09 (d, 2H), 6.49 (d,

1H), 4.79 (m, 1H), 3.78 (m, 2H), 2.94 (m, 2H), 2.60 (m, 2H), 2.44 (m, 2H), 1.60 (m, 2H). ES-MS m/z 369.2 $(C_{21}H_{21}ClN_2O_2 + 1)^+$.

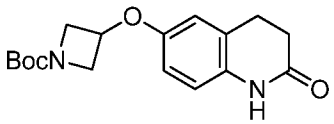
3. PREPARATION OF 6-((1-(3-(3-CHLOROPHENYL)PROPYL)AZETIDIN-3-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 24, (SCHEME 2).

Scheme 2



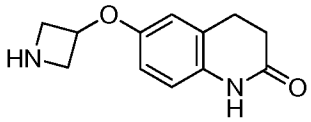
24

a. PREPARATION OF TERT-BUTYL 3-((2-OXO-1,2,3,4-TETRAHYDROQUINOLIN-6-YL)OXY)AZETIDINE-1-CARBOXYLATE (SCHEME 2).



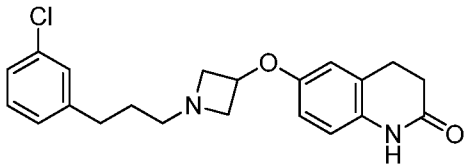
[001069] A mixture of tert-butyl 3-(tosyloxy)azetidine-1-carboxylate (5.4 g, 17 mmol), *6*-hydroxy-*3,4*-dihydroquinolin-2(1H)-one (2.99 g, 18 mmol), DBU (4.1 mL, 27 mmol) and anhydrous isopropanol (15 mL) was heated at 90 °C for 3 d. An yellowish brown suspension was obtained, which was cooled to room temperature. The mixture was diluted with brine (20 mL) and cold water (20 mL), which was extracted with ethyl acetate. The organic extract was dried over sodium sulfate and evaporated. The resulting substance was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a gradient solvent mixture of dichloromethane:methanol (100:0 to 5:95) yield the title compound that was used in the next step. Yield: 3.0 g (51.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 6.76 (b. s, 1H), 6.70 (s, 1H), 6.62 (b. s, 1H), 4.89 (b. s, 1H), 4.27 (b. s, 2H), 3.75 (b. s, 2H), 2.83 (b. m, 2H), 2.40 (b. m, 2H), 1.39 (s, 9H).

b. PREPARATION OF 6-(AZETIDIN-3-YLOXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (SCHEME 2).



[001070] To a solution of tert-butyl 3-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)azetidine-1-carboxylate (2.99 g, 9.4 mmol) in anhydrous dichloromethane (45 mL) was added drop wise trimethylsilyltriflate (2.55 mL, 14 mmol) at room temperature. The solution became a white suspension in few minutes, which was stirred for 2 h. The mixture was filtered and the precipitate collected was washed with anhydrous diethyl ether. A white powder of the secondary amine salt of triflic acid was obtained that was used in the next step ($C_{12}H_{14}N_2O_2 \cdot CF_3SO_3H$). Yield: 3.3 g (95.4 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.97 (s, 1H), 8.95 (b. s, 1H), 8.70 (b. s, 1H), 6.80 (d, 1H), 6.74 (s, 1H), 6.68 (m, 1H), 4.98 (m, 1H), 4.45 (b. s, 2H), 3.97 (b. s, 2H), 2.85 (t, 2H), 2.41 (t, 2H).

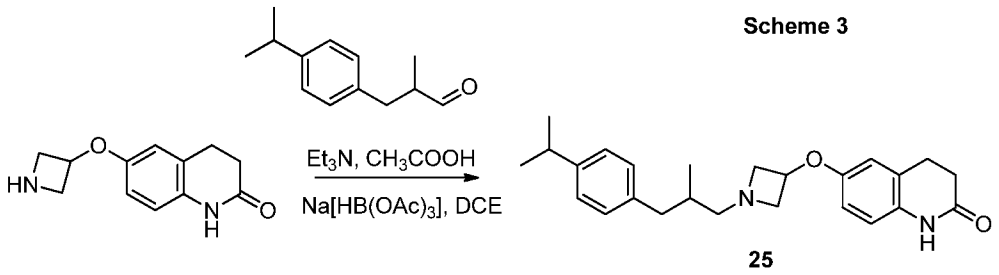
c. PREPARATION OF COMPOUND 24 (SCHEME 2).



[001071] A suspension of 6-(azetidin-3-yloxy)-3,4-dihydroquinolin-2(1H)- (0.3 g, 0.81 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.34 mL, 2.4 mmol) was added to the mixture, which was followed by the addition of 3-(3-chlorophenyl)propanal (0.15 mL, 0.98 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.26 g, 1.22 mmol) were added to the reaction mixture, which was stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate. The organic solution was dried over sodium sulfate and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.14 g (46.3 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.91 (s, 1H), 7.27 (m, 3H), 7.18 (d, 1H), 6.75 (d, 1H), 6.68 (s, 1H), 6.61 (m, 1H), 4.69 (m, 1H), 3.72 (t, 2H), 2.89 (t, 2H), 2.81 (t, 2H), 2.60 (t, 2H), 2.40 (m, 4H), 1.58 (m, 2H). ES-MS m/z 371.2 $(C_{21}H_{23}ClN_2O_2 + 1)^+$.

4. PREPARATION OF 6-((1-(3-(4-ISOPROPYLPHENYL)-2-METHYLPROPYL)AZETIDIN-3-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 25, SCHEME 3).

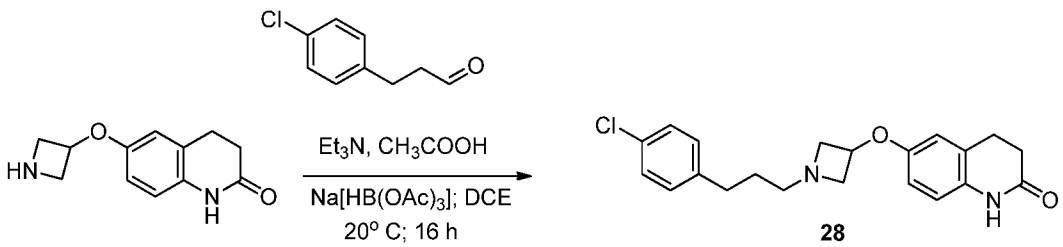
Scheme 3



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[001072] A suspension of 6-(azetidin-3-yloxy)quinolin-2(1H)-one (0.3 g, 0.58 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.34 mL, 2.4 mmol) was added to the mixture, which was followed by the addition of 3-(4-isopropylphenyl)-2-methylpropanal (0.15 mL, 0.98 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.26 g, 1.22 mmol) were added to the reaction mixture and later stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.14 g (61.7 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.63 (s, 1H), 7.84 (d, 1H), 7.24 (d, 1H), 7.06 (m, 6H), 6.49 (d, 1H), 4.80 (m, 1H), 3.81 (m, 2H), 2.98 (m, 2H), 2.78 (m, 1H), 2.72 (m, 1H), 2.45 (m, 1H), 2.27 (m, 2H), 1.65 (b. s, 1H), 1.19 (d, 6H), 0.78 (d, 3H). ES-MS m/z 391.3 $(C_{25}H_{30}N_2O_2 + 1)^+$.

5. PREPARATION OF 6-((1-(3-(P-TOLYL)PROPYL)AZETIDIN-3-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 28, SCHEME 4).



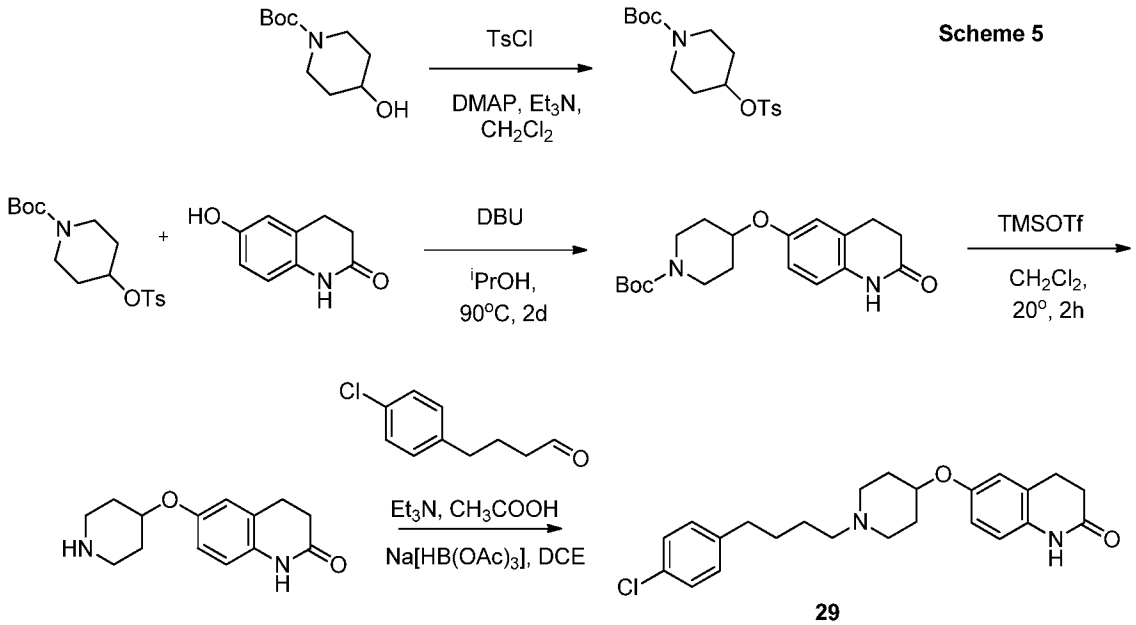
28

[001073] A suspension of 6-(azetidin-3-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 0.82 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.34 mL, 2.4 mmol) was added to the mixture, which was followed by the addition of 3-(4-chlorophenyl)propanal (0.28 mL, 0.98 mmol). Further, acetic acid (0.09 mL) and

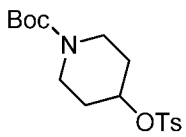
sodium triacetoxyborohydride (0.26 g, 1.22 mmol) were added to the reaction mixture and later stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.1). A microcrystalline solid product was obtained. Yield: 0.27 g (89.4 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1H), 7.29 (d, 2H), 7.18 (d, 2H), 6.75 (d, 1H), 6.66 (s, 1H), 6.56 (m, 1H), 4.66 (m, 1H), 3.69 (b. t, 2H), 2.88 (b. t, 2H), 2.80 (t, 2H), 2.55 (t, 2H), 2.39 (m, 4H), 1.54 (m, 2H). ES-MS m/z 369.1 $(C_{21}H_{23}ClN_2O_2 - 1)^-$.

6. PREPARATION OF 6-((1-(4-(4-CHLOROPHENYL)BUTYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 29, SCHEME 5).

Scheme 5



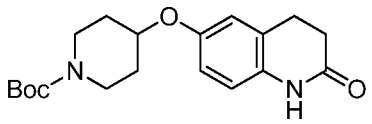
a. PREPARATION OF TERT-BUTYL 4-(TOSYLOXY)PIPERIDINE-1-CARBOXYLATE (SCHEME 5).



[001074] To a mixture of N-Boc-*4*-hydroxy piperidine (15.0 g, 74.5 mmol), DMAP (0.30 g, 2.4 mmol), and Et_3N (15.6 mL, 112 mmol) in anhydrous dichloromethane (180 mL) was added *p*-toluenesulfonylchloride (17.04 g, 89.4 mmol) at 0 °C. After the addition, the mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with brine (20 mL),

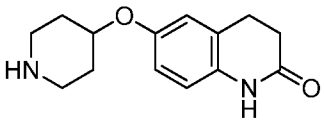
sodium carbonate solution (10 mL) and water (20 mL). The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 8 g) using a gradient solvent mixture of hexane:ethylacetate (100:5 to 50:50) for use in the next step. Yield: 22.2 g (83.8 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, 2H), 7.49 (d, 2H), 4.69 (b. s, 1H), 3.49 (b. m, 2H), 3.15 (b. m, 2H), 1.70 (b. m, 2H), 1.51 (b. m, 2H), 1.38 (s, 9H).

b. PREPARATION OF TERT-BUTYL 4-((2-OXO-1,2,3,4-TETRAHYDROQUINOLIN-6-YL)OXY)PIPERIDINE-1-CARBOXYLATE (EXAMPLE A4) (SCHEME 5).



[001075] A mixture of tert-butyl 4-(tosyloxy)piperidine-1-carboxylate (6.0 g, 17 mmol), *6*-hydroxy-*3,4*-dihydroquinolin-2(1H)-one **8** (2.75 g, 17 mmol), DBU (3.8 mL, 25 mmol) and anhydrous isopropanol (15 mL) was heated at 90 °C for 2 d. A pale brown suspension was obtained, which was cooled to room temperature and filtered. The precipitate was washed with isopropanol. About 2.5 g of product, as a white precipitate was isolated. The filtrate was diluted with water and brine and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated on a rotary evaporator. The resulting substance was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a gradient solvent mixture of dichloromethane:methanol (100:0 to 5:95) for use in the next step. Yield: 1.32 g. Total yield = 3.82 g (65.3 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 6.83 (s, 1H), 6.76 (s, 2H), 4.42 (b. s, 1H), 3.64 (b. m, 2H), 3.15 (b. m, 2H), 2.83 (t, 2H), 2.40 (t, 2H), 1.91 (b. m, 2H), 1.49 (b. m, 2H), 1.41 (s, 9H).

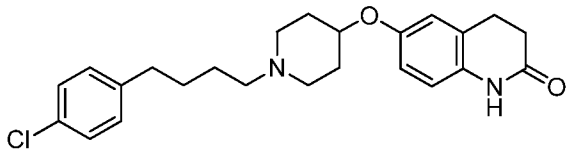
c. PREPARATION OF 6-(PIPERIDIN-4-YLOXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (SCHEME 5).



[001076] To a solution of tert-butyl 4-((2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)oxy)piperidine-1-carboxylate (3.7 g, 10.7 mmol) in anhydrous dichloromethane (55 mL) was added drop wise trimethylsilyltriflate (2.90 mL, 16 mmol) at room temperature. A pale yellow suspension was obtained in a few minutes, which was stirred for 12 h. The resulting mixture was evaporated on a rotary evaporator under vacuum. The residue obtained was

washed with anhydrous diethyl ether (3 × 5 mL) to remove any soluble side products. The crude product was triturated with dichloromethane to obtain a pale yellow precipitate, which was filtered and washed with ether for use in the next step. Yield: 3.8 g (89.8 %; based on $C_{14}H_{18}N_2O_2.CF_3SO_3H$). ^1H NMR (400 MHz, DMSO-d_6): δ 9.95 (s, 1H), 8.36 (b. s, 2H), 6.86 (s, 1H), 6.79 (s, 2H), 4.51 (m, 1H), 3.23 (b. s, 2H), 3.12 (b. s, 2H), 2.82 (t, 2H), 2.45 (t, 2H), 2.04 (b. m, 2H), 1.77 (b. m, 2H).

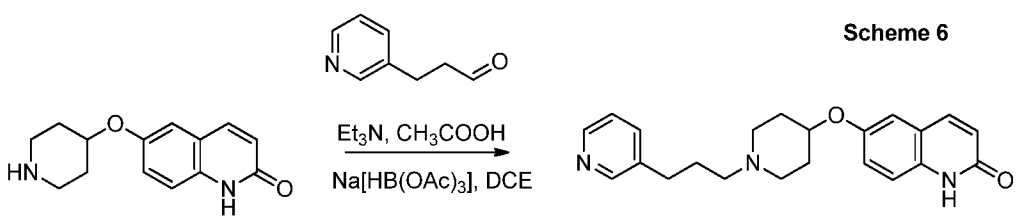
7. PREPARATION OF 6-((1-(4-(4-CHLOROPHENYL)BUTYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 29, SCHEME 5).



[001077] A suspension of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of 4-(4-chlorophenyl)butanal (0.3 mL, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture and later stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (2 × 30 mL). The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.23 g (73.6 %). ^1H NMR (400 MHz, DMSO-d_6): δ 9.86 (s, 1H), 7.72 (d, 2H), 7.20 (d, 2H), 6.78 (s, 1H), 6.72 (m, 1H), 4.21 (b. s, 1H), 2.80 (t, 2H), 2.65 (b. s, 2H), 2.57 (t, 2H), 2.49 (t, 2H), 2.28 (b. s, 2H), 2.15 (b. s, 2H), 1.85 (b. m, 2H), 1.52 (m, 4H), 1.41 (b. m, 2H). ES-MS m/z 413.0 $(C_{24}H_{29}ClN_2O_2 + 1)^+$.

8. PREPARATION OF 6-((1-(3-(PYRIDIN-3-YL)PROPYL)PIPERIDIN-4-YL)OXY)QUINOLIN-2(1H)-ONE (COMPOUND 31, SCHEME 6).

Scheme 6

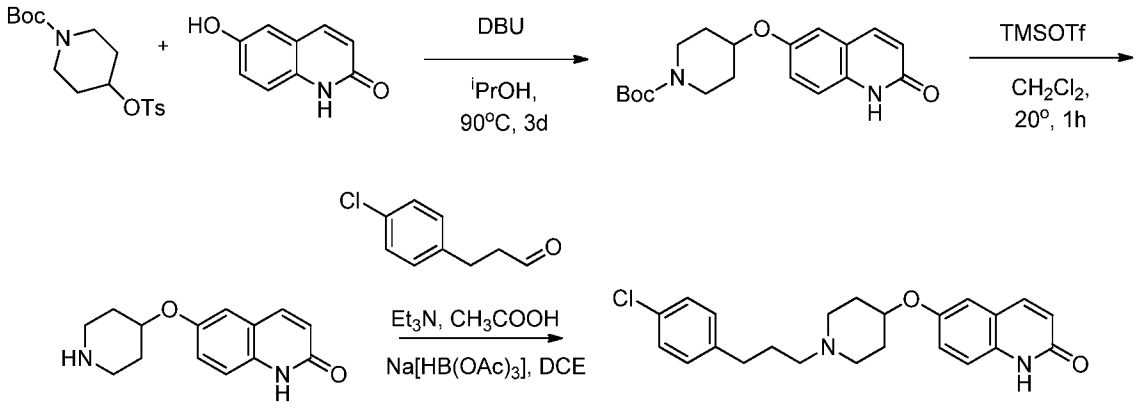


31

[001078] A suspension of 6-(piperidin-4-yloxy)quinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at rt. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of 3-(pyridin-3-yl)propanal (0.121 g, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture and later stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (2 × 30 mL). The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.175 g (63.3 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.76 (s, 1H), 8.62 (s, 1H), 8.44 (s, 1H), 7.89 (d, 1H), 7.34 (m, 1H), 6.78 (m, 3H), 6.58 (d, 1H), 6.47 (m, 1H), 4.25 (b. s, 1H), 3.16 (d, 2H), 2.83 (t, 2H), 2.73 (b. m, 2H), 2.41 (t, 2H), 2.29 (t, 2H), 1.91 (b. m, 2H), 1.65 (b. m, 2H). ES-MS m/z 364.1 $(C_{22}H_{25}N_3O_2 + 1)^+$.

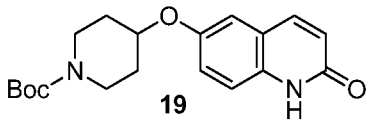
9. Preparation of 6-((1-(3-(4-chlorophenyl)propyl)piperidin-4-yl)oxy)quinolin-2(1H)-one (Compound 34, Scheme 7).

Scheme 7



34

a. Preparation of tert-butyl 4-((2-oxo-1,2-dihydroquinolin-6-yl)oxy)piperidine-1-carboxylate (Scheme 7).

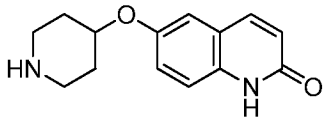


19

[001079] A mixture of tert-butyl 4-(tosyloxy)piperidine-1-carboxylate (6.0 g, 17 mmol), *6*-hydroxyquinolin-2(1H)-one (2.72 g, 17 mmol), DBU (3.8 mL, 25 mmol) and anhydrous isopropanol (15 mL) was heated at 90 °C for 3 d. A pale brown suspension was obtained,

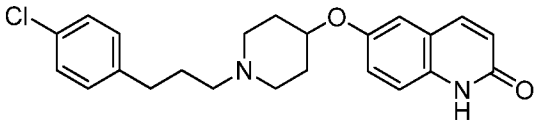
which was cooled to room temperature and filtered. The precipitate was washed with isopropanol and diethyl ether. About 1.63 g of product, as a white precipitate was isolated. The filtrate was diluted with water and brine and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated on a rotary evaporator. The resulting substance was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a gradient solvent mixture of dichloromethane:methanol (100:0 to 5:95) and was used in the next step. Yield: 1.30 g. Total yield = 2.93 g (50.4 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.62 (s, 1H), 7.78 (d, 1H), 7.28 (s, 1H), 7.26 (m, 2H), 6.52 (d, 1H), 4.52 (b. s, 1H), 3.66 (b. m, 2H), 3.22 (b. m, 2H), 1.95 (b. m, 2H), 1.55 (b. m, 2H), 1.41 (s, 9H).

b. PREPARATION OF 6-(PIPERIDIN-4-YLOXY)QUINOLIN-2(1H)-ONE (SCHEME 7).



[001080] To a mixture of tert-butyl 4-((2-oxo-1,2-dihydroquinolin-6-yl)oxy)piperidine-1-carboxylate (1.64 g, 4.8 mmol) in anhydrous dichloromethane (25 mL) was added drop wise trimethylsilyltriflate (1.29 mL, 7.1 mmol) at rt. A white suspension was obtained in ten minutes, which was stirred for an hour. The resulting mixture was filtered and the precipitate was washed with anhydrous dichloromethane (2 × 3 mL) to remove any soluble side products for use in the next step. Yield: 1.46 g (77.7 %; based on $C_{14}H_{16}N_2O_2.CF_3SO_3H$). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.69 (s, 1H), 8.38 (b. s, 2H), 7.81 (d, 1H), 7.32 (s, 1H), 7.22 (m, 2H), 6.51 (d, 1H), 5.16 (b. s), 4.58 (b. s, 1H), 3.27 (b. m, 2H), 3.09 (b. m, 2H), 2.09 (b. m, 2H), 1.82 (b. m, 2H).

c. PREPARATION OF 6-((1-(3-(4-CHLOROPHENYL)PROPYL)PIPERIDIN-4-YL)OXY)QUINOLIN-2(1H)-ONE (COMPOUND 34, SCHEME 7).

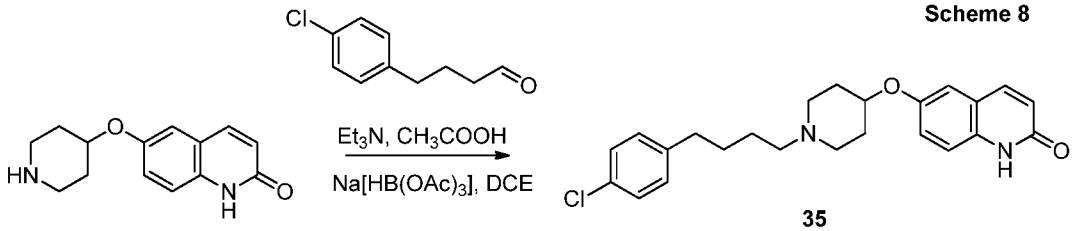


[001081] A suspension of 6-(piperidin-4-yloxy)quinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of 3-(4-chlorophenyl)propanal (0.31 mL, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture and later stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and

brine (10 mL). The bilayer mixture was extracted with ethyl acetate (80 mL) and later washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.165 g (54.6 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.65 (s, 1H), 7.82 (d, 1H), 7.34 (d, 2H), 7.25 (m, 4H), 7.18 (m, 1H), 6.47 (d, 1H), 4.35 (b. s, 1H), 2.68 (b. s, 2H), 2.59 (t, 2H), 2.31 (b. s, 2H), 2.15 (b. s, 2H), 1.93 (b. s, 2H), 1.71 (b. s, 2H), 1.62 (b. s, 2H). ES-MS m/z 397.5 $(C_{23}H_{25}ClN_2O_2 + 1)^+$.

10. PREPARATION OF 6-((1-(4-(4-CHLOROPHENYL)BUTYL)PIPERIDIN-4-YL)OXY)QUINOLIN-2(1H)-ONE (COMPOUND 35, SCHEME 8).

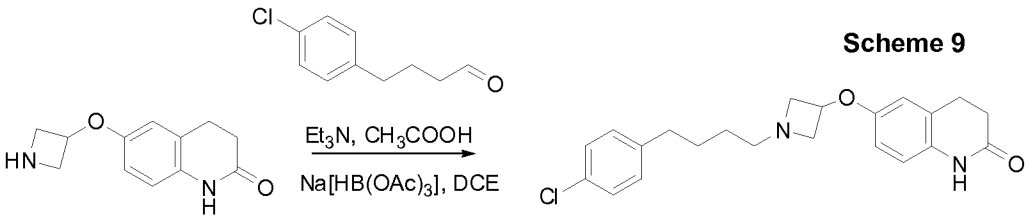
Scheme 8



35

[001082] A suspension of 6-(piperidin-4-yloxy)quinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at rt. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of 4-(4-chlorophenyl)butanal (0.33 mL, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture, and stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (60 mL) and later washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.14 g (44.8 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.62 (s, 1H), 7.82 (d, 1H), 7.33 (d, 2H), 7.24 (m, 3H), 7.16 (m, 2H), 6.48 (d, 1H), 4.36 (b. s, 1H), 2.70 (b. s, 2H), 2.60 (m, 2H), 2.39 (b. s, 2H), 2.18 (b. s, 2H), 1.93 (b. s, 2H), 1.57 (b. m, 4H), 1.44 (b. s, 2H). ES-MS m/z 411.5 $(C_{24}H_{27}ClN_2O_2 + 1)^+$.

11. PREPARATION OF 6-((1-(4-(4-CHLOROPHENYL)BUTYL)AZETIDIN-3-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 36, SCHEME 9).

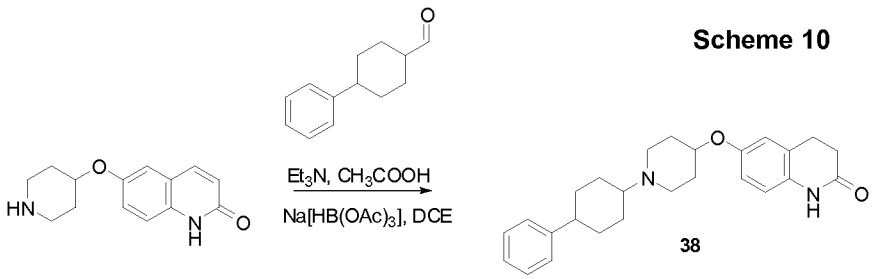


Scheme 9

36

[001083] A suspension of 6-(azetidin-3-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 0.8 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.34 mL, 2.4 mmol) was added to the mixture, which was followed by the addition of 4-(4-chlorophenyl)butanal (0.36 mL, 0.98 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture, and stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (2 × 50 mL), which was washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.143 g (45.6 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.91 (s, 1H), 7.32 (d, 2H), 7.22 (d, 2H), 6.76 (d, 1H), 6.68 (s, 1H), 6.60 (m, 1H), 4.66 (b. s, 1H), 3.68 (b. m, 2H), 2.84 (b. m, 4H), 2.55 (m, 2H), 2.47 (m, 4H), 1.55 (m, 2H), 1.29 (m, 2H). ES-MS m/z 385.5 $(C_{22}H_{25}ClN_2O_2 + 1)^+$.

12. PREPARATION OF 6-((1-(4-PHENYLCYCLOHEXYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 38, SCHEME 10).



Scheme 10

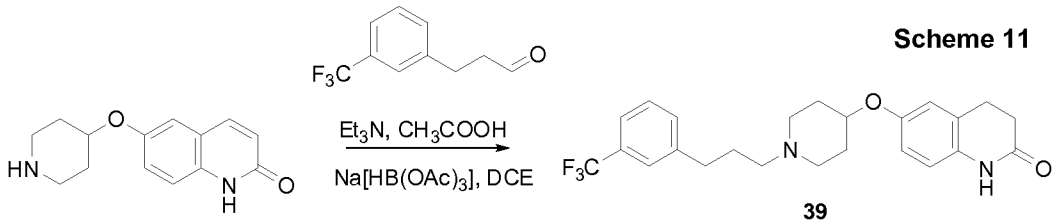
38

[001084] A suspension of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at rt. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of *4*-phenylcyclohexanone (0.16 g, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture, and stirred for

16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (60 mL), which was washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.11 g (35.9 %). Some product was found to be present in the filtrate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.26 (m, 4H), 7.22 (m, 1H), 6.80 (s, 1H), 6.75 (s, 2H), 4.27 (b. s, 1H), 2.82 (b. s, 4H), 2.40 (b. s, 1H), 2.40 (m, 2H), 2.18 (b. m, 2H), 1.93 (b. m, 6H), 1.55 (b. m, 6H). ES-MS m/z 405.2 $(C_{26}H_{32}N_2O_2 + 1)^+$.

13. PREPARATION OF 6-((1-(3-(3-(TRIFLUOROMETHYL)PHENYL)PROPYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 39, SCHEME 11).

Scheme 11

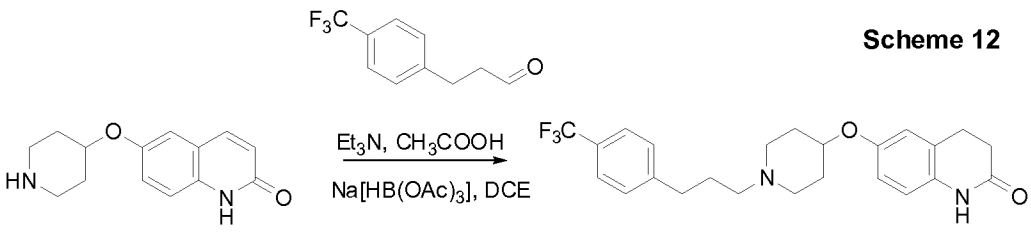


39

[001085] A suspension of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.2 g, 0.5 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.21 mL, 1.5 mmol) was added to the mixture, which was followed by the addition of *3*-(*3*-(trifluoromethyl)phenyl)propanal (0.1 g, 0.5 mmol). Further, acetic acid (0.06 mL) and sodium triacetoxyborohydride (0.16 g, 0.75 mmol) were added to the reaction mixture, and stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (50 mL), which was washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.055 g (25.2 %). Some product was found to be present in the filtrate. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.58 (s, 1H), 7.53 (b. s, 3H), 6.80 (s, 1H), 6.74 (b. s, 2H), 4.24 (b. s, 1H), 2.82 (t, 2H), 2.70 (m, 4H), 2.38 (t, 2H), 2.29 (b. s, 2H), 2.22 (b. s, 2H), 1.88 (b. s, 2H), 1.76 (b. s, 2H), 1.59 (b. s, 2H). ES-MS m/z 433.3 $(C_{24}H_{27}F_3N_2O_2 + 1)^+$.

14. PREPARATION OF 6-((1-(3-(4-(TRIFLUOROMETHYL)PHENYL)PROPYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 40, SCHEME 12).

Scheme 12

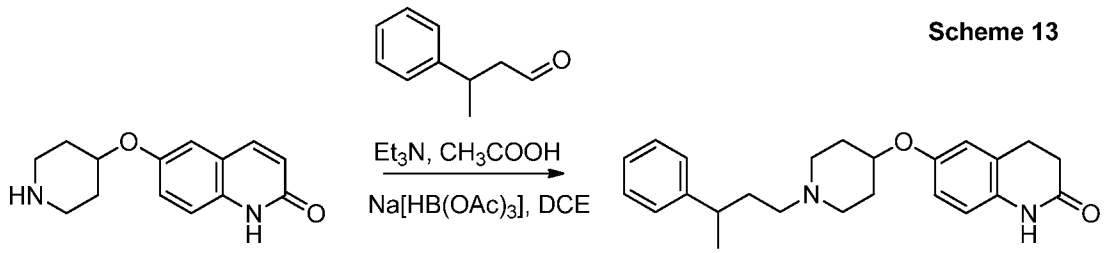


40

[001086] A suspension of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at room temperature. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of *3*-(*4*-(trifluoromethyl)phenyl)propanal (0.184 g, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture, and stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (50 mL), which was washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). The product was triturated with ether and filtered. Yield: 0.145 g (44.3 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.64 (d, 2H), 7.45 (d, 2H), 6.80 (s, 1H), 6.74 (s, 2H), 4.24 (b. s, 1H), 2.82 (t, 2H), 2.68 (m, 4H), 2.39 (t, 2H), 2.29 (b. s, 2H), 2.16 (b. s, 2H), 1.88 (b. s, 2H), 1.76 (b. s, 2H), 1.60 (b. s, 2H). ES-MS m/z 433.30 $(C_{24}H_{27}F_3N_2O_2 + 1)^+$.

15. PREPARATION OF 41 (SCHEME 13).

Scheme 13



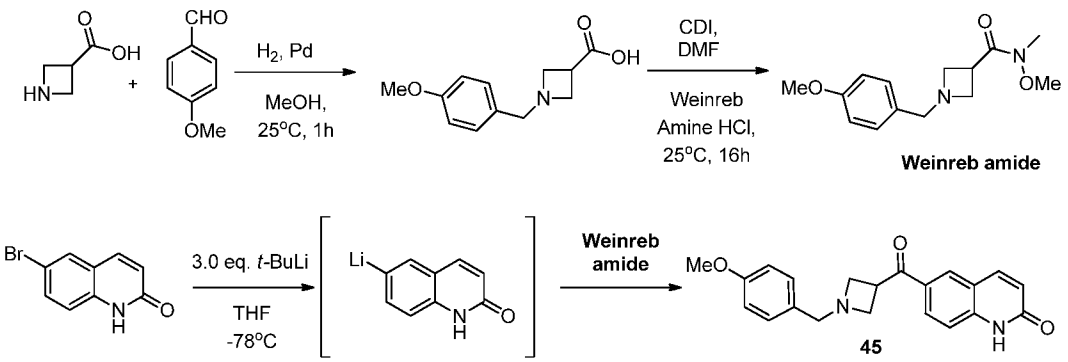
41

[001087] A suspension of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 0.76 mmol) and anhydrous dichloroethane (10 mL) was stirred at rt. Triethyl amine (0.32 mL, 2.3 mmol) was added to the mixture, which was followed by the addition of *3*-phenylbutanal (0.135 g, 0.91 mmol). Further, acetic acid (0.09 mL) and sodium triacetoxyborohydride (0.24 g, 1.1 mmol) were added to the reaction mixture, and stirred for 16 h. The resulting mixture

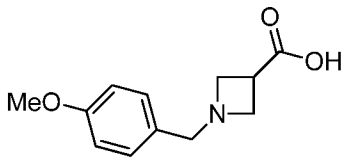
was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (50 mL), which was washed with brine. The organic solution was dried over Na_2SO_4 and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a solvent mixture of dichloromethane:methanol:ammonia (95:5:0.05). An oily substance was obtained. Yield: 0.19 g (66.3 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.90 (s, 1H), 7.29 (m, 2H), 7.23 (m, 2H), 7.17 (m, 1H), 6.78 (s, 1H), 6.73 (s, 2H), 4.22 (b. s, 1H), 2.81 (t, 2H), 2.73 (m, 1H), 2.62 (b. s, 2H), 2.39 (t, 2H), 2.23 (b. s, 2H), 2.12 (b. s, 2H), 1.86 (b. s, 2H), 1.71 (b. s, 2H), 1.57 (b. s, 2H), 1.20 (d, 3H). ES-MS m/z 379.3 $(C_{24}H_{30}N_2O_2 + 1)^+$.

16. Preparation of 6-(1-(4-methoxybenzyl)azetidine-3-carbonyl)quinolin-2(1H)-one (Compound 45, Scheme 14).

Scheme 14

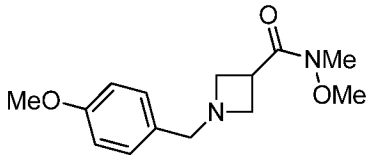


a. Preparation of 1-(4-methoxybenzyl)azetidine-3-carboxylic acid (Scheme 14).



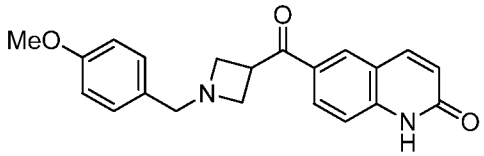
[001088] A mixture of azetidine-*3*-carboxylic acid (1.0 g, 10 mmol), *4*-methoxybenzaldehyde (1.9 mL, 15 mmol), palladium on activated carbon (wet 10% Pd/C 0.5 g), and anhydrous methanol (20 mL) was stirred under hydrogen gas (1 atm) at 25 °C for 1 h. The resulting mixture was filtered and the filtrate was evaporated on a rotary evaporator. The residue obtained was dissolved in THF and evaporated. The residue was triturated with ethyl acetate to obtain a white solid, which was filtered and dried under vacuum for use in the next step. Yield = 1.80 g (82.0 %).

b. PREPARATION OF N-METHOXY-1-(4-METHOXYBENZYL)-N-METHYLAZETIDINE-3-CARBOXAMIDE (SCHEME 14).



[001089] To a solution of *1*-(*4*-methoxybenzyl)azetidine-*3*-carboxylic acid (1.8 g, 8.1 mmol) in DMF (10 mL) was added CDI (1.8 g, 9.72 mmol) at room temperature. After 15 min, Weinreb amine hydrochloride salt (1.2 g, 10.13 mmol) and triethyl amine (1.8 mL, 11.34 mmol) were added to the reaction mixture and stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with dichloromethane (60 mL) and later washed with brine. The organic solution was dried over $MgSO_4$ and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 40 g) using a gradient solvent mixture of dichloromethane to dichloromethane:methanol (90:10). The resulting product contained DMF, which was removed by water wash of a dichloromethane solution followed by drying with $MgSO_4$, and evaporating to an oily residue that was used in the next step. Yield: 1.60 g (74.0 %).

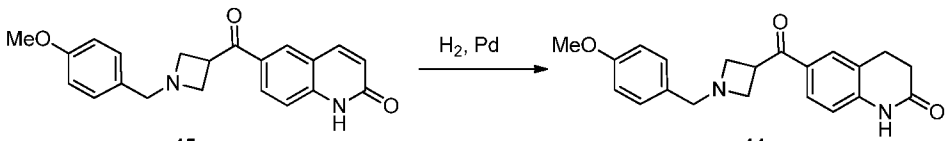
c. PREPARATION OF 6-(1-(4-METHOXYBENZYL)AZETIDINE-3-CARBONYL)QUINOLIN-2(1H)-ONE (COMPOUND 45, SCHEME 14).



[001090] To a solution of *6*-bromoquinolin-2(1H)-one (1.4 g, 6.25 mmol) in anhydrous THF (30 mL) at -78 °C, was added drop wise a 1.7 M pentane solution of *tert*-BuLi (12.8 mL, 21.88 mol). After 20 min, a THF solution of N-methoxy-1-(4-methoxybenzyl)-N-methylazetidine-3-carboxamide (1.6 g, 6.05 mmol) was added slowly to the reaction mixture. The resulting mixture was stirred and warmed up to 25 °C over 2 h. The reaction was quenched by the slow addition of saturated ammonium chloride solution, which was extracted with dichloromethane. The extract was dried over $MgSO_4$ and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 40 g) using a gradient solvent mixture of dichloromethane to dichloromethane:methanol (90:10) to obtain pure product that was used in the next step. Yield: 0.4 g (20.0 %).

17. PREPARATION OF 6-(1-(4-METHOXYBENZYL)AZETIDINE-3-CARBONYL)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 44, SCHEME 15).

Scheme 15

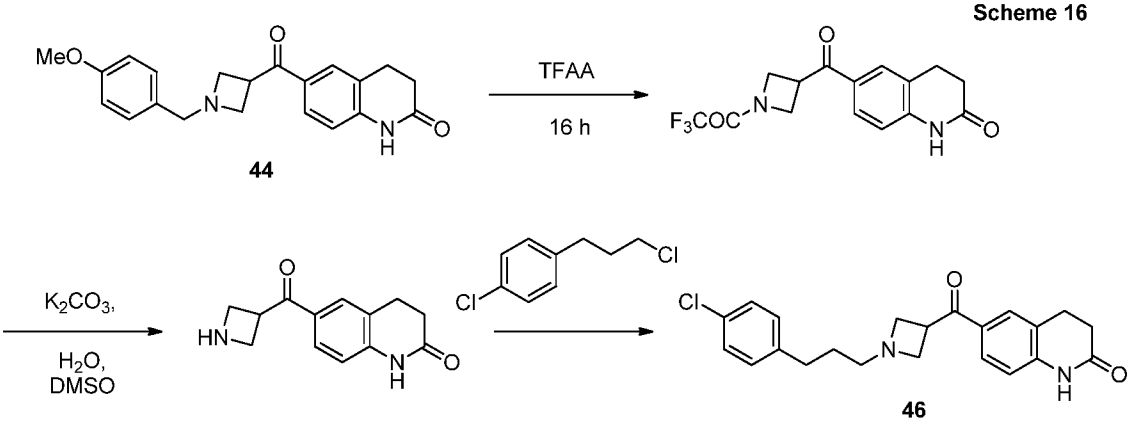


45 44

[001091] A suspension of 6-(1-(4-methoxybenzyl)azetidine-3-carbonyl)quinolin-2(1H)-one (0.65 g, 1.9 mmol), ethanol (30 mL), and palladium on activated carbon (wet 10% Pd/C 0.10 g) was stirred under hydrogen gas (45 psi) at 25 °C for 16 h. The resulting mixture was filtered and the filtrate was evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 40 g) using a gradient solvent mixture of dichloromethane to dichloromethane:methanol (90:10) to obtain pure product that was used in the next step. Yield = 0.25 g (39.0 %).

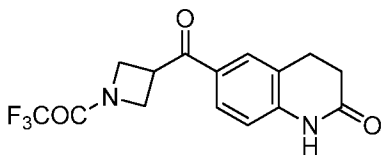
18. PREPARATION OF 6-(1-(3-(4-CHLOROPHENYL)PROPYL)AZETIDINE-3-CARBONYL)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 46, SCHEME 16).

Scheme 16



44 46

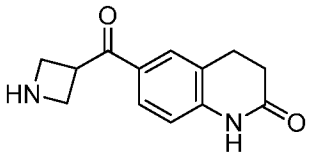
a. PREPARATION OF 6-(1-(2,2,2-TRIFLUOROACETYL)AZETIDINE-3-CARBONYL)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (SCHEME 16).



[001092] 6-(1-(4-methoxybenzyl)azetidine-3-carbonyl)-3,4-dihydroquinolin-2(1H)-one (0.20 g, 0.57 mmol) was dissolved in trifluoroacetic anhydride and stirred at 25 °C for 16 h. The mixture was evaporated to dryness. The residue was dissolved in THF and ethyl acetate, which was washed with brine, dried over $MgSO_4$, and evaporated. A mixture of diamide and

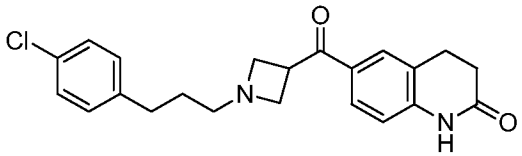
monoamide products were obtained, which was carried over to the next step without further purification.

19. PREPARATION OF 6-(AZETIDINE-3-CARBONYL)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (SCHEME 16).



[001093] To a solution of 6-(1-(2,2,2-trifluoroacetyl)azetidine-3-carbonyl)-3,4-dihydroquinolin-2(1H)-one (mixture obtained from previous step) in DMSO:water (7:3, 10 mL) was added potassium carbonate (4 eq). The reaction mixture was heated at 80 °C for 16 h. The resulting mixture was extracted with dichloromethane, which was dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a gradient solvent mixture of dichloromethane:methanol:ammonia (95:5:0) to dichloromethane:methanol:ammonia (85:15:1) to obtain pure product that was used in the next step. Yield = 0.042 g.

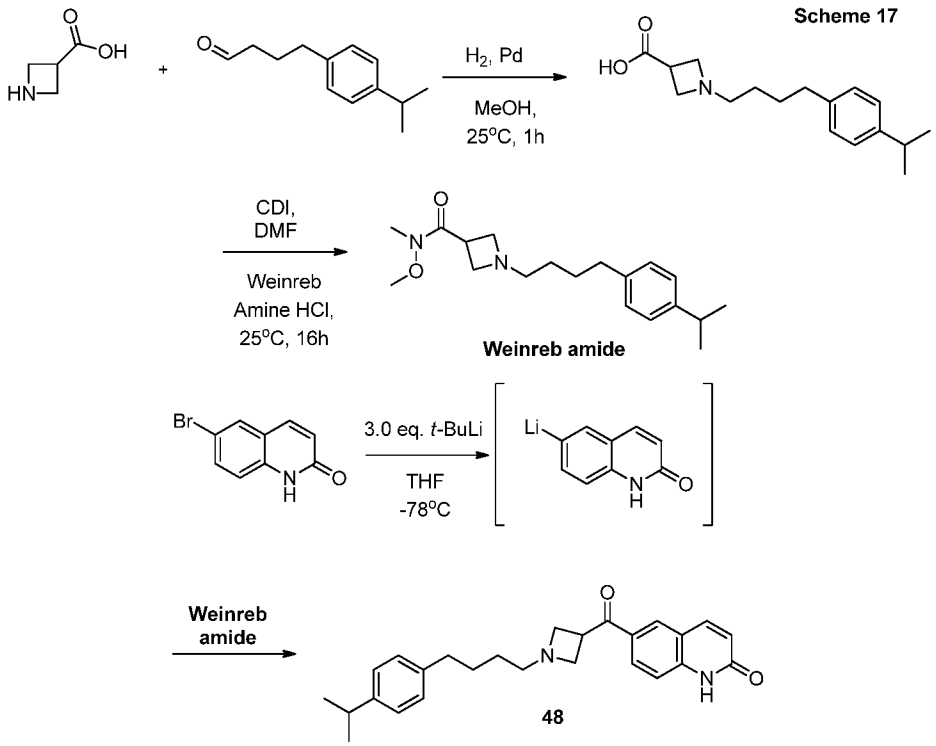
20. PREPARATION OF 6-(1-(3-(4-CHLOROPHENYL)PROPYL)AZETIDINE-3-CARBONYL)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 46, SCHEME 16).



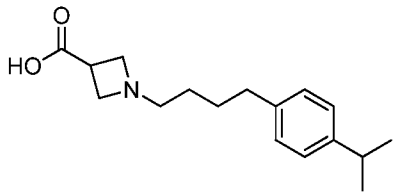
[001094] A mixture of 6-(azetidine-3-carbonyl)-3,4-dihydroquinolin-2(1H)-one (0.025 g, 0.075 mmol), *1*-chloro-*4*-(*3*-chloropropyl)benzene (0.028 g, 0.15 mmol), potassium carbonate (0.040 g, 0.30 mmol), and sodium iodide (0.005 g), in DMSO:water (1:1, 2 mL) was heated at 90 °C for 16 h. The resulting mixture was extracted with ethyl acetate, which was dried over $MgSO_4$, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using a gradient solvent mixture of dichloromethane:methanol:ammonia (95:5:0) to dichloromethane:methanol:ammonia (90:10:1) to obtain pure title product. Yield = 0.008 g.

21. Preparation of 6-(1-(4-(4-isopropylphenyl)butyl)azetidine-3-carbonyl)quinolin-2(1H)-one (Compound 48, Scheme 17).

Scheme 17

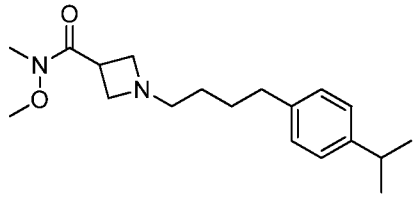


a. Preparation of 1-(4-(4-isopropylphenyl)butyl)azetidine-3-carboxylic acid (Scheme 17).



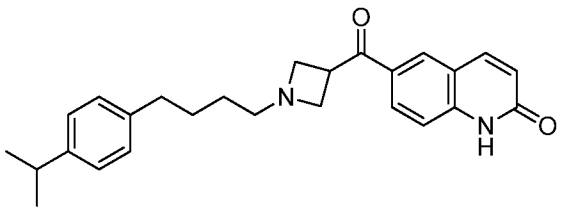
[001095] A mixture of azetidine-*3*-carboxylic acid (1.8 g, 18 mmol), *4*-(*4*-isopropylphenyl)butanal (3.8 g, 20 mmol), palladium on activated carbon (wet 10% Pd/C 0.8 g), and anhydrous methanol (40 mL) was stirred under hydrogen gas (1 atm) at 25 °C for 3 h. The resulting mixture was filtered and the filtrate was evaporated on a rotary evaporator. The residue was dissolved in a mixture of THF and ethyl acetate (1:1; 60 mL), and filtered to remove a small quantity of insoluble material (0.2 g). The filtrate was evaporated on a rotary evaporator. The oily residue obtained was washed with hexane and dried under vacuum and used for the next step. Yield = 3.50 g (70.0 %).

b. PREPARATION OF 1-(4-(4-ISOPROPYLPHENYL)BUTYL)-N-METHOXY-N-METHYLAZETIDINE-3-CARBOXAMIDE (SCHEME 17).



[001096] To a solution of the 1-(4-(4-isopropylphenyl)butyl)azetidine-3-carboxylic acid (3.5 g, 12.7 mmol) in THF (60 mL) was added CDI (2.5 g, 15.24 mmol) at room temperature. After 60 min, Weinreb amine hydrochloride salt (1.7 g, 17.78 mmol) and triethyl amine (2.8 mL, 20.32 mmol) were added to the reaction mixture and stirred for 16 h. The resulting mixture was treated with few drops of sodium carbonate solution and brine (10 mL). The bilayer mixture was extracted with ethyl acetate (60 mL) and later washed with brine. The organic solution was dried over $MgSO_4$ and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 40 g) using a gradient solvent mixture of dichloromethane to dichloromethane:methanol (90:10) and used for the next step. Yield: 1.90 g (48.0 %).

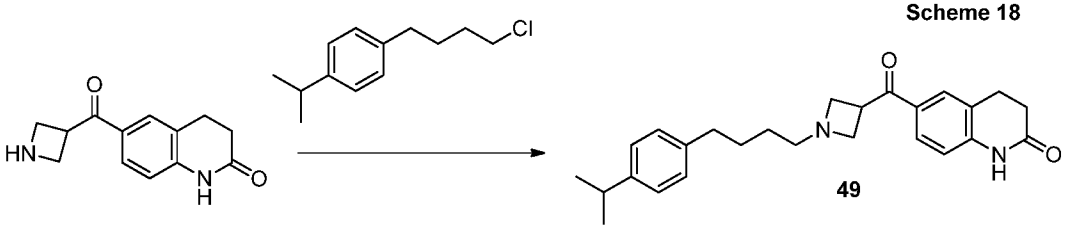
c. PREPARATION OF 6-(1-(4-(4-ISOPROPYLPHENYL)BUTYL)AZETIDINE-3-CARBONYL)QUINOLIN-2(1H)-ONE (COMPOUND 48, SCHEME 17).



[001097] To a solution of *6*-bromoquinolin-2(1H)-one (1.3 g, 6.0 mmol) in anhydrous THF (40 mL) at -78 °C, was added drop wise a 1.7 M pentane solution of *tert*-BuLi (11.5 mL, 19.80 mol). After 20 min, a THF solution (20 mL) of 1-(4-(4-isopropylphenyl)butyl)-N-methoxy-N-methylazetidine-3-carboxamide (1.9 g, 6.0 mmol) was added slowly to the reaction mixture. The resulting mixture was stirred and warmed up to 25 °C over 2 h. The reaction was quenched by the slow addition of saturated ammonium chloride solution, which was extracted with dichloromethane. The extract was dried over $MgSO_4$ and evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 40 g) using a gradient solvent mixture of dichloromethane to dichloromethane:methanol (90:10) to obtain pure title product. Yield: 0.150 g (6.24 %).

22. Preparation of 6-(1-(4-(4-isopropylphenyl)butyl)azetidine-3-carbonyl)-3,4-dihydroquinolin-2(1H)-one (Compound 49, Scheme 18).

Scheme 18

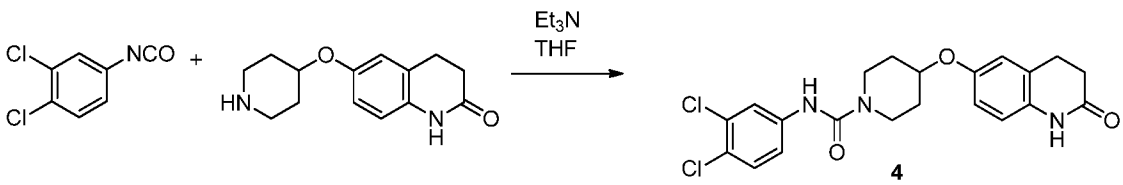


49

[001098] A suspension of 6-(1-(4-(4-isopropylphenyl)butyl)azetidine-3-carbonyl)quinolin-2(1H)-one (0.150 g, 0.37 mmol), ethanol (30 mL), and palladium on activated carbon (wet 10% Pd/C 0.10 g) was stirred under hydrogen gas (45 psi) at 25 °C for 16 h. The resulting mixture was filtered and the filtrate was evaporated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 2 g) using a gradient solvent mixture of dichloromethane:methanol:ammonia (95:5:0) to dichloromethane:methanol:ammonia (90:10:1) to obtain pure title product. Yield = 0.061 g (40.4 %).

23. Preparation Of N-(3,4-Dichlorophenyl)-4-((2-Oxo-1,2,3,4-Tetrahydroquinolin-6-Yl)Oxy)Piperidine-1-Carboxamide (Compound 4, Scheme 19)

Scheme 19



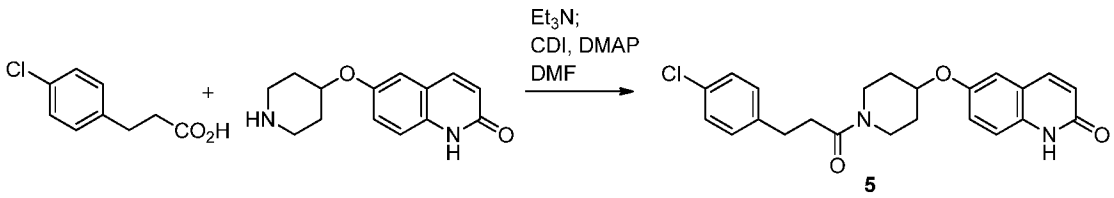
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[001099] To a solution of 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.21 g, 0.53 mmol) in anhydrous tetrahydrofuran (5 mL) at 20 °C was added triethyl amine (0.22 mL, 1.6 mmol) followed by *3,4*-(dichloro)phenylisocyanate (0.199 g, 1.1 mmol). After 5 h, the mixture was treated with brine (10 mL) and extracted with ethyl acetate (40 mL). The solution was dried over Na_2SO_4 and evaporated on a rotavap. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 8 g) using gradient dichloromethane:methanol solvent mixture (100:0 to 95:5). The product was triturated with ether and filtered. Yield: 0.114 g (49.5 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H),

8.83 (s, 1H), 7.85 (s, 1H), 7.46 (m, 2H), 6.82 (s, 1H), 6.80 (m, 2H), 4.48 (m, 1H), 3.79 (m, 2H), 3.27 (m, 2H), 2.84 (t, 2H), 2.41 (t, 2H), 1.93 (m, 2H), 1.57 (m, 2H). ES-MS m/z 434.10 $(C_{21}H_{21}Cl_2N_3O_3 + 1)^+$.

24. PREPARATION OF 6-((1-(3-(4-CHLOROPHENYL)PROPANOYL)PIPERIDIN-4-YL)OXY)QUINOLIN-2(1H)-ONE (COMPOUND 5, SCHEME 20):

Scheme 20

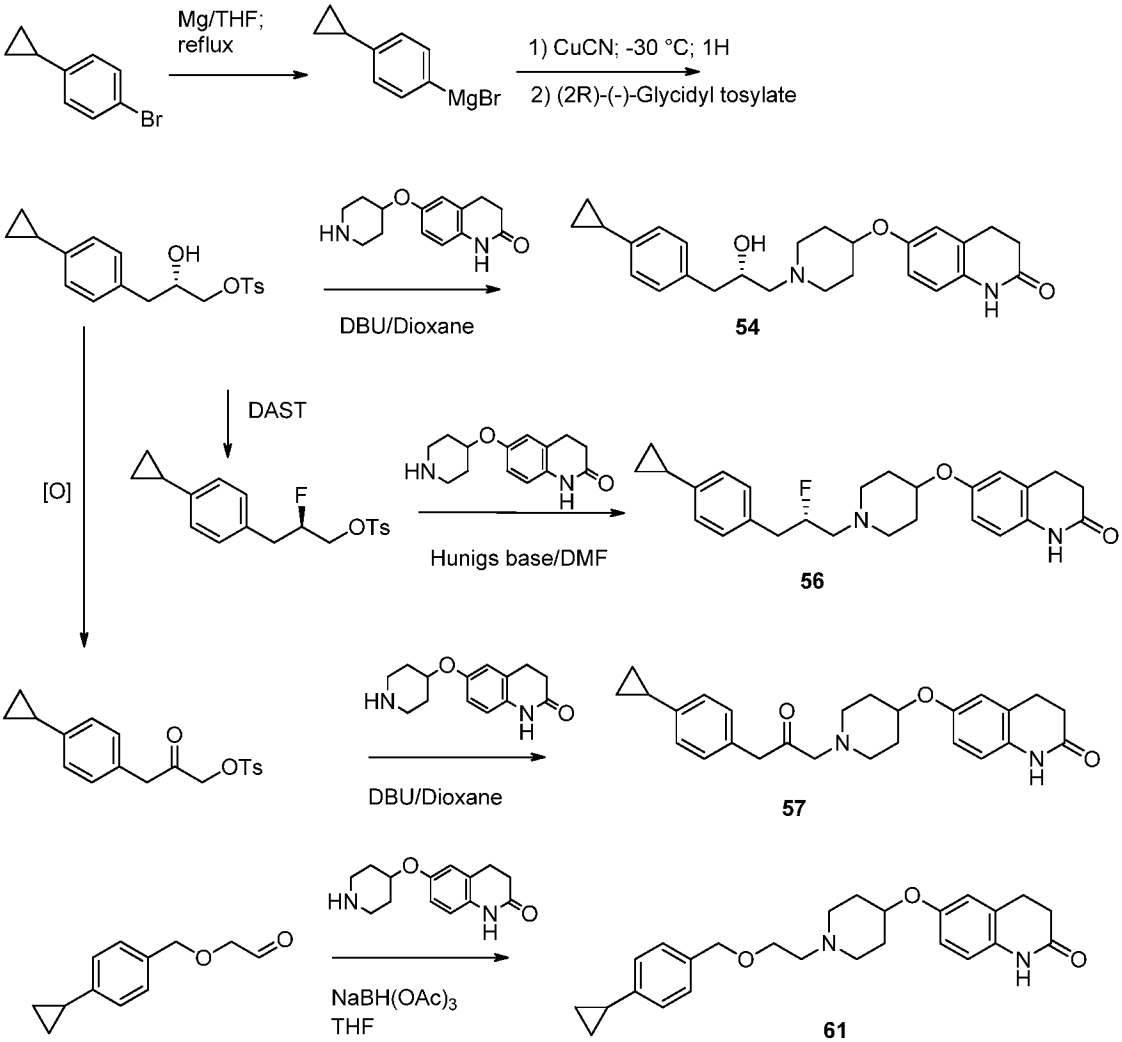


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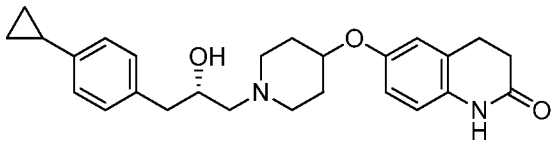
[001100] A mixture of *3-(4*-chlorophenyl)propanoic acid (0.146 g, 0.8 mmol), *4*-(dimethylamino)-pyridine (0.005 g, 0.04 mmol) and *1,1'*-carbonyldiimidazole (0.128 g, 0.8 mmol) was stirred in DMF at 20 °C. After an hour, 6-(piperidin-4-yloxy)quinolin-2(1H)-one (0.26 g, 0.66 mmol) was added to the reaction mixture followed by triethyl amine (0.28 mL, 1.98 mmol), and stirred for 15 h. The clear mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 30 mL). The organic solution was washed with brine, dried over Na_2SO_4 and evaporated on a rotavap. The residue was purified by flash column chromatography on silica gel (230-400 mesh; 12 g) using dichloromethane:methanol solvent mixture (95:5). The product was triturated with ether and filtered. Yield: 0.16 g (59.0 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.63 (s, 1H), 7.82 (d, 1H), 7.26 (m, 7H), 6.49 (d, 1H), 4.57 (m, 1H), 3.87 (m, 1H), 3.69 (m, 1H), 3.25 (m, 2H), 2.87 (m, 2H), 2.65 (m, 2H), 1.89 (b.s, 2H), 1.51 (b.m, 2H). ES-MS m/z 411.15 $(C_{23}H_{23}ClN_2O_3 + 1)^+$.

25. PREPARATION OF (S)-6-((1-(3-(4-CYCLOPROPYLPHENYL)-2-HYDROXYPROPYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 54), (S)-6-((1-(3-(4-CYCLOPROPYLPHENYL)-2-FLUOROPROPYL)-PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 56), 6-((1-(3-(4-CYCLOPROPYLPHENYL)-2-OXOPROPYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 57), AND 6-((1-(2-((4-CYCLOPROPYLBENZYL)OXY)ETHYL)PIPERIDIN-4-YL)OXY)-3,4-DIHYDROQUINOLIN-2(1H)-ONE (COMPOUND 61) [SCHEME 21]

Scheme 21



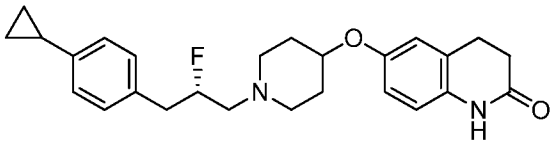
a. Preparation of 54 (Scheme 21)



[001101] **Step 1**: The tosylate compound (S)-3-(4-cyclopropylphenyl)-2-hydroxypropyl 4-methylbenzenesulfonate was prepared starting from grignard reagent (4-cyclopropylphenyl)magnesium bromide and R-glycidyl tosylate in the presence of CuCN.

[001102] **Step 2**: A mixture of tosylate compound (0.45 g, 1.3 mmol), **16** (0.32 g, 1.3 mmol), DBU (0.3 mL, 1.5 eq.) and dioxane (5 mL) was heated at 90 °C for 24 h. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and water. The organic layer was separated, washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified on silica gel (12 g, 280-400 mesh) using dichloromethane: methanol (9:1). Yield: 60 mg. ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 0.61 (q, 2 H), 0.83 - 0.98 (m, 2 H), 1.66 (s, 3 H), 1.80 - 2.01 (m, 2 H), 2.32 - 2.45 (m, 2 H), 2.53 - 2.73 (m, 3 H), 2.73 - 2.94 (m, 3 H), 3.38 - 3.71 (m, 4 H), 3.85 (br. s., 1 H), 4.30 (br. s., 1 H), 5.19 (d, 1 H), 6.66 - 6.86 (m, 3 H), 6.93 - 7.03 (m, 2 H), 7.05 - 7.17 (m, 2 H), 9.89 (s, 1 H).

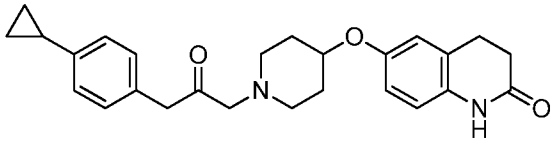
b. Preparation of 56 (Scheme 21)



[001103] **Step 1**: The tosylate compound, (S)-3-(4-cyclopropylphenyl)-2-hydroxypropyl 4-methylbenzenesulfonatehydroxyl was treated with DAST (2 eq) in dichloromethane at 0 °C. The reaction mixture after addition was warmed up to room temperature and stirred for an hour. The mixture was treated with brine and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified on silica gel (12 g, 280-400 mesh) using dichloromethane:methanol mixture as eluent to obtain (R)-3-(4-cyclopropylphenyl)-2-fluoropropyl 4-methylbenzenesulfonate. **Step 2**: A mixture of (R)-3-(4-cyclopropylphenyl)-2-fluoropropyl 4-methylbenzenesulfonate. (1 eq), 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (1 eq), DBU (1.5 eq.) and dioxane (5 mL) was heated at 90 °C for 24 h. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and water. The organic layer was separated, washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified on silica gel (12 g, 280-400

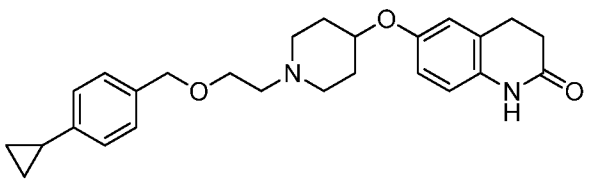
mesh) using dichloromethane: methanol (9:1) to obtain **56**. ^{1}H NMR (500 MHz, $CHCl_3$-*d*) δ ppm 0.56 - 0.64 (m, 2 H), 0.83 - 0.91 (m, 2 H), 1.63 - 1.97 (m, 6 H), 2.31 (s, 2 H), 2.41 - 2.59 (m, 3 H), 2.71 (d, 2 H), 2.79 - 2.90 (m, 3 H), 4.09 - 4.21 (m, 1 H), 4.46 - 4.68 (m, 1 H), 4.69 - 4.88 (m, 1 H), 6.55 - 6.70 (m, 3 H), 6.95 (t, 2 H), 7.01 - 7.10 (m, 2 H), 7.90 (s, 1H).

c. **Preparation of 57 (Scheme 21)**



[001104] A mixture of 3-(4-cyclopropylphenyl)-2-oxopropyl 4-methylbenzenesulfonate (0.5 g, 1.45 mmol; obtained by Dess-Martin oxidation of (S)-3-(4-cyclopropylphenyl)-2-hydroxypropyl 4-methylbenzenesulfonate), 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (400 mg, 1.6 mmol), Hunig's base (0.4 mL, 1.5 eq) was heated at 90 °C for 16 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over Na_2SO_4 and evaporated. The obtained residue was purified by silica gel chromatography using silica (12 g, 280-400 mesh) and gradient dichloromethane:methanol (100:0 to 90:10) as eluant mixture to obtain **57**. Yield: 60 mg. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.55 - 0.63 (m, 2 H) 0.82 - 0.92 (m, 2 H) 1.70 - 1.84 (m, 3 H) 1.86 - 1.96 (m, 2 H) 2.22 - 2.34 (m, 2 H) 2.53 (dd, 2 H) 2.56 - 2.66 (m, 2 H) 2.79 - 2.89 (m, 2 H) 3.14 (s, 2 H) 3.62 (s, 2 H) 4.11 - 4.22 (m, 1 H), 6.54 - 6.69 (m, 3 H) 6.95 (d, 2 H) 7.04 (d, 2 H) 7.91 (s, 1 H).

d. **Preparation of 61 (Scheme 21)**



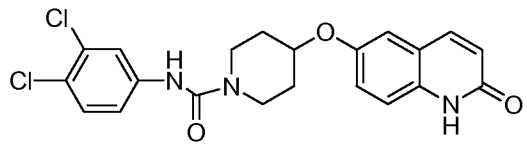
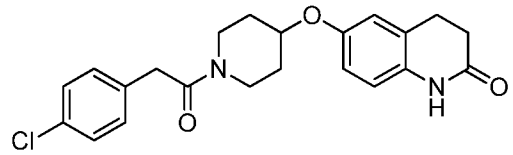
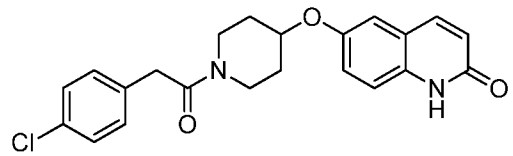
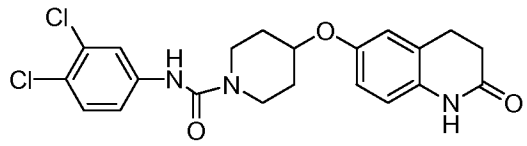
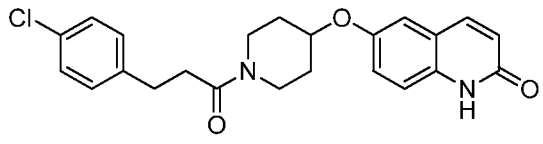
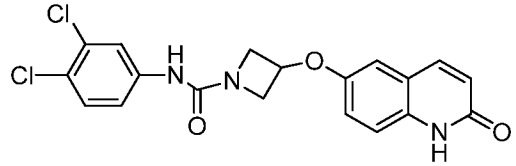
[001105] A mixture of 2-((4-cyclopropylbenzyl)oxy)acetaldehyde (0.2 g, 1.05 mmol), sodium trisacetoxy borohydride (0.37 g, 1.2 mmol), and 6-(piperidin-4-yloxy)-3,4-dihydroquinolin-2(1H)-one (0.3 g, 1.2 mmol) in THF solvent was stirred at room temperature for 5 h. The resulting mixture was treated with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic extract was washed with brine, dried over Na_2SO_4, and evaporated. The residue obtained was purified on silica gel (12 g, 280-400 mesh) using dichloromethane:methanol (9:1) as eluent to obtain **61**. Yield: 40 mg. ^{1}H NMR (500 MHz,

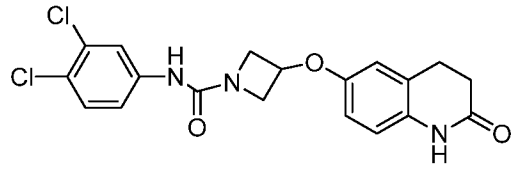
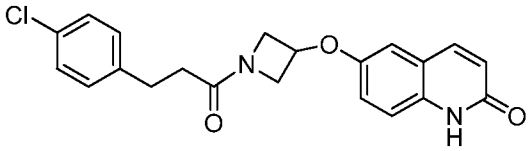
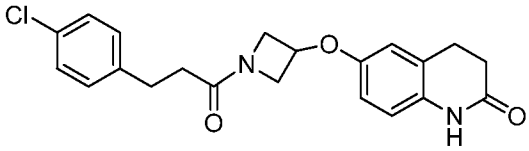
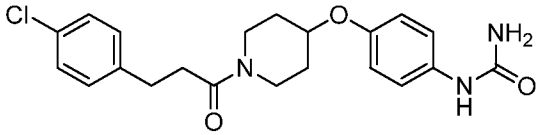
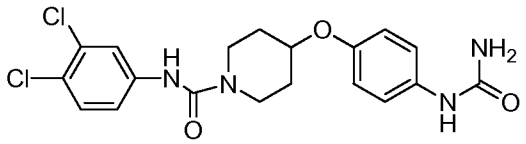
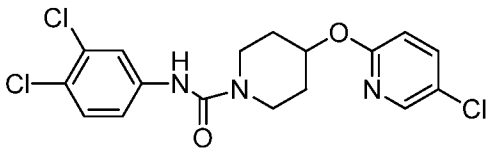
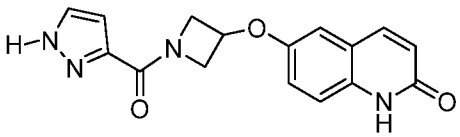
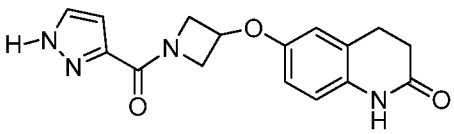
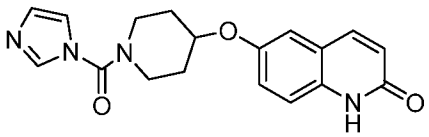
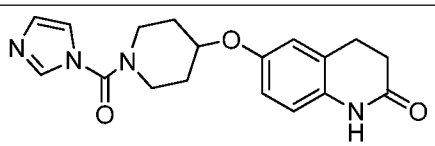
DMSO-d_6) δ ppm 0.58 - 0.69 (m, 2 H) 0.86 - 0.96 (m, 2 H) 1.48 - 1.61 (m, 2 H) 1.80 - 1.94 (m, 3 H) 2.16 - 2.28 (m, 2 H) 2.38 (dd, 2 H) 2.44 - 2.56 (m, 2 H) 2.64 - 2.74 (m, 2 H) 2.76 - 2.85 (m, 2 H) 3.49 (t, 2 H) 4.15 - 4.26 (m, 1 H) 4.39 (s, 2 H) 6.64 - 6.82 (m, 3 H) 7.03 (d, 2 H) 7.18 (d, 2 H) 9.87 (s, 1 H)

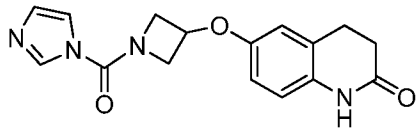
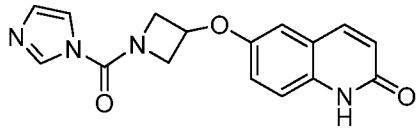
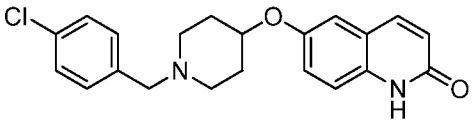
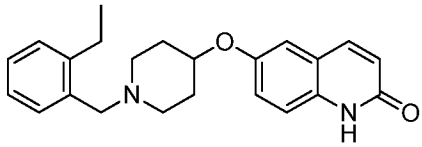
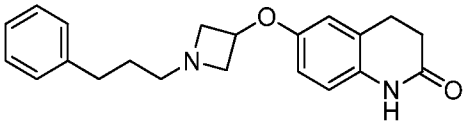
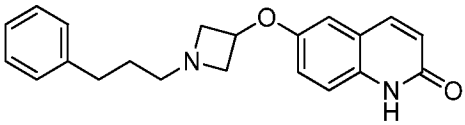
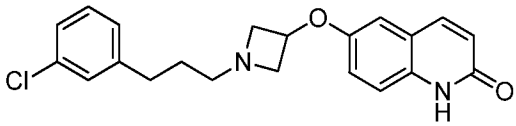
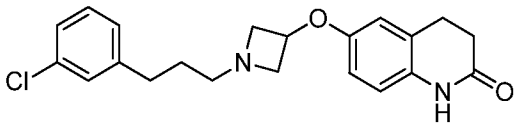
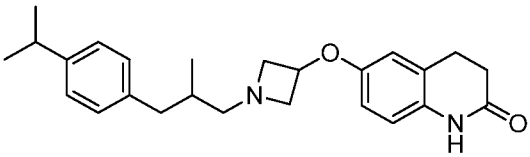
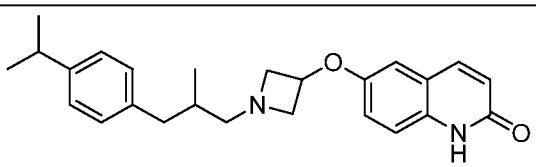
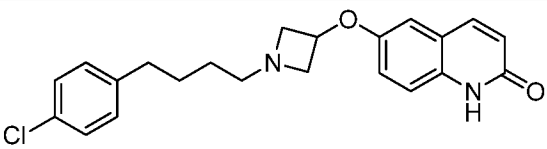
26. EXAMPLE COMPOUNDS.

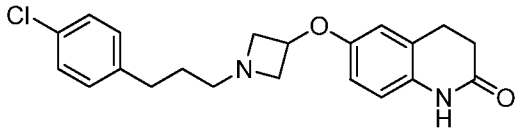
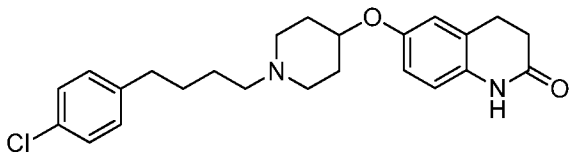
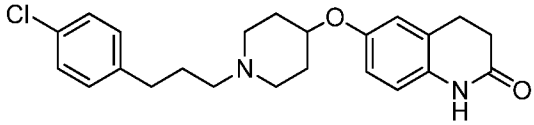
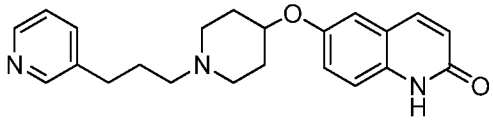
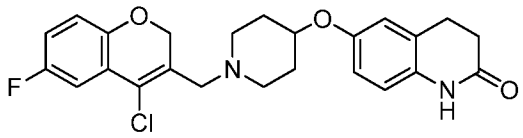
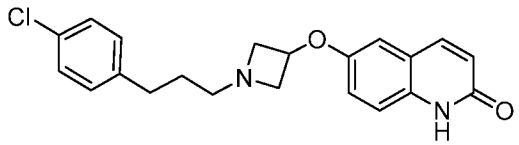
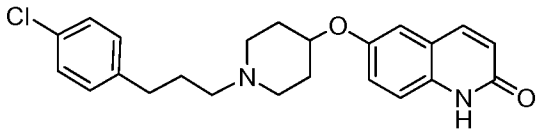
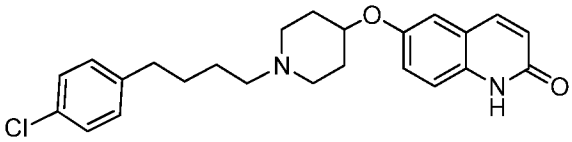
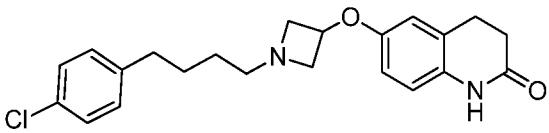
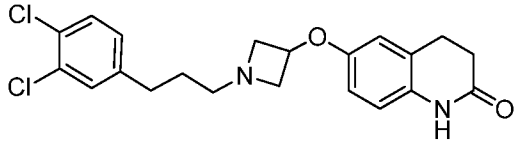
[001106] Table 1 below lists specific compounds, preferred synthetic route(s), and characterization data. The compounds in Table 1 were synthesized with methods identical or analogous to those described herein. The requisite starting materials were commercially available, described in the literature, or readily synthesized by one skilled in the art of organic synthesis.

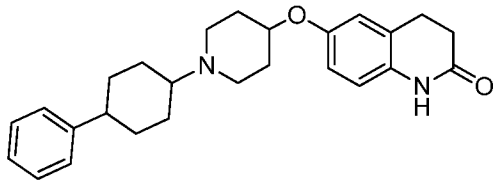
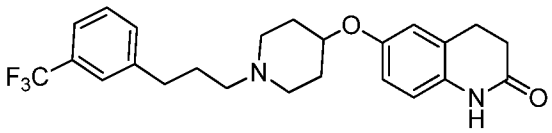
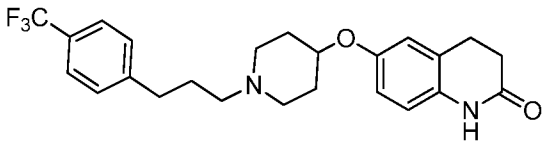
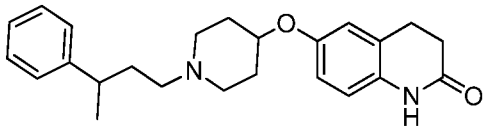
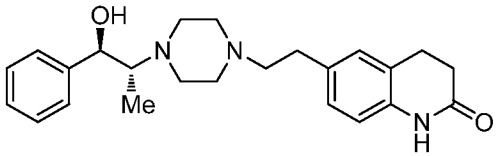
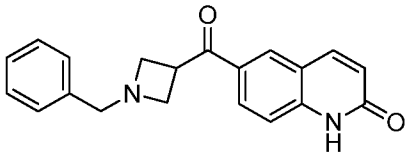
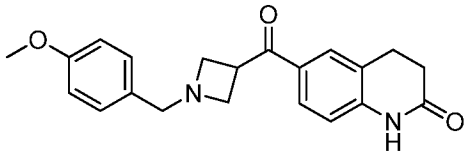
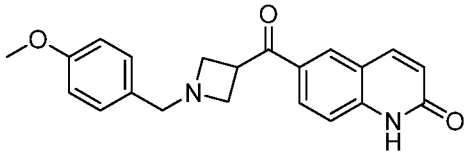
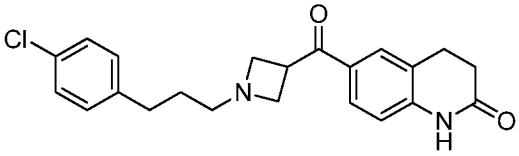
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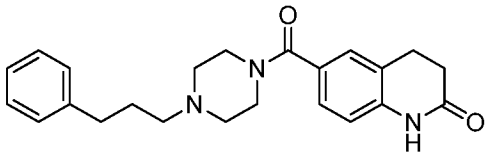
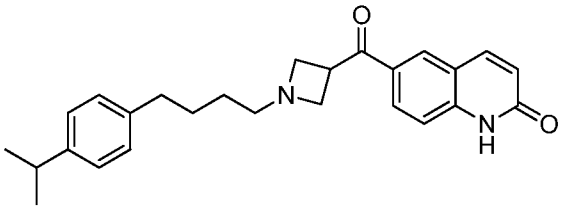
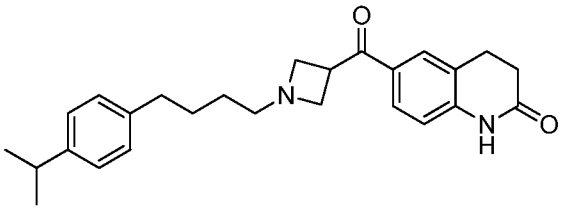
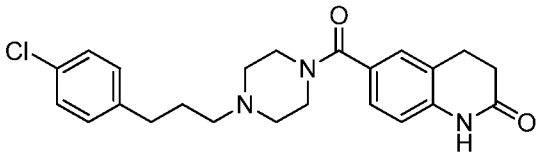
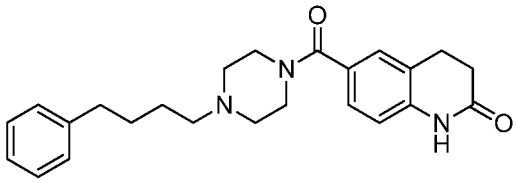
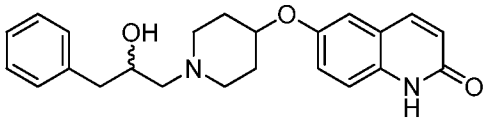
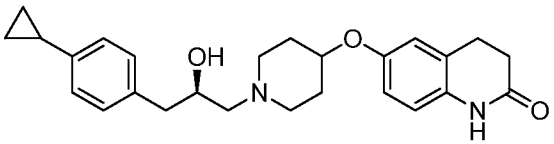
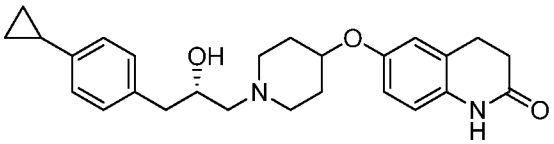
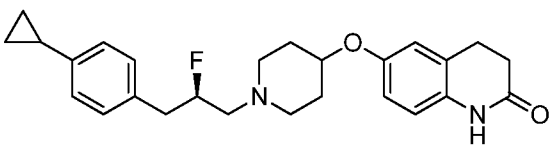
No.	Structure	Synthetic Route Reference	Parent MW
1		Scheme 19, Page 402	432.3
2		Scheme 20, Page 403	398.9
3		Scheme 20, Page 403	396.9
4		Scheme 19, Page 402	434.3
5		Scheme 20, Page 403	410.9
6		Scheme 19, Page 402	404.3

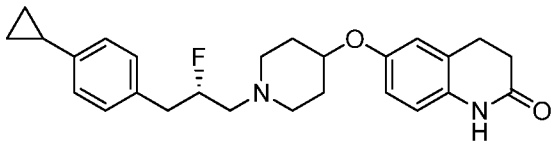
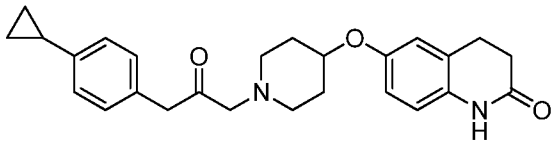
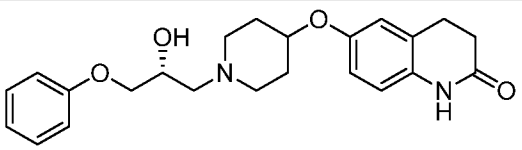
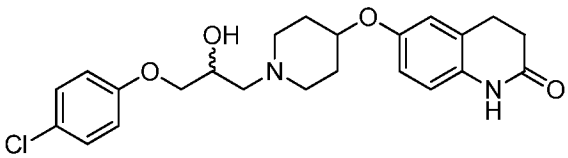
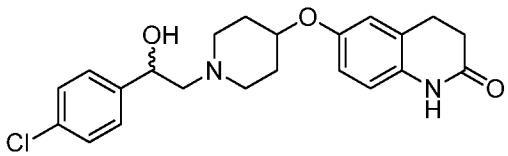
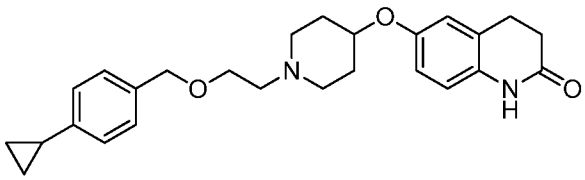
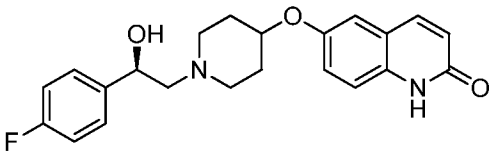
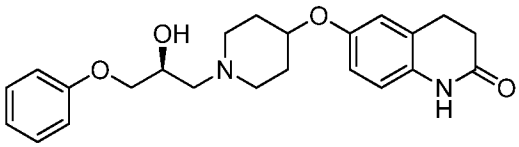
No.	Structure	Synthetic Route Reference	Parent MW
7		Scheme 19, Page 402	406.3
8		Scheme 20, Page 403	382.8
9		Scheme 20, Page 403	384.9
10		Scheme 20, Page 403	401.9
11		Scheme 19, Page 402	423.3
12		Scheme 19, Page 402	400.7
13		Scheme 20, Page 403	310.3
14		Scheme 20, Page 403	312.1
15		Scheme 19, Page 402	338.4
16		Scheme 19, Page 402	340.4

No.	Structure	Synthetic Route Reference	Parent MW
17		Scheme 19, Page 402	312.3
18		Scheme 19, Page 402	310.3
19		Scheme 1, Page 381	368.9
20		Scheme 1, Page 381	362.5
21		Scheme 1, Page 381	336.4
22		Scheme 1, Page 381	334.4
23		Scheme 1, Page 381	368.9
24		Scheme 1, Page 381	370.9
25		Scheme 3, Page 386	Article I. 392.5
26		Scheme 3, Page 386	390.5
27		Scheme 1, Page 381	382.9

No.	Structure	Synthetic Route Reference	Parent MW
28		Scheme 4, Page 386	370.9
29		Scheme 5, Page 387	412.2
30		Scheme 5, Page 387	398.9
31		Scheme 6, Page 389	363.5
32		Scheme 7, Page 390	442.9
33		Scheme 7, Page 390	368.9
34		Scheme 7, Page 390	396.9
35		Scheme 8, Page 391	410.9
36		Scheme 9, Page 392	384.9
37		Scheme 9, Page 392	405.3

No.	Structure	Synthetic Route Reference	Parent MW
38		Scheme 10, Page 393	404.5
39		Scheme 11, Page 394	432.5
40		Scheme 12, Page 395	432.5
41		Scheme 13, Page 395	378.5
42		Scheme 21, Page 404	393.5
43		Scheme 14, Page 396	318.4
44		Scheme 15, Page 398	350.4
45		Scheme 14, Page 396	348.4
46		Scheme 16, Page 398	382.9

No.	Structure	Synthetic Route Reference	Parent MW
47		Scheme 16, Page 398	377.5
48		Scheme 17, Page 400	402.5
49		Scheme 18, Page 401	404.5
50		Scheme 16, Page 398	411.9
51		Scheme 16, Page 398	391.5
52		Scheme 21, Page 404	378.5
53		Scheme 21, Page 404	420.5
54		Scheme 21, Page 404	420.5
55		Scheme 21, Page 404	422.5

No.	Structure	Synthetic Route Reference	Parent MW
56		Scheme 21, Page 404	422.5
57		Scheme 21, Page 404	418.5
58		Scheme 21, Page 404	396.5
59		Scheme 21, Page 404	430.9
60		Scheme 21, Page 404	400.9
61		Scheme 21, Page 404	420.5
62		Scheme 21, Page 404	382.4
63		Scheme 21, Page 404	396.5

27. Generation of GluN1/GluN2B receptors expressed in Xenopus cell line

[001107] Stage V and VI oocytes were surgically removed from the ovaries of large, well-fed and healthy *Xenopus laevis* anesthetized with 3-amino-benzoic acid ethyl ester (3 gm/l). Clusters of isolated oocytes were incubated with 292 U/ml Worthington (Freehold, NJ) type

IV collagenase or 1.3 mg/ml collagenase (Life Technologies, Gaithersburg, MD; 17018–029) for 2 hr in Ca^{2+}-free solution comprised of (in mM) 115 NaCl, 2.5 KCl, and 10 HEPES, pH 7.5, with slow agitation to remove the follicular cell layer. Oocytes were then washed in the same solution supplemented with 1.8 mM $CaCl_2$ and maintained in Barth's solution comprised of (in mM): 88 NaCl, 1 KCl, 2.4 $NaHCO_3$, 10 HEPES, 0.82 $MgSO_4$, 0.33 $Ca(NO_3)_2$, and 0.91 $CaCl_2$, and supplemented with 100 μg/ml gentamycin, 10 μg/ml streptomycin, and 10 μg/ml penicillin. Oocytes were manually defolliculated and injected within 24 hrs of isolation with 3-5 ng of GluN1 subunit cRNA and 7-10 ng of GluN2B cRNA subunit in a 50 nl volume, and incubated in Barth's solution at 18°C for 2–7 d. Glass injection pipettes had tip sizes ranging from 10-20 microns, and were backfilled with mineral oil. cRNA was synthesized from linearized template cDNA for human and rat glutamate receptor subunits according to manufacturer specifications (Ambion).

28. CELL-BASED FUNCTIONAL ASSAY

[001108] Two electrode voltage-clamp recordings were made 2–7 days post-injection. Oocytes were placed in a dual-track Plexiglas recording chamber with a single perfusion line that splits in a Y-configuration to perfuse two oocytes. Dual recordings were made at room temperature (23 °C) using two Warner OC725B two-electrode voltage clamp amplifiers, arranged as recommended by the manufacturer. Glass microelectrodes (1-10 megaohms) were filled with 300 mM KCl (voltage electrode) or 3 M KCl (current electrode). The bath clamps communicated across silver chloride wires placed into each side of the recording chamber, both of which were assumed to be at a reference potential of 0 mV. Oocytes were perfused with a solution comprised of (in mM) 90 NaCl, 1 KCl, 10 HEPES, 10 EDTA and 0.5 $BaCl_2$; pH was adjusted by addition of 1-3 M NaOH of HCl. Oocytes were recorded under voltage clamp at -40 mV. Final concentrations for glutamate and glycine were 50 μM and 30 μM, respectively. Recordings were made at pH 6.9 and pH 7.6.

29. DATA ANALYSIS

[001109] Concentration-response curves for experimental compounds were obtained by applying in successive fashion maximal glutamate/glycine, followed by glutamate/glycine plus variable concentrations of experimental compounds. Dose response curves consisting of 4 to 8 concentrations were obtained in this manner. The baseline leak current at -40 mV was measured before and after recording, and the full recording linearly corrected for any change in leak current. The level of inhibition by applied experimental compounds was expressed as a percent of the initial glutamate response, and averaged together across oocytes from

multiple experiments. Results were pooled, and the average percent responses at antagonist concentrations were fit by the equation:

Percent Response = (100 - minimum) / (1 + ([conc] / IC_{50})^{nH}) + minimum,

where *minimum* is the residual percent response in saturating concentration of the disclosed compounds, IC_{50} is the concentration of antagonist that causes half of the achievable inhibition, and *nH* is a slope factor describing steepness of the inhibition curve. *Minimum* was constrained to be between 0 and 20. The pH Boost ratio was calculated by dividing the IC_{50} measured in recordings performed at pH 7.6 by the IC_{50} measured in recordings performed at pH 6.9.

30. Activity of Compounds in Cell-based Assays

[001110] Table III below lists specific compounds as well as experimentally determined NMDA activity in a cell-based assay. The NMDA activity was determined using the electrophysiological NMDA receptor activity assays in Xenopus laevis oocytes as described above, wherein the Xenopus oocytes were injected with cRNA encoding human GluN1a and GluN2B subunits. The compounds in Table 2 were synthesized with methods identical or analogous to those described herein. The compound numbers in Table 2 correspond to the compound numbers used in Table 1.

Table 2.

No.	IC_{50} (pH 7.6)	nH	Y_{max}	IC_{50} (pH 6.9)	nH	Y_{max}	IC_{50} 7.6/6.9	No. of oocytes	
								pH 7.6	pH 6.9
1	0.025	-0.93	8.1	0.011	-0.56	0.0	2.3	18	20
2	9.44	-1.07	0.0	4.33	-0.77	10.9	2.2	5	10
3	2.65	-1.51	17.3	1.83	-0.93	14.1	1.5	11	13
4	0.153	-0.95	16.0	0.196	-0.86	0.0	0.8	20	16
5	0.052	-1.07	0.0	0.021	-0.76	0.0	2.5	16	19
6	0.042	-0.74	0.0	0.039	-0.68	0.0	1.1	15	15
7	0.280	-1.11	14.0	0.169	-0.51	1.3	1.7	18	20
8	0.752	-0.93	0.0	0.316	-0.56	0.0	2.4	17	20
9	2.106	-1.20	8.7	1.164	-0.87	2.2	1.8	10	11
10	0.652	-0.89	2.6	0.331	-0.61	0.0	2.0	13	19
11	0.199	-1.00	18.7	0.280	-0.69	0.0	0.7	18	18
12	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	NA	0	5
13	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	NA	0	5
14	n.d.	n.d.	n.d.	> 1*	n.a.	n.a.	NA	0	2

No.	IC_{50} (pH 7.6)	nH	Y_{max}	IC_{50} (pH 6.9)	nH	Y_{max}	IC_{50} 7.6/6.9	No. of oocytes	
								pH 7.6	pH 6.9
15	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	NA	0	12
16	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	n.a.	0	12
17	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	NA	0	10
18	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	NA	0	10
19	36.5	-0.92	20.0	33.4	-0.75	0.0	2.5	9	12
20	n.d.	n.d.	n.d.	> 1*	n.a.	n.a.	NA	0	7
21	0.170	-0.78	10.0	0.128	-0.33	0.0	1.3	15	16
22	0.387	-0.74	6.2	0.137	-0.62	0.0	2.8	18	20
23	0.279	-1.08	18.6	0.082	-0.71	8.3	3.4	16	16
24	0.172	-1.75	17.3	0.126	-0.69	3.4	1.4	14	16
25	0.341	-0.91	1.9	0.129	-0.79	0.0	2.6	13	14
26	0.414	-1.46	7.1	0.104	-0.87	10.0	4.0	12	12
27	0.009	-2.05	19.3	0.004	-1.25	14.2	2.3	16	15
28	0.113	-0.91	10.0	0.064	-0.87	10.0	1.8	9	9
29	0.037	-2.82	18.7	0.007	-2.00	19.1	5.5	13	9
30	0.011	-0.92	7.6	0.003	-0.60	0.0	4.4	19	16
31	0.458	-1.02	8.9	0.226	-0.58	0.0	2.0	17	1
32	n.d.	n.d.	n.d.	> 10*	n.a.	n.a.	NA	0	6
33	0.185	-0.82	7.2	0.038	-0.65	0.0	4.8	15	17
34	0.010	-1.27	14.2	0.002	-0.82	9.3	5.7	26	31
35	0.011	-1.28	9.8	0.005	-0.71	0.0	2.3	15	20
36	0.020	-1.00	20.0	0.012	-0.94	10.0	1.7	9	11
37	0.307	-1.21	18.8	0.043	-0.58	0.0	7.2	22	41
38	0.722	-1.14	0.0	0.298	-0.65	0.0	2.6	16	17
39	0.348	-0.90	3.5	0.068	-0.88	10.0	5.1	31	29
40	0.024	-0.90	5.2	0.006	-0.80	7.5	4.2	19	20
41	0.069	-1.02	14.8	0.047	-0.62	3.2	1.5	19	20
42	> 10*	n.d.	n.d.	> 10*	n.d.	n.d.	n.a.	5	5
43	n.d.	n.d.	n.d.	> 1*	n.d.	n.d.	n.a.	0	5
44	n.d.	n.d.	n.d.	> 1*	n.d.	n.d.	n.a.	0	8
45	n.d.	n.d.	n.d.	> 1*	n.d.	n.d.	n.a.	0	5
46	0.023	-1.14	10.0	0.012	-1.36	10.0	1.9	9	9
47	1.046	-0.79	0.0	0.483	-0.67	0.0	2.2	15	20
48	0.008	-0.77	12.5	0.003	-0.74	10.3	3.0	33	39

No.	IC_{50} (pH 7.6)	nH	Y_{max}	IC_{50} (pH 6.9)	nH	Y_{max}	IC_{50} 7.6/6.9	No. of oocytes	
								pH 7.6	pH 6.9
49	0.009	-1.24	9.8	0.005	-0.64	5.8	1.7	12	11
50	0.953	-0.83	10.0	0.375	-0.57	0.0	2.5	12	16
51	3.079	-0.61	0.0	0.939	-0.57	0.0	3.3	16	19
52	0.108	-0.77	0.0	0.090	-0.78	0.0	1.2	14	16
53	2.245	-0.78	0.0	1.012	-0.70	0.0	2.2	14	16
54	0.193	-0.85	0.0	0.049	-0.95	0.0	3.9	11	11
55	1.072	-0.94	0.0	0.221	-0.82	0.0	4.9	20	24
56	0.746	-0.82	0.0	0.225	-0.72	0.0	3.3	10	14
57	0.844	-0.92	9.0	0.408	-0.70	0.0	2.1	13	13
58	0.138	-0.82	0.0	0.057	-0.86	0.0	2.4	15	14
59	0.058	-0.92	10.0	0.017	-0.73	10.0	3.4	12	11
60	0.781	-0.79	0.0	0.466	-0.57	0.0	1.7	14	20
61	0.020	-0.85	3.0	0.007	-0.84	1.4	2.9	36	30
62	0.633	-0.92	10.0	0.616	-0.84	10.0	1.0	12	15
63	0.047	-0.88	1.0	0.021	-0.90	0.0	2.2	34	29

*"n.d." indicates not determined or not tested in the assay; "n.a." indicates not applicable; IC_{50} is given in μM.

31. NMDA Receptor Subunit Selectivity

[001111] To evaluate NMDA receptor subunit selectivity, Xenopus oocytes were injected with cRNA encoding either human or rat GluN1a plus either GluN2A, GluN2C or GluN2D subtype of NMDA receptors using the protocol described above. After application of glutamate (100 μM) and glycine (30 μM) for one minute, the indicated concentration of antagonist was perfused, with 100 μM glutamate and 30 μM glycine, onto the oocyte for two minutes. Following this time period, the remaining current in the presence of the antagonist was measured and compared to the maximal current obtained with 100 μM glutamate and 30 μM glycine alone (defined as 100%). Results of the GluN2 selectivity assay, shown as percent receptor activation remaining after antagonist application, are provided in Table 3 below.

TABLE 3.*

No.	GluN2A				GluN2C			
	Conc. Tested (sp)	% Current Remaining	SD	n	Conc. Tested (sp)	% Current Remaining	SD	n
1	10 μM (Rat)	80.4	1.1	4	n.d.	n.d.	n.d.	n.d.
4	10 μM (Rat)	77.3	11.2	5	3 μM (Rat)	80	5.4	6
5	10 μM	108	4.5	3	3 μM (Rat)	84.4	6.3	4
6	10 μM	109	5.3	3	n.d.	n.d.	n.d.	n.d.
22	3 μM	95.6	3.2	4	3 μM (Rat)	87.5	8.6	4
26	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
28	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
30	3 μM	89.2	18.1	3	3 μM (Rat)	104.4	14.7	4
31	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
35	3 μM	96.3	16.3	4	3 μM (Rat)	91.7	4.8	4, 4
36	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
40	3 μM	102.7	6.1	4	3 μM (Rat)	92.4	0.7	4
46	n.d.	n.d.	n.d.	n.d.	3 μM (Rat)	89.3	5.9	4
48	n.d.	n.d.	n.d.	n.d.	3 μM (Rat)	92.7	2.6	4
54	10 μM	102.1	4.9	4	10 μM (Rat)	89.0	1.9	4
58	3 μM	106.4	4.9	4	3 μM (Rat)	97.2	0.8	4
59	3 μM	102.4	5.5	3	3 μM (Rat)	97.7	0.6	4
61	3 μM	95.9	1.0	2	3 μM (Rat)	94.7	3.3	2

*"n.d." indicates not determined or not tested in the assay; "sp" indicates species (Human if not specified).

TABLE 3 (CONTINUED).*

No.	GluN2D			
	Conc Tested (sp)	% Current. Remaining	SD	n
1	10 μM (Rat)	83.9	8.7	6
4	10 μM (Rat)	89.3	3.0	6
5	10 μM (Rat)	88.9	4.5	6
6	n.d.	n.d.	n.d.	n.d.
22	3 μM	98.5	0.9	4
26	10 μM	109	5.3	4
28	10 μM	95.0	2.8	4
30	3 μM	89.4	4.9	4
31	10 μM	98	6.6	3
35	3 μM	94.2	2.9	4
36	10 μM	97.0	17.0	4
40	3 μM	101.4	3.3	3
46	n.d.	n.d.	n.d.	n.d.
48	n.d.	n.d.	n.d.	n.d.
54	10 μM	112.2	2.5	4
58	3 μM	98.8	1.3	4
59	3 μM	97.5	0.6	3
61	3 μM	100.3	5.2	2

*"n.d." indicates not determined or not tested in the assay; "sp" indicates species(Human if not specified).

32. hERG AND α_1-ADRENERGIC BINDING STUDIES

[001112] Binding to the human ether-a-go-go potassium channel (hERG) expressed in HEK293 cells by displacement of 1.5 nM [3H]-astemizole was evaluated. Each result represents the average of displacement binding experiments done in duplicate at 0.3, 1, 3, or 10 μM of the test compound.

[001113] Binding to percent displacement of 0.25 nM [3H]-prazosin from Wistar rat brain membranes was also evaluated. Each result represents the average of displacement binding

experiments done in duplicate at 1 μM of the test compound. hERG and α_1-Adrenergic binding (% displacement) data are provided in Table 4 below.

TABLE 4.

No.	hERG Binding % Displacement (±SD)				α1-Adrenergic (%) at 1 μM)
	0.3 μM	1 μM	3 μM	10 μM	
1	17.6 (6.7)		8.2 (4.1)		≤ 0
5	34.5 (3.1)		72.3 (4.7)		8
6	16.8 (4.4)		11.1 (3.3)		≤ 0
7	10.0 (4.2)		10.3 (5.6)		
9	14.4 (5.6)		45.7 (7.3)		7
10	5.7 (1.6)		35.7 (4.7)		≤ 0
11	24.1 (2.0)		9.2 (3.0)		≤ 0
21	49.4 (4.0)		68.8 (4.8)		75
22	55.2 (1.2)		78.7 (8.3)		
23	43.4 (8.3)		70.3 (10.4)		
24	33.5 (8.1)		67.8 (3.2)		
25	15.8 (3.7)		30.6 (3.5)		42
26	11.2 (9.3)		22.9 (6.1)		56
27	60.7 (3.6)		78.6 (2.3)		
28	43.8 (4.5)		65.5 (6.6)		
29	50.4 (6.8)		82.5 (2.3)		85
30	61.3 (1.2)		82.9 (2.8)		77
31	21.4 (5.9)		43.9 (11.6)		10
32	5.5 (7.5)		3.8 (4.7)		
33	60.2 (4.7)		78.7 (5.9)		70
34	82.0 (3.0)		94.3 (2.0)		60
35	64.4 (5.6)		85.0 (1.6)		76
36	30.6 (3.1)		59.1 (5.8)		70
37	35.8 (2.5)		53.9 (4.6)		
38	29.2 (4.3)		61.1 (5.7)		86
39	35.9 (3.6)		63.5 (5.5)		87
40	34.9 (5.8)		70.3 (4.6)		52
41	31.7 (8.0)		65.8 (3.3)		53
42	13.7 (4.3)		29.7 (10.7)		26
46	30.2 (3.2)	51.6 (4.3)	82.4 (5.7)	92.8 (1.4)	26
47	28.4 (4.1)		63.9 (10.0)		

No.	hERG Binding % Displacement (±SD)				α1-Adrenergic (%) at 1 μM)
	0.3 μM	1 μM	3 μM	10 μM	
48	26.5 (2.8)	41.6 (8.8)	53.3 (12.8)	56.2 (12.4)	15
49	30.5 (10.9)	51.1 (9.2)	68.2 (12.0)	85.0 (5.3)	≤ 0
50	50.7 (3.3)		83.1 (6.0)		≤ 0
51	49.3 (4.2)		82.9 (2.6)		
52	31.2 (1.7)		71.6 (1.4)		40
53	22.0 (4.4)		45.3 (6.2)		9
54	4.0 (6.3)	1.3 (10.9)	43.9 (5.6)	58.5 (10.5)	7
55	30.5 (3.0)		59.0 (9.5)		6
56	25.2 (5.0)		40.0 (7.4)		≤ 0
57	26.2 (5.5)		40.8 (1.5)		≤ 0
58	24.9 (10.1)	47.3 (7.0)	79.8 (13.4)	91.2 (1.6)	25
59	59.5 (3.3)	74.1 (7.1)	90.6 (1.9)	93.2 (1.5)	47
60	n.d.		n.d.		80
61	22.1 (7.0)		52.7 (4.9)		

*"n.d." indicates not determined or not tested in the assay.

33. PROSPECTIVE IN VITRO NONCOMPETITIVE NMDA RECEPTOR BLOCK ASSAY

[001114] Generally, NMDA receptor antagonists are competitive antagonists, uncompetitive channel blockers, and non-competitive antagonists. The compounds described in the preceding examples would be expected to exhibit certain NMDA receptor *in vitro* characteristics in various cell models known to the skilled person. A suitable assay for determination of the mechanism of action is a noncompetitive block assay. Briefly, *Xenopus* oocytes, injected with GluN2B-NMDA receptors as previous described, are perfused with (1) glutamate and glycine at various concentrations or (2) glutamate, glycine, with the antagonist compound. For example, if increasing glutamate and increasing glycine cannot overcome the block by the test compound, these results would suggest the test compound is a noncompetitive antagonist, binding to site other that agonist binding site. Compounds of the present invention are expected as a class to show noncompetitive NMDA receptor blockade.

34. PROSPECTIVE *IN VIVO* EFFECTS

[001115] In vivo efficacy for disclosed compounds and products of disclosed methods of making can be measured in a number of preclinical rat or mouse behavioral model known as

the forced swim test, or in a preclinical rat or mouse model of cerebral ischemia or stroke, known as the middle cerebral artery occlusion model.

[001116] For example, rodents, such as mice or rats, can be tested in a Forced Swim Test. Here, the animal is taken from their home cage and administerd a drug or vehicle control solution. At a defined period of time post administration the mouse or rat will be placed into a chamber of water of defined diameter appropriate for the species and deep enough to prevent the animal from touching the bottom. The water is kept at 25 °C. The swimming behavior can be observed directly or videotaped for later viewing. The animal is allowed to swim for 6 minutes and the immobility time is counted and recorded. Immobility refers to the time that the animal spends floating or engaged in minimal activity to keep afloat. The total immobility times for each animal will be recorded and can be used as an endpoint measured for effects of drug in the experiment. Compounds that inhibit NMDA receptors including those that are selective for GluN2B receptors can decrease the total immobility time (*Eur J Pharm* 1999, 375: 31; *Pharm Bioch Behav* 1995, 52: 621; *Biol Psych* 2008, 63: 349; *Science* 2010, 329: 959).

35. Prophetic Pharmaceutical Composition Examples

[001117] "Active ingredient" as used throughout these examples relates to one or more disclosed compounds, a product of a disclosed method of making, or a pharmaceutically acceptable salt, solvate, polymorph, hydrate and the stereochemically isomeric form thereof. The following examples of the formulation of the compounds of the present invention in tablets, suspension, injectables and ointments are prophetic.

[001118] Typical examples of recipes for the formulation of the invention are as given below. Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension, ointments, suppositories or chewable tablet form employing the disclosed compounds in desired dosage amounts in accordance with the present invention. Various conventional techniques for preparing suitable dosage forms can be used to prepare the prophetic pharmaceutical compositions, such as those disclosed herein and in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.) and Martindale The Extra Pharmacopoeia (London The Pharmaceutical Press). The disclosure of this reference is hereby incorporated herein by reference.

a. Pharmaceutical Composition for Oral Administration

[001119] A tablet can be prepared as follows:

Component	Amount
Active ingredient	10 to 500 mg
Lactose	100 mg
Crystalline cellulose	60 mg
Magnesium stearate	5
Starch (e.g. potato starch)	Amount necessary to yield total weight indicated below
Total (per capsule)	1000 mg

[001120] Alternatively, about 100 mg of a disclosed compound, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (e.g. from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate are used per tablet. The mixture of active component, lactose and starch is granulated with a 5% solution (m/m) of the PVP in water. After drying, the granules are mixed with magnesium stearate for 5 min. This mixture is moulded using a customary tablet press (e.g. tablet format: diameter 8 mm, curvature radius 12 mm). The moulding force applied is typically about 15 kN.

[001121] Alternatively, a disclosed compound can be administered in a suspension formulated for oral use. For example, about 100-5000 mg of the desired disclosed compound, 1000 mg of ethanol (96%), 400 mg of xanthan gum, and 99 g of water are combined with stirring. A single dose of about 10-500 mg of the desired disclosed compound according can be provided by 10 ml of oral suspension.

[001122] In these Examples, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds. In some circumstances it may be desirable to use a capsule, e.g. a filled gelatin capsule, instead of a tablet form. The choice of tablet or capsule will depend, in part, upon physicochemical characteristics of the particular disclosed compound used.

[001123] Examples of alternative useful carriers for making oral preparations are lactose, sucrose, starch, talc, magnesium stearate, crystalline cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl cellulose, glycerin, sodium alginate, gum arabic, etc. These alternative carriers can be substituted for those given above as required for desired dissolution, absorption, and manufacturing characteristics.

[001124] The amount of a disclosed compound per tablet for use in a pharmaceutical composition for human use is determined from both toxicological and pharmacokinetic data obtained in suitable animal models, e.g. rat and at least one non-rodent species, and adjusted

based upon human clinical trial data. For example, it could be appropriate that a disclosed compound is present at a level of about 10 to 1000 mg per tablet dosage unit.

b. PHARMACEUTICAL COMPOSITION FOR INJECTABLE USE

[001125] A parenteral composition can be prepared as follows:

Component	Amount
Active ingredient	10 to 500 mg
Sodium carbonate	560 mg*
Sodium hydroxide	80 mg*
Distilled, sterile water	Quantity sufficient to prepare total volume indicated below.
Total (per capsule)	10 ml per ampule

* Amount adjusted as required to maintain physiological pH in the context of the amount of active ingredient, and form of active ingredient, e.g. a particular salt form of the active ingredient.

[001126] Alternatively, a pharmaceutical composition for intravenous injection can be used, with composition comprising about 100-5000 mg of a disclosed compound, 15 g polyethylenglycol 400 and 250 g water in saline with optionally up to about 15% Cremophor EL, and optionally up to 15% ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid are used. The preparation of such an injectable composition can be accomplished as follows: The disclosed compound and the polyethylenglycol 400 are dissolved in the water with stirring. The solution is sterile filtered (pore size 0.22 μm) and filled into heat sterilized infusion bottles under aseptic conditions. The infusion bottles are sealed with rubber seals.

[001127] In a further example, a pharmaceutical composition for intravenous injection can be used, with composition comprising about 10-500 mg of a disclosed compound, standard saline solution, optionally with up to 15% by weight of Cremophor EL, and optionally up to 15% by weight of ethyl alcohol, and optionally up to 2 equivalents of a pharmaceutically suitable acid such as citric acid or hydrochloric acid. Preparation can be accomplished as follows: a desired disclosed compound is dissolved in the saline solution with stirring. Optionally Cremophor EL, ethyl alcohol or acid are added. The solution is sterile filtered (pore size 0.22 μm) and filled into heat sterilized infusion bottles under aseptic conditions. The infusion bottles are sealed with rubber seals.

[001128] In this Example, active ingredient can be replaced with the same amount of any of the compounds according to the present invention, in particular by the same amount of any of the exemplified compounds.

[001129] The amount of a disclosed compound per ampule for use in a pharmaceutical composition for human use is determined from both toxicological and pharmacokinetic data obtained in suitable animal models, e.g. rat and at least one non-rodent species, and adjusted based upon human clinical trial data. For example, it could be appropriate that a disclosed compound is present at a level of about 10 to 1000 mg per tablet dosage unit.

[001130] Carriers suitable for parenteral preparations are, for example, water, physiological saline solution, etc. which can be used with tris(hydroxymethyl)aminomethane, sodium carbonate, sodium hydroxide or the like serving as a solubilizer or pH adjusting agent. The parenteral preparations contain preferably 50 to 1000 mg of a disclosed compound per dosage unit.

[001131] It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

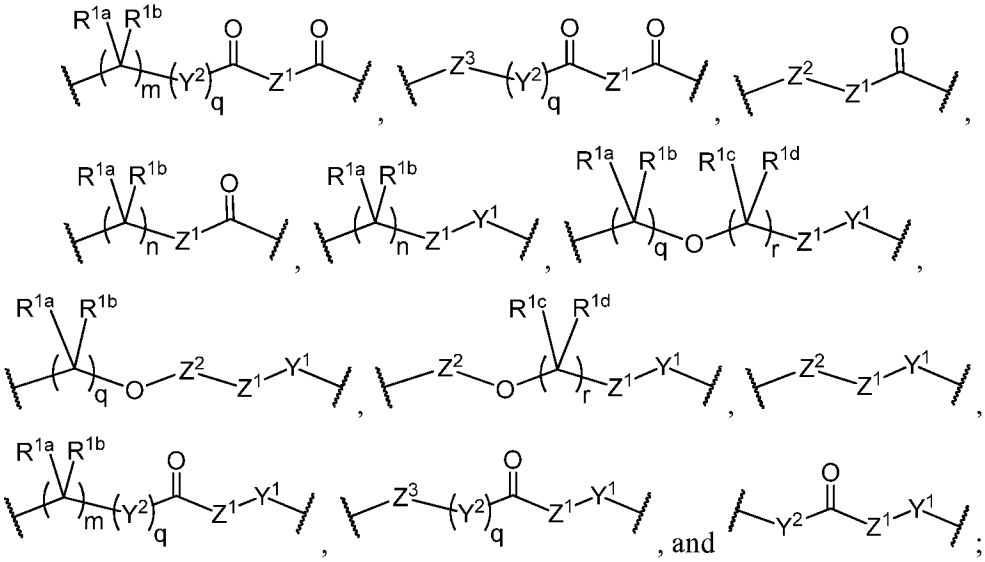
What is claimed is:

1. A compound having a structure represented by a formula:

$$Ar^1—L—Ar^2,$$

wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;

wherein L is selected from:



, and ;

wherein each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl;

wherein m is an integer from 1-3;

wherein n is an integer from 1-4;

wherein q is an integer from 0-1;

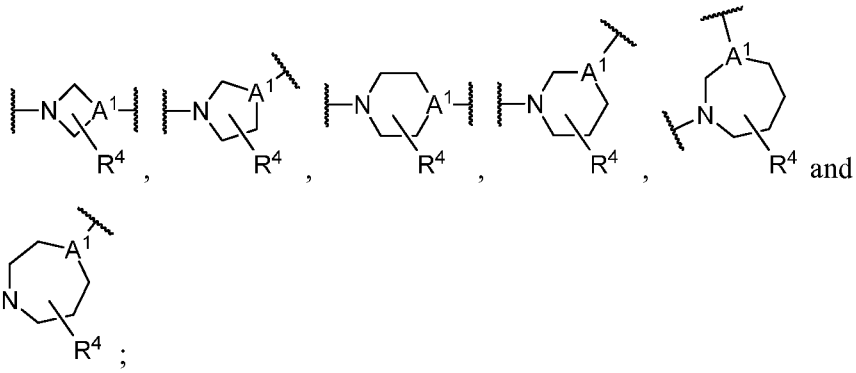
wherein r is an integer from 0-1;

wherein Y^1, when present, is selected from —O— and —$CR^{2a}R^{2b}$—;

wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl;

wherein Y^2, when present, is —NH—;

wherein Z^1, when present, is a 4- to 7-membered hetercycloalkyl selected from:



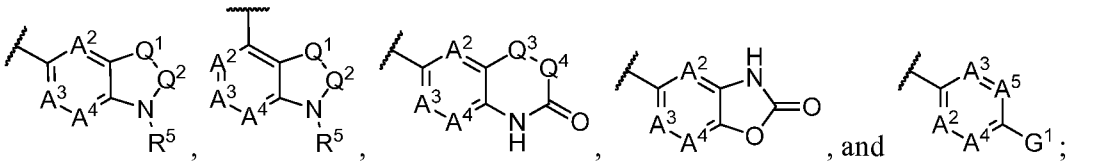
wherein A^1 is N or CR^3;

wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl;

wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;

wherein Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;;

wherein Ar^2 is selected from:



wherein A^2 is selected from N and CR^{6a}; wherein A^3, when present, is selected from N and CR^{6b}; and wherein A^4, when present, is selected from N and CR^{6c}; and wherein A^5, when present, is selected from N and CR^{6d};

wherein each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino;

wherein Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —N=, —NR^{8a}—, and (C=O);

wherein Q^2, when present, is selected from =N—, =CR^{7c}—, —NR^{8b}—, (C=NH), (S=O), (SO_2), (C=S), and (C=O); provided that Q^1 and Q^2 are not

simultaneously (C=O);

wherein Q^3, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —N=, —NR^{8a}—, and —NR^{8a}—;

wherein Q^4, when present, is selected from =CR^{7c}—, —$CR^{7c}R^{7d}$—, —O—, —S—, —NR^{8b}—, and (C=O); provided that Q^3 and Q^4 are not simultaneously —NR^{8a}— and —NR^{8b}—, respectively, or that or Q^3 and Q^4 are not simultaneously —O— or —S—;

wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino;

wherein each of R^{8a} and R^{8b}, when present is independently selected from hydrogen and C1-C8 alkyl;

wherein G^1, when present, is selected from —OH, —NHR^9, —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$, —OR^9, —NH(C=O)R^9; —NH(C=O)OR^9; and —NH(C=O)$NR^{10a}R^{10b}$;

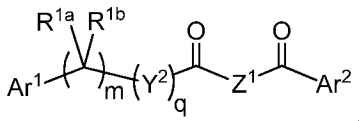
wherein each of R^9, when present, is selected from C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl;

wherein each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl;

wherein R^5, when present, is selected from hydrogen, C1-C2 monohaloalkyl, C1-C2 polyhaloalkyl, and C1-C2 alkyl;

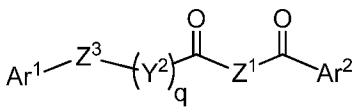
or a pharmaceutically acceptable salt, solvate, or polymorph thereof.

2. The compound of claim 1, wherein the compound has a structure represented by a formula:



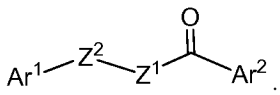
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3. The compound of claim 1, wherein the compound having a structure represented by a formula:

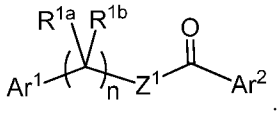


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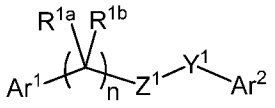
4. The compound of claim 1, wherein the compound having a structure represented by a formula:



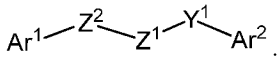
5. The compound of claim 1, wherein the compound having a structure represented by a formula:



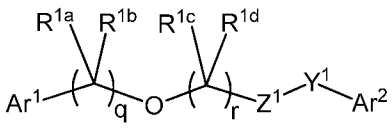
6. The compound of claim 1, wherein the compound having a structure represented by a formula:



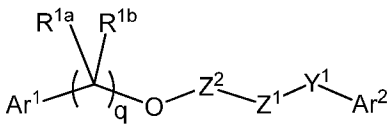
7. The compound of claim 1, wherein the compound having a structure represented by a formula:



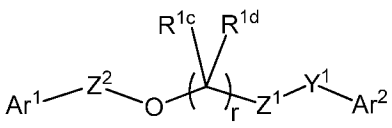
8. The compound of claim 1, wherein the compound having a structure represented by a formula:



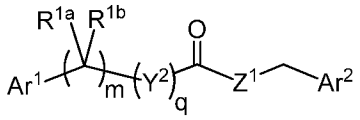
9. The compound of claim 1, wherein the compound having a structure represented by a formula:



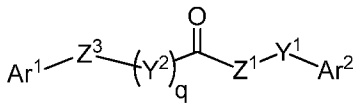
10. The compound of claim 1, wherein the compound having a structure represented by a formula:



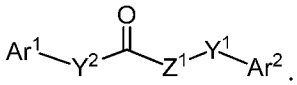
11. The compound of claim 1, wherein the compound having a structure represented by a formula:



12. The compound of claim 1, wherein the compound having a structure represented by a formula:



13. The compound of claim 1, wherein the compound having a structure represented by a formula:

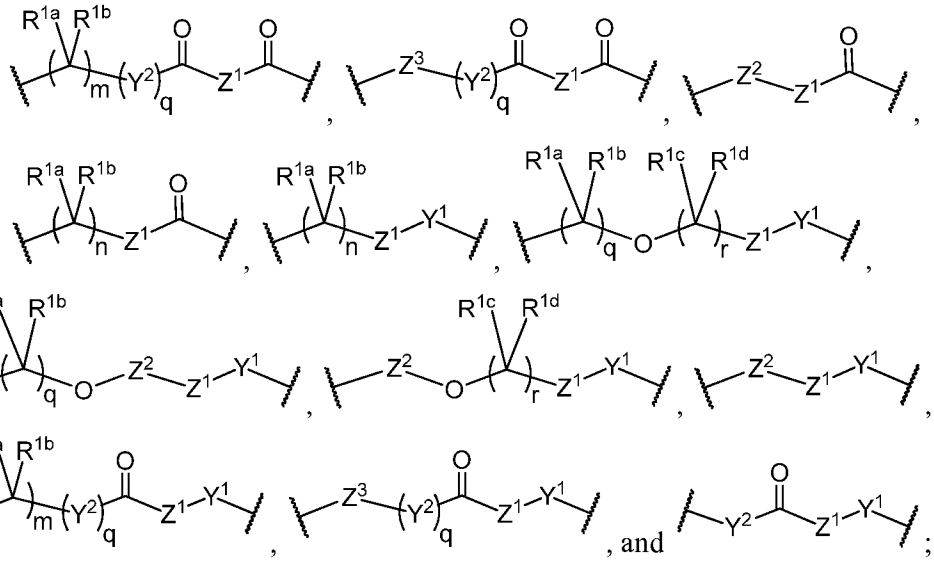


14. A pharmaceutical composition comprising an effective amount of a compound having a structure represented by a formula:

Ar^1—L—Ar^2,

wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;

wherein L is selected from:



wherein each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl;

wherein m is an integer from 1-3;

wherein n is an integer from 1-4;

wherein q is an integer from 0-1;

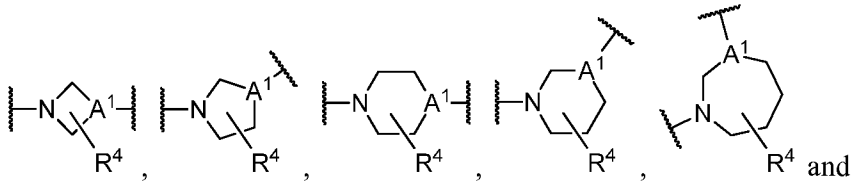
wherein r is an integer from 0-1;

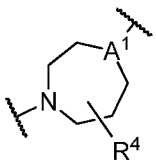
wherein Y^1, when present, is selected from —O— and —$CR^{2a}R^{2b}$—;

wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl;

wherein Y^2, when present, is —NH—;

wherein Z^1, when present, is a 4- to 7-membered hetercycloalkyl selected from:





;

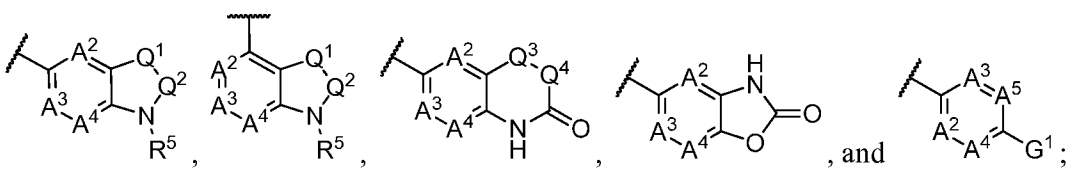
wherein A^1 is N or CR^3;

wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl;

wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;

wherein Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;;

wherein Ar^2 is selected from:



;

wherein A^2 is selected from N and CR^{6a}; wherein A^3, when present, is selected

from N and CR^{6b}; and wherein A^4, when present, is selected from N and CR^{6c}; and wherein A^5, when present, is selected from N and CR^{6d};

wherein each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino;

wherein Q^1, when present, is selected from $—CR^{7a}═$, $—CR^{7a}R^{7b}—$, —O—, —S—, —N═, $—NR^{8a}—$, and (C═O);

wherein Q^2, when present, is selected from ═N—, $═CR^{7c}—$, $—NR^{8b}—$, (C═NH), (S═O), (SO_2), (C═S), and (C═O); provided that Q^1 and Q^2 are not simultaneously (C═O);

wherein Q^3, when present, is selected from $—CR^{7a}═$, $—CR^{7a}R^{7b}—$, —O—, —S—, —N═, $—NR^{8a}—$, and $—NR^{8a}—$;

wherein Q^4, when present, is selected from $═CR^{7c}—$, $—CR^{7c}R^{7d}—$, —O—, —S—, $—NR^{8b}—$, and (C═O); provided that Q^3 and Q^4 are not simultaneously $—NR^{8a}—$ and $—NR^{8b}—$, respectively, or that or Q^3 and Q^4 are not simultaneously —O— or —S—;

wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino;

wherein each of R^{8a} and R^{8b}, when present is independently selected from hydrogen and C1-C8 alkyl;

wherein G^1, when present, is selected from —OH, $—NHR^9$, —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$, $—OR^9$, $—NH(C═O)R^9$; $—NH(C═O)OR^9$; and $—NH(C═O)NR^{10a}R^{10b}$;

wherein each of R^9, when present, is selected from C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl;

wherein each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl;

wherein R^5, when present, is selected from hydrogen, C1-C2 monohaloalkyl, C1-C2 polyhaloalkyl, and C1-C2 alkyl;

or a pharmaceutically acceptable salt, solvate, or polymorph thereof, and a

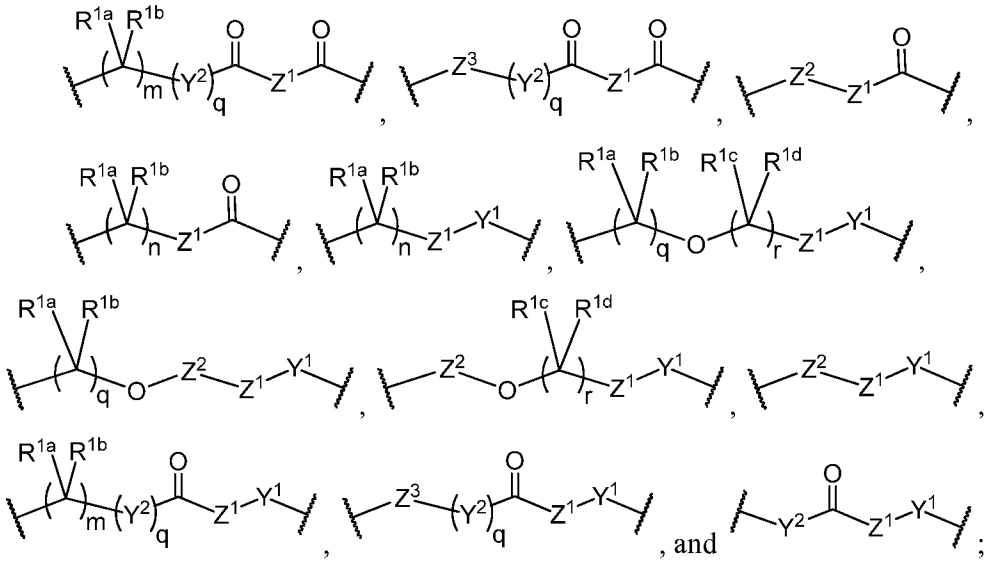
pharmaceutically acceptable carrier.

15. A method for the treatment of a neurological and/or psychiatric disorder associated with NMDA receptor function in a mammal comprising the step of administering to the mammal an effective amount of at least one compound having a structure represented by a formula:

$$Ar^1—L—Ar^2,$$

wherein Ar^1 is selected from phenyl and heterocyclyl; and wherein Ar^1 is substituted with 0-2 groups independently selected from halogen, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;

wherein L is selected from:



wherein each occurrence of R^{1a}, R^{1b}, R^{1c}, and R^{1d}, when present, is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl;

wherein m is an integer from 1-3;

wherein n is an integer from 1-4;

wherein q is an integer from 0-1;

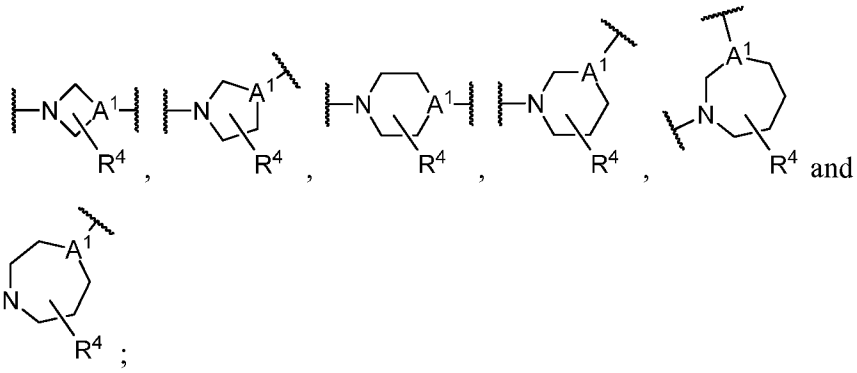
wherein r is an integer from 0-1;

wherein Y^1, when present, is selected from —O— and —$CR^{2a}R^{2b}$—;

wherein each of R^{2a} and R^{2b} is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, and C1-C3 alkyl;

wherein Y^2, when present, is —NH—;

wherein Z^1, when present, is a 4- to 7-membered hetercycloalkyl selected from:



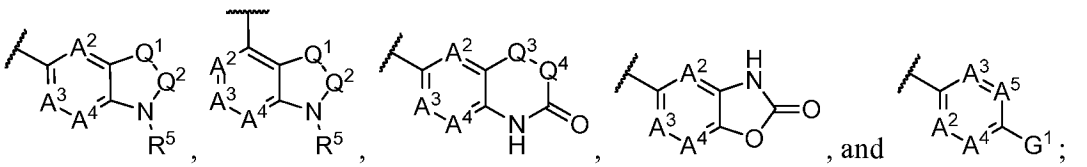
wherein A^1 is N or CR^3;

wherein R^3 is selected from hydrogen, halogen, —OH, and C1-C3 alkyl;

wherein each occurrence of R^4 is independently selected from hydrogen, halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;

wherein Z^2, when present, is a 3- to 7-membered cycloalkyl substituted with 0-2 groups independently selected from halogen, —NH_2, —OH, —CN, C1-C4 alkyl, C1-C4 monohaloalkyl, C1-C4 polyhaloalkyl, C1-C4 alkoxy, C1-C4 alkylamino, and C1-C4 dialkylamino;;

wherein Ar^2 is selected from:



wherein A^2 is selected from N and CR^{6a}; wherein A^3, when present, is selected from N and CR^{6b}; and wherein A^4, when present, is selected from N and CR^{6c}; and wherein A^5, when present, is selected from N and CR^{6d};

wherein each of R^{6a}, R^{6b}, R^{6c}, and R^{6d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino;

wherein Q^1, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —N=, —NR^{8a}—, and (C=O);

wherein Q^2, when present, is selected from =N—, =CR^{7c}—, —NR^{8b}—, (C=NH), (S=O), (SO_2), (C=S), and (C=O); provided that Q^1 and Q^2 are not simultaneously (C=O);

wherein Q^3, when present, is selected from —CR^{7a}=, —$CR^{7a}R^{7b}$—, —O—, —S—, —N=, —NR^{8a}—, and —NR^{8a}—;

wherein Q^4, when present, is selected from =CR^{7c}—, —$CR^{7c}R^{7d}$—, —O—, —S—, —NR^{8b}—, and (C=O); provided that Q^3 and Q^4 are not simultaneously —NR^{8a}— and —NR^{8b}—, respectively, or that or Q^3 and Q^4 are not simultaneously —O— or —S—;

wherein each of R^{7a}, R^{7b}, R^{7c}, and R^{7d}, when present, is independently selected from hydrogen, halogen, —CN, C1-C3 alkyl, C1-C3 monohaloalkyl, C1-C3 polyhaloalkyl, C1-C3 alkoxy, C1-C3 alkylamino, and C1-C3 dialkylamino;

wherein each of R^{8a} and R^{8b}, when present is independently selected from hydrogen and C1-C8 alkyl;

wherein G^1, when present, is selected from —OH, —NHR^9, —NH(C1-C6 alkyl)$NR^{10a}R^{10b}$, —OR^9, —NH(C=O)R^9; —NH(C=O)OR^9; and —NH(C=O)$NR^{10a}R^{10b}$;

wherein each of R^9, when present, is selected from C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl;

wherein each of R^{10a} and R^{10b}, when present, is independently selected from hydrogen, C1-C3 alkyl, C1-C3 monohaloalkyl, and C1-C3 polyhaloalkyl;

wherein R^5, when present, is selected from hydrogen, C1-C2 monohaloalkyl, C1-C2 polyhaloalkyl, and C1-C2 alkyl;

or a pharmaceutically acceptable salt, solvate, or polymorph thereof.

16. The method of claim 15, wherein the mammal is a human.

17. The method of claim 15, wherein the effective amount is a therapeutically effective amount.

18. The method of claim 15, wherein the effective amount is a prophylactically effective amount.

19. The method of claim 15, further comprising the step of identifying the subject in need of treatment of the disorder.

20. The method of claim 15, wherein the subject has been diagnosed with a need for treatment of the disorder prior to the administering step.
21. The method of claim 15, wherein the disorder is selected from autism, dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, including the positive and negative symptoms thereof and cognitive dysfunction related to schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, and psychotic depression.
22. The method of claim 15, wherein the disorder is selected from dementia, delirium, amnestic disorders, age-related cognitive decline, schizophrenia, psychosis including schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, substance-related disorder, movement disorders, epilepsy, including absence epilepsy, chorea, pain, migraine, diabetes, dystonia, obesity, eating disorders, brain edema, sleep disorder, narcolepsy, anxiety, affective disorder, panic attacks, unipolar depression, bipolar disorder, psychotic depression, autism, panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, and substance-induced anxiety disorder.
23. The method of claim 15, wherein the disorder is selected from absence epilepsy, cognitive disorders, age-related cognition decline, learning deficit, intellectual impairment disorders, cognition impairment in schizophrenia, cognition impairment in Alzheimer's disease, and mild cognitive impairment.