QUINOLINE DERIVATIVES AS MODULATORS OF MAS-RELATED G-PROTEIN RECEPTOR X2 AND RELATED PRODUCTS

BACKGROU

Technical Field

The invention relates to modulators of the Mas-related G-protein coupled receptor X2, to products containing the same, as well as to methods of their use and preparation.

Description of the Related Art

Mas-related G-protein receptors (MRGPRs) are a group of orphan receptors with limited expression in very specialized tissues. Very little is known about the function of most of these receptors. There are eight related receptors in this class expressed in humans, only four of which have readily identifiable orthologs in other species (*i.e.*, MRGPR D, E, F and G). Some of the other four receptors (MRGPR X1, X2, X3 and X4) have counterparts in higher species including dogs and horses, but they do not have a single corresponding ortholog in rodents.

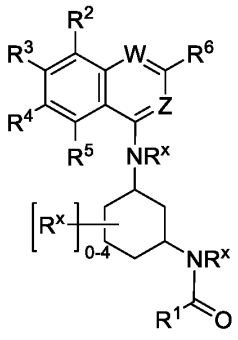
BRIEF SUMMARY

This invention is based, in part, on the identification of MRGPRX2 or MRGPRX2 ortholog modulator compounds. Among rodent orthologs, mouse mrgprb2 and rat mrgprb3 correspond functionally to human MRGPRX2 in mast cells. MRGPRX2 and its ortholog receptors mediate disorders including pseudo-allergic drug reactions, chronic itch (*e.g.*, pruritus), inflammation disorders, pain disorders, a cancer associated condition, skin disorders, wound healing, cardiovascular disease, and lung inflammation/COPD. In one embodiment, expression of MRGPRX2 and its orthologs is largely restricted to mast cells. Mast cells are innate immune cells that primarily reside at sites exposed to the external environment, such as the skin, oral/gastrointestinal mucosa and respiratory tract. Mast cells express numerous receptors that respond to mechanical and chemical stimuli. Upon activation, classically by IgE, mast cells release pre-formed mediators from granules (e.g., histamine, proteases, and heparin) and

newly synthesized mediators (e.g., thromboxane, prostaglandin D2, leukotriene C4, tumor necrosis factor alpha, eosinol chemotactor factor, and platelet-activating factor) that elicit allergic and inflammatory responses. Histamine dilates post-capillary venules, activates the endothelium, and increases blood vessel permeability. This causes local edema, warmth, redness, and chemotaxis of other inflammatory cells to the site of release. Histamine also contributes to neuronal sensitization that leads to pain or itch. MRGPRX2 and its orthologs mediate immunoglobulin E (IgE) independent activation of mast cells. MRGPRX2 and its orthologs are receptors for (or sensitive to activation by) various ligands, including basic secretagogues (small cationic molecules), certain drugs (e.g., cationic peptidergic drugs), neuropeptides, and antimicrobial peptides, and thus are important for non-IgE mediated pseudo-allergic reactions, inflammation, pain, and itch conditions. Mast cells may also contribute to the progression of autoimmune disorders by promoting chronic inflammation in the local tissue microenvironment and ultimately polarizing toward a T_h17 immune response. Thus, modulating MRGPRX2 or MRGPRX2 orthologs allows for treatment of autoimmune diseases, pseudo-allergic drug reactions, pain, itch, and inflammatory disorders such as inflammatory bowel disease, urticaria, sinusitis, asthma, rosacea, endometriosis, and other MRGPRX2 or MRGPRX2 ortholog dependent conditions as explained in more detail below.

In one embodiment is provided a method of treating a MRGPRX2 or a MRGPRX2 ortholog dependent condition by administering to a subject in need thereof an effective amount of the pharmaceutical composition of the modulator compounds of the present invention.

Accordingly, in an embodiment, is provided a compound having structure (I):



(I)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein W, Z, R^1, R^2, R^3, R^4, R^5, R^6 and R^x are as defined herein.

In other embodiments, compounds are provided having formula (Ia), (Ib), (Ic), (Id), (1e) or (If) as defined herein, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

In yet other embodiments, pharmaceutical compositions are provided comprising a carrier or excipient and a compound having structure (I), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

In specific embodiments, pharmaceutical compositions are provided comprising substructures of structure (I) with formula (Ia), (Ib), (Ic), (Id), (1e) or (If) as defined herein or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

In another embodiment, methods are provided for treating an MRGPRX2 or a MRGPRX2 ortholog dependent condition by administering to a subject in need thereof an effective amount of a compound having structure (I), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

In some embodiments, the MRGPRX2 or a MRGPRX2 ortholog dependent condition is one or more of a pseudo-allergic reaction, itch associated condition, a pain associated condition, a cancer associated condition, an inflammation-associated condition, or an autoimmune disorder.

In one embodiment, the methods of treating the MRGPRX2 or the MRGPRX2 ortholog dependent condition are provided which comprise of administering an effective amount of a compound of structure (I) with formula (Ia), (Ib), (Ic), (Id), (1e) or (If) as defined herein, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

In another embodiment, compounds are provided having one or more of the structures disclosed herein, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof.

DETAILED DESCRIPTION

As mentioned above, the invention relates to modulators of MRGPRX2 (or MRGPRX2 ortholog), to products containing the same, as well as to methods of their use and preparation. This invention is based, in part, on the identification of MRGPRX2

modulator compounds and MRGPRX2 ortholog modulator compounds. MRGPRX2 and MRGPRX2 orthologs are expressed in mast cells. MRGPRX2 and MRGPRX2 orthologs are receptors for (or sensitive to activation by) a diverse group of ligands, including basic secretagogues, certain drugs, neuropeptides, antimicrobial peptides, and thus are important for pseudo-allergic reactions, itch, pain, or inflammatory disorders upon exposure.

MRGPRs appear to be sensory receptors that recognize their external environment to exogenous or endogenous signals/chemicals. These receptors likely respond to multiple chemical ligands/agonists. For example, MRGPRX2 recognizes Compound 48/80, Substance P, mastoparan, icatibant, ciprofloxacin, and tracurium as agonist signals. In certain embodiments, molecules of this invention modulate MRGPRX2 by functioning as inverse agonists that are capable of blocking multiple chemical entities, and/or as competitive antagonists that can specifically block individual ligands. In one embodiment, such modulations are selective against other MRGPRs, such as MRGPR X1, X3 and/or X4.

Definitions

As used herein, the following terms have the meaning defined below, unless the context indicates otherwise.

"Modulating" MRGPRX2 means that the compound interacts with MRGPRX2 or MRGPRX2 orthologs in a manner such that it functions as an inverse agonist to the receptor, and/or as a competitive antagonist to the receptor. In one embodiment, such modulation is partially or fully selective against other MRGPRs, such as MRGPR X1, X3 and/or X4.

"MRGPR" refers to one or more of the Mas-related G protein coupled receptors, which are a group of orphan receptors with limited expression in very specialized tissues (e.g., in mast cells and dorsal root ganglia) and barrier tissues. There are eight related receptors in this class expressed in humans, only 4 of which have readily identifiable orthologs in other species (i.e., MRGPR D, E, F and G). The other four receptors (MRGPR X1, X2, X3 and X4) have no single ortholog, based on homology, in non-human species. Among rodent receptors, mouse mrgprb2 and rat mrgprb3 correspond functionally to human MRGPRX2 on mast cells.

"MRGPRX2," also referred to as "MRGX2," or "MGRG3," refers to a member of the MRGPR family that is expressed on mast cells and capable of mediating IgE independent activation (e.g., mast cell degranulation) in response to ligand binding. An exemplary human MRGPRX2 amino acid sequence is set forth in Uniprot Q96LB1.

"Effective amount" refers to a quantity of a specified agent sufficient to achieve a desired effect in a subject being treated with that agent. Ideally, an effective amount of an agent is an amount sufficient to inhibit or treat the disease without causing substantial toxicity in the subject. The effective amount of an agent will be dependent on the subject being treated, the severity of the affliction, and the manner of administration of the pharmaceutical composition. Methods of determining an effective amount of the disclosed compound sufficient to achieve a desired effect in a subject will be understood by those of skill in the art in light of this disclosure.

"Alkyl" means a saturated or unsaturated straight chain or branched alkyl group having from 1 to 8 carbon atoms, in some embodiments from 1 to 6 carbon atoms, in some embodiments from 1 to 4 carbon atoms, and in some embodiments from 1 to 3 carbon atoms. Examples of saturated straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl-, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. An unsaturated alkyl includes alkenyl and alkynyl as defined below.

"Alkenyl" means a straight chain or branched alkenyl group having from 2 to 8 carbon atoms, in some embodiments from 2 to 6 carbon atoms, in some embodiments from 2 to 4 carbon atoms, and in some embodiments from 2 to 3 carbon atoms. Alkenyl groups are unsaturated hydrocarbons that contain at least one carbon-carbon double bond. Examples of lower alkenyl groups include, but are not limited to, vinyl, propenyl, butenyl, pentenyl, and hexenyl.

"Alkynyl" means a straight chain or branched alkynyl group having from 2 to 8 carbon atoms, in some embodiments from 2 to 6 carbon atoms, in some embodiments from 2 to 4 carbon atoms, and in some embodiments from 2 to 3 carbon atoms. Alkynyl groups are unsaturated hydrocarbons that contain at least one carbon-carbon triple bond. Examples of alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

"Halo" or "halogen" refers to fluorine, chlorine, bromine, and iodine.

"Hydroxy" refers to –OH.

"Cyano" refers to –CN.

Amino refers to $–NH_2$, -NHalkyl or $N(alkyl)_2$, wherein alkyl is as defined above. Examples of amino include, but are not limited to – NH_2, $-NHCH_3$, $–N(CH_3)_2$, and the like.

"Haloalkyl" refers to alkyl as defined above with one or more hydrogen atoms replaced with halogen. Examples of lower haloalkyl groups include, but are not limited to, $–CF_3$, $–CHF_2$, and the like.

"Alkoxy" refers to alkyl as defined above joined by way of an oxygen atom (i.e., –O–alkyl). Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, n-butoxy, isopropoxy, sec-butoxy, tert-butoxy, and the like.

"Haloalkoxy" refers to haloalkyl as defined above joined by way of an oxygen atom (i.e., –O–haloalkyl). Examples of lower haloalkoxy groups include, but are not limited to, $–OCF_3$, and the like.

"Cycloalkyl" refers to alkyl groups forming a ring structure, which can be substituted or unsubstituted, wherein the ring is either completely saturated, partially unsaturated, or fully unsaturated, wherein if there is unsaturation, the conjugation of the pi-electrons in the ring do not give rise to aromaticity. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like.

"Aryl" groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Representative aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons in the ring portions of the groups. The terms "aryl" and "aryl groups" include fused rings wherein at least one ring, but not necessarily all rings, are aromatic, such as fused aromatic-aliphatic ring systems (e.g.,

indanyl, tetrahydronaphthyl, and the like). In one embodiment, aryl is phenyl or naphthyl, and in another embodiment aryl is phenyl.

"Carbocycle" refers to alkyl groups forming a ring structure, which can be substituted or unsubstituted, wherein the ring is either completely saturated, partially unsaturated, or fully unsaturated, wherein if there is unsaturation, the conjugation of the pi-electrons in the ring may give rise to aromaticity. In one embodiment, carbocycle includes cycloalkyl as defined above. In another embodiment, carbocycle includes aryl as defined above.

"Heterocycle" refers to aromatic and non-aromatic ring moieties containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, S, or P. In some embodiments, heterocyclyl include 3 to 20 ring members, whereas other such groups have 3 to 15 ring members. At least one ring contains a heteroatom, but every ring in a polycyclic system need not contain a heteroatom. For example, a dioxolanyl ring and a benzdioxolanyl ring system (methylenedioxyphenyl ring system) are both heterocyclyl groups within the meaning herein.

Heterocyclyl groups also include fused ring species including those having fused aromatic and non-aromatic groups. A heterocyclyl group also includes polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl, and also includes heterocyclyl groups that have substituents, including but not limited to alkyl, halo, amino, hydroxy, cyano, carboxy, nitro, thio, or alkoxy groups, bonded to one of the ring members. A heterocyclyl group as defined herein can be a heteroaryl group or a partially or completely saturated cyclic group including at least one ring heteroatom. Heterocyclyl groups include, but are not limited to, pyrrolidinyl, furanyl, tetrahydrofuranyl, dioxolanyl, piperidinyl, piperazinyl, morpholinyl, pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, thiophenyl, benzothiophenyl, benzofuranyl, dihydrobenzofuranyl, indolyl, dihydroindolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups.

In one embodiment, heterocyclyl includes heteroaryl.

"Heteroaryl" refers to aromatic ring moieties containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, pyrazinyl, pyrimidinyl, thienyl, triazolyl, tetrazolyl, triazinyl, thiazolyl, thiophenyl, oxazolyl, isoxazolyl, benzothiophenyl, benzofuranyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, azabenzimidazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthalenyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinoxalinyl, and quinazolinyl groups. The terms "heteroaryl" and "heteroaryl groups" include fused ring compounds such as wherein at least one ring, but not necessarily all rings, are aromatic, including tetrahydroquinolinyl, tetrahydroisoquinolinyl, indolyl, and 2,3-dihydro indolyl.

"Isomer" is used herein to encompass all chiral, diastereomeric or racemic forms of a structure (also referred to as a stereoisomer, as opposed to a structural or positional isomer), unless a particular stereochemistry or isomeric form is specifically indicated. Such compounds can be enriched or resolved optical isomers at any or all asymmetric atoms as are apparent from the depictions, at any degree of enrichment. Both racemic and diastereomeric mixtures, as well as the individual optical isomers can be synthesized so as to be substantially free of their enantiomeric or diastereomeric partners, and these are all within the scope of certain embodiments of the invention. The isomers resulting from the presence of a chiral center comprise a pair of nonsuperimposable- isomers that are called "enantiomers." Single enantiomers of a pure compound are optically active (i.e., they are capable of rotating the plane of plane polarized light and designated R or S).

"Isolated optical isomer" means a compound which has been substantially purified from the corresponding optical isomer(s) of the same formula. For example, the isolated isomer may be at least about 80%, at least 80% or at least 85% pure by weight. In other embodiments, the isolated isomer is at least 90% pure or at least 98% pure, or at least 99% pure by weight.

"Substantially enantiomerically or diastereomerically" pure means a level of enantiomeric or diastereomeric enrichment of one enantiomer with respect to the

other enantiomer or diastereomer of at least about 80%, and more specifically in excess of 80%, 85%, 90%, 95%, 98%, 99%, 99.5% or 99.9%.

The terms "racemate" and "racemic mixture" refer to an equal mixture of two enantiomers. A racemate is labeled "(±)" because it is not optically active (i.e., will not rotate plane-polarized light in either direction since its constituent enantiomers cancel each other out). All compounds with an asterisk (*) adjacent to a tertiary or quaternary carbon are optically active isomers, which may be purified from the respective racemate and/or synthesized by appropriate chiral synthesis.

A "hydrate" is a compound that exists in combination with water molecules. The combination can include water in stoichiometric quantities, such as a monohydrate or a dihydrate, or can include water in random amounts. As the term is used herein a "hydrate" refers to a solid form; that is, a compound in a water solution, while it may be hydrated, is not a hydrate as the term is used herein.

A "solvate" is similar to a hydrate except that a solvent other than water is present. For example, methanol or ethanol can form an "alcoholate", which can again be stoichiometric or non-stoichiometric. As the term is used herein a "solvate" refers to a solid form; that is, a compound in a solvent solution, while it may be solvated, is not a solvate as the term is used herein.

"Isotope" refers to atoms with the same number of protons but a different number of neutrons, and an isotope of a compound of structure (I) includes any such compound wherein one or more atoms are replaced by an isotope of that atom. For example, carbon 12, the most common form of carbon, has six protons and six neutrons, whereas carbon 13 has six protons and seven neutrons, and carbon 14 has six protons and eight neutrons. Hydrogen has two stable isotopes, deuterium (one proton and one neutron) and tritium (one proton and two neutrons). While fluorine has a number of isotopes, fluorine-19 is longest-lived. Thus, an isotope of a compound having the structure of structure (I) includes, but not limited to, compounds of structure (I) wherein one or more carbon 12 atoms are replaced by carbon-13 and/or carbon-14 atoms, wherein one or more hydrogen atoms are replaced with deuterium and/or tritium, and/or wherein one or more fluorine atoms are replaced by fluorine-19.

"Salt" generally refers to an organic compound, such as a carboxylic acid or an amine, in ionic form, in combination with a counter ion. For example, salts formed

between acids in their anionic form and cations are referred to as "acid addition salts". Conversely, salts formed between bases in the cationic form and anions are referred to as "base addition salts."

The term "pharmaceutically acceptable" refers to an agent that has been approved for human consumption and is generally non-toxic. For example, the term "pharmaceutically acceptable salt" refers to nontoxic inorganic or organic acid and/or base addition salts (see, e.g., Lit et al., Salt Selection for Basic Drugs, Int. J. Pharm., 33, 201-217, 1986) (incorporated by reference herein).

Pharmaceutically acceptable base addition salts of compounds of the invention include, for example, metallic salts including alkali metal, alkaline earth metal, and transition metal salts such as, for example, calcium, magnesium, potassium, sodium, and zinc salts. Pharmaceutically acceptable base addition salts also include organic salts made from basic amines such as, for example, *N,N*'dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine.

Pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of inorganic acids include hydrochloric, hydrobromic, hydriodic, nitric, carbonic, sulfuric, and phosphoric acids. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, aromatic aliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids, examples of which include formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, 4-hydroxybenzoic, phenylacetic, mandelic, hippuric, malonic, oxalic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, panthothenic, trifluoromethanesulfonic, 2-hydroxyethanesulfonic, p-toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, alginic, β-hydroxybutyric, salicylic, galactaric, and galacturonic acid.

The compounds of the disclosure (*i.e.*, compounds of structure (I) and embodiments thereof), or their pharmaceutically acceptable salts may contain one or more centers of geometric asymmetry and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. Embodiments thus

include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also included.

Although pharmaceutically unacceptable salts are not generally useful as medicaments, such salts may be useful, for example as intermediates in the synthesis of compounds having the structure (I), for example in their purification by recrystallization.

As used herein, the phrase "MRGPRX2 dependent condition" means a condition where the activation, over sensitization, or desensitization of MRGPRX2 or its orthologs by a natural or synthetic ligand initiates, mediates, sustains, or augments a pathological condition. For example, it is known that some cationic peptidergic drugs cause pseudo-allergic reactions in patients where MRGPRX2 is sensitive to (or activated by) secretagogues, cationic peptidergic drugs, including icatibant, leuprolide, or ganirelix, neutral and anionic peptidergic drugs (e.g., exenatide, glucagon, liraglutide, enfuviritide, colistimethate), non-steroidal agonist (atracurium mivacurium), non-steroidal antagonist drugs, neuropeptides, and antimicrobial peptides. Moreover, overexpression of MRGPRX2 and/or overactivity MRGPRX2 may also render mast cells more susceptible to activation by endogenous and/or exogenous ligands. Without limited by theory, it is to be understood that by modulating MRGPRX2, pseudo-allergic reactions, itch, pain, inflammatory or autoimmune disorders can be eased.

In some embodiments, the MRGPRX2 dependent condition is a condition that is caused by IgE independent activation of MRGPRX2 or its orthologs. IgE independent activation of MRGPRX2 is capable of inducing mast cell degranulation. For example, IgE independent mast cell activation is associated with some cases of chronic urticaria and

other mast cell mediated conditions, which are not responsive to current anti-IgE or antihistamine therapies. Thus, the compounds of the present disclosure may be used for treating an MRGPRX2 dependent condition caused by IgE independent activation of MRGPRX2 and that would benefit from modulating MRGPRX2.

In some embodiments, the MRGPRX2 dependent condition is an itch associated condition, a pain associated condition, a cancer associated condition, a pseudo-allergic reaction, or an autoimmune or inflammatory disorder in humans or other mammals.

As used herein the phrase "pseudo-allergic reaction" refers to an IgE-independent allergic reaction, characterized by histamine release, inflammation, airway contraction, or any combination thereof. A pseudo-allergic reaction may be an analphylactic reaction. A pseudo-allergic reaction may be caused by a range of cationic substances, collectively called basic secretagogues, including inflammatory peptides and drugs associated with allergic-type reactions. Thus, in one embodiment, the method of present invention is provided to treat a pseudo-allergic reaction, such as pseudo-allergic reactions caused by secretagogues, cationic peptidergic drugs, anionic peptidergic drugs, neutral peptidergic drugs, non-steroidal antagonist drugs, neuropeptides, and antimicrobial peptides. In one embodiment, the pseudo-allergic reaction is caused by MCD peptide, Substance P, VIP, PACAP, dynorphin, somatostatin, Compound 48/80, cortistatin-14, mastoparan, melettin, cathelicidin peptides, ciprofloxacin, vancomycin, leuprolide, goserelin, histrelin, triptorelin, cetrorelix, ganirelix, degarelix, octreotide, lanreotide, pasireotide, sermorelin, tesamorelin, icatibant, glatiramer acetate, teriparatide, pramlintide, bleomycin, exenatide, glucagon, liraglutide, enfuvirtide, colistimethate, succinylcholine, tubocurarine, atracurium, mivacurium, and rocuronium.

As used herein, the phrase "itch associated condition" means pruritus (including acute and chronic pruritus) associated with any condition. The itch sensation can originate, *e.g.,* from the peripheral nervous system (*e.g.*, dermal or neuropathic itch) or from the central nervous system (*e.g.*, neuropathic, neurogenic or psychogenic itch). Thus, in one embodiment, the method of present invention is provided to treat an itch associated condition, such as chronic itch; contact dermatitis; Allergic blepharitis; Anaphylaxis; Anaphylactoid drug reactions; Anaphylactic shock; Anemia; Atopic dermatitis; Bullous pemphigoid; Candidiasis; Chicken pox; end-stage renal failure;

hemodialysis; Cholestatic pruritis; Chronic urticaria; Contact dermatitis, Dermatitis herpetiformis; Diabetes; Drug allergy, Dry skin; Dyshidrotic dermatitis; Ectopic eczema; Eosinophilic fasciitis; Epidermolysis bullosa; Erythrasma; Food allergy; Folliculitis; Fungal skin infection; Hemorrhoids; Herpes; HIV infection; Hodgkin's disease; Hyperthyroidism; Iodinated contrast dye allergy; Iron deficiency anemia; Kidney disease; Leukemia, porphyrias; Lymphoma; Mast cell activation syndrome, Malignancy; Mastocystosis; Multiple myeloma; Neurodermatitis; Onchocerciasis; Paget's disease; Pediculosis; Polycythemia rubra vera; Prurigo nodularis; Lichen Planus; Lichen Sclerosis; Pruritus ani; Pseudo-allergic reactions; Pseudorabies; Psoriasis; Rectal prolapse; Sarcoidosis granulomas; Scabies; Schistosomiasis; Scleroderma, Severe stress, Stasia dermatitis; Swimmer's itch; Thyroid disease; Tinea cruris; Uremic Pruritus; Rosacea; Cutaneous amyloidosis; Scleroderma; Acne; wound healing; burn healing; ocular itch; and Urticaria.

As used herein, the phrase “pain associated condition” means any pain due to a medical condition. Thus, in one embodiment, the method of present invention is provided to treat a pain associated condition, such as Acute Pain, Advanced Prostate Cancer, AIDS-Related Pain, Ankylosing Spondylitis, Arachnoiditis, Arthritis, Arthrofibrosis, Ataxic Cerebral Palsy, Autoimmune Atrophic Gastritis, Avascular Necrosis, Back Pain, Behcet’s Disease (Syndrome), Burning Mouth Syndrome, Bursitis, Cancer Pain, Carpal Tunnel, Cauda Equina Syndrome, Central Pain Syndrome, Cerebral Palsy, Cervical Stenosis, Charcot-Marie-Tooth (CMT) Disease, Chronic Fatigue Syndrome (CFS), Chronic Functional Abdominal Pain (CFAP), Chronic Pain, Chronic Pancreatitis, Chronic Pelvic Pain Syndrome, Collapsed Lung (Pneumothorax), Complex Regional Pain Syndrome (RSD), Corneal Neuropathic Pain, Crohn’s Disease, Degenerative Disc Disease, Dental Pain, Dercum’s Disease, Dermatomyositis, Diabetic Peripheral Neuropathy (DPN), Dystonia, Ehlers-Danlos Syndrome (EDS), Endometriosis, Eosinophilia-Myalgia Syndrome (EMS), Erythromelalgia, Fibromyalgia, Gout, Headaches, Herniated disc, Hydrocephalus, Intercostal Neuraligia, Interstitial Cystitis, Irritable Bowel syndrome (IBS), Juvenile Dermatositis (Dermatomyositis), Knee Injury, Leg Pain, Loin Pain-Haematuria Syndrome, Lupus, Lyme Disease, Medullary Sponge Kidney (MSK), Meralgia Paresthetica, Mesothelioma, Migraine, Musculoskeletal pain, Myofascial Pain, Myositis, Neck Pain, Neuropathic Pain, Occipital Neuralgia, Osteoarthritis, Paget’s Disease, Parsonage Turner Syndrome, Pelvic Pain, Periodontitis Pain, Peripheral Neuropathy,

Phantom Limb Pain, Pinched Nerve, Polycystic Kidney Disease, Polymyalgia Rhuematica, Polymyositis, Porphyria, Post Herniorraphy Pain Syndrome, Post Mastectomy, Postoperative Pain, Pain Syndrome, Post Stroke Pain, Post Thorocotomy Pain Syndrome, Postherpetic Neuralgia (Shingles), Post-Polio Syndrome, Primary Lateral Sclerosis, Psoriatic Arthritis, Pudendal Neuralgia, Radiculopathy, Raynaud's Disease, Rheumatoid Arthritis (RA), Sacroiliac Joint Dysfunction, Sarcoidosi, Scheuemann's Kyphosis Disease, Sciatica, Scoliosis, Shingles (Herpes Zoster), Sjogren's Syndrome, Spasmodic Torticollis, Sphincter of Oddi Dysfunction, Spinal Cerebellum Ataxia (SCA Ataxia), Spinal Cord Injury, Spinal Stenosis, Syringomyelia, Tarlov Cysts, Transverse Myelitis, Trigeminal Neuralgia, Neuropathic Pain, Ulcerative Colitis, Vascular Pain and Vulvodynia.

As used herein, the term "autoimmune disorder", or "inflammatory disorder" means a disease or disorder arising from and/or directed against an individual's own tissues or organs, or a co-segregate or manifestation thereof, or resulting condition therefrom. Typically, various clinical and laboratory markers of autoimmune diseases may exist including, but not limited to, hypergammaglobulinemia, high levels of autoantibodies, antigen-antibody complex deposits in tissues, clinical benefit from corticosteroid or immunosuppressive treatments, and lymphoid cell aggregates in affected tissues. Thus, in one embodiment, the method of present invention is provided to treat an autoimmune disorder, such as chronic inflammation, mast cell activation syndrome, Multiple Sclerosis, Steven Johnson's Syndrome, Toxic Epidermal Necrolysis, appendicitis, bursitis, cutaneous lupus, colitis, cystitis, dermatitis, phlebitis, reflex sympathetic dystrophy/complex regional pain syndrome (rsd/crps), rhinitis, tendonitis, tonsillitis, acne vulgaris, sinusitis, rosacea, psoriasis, graft-versus-host disease, reactive airway disorder, asthma, airway infection, allergic rhinitis, autoinflammatory disease, celiac disease, chronic prostatitis, diverticulitis, glomerulonephritis, hidradenitis suppurativa, hypersensitivities, intestinal disorder, epithelial intestinal disorder, inflammatory bowel disease, irritable bowel syndrome, Crohn's Disease, ulcerative colitis, lupus erythematous, interstitial cystitis, otitis, pelvic inflammatory disease, endometrial pain, reperfusion injury, rheumatic fever, rheumatoid arthritis, sarcoidosis, transplant rejection, psoriasis, lung inflammation, chronic obstructive pulmonary disease, permanent sputum eosiniophilia, eosinophilic leukemia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic duodenitis, eosinophilic gastroenteritis,

mast cell gastrointestinal disease, hypereosinophilic syndrome, aspirin-exacerbated respiratory disease, nasal polyposis, chronic rhinosinusitis, antibody-dependent cell-mediated cytotoxicity, neurofibromatosis, swannamatoisis, tubulointerstitial nephritis, glomerulonephritis, diabetic nephropathy, allograft rejection, amyloidosis, renovascular ischemia, reflux nephropathy, polycystic kidney disease, liver fibrosis/cirrhosis, autoimmune liver disease, Biliary atresia, acute and chronic Hepatitis B and C virus, Liver tumors and cancer, Alcoholic liver disease, Polycystic liver disease, Liver cholangiocarcinoma, neuromyelitis optica spectum disorder, cardiovascular disease, inflammation induced by bacterial or viral infection, inflammation associated with SARS-CoV-2 infection or its variants and Coronavirus Disease 2019 (COVID-19), acute respiratory distress syndrome, pneumonia, Long/Long-Term/Chronic COVID, Post-Acute Sequelae of COVID-19 (PASC), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS "Brain Fog") and vasculitis.

As used herein the phrase "cancer associated condition" means any disease arising from the proliferation of malignant cancerous cells. Thus, in one embodiment, the method of present invention is provided to treat a cancer/tumor associated condition, such as adenoid cystic carcinoma, adrenal gland tumor, amyloidosis, anal cancer, appendix cancer, astrocytoma, ataxia-telangiectasia, beckwith-wiedemann syndrome, cholangiocarcinoma, birt-hogg-dube syndrome, bone cancer, brain stem glioma, brain tumor, breast cancer (inflammatory, metastatic, male), prostrate, basal cell, melanoma, colon, colorectal, bladder, kidney cancer, lacrimal gland cancer, laryngeal and hypopharyngeal cancer, lung cancer (non-small cell, small cell), leukemia (acute lymphoblastic, acute lymphocytic, acute myeloid, B cell prolymphocytic, chronic lymphocytic, chronic myeloid, chronic T cell lymphocytic, eosinophilic), Liver Cancer, Li-Fraumei syndrome, lymphoma (Hodgkin and non-hodgkin), lynch syndrome, mastocytosis, medulloblastoma, meningioma, mesothelioma, multiple endocrine neoplasia, multiple myeloma, MUTYH-associated polyposis, myelodyspastic syndrome, nasal cavity and paranasal sinus cancer, neurobastoma, neuroendocrine tyymors, neurofibromatosis, penile cancer, parathyroid cancer, ovarian fallopian tube and peritoneal cancer, osteosarcoma, pituitary gland tumor, pleupulmonary blastoma, oral and oropharyngeal , thyroid, uterine, pancreatic, carney complex, brain and spinal cord cancer, cervical cancer, cowden syndrome, craniopharyngioma, desmoid tumor,

desmoplatic infantile ganglioglioma, ependymoma, esophageal cancer, ewing sarcoma, eye cancer, eyelid cancer, familial adenomatous polyposis, familial GIST, familial malignant melanoma, familial pancreatic cancer, gallbladder cancer, gastrointestinal stromal tumor, germ cell tumor, gestational trophoblastic disease, head and neck cancer, hereditary breast and ovarian cancer, hereditary diffuse gastric cancer, hereditary, leiomyomastosis and renal cell cancer, hereditary pancreatitis, herediatary papillary renal carcinoma, hereditary mixed polyposis syndrome, HIV/AIDS related cancers, retinoblastoma, rhabdomyosarcoma, salivary glanc cancer, Kaposi sarcoma, small bowel cancer, stomach cancer, testicular cancer, thymoma and thymic carcinoma, thyroid cancer, vaginal cancer, culver cancer, werner syndrome and Xeroderma pigmentosum.

As used herein, the term "administration" refers to providing a compound, or a pharmaceutical composition comprising the compound as described herein. The compound or composition can be administered by another person to the subject or it can be self-administered by the subject. Non-limiting examples of routes of administration are oral, parenteral (*e.g.*, intravenous), or topical.

As used herein, the term "treatment" refers to an intervention that ameliorates a sign or symptom of a disease or pathological condition. As used herein, the terms "treatment", "treat" and "treating," with reference to a disease, pathological condition or symptom, also refers to any observable beneficial effect of the treatment. The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease, a slower progression of the disease, a reduction in the number of relapses of the disease, an improvement in the overall health or well-being of the subject, or by other parameters well known in the art that are specific to the particular disease. A prophylactic treatment is a treatment administered to a subject who does not exhibit signs of a disease or exhibits only early signs, for the purpose of decreasing the risk of developing pathology. A therapeutic treatment is a treatment administered to a subject after signs and symptoms of the disease have developed.

As used herein, the term "subject" refers to an animal (*e.g.*, a mammal, such as a human, dog or horse), and thus veterinary use is an application specifically contemplated herein. A subject to be treated according to the methods described

herein may be one who has been diagnosed with a MRGPRX2 dependent condition or MRGPRX2 ortholog dependent condition, such as a pseudo-allergic reaction, an itch associated condition, a pain associated condition, a cancer associated condition, an inflammatory or autoimmune disorder. Diagnosis may be performed by any method or technique known in the art. One skilled in the art will understand that a subject to be treated according to the present disclosure may have been subjected to standard tests or may have been identified, without examination, as one at risk due to the presence of one or more risk factors associated with the disease or condition. The term "patient" may be used interchangeably with the term "subject." A subject may refer to an adult or pediatric subject.

The Federal Food, Drug, and Cosmetic Act defines "pediatric" as a subject aged 21 or younger at the time of their diagnosis or treatment. Pediatric subpopulations are further characterized as: (i) neonates – from birth through the first 28 days of life; (ii) infants – from 29 days to less than 2 years; (iii) children – 2 years to less than 12 years; and (iv) adolescents – aged 12 through 21. Despite the definition, depending on the susceptible patient population and clinical trial evaluation, an approved regulatory label may include phrasing that specifically modifies the range of a pediatric population, such as, for example, pediatric patients up to 22 years of age.

In another embodiment, the method of treating a subject having a MRGPRX2 dependent condition (e.g., an itch associated condition, a pain associated condition, a pseudo-allergic reaction, or an inflammatory or autoimmune disorder) described herein further comprises administering to the subject a pharmaceutically effective amount of a second therapeutic agent. In one embodiment, the itch associated condition is a pseudo-allergic condition.

In one embodiment, the second therapeutic agent is an antihistamine, such as an H1 receptor antagonist or an H2 receptor antagonist. In one embodiment, the second therapeutic agent is an H1 receptor antagonist antihistamine, such as levocetirizine, loratadine, fexofenadine, cetirizine, desloratadine, olopatadine, diphenhydramine, cyproheptadine or hydroxyzine pamoate. In one embodiment, the second therapeutic agent is a H2 receptor antagonist, such as cimetidine, nizatidine, ranitidine or famotidine. In one embodiment, the second therapeutic agent is a leukotriene receptor antagonist or leukotriene synthesis inhibitor, such as montelukast,

zafirlukast, pranlukast, or 5-lipoxygenase inhibitor (e.g., zileuton, hypericum perforatum). In one embodiment, the second therapeutic agent is an immunomodulatory agent such as Omalizumab or immunoglobulin therapy. In one embodiment, the second therapeutic agent is a corticosteroid, such as hydrocortisone, cortisone, ethamethasoneb, triamcinolone, prednisone, prednisolone, or fludrocortisone. In one embodiment, the second therapeutic agent is a tricylic antidepressant that can relieve itch such as doxepin, amitriptyline or nortriptyline. In one embodiment, the second therapeutic agent is an anti-inflammatory drug such as dapsone, sulfasalazine, hydroxycholoroquine or colchicine. In one embodiment, the second therapeutic agent is an immunosuppressant such as cyclosporine, methotrexate, mycophenolic acid or tacromilus.

The second therapeutic agent may be administered simultaneously, separately, or sequentially with the compounds of the present disclosure. If administered simultaneously, the second therapeutic agent and compound of the present disclosure may be administered in separate dosage forms or in the same dosage form.

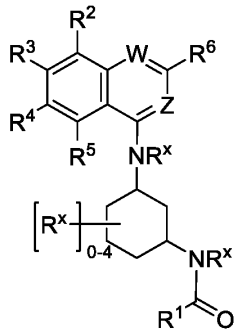
In another embodiment, a method of treating a subject having an itch associated condition is provided, the method comprising administering to the subject a pharmaceutically effective amount of a compound having structure (I) or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, or a pharmaceutical composition thereof. In one embodiment, the itch associated condition is urticaria, pruritus, atopic dermatitis, dry skin, psoriasis, contact dermatitis, or eczema.In another embodiment, a method of treating a subject having an inflammation or autoimmune associated condition is provided, the method comprising administering to the subject a pharmaceutically effective amount of a compound having structure (I) or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, or a pharmaceutical composition thereof. In one embodiment, the inflammation or autoimmune associated condition is sinusitis, asthma, rosacea, or endometriosis.

In another embodiment, a method of treating a subject having a pain associated condition is provided, the method comprising administering to the subject a pharmaceutically effective amount of a compound having structure (I) or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, or a pharmaceutical composition thereof. In one embodiment, the pain associated

coniditon is chronic pelvic pain syndrome, endometriosis pain, fibromyalgia, migraine or postoperative pain.

Compounds

As detailed above, the present disclosure provides compounds showing significant activity as MRGPRX2 antagonists. Accordingly, one embodiment provides a compound having the following structure (I):



(I)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^1 is cycloalkyl, aryl, heterocyclyl, $-(CH_2)_nQ$, -CHQR, $-(CH=CH)_nQ$, or $-CQ(R)_2$, where Q is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, -OR, $-CH_2C(O)OR$, -C(O)OR, -C(O)NHR, -OC(O)R, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)S(O)_2R$, and where R^1 and/or Q is optionally substituted with one or more R^q;

each R is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-N(R)_2$, alkylamino, $-(CH_2)_nR'$, X, aryl, cycloalkyl, heteroaryl, or heterocyclyl, or two R groups together with the atom to which it is attached forms a double bond, carbocyle or heterocycle, wherein R is optionally substituted with one or more of X, haloalkyl, or haloalkoxy;

each R^q is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, oxo, -OR, -SR, $-O(CH_2)_nR$, $-OX_3$, $-OX_2H$, $-O(X)H_2$, -C(O)OR, -C(O)R, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(O)_2$, =NH, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $S(O)_2R$, $-B(OR)_2$, -C(H)Q'R, $-O(CH_2)_nQ'$, or $-(CH_2)_nQ'$, where Q' is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, OR', -C(O)OR', -OC(O)R', X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, $-C(CH_3)_2X$, $-C(CH_3)_2OH$, -CN, $-N(R')_2$, -N(R')C(O)R', or $-N(R')S(O)_2R'$, and where R^q and/or Q' is optionally substituted with one or more R^Y;

R^2, R^3, R^4, R^5, and R^6 are independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, -OR, -C(O)OR, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, $C(X)_2R$, $-C(X)(R)_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, or $S(O)_2R$;

each R^x is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, -OR, -C(O)OR, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, or $S(O)_2R$, or R^X together with R^1 forms a heterocyclic ring;

each R^Y is independently C_{1-6} alkyl, cycloalkyl, oxo, X, $-CX_3$, -OR, or -C(O)OR;

W is N or CR^w;

Z is N or CR^z;

R^w is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocyclyl;

R^z is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, or heterocyclyl;

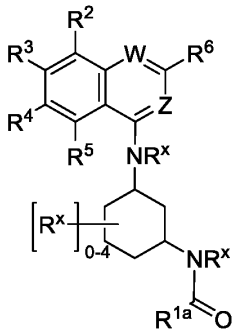
each R' is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, -OR, aryl, cycloalkyl, heteroaryl, or heterocyclyl;

each X is independently F, Cl, Br, or I; and

each n is independently 0, 1, 2, 3, 4 or 5.

In some embodiments, R is C_{1-6} alkyl optionally substituted with one or more of X, haloalkyl, or haloalkoxy.

In yet another embodiment, are provided compounds of formula (1a):



(Ia)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^{1a} is cycloalkyl, $-(CH_2)_nQ$, -CHQR, or $-CQ(R)_2$,

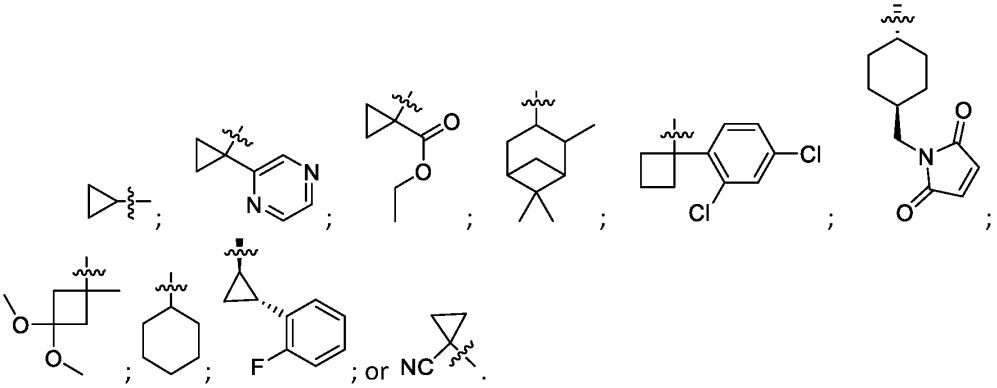
Q is cycloalkyl, -OR, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, or $-N(R)S(O)_2R$, and

where R^{1a} and/or Q is optionally substituted with one or more R^q.

In one embodiment, R^{1a} is cycloalkyl.

In some embodiments, R^{1a} and/or Q is substituted with one or more R^q. In other embodiments, the substituents are selected from C_{1-6} alkyl, C_{2-6} alkenyl, aryl, cycloalkyl, heterocyclyl, -OR, $-O(CH_2)_nR$, $-OX_3$, $-OX_2H$, $-O(X)H_2$, -C(O)OR, -C(O)R, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $S(O)_2R$, -C(H)Q'R, or $-(CH_2)_nQ'$, where Q' is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, OR', -C(O)OR', -OC(O)R', X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R')_2$, -N(R')C(O)R', or $-N(R')S(O)_2R'$. In yet other embodiments, the substituents are C_{1-6} alkyl, aryl, heterocyclyl, -OR, -CN, -C(O)OR, or $-(CH_2)_nQ'$.

In yet other embodiments, R^{1a} optionally substituted with one or more R^q has one of the following structures:

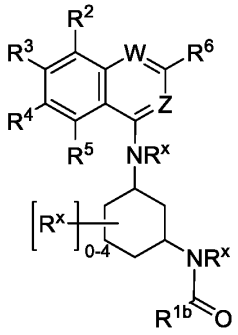


In yet other embodiments, R^4 and R^6 are independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, OR, -C(O)OR, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, or $S(O)_2R$. In some embodiments, R^6 is X, $-CX_3$, $-CX_2H$, or $-C(X)H_2$. In yet other embodiments, R^6 is $-CF_3$, $-CF_2H$, or CFH_2.

In one embodiment, R^x is H.

In another embodiment, a compound of formula (1a) is provided where W is N and Z is CH. In yet another embodiment, a compound of formula (1a) is provided where W is CH and Z is N.

In one embodiment, are provided compounds of formula (1b):



(Ib)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^{1b} is aryl, $-(CH_2)_nQ$, -CHQR, and $-CQ(R)_2$,

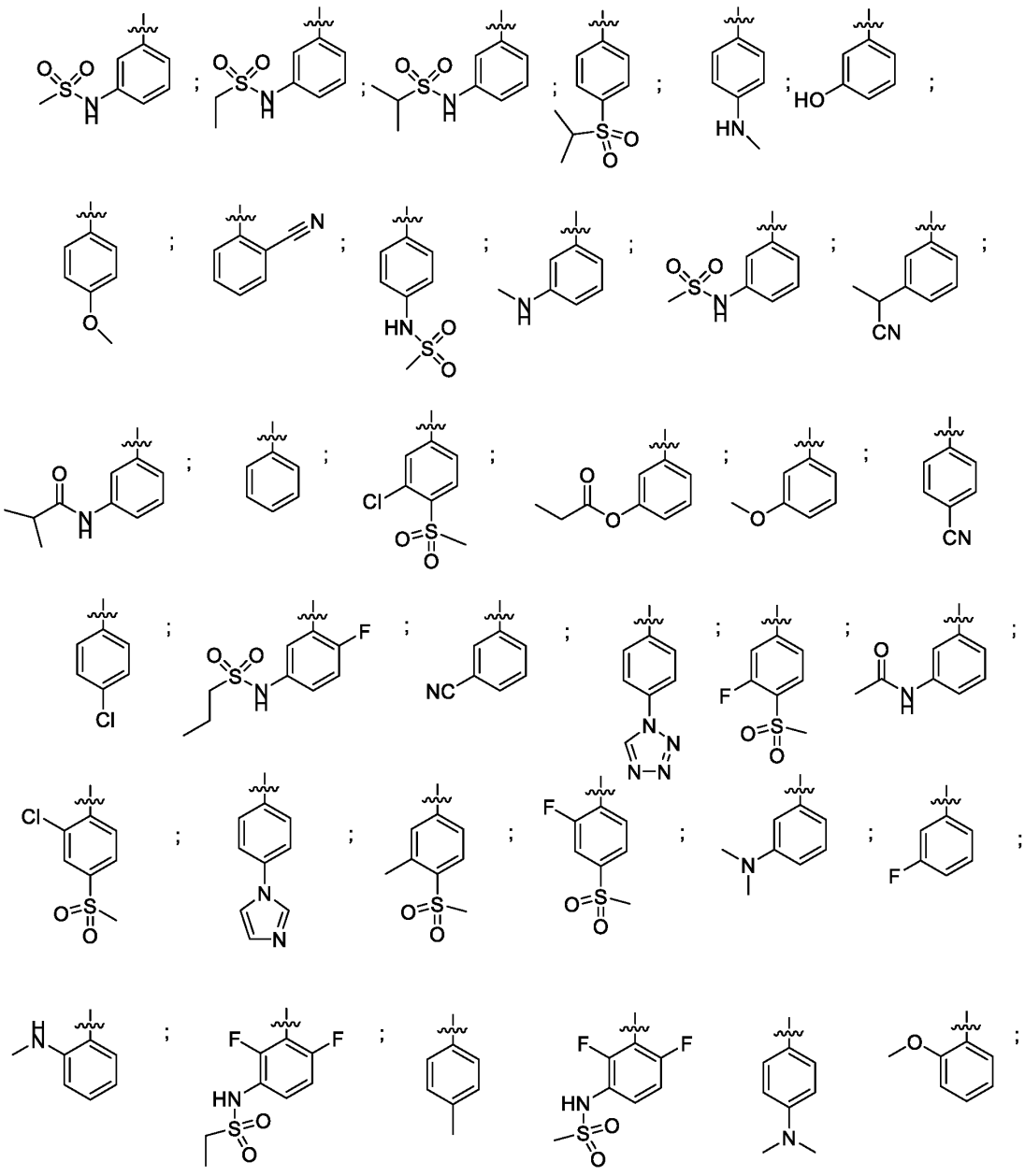
where Q is aryl, -OR, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, or $-N(R)S(O)_2R$, and

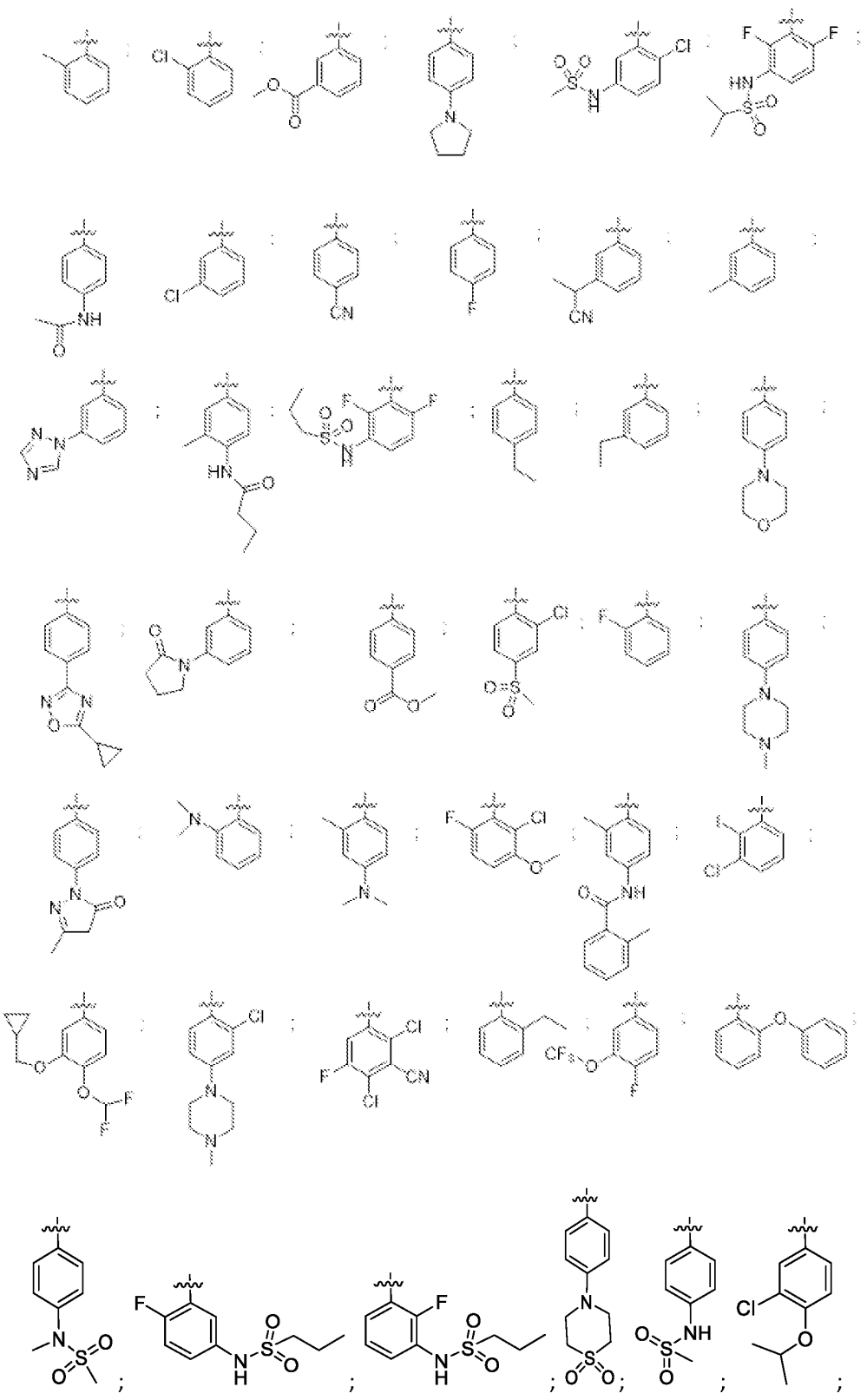
where R^{1b} and/or Q is optionally substituted with one or more R^q.

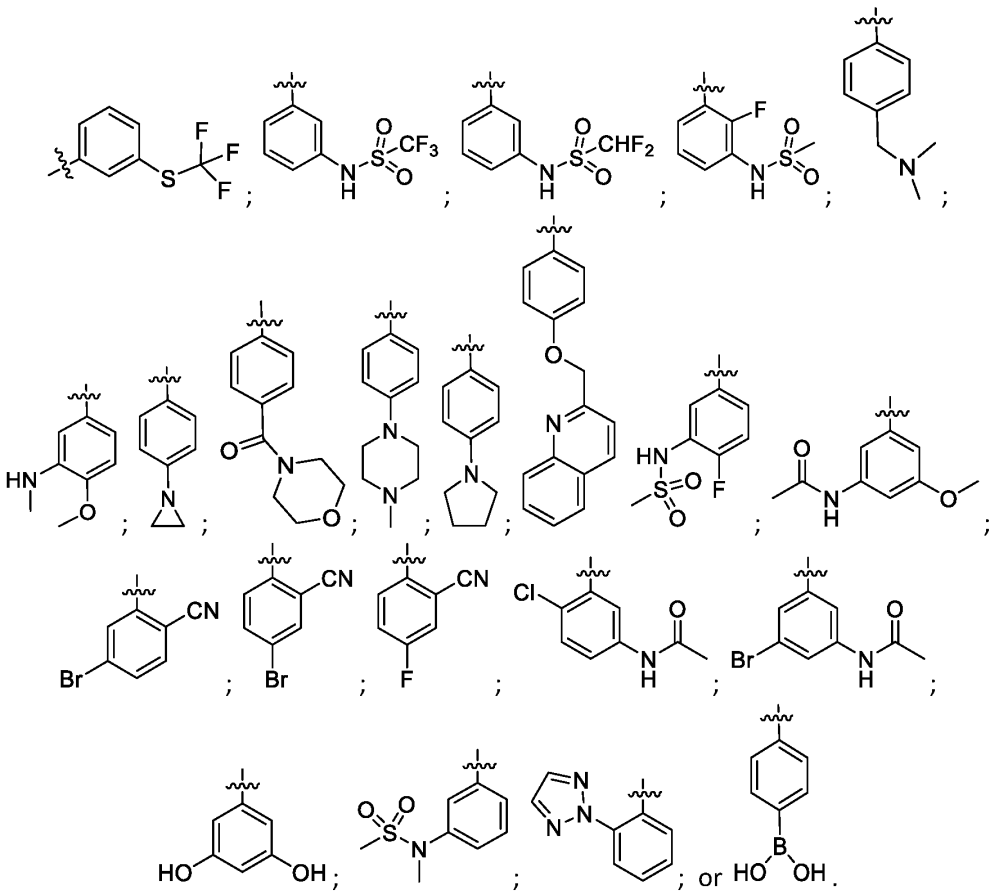
In one embodiment, R^{1b} is aryl. In another embodiment, R^{1b} is phenyl.

In some embodiments, R^{1b} and/or Q is substituted with one or more R^q. In other embodiments, the substituents are selected from C_{1-6} alkyl, C_{2-6} alkenyl, aryl, cycloalkyl, heterocyclyl, -OR, -SR, $-O(CH_2)_nR$, $-OX_3$, $-OX_2H$, $-O(X)H_2$, -C(O)OR, -C(O)R, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $S(O)_2R$, $-B(OR)_2$, -C(H)Q'R, or $-(CH_2)_nQ'$ where Q' is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, OR', -C(O)OR', -OC(O)R', X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R')_2$, -N(R')C(O)R', or $-N(R')S(O)_2R'$, and where R^q and/or Q' is optionally substituted with one or more R^Y.

In yet other embodiments, R^{1b} optionally substituted with one or more R^q has one of the following structures:







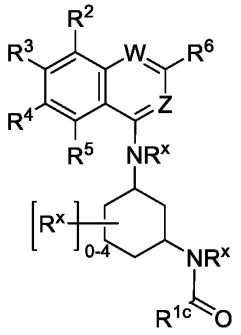
In yet other embodiments, R^4 and R^6 are independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, -OR, -C(O)OR, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, or $S(O)_2R$. In specific embodiments, R^6 is X, $-CX_3$, $-CX_2H$, or $-C(X)H_2$.

In some embodiments, R^6 is $–CF_3$, $-CF_2H$, or CFH_2.

In one embodiment, R^x is H.

In another embodiment, a compound of formula (1b) is provided where W is N and Z is CH. In yet another embodiment, a compound of formula (1b) is provided where W is CH and Z is N.

In one embodiment, are provided compounds of formula (1c):



(Ic)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^{1c} is heterocyclyl, $-(CH_2)_nQ$, -CHQR, or $-CQ(R)_2$,

where Q is heterocyclyl, -OR, -C(O)OR, -OC(O)R, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, or $-N(R)S(O)_2R$, and

where R^{1c} and/or Q is optionally substituted with one or more R^q.

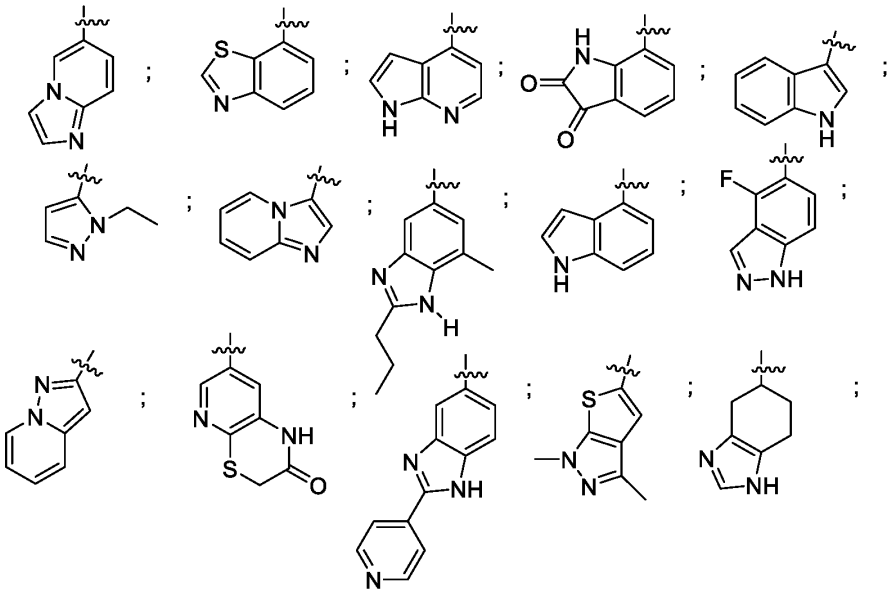
In one embodiment, R^{1c} is heterocyclyl.

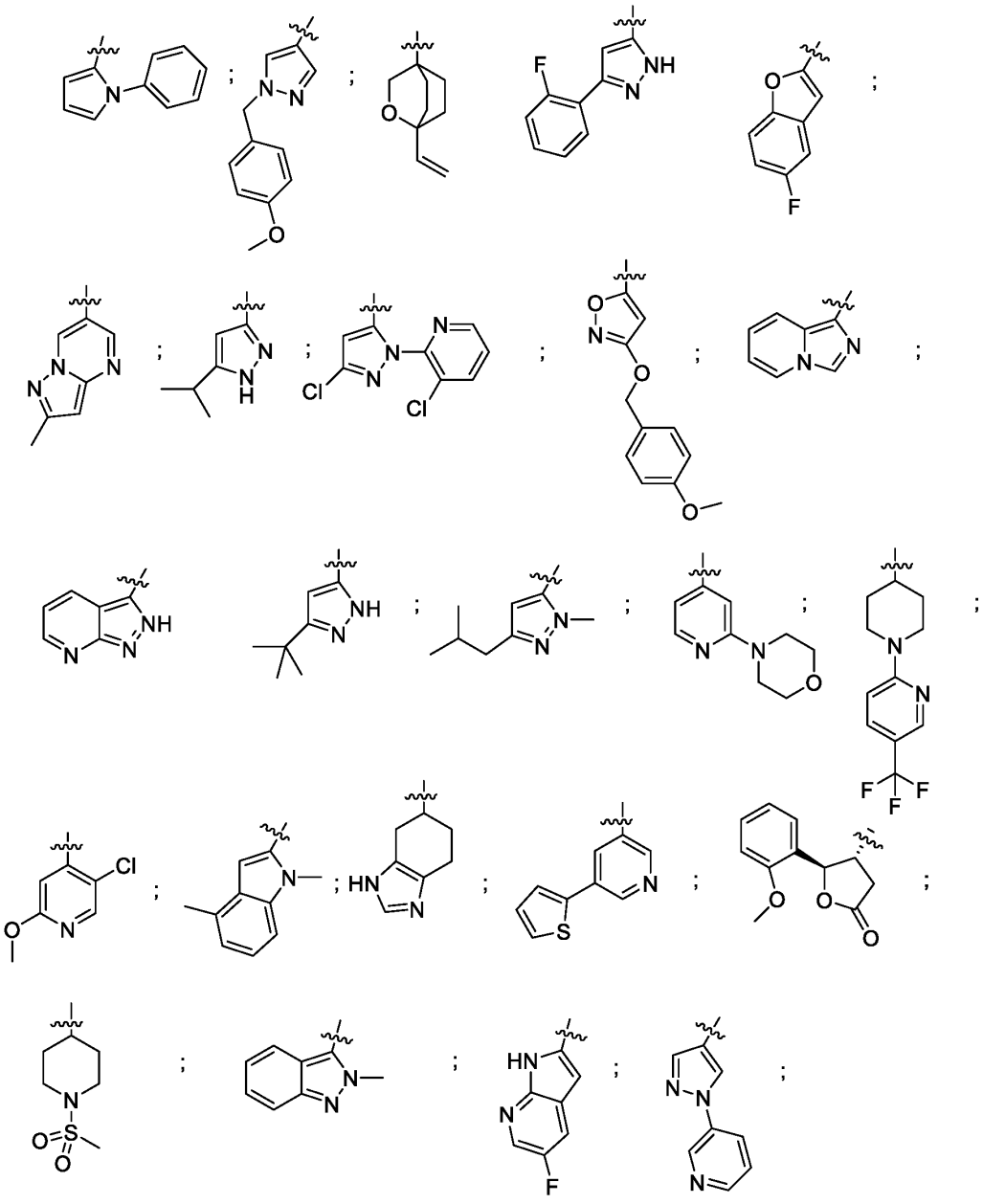
In another embodiment, heterocyclyl is aromatic and non-aromatic ring moieties containing 3 or more ring members, of which one or more is a heteroatom and wherein the heteroatom is selected from N, O, S, or P.

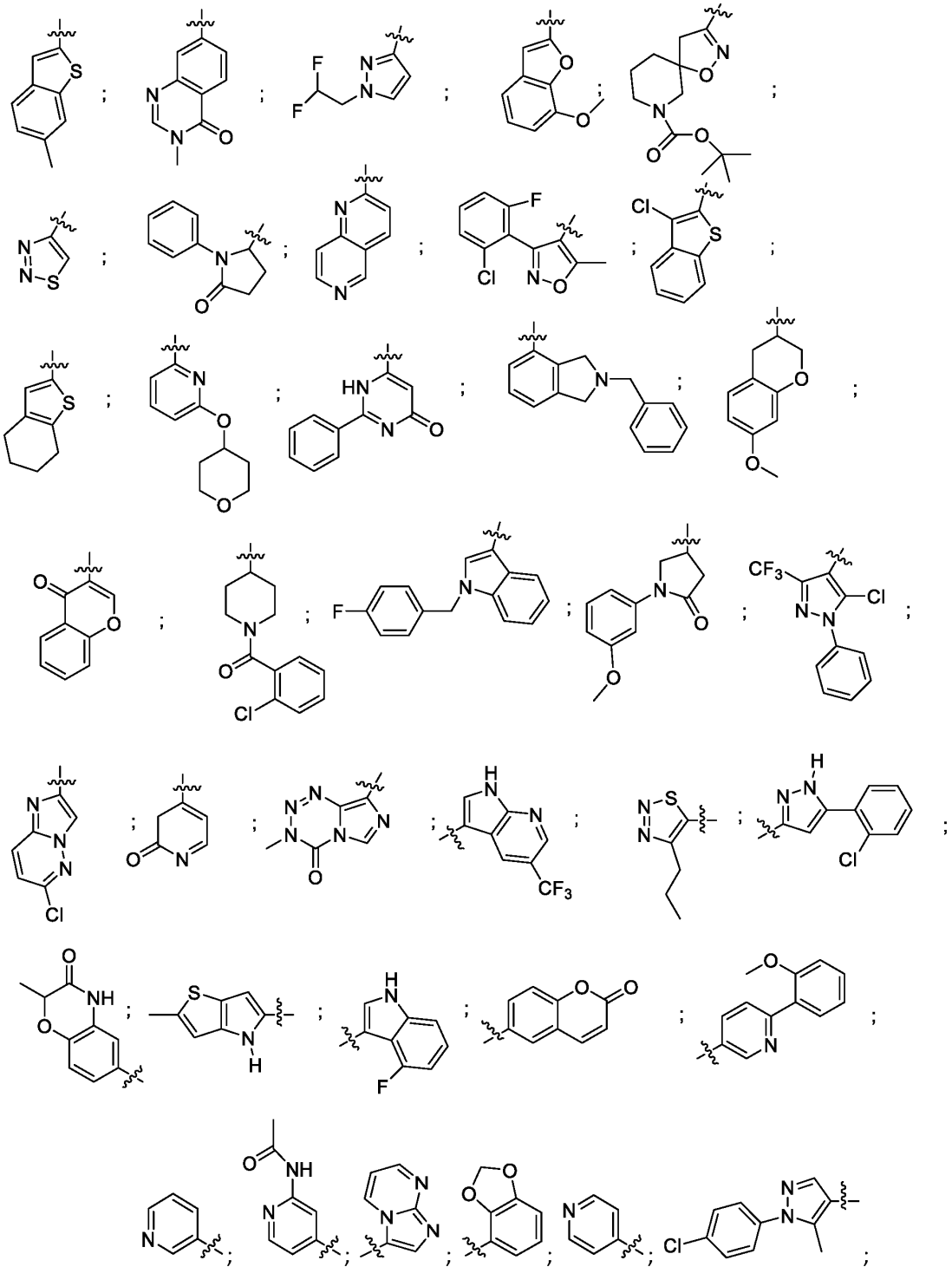
In some embodiments, R^{1c} and/or Q is substituted with one or more R^q.

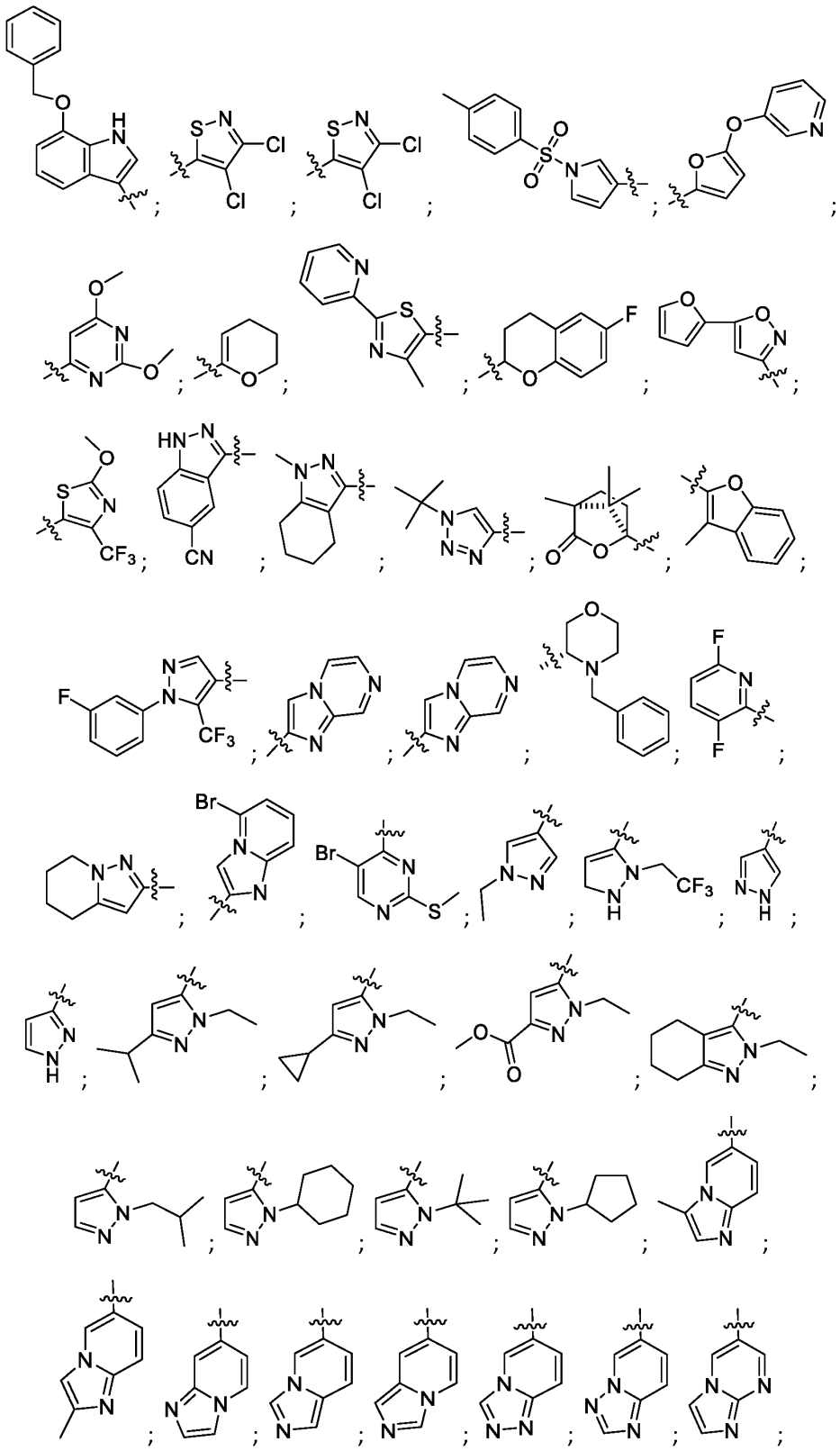
In other embodiments, the substituents are selected from C_{1-6} alkyl, C_{2-6} alkenyl, aryl, cycloalkyl, heterocyclyl, -OR, -SR, $-O(CH_2)_nR$, $-OX_3$, $-OX_2H$, $-O(X)H_2$, -C(O)OR, -C(O)R, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(O)_2$, =NH, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, $S(O)_2R$, -C(H)Q'R, or $-(CH_2)_nQ'$ where Q' is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, OR', -C(O)OR', -OC(O)R', X, $-CX_3$, $-CX_2H$, $-C(CH_3)_2X$, $-C(CH_3)_2OH$, $-C(X)H_2$, -CN, $-N(R')_2$, $-N(R')C(O)R'$, or $-N(R')S(O)_2R'$, and where R^q and/or Q' is optionally substituted with one or more R^Y.

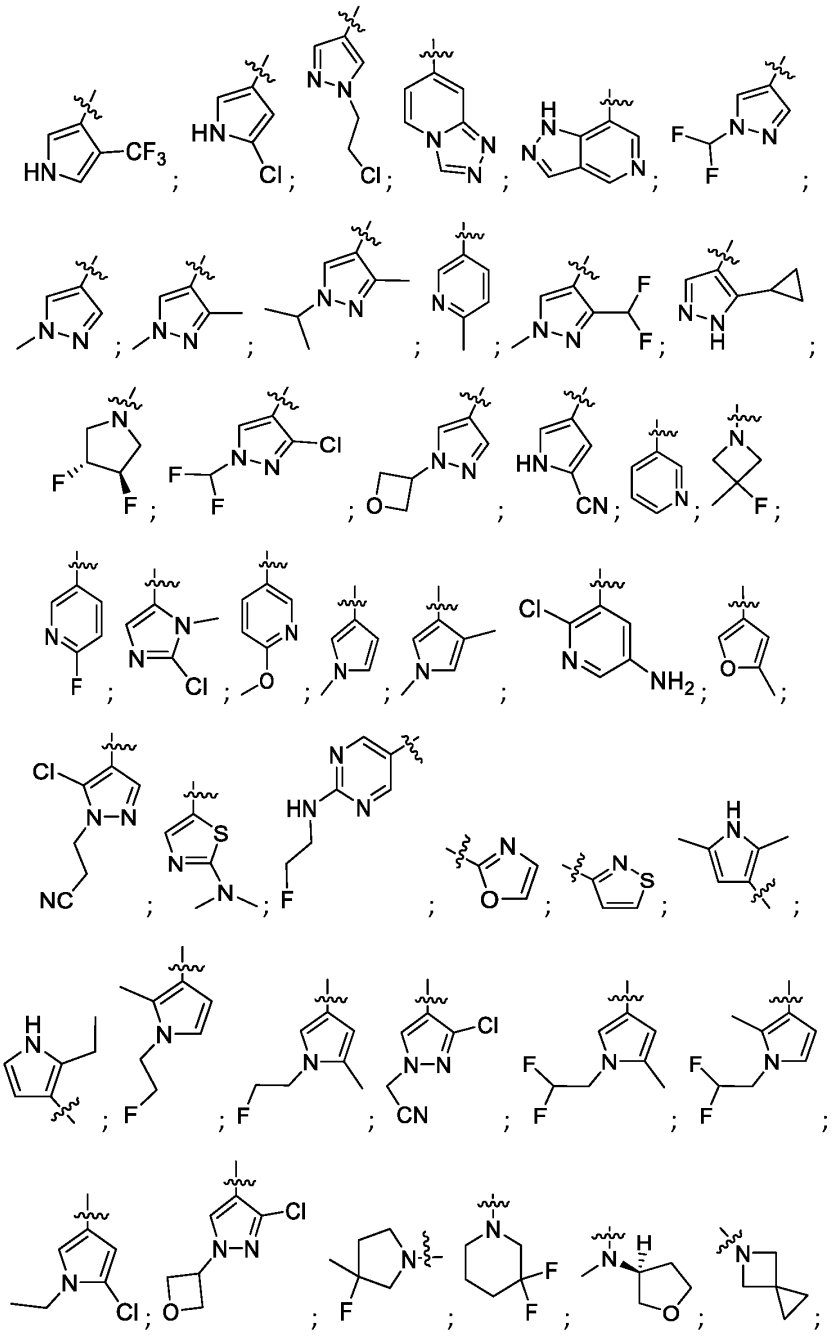
In some embodiments, R^{1c} optionally substituted with one or more R^q has one of the following structures:

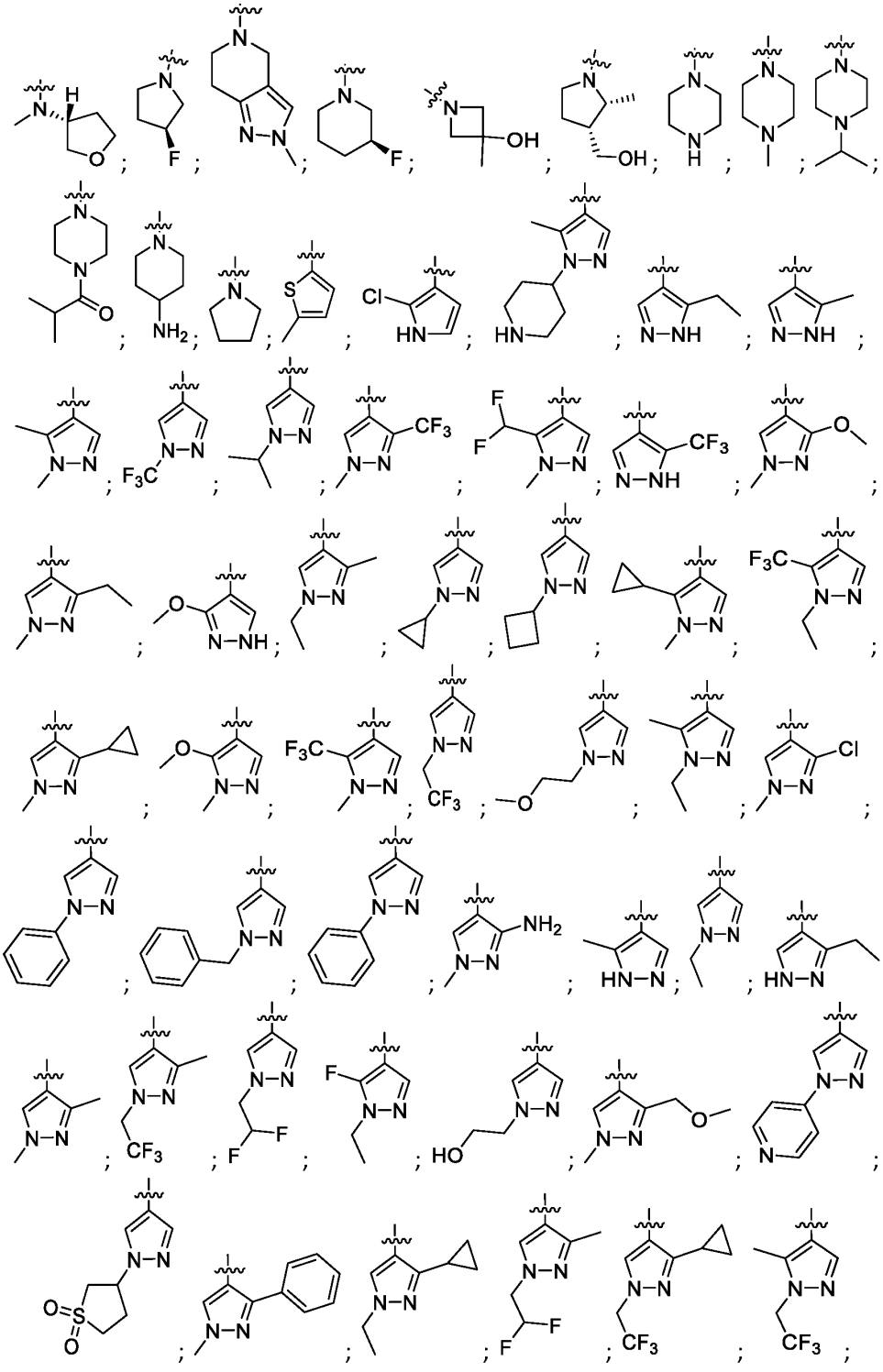


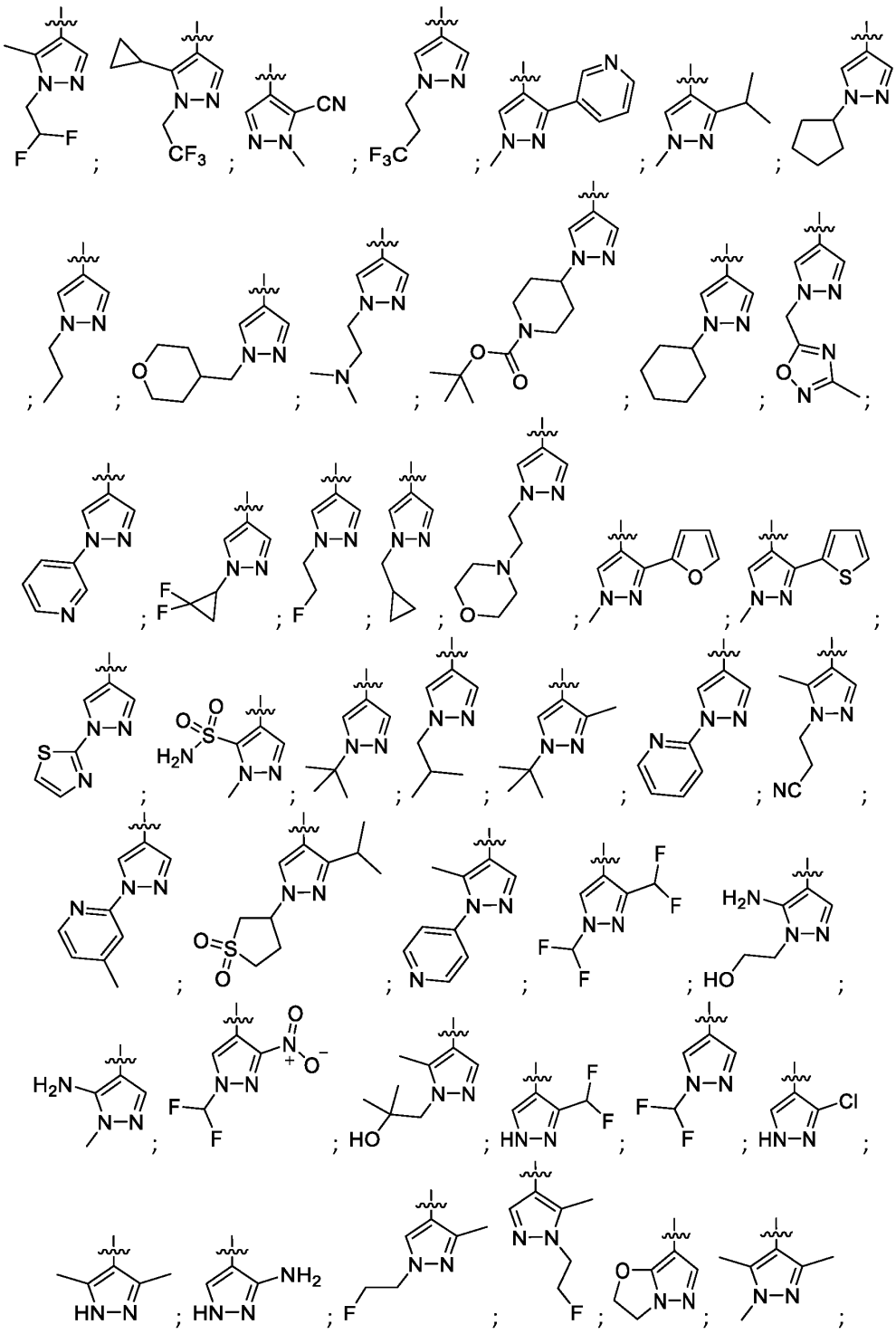


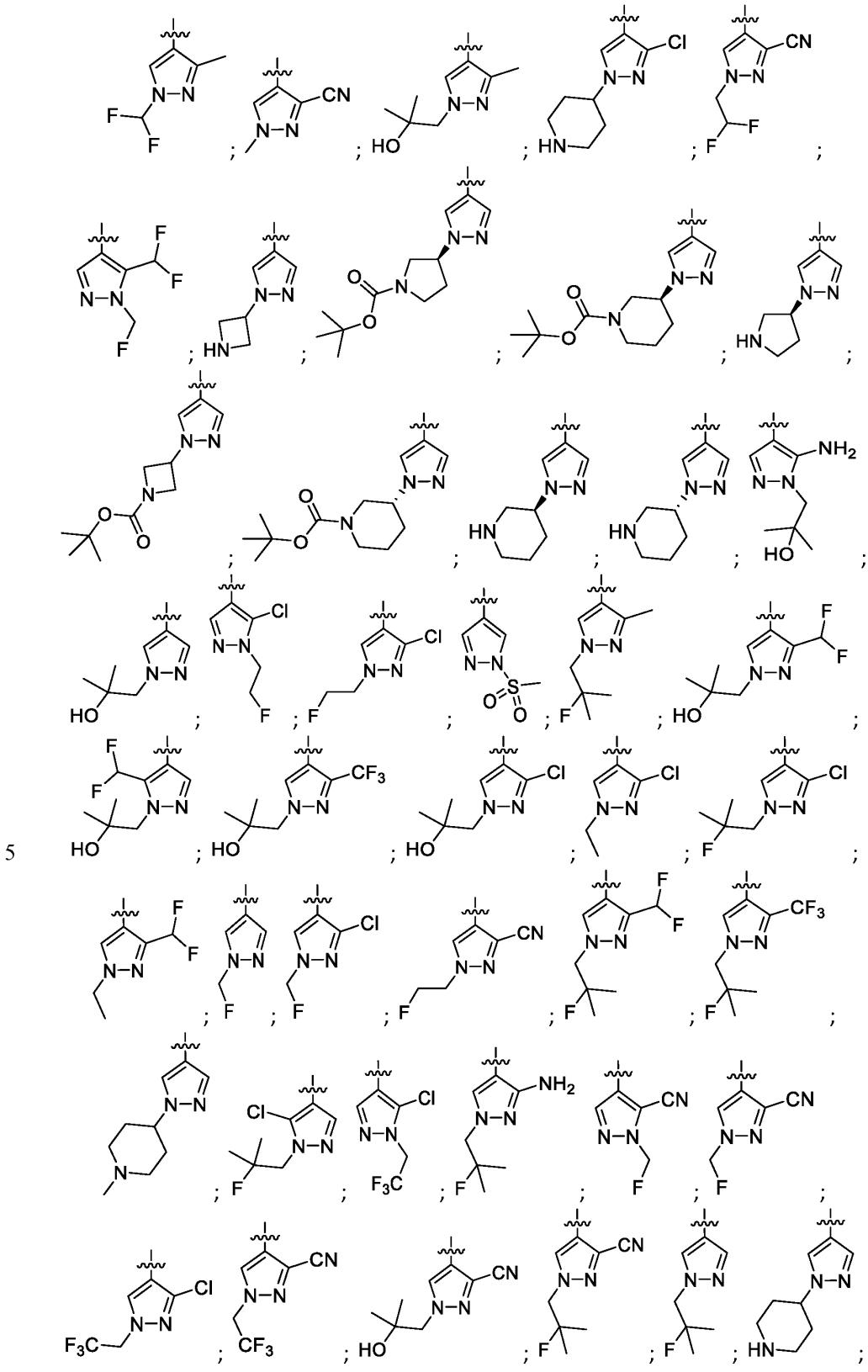


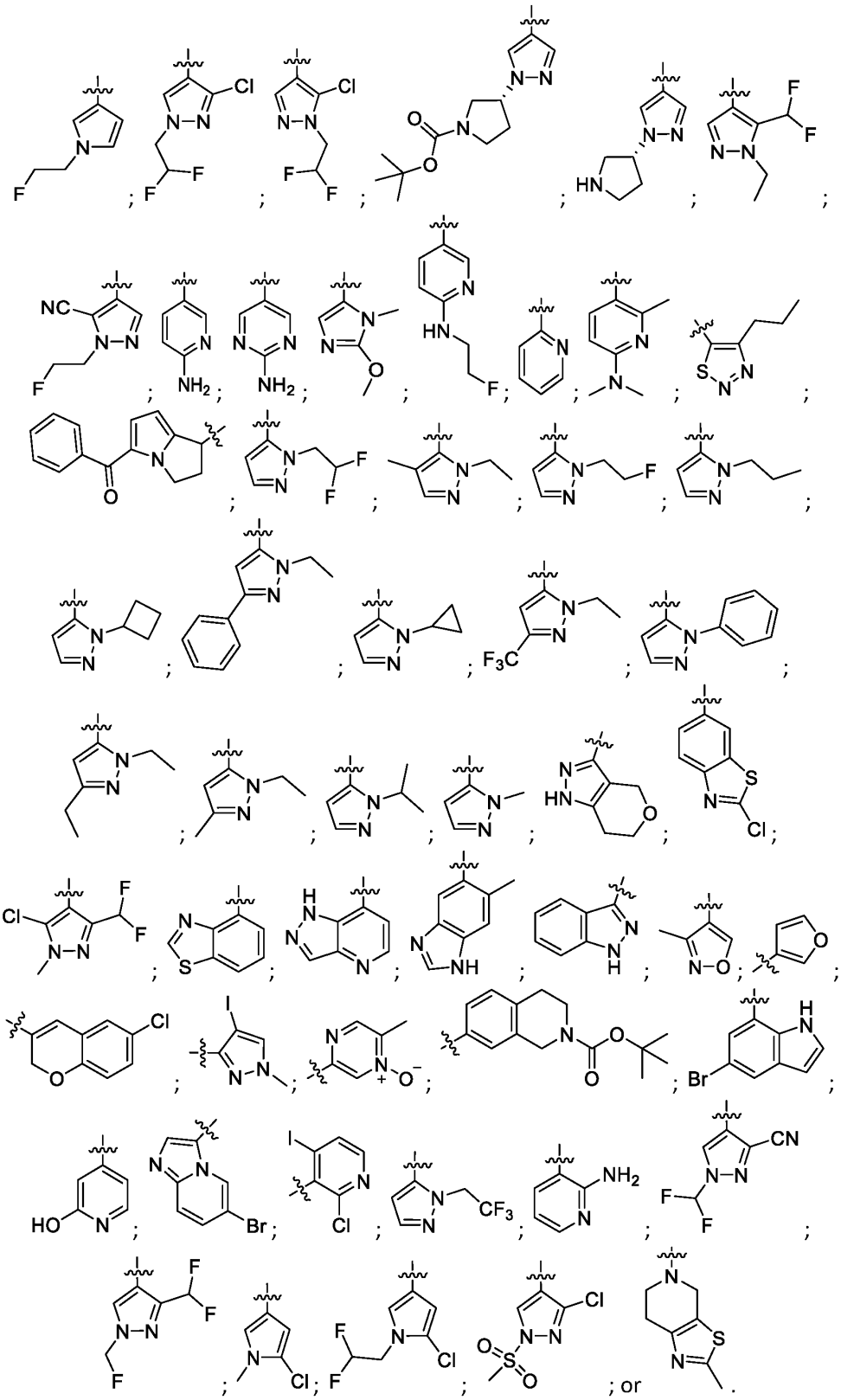












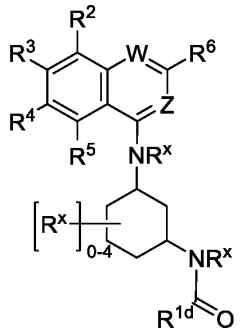
In yet other embodiments, R^4 and R^6 are at each occurrence, independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, -OR, -C(O)OR, -OC(O)R, X, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, $-N(R)S(O)_2R$, or $S(O)_2R$.

In specific embodiments, R^6 is X, $-CX_3$, $-CX_2H$, or $-C(X)H_2$. In yet other embodiments, R^6 is $-CF_3$, $-CF_2H$, or CFH_2.

In one embodiment, R^x is H.

In another embodiment, a compound of formula (1c) is provided where W is N and Z is CH. In yet another embodiment, a compound of formula (1c) is provided where W is CH and Z is N.

In one embodiment, are provided compounds of formula (1d):



(Id)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^{1d} is $CQ(R)_2$,

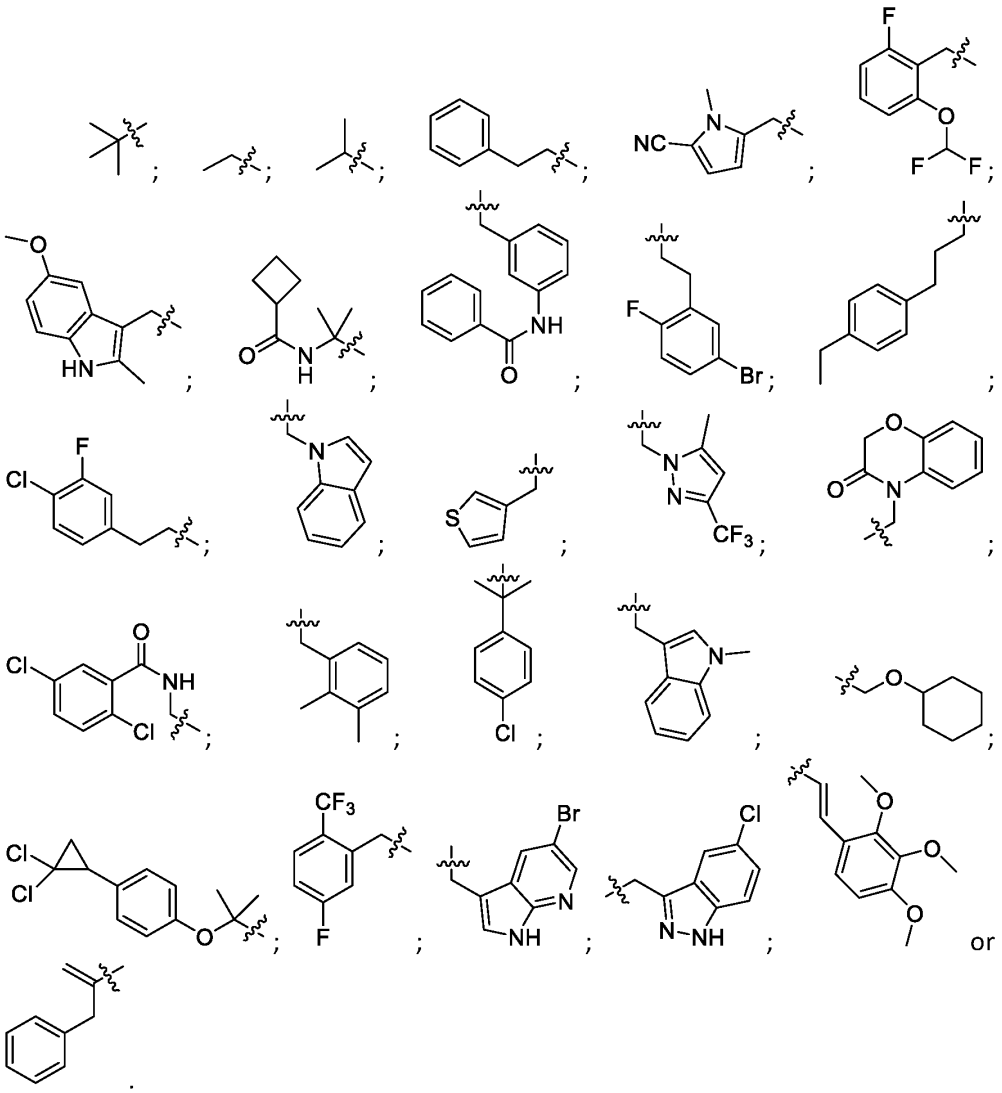
where Q is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, -OR, $-CH_2C(O)OR$, -C(O)OR, -C(O)NHR, -OC(O)R, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)S(O)_2R$, and

where R^{1d} and/or Q is optionally substituted with one or more R^q.

In specific embodiments, Q is selected from C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl and N(R)C(O)R.

In other embodiments, R is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkylamino, $-(CH_2)_nR'$, X, H, aryl, cycloalkyl, or heterocyclyl.

In some embodiments, R^{1d} optionally substituted with one or more R^q has one of the following structures:

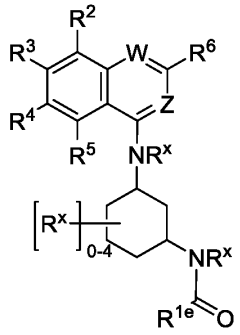


In one embodiment, R^6 is X, $-CX_3$, $-CX_2H$, or $-C(X)H_2$. In yet other embodiments, R^6 is $-CF_3$, $-CF_2H$, or CFH_2.

In one embodiment, R^x is H.

In another embodiment, a compound of formula (1d) is provided where W is N and Z is CH. In yet another embodiment, a compound of formula (1d) is provided where W is CH and Z is N.

In one embodiment, are provided compounds of formula (1e):



(Ie)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^{1e} is -CHQR,

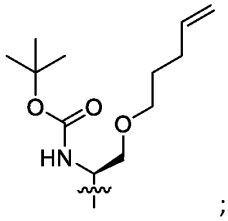
where Q is C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, -OR, $-CH_2C(O)OR$, -C(O)OR, -C(O)NHR, -OC(O)R, $-CX_3$, $-CX_2H$, $-C(X)H_2$, -CN, $-N(R)_2$, -N(R)C(O)R, -N(R)C(O)OR, or $-N(R)S(O)_2R$, and

where each R^{1e} and/or Q is optionally substituted with one or more R^q.

In specific embodiments, Q is selected from C_{1-6} alkyl, aryl, cycloalkyl, heterocyclyl, -N(R)C(O)R and -N(R)C(O)OR.

In other embodiments, R is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, alkylamino, $-(CH_2)_nR'$, X, aryl, cycloalkyl, or heterocyclyl.

In some embodiments, R^{1e} optionally substituted with one or more R^q has one of the following structures: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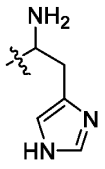
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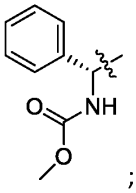
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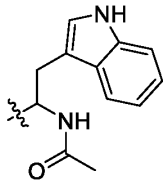
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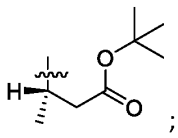
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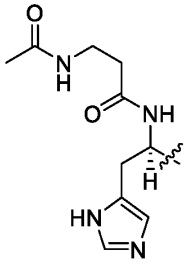
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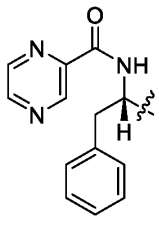
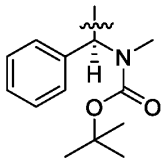
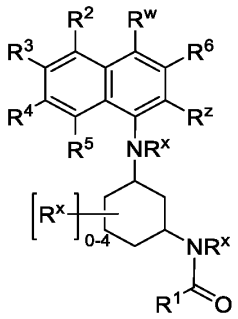

; or

.

In specific embodiments, R^6 is X, $-CX_3$, $-CX_2H$, or $-C(X)H_2$. In yet other embodiments, R^6 is $-CF_3$, $-CF_2H$, or CFH_2.

In one embodiment, R^x is H.

In another embodiment, a compound of formula (1e) is provided where W is N and Z is CH. In yet another embodiment, a compound of formula (1e) is provided where W is CH and Z is N.

In one embodiment, are provided compounds of formula (1f):



(If)

or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein:

R^W or R^z is independently C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, H, aryl, cycloalkyl, heteroaryl, or heterocyclyl.

In specific embodiments, R^6 is X, $-CX_3$, $-CX_2H$, or $-C(X)H_2$. In yet other embodiments, R^6 is $-CF_3$, $-CF_2H$, or CFH_2.

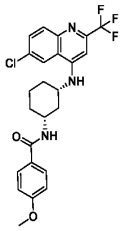
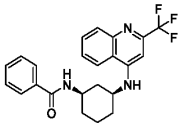
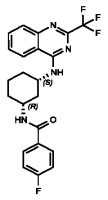
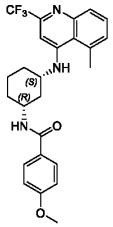
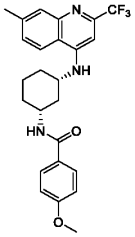
In a specific embodiment, R^W and R^z are both H.

In another embodiment, R^x is H.

In one embodiment, a compound is selected from any one of the compounds listed in the following Table, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or istotope thereof.

Table

Representative compounds having Structure (I)

Structure	Cpd No.
	Ex. 1
	Ex. 2
	Ex. 3
	Ex. 4
	Ex. 5

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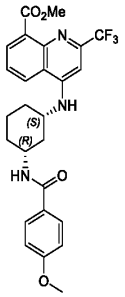
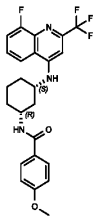
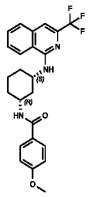
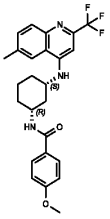
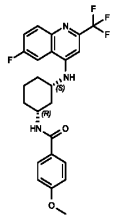
	Ex. 6
	1-1
	1-2
	1-3
	1-4

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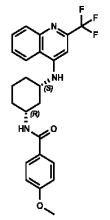
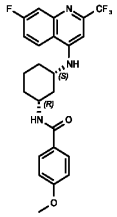
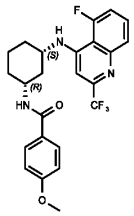
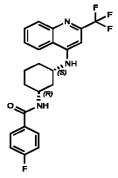
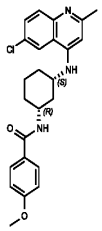
	1-5
	1-6
	1-7
	1-8
	1-9

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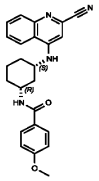
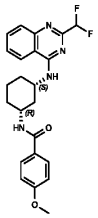
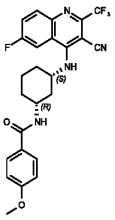
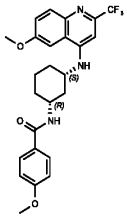
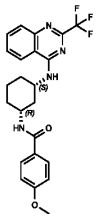
	1-10
	1-11
	1-12
	1-13
	1-14

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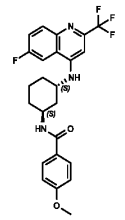
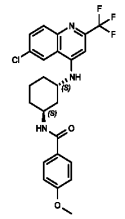
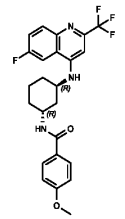
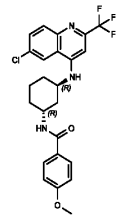
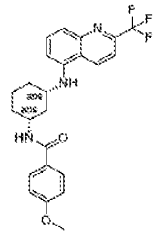
	1-15
	1-16
	1-17
	1-18
	Ex. 7

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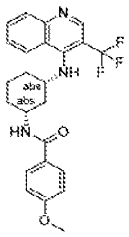
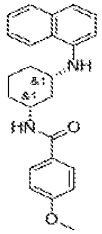
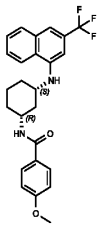
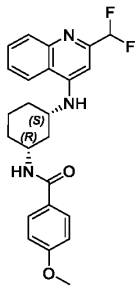
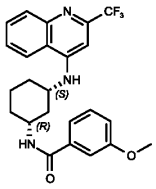
	Ex. 8
	2-1
	2-2
	Ex. 9
	Ex. 10

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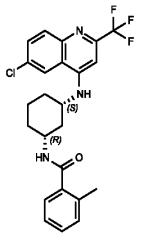
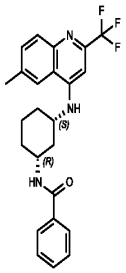
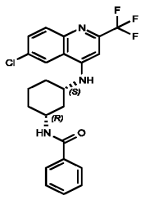
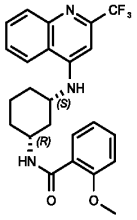
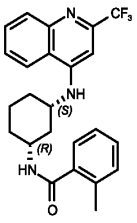
	Ex. 11
	Ex. 12
	Ex. 13
	3-1
	3-2

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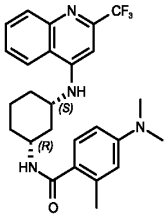
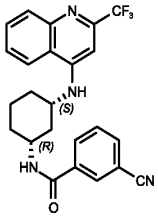
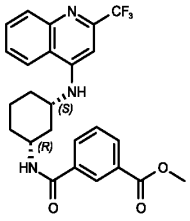
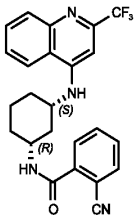
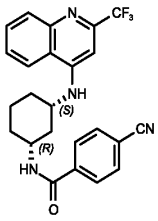
	3-3
	3-4
	3-5
	3-6
	3-7

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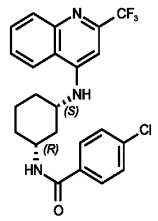
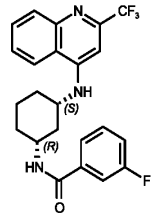
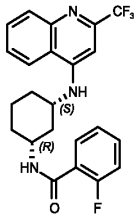
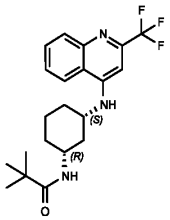
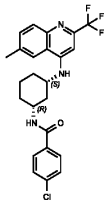
	3-8
	3-9
	3-10
	3-11
	3-12

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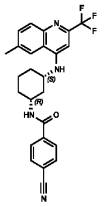
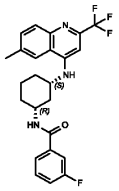
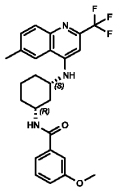
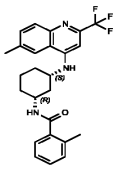
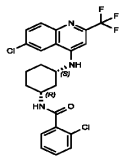
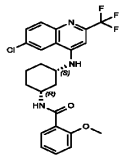
	3-13
	3-14
	3-15
	3-16
	3-17
	3-18

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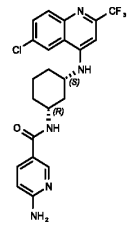
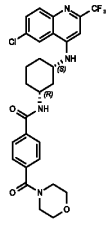
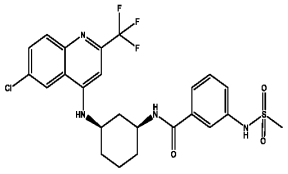
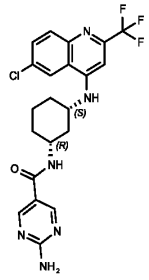
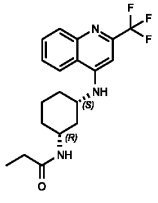
	3-19
	3-20
	Ex. 14
	Ex. 15
	Ex. 16

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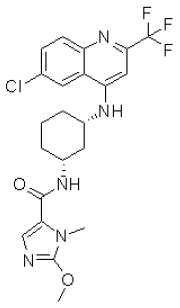
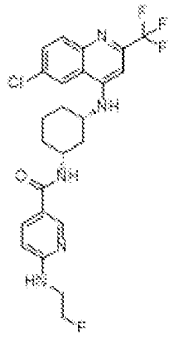
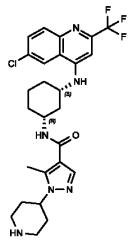
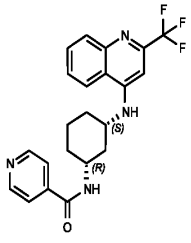
	Ex. 17
	Ex. 18
	Ex. 19
	4-1

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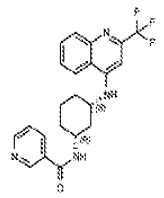
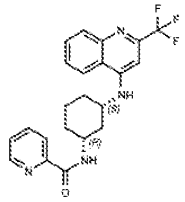
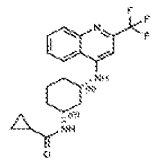
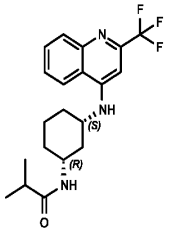
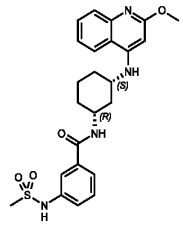
	4-2
	4-3
	4-4
	4-5
	4-6

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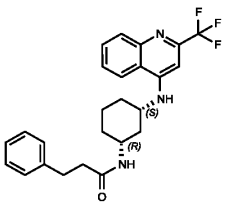
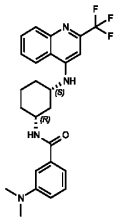
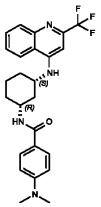
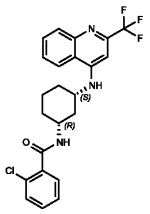
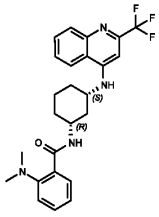
	4-7
	4-8
	4-9
	4-10
	4-11

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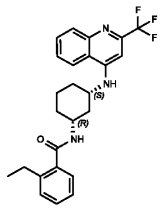
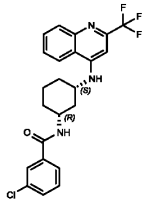
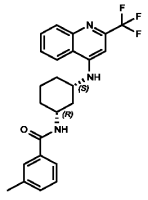
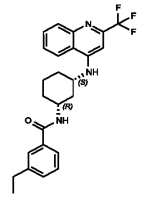
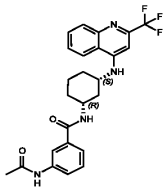
	4-12
	4-13
	4-14
	4-15
	4-16

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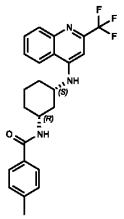
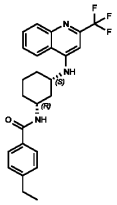
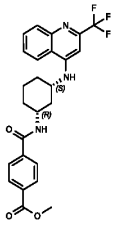
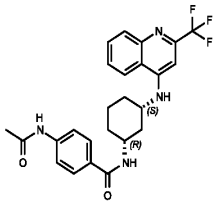
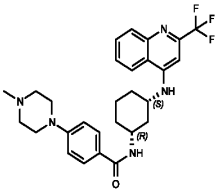
	4-17
	4-18
	4-19
	4-20
	4-21

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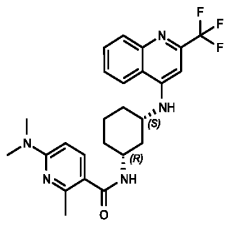
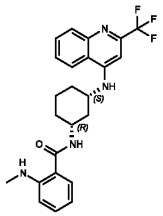
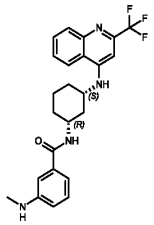
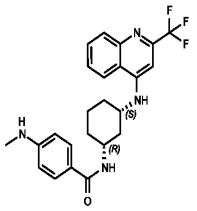
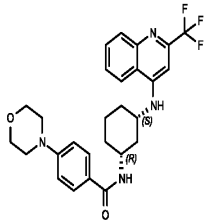
	4-22
	4-23
	4-24
	4-25
	4-26

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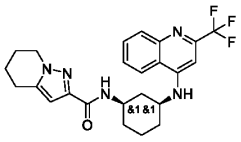
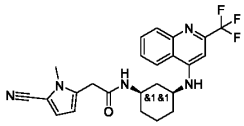
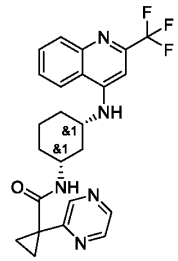
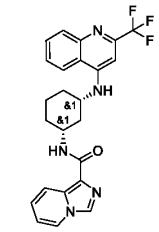
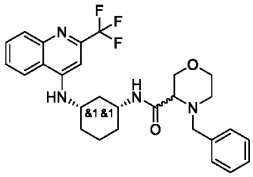
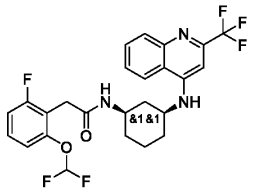
	4-27
	4-28
	4-29
	4-30
	4-31
	4-32

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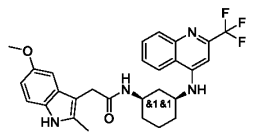
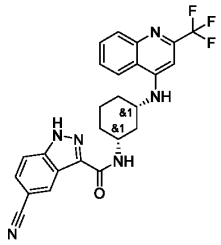
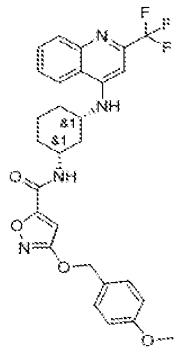
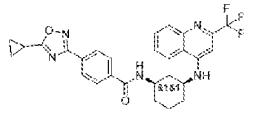
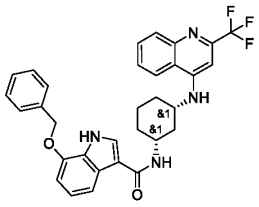
	4-33
	4-34
	4-35
	4-36
	4-37

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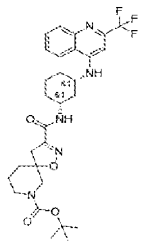
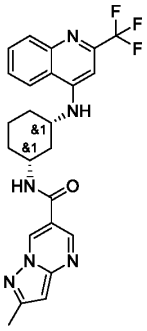
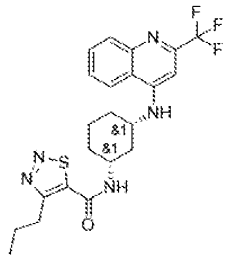
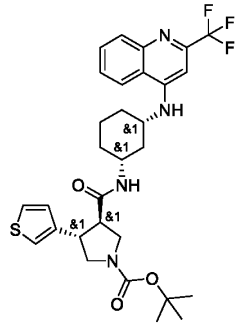
	4-38
	4-39
	4-40
	4-41

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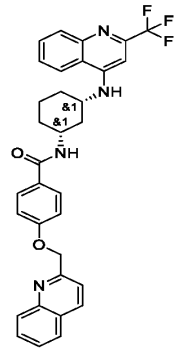
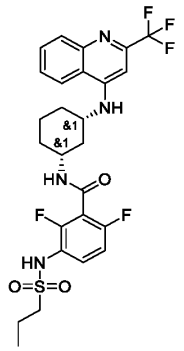
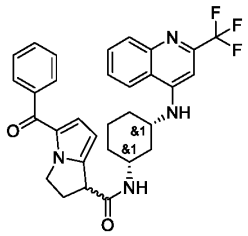
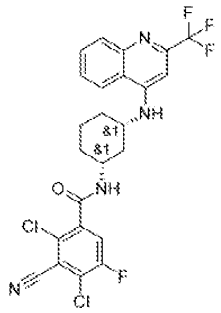
	4-42
	4-43
	4-44
	4-45

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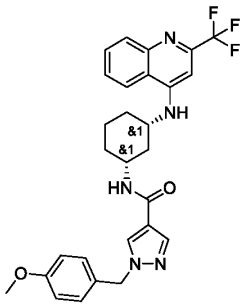
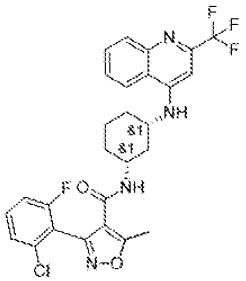
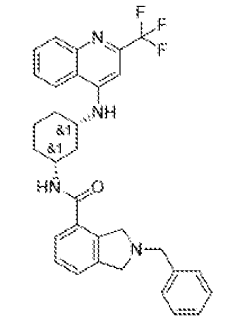
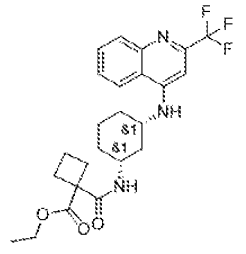
	4-46
	4-47
	4-48
	4-49

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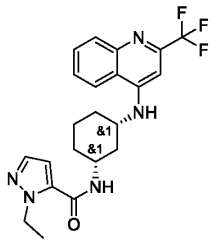
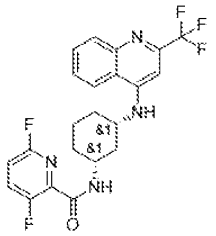
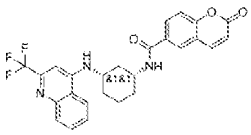
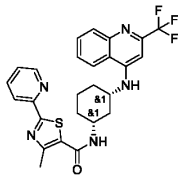
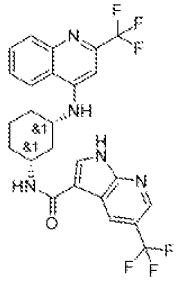
	4-50
	4-51
	4-52
	4-53
	4-54

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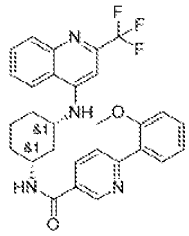
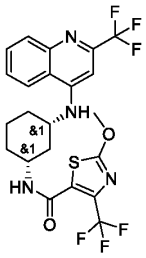
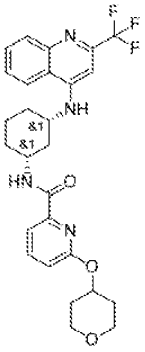
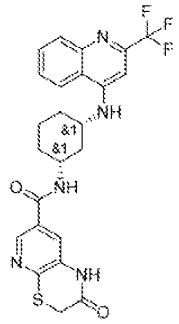
	4-55
	4-56
	4-57
	4-58

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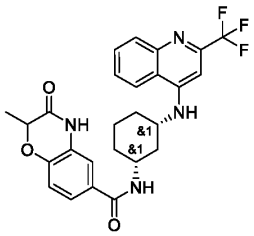
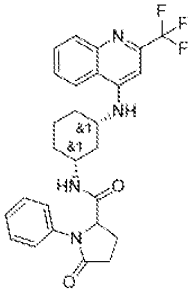
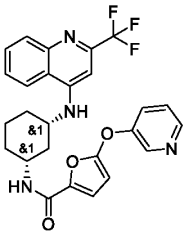
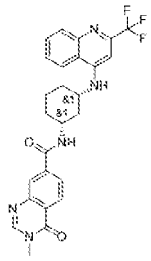
	4-59
	4-60
	4-61
	4-62

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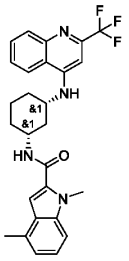
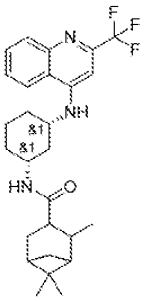
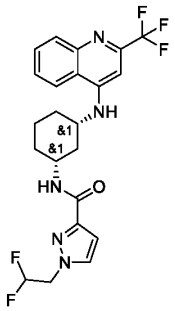
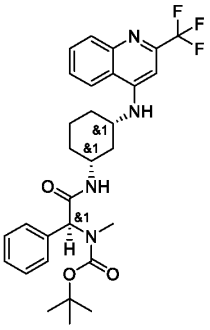
	4-63
	4-64
	4-65
	4-66

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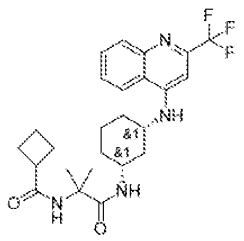
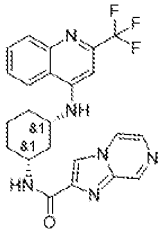
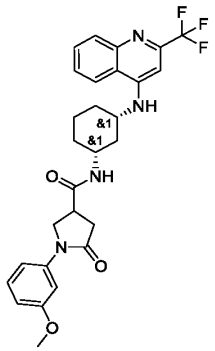
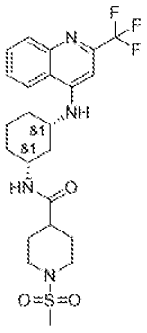
	4-67
	4-68
	4-69
	4-70

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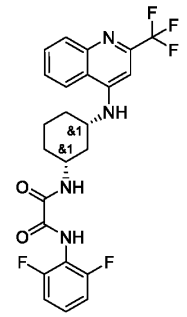
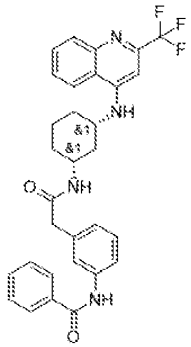
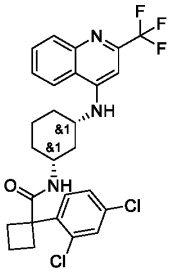
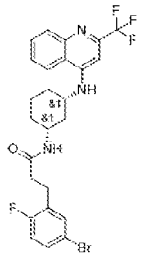
	4-71
	4-72
	4-73
	4-74

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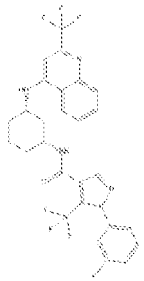
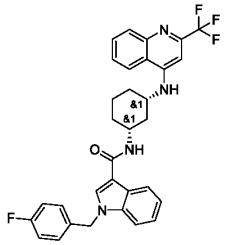
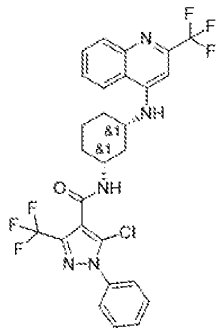
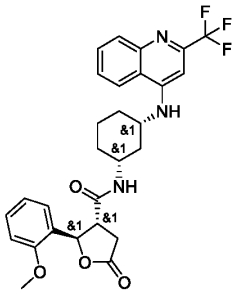
	4-75
	4-76
	4-77
	4-78

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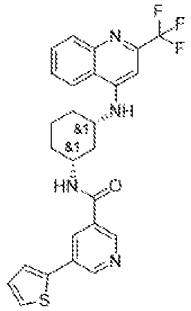
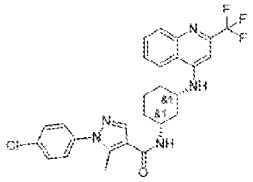
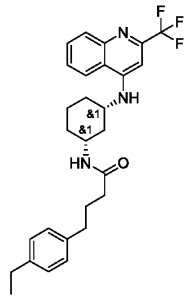
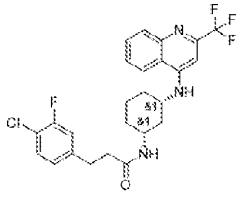
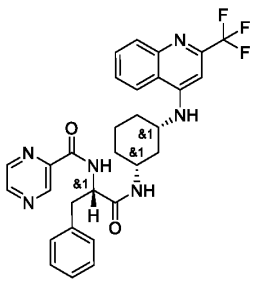
	4-79
	4-80
	4-81
	4-82
	4-83

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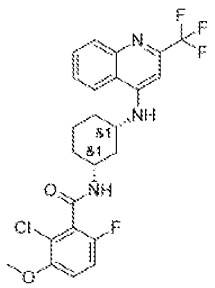
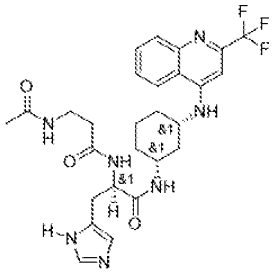
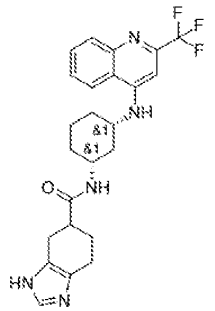
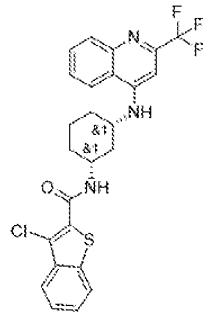
	4-84
	4-85
	4-86
	4-87

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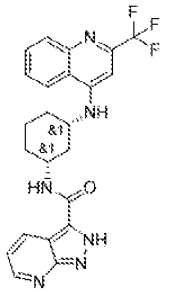
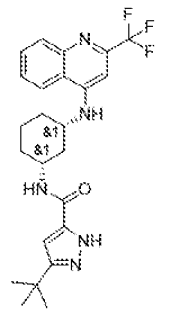
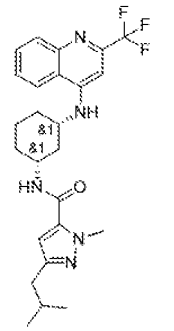
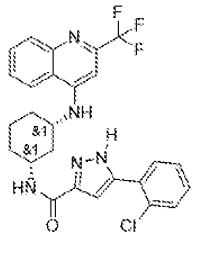
	4-88
	4-89
	4-90
	4-91

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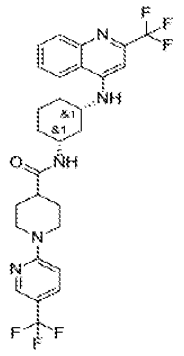
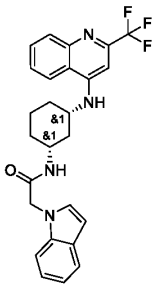
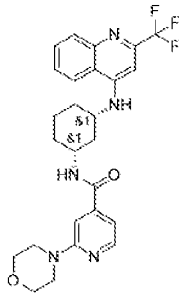
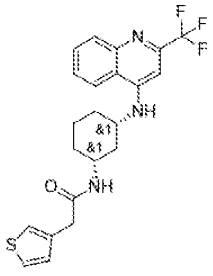
	4-92
	4-93
	4-94
	4-95

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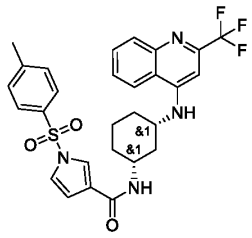
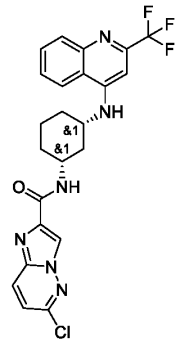
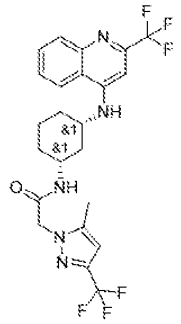
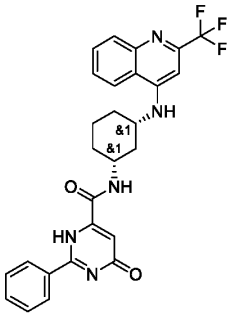
	4-96
	4-97
	4-98
	4-99

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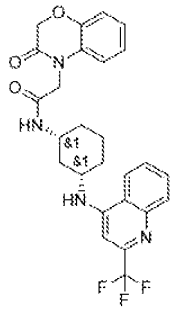
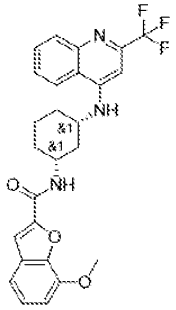
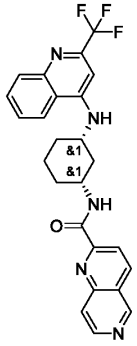
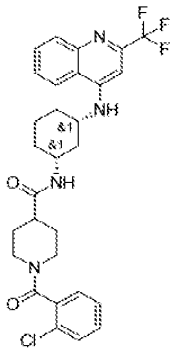
	4-100
	4-101
	4-102
	4-103

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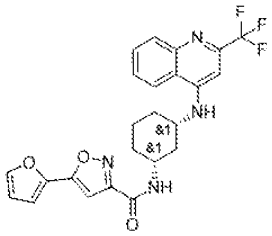
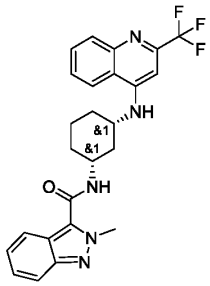
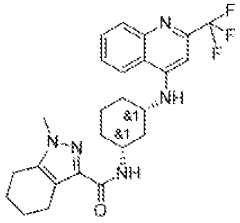
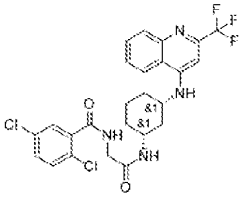
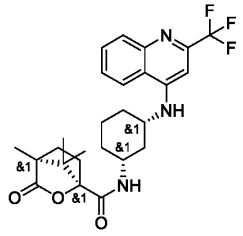
	4-104
	4-105
	4-106
	4-107
	4-108

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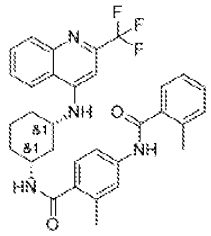
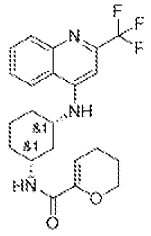
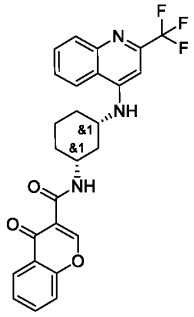
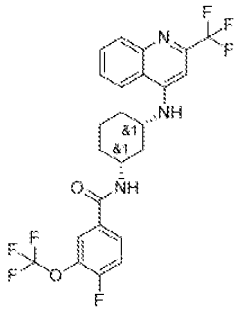
	4-109
	4-110
	4-111
	4-112

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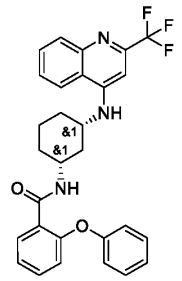
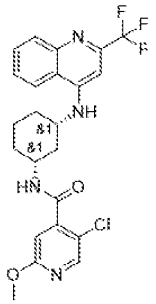
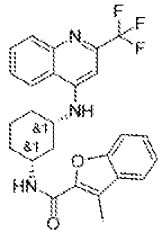
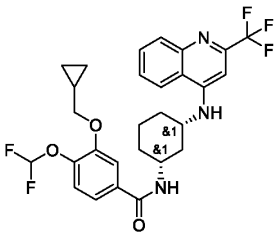
	4-113
	4-114
	4-115
	4-116

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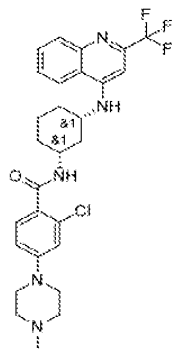
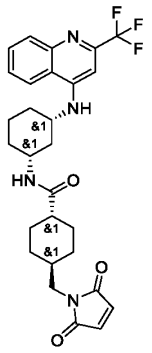
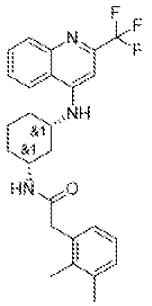
	4-117
	4-118
	4-119

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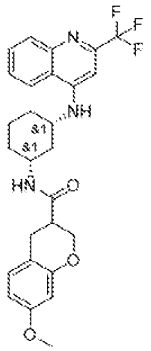
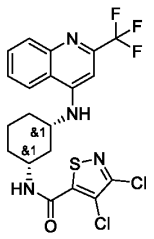
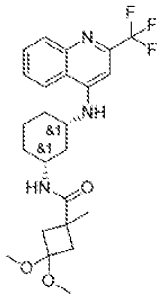
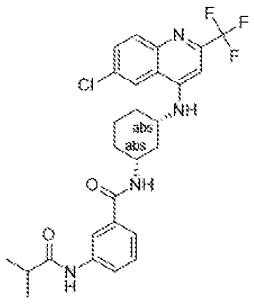
	4-120
	4-121
	4-122
	4-123

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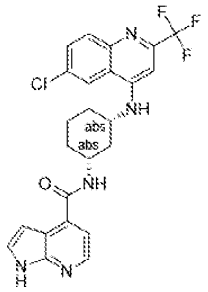
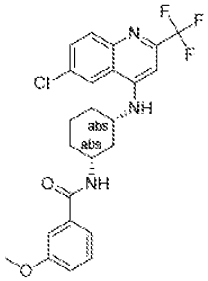
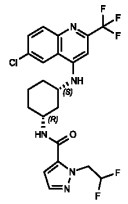
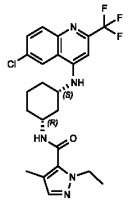
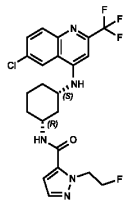
	4-124
	4-125
	4-126
	4-127
	4-128

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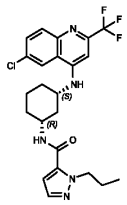
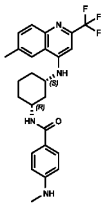
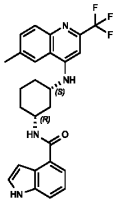
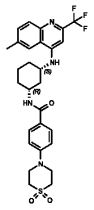
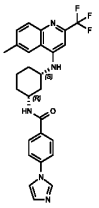
	4-129
	4-130
	4-131
	4-132
	4-133

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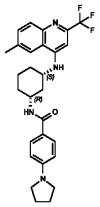
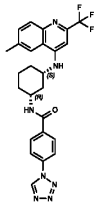
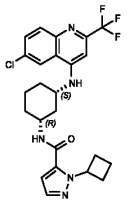
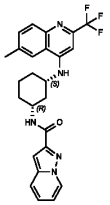
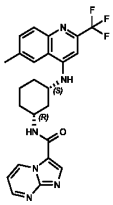
	4-134
	4-135
	4-136
	4-137
	4-138

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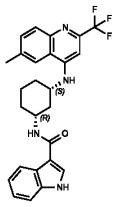
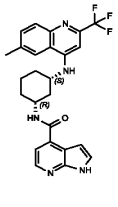
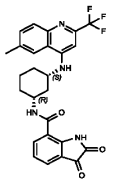
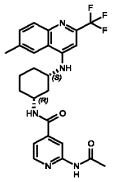
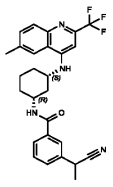
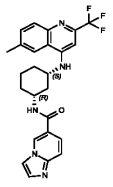
	4-139
	4-140
	4-141
	4-142
	4-143
	4-144

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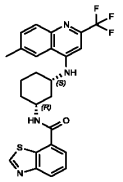
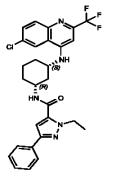
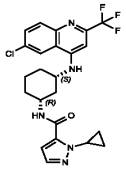
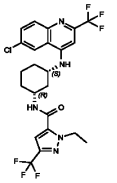
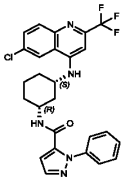
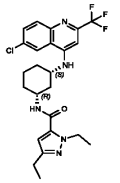
	4-145
	4-146
	4-147
	4-148
	4-149
	4-150

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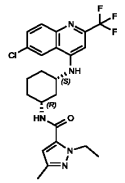
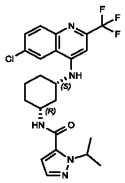
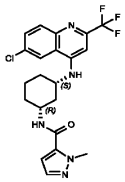
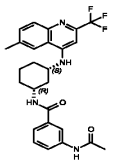
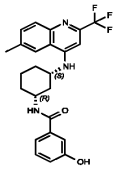
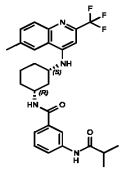
	4-151
	4-152
	4-153
	4-154
	4-155
	4-156

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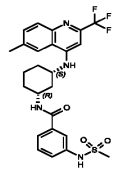
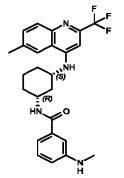
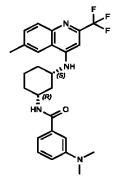
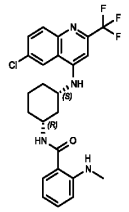
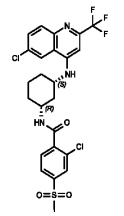
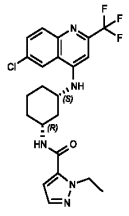
	4-157
	4-158
	4-159
	4-160
	4-161
	4-162

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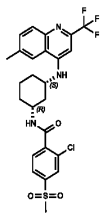
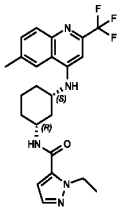
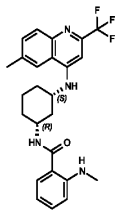
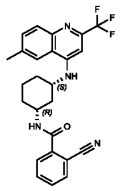
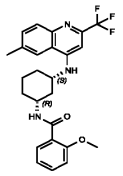
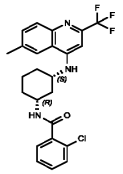
	4-163
	4-164
	4-165
	4-166
	4-167
	4-168

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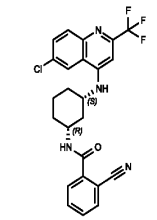
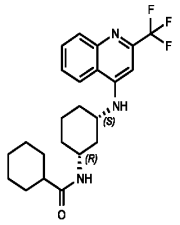
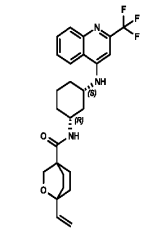
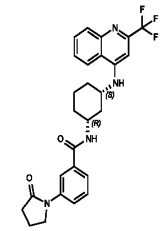
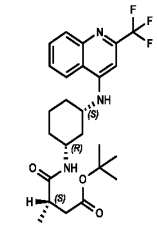
	4-169
	4-170
	4-171
	4-172
	4-173

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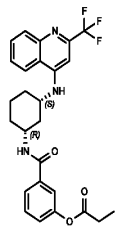
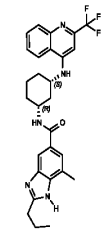
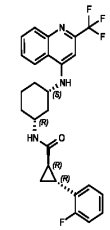
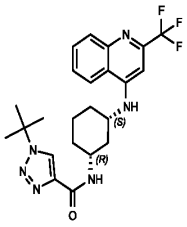
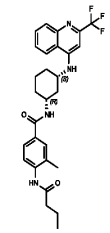
	4-174
	4-175
	4-176
	4-177
	4-178

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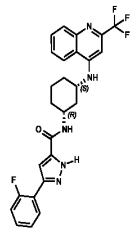
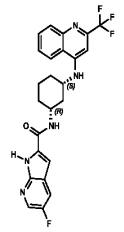
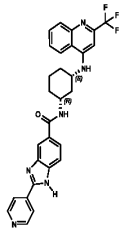
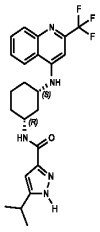
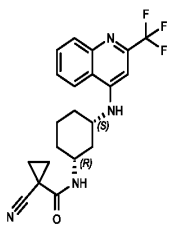
	4-179
	4-180
	4-181
	4-182
	4-183

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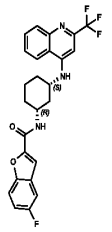
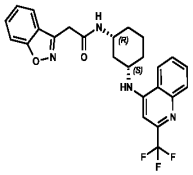
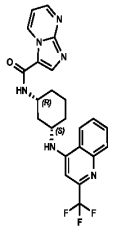
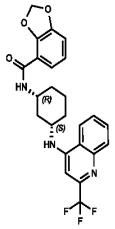
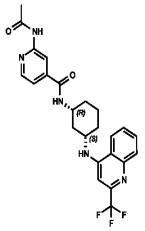
	4-184
	4-185
	4-186
	4-187
	4-188

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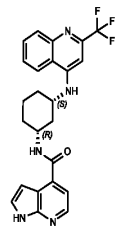
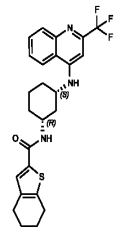
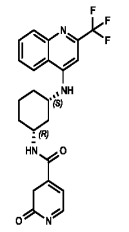
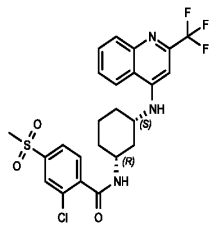
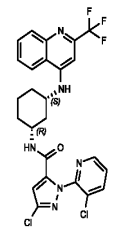
	4-189
	4-190
	4-191
	4-192
	4-193

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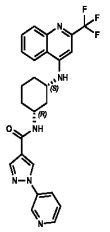
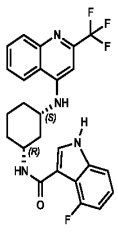
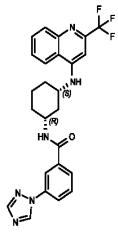
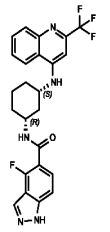
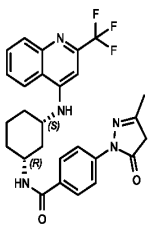
	4-194
	4-195
	4-196
	4-197
	4-198

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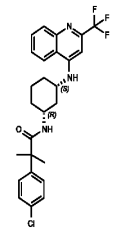
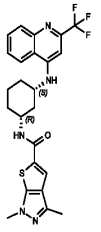
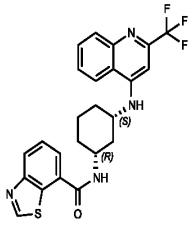
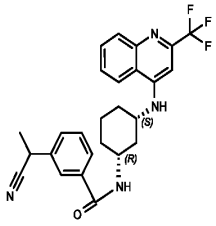
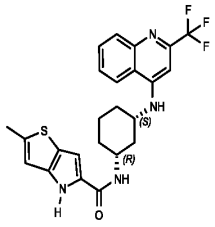
	4-199
	4-200
	4-201
	4-202
	4-203

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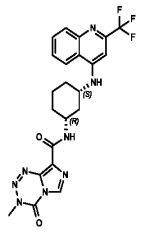
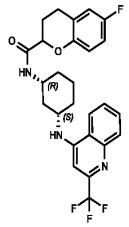
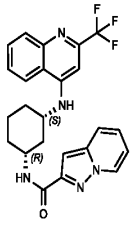
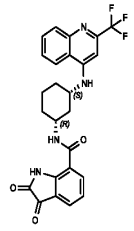
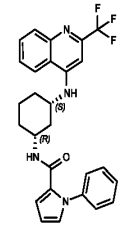
	4-204
	4-205
	4-206
	4-207
	4-208

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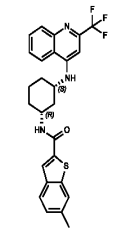
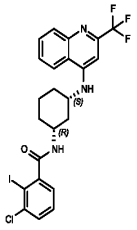
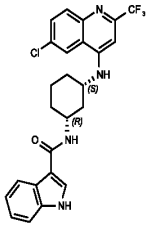
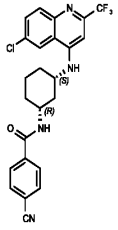
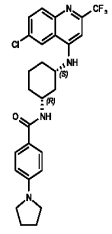
	4-209
	4-210
	4-211
	4-212
	4-213

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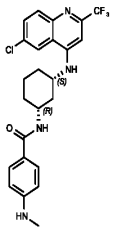
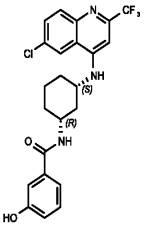
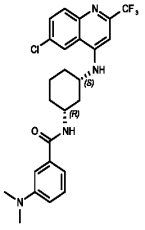
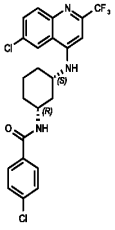
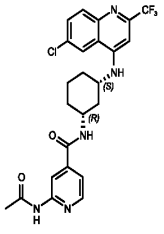
	4-214
	4-215
	4-216
	4-217
	4-218

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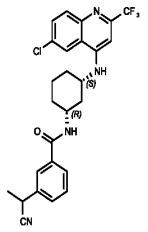
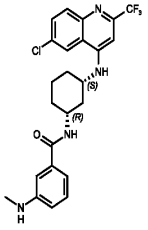
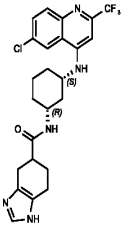
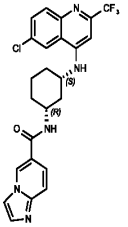
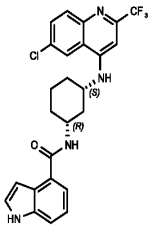
	4-219
	4-220
	4-221
	4-222
	4-223

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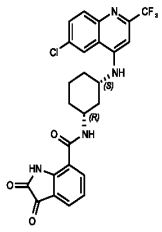
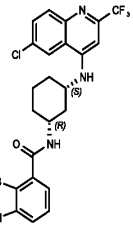
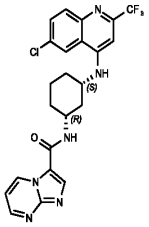
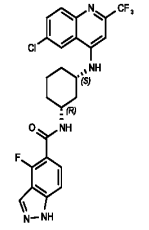
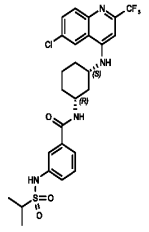
	4-224
	4-225
	4-226
	4-227
	4-228

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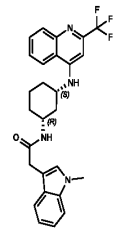
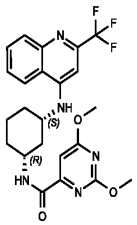
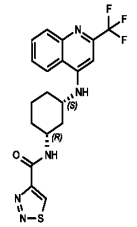
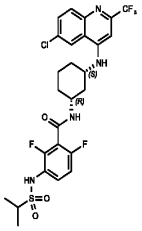
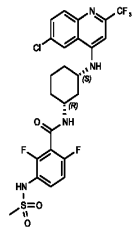
	4-229
	4-230
	4-231
	4-232
	4-233

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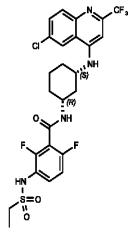
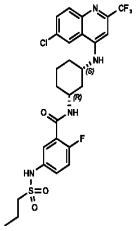
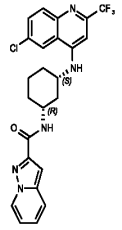
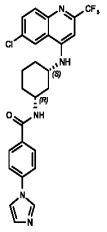
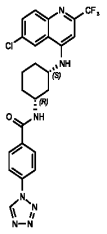
	4-234
	4-235
	4-236
	4-237
	4-238

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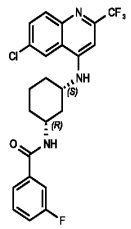
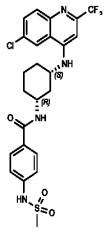
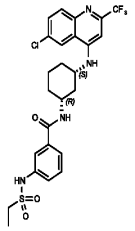
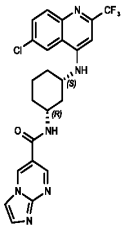
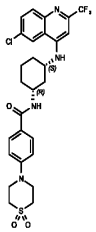
	4-239
	4-240
	4-241
	4-242
	4-243

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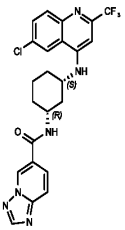
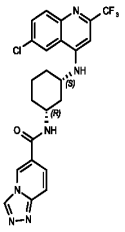
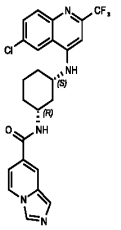
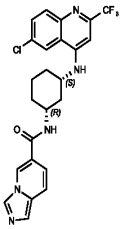
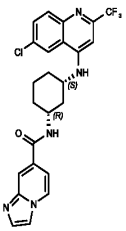
	4-244
	4-245
	4-246
	4-247
	4-248

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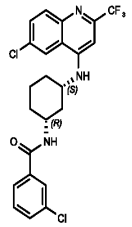
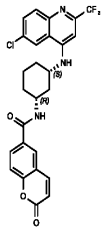
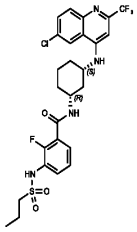
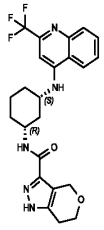
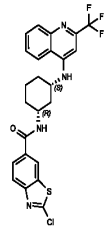
	4-249
	4-250
	4-251
	4-252
	4-253

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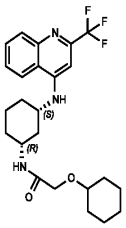
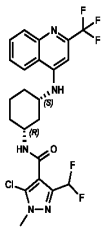
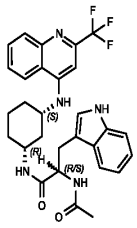
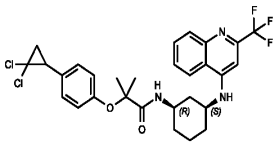
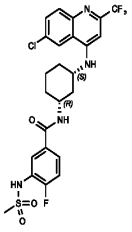
	4-254
	4-255
	4-256
	4-257
	4-258

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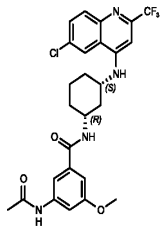
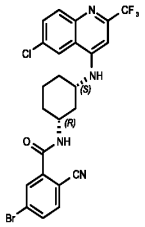
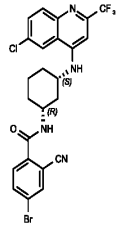
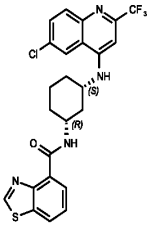
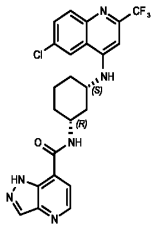
	4-259
	4-260
	4-261
	4-262
	4-263

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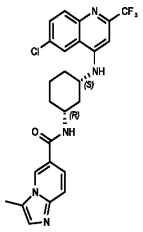
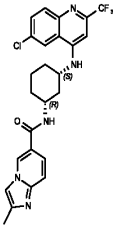
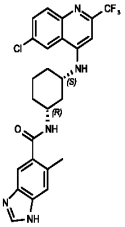
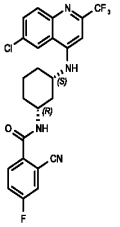
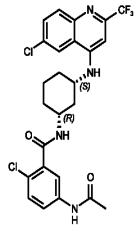
	4-264
	4-265
	4-266
	4-267
	4-268

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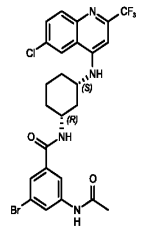
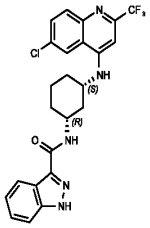
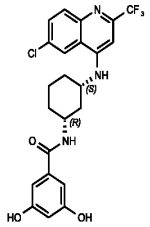
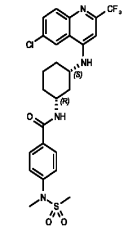
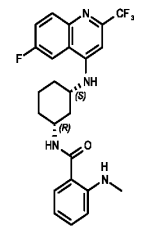
	4-269
	4-270
	4-271
	4-272
	4-273

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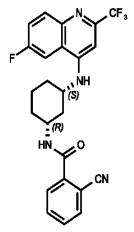
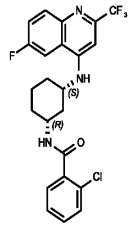
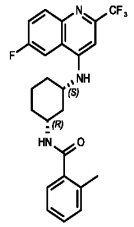
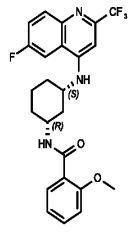
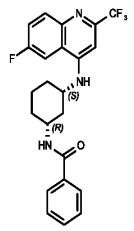
	4-274
	4-275
	4-276
	4-277
	4-278

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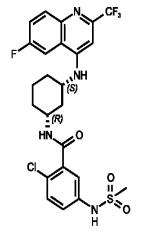
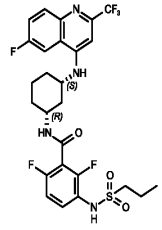
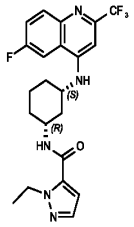
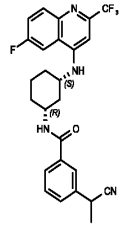
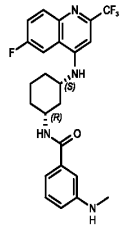
	4-279
	4-280
	4-281
	4-282
	4-283

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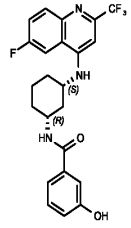
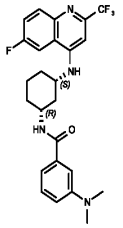
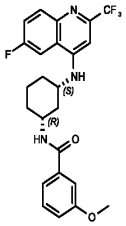
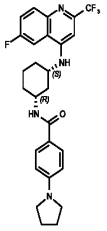
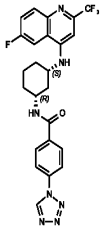
	4-284
	4-285
	4-286
	4-287
	4-288

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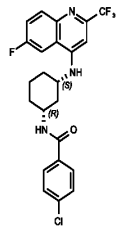
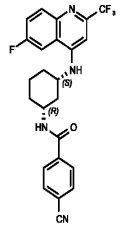
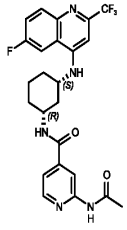
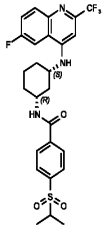
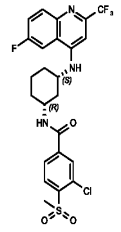
	4-289
	4-290
	4-291
	4-292
	4-293

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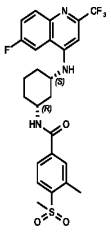
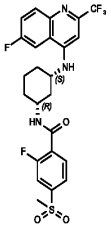
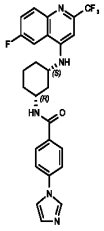
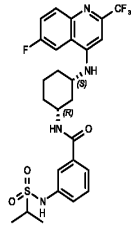
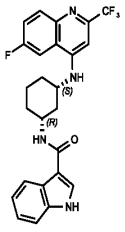
	4-294
	4-295
	4-296
	4-297
	4-298

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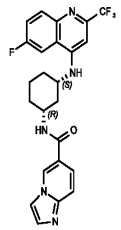
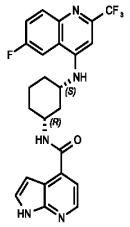
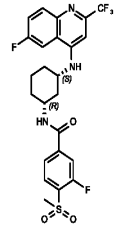
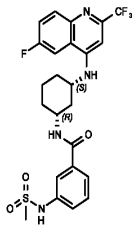
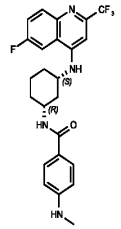
	4-299
	4-300
	4-301
	4-302
	4-303

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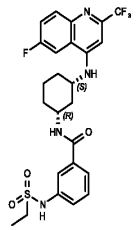
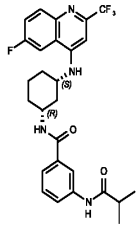
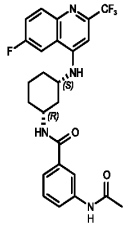
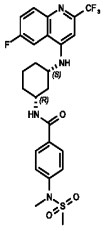
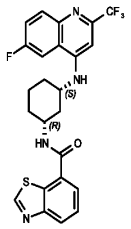
	4-304
	4-305
	4-306
	4-307
	4-308

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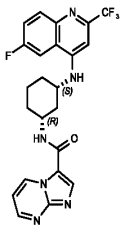
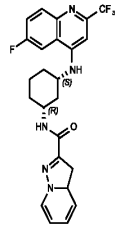
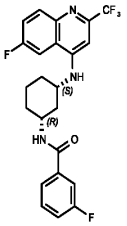
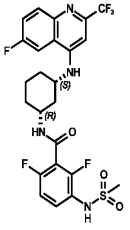
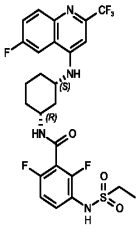
	4-309
	4-310
	4-311
	4-312
	4-313

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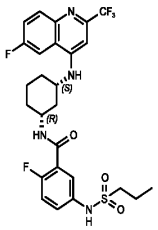
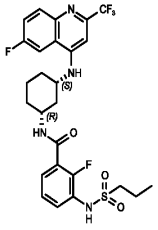
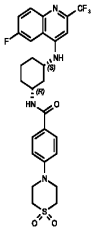
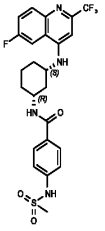
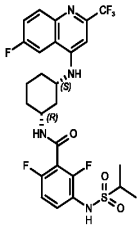
	4-314
	4-315
	4-316
	4-317
	4-318

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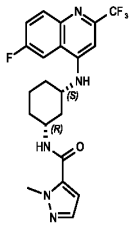
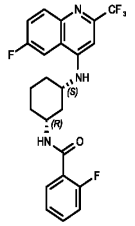
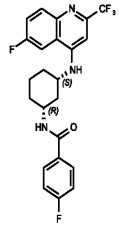
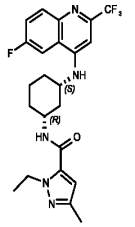
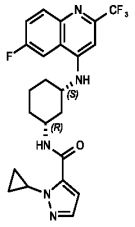
	4-319
	4-320
	4-321
	4-322
	4-323

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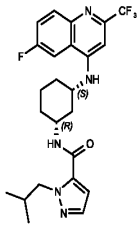
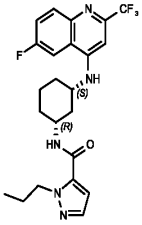
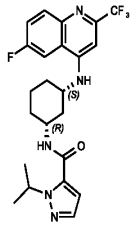
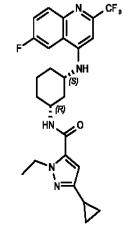
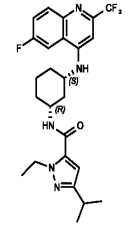
	4-324
	4-325
	4-326
	4-327
	4-328

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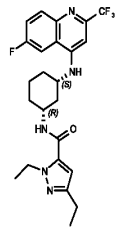
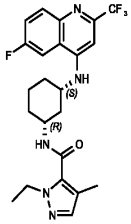
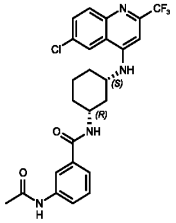
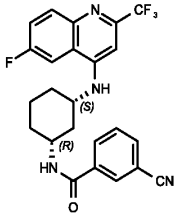
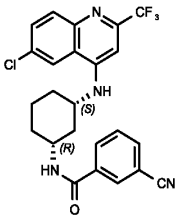
	4-329
	4-330
	4-331
	4-332
	4-333

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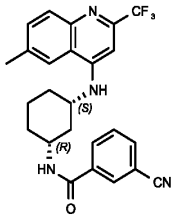
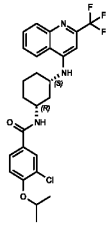
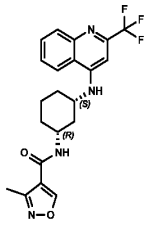
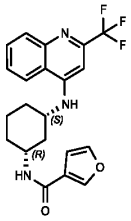
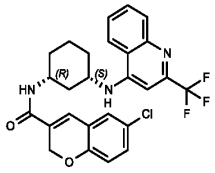
	4-334
	4-335
	4-336
	4-337
	4-338

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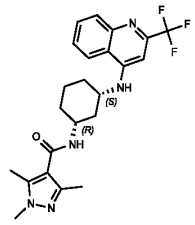
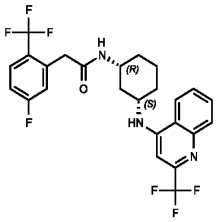
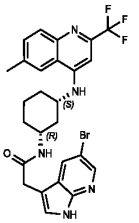
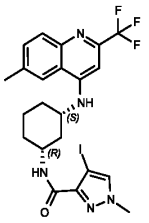
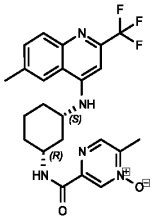
	4-339
	4-340
	4-341
	4-342
	4-343

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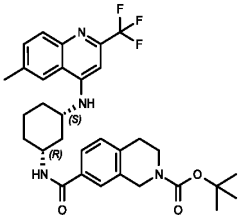
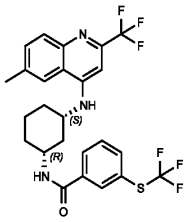
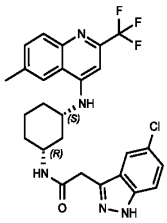
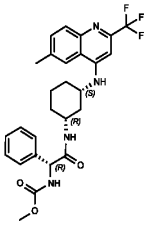
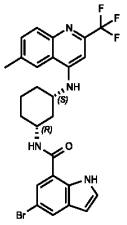
	4-344
	4-345
	4-346
	4-347
	4-348

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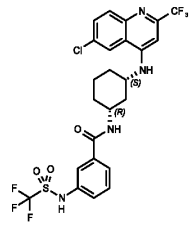
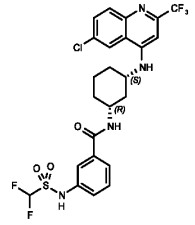
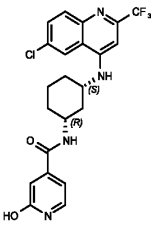
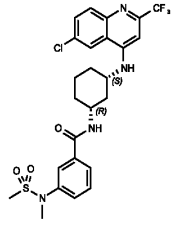
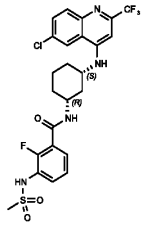
	4-349
	4-350
	4-351
	4-352
	4-353

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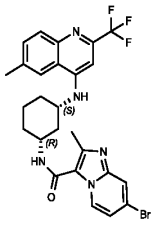
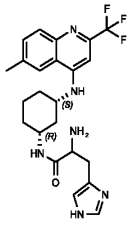
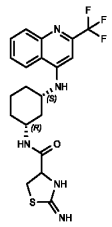
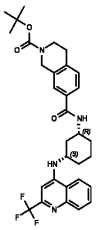
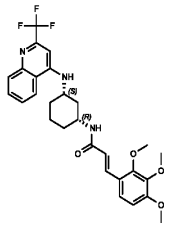
	4-354
	4-355
	4-356
	4-357
	4-358

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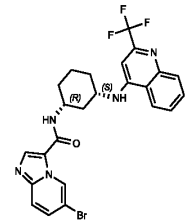
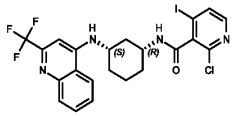
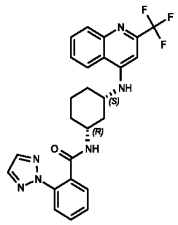
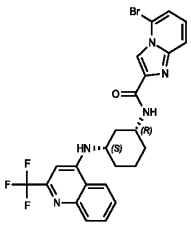
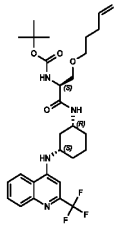
	4-359
	4-360
	4-361
	4-362
	4-363

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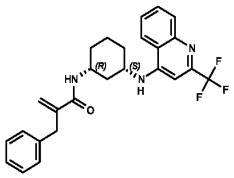
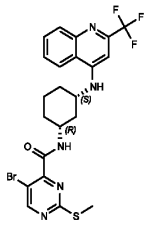
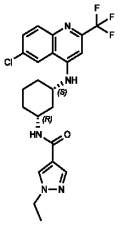
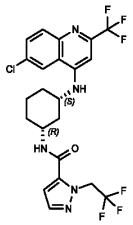
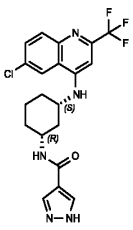
	4-364
	4-365
	4-366
	4-367
	4-368

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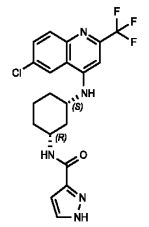
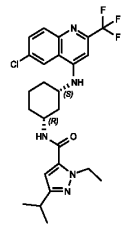
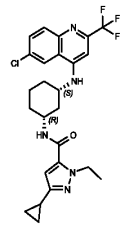
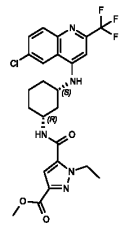
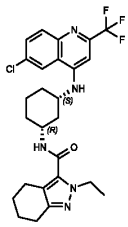
	4-369
	4-370
	4-371
	4-372
	4-373

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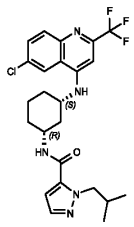
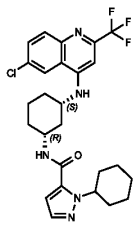
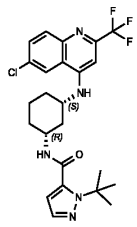
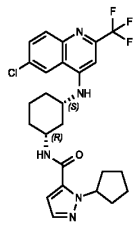
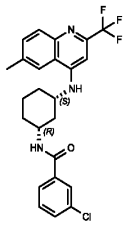
	4-374
	4-375
	4-376
	4-377
	4-378

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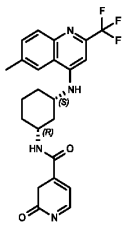
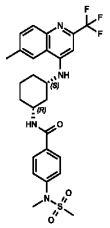
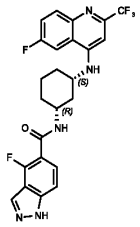
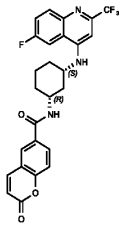
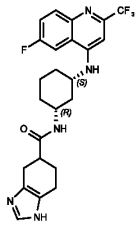
	4-379
	4-380
	4-381
	4-382
	4-383

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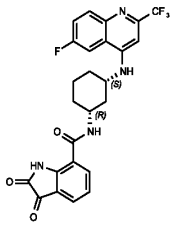
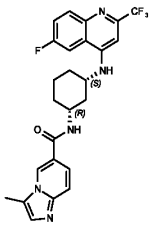
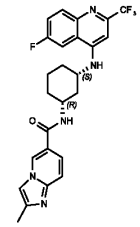
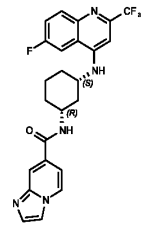
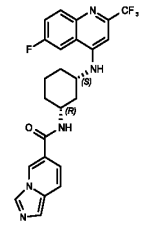
	4-384
	4-385
	4-386
	4-387
	4-388

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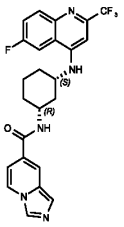
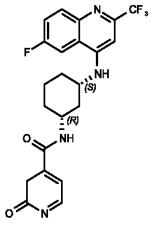
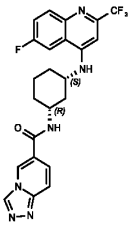
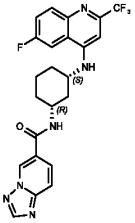
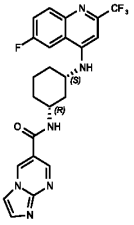
	4-389
	4-390
	4-391
	4-392
	4-393

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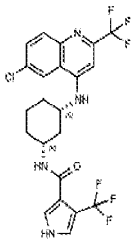
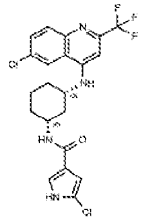
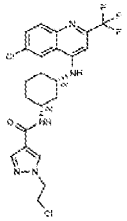
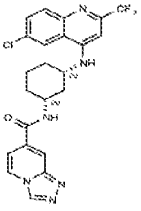
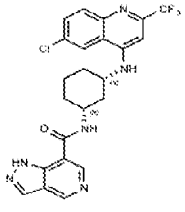
	4-394
	4-395
	4-396
	4-397
	4-398

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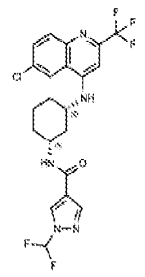
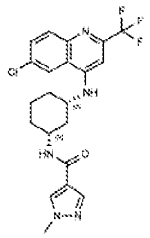
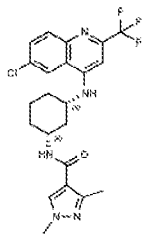
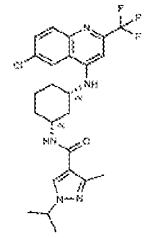
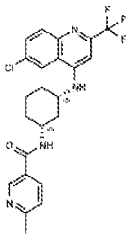
	4-399
	4-400
	4-401
	4-402
	4-403

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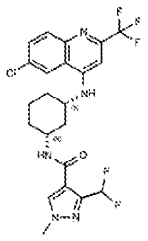
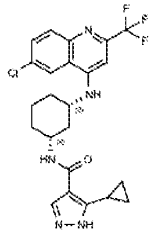
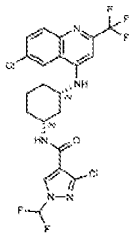
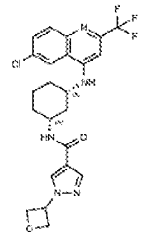
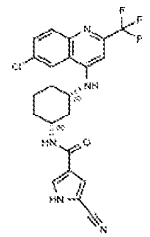
	4-404
	4-405
	4-406
	4-407
	4-408

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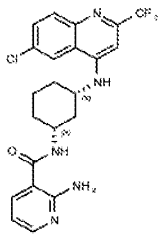
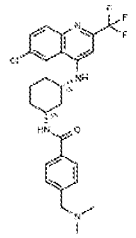
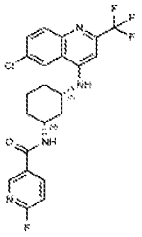
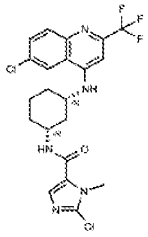
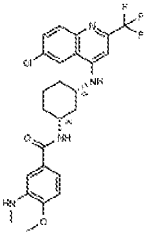
	4-409
	4-410
	4-411
	4-412
	4-413

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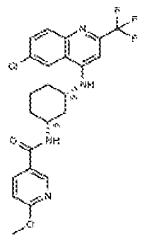
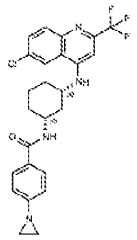
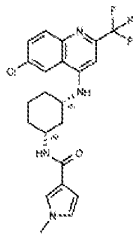
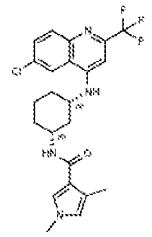
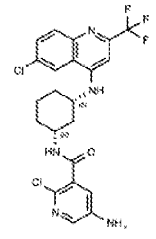
	4-414
	4-415
	4-416
	4-417
	4-418

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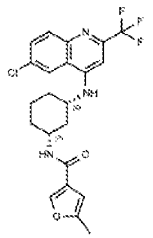
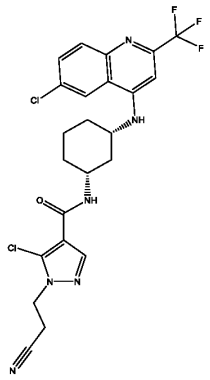
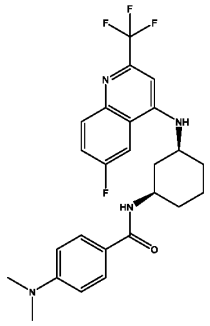
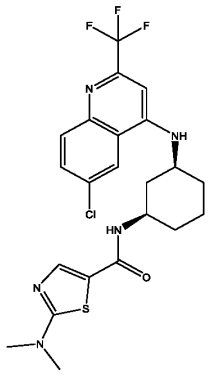
	4-419
	4-420
	4-421
	4-422

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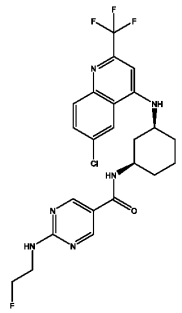
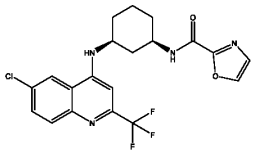
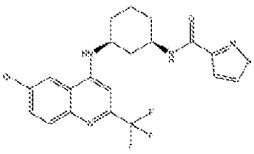
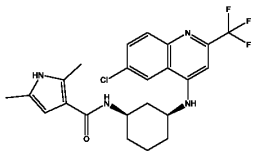
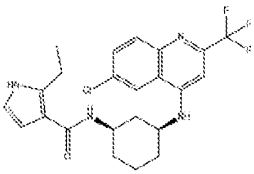
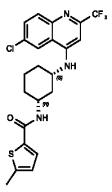
	4-423
	4-424
	4-425
	4-426
	4-427
	4-428

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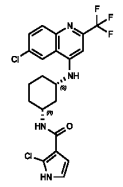
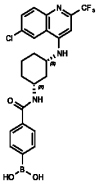
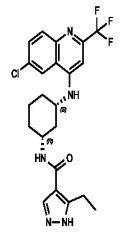
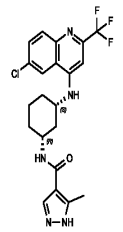
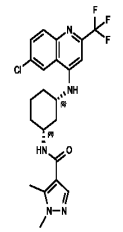
	4-429
	4-430
	4-431
	4-432
	4-433

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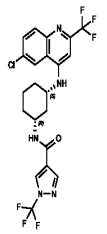
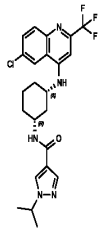
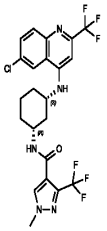
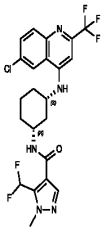
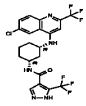
	4-434
	4-435
	4-436
	4-437
	4-438

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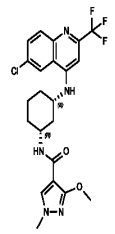
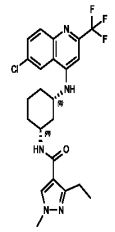
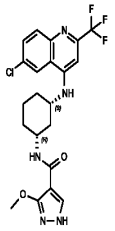
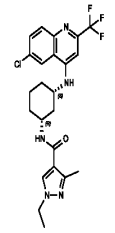
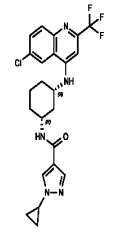
	4-439
	4-440
	4-441
	4-442
	4-443

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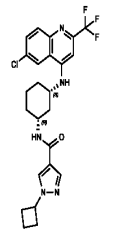
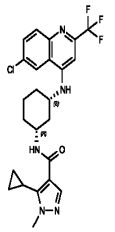
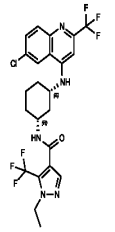
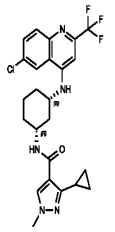
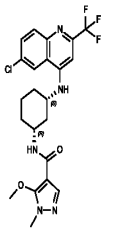
	4-444
	4-445
	4-446
	4-447
	4-448

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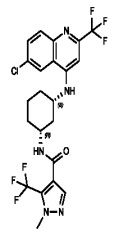
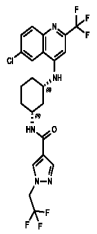
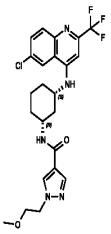
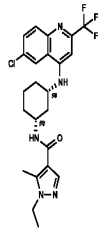
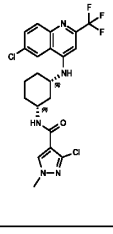
	4-449
	4-450
	4-451
	4-452
	4-453

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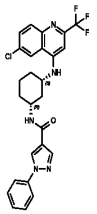
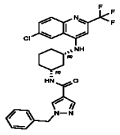
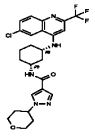
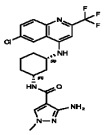
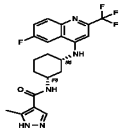
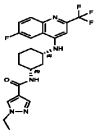
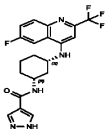
	4-454
	4-455
	4-456
	4-457
	4-458
	4-459
	4-460

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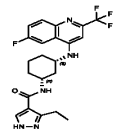
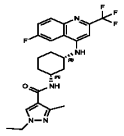
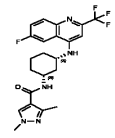
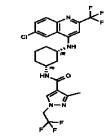
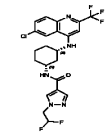
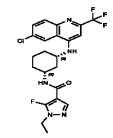
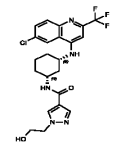
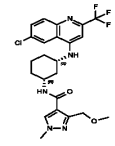
	4-461
	4-462
	4-463
	4-464
	4-465
	4-466
	4-467
	4-468

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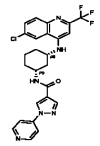
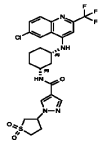
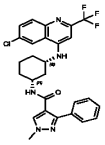
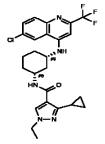
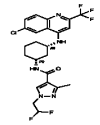
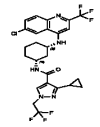
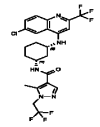
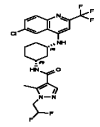
	4-469
	4-470
	4-471
	4-472
	4-473
	4-474
	4-475
	4-476

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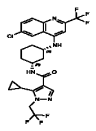
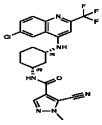
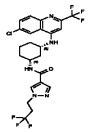
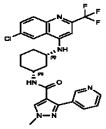
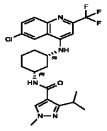
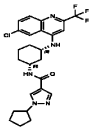
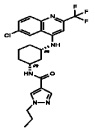
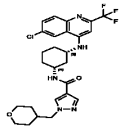
	4-477
	4-478
	4-479
	4-480
	4-481
	4-482
	4-483
	4-484

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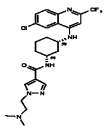
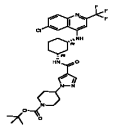
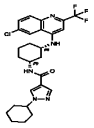
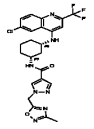
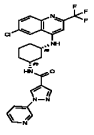
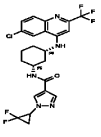
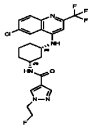
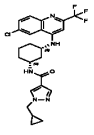
	4-485
	4-486
	4-487
	4-488
	4-489
	4-490
	4-491
	4-492

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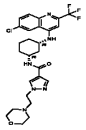
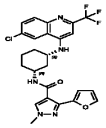
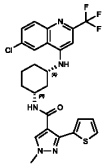
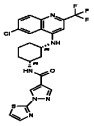
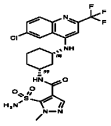
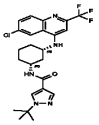
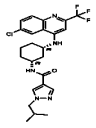
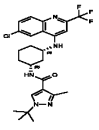
	4-493
	4-494
	4-495
	4-496
	4-497
	4-498
	4-499
	4-500

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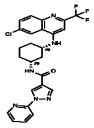
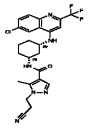
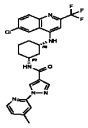
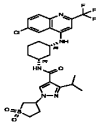
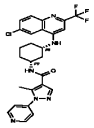
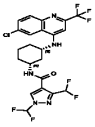
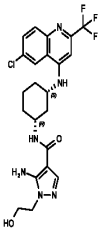
	4-501
	4-502
	4-503
	4-504
	4-505
	4-506
	4-507

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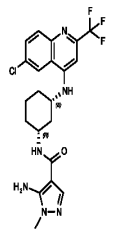
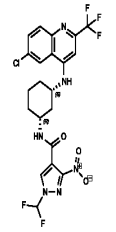
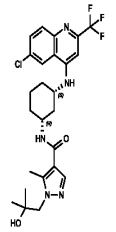
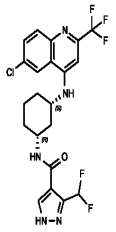
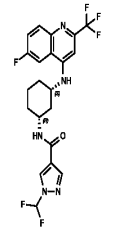
	4-508
	4-509
	4-510
	4-511
	4-512

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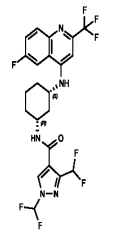
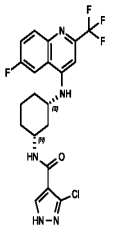
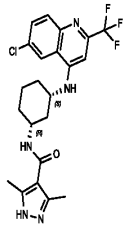
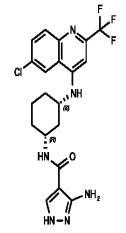
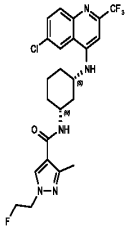
	4-513
	4-514
	4-515
	4-516
	4-517

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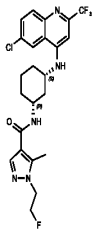
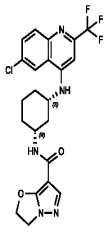
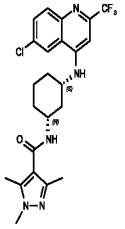
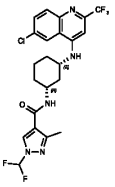
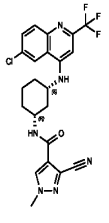
	4-518
	4-519
	4-520
	4-521
	4-522

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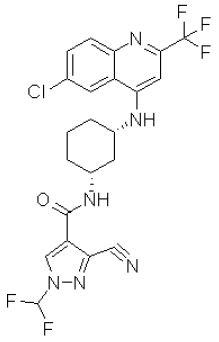
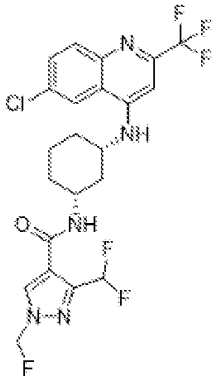
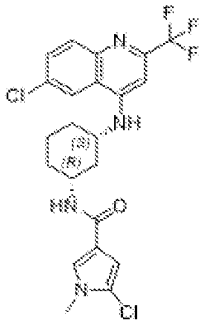
	Ex. 21
	Ex. 22
	Ex. 23

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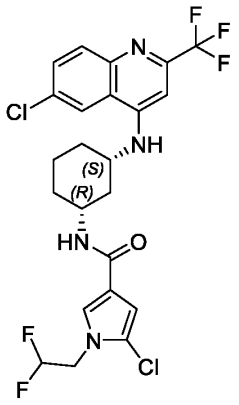
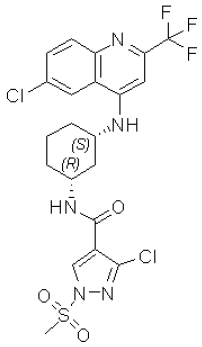
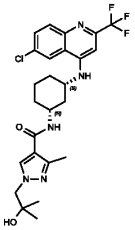
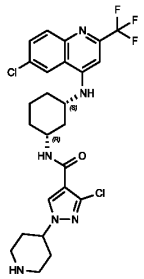
	Ex. 24
	Ex. 25
	Ex. 26
	Ex. 27

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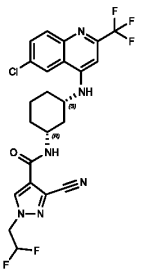
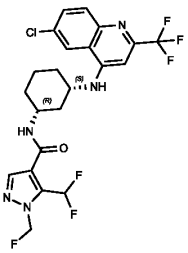
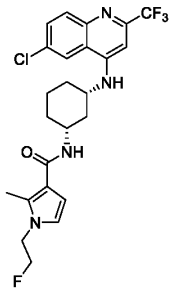
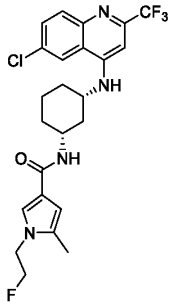
	Ex. 28
	Ex. 29
	5-1
	5-2

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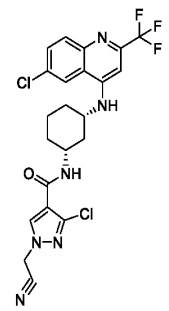
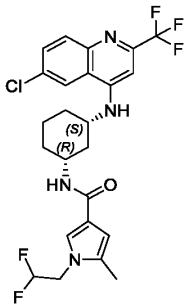
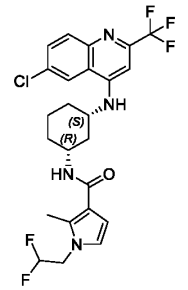
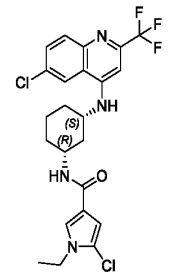
	5-3
	5-4
	5-5
	5-6

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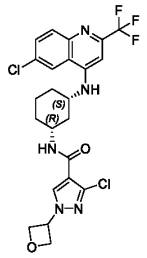
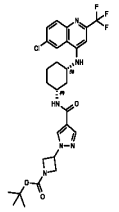
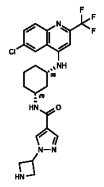
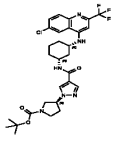
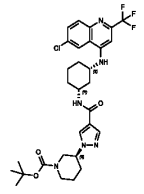
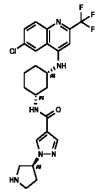
	5-7
	5-8
	5-9
	5-10
	5-11
	5-12

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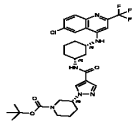
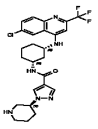
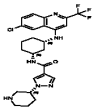
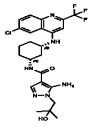
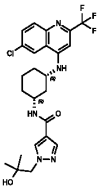
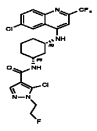
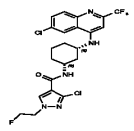
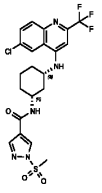
	5-13
	5-14
	5-15
	5-16
	5-17
	5-18
	5-19
	5-20

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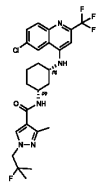
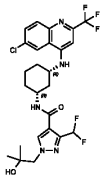
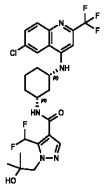
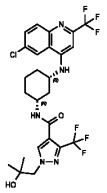
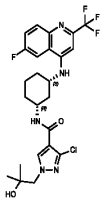
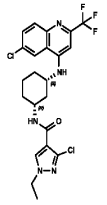
	5-21
	5-22
	5-23
	5-24
	5-25
	5-26

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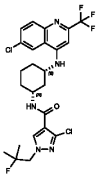
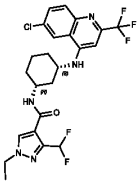
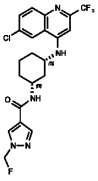
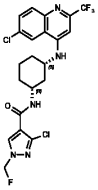
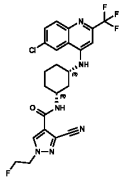
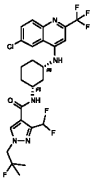
	5-27
	5-28
	5-29
	5-30
	5-31
	5-32

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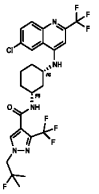
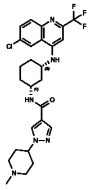
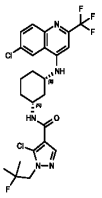
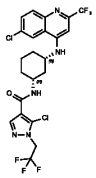
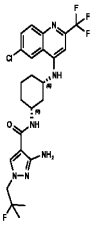
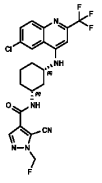
	5-33
	5-34
	5-35
	5-36
	5-37
	5-38

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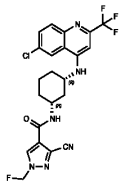
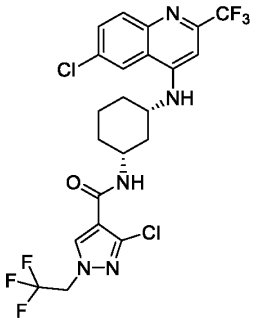
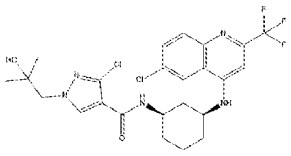
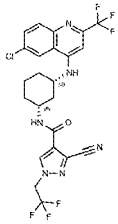
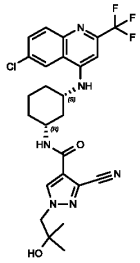
	5-39
	Ex. 30
	Ex. 31
	Ex. 32
	Ex. 33

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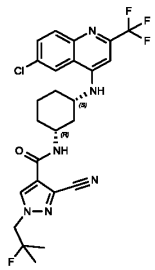
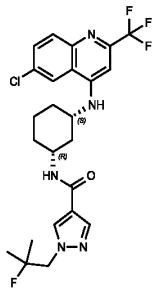
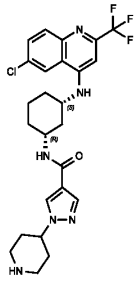
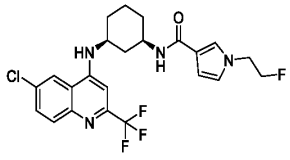
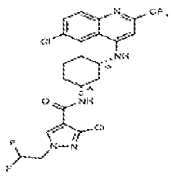
	Ex. 34
	Ex. 35
	Ex. 36
	Ex. 37
	Ex. 38

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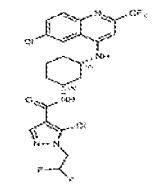
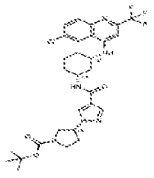
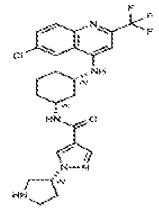
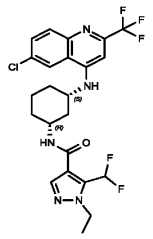
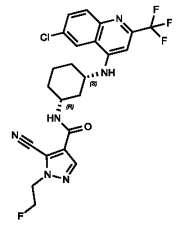
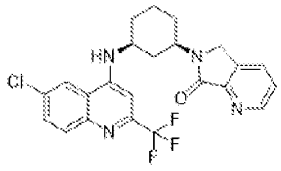
	Ex. 39
	Ex. 40
	Ex. 41
	Ex. 42
	6-1
	Ex. 43

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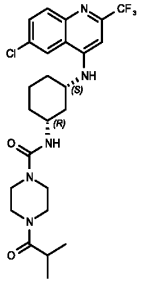
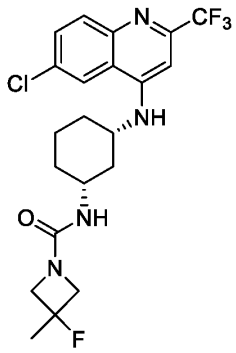
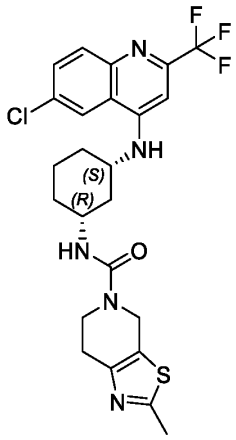
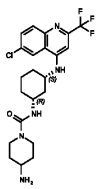
	Ex. 44
	Ex. 45
	Ex. 46
	8-1

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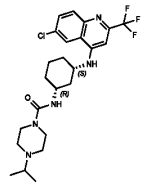
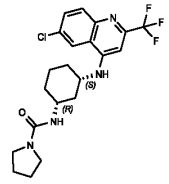
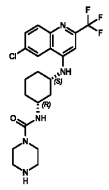
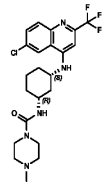
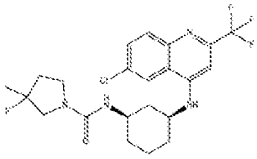
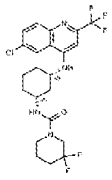
	8-2
	8-3
	8-4
	8-5
	8-6
	8-7

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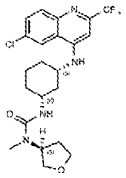
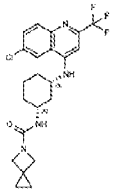
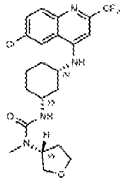
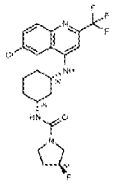
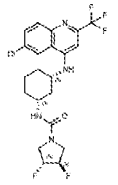
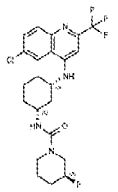
	8-8
	8-9
	8-10
	8-11
	8-12
	8-13

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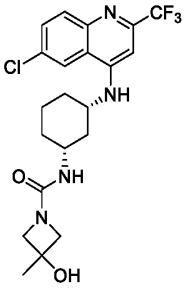
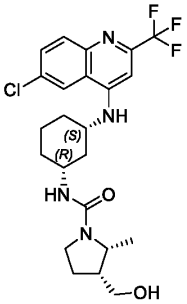
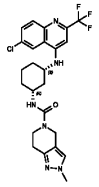
	8-14
	8-15
	8-16

In another embodiment, representative compounds of structure (I), as well as formulas (Ia) through (1f) as applicable, include, but not limited to, any one of the compounds listed below in their IUPAC names as well as a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof:

N-[(1R,3S)-3-{[8-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

4-methoxy-N-[(1R,3S)-3-{[3-(trifluoromethyl)isoquinolin-1-yl]amino}cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

4-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[7-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1R,3S)-3-{[5-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

4-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-[(6-chloro-2-methylquinolin-4-yl)amino]cyclohexyl]-4-methoxybenzamide;

N-[(1R,3S)-3-[(2-cyanoquinolin-4-yl)amino]cyclohexyl]-4-methoxybenzamide;

N-[(1R,3S)-3-{[2-(difluoromethyl)quinazolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1R,3S)-3-{[3-cyano-6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

4-methoxy-N-[(1R,3S)-3-{[6-methoxy-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinazolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1S,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1S,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1R,3R)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1R,3R)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinazolin-4-yl]amino}cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[5-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[7-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

methyl 4-{[(1S,3R)-3-(4-methoxybenzamido)cyclohexyl]amino}-2-(trifluoromethyl)quinoline-8-carboxylate;

4-methoxy-N-[(1R,3S)-3-[(naphthalen-1-yl)amino]cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[3-(trifluoromethyl)naphthalen-1-yl]amino}cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-5-yl]amino}cyclohexyl]benzamide;

4-methoxy-N-[(1R,3S)-3-{[3-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[2-(difluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxybenzamide;

2-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-(dimethylamino)-2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-cyano-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

methyl 3-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}benzoate;

2-cyano-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-cyano-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2,2-dimethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

4-chloro-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-cyano-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-fluoro-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-methoxy-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-methyl-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methoxybenzamide;

6-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(morpholine-4-carbonyl)benzamide;

3-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methylbenzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-4-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-2-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclopropanecarboxamide;

2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

3-methanesulfonamido-N-[(1R,3S)-3-[(2-methoxyquinolin-4-yl)amino]cyclohexyl]benzamide;

3-phenyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

3-(dimethylamino)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-(dimethylamino)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-(dimethylamino)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-ethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-ethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-acetamido-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-ethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

methyl 4-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}benzoate;

4-acetamido-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-(4-methylpiperazin-1-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

6-(dimethylamino)-2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

2-(methylamino)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-(methylamino)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-(methylamino)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-(morpholin-4-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4H,5H,6H,7H-pyrazolo[1,5-a]pyridine-2-carboxamide;

2-(5-cyano-1-methyl-1H-pyrrol-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

1-(pyrazin-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclopropane-1-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,5-a]pyridine-1-carboxamide;

4-benzyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]morpholine-3-carboxamide;

2-[2-(difluoromethoxy)-6-fluorophenyl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

2-(5-methoxy-2-methyl-1H-indol-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

5-cyano-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-indazole-3-carboxamide;

3-[(4-methoxyphenyl)methoxy]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2-oxazole-5-carboxamide;

4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

7-(benzyloxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-3-carboxamide;

tert-butyl 3-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1-oxa-2,7-diazaspiro[4.5]dec-2-ene-7-carboxylate;

2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide;

4-propyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2,3-thiadiazole-5-carboxamide;

tert-butyl (3S,4R)-3-(thiophen-3-yl)-4-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}pyrrolidine-1-carboxylate;

4-[(quinolin-2-yl)methoxy]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2,6-difluoro-3-(propane-1-sulfonamido)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

5-benzoyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dihydro-1H-pyrrolizine-1-carboxamide;

2,4-dichloro-3-cyano-5-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

1-[(4-methoxyphenyl)methyl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

3-(2-chloro-6-fluorophenyl)-5-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2-oxazole-4-carboxamide;

2-benzyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dihydro-1H-isoindole-4-carboxamide;

ethyl 1-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}cyclobutane-1-carboxylate;

1-ethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

3,6-difluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-2-carboxamide;

2-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-chromene-6-carboxamide;

4-methyl-2-(pyridin-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-thiazole-5-carboxamide;

5-(trifluoromethyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-3-carboxamide;

6-(2-methoxyphenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

2-methoxy-4-(trifluoromethyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-thiazole-5-carboxamide;

6-(oxan-4-yloxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-2-carboxamide;

2-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H,2H,3H-pyrido[2,3-b][1,4]thiazine-7-carboxamide;

2-methyl-3-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,4-dihydro-2H-1,4-benzoxazine-6-carboxamide;

5-oxo-1-phenyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrrolidine-2-carboxamide;

5-(pyridin-3-yloxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]furan-2-carboxamide;

3-methyl-4-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,4-dihydroquinazoline-7-carboxamide;

1,4-dimethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-2-carboxamide;

2,6,6-trimethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]bicyclo[3.1.1]heptane-3-carboxamide;

1-(2,2-difluoroethyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-3-carboxamide;

tert-butyl N-methyl-N-[(S)-phenyl({[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl})methyl]carbamate;

2-(cyclobutylformamido)-2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrazine-2-carboxamide;

1-(3-methoxyphenyl)-5-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrrolidine-3-carboxamide;

1-methanesulfonyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]piperidine-4-carboxamide;

N-(2,6-difluorophenyl)-N'-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]ethanediamide;

N-[3-({[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}methyl)phenyl]benzamide;

1-(2,4-dichlorophenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclobutane-1-carboxamide;

3-(5-bromo-2-fluorophenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

1-(3-fluorophenyl)-5-(trifluoromethyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

1-[(4-fluorophenyl)methyl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-3-carboxamide;

5-chloro-1-phenyl-3-(trifluoromethyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

(2R,3R)-2-(2-methoxyphenyl)-5-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]oxolane-3-carboxamide;

5-(thiophen-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

1-(4-chlorophenyl)-5-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

4-(4-ethylphenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]butanamide;

3-(4-chloro-3-fluorophenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

(2S)-3-phenyl-2-[(pyrazin-2-yl)formamido]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

2-chloro-6-fluoro-3-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

(2R)-2-(3-acetamidopropanamido)-3-(1H-imidazol-5-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4,5,6,7-tetrahydro-1H-1,3-benzodiazole-6-carboxamide;

3-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-benzothiophene-2-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-pyrazolo[3,4-b]pyridine-3-carboxamide;

3-tert-butyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

1-methyl-3-(2-methylpropyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

3-(2-chlorophenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

1-[5-(trifluoromethyl)pyridin-2-yl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]piperidine-4-carboxamide;

2-(1H-indol-1-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

2-(morpholin-4-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-4-carboxamide;

2-(thiophen-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

1-(4-methylbenzenesulfonyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrole-3-carboxamide;

6-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-b]pyridazine-2-carboxamide;

2-[5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

6-oxo-2-phenyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,6-dihydropyrimidine-4-carboxamide;

2-(3-oxo-3,4-dihydro-2H-1,4-benzoxazin-4-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

7-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-benzofuran-2-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,6-naphthyridine-2-carboxamide;

1-(2-chlorobenzoyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]piperidine-4-carboxamide;

5-(furan-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2-oxazole-3-carboxamide;

2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-indazole-3-carboxamide;

1-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4,5,6,7-tetrahydro-1H-indazole-3-carboxamide;

2-[(2,5-dichlorophenyl)formamido]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

(1R,4S)-4,7,7-trimethyl-3-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-oxabicyclo[2.2.1]heptane-1-carboxamide;

2-methyl-4-(2-methylbenzamido)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,4-dihydro-2H-pyran-6-carboxamide;

4-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4H-chromene-3-carboxamide;

4-fluoro-3-(trifluoromethoxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-phenoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

5-chloro-2-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-4-carboxamide;

3-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-benzofuran-2-carboxamide;

3-(cyclopropylmethoxy)-4-(difluoromethoxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-chloro-4-(4-methylpiperazin-1-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

(1r,4r)-4-[(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)methyl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclohexane-1-carboxamide;

2-(2,3-dimethylphenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

7-methoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,4-dihydro-2H-1-benzopyran-3-carboxamide;

3,4-dichloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2-thiazole-5-carboxamide;

3,3-dimethoxy-1-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclobutane-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(2-methylpropanamido)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methoxybenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-4-methyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-propyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(methylamino)benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-4-carboxamide;

4-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-(1H-imidazol-1-yl)-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(pyrrolidin-1-yl)benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(1H-1,2,3,4-tetrazol-1-yl)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclobutyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrazolo[1,5-a]pyridine-2-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrimidine-3-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-3-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dioxo-2,3-dihydro-1H-indole-7-carboxamide;

2-acetamido-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-4-carboxamide;

3-(1-cyanoethyl)-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-benzothiazole-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-3-phenyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclopropyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-phenyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-diethyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-3-methyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(propan-2-yl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrazole-5-carboxamide;

3-acetamido-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-hydroxy-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(2-methylpropanamido)benzamide

3-methanesulfonamido-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(methylamino)benzamide;

3-(dimethylamino)-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-(methylamino)benzamide;

2-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonylbenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-1H-pyrazole-5-carboxamide;

2-chloro-4-methanesulfonyl-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

1-ethyl-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-(methylamino)benzamide;

2-cyano-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-methoxy-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-chloro-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-cyanobenzamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclohexanecarboxamide;

1-ethenyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-oxabicyclo[2.2.2]octane-4-carboxamide;

3-(2-oxopyrrolidin-1-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

tert-butyl (3S)-3-methyl-3-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}propanoate;

3-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}phenyl propanoate;

4-methyl-2-propyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-1,3-benzodiazole-6-carboxamide;

(1R,2R)-2-(2-fluorophenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclopropane-1-carboxamide;

1-tert-butyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-1,2,3-triazole-4-carboxamide;

4-butanamido-3-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-(2-fluorophenyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

5-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

2-(pyridin-4-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-1,3-benzodiazole-6-carboxamide;

3-(propan-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

1-cyano-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]cyclopropane-1-carboxamide;

5-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-benzofuran-2-carboxamide;

2-(1,2-benzoxazol-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrimidine-3-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-1,3-benzodioxole-4-carboxamide;

2-acetamido-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-4-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4,5,6,7-tetrahydro-1-benzothiophene-2-carboxamide;

2-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dihydropyridine-4-carboxamide;

2-chloro-4-methanesulfonyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-chloro-1-(3-chloropyridin-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

1-(pyridin-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

4-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-3-carboxamide;

3-(1H-1,2,4-triazol-1-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-indazole-5-carboxamide;

4-(3-methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-(4-chlorophenyl)-2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

1,3-dimethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-thieno[2,3-c]pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-benzothiazole-7-carboxamide;

3-(1-cyanoethyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4H-thieno[3,2-b]pyrrole-5-carboxamide;

3-methyl-4-oxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3H,4H-imidazo[4,3-d][1,2,3,5]tetrazine-8-carboxamide;

6-fluoro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,4-dihydro-2H-1-benzopyran-2-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrazolo[1,5-a]pyridine-2-carboxamide;

2,3-dioxo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dihydro-1H-indole-7-carboxamide;

1-phenyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrole-2-carboxamide;

6-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-benzothiophene-2-carboxamide;

3-chloro-2-iodo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-cyanobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(pyrrolidin-1-yl)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(methylamino)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-hydroxybenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(dimethylamino)benzamide;

4-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-acetamidopyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(1-cyanoethyl)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(methylamino)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4,5,6,7-tetrahydro-1H-1,3-benzodiazole-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dioxo-2,3-dihydro-1H-indole-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-benzothiazole-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrimidine-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-fluoro-2H-indazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(propane-2-sulfonamido)benzamide;

2-(1-methyl-1H-indol-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

2,6-dimethoxy-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrimidine-4-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2,3-thiadiazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,6-difluoro-3-(propane-2-sulfonamido)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,6-difluoro-3-methanesulfonamidobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-ethanesulfonamido-2,6-difluorobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-fluoro-5-(propane-1-sulfonamido)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrazolo[1,5-a]pyridine-2-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(1H-imidazol-1-yl)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(1H-1,2,3,4-tetrazol-1-yl)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-fluorobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonamidobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-ethanesulfonamidobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrimidine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-[1,2,4]triazolo[1,5-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,5-a]pyridine-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,5-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-7-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-oxo-2H-chromene-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-fluoro-3-(propane-1-sulfonamido)benzamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H,4H,6H,7H-pyrano[4,3-c]pyrazole-3-carboxamide;

2-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-benzothiazole-6-carboxamide;

2-(cyclohexyloxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

5-chloro-3-(difluoromethyl)-1-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

2-acetamido-3-(1H-indol-3-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-fluoro-3-methanesulfonamidobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-acetamido-5-methoxybenzamide;

5-bromo-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-cyanobenzamide;

4-bromo-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-cyanobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-benzothiazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-pyrazolo[4,3-b]pyridine-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methylimidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methyl-1H-1,3-benzodiazole-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-cyano-4-fluorobenzamide;

2-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-acetamidobenzamide;

3-bromo-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-acetamidobenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-indazole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,5-dihydroxybenzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(N-methylmethanesulfonamido)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-(methylamino)benzamide;

2-cyano-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-chloro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methylbenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methoxybenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-chloro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methanesulfonamidobenzamide;

2,6-difluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(propane-1-sulfonamido)benzamide;

1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

3-(1-cyanoethyl)-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(methylamino)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-hydroxybenzamide;

3-(dimethylamino)-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methoxybenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(pyrrolidin-1-yl)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(1H-1,2,3,4-tetrazol-1-yl)benzamide;

4-chloro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-cyano-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-acetamido-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(propane-2-sulfonyl)benzamide;

3-chloro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonylbenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonyl-3-methylbenzamide;

2-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonylbenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(1H-imidazol-1-yl)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(propane-2-sulfonamido)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-3-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrolo[2,3-b]pyridine-4-carboxamide;

3-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonylbenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methanesulfonamidobenzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(methylamino)benzamide;

3-ethanesulfonamido-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(2-methylpropanamido)benzamide;

3-acetamido-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(N-methylmethanesulfonamido)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-benzothiazole-7-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrimidine-3-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3H,3aH-pyrazolo[1,5-a]pyridine-2-carboxamide;

3-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2,6-difluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methanesulfonamidobenzamide;

3-ethanesulfonamido-2,6-difluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

2-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(propane-1-sulfonamido)benzamide;

2-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(propane-1-sulfonamido)benzamide;

4-(1,1-dioxo-1λ^6-thiomorpholin-4-yl)-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methanesulfonamidobenzamide;

2,6-difluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(propane-2-sulfonamido)benzamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrazole-5-carboxamide;

2-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

4-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-1H-pyrazole-5-carboxamide;

1-cyclopropyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-methylpropyl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-propyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(propan-2-yl)-1H-pyrazole-5-carboxamide;

3-cyclopropyl-1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(propan-2-yl)-1H-pyrazole-5-carboxamide;

1,3-diethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methyl-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-acetamidobenzamide;

3-cyano-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyanobenzamide;

3-cyano-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-chloro-4-(propan-2-yloxy)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

3-methyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2-oxazole-4-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]furan-3-carboxamide;

6-chloro-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-chromene-3-carboxamide;

1,3,5-trimethyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

2-[5-fluoro-2-(trifluoromethyl)phenyl]-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

2-{5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl}-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

4-iodo-1-methyl-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-3-carboxamide;

2-methyl-5-{[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}pyrazin-1-ium-1-olate;

tert-butyl 7-{[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-[(trifluoromethyl)sulfanyl]benzamide;

2-(5-chloro-2H-indazol-3-yl)-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]acetamide;

methyl N-[(R)-{[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}(phenyl)methyl]carbamate;

5-bromo-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-indole-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(trifluoromethanesulfonamido)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(difluoromethanesulfonamido)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-hydroxypyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(N-methylmethanesulfonamido)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-fluoro-3-methanesulfonamidobenzamide;

7-bromo-2-methyl-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-3-carboxamide;

2-amino-3-(1H-imidazol-5-yl)-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

2-amino-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4,5-dihydro-1,3-thiazole-4-carboxamide;

tert-butyl 7-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1,2,3,4-tetrahydroisoquinoline-2-carboxylate;

(2E)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(2,3,4-trimethoxyphenyl)prop-2-enamide;

6-bromo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-3-carboxamide;

2-chloro-4-iodo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

2-(2H-1,2,3-triazol-2-yl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

5-bromo-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-2-carboxamide;

tert-butyl N-[(1S)-2-(pent-4-en-1-yloxy)-1-{[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}ethyl]carbamate;

2-benzyl-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]prop-2-enamide;

5-bromo-2-(methylsulfanyl)-N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrimidine-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-3-(propan-2-yl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyclopropyl-1-ethyl-1H-pyrazole-5-carboxamide;

methyl 5-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1-ethyl-1H-pyrazole-3-carboxylate;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-ethyl-4,5,6,7-tetrahydro-2H-indazole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-methylpropyl)-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclohexyl-1H-pyrazole-5-carboxamide;

1-tert-butyl-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclopentyl-1H-pyrazole-5-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-oxo-2,3-dihydropyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-methyl-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(N-methylmethanesulfonamido)benzamide;

4-fluoro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-indazole-5-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-oxo-2H-chromene-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4,5,6,7-tetrahydro-1H-1,3-benzodiazole-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,3-dioxo-2,3-dihydro-1H-indole-7-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methylimidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methylimidazo[1,2-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyridine-7-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,5-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,5-a]pyridine-7-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-oxo-2,3-dihydropyridine-4-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-[1,2,4]triazolo[4,3-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-[1,2,4]triazolo[1,5-a]pyridine-6-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]imidazo[1,2-a]pyrimidine-6-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(trifluoromethyl)-1H-pyrrole-3-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-chloroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-[1,2,4]triazolo[4,3-a]pyridine-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H-pyrazolo[4,3-c]pyridine-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(difluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-1-(propan-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-6-methylpyridine-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyclopropyl-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(difluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(oxetan-3-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyano-1H-pyrrole-3-carboxamide;

2-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-[(dimethylamino)methyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-6-fluoropyridine-3-carboxamide;

2-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-imidazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methoxy-3-(methylamino)benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-6-methoxypyridine-3-carboxamide;

4-(aziridin-1-yl)-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrrole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,4-dimethyl-1H-pyrrole-3-carboxamide;

5-amino-2-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyridine-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methylfuran-3-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-cyanoethyl)-1H-pyrazole-4-carboxamide;

4-(dimethylamino)-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]benzamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-(dimethylamino)-1,3-thiazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-[(2-fluoroethyl)amino]pyrimidine-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-oxazole-2-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,2-thiazole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2,5-dimethyl-1H-pyrrole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-ethyl-1H-pyrrole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methylthiophene-2-carboxamide;

2-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrrole-3-carboxamide;

(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}phenyl)boronic acid;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-ethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,5-dimethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(propan-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methoxy-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-ethyl-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methoxy-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclopropyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclobutyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyclopropyl-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyclopropyl-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methoxy-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-5-methyl-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-phenyl-1H-pyrazole-4-carboxamide;

1-benzyl-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(oxan-4-yl)-1H-pyrazole-4-carboxamide;

3-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methyl-1H-pyrazole-4-carboxamide;

1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

5-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

1-ethyl-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-5-fluoro-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxyethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(methoxymethyl)-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(1,1-dioxo-1λ^6-thiolan-3-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-3-phenyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyclopropyl-1-ethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyclopropyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-5-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyclopropyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyano-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(3,3,3-trifluoropropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-3-(pyridin-3-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-3-(propan-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclopentyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-propyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[(oxan-4-yl)methyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[2-(dimethylamino)ethyl]-1H-pyrazole-4-carboxamide;

tert-butyl 4-(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-cyclohexyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(pyridin-3-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluorocyclopropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(cyclopropylmethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[2-(morpholin-4-yl)ethyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(furan-2-yl)-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-3-(thiophen-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(1,3-thiazol-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-5-sulfamoyl-1H-pyrazole-4-carboxamide;

1-tert-butyl-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-methylpropyl)-1H-pyrazole-4-carboxamide;

1-tert-butyl-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(pyridin-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-cyanoethyl)-5-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(4-methylpyridin-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(1,1-dioxo-1λ^6-thiolan-3-yl)-3-(propan-2-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methyl-1-(pyridin-4-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3-bis(difluoromethyl)-1H-pyrazole-4-carboxamide;

5-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxyethyl)-1H-pyrazole-4-carboxamide;

5-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(difluoromethyl)-3-nitro-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-5-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(difluoromethyl)-1H-pyrazole-4-carboxamide;

1-(difluoromethyl)-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

1,3-bis(difluoromethyl)-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,5-dimethyl-1H-pyrazole-4-carboxamide;

5-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-5-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2H,3H-pyrazolo[3,2-b][1,3]oxazole-7-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1,3,5-trimethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(difluoromethyl)-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methanesulfonamidobenzamide;

2-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrimidine-5-carboxamide;

N-[(1R,3S)-3-{[2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]propanamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methoxy-1-methyl-1H-imidazole-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-6-[(2-fluoroethyl)amino]pyridine-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-methyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-2-methyl-1H-pyrrole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-5-methyl-1H-pyrrole-3-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-cyanoethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-5-methyl-1H-pyrrole-3-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-2-methyl-1H-pyrrole-3-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-1H-pyrrole-3-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(oxetan-3-yl)-1H-pyrazole-4-carboxamide;

tert-butyl 3-(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1H-pyrazol-1-yl)azetidine-1-carboxylate;

1-(azetidin-3-yl)-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1H-pyrazole-4-carboxamide;

tert-butyl (3S)-3-(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate;

tert-butyl (3S)-3-(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[(3S)-pyrrolidin-3-yl]-1H-pyrazole-4-carboxamide;

tert-butyl (3R)-3-(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1H-pyrazol-1-yl)piperidine-1-carboxylate;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[(3S)-piperidin-3-yl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[(3R)-piperidin-3-yl]-1H-pyrazole-4-carboxamide;

5-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methanesulfonyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoro-2-methylpropyl)-3-methyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(difluoromethyl)-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(difluoromethyl)-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-fluoro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-ethyl-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(difluoromethyl)-1-ethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(fluoromethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(fluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(2-fluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(difluoromethyl)-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoro-2-methylpropyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(1-methylpiperidin-4-yl)-1H-pyrazole-4-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

3-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyano-1-(fluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(fluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(difluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(difluoromethyl)-1-(fluoromethyl)-1H-pyrazole-4-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methyl-1H-pyrrole-3-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-1H-pyrrole-3-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-methanesulfonyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-3-methyl-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(difluoromethyl)-1-(fluoromethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyano-1-(2-fluoroethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(2-hydroxy-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-cyano-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2-fluoroethyl)-1H-pyrrole-3-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide;

3-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide;

tert-butyl (3R)-3-(4-{[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]carbamoyl}-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-[(3R)-pyrrolidin-3-yl]-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-(difluoromethyl)-1-ethyl-1H-pyrazole-4-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-cyano-1H-pyrazole-4-carboxamide;

6-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5H,6H,7H-pyrrolo[3,4-b]pyridin-7-one;

4-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]piperidine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(propan-2-yl)piperazine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrrolidine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]piperazine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-methylpiperazine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-fluoro-3-methylpyrrolidine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,3-difluoropiperidine-1-carboxamide;

1-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-3-[(3R)-oxolan-3-yl]urea;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5-azaspiro[2.3]hexane-5-carboxamide;

1-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-methyl-3-[(3S)-oxolan-3-yl]urea;

(3S)-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-fluoropyrrolidine-1-carboxamide;

(3R,4R)-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3,4-difluoropyrrolidine-1-carboxamide;

(3S)-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-fluoropiperidine-1-carboxamide;

5-chloro-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-1-(propan-2-yl)-1H-pyrrole-3-carboxamide;

(2R,3R)-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-(hydroxymethyl)-2-methylpyrrolidine-1-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methyl-2H,4H,5H,6H,7H-pyrazolo[4,3-c]pyridine-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-2-methyl-4H,5H,6H,7H-[1,3]thiazolo[5,4-c]pyridine-5-carboxamide;

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-4-(2-methylpropanoyl)piperazine-1-carboxamide; and

N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-3-fluoro-3-methylazetidine-1-carboxamide.

In certain embodiments, the invention provides a pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable carrier, diluent, or excipient. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which can be in the form of an ampoule, capsule, sachet, paper, or other container. When the active compound is mixed with a carrier, or when the carrier serves as a diluent, it can be solid, semi-solid, or liquid material that acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid carrier, for example contained in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatin, lactose, terra alba, sucrose, dextrin, magnesium carbonate, sugar, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid, or lower alkyl ethers of cellulose,

silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose, and polyvinylpyrrolidone. Similarly, the carrier or diluent can include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

As used herein, the term "pharmaceutical composition" refers to a composition containing one or more of the compounds described herein, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof, formulated with a pharmaceutically acceptable carrier, which can also include other additives, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); for administration to a pediatric subject (*e.g.*, solution, syrup, suspension, elixir, powder for reconstitution as suspension or solution, dispersible/effervescent tablet, chewable tablet, lollipop, freezer pops, troches, oral thin strips, orally disintegrating tablet, orally disintegrating strip, and sprinkle oral powder or granules); or in any other formulation described herein, including spray dry dispersions (e.g., a single-phase, amorphous molecular dispersion of a compound as described herein in a polymer matrix). Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington: The Science and Practice of Pharmacy, 21st Ed., Gennaro, Ed., Lippencott Williams & Wilkins (2005) and in The United States Pharmacopeia: The National Formulary (USP 36 NF31), published in 2013.

In certain embodiments, the invention provides a pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, is in an amorphous form. In other embodiments the compound, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, is

micronized. In still other embodiments the compound, or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, is crystalline.

In certain embodiments, the invention provides a pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, wherein the compound, or the pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, has a distribution of particle sizes. For example, in some embodiments a D_{50} particle size distribution of the compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, ranges from about 500 nm to about 500 μm. In other embodiments, the D_{50} particle size distribution of the compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, ranges from about 500 nm to about 1 μm, or from about 1 μm to about 50 μm, or from about 50 μm to about 100 μm, or from about 100 μm to about 150 μm. In still other embodiments, the D_{50} particle size distribution of the compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, ranges from about 1 μm to about 10 μm, or from about 2 μm to about 8 μm, or from about 3 μm to about 7 μm.

In certain embodiments, a D_{90} particle size distribution of the compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, ranges from about 1 μm to about 1000 μm. In other embodiments, the D_{90} particle size distribution of the compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, ranges from about 2 μm to about 100 μm, or from about 100 μm to about 200 μm, or from about 200 μm to about 300 μm, or from about 300 μm to about 400 μm, or from about 400 μm to about 500 μm, or from about 500 μm to about 600 μm, or from about 600 μm to about 700 μm, or from about 700 μm to about 800 μm, or from about 800 μm to about 900 μm, or from about 900 μm to about 1000 μm. In still other embodiments, the D_{90} particle size distribution of the compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof,

ranges from about 5 μm to about 25 μm, or from about 7 μm to about 23 μm, or from about 9 μm to about 21 μm, or from about 11 μm to about 19 μm.

In some embodiments, the pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, with at least one pharmaceutically acceptable carrier, diluent, or excipient further comprises a second therapeutic agent.

In one embodiment, the second therapeutic agent is an antihistamine, such as an H1 receptor antagonist or an H2 receptor antagonist. In one embodiment, the second therapeutic agent is an H1 receptor antagonist antihistamine, such as levocetirizine, loratadine, fexofenadine, cetirizine, desloratadine, olopatadine, diphenhydramine, cyproheptadine or hydroxyzine pamoate. In one embodiment, the second therapeutic agent is a H2 receptor antagonist, such as cimetidine, nizatidine, ranitidine or famotidine. In one embodiment, the second therapeutic agent is a leukotriene receptor antagonist or leukotriene synthesis inhibitor, such as montelukast, zafirlukast, pranlukast, or 5-lipoxygenase inhibitor (e.g., zileuton, hypericum perforatum). In one embodiment, the second therapeutic agent is an immunomodulatory agent such as Omalizumab or immunoglobulin therapy. In one embodiment, the second therapeutic agent is a corticosteroid, such as hydrocortisone, cortisone, ethamethasoneb, triamcinolone, prednisone, prednisolone, or fludrocortisone. In one embodiment, the second therapeutic agent is a tricylic antidepressant that can relieve itch such as doxepin, amitriptyline or nortriptyline. In one embodiment, the second therapeutic agent is an anti-inflammatory drug such as dapsone, sulfasalazine, hydroxycholoroquine or colchicine. In one embodiment, the second therapeutic agent is an immunosuppressant such as cyclosporine, methotrexate, mycophenolic acid or tacromilus.

In one embodiment, the second therapeutic agent is an H1 receptor antagonist antihistamine, such as levocetirizine, loratadine, fexofenadine, cetirizine, desloratadine, olopatadine, diphenhydramine, cyproheptadine or hydroxyzine pamoate. In one embodiment, the second therapeutic agent is a H2 receptor antagonist, such as cimetidine, nizatidine, ranitidine or famotidine. In one embodiment, the second therapeutic agent is a leukotriene receptor antagonist or leukotriene synthesis inhibitor, such as montelukast, zafirlukast, pranlukast, or 5-lipoxygenase inhibitor (e.g., zileuton,

hypericum perforatum). In one embodiment, the second therapeutic agent is an immunomodulatory agent such as Omalizumab or immunoglobulin therapy. In one embodiment, the second therapeutic agent is a corticosteroid, such as hydrocortisone, cortisone, ethamethasoneb, triamcinolone, prednisone, prednisolone, or fludrocortisone. In one embodiment, the second therapeutic agent is a tricylic antidepressant that can relieve itch such as doxepin, amitriptyline or nortriptyline. In one embodiment, the second therapeutic agent is an anti-inflammatory drug such as dapsone, sulfasalazine, hydroxycholoroquine or colchicine. In one embodiment, the second therapeutic agent is an immunosuppressant such as cyclosporine, methotrexate, mycophenolic acid or tacromilus.

As used herein, the term "pharmaceutically acceptable carrier" refers to any ingredient other than the disclosed compounds, or a pharmaceutically acceptable isomer, racemate, hydrate, solvate, isotope or salt thereof (e.g., a carrier capable of suspending or dissolving the active compound) and having the properties of being nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspending or dispersing agents, sweeteners, or waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

In certain embodiments, the invention provides a pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, and at

least one polymeric carrier. In some embodiments, the pharmaceutical composition is in the form of an amorphous solid dispersion including at least one polymeric carrier.

In some embodiments, the polymeric carrier comprises at least one selected from the group consisting of an enteric polymer, a hydrophilic polymer, a surfactant, an amphiphilic polymer, and combinations thereof.

In some embodiments, the pharmaceutical composition contains a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, and a polymeric carrier comprising at least one selected from the group consisting of a methacrylate polymer, a hydroxylpropyl methyl cellulose phthalate (HPMCP) polymer, a hydroxypropyl methyl cellulose acetate-succinate (HPMCAS) polymer, a cellulose acetylate phthalate (CAP) polymer, a starch, a sodium carboxymethyl cellulose polymer, a sodium alginate polymer, a polyethylene glycol (PEG), a polyvinyl pyrollidone (PVP), a hydroxy propyl methyl cellulose (HPMC) polymer, a polyvinvyl alcohol (PVA), a beta-cyclodextrin polymer, a mannitol polymer, a chitosan polymer, a carrageenan polymer, a hydroxypropylcellulose (HPC) polymer, a polyethylene-polypropylene glycol, a lecithin, a bile salt, a lauroyl polyoxyl-32 glyceride, a polyethylene oxide (PEO) / polypropylene glycol (PPG) copolymer, a PEG-modified starch, a vinyl acetate/vinylpyrrolidone random copolymer, a polyacrylic acid, a polyacrylate, and a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (PCL-PVAc-PEG) graft copolymer.

In some embodiments, the pharmaceutical composition contains a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, and a polymeric carrier comprising at least one selected from the group consisting of a hydroxy propyl methyl cellulose (HPMC) polymer, a hydroxypropyl methyl cellulose acetate-succinate (HPMCAS) polymer, a polyvinyl pyrollidone (PVP) and a hydroxypropylcellulose (HPC) polymer. In more specific embodiments, the polymeric carrier comprises a hydroxypropyl methyl cellulose acetate-succinate (HPMCAS) polymer. For example, in some embodiments the polymeric carrier comprises HPMCAS-MG.

In some embodiments, the pharmaceutical composition comprises a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, and at least one polymeric carrier, such

that a mass ratio of the compound to the polymeric carrier that ranges from about 1:100 to about 50:1. For example, in some embodiments the mass ratio of the compound to the polymeric carrier ranges from about 1:100 to about 1:50; or from about 1:50 to about 1:10; or from about 1:10 to about 1:1, or from about 1:1 to about 10:1, or from about 10:1 to about 20:1, or from about 20:1 to about 50:1. In other embodiments, the mass ratio of the compound to the polymer carrier ranges from about 1:1 to about 1:5.

In some embodiments, the pharmaceutical composition comprises a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, and at least one polymeric carrier, such that a weight percent of the compound ranges from about 2% to about 70% relative to a combined mass of the compound and the polymeric carrier. In other embodiments, the weight percent of the compound ranges from about 2% to about 10%, or from about 10% to about 20%, or from about 15% to about 25%, or from about 20% to about 30%, or from about 30% to about 40%, or from about 40% to about 50%, or from about 50% to about 60%, or from about 60% to about 70%, relative to a combined mass of the compound and the polymeric carrier.

In certain embodiments, the invention provides a pharmaceutical composition further comprising at least one pharmaceutically acceptable excipient. For example, in some embodiments the pharmaceutical composition comprises a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, at least one polymeric carrier as described above, and at least one pharmaceutically acceptable excipient. Pharmaceutically acceptable excipients may include, for example, fillers, binders, disintegrants, surfactants, lubricants, glidants, capsule shells, and mixtures thereof. Fillers may include, for example, mannitol, a microcrystalline cellulose (MCC), a silicified microcrystalline cellulose (SMCC) and mixtures thereof. Binders may include, for example, a hydroxypropylmethylcellulose (HPMC), a povidone, and mixtures thereof. Disintegrants may include, for example, a sodium starch glycolate (SSG), a croscarmellose sodium (CCS), and mixtures thereof. Surfactants may include, for example, sodium lauryl sulfate (SLS), a polaxamer, and mixtures thereof. Lubricants may include, for example, magnesium stearant (MS), sodium stearyl fumarate (SSF), and mixtures thereof. Glidants may include, for example, silicon dioxide, talc, and mixtures

thereof. Capsule shells may include, for example, an HPMC capsule or a gelatin capsule. Surfactants may include, for example, sodium lauryl sulfate (SLS).

In some embodiments, the pharmaceutical composition comprises at least one solvent. Solvents may include, for example, water and organic solvents (such as dimethylsulfoxide and the like).

The formulations can be mixed with auxiliary agents which do not deleteriously react with the active compounds. Such additives can include wetting agents, emulsifying and suspending agents, salt for influencing osmotic pressure, buffers and/or coloring substances, preserving agents, sweetening agents, or flavoring agents. The compositions can also be sterilized if desired.

The route of administration can be any route which effectively transports the active compound of the invention to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal, or parenteral, including intravenous, subcutaneous and/or intramuscular. In one embodiment, the route of administration is oral. In another embodiment, the route of administration is topical.

Dosage forms can be administered once a day, or more than once a day, such as twice or thrice daily. Alternatively, dosage forms can be administered less frequently than daily, such as every other day, or weekly, if found to be advisable by a prescribing physician or drug's prescribing information. Dosing regimens include, for example, dose titration to the extent necessary or useful for the indication to be treated, thus allowing the patient's body to adapt to the treatment, to minimize or avoid unwanted side effects associated with the treatment, and/or to maximize the therapeutic effect of the present compounds. Other dosage forms include delayed or controlled-release forms. Suitable dosage regimens and/or forms include those set out, for example, in the latest edition of the Physicians' Desk Reference, incorporated herein by reference.

Proper dosages for pediatric patients can be determined using known methods, including weight, age, body surface area, and models such as Simcyp® Pediatric Simulation modeling (CERTARA, Princeton, N.J.) which can be used to establish a pharmacokinetic approach for dosing that takes into account patient age, ontogeny of the clearance pathways to eliminate a compound of any one of formulas (Ia) through (1f), and body surface area (BSA). In one embodiment, the dosage form is formulated

to provide a pediatric dose from about 30% to about 100% of an adult dose, or about 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% of an adult dose.

In one embodiment, the invention provides an oral pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable oral carrier, diluent, or excipient. In another embodiment, the invention provides a topical pharmaceutical composition comprising a compound of structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof, together with at least one pharmaceutically acceptable topical carrier, diluent, or excipient. For example, the oral pharmaceutical composition is provided to treat cholestatic pruritus, wherein the dosage regimen is, for example, once a day. In one embodiment, the topical pharmaceutical composition is provided to treat atopic dermatitis.

In another embodiment, there are provided methods of making a composition of a compound described herein including formulating a compound of the invention with a pharmaceutically acceptable carrier or diluent. In some embodiments, the pharmaceutically acceptable carrier or diluent is suitable for oral administration. In some such embodiments, the methods can further include the step of formulating the composition into a tablet or capsule. In other embodiments, the pharmaceutically acceptable carrier or diluent is suitable for parenteral administration. In some such embodiments, the methods further include the step of lyophilizing the composition to form a lyophilized preparation. In some embodiments, the composition is formulated into a pediatric dosage form suitable for treating a pediatric subject.

In certain embodiments, the invention provides a compound having structure (I) or any one of formulas (Ia) through (1f), or a pharmaceutically acceptable salt, isomer, hydrate, solvate or isotope thereof. Such compounds can be synthesized using standard synthetic techniques known to those skilled in the art. For example, compounds of the present invention can be synthesized using appropriately modified synthetic procedures set forth in the following Examples and Reaction Schemes.

To this end, the reactions, processes, and synthetic methods described herein are not limited to the specific conditions described in the following experimental

section, but rather are intended as a guide to one with suitable skill in this field. For example, reactions may be carried out in any suitable solvent, or other reagents to perform the transformation[s] necessary. Generally, suitable solvents are protic or aprotic solvents which are substantially non-reactive with the reactants, the intermediates or products at the temperatures at which the reactions are carried out (i.e., temperatures which may range from the freezing to boiling temperatures). A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction, suitable solvents for a particular work-up following the reaction may be employed.

All reagents, for which the synthesis is not described in the experimental part, are either commercially available, or are known compounds or may be formed from known compounds by known methods by a person skilled in the art. The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to a person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallization. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash column chromatography, using purpose-made or prepacked silica gel cartridges and eluents such as gradients of solvents such as heptane, ether, ethyl acetate, acetonitrile, ethanol and the like. In some cases, the compounds may be purified by preparative HPLC using methods as described.

Purification methods as described herein may provide compounds of the present invention which possess a sufficiently basic or acidic functionality in the form of a salt, such as, in the case of a compound of the present invention which is sufficiently basic, a trifluoroacetate or formate salt, or, in the case of a compound of the present invention which is sufficiently acidic, an ammonium salt. A salt of this type can either be transformed into its free base or free acid form, respectively, by various methods known to a person skilled in the art, or be used as salts in subsequent biological assays. It is to be understood that the specific form of a compound of the present invention as isolated and as described herein is not necessarily the only form in which said compound can be applied to a biological assay in order to quantify the specific biological activity.

Chemical names were generated using the ChemDraw naming software (Version 17.0.0.206) by PerkinElmer Informatics, Inc. In some cases, generally accepted names of commercially available reagents were used in place of names generated by the naming software.

EXAMPLES

General Methods

^{1}H NMR (400 MHz) spectra were obtained in solution of deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or dimethyl sulfoxide – D6 (DMSO). HPLC retention times, purities, and mass spectra (LCMS) were obtained using one of the following methods:

Method 1: Agilent 1260 Infinity II System equipped with an Agilent Poroshell 120 EC-18, 2.7 µm, 4.6 x 100 mm column at 30 °C, using H_2O with 0.1% formic acid as the mobile phase A, and MeCN with 0.1% formic acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5-95% mobile phase B over 12 min then held at 95% for 1.8 min, then return to 10% mobile phase B over 0.2 min. The flow rate was 1 mL/min.

Method 2: SHIMADZU LCMS-2020 System equipped with a Kinetex EVO C18 2.1X30 mm column, (5um particles), using H_2O with 0.0375% Trifluoroacetic Acid as the mobile phase A, and MeCN with 0.01875% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00 min and 5-90% B at 0.00-0.80 min, 90-95% B at 0.80-0.12 min, and then 95-5%B in 0.01 min, hold on 5% B for 0.34 min, the flow rate was 1.5 ml/min.

Method 3: Agilent 1200 System equipped with a Kinetex C18 50*2.1 mm column, (5um particles), using H_2O with 0.037% Trifluoroacetic Acid as the mobile phase A, and MeCN with 0.018% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00 min and 5-90% B at 0.00-0.80 min, 90-95% B at 0.80-0.12 min, and then 95-5%B in 0.01 min, hold on 5% B for 0.34 min, the flow rate was 1.5 ml/min.

Method 4: SHIMADZU LCMS-2020 System equipped with a Kinetex EVO C18 2.1X30 mm column, (5um particles), using H_2O with 0.0375% Trifluoroacetic Acid as the

mobile phase A, and MeCN with 0.01875% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00min and 5-90% B at 0.00-0.80 min, 90-95% B at 0.80-0.12 min, and then 95-5%B in 0.01 min, hold on 5% B for 0.34 min, the flow rate was 1.5 ml/min.

Method 5: Agilent 1200 System equipped with an Xbridge Shield RP18 2.1*50 mm column (5um particles), using H_2O with 10 mM NH_4HCO_3 as the mobile phase A, and MeCN as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5-95 %B in 0.30 min and 30-95% B at 0.30-0.80 min, hold on 95% B for 0.4 min, and then 95-5%B in 0.01 min, the flow rate was 1.5 ml/min.

Method 6: SHIMADZU LCMS-2020 System equipped with a Kinetex EVO C18 2.1X30 mm column, (5um particles), using H2O with 0.0375% Trifluoroacetic Acid as the mobile phase A, and MeCN with 0.01875% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00min and 5-90% B at 0.00-0.80 min, 90-95% B at 0.80-0.12 min, and then 95-5%B in 0.01 min, hold on 5% B for 0.34 min, the flow rate was 1.5 ml/min.

Method 7: SHIMADZU LCMS-2020 System equipped with a Chromolith@Flash RP-18E 25-2 MM column, using H_2O with 0.0375% Trifluoroacetic Acid as the mobile phase A, and MeCN with 0.01875% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00 min and 5-90% B at 0.00-0.80 min, 90-95% B at 0.80-0.12 min, and then 95-5%B in 0.01 min, hold on 5% B for 0.34 min, the flow rate was 1.5 ml/min.

Method 8: SHIMADZU LCMS-2020 System equipped with a Kinetex EVO C18 2.1X30 mm column, (5um particles), using H_2O with 0.0375% Trifluoroacetic Acid as the mobile phase A, and MeCN with 0.01875% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00 min and 5-90% B at 0.00-0.80 min, 90-95% B at 0.80-0.12 min, and then 95-5%B in 0.01 min, hold on 5% B for 0.34 min, the flow rate was 1.5 ml/min.

Method 9: Agilent 1290 Infinity II System equipped with an Agilent Poroshell 120 EC-18, 2.7 µm, 4.61 x 100 mm column at 35 °C, using H_2O with 0.1% formic acid as the mobile phase A, and MeCN with 0.1% formic acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5-95% mobile phase B over 8.0

min then held at 95% for 1.8 mins, then return to 20% mobile phase B over 0.2 min. The flow rate was 0.7 mL/min.

Method 10: Agilent 1260 Infinity II System equipped with an Agilent Poroshell 120 EC-18, 2.7 µm, 4.6 x 100 mm column at 30 °C, using H_2O with 0.1% formic acid as the mobile phase A, and MeCN with 0.1% formic acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5-95% mobile phase B over 5 min then held at 95% for 1.8 min, then return to 20% mobile phase B over 0.2 min. The flow rate was 1 mL/min.

Method 11: Agilent 1290 Infinity II System equipped with an Agilent Poroshell 120 EC-18, 1.9 µm, 2.1 x 50 mm column at 35 °C, using H_2O with 0.1% formic acid as the mobile phase A, and MeCN with 0.1% formic acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 20-95% mobile phase B over 0.8 min then held at 95% for 0.7 mins, then return to 20% mobile phase B over 0.7 min. The flow rate was 0.7 mL/min.

Method 12: SHIMADZU LCMS-2020 System equipped with a Kinetex EVO C18 2.1X30mm, (2.6um particles), using H2O with 0.0375% Trifluoroacetic Acid as the mobile phase A, and MeCN with 0.01875% Trifluoroacetic Acid as the mobile phase B. An ESI detector in positive mode was used. The gradient was 5% B at 0.00min and 5-95% B at 0.00-0.8 min, 95-95% B at 0.80-1.09 min, and then 95-5%B in 0.01min, hold on 5% B for 0.1min, the flow rate was 1.5 ml/min.

Method 13: Agilent 1200\G1956A equipped with Kinetex EVO C18 30*2.1mm,5um column, using H2O with 0.0375% TFA as mobile phase A, and MeCN with 0.01875% TFA as mobile phase B. The gradient was 5-95% mobile phase B for 0.8 min, held at 95% for 0.4 min, then returned to 5% mobile phase B for 0.01 min, held at 5% for 0.29 min. The flow rate was 1.5 mL/min. An ESI detector in positive mode was used.

Method 14: SHIMADZU LCMS-2020 equipped with Kinetex® EVO C18 2.1x30mm 5um column, using H2O with 0.0375% TFA as mobile phase A, and MeCN with 0.01875% TFA as mobile phase B. The gradient was 5-95% mobile phase B for 0.8 min, held at 95% for 0.15 min, then returned to 5% mobile phase B for 0.01 min, held at 5% for 0.04 min. The flow rate was 2 mL/min. An ESI detector in positive mode was used.

Method 15: Agilent 1100\G1956A equipped with Kinetex@ 5um EVO C18 30*2.1mm column, using H2O with 0.0375% TFA as mobile phase A, and MeCN with 0.01875% TFA as mobile phase B. The gradient was 5-95% mobile phase B for 0.8 min, held at 95% for 0.4 min, then returned to 5% mobile phase B for 0.01 min, held at 5% for 0.29 min. The flow rate was 1.5 mL/min. An ESI detector in positive mode was used.

Method 16: SHIMADZU LCMS-2020 equipped with Kinetex EVO C18 2.1X30mm,5um column, using H2O with 0.0375% TFA as mobile phase A, and MeCN with 0.01875% TFA as mobile phase B. The gradient was 5-95% mobile phase B for 0.8 min, held at 95% for 0.4 min, then returned to 5% mobile phase B for 0.01 min, held at 5% for 0.04 min. The flow rate was 1.5 mL/min. An ESI detector in positive mode was used.

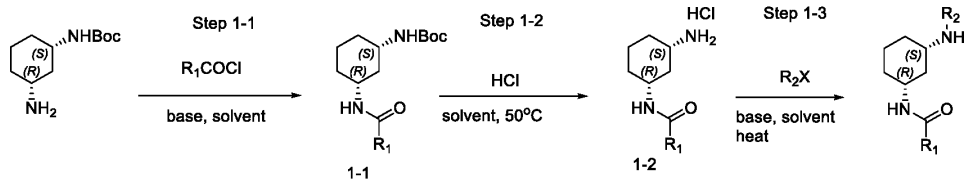
The pyridine, dichloromethane (DCM), tetrahydrofuran (THF), and toluene used in the procedures were from Aldrich Sure-Seal bottles kept under nitrogen (N_2). Other solvents were used as is. All reactions were stirred magnetically, and temperatures are external reaction temperatures. Chromatographies were typically carried out using a Combiflash Rf flash purification system (Teledyne Isco) equipped with Redisep (Teledyne Isco) Rf Gold Normal-Phase silica gel (SiO_2) columns or by using a similar system.

Preparative HPLC purifications were typically performed using one of the following systems: 1) Waters System equipped with a Waters 2489 uv/vis detector, an Aquity QDA detector, a Waters xBridge Prep C18 5 µm OBD, 30 X 150 mm column, and eluting with various gradients of H_2O/ MeCN (0.1% formic acid) at a 30 mL/min flow rate, 2) Teledyne Isco ACCQPrep® HP150 UV system equipped with a Waters xBridge Prep C18 5 µm OBD, 30 X 150 mm column, and eluting with various gradients of H_2O/ MeCN (0.1% formic acid) at a 42.5 mL/min flow rate, or 3) column: Phenomenex Synergi C18 150X30 mm- 4µm; mobile phase: [H_2O (0.225%formic acid)-MeCN];B%: 55%-85%,12min) and were typically concentrated using a Genevac EZ-2.

The following additional abbreviations are used: ethyl acetate (EA), triethylamine (TEA), water (H_2O), sodium chloride (NaCl), Hydrochloric acid (HCl), methanol (MeOH), dimethyl sulfoxide (DMSO), silica gel (SiO_2), diisobutylaluminium hydride (DIBAL), trifluoroacetic acid (TFA), 4-dimethylaminopyridine (DMAP), diphenylphosphoryl azide (DPPA), benzoyl peroxide (BPO), 1,1'-

bis(diphenylphosphino)ferrocene (dppf), bis(pinacolato)diboron (B_2pin_2), tetrahydrofuran (THF), 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO), hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU), hydroxybenzotriazole (HOBt), *N*-methyl morpholine (NMM), *N*-Bromosuccinimide (NBS), diisopropylethyl amine (DIPEA or DIEA), diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD), 2-[2-(dicyclohexylphosphino)phenyl]-*N*-methylindole (CM-Phos), triflic acid (TfOH), l-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), isopropanol (IPA), dimethylformamide (DMF), dimethyl acetamide (DMA), dichloromethane (DCM), 1,2-dichloroethane (DCE), acetonitrile (MeCN or ACN), 1,1'-thiocarbonyldiimidazole (TCDI), petroleum ether (PE), polyphosphoric acid (PPA), not determined (ND), retention time (RT, tr, or t_R), molecular weight (mw), room temperature (rt), hour (h), and not applicable (N/A).

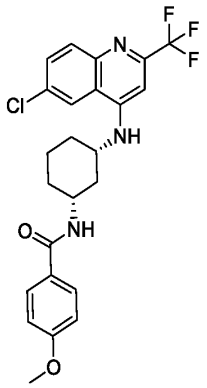
Scheme 1



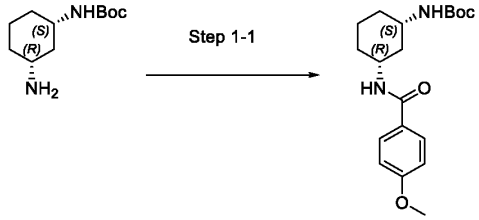
Reagents: Step 1-1. R_1COCl, base (DIPEA), solvent (DCM); Step 1-2. HCl, solvent (1,4-dioxane); Step 1-3. R_2X, base (DIPEA), solvent (DMSO, NMP), heat

EXAMPLE 1

SYNTHESIS OF EXAMPLE 1



Step 1-1. Synthesis of tert-butyl ((1S,3R)-3-(4-methoxybenzamido)cyclohexyl)carbamate

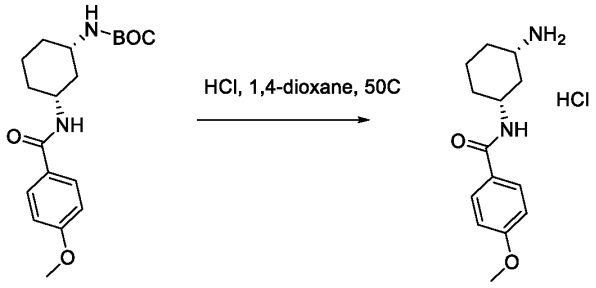


To a stirring ice-cold solution of (1S,3R)-3-Amino-1-(Boc-amino)cyclohexane (1.142 g, 1.0 equiv., 5.329 mmol) in DCM (30 mL) was added with DIPEA (1.377 g, 1.9 mL, 2.0 equiv., 10.66 mmol), followed by slow addition of 4-methoxybenzoyl chloride (955 mg, 758 µL, 1.05 equiv., 5.60 mmol). The resulting mixture was allowed to stir at room temperature. After stirring for 18 hours, the reaction mixture was filtered, and the filter cake was washed with DCM and dried under high vacuum to yield tert-butyl ((1S,3R)-3-(4-methoxybenzamido)cyclohexyl)carbamate (1.659 g, 4.761 mmol, 89 % yield).

LCMS-ESI (m/z) calculated: 348.44; found 349.2 $[M+H]^+$, RT = 4.239 min (Method 10).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.09 (d, J = 7.9 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.1 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.71 (m, 1H), 3.31 – 3.22 (m, 1H), 1.93 (d, J = 12.0 Hz, 1H), 1.77 – 1.68 (m, 3H), 1.38 (s, 9H), 1.31 – 1.17 (m, 3H), 1.11 – 1.01 (m, 1H).

Step 1-2. Synthesis of N-((1R,3S)-3-aminocyclohexyl)-4-methoxybenzamide



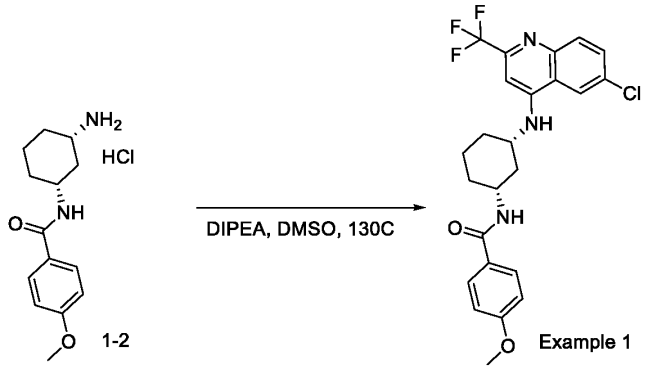
To a stirred suspension of tert-butyl ((1S,3R)-3-(4-methoxybenzamido)cyclohexyl)-carbamate (1.654 g, 1 Eq, 4.747 mmol) in EtOH (40 mL) was added 1.25M hydrogen chloride in 1,4-dioxane (1.731 g, 37.97 mL, 1.25 molar,

10 Eq, 47.47 mmol). The resulting mixture was stirred at 50 °C for 17 hours. The reaction mixture was directly concentrated to yield a white solid, which was further dried under high vacuum to yield N-((1R,3S)-3-aminocyclohexyl)-4-methoxybenzamide hydrochloride (1.331 g, 4.674 mmol, 98 %) that was used without further purification in the next step.

LCMS-ESI (m/z) calculated: 248.44; found 249.2 $[M+H]^+$, RT = 1.665 min (Method 10).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.26 (d, J = 7.9 Hz, 1H), 8.09 (s, 3H), 7.84 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 3.91 – 3.81 (m, 1H), 3.80 (s, 3H), 3.13 – 3.05 (m, 1H), 2.12 (d, J = 11.6 Hz, 1H), 1.91 (d, J = 12.0 Hz, 1H), 1.78 (d, J = 12.0 Hz, 2H), 1.44 – 1.21 (m, 4H).

Step 1-3. Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-4-methoxybenzamide (Example 1)



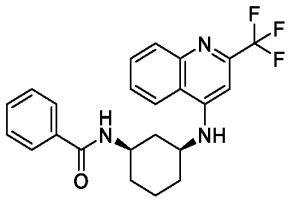
A pressure vial containing a solution of 4,6-dichloro-2-(trifluoromethyl)quinoline (56 mg, 1.0 equiv., 0.21 mmol) and N-((1R,3S)-3-aminocyclohexyl)-4-methoxybenzamide hydrochloride (60 mg, 1.0 equiv., 0.21 mmol) in DMSO (2 mL) was charged with DIPEA (0.11 g, 0.15 mL, 4.0 equiv., 0.84 mmol). The vial was closed and the resulting solution was stirred at 130 °C. After stirring for 20 h at 130 °C, the reaction mixture was cooled to room temperature. The reaction mixture was filtered, and the filtrate was purified by prep HPLC (ISCO ACCQPrep 150) to yield N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-4-methoxybenzamide (20 mg, 42 µmol, 20 % yield).

LCMS-ESI (m/z) calculated: 477.91; found 478.2 $[M+H]^+$, RT = 7.477 min (Method 9).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.61 (s, 1H), 8.18 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.83 (d, J = 8.5 Hz, 2H), 7.74 (dd, J = 9.0, 2.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.01 – 6.89 (m, 3H), 4.07 – 3.98 (m, 1H), 3.92 – 3.84 (m, 1H), 3.80 (s, 3H), 2.16 (d, J = 11.9 Hz, 1H), 1.97 (d, J = 12.3 Hz, 1H), 1.91 – 1.78 (m, 2H), 1.60 – 1.47 (m, 2H), 1.44 – 1.29 (m, 2H).

EXAMPLE 2

SYNTHESIS OF EXAMPLE 2



Step 1-1. Synthesis of tert-butyl ((1S,3R)-3-benzamidocyclohexyl)carbamate

To an ice-cold solution of (1S,3R)-3-amino-1-(Boc-amino)cyclohexane (1.238 g, 1 Eq, 5.777 mmol) in DCM (30 mL) was added DIPEA (1.493 g, 2.0 mL, 2 Eq, 11.55 mmol), followed by benzoyl chloride (853 mg, 704 µL, 1.05 Eq, 6.07 mmol). The resulting mixture was allowed to stir at room temperature for 1 h. The reaction mixture was filtered, and the filter cake was washed with DCM and dried under high vacuum to yield tert-butyl ((1S,3R)-3-benzamidocyclohexyl)carbamate (1.575 g, 4.946 mmol, 86 % yield).

LCMS-ESI (m/z) calculated: 318.30; found 319.2 $[M+H]^+$, RT = 4.237 min (Method 10).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.26 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 7.5 Hz, 2H), 7.53 – 7.42 (m, 3H), 6.84 (d, J = 8.0 Hz, 1H), 3.84 – 3.74 (m, 1H), 3.31 – 3.23 (m, 1H), 1.95 (d, J = 12.0 Hz, 1H), 1.79 – 1.68 (m, 3H), 1.38 (s, 9H), 1.31 – 1.17 (m, 3H), 1.11 – 1.02 (m, 1H).

Step 1-2. Synthesis of N-((1R,3S)-3-aminocyclohexyl)benzamide hydrochloride

To a stirred white suspension of tert-butyl ((1S,3R)-3-benzamidocyclohexyl)-carbamate (1.570 g, 1 Eq, 4.931 mmol) in 1,4-dioxane (35 mL) was added 4M hydrogen chloride in 1,4-dioxane (10 Eq, 49.31 mmol). The resulting mixture was heated at 50 °C for 19 h. The reaction mixture was directly concentrated and dried under high vacuum to yield N-((1R,3S)-3-aminocyclohexyl)benzamide hydrochloride (1.201 g, 4.714 mmol, 96 % yield).

LCMS-ESI (m/z) calculated: 218.30; found 219.2 $[M+H]^+$, RT = 0.261 min (Method 11).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.42 (d, J = 7.9 Hz, 1H), 8.11 (s, 3H), 7.85 (d, J = 7.5 Hz, 2H), 7.55 – 7.41 (m, 3H), 3.93 – 3.80 (m, 1H), 3.18 – 3.04 (m, 1H), 2.14 (d, J = 11.8 Hz, 1H), 1.92 (d, J = 12.0 Hz, 1H), 1.79 (d, J = 11.4 Hz, 2H), 1.48 – 1.20 (m, 4H).

Step 1-3. Synthesis of N-((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl) benzamide (Example 2)

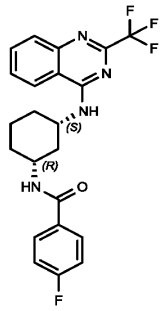
To a solution of 4-chloro-2-(trifluoromethyl)quinoline (55 mg, 1 Eq, 0.24 mmol) and N-((1R,3S)-3-aminocyclohexyl)benzamide hydrochloride (60 mg, 1 Eq, 0.24 mmol) in DMSO (2 mL) was added DIPEA (0.12 g, 0.16 mL, 4 Eq, 0.94 mmol). The vial was capped and the resulting solution was stirred at 130 °C for 18 h. The reaction mixture was cooled to room temperature, passed through a syringe filter, and the filtrate was purified by prep HPLC (ISCO ACCQPrep 150) to yield N-((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl) benzamide (13.4 mg, 32.4 µmol, 14 % yield).

LCMS-ESI (m/z) calculated: 413.44; found 414.3 $[M+H]^+$, RT = 5.687 min (Method 9).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.42 (d, J = 8.5 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.92 – 7.80 (m, 3H), 7.73 (t, J = 7.6 Hz, 1H), 7.58 – 7.37 (m, 5H), 6.90 (s, 1H), 4.10 – 3.99 (m, 1H), 3.93 – 3.82 (m, 1H), 2.19 (d, J = 12.0 Hz, 1H), 2.01 – 1.80 (m, 3H), 1.56 (q, J = 12.1 Hz, 2H), 1.46 – 1.29 (m, 2H).

EXAMPLE 3

SYNTHESIS OF EXAMPLE 3



Step 1-1. Synthesis of tert-butyl N-[(1S,3R)-3-[(4-fluorobenzoyl)amino]cyclohexyl]carbamate

To a solution of tert-butyl N-[(1S,3R)-3-aminocyclohexyl]carbamate (0.8 g, 3.7 mmol, 1 eq) and TEA (567 mg, 5.60 mmol, 779 uL, 1.5 eq) in DCM (5 mL) was added 4-fluorobenzoyl chloride (592 mg, 3.73 mmol, 448 uL, 1 eq) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H_2O (50 mL) and EA (50 mL). The mixture was filtered, and the resulting cake was concentrated under reduced pressure to give crude product. The filtered liquor was extracted with EA (50 mL x 2). The combined organic layers were washed with sat.aq NaCl (50 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl N-[(1S,3R)-3-[(4-fluorobenzoyl)amino]cyclohexyl]carbamate (1.26 g, crude) that was used in the next step without further purification.

LCMS-ESI (m/z) calculated: 336.40; found 237.2 $[M+H-Boc]^+$, RT = 0.9 min (Method 2).

^1H NMR (400 MHz, DMSO-d6) δ = 8.30 (d, J = 8.0 Hz, 1H), 7.92 - 7.88 (m, 2H), 7.30 - 7.24 (m, 2H), 6.85 (d, J = 8.0 Hz, 1H), 3.81 - 3.73 (m, 1H), 3.27 - 3.28 (m, 1H), 1.95 (d, J = 11.2 Hz, 1H), 1.78 - 1.71 (m, 3H), 1.37 (s, 9H), 1.31- 1.02 (m, 4H).

Step 1-2. Synthesis of N-[(1R,3S)-3-aminocyclohexyl]-4-fluoro-benzamide

A sample of tert-butyl N-[(1S,3R)-3-[(4-fluorobenzoyl)amino]cyclohexyl]carbamate (1.16 g, 3.45 mmol, 1 eq) was added to HCl/MeOH (4 M, 15 mL, 17.40 eq) at 25 °C. The mixture was stirred at 25 °C for 1h. The

reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in MeOH (50 mL), and then resin(base) was added and filtered to remove the insoluble particles. The mother liquor was concentrated under reduced pressure to give crude product N-[(1R,3S)-3-aminocyclohexyl]-4-fluoro-benzamide (0.81 g, 3.43 mmol, 99.41% yield) that was used in the next step without further purification.

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.52- 8.46 (m, 1H), 7.96 - 7.92 (m, 2H), 7.30 - 7.25 (m, 2H), 3.85 - 3.83 (m, 1H), 3.06-3.01 (m, 1H), 2.14 (d, J = 10.8 Hz, 1H), 1.93 (d, J = 11.2 Hz, 1H), 1.78 - 1.76 (m, 2H), 1.49 - 1.26 (m, 4H).

Step 1-3. Synthesis of 4-fluoro-N-[(1R,3S)-3-[[2-(trifluoromethyl)quinazolin-4-yl]amino]cyclohexyl]benzamide (Example 3)

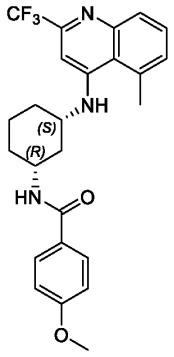
A mixture of 4-chloro-2-(trifluoromethyl)quinazoline (80 mg, 344 umol, 1 eq), N-[(1R,3S)-3-aminocyclohexyl]-4-fluorobenzamide (163 mg, 688 umol, 2 eq) and DIEA (222 mg, 1.72 mmol, 300 uL, 5 eq) in DMSO (2 mL) was stirred at 120 °C for 1 h. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 um; mobile phase: [water(0.225%FA)-ACN];B%: 50%-70%,10min) and lyophilized to afford 4-fluoro-N-[(1R,3S)-3-[[2-(trifluoromethyl)-quinazolin-4-yl]amino]cyclohexyl]benzamide (60 mg, 138 umol, 40% yield).

LCMS-ESI (m/z) calculated: 432.4; found 433.2 $[M+H\text{-}Boc]^+$, RT = 0.941 min (Method 2).

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.54 (d, J = 8.0 Hz, 1H), 8.45 - 8.38 (m, 2H), 7.93 - 7.81 (m, 4H), 7.69 - 7.65 (m, 1H), 7.31 - 7.25 (m, 2H), 4.34 - 4.29 (m, 1H), 4.00 - 3.89 (m, 1H), 2.19 (d, J = 11.6 Hz, 1H), 1.99 - 1.85 (m, 3H), 1.62 - 1.30 (m, 4H).

EXAMPLE 4

SYNTHESIS OF EXAMPLE 4



Step 1-3. Synthesis of 4-methoxy-N-[(1R,3S)-3-[[5-methyl-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]benzamide

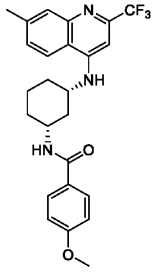
A mixture of 4-chloro-5-methyl-2-(trifluoromethyl)quinoline (120 mg, 489 umol, 1 eq), N-[(1R,3S)-3-aminocyclohexyl]-4-methoxy-benzamide (170 mg, 685 umol, 1.4 eq) and DIEA (189mg, 1.47 mmol, 255 uL, 3 eq) in NMP (1 mL) was stirred at 120 °C for 16 h. The mixture was cooled to rt, filtered and concentrated. The filtrate was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(0.225%FA)- ACN];B%: 32%-62%,10min) and lyophilized to afford 4-methoxy-N-[(1R,3S)-3-[[5-methyl-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl] benzamide (8.7 mg, 19 umol, 4% yield).

LCMS-ESI (m/z) calculated: 457.5; found 458.1 $[M+H]^+$, RT = 0.846 min (Method 8).

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.44 - 8.38 (m, 1H), 8.18 (br d, J = 7.6 Hz, 1H), 7.84 (d, J = 8.9 Hz, 2H), 7.70 (d, J = 8.1Hz, 1H), 7.58 - 7.51 (m, 1H), 7.28 (d, J = 7.0 Hz, 1H), 6.97 (d, J = 8.9 Hz, 2H), 6.90 - 6.85 (m, 1H), 6.31 (br d, J = 7.5 Hz, 1H), 4.06 - 3.95 (m, 1H), 3.85 - 3.75 (m, 4H), 2.96 - 2.90 (m, 3H), 2.32 - 2.24 (m, 1H), 2.11 - 2.03 (m, 1H), 1.89 (br d, J = 10.8 Hz, 1H), 1.81 (br d, J = 13.1 Hz, 1H), 1.61 - 1.45 (m, 2H), 1.39 - 1.26 (m, 2H).

EXAMPLE 5

SYNTHESIS OF EXAMPLE 5



Synthesis of 4-chloro-7-methyl-2-(trifluoromethyl)quinoline

A mixture of 7-methyl-2-(trifluoromethyl)quinolin-4-ol (150 mg, 660 umol, 1 eq) and $POCl_3$ (2.02 g, 13.2 mmol, 1.23 mL, 20 eq) in ACN (1 mL) was stirred at 90 °C for 2 h. The mixture was cooled to 20 °C and slowly poured into water (20 mL), extracted with EtOAc (20 mL) and the organic layer was collected and concentrated under reduced pressure to afford crude 4-chloro-7-methyl-2-(trifluoromethyl)quinoline (150 mg) that was used without further purification.

LCMS-ESI (m/z) calculated: 245.6; found 246.0 $[M+H]^+$, RT = 1.018 min (Method 2).

Step 1-2. Synthesis of 4-methoxy-N-[(1R,3S)-3-[[7-methyl-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]benzamide

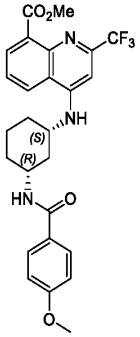
A mixture of 4-chloro-7-methyl-2-(trifluoromethyl)quinoline (150 mg, 611 umol, 1 eq) , N-[(1R,3S)-3-aminocyclohexyl]-4-methoxy-benzamide (227 mg, 914 umol, 1.5 eq) and DIEA (237 mg, 1.83 mmol, 319 uL, 3 eq) in NMP (0.5 mL) was stirred at 120 °C for 16 h. The mixture was cooled to rt, filtered and concentrated. The filtrate was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 um; mobile phase: [water (0.225%FA)- ACN];B%: 32%-62%,10 min) and lyophilized to afford4-methoxy-N-[(1R,3S)-3-[[7-methyl-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl] benzamide (23.5 mg, 51 umol, 8%).

LCMS-ESI (m/z) calculated: 457.49; found 458.1 $[M+H]^+$, RT = 0.818 min (Method 2).

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.31 (d, J = 8.8 Hz, 1H), 8.21 - 8.13 (m, 1H), 7.83 (d, J = 8.8 Hz, 2H), 7.67 (s, 1H), 7.39 (dd, J = 1.3, 8.7 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 4.07 - 3.96 (m, 1H), 3.80 (s, 4H), 2.47 (s, 3H), 2.20 - 2.12 (m, 1H), 2.00 - 1.93 (m, 1H), 1.91 - 1.78 (m, 2H), 1.61 - 1.47 (m, 2H), 1.45 - 1.27 (m, 2H).

EXAMPLE 6

SYNTHESIS OF EXAMPLE 6



Step 1-1: Synthesis of N-[(1R,3S)-3-[[8-bromo-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-4-methoxy-benzamide

To a solution of 8-bromo-4-chloro-2-(trifluoromethyl)quinoline (60 mg, 193 umol, 1 eq) in DMSO (1 mL) were added N- [(1R,3S)-3-aminocyclohexyl]-4-methoxy-benzamide (52.8 mg, 213 umol, 1.1 eq) and DIEA (50.0 mg, 386 umol, 67 uL, 2 eq) . The mixture was stirred at 125 °C for 12 h. The reaction mixture was added to water (20 mL) and extracted with EA (20 mL × 2). The combined organics were washed with brine, dried by Na_2SO_4 and conentrated in vacuo to give the residue. The residue was purified by prep-TLC (SiO_2, PE: EA = 2:1) to afford N-[(1R,3S)-3-[[8-bromo-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-4-methoxy-benzamide (60 mg, 115 umol, 59% yield).

LCMS-ESI (m/z) calculated: 522.6; found 522.1/524.1 $[M+H]^+$, RT = 0.977 min (Method 2).

Step 1-2: Synthesis of 4-[[(1S,3R)-3-[(4-methoxybenzoyl)amino]cyclohexyl]amino]-2-(trifluoromethyl)quinoline-8-carboxylate

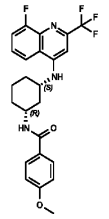
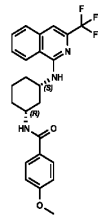
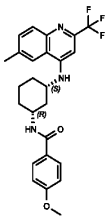
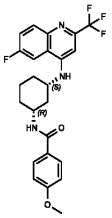
To a solution of N-[(1R,3S)-3-[[8-bromo-2-(trifluoromethyl)-4-quinolyl]amino] cyclohexyl]-4-methoxy-benzamide (60 mg, 115 umol, 1 eq) , Et_3N (34.9 mg, 345 umol, 48 uL, 3 eq) in MeOH (10 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (9.4 mg, 11.5 umol, 0.1 eq) at 25 °C. The suspension was degassed under vacuum and purged with CO several times. The reaction was heated to 70 °C and stirred under a CO (50 psi) atmosphere for 16 h. The reaction mixture was cooled to room temperature and Et_3N (34.9 mg, 345 umol, 48 uL, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (28.1 mg, 34.5 umol, 0.3 eq) were added. The suspension was degassed under vacuum and purged with CO several times and then warmed to 70 °C and stirred under a CO (50 psi) atmosphere for 16 h. To the reaction mixture was added thiourea (resin) (1 g) and stirred at 20 °C for 2 h. The reaction mixture was filtered and the filter cake was washed with MeOH (10 mL × 3). The filtrate was concentrated in vacuo to give a residue that was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(0.225% FA)-ACN];B%: 35%-65%,10min) to afford methyl 4-[[(1S,3R)-3-[(4-methoxybenzoyl)amino]cyclohexyl]amino]-2-(trifluoromethyl) quinoline-8-carboxylate (7.4 mg, 14.8 umol, 13% yield).

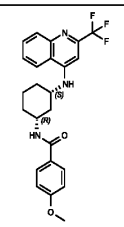
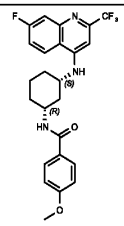
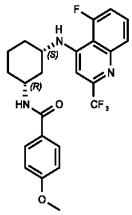
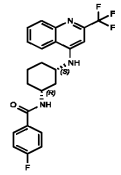
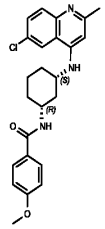
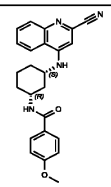
LCMS-ESI (m/z) calculated: 501.5; found 502.3 $[M+H]^+$, RT = 0.980 min (Method 2).

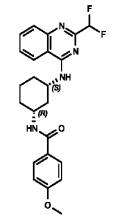
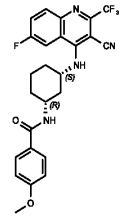
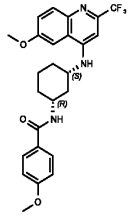
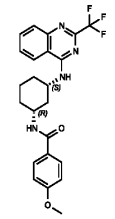
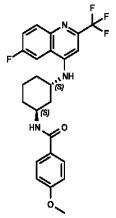
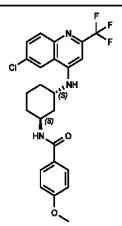
^1H NMR (400MHz, DMSO) δ = 8.56 (d, J=7.6 Hz, 1H), 8.18 (d, J=7.8 Hz, 1H), 7.89 - 7.80 (m, 3H), 7.59 (dd, J=7.2, 8.4 Hz, 1H), 7.53 (d, J=8.2 Hz, 1H), 7.00 - 6.94 (m, 3H), 4.09 - 3.96 (m, 1H), 3.87 (s, 4H), 3.80 (s, 3H), 2.17 (br d, J=11.9 Hz, 1H), 1.97 (br d, J=11.5 Hz, 1H), 1.92 - 1.77 (m, 2H), 1.55 (q, J=12.0 Hz, 2H), 1.46 - 1.26 (m, 2H).

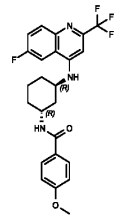
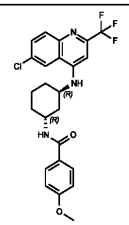
The compounds listed in Table 1 were made using the procedures of Scheme 1.

Table 1

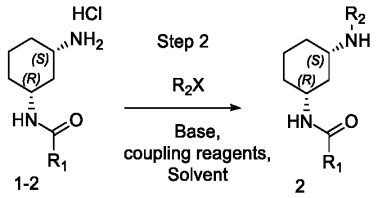
Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	1-1	9.083	461.461	462.2	$[M+H]^+$	Method 1
	1-2	10.403	443.47	444.2	$[M+H]^+$	Method 1
	1-3	7.746	457.497	458.3	$[M+H]^+$	Method 1
	1-4	8.975	461.461	462.2	$[M+H]^+$	Method 1

Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	1-5	7.213	443.47	444.2	$[M+H]^+$	Method 1
	1-6	0.889	461.461	462.2	$[M+H]^+$	Method 4
	1-7	0.936	461.461	462.2	$[M+H]^+$	Method 4
	1-8	1.031	431.435	432.2	$[M+H]^+$	Method 2
	1-9	5.884	423.94	424.2	$[M+H]^+$	Method 1
	1-10	6.871	400.48	401.3	$[M+H]^+$	Method 1

Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	1-11	7.143	426.47	427.2	$[M+H]^+$	Method 1
	1-12	9.471	486.47	487.2	$[M+H]^+$	Method 1
	1-13	7.878	473.5	474.2	$[M+H]^+$	Method 1
	1-14	12.167	444.46	445.2	$[M+H]^+$	Method 1
	1-15	9.339	461.46	462.2	$[M+H]^+$	Method 1
	1-16	10.064	477.91	478.2	$[M+H]^+$	Method 1

Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	1-17	9.356	461.46	462.2	$[M+H]^+$	Method 1
	1-18	10.077	477.91	478.2	$[M+H]^+$	Method 1

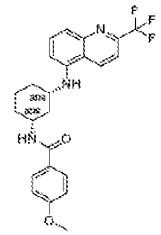
Scheme 2



Reagents: Base (t-Bu-ONa, TEA, Cs_2CO_3…), Coupling Reagent ($Pd(OAc)_2$, 1-BuXPhosPd, $Pd(dppf)Cl_2$), solvent (1,4-dioxane)

EXAMPLE 7

SYNTHESIS OF EXAMPLE 7



Step 2: Synthesis of 4-methoxy-N-((1R,3S)-3-((2-(trifluoromethyl)quinolin-5-yl)amino)cyclohexyl)benzamide

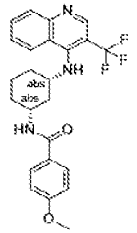
A mixture of 5-bromo-2-(trifluoromethyl)quinoline (97 mg, 1 Eq, 351 µmol), N-((1R,3S)-3-aminocyclohexyl)-4-methoxybenzamide hydrochloride (100 mg, 1 Eq, 351 µmol), cesium carbonate (343 mg, 3 Eq, 1.05 mmol), palladium(II) acetate (3.9 mg, 0.05 Eq, 17.6 µmol), and BINAP (22 mg, 0.10 Eq, 35 µmol) in 1,4-dioxane (3 mL) was degassed with nitrogen for 5 min. The vial was capped and the resulting mixture was heated at 100 °C. After stirring for 20 hours at 100 °C, the reaction mixture was cooled to room temperature, passed through a syringe filter, and the filtrate was directly loaded/purified by prep HPLC (ISCO ACCQPrep 150). to afford 4-methoxy-N-((1R,3S)-3-((2-(trifluoromethyl)quinolin-5-yl)amino)cyclohexyl)benzamide (49 mg, 111 µmol, 32 % yield).

LCMS-ESI (m/z) calculated: 443.47; found 444.2 $[M+H]^+$, RT = 0.987 min (Method 11).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, *J* = 8.8 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.81 (dd, *J* = 8.7, 6.8 Hz, 3H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.43 (d, *J* = 7.6 Hz, 1H), 4.02 – 3.92 (m, 1H), 3.79 (s, 3H), 3.65 – 3.56 (m, 1H), 2.27 (d, *J* = 12.1 Hz, 1H), 2.09 – 2.03 (m, 1H), 1.92 – 1.80 (m, 2H), 1.56 – 1.27 (m, 4H).

EXAMPLE 8

SYNTHESIS OF EXAMPLE 8



Step 2: Synthesis of 4-methoxy-N-((1R,3S)-3-((3-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)benzamide

A mixture of 4-bromo-3-(trifluoromethyl)quinoline (97 mg, 1 Eq, 351 µmol), N-((1R,3S)-3-aminocyclohexyl)-4-methoxybenzamide hydrochloride (100 mg, 1 Eq, 351 µmol), cesium carbonate (343 mg, 3 Eq, 1.05 mmol), palladium(II) acetate (3.9 mg, 0.05

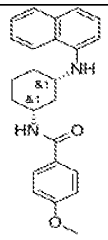
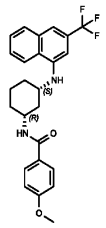
Eq, 17.6 µmol), and BINAP (22 mg, 0.10 Eq, 35.1 µmol) in 1,4-dioxane (3 mL) was degassed with nitrogen. The vial was capped and the resulting mixture was heated at 100 °C. After stirring for 20 h, the reaction mixture was cooled to room temperature, passed through a syringe filter, and the filtrate was directly loaded/purified by prep HPLC (ISCO ACCQPrep 150) to afford 4-methoxy-N-((1R,3S)-3-((3-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)benzamide (6.5 mg, 15 µmol, 4 % yield).

LCMS-ESI (m/z) calculated: 443.47; found 444.2 $[M+H]^+$, RT = 0.488 min (Method 11).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.37 (d, *J* = 8.6 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 3H), 7.61 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.03 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 5H), 2.07 (d, *J* = 12.0 Hz, 1H), 1.95 (d, *J* = 12.5 Hz, 1H), 1.80 (d, *J* = 9.0 Hz, 2H), 1.65 – 1.47 (m, 2H), 1.37 – 1.24 (m, 2H).

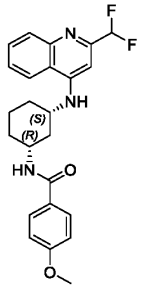
The compounds listed in Table 2 were made using the procedures of Scheme 2.

Table 2

Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	2-1	0.691	374.484	375.2	$[M+H]^+$	Method 7
	2-2	1.09	442.482	443.2	$[M+H]^+$	Method 5

EXAMPLE 9

SYNTHESIS OF EXAMPLE 9



Synthesis of 2-(difluoromethyl)quinolin-4-ol

To PPA (26.9 mmol, 10 mL, 5.00 eq) was added aniline (0.5 g, 5.37 mmol, 490 uL, 1 eq) and ethyl 4,4-difluoro-3-oxobutanoate (892 mg, 5.37 mmol, 1 eq) at 140 °C. The reaction mixture was stirred at 140 °C for 12 h. The reaction mixture was cooled to room temperature, poured into water (50 mL) and extracted with ethyl acetate (4 X 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under vacuo to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=1:2) to afford 2-(difluoromethyl)quinolin-4-ol (0.2 g, 1.02 mmol, 19% yield).

LCMS-ESI (m/z) calculated: 195.17; found 196.4 $[M+H]^+$, RT = 0.777 min (Method 2).

Synthesis of 4-chloro-2-(difluoromethyl) quinoline

To a solution of 2-(difluoromethyl)quinolin-4-ol (200 mg, 1.02 mmol, 1 eq) in DCE (3 mL) at 0 °C was added $POCl_3$ (430 mg, 2.80 mmol, 261 uL, 2.74 eq) dropwise. The reaction mixture was then heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to give a brown oil. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate=10:1) to give 4-chloro-2-(difluoromethyl)quinoline (200 mg, 936 umol, 91% yield).

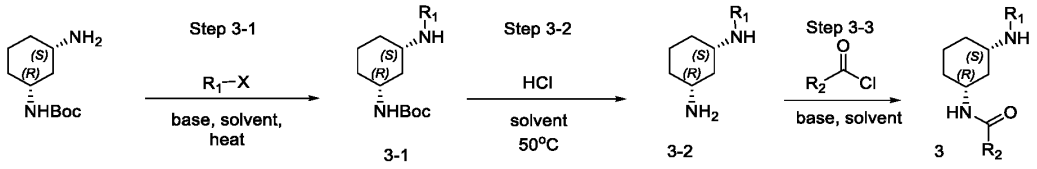
LCMS-ESI (m/z) calculated: 213.61 found 214.0 $[M+H]^+$, RT = 0.930 min (Method 2).

Step 2: Synthesis of N-[(1R,3S)-3-[[2-(difluoromethyl)-4-quinolyl]amino]cyclohexyl]-4-methoxy-benzamide

A mixture of 4-chloro-2-(difluoromethyl)quinoline (30 mg, 140 umol, 1 eq), N-[(1R,3S)-3-aminocyclohexyl]-4-methoxybenzamide (35 mg, 140 umol, 1 eq), [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium; ditert-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (22 mg, 28 umol, 0.2 eq) and t-BuONa (27 mg, 281 umol, 2 eq) in tert-amyl alcohol (1 mL) was heated at 100 °C for 3 h. The reaction mixture was cooled to room temperature, poured into water (10 mL), extracted with ethyl acetate (2 x 10 mL) and the combined organics were dried and concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge 150*25mm* 5um;mobile phase:[water(10mM NH4HCO3)-ACN];B%: 32%-62%,8min) to afford N-[(1R,3S)-3-[[2-(difluoromethyl)-4-quinolyl]amino]cyclohexyl]-4-methoxy-benzamide (3 mg, 6.7 umol, 5% yield).

LCMS-ESI (m/z) calculated: 425.47 found 426.2 $[M+H]^+$, RT = 0.797 min (Method 2).

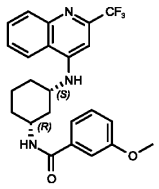
Scheme 3



Reagents: Step 3-1. R_1X, base (DIPEA), solvent (DMSO, NMP), 130 °C; Step 3-2. HCl, solvent (1,4-dioxane); Step 3-3. R_2COCl, base (DIPEA), solvent (DMF)

EXAMPLE 10

SYNTHESIS OF EXAMPLE 10



Step 3-1. Synthesis of tert-butyl ((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamate

To a solution of 4-chloro-2-(trifluoromethyl)quinoline (1.08 g, 1 Eq, 4.65 mmol) and tert-butyl ((1R,3S)-3-aminocyclohexyl)carbamate (0.996 g, 1 Eq, 4.65 mmol) in DMSO (12 mL) was added DIPEA (2.40 g, 3.2 mL, 4 Eq, 18.6 mmol). The vial was capped and the resulting solution was heated at 130 °C. After stirring for 3 hours at 130 °C, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with water and extracted with EtOAc (3 x 20 mL). The organic layers were combined, washed with brine, and concentrated under reduced pressure. The residue was purified by flash column chromatography (ISCO Gold 120g, 0-80% EtOAc/hexanes) to yield tert-butyl ((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamate (0.584 g, 1.43 mmol, 31 % yield).

LCMS-ESI (m/z) calculated: 409.45 found 410.3 $[M+H]^+$, RT = 4.976 min (Method 10).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 6.94 – 6.75 (m, 2H), 3.81 – 3.70 (m, 1H), 3.52 – 3.39 (m, 1H), 2.07 (d, J = 12.0 Hz, 1H), 1.91 (d, J = 12.2 Hz, 1H), 1.84 – 1.71 (m, 2H), 1.50 – 1.28 (m, 12H), 1.17 – 1.07 (m, 1H).

Step 3-2. Synthesis of (1S,3R)-N1-(2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride

To a stirred suspension of tert-butyl ((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamate (580 mg, 1 Eq, 1.42 mmol) in 1,4-dioxane (10 mL) was added 4M hydrogen chloride in 1,4-dioxane (3.54 mL, 4.00 molar, 10 Eq, 14.2

mmol). The resulting mixture was stirred at 50 °C for 16 h. The reaction mixture was filtered, and the resulting filter cake was washed with diethyl ether and dried under high vacuum to yield (1S,3R)-N1-(2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (491 mg, 1.42 mmol, 100 %).

LCMS-ESI (m/z) calculated: 309.2 found 310.2 $[M+H]^+$, RT = 1.294 min (Method 10).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, *J* = 8.5 Hz, 1H), 8.22 (s, 4H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 4.06 – 3.94 (m, 1H), 3.32 – 3.20 (m, 1H), 2.25 (d, *J* = 11.7 Hz, 1H), 2.03 – 1.81 (m, 3H), 1.68 – 1.56 (m, 1H), 1.54 – 1.41 (m, 2H), 1.39 – 1.27 (m, 1H).

Step 3-3. Synthesis of 3-methoxy-N-((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)benzamide

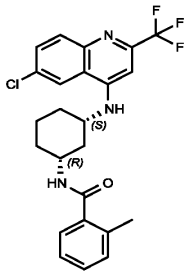
To the solution of (1S,3R)-N1-(2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine (20 mg, 1 Eq, 65 µmol) and DIEA (25 mg, 3 Eq, 0.19 mmol) in DMF (1.5 mL) was added 3-(methoxycarbonyl)benzoic acid chloride (12 mg, 1.2 Eq, 78 µmol). The reaction mixture was stirred at 25 °C for 18 h. The crude mixture was purified by Waters prep HPLC (20-90% 0.1% formic acid in MeCN and 0.1% formic acid in water) to yield 3-methoxy -N-((1R,3S)-3-((2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)benzamide (8.4 mg, 19 µmol, 29 % yield).

LCMS-ESI (m/z) calculated: 443.47 found 444.20 $[M+H]^+$, RT = 7.592 min (Method 1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (d, *J* = 8.5 Hz, 1H), 8.32 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.52 – 7.30 (m, 4H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.90 (s, 1H), 4.05 (d, *J* = 11.8 Hz, 1H), 3.88 (d, *J* = 7.9 Hz, 1H), 3.80 (d, *J* = 1.8 Hz, 3H), 2.19 (d, *J* = 12.1 Hz, 1H), 1.99 (d, *J* = 12.2 Hz, 1H), 1.87 (dd, *J* = 25.2, 12.8 Hz, 2H), 1.72 – 1.53 (m, 2H), 1.51 – 1.20 (m, 2H).

EXAMPLE 11

SYNTHESIS OF EXAMPLE 11



Step 3-1. Synthesis of tert-butyl ((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl) amino)cyclohexyl)carbamate

To a stirring solution of 4,6-dichloro-2-(trifluoromethyl)quinoline (1.241 g, 1 Eq, 4.666 mmol) and tert-butyl ((1R,3S)-3-aminocyclohexyl)carbamate (1.0 g, 1 Eq, 4.666 mmol) in DMSO (6 mL) was added DIPEA (2.41 g, 3.30 mL, 4 Eq, 18.7 mmol). The vial was capped and heated at 130 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with water (10 mL) and extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with brine, and concentrated in vacuo. The crude residue was purified by flash silica gel column chromatography (0-100% 10% MeOH in EtOAc and hexanes) to afford tert-butyl ((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamate (1.229 g, 2.768 mmol, 59 % yield).

Step 3-2. Synthesis of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride

To tert-butyl ((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl) carbamate (1.229 g, 1 Eq, 2.768 mmol) in 1,4-Dioxane (10 mL) was added 4M hydrogen chloride in 1,4-dioxane (1.51 g, 10.4 mL, 4.00 molar, 15 Eq, 41.5 mmol). The vial was capped and was heated at 50 °C for 14 h. The reaction mixture was cooled to room temperature, filtered, and the filter cake was washed with diethyl ether (2 x 10 mL) and dried under high vacuum to yield (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (1.15 g, 3.02 mmol, 100 % yield).

LCMS-ESI (m/z) calculated: 343.1 found 344.1 $[M+H]^+$, RT = 0.66 min (Method 11)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.91 – 7.84 (m, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 6.97 (s, 1H), 3.97 – 3.85 (m, 1H), 3.57 (s, 3H), 3.31 – 3.19 (m, 1H), 2.30 – 2.22 (m, 1H), 2.04 – 1.89 (m, 2H), 1.88 – 1.79 (m, 1H), 1.64 – 1.27 (m, 4H).

Step 3-3. Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-2-methylbenzamide

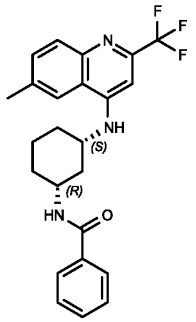
To a solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (60 mg, 1 Eq, 0.16 mmol) in DMF (2 mL) was added DIPEA (0.11 mL, 4 Eq, 0.63 mmol), followed by 2-methylbenzoyl chloride (26 mg, 22 µL, 1.05 Eq, 0.17 mmol). The resulting mixture was allowed to stir at room temperature for 1 h. The reaction mixture was passed through a syringe filter, and the filtrate was directly loaded/purified by prep HPLC (ISCO ACCQPrep 150) to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-2-methylbenzamide (20 mg, 43 µmol, 27 % yield).

LCMS-ESI (m/z) calculated: 461.91 found 462.2 $[M+H]^+$, RT = 1.025 min (Method 11)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.32 – 7.19 (m, 4H), 6.96 (s, 1H), 4.05 – 3.86 (m, 2H), 2.32 (s, 3H), 2.17 (d, *J* = 12.1 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.81 (d, *J* = 13.3 Hz, 1H), 1.60 – 1.45 (m, 2H), 1.39 – 1.22 (m, 2H).

EXAMPLE 12

SYNTHESIS OF EXAMPLE 12



Step 3-1. Synthesis of tert-butyl ((1R,3S)-3-((6-methyl-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamate

To a solution of tert-butyl ((1R,3S)-3-aminocyclohexyl)carbamate (1.0 g, 1 Eq, 4.7 mmol) and 4-chloro-6-methyl-2-(trifluoromethyl)quinoline (1.1 g, 1 Eq, 4.7 mmol) in DMSO (12 mL) was added DIPEA (1.2 g, 1.6 mL, 2 Eq, 9.3 mmol). The vial was capped and the resulting solution was heated at 130 °C. After stirring for 3 h at 130 °C, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3x10 mL). The organic layers were combined, washed with brine and concentrated under reduced pressure. The residue was dissolved in DCM and purified by flash column chromatography (ISCO Gold 120g, 0-80% EtOAc/hexanes, 11 CV ramp) to afford tert-butyl ((1R,3S)-3-((6-methyl-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamate (1.3 g, 3.1 mmol, 66 % yield).

LCMS-ESI (m/z) calculated: 423.48 found 424.2 $[M+H]^+$, RT = 5.092 min (Method 10).

Step 3-2. Synthesis of (1S,3R)-N1-(6-methyl-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride

To tert-butyl ((1R,3S)-3-((6-methyl-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl) carbamate (1.3 g, 1 Eq, 3.1 mmol) in 1,4-Dioxane (10 mL) was added 4M hydrogen chloride in 1,4-dioxane (7.7 mL, 4.00 molar, 10 Eq, 31 mmol). The reaction mixture was heated at 50 °C for 18 h, cooled to room temperature, filtered,

and the filter cake was washed with diethyl ether and dried under high vacuum to afford (1S,3R)-N1-(6-methyl-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (1.1 g, 3.1 mmol, 100 % yield).

LCMS-ESI (m/z) calculated: 323.82 found 324.2 $[M+H]^+$, RT = 2.28 min (Method 10).

Step 3-3. Synthesis of N-((1R,3S)-3-((6-methyl-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)benzamide

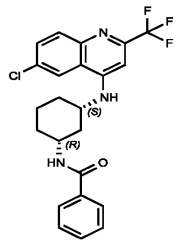
To a solution of (1S,3R)-N1-(6-methyl-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (75 mg, 1 Eq, 0.21 mmol) in DMF (1.5 mL) was added DIPEA (0.15 mL, 4 Eq, 0.83 mmol), followed by benzoyl chloride (31 mg, 1.05 Eq, 0.22 mmol). The resulting mixture was allowed to stir at room temperature for 18 h. The reaction mixture was passed through a syringe filter, and the filtrate was directly loaded/purified by prep HPLC (ISCO ACCQPrep 150) to afford N-((1R,3S)-3-((6-methyl-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl) benzamide (9.1 mg, 21 µmol, 10 % yield).

LCMS-ESI (m/z) calculated: 427.47 found 428.3 $[M+H]^+$, RT = 0.848 min (Method 11)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (d, J = 7.9 Hz, 1H), 8.21 (s, 1H), 7.89 – 7.71 (m, 3H), 7.60 – 7.40 (m, 4H), 7.24 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 4.09 – 3.98 (m, 1H), 3.89 – 3.79 (m, 1H), 2.49 (s, 3H), 2.19 (d, J = 12.0 Hz, 1H), 2.01 – 1.79 (m, 3H), 1.62 – 1.48 (m, 2H), 1.45 – 1.30 (m, 2H).

EXAMPLE 13

SYNTHESIS OF EXAMPLE 13



Step 3-3. Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)benzamide

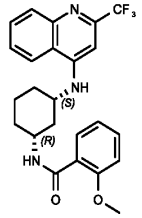
To a solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (45 mg, 1 Eq, 0.12 mmol) in DMF (1.5 mL) was added DIPEA (83 µL, 4 Eq, 0.47 mmol), followed by benzoyl chloride (17 mg, 1.05 Eq, 0.12 mmol). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was passed through a syringe filter, and the filtrate was directly loaded/purified by prep HPLC (ISCO ACCQPrep 150) to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl)benzamide (5 mg, 0.01 mmol, 9 % yield).

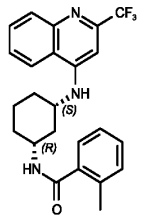
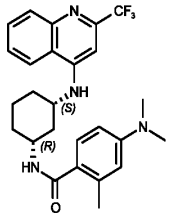
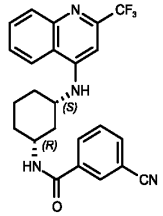
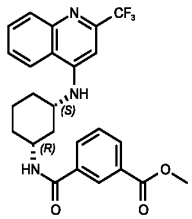
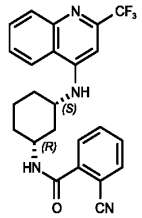
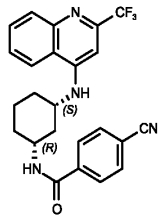
LCMS-ESI (m/z) calculated: 447.89 found 448.2 $[M+H]^+$, RT = 1.000 min (Method 11)

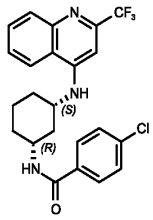
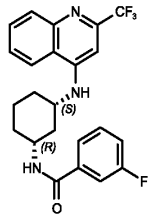
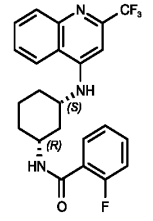
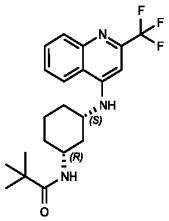
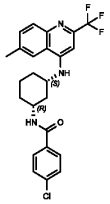
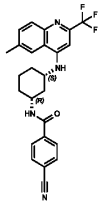
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.34 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.53 – 7.42 (m, 4H), 6.95 (s, 1H), 4.09 – 4.01 (m, 1H), 3.93 – 3.84 (m, 1H), 2.17 (d, *J* = 12.0 Hz, 1H), 1.97 (d, *J* = 12.2 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.60 – 1.50 (m, 2H), 1.43 – 1.30 (m, 2H).

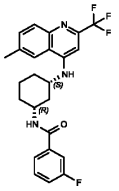
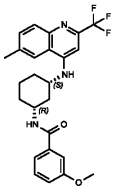
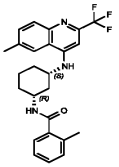
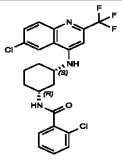
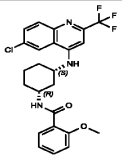
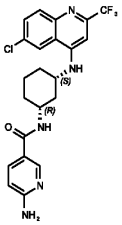
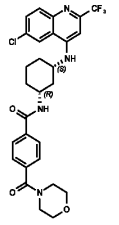
The compounds listed in Table 3 were made using the procedures of Scheme 3.

Table 3

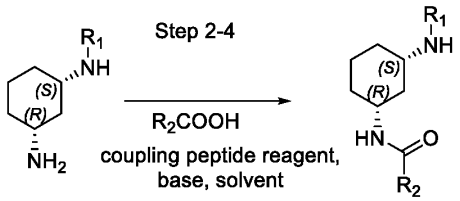
Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	3-1	7.906	443.47	444.2	$[M+H]^+$	Method 1

	3-2	7.606	427.47	428.2	$[M+H]^+$	Method 1
	3-3	7.317	470.54	471.2	$[M+H]^+$	Method 1
	3-4	7.497	438.45	439.2	$[M+H]^+$	Method 1
	3-5	7.717	471.48	472.2	$[M+H]^+$	Method 1
	3-6	6.927	438.45	439.2	$[M+H]^+$	Method 1
	3-7	7.419	438.45	439.2	$[M+H]^+$	Method 1

	3-8	8.449	447.89	448.2	$[M+H]^+$	Method 1
	3-9	7.849	431.43	432.2	$[M+H]^+$	Method 1
	3-10	7.715	431.43	432.2	$[M+H]^+$	Method 1
	3-11	7.789	393.45	394.1	$[M+H]^+$	Method 6
	3-12	8.807	461.91	462.3	$[M+H]^+$	Method 1
	3-13	7.813	452.48	453.2	$[M+H]^+$	Method 1

	3-14	8.214	445.46	446.2	$[M+H]^+$	Method 1
	3-15	7.931	457.50	458.3	$[M+H]^+$	Method 1
	3-16	8.050	441.50	442.3	$[M+H]^+$	Method 1
	3-17	10.007	482.33	482.2	$[M+H]^+$	Method 1
	3-18	10.269	477.91	478.2	$[M+H]^+$	Method 1
	3-19	6.287	463.89	464.2	$[M+H]^+$	Method 1
	3-20	8.298	561	561.2	$[M+H]^+$	Method 1

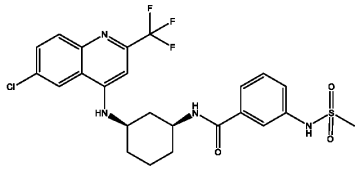
Scheme 4



Reagents: Step 2-4. R_2COOH, peptide coupling reaction (HATU), base (DIPEA), solvent (DMF)

EXAMPLE 14

SYNTHESIS OF EXAMPLE 14



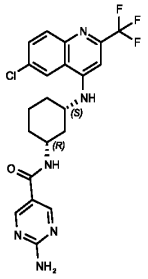
Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-(methylsulfonamido)benzamide

To a stirring solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (90 mg, 1 Eq, 0.24 mmol) in DMF (2 mL) were added 3-(methylsulfonamido)benzoic acid (51 mg, 1 Eq, 0.24 mmol), HATU (0.10 g, 1.1 Eq, 0.26 mmol) and N-ethyl-N-isopropylpropan-2-amine (DIPEA) (92 mg, 0.12 mL, 3 Eq, 0.71 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered and purified by reversed phase prep HPLC (35-->55% 0.1% formic acid in MeCN and 0.1% formic acid in H_2O) to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-(methylsulfonamido)benzamide (66 mg, 123 µmol, 52 % yield).

LCMS-ESI (m/z) calculated: 540.99 found 541.2 $[M+H]^+$, RT = 0.906 min (Method 11)

EXAMPLE 15

SYNTHESIS OF EXAMPLE 15



Synthesis of 2-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl] pyrimidine-5-carboxamide

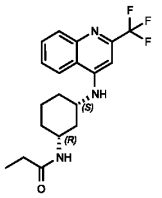
To a solution of 2-aminopyrimidine-5-carboxylic acid (12 mg, 1 Eq, 87 µmol) in DMF (2 mL) was added HATU (50 mg, 1.5 Eq, 0.13 mmol). The resulting solution was stirred at room temperature for 10 minutes. To the mixture was added (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine (30 mg, 1 Eq, 87 µmol). The resulting mixture was stirred at room temperature for 19 h. The crude mixture was directly purified by prep HPLC to afford 2-amino-N-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]pyrimidine-5-carboxamide (33 mg, 71 µmol, 82 % yield)

LCMS-ESI (m/z) calculated: 464.88 found 465.2 $[M+H]^+$, RT = 7.332 min (Method 1)

^{1}H NMR (400 MHz, DMSO) δ 8.67 (d, *J* = 1.6 Hz, 2H), 8.61 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.74 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.18 (s, 2H), 6.94 (s, 1H), 4.12 – 3.76 (m, 2H), 2.18 (d, *J* = 12.0 Hz, 1H), 1.98 (d, *J* = 12.1 Hz, 1H), 1.86 (dd, *J* = 26.2, 13.0 Hz, 2H), 1.53 (dq, *J* = 23.5, 12.6, 11.9 Hz, 2H), 1.45 – 1.18 (m, 2H).

EXAMPLE 16

SYNTHESIS OF EXAMPLE 16



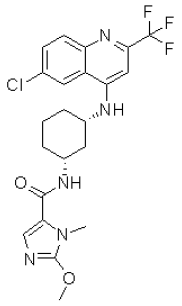
Synthesis of N-[(1R,3S)-3-[[2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl] propanamide

To a mixture of propionic acid (5 mg, 64 umol, 5 uL, 1 eq) in DMF (2 mL) were added DIPEA (8 mg, 64 umol, 11.10 uL, 1 eq), (1S,3R)-N1-[2-(trifluoromethyl)-4-quinolyl]cyclohexane-1,3-diamine (25 mg, 70 umol, 1.1 eq, HCl) and HATU (24 mg, 64 umol, 1 eq). The reaction mixture was stirred at 30 °C for 12 hr. The reaction mixture was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150*50mm*3 um; mobile phase: [water(0.225%FA)-ACN];B%: 30%-50%,10min) to yield N-[(1R,3S)-3-[[2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]propanamide (3 mg, 7 umol, 12% yield).

LCMS-ESI (m/z) calculated: 365.4 found 366.1 $[M+H]^+$, RT = 0.731 min (Method 6).

EXAMPLE 17

SYNTHESIS OF EXAMPLE 17



N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-2-methoxy-1-methyl-1H-imidazole-5-carboxamide

To a stirred solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (120 mg, 1 Eq, 316 µmol) in DMF (5 mL) were added 2-chloro-1-methyl-1H-imidazole-5-carboxylic acid (50.7 mg, 1 Eq, 316 µmol), HATU (120 mg, 1 Eq, 316 µmol), and DIPEA (163 mg, 0.22 mL, 4 Eq, 1.26 mmol). The resulting mixture was allowed to stir at room temperature. After stirring for 1 hour, the reaction mixture was filtered, and the filtrate was directly loaded/purified by prep HPLC (ISCO ACCQPrep 150) to afford 2-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl)-1-methyl-1H-imidazole-5-carboxamide (83.9 mg, 173 µmol, 54.7 %).

LCMS-ESI (m/z) calculated: 485.1 found 486.2[M+H]+, RT = 9.057 min (Method 1).

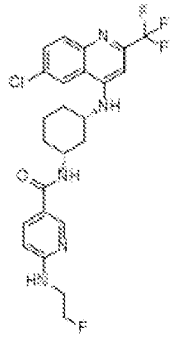
To a solution of 2-chloro-N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-methyl-imidazole-4-carboxamide (20 mg, 1 Eq, 41.13 umol) in 2-methylbutan-2-ol (2 mL) was added CH_3ONa (5.4 M, 3 Eq, 22.85 uL). The resulting solution was heated at 70 °C for 23 hours. The reaction mixture was cooled to room temperature and was directly purified by prep-HPLC to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl) -4-quinolyl]amino]-cyclohexyl]-2-methoxy-3-methyl-imidazole-4-carboxamide (3.0 mg, 5.67 umol, 14% yield).

LCMS-ESI (m/z) calculated: 481.9 found 482.3[M+H]$^+$, RT = 0.472 min (Method 2).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.62-8.58 (m, 1H), 8.37 - 8.29 (m, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.76-7.71 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 6.92 (s, 1H), 3.95 (s, 4H), 3.88 - 3.80.

EXAMPLE 18

SYNTHESIS OF EXAMPLE 18



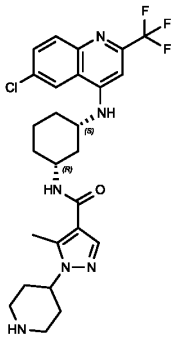
Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-6-((2-fluoroethyl)amino)nicotinamide

A solution of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-6-fluoronicotinamide 4-411 (50 mg, 1 Eq, 0.11 mmol in NMP (4 mL) was charged with 2-fluoroethan-1-amine (6.8 mg, 1 Eq, 0.11 mmol), and DIPEA (42 mg, 56 µL, 3 Eq, 0.32 mmol). The resulting yellow solution was allowed to stir at 75°C for 18 hours. The reaction mixture was cooled to room temperature and was directly purified by prep-HPLC to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-6-((2-fluoroethyl)amino)nicotinamide (9.0 mg, 18 µmol, 16 % yield).

LCMS-ESI (m/z) calculated: 509.93; found 510.2 [M+H]$^+$, tR = 7.013 min (Method 1).

EXAMPLE 19

SYNTHESIS OF EXAMPLE 19



Synthesis of tert-butyl 4-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-5-methyl-1H-pyrazol-1-yl)piperidine-1-carboxylate

A solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (80 mg, 1 Eq, 0.21 mmol) and DIPEA (0.15 mL, 4 Eq, 0.84 mmol) in DMF (4 mL) was charged with HATU (80 mg, 1 Eq, 0.21 mmol) and 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-5-methyl-1H-pyrazole-4-carboxylic acid (65 mg, 1 Eq, 0.21 mmol). The resulting solution was stirred at room temperature for 1 hour. The crude mixture was directly purified by prep-HPLC to afford tert-butyl 4-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-5-methyl-1H-pyrazol-1-yl)piperidine-1-carboxylate (83.4 mg, 131 µmol, 62 % yield).

LCMS-ESI (m/z) calculated: 634.26; found 635.3 $[M+H]^+$, tR = 10.514 min (Method 1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.89 (d, *J* = 9.3 Hz, 2H), 7.80 – 7.70 (m, 2H), 7.48 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 2.8 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 4.08 – 3.92 (m, 3H), 3.85 (d, *J* = 10.0 Hz, 1H), 3.41 (s, 4H), 2.90 (s, 2H), 2.12 (d, *J* = 11.7 Hz, 1H), 1.96 (d, *J* = 12.4 Hz, 1H), 1.89 – 1.73 (m, 6H), 1.54 – 1.25 (m, 13H).

Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-5-methyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide

A solution of tert-butyl 4-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-5-methyl-1H-pyrazol-1-yl)piperidine-1-carboxylate (78.9 mg, 1 Eq, 0.12 mmol) in 1,4-dioxane (5 mL) was charged with a solution of hydrogen chloride in 1,4-dioxane (4.0 M, 311 µL, 10 Eq, 1.24 mmol). The resulting

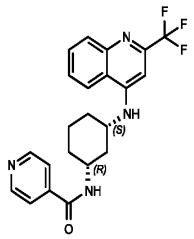
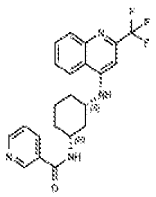
suspension was heated at 50°C for 3 hours. The reaction mixture was subsequently cooled to room temperature, filtered, and the filter cake was washed with diethyl ether and dried to yield N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-5-methyl-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide (57.8 mg, 108 µmol, 87.0 %).

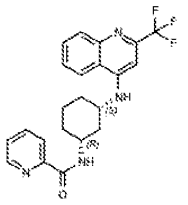
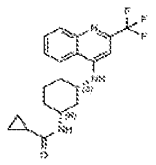
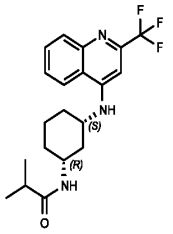
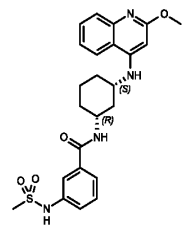
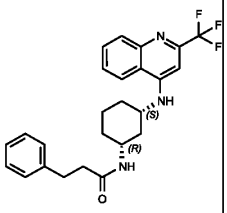
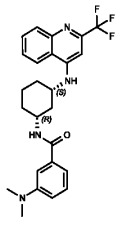
LCMS-ESI (m/z) calculated: 534.21; found 535.3 $[M+H]^+$, tR = 5.987 min (Method 1).

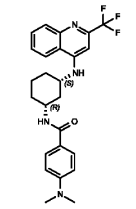
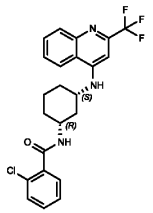
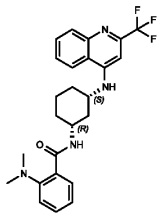
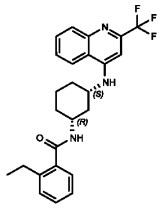
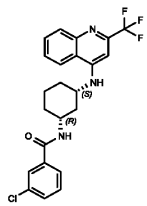
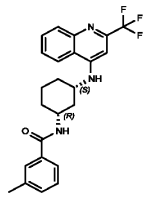
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (d, *J* = 10.9 Hz, 1H), 8.81 (d, *J* = 11.1 Hz, 1H), 8.66 (s, 1H), 7.97 – 7.88 (m, 2H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.73 (dd, *J* = 23.2, 8.4 Hz, 2H), 6.97 (s, 1H), 4.57 – 4.47 (m, 1H), 4.02 – 3.85 (m, 2H), 3.37 (d, *J* = 12.3 Hz, 2H), 3.06 (q, *J* = 12.9, 12.1 Hz, 2H), 2.51 (s, 3H), 2.24 – 2.08 (m, 3H), 1.96 (d, *J* = 13.3 Hz, 3H), 1.82 (t, *J* = 12.6 Hz, 2H), 1.60 – 1.46 (m, 2H), 1.44 – 1.35 (m, 1H), 1.34 – 1.23 (m, 1H).

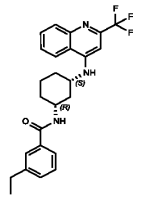
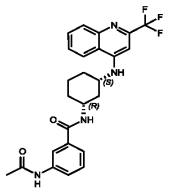
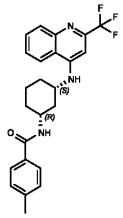
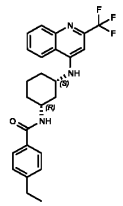
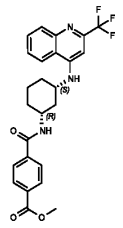
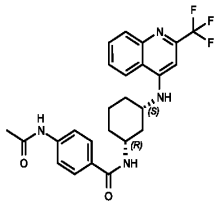
The compounds listed in Table 4 were made using the procedures of Scheme 4

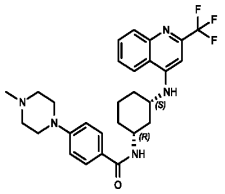
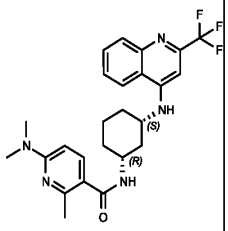
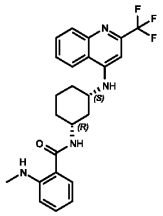
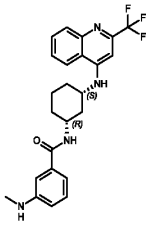
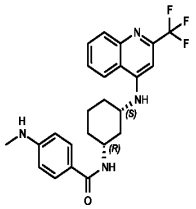
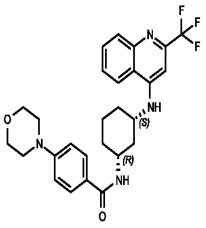
Table 4

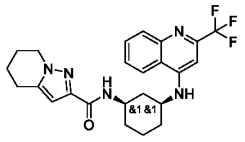
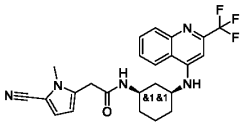
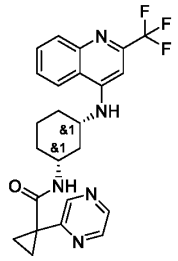
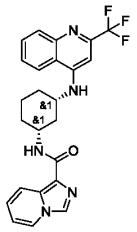
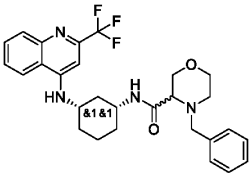
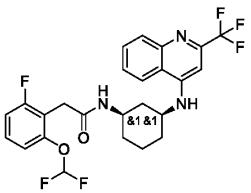
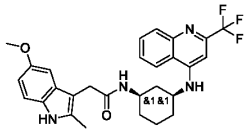
Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	4-1	0.712	414.432	415.1	$[M+H]^+$	Method 6
	4-2	0.715	414.432	415.1	$[M+H]^+$	Method 6

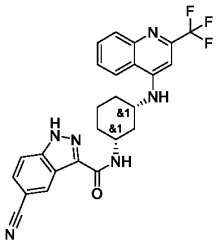
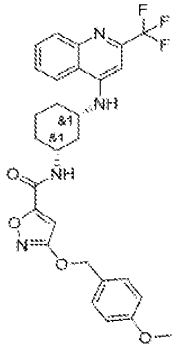
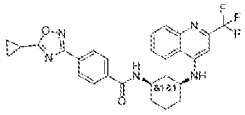
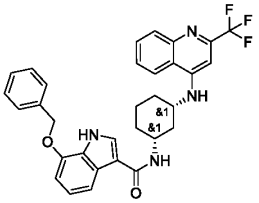
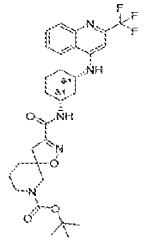
	4-3	0.787	414.432	415.1	$[M+H]^+$	Method 6
	4-4	0.749	377.411	378.1	$[M+H]^+$	Method 6
	4-5	0.762	379.427	380.1	$[M+H]^+$	Method 6
	4-6	4.718	468.57	469.2	$[M+H]^+$	Method 1
	4-7	0.820	441.498	442.1	$[M+H]^+$	Method 6
	4-8	0.798	456.513	457.3	$[M+H]^+$	Method 3

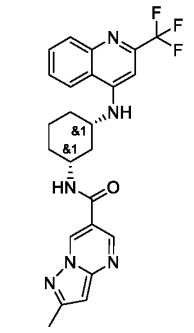
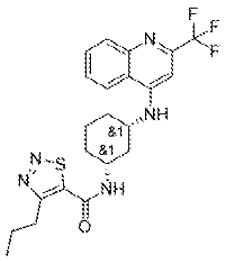
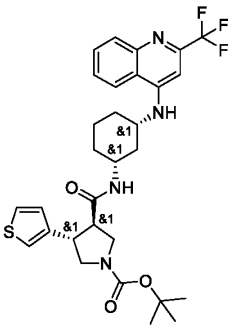
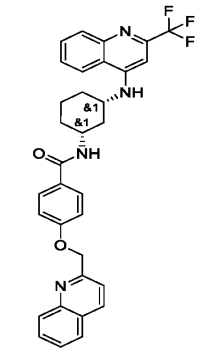
	4-9	0.835	456.513	457.3	$[M+H]^+$	Method 3
	4-10	0.820	447.89	448.1	$[M+H]^+$	Method 6
	4-11	0.732	456.513	457.1	$[M+H]^+$	Method 6
	4-12	0.825	441.498	442.1	$[M+H]^+$	Method 6
	4-13	0.839	447.89	448.1	$[M+H]^+$	Method 6
	4-14	0.826	427.471	428.1	$[M+H]^+$	Method 6

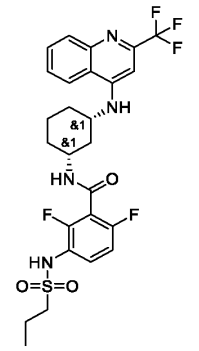
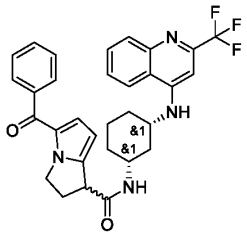
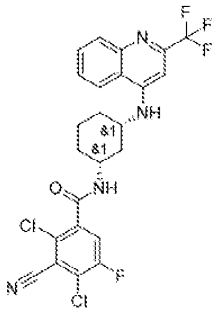
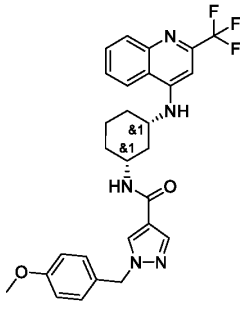
	4-15	0.849	441.498	442.1	$[M+H]^+$	Method 6
	4-16	0.773	470.496	471.1	$[M+H]^+$	Method 6
	4-17	0.820	427.471	428.1	$[M+H]^+$	Method 6
	4-18	0.841	441.498	442.1	$[M+H]^+$	Method 6
	4-19	0.820	471.48	472.1	$[M+H]^+$	Method 6
	4-20	0.766	470.496	471.1	$[M+H]^+$	Method 6

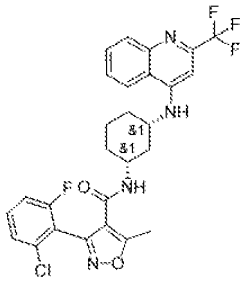
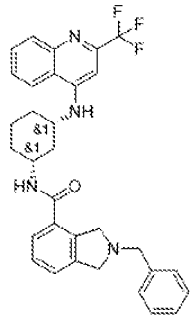
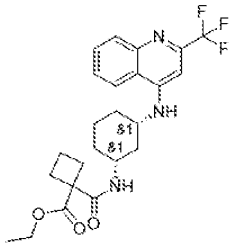
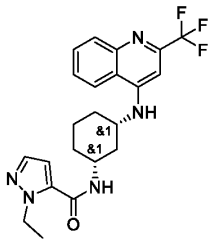
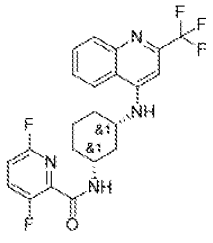
	4-21	0.710	511.593	512.2	[M+H]$^+$	Method 6
	4-22	0.738	471.528	472.3	[M+H]$^+$	Method 4
	4-23	0.806	442.486	443.1	[M+H]$^+$	Method 6
	4-24	0.734	442.486	443.1	[M+H]$^+$	Method 6
	4-25	0.770	442.486	443.1	[M+H]$^+$	Method 6
	4-26	0.800	498.55	499.2	[M+H]$^+$	Method 6

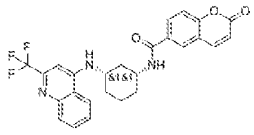
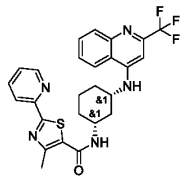
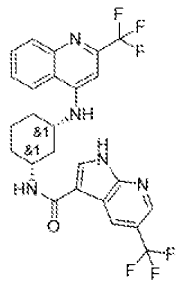
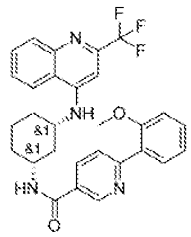
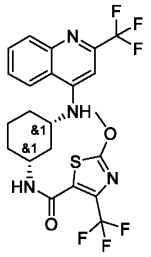
	4-27	0.833	457.501	458	$[M+H]^+$	Method 2
	4-28	0.815	455.485	456	$[M+H]^+$	Method 2
	4-29	0.804	455.485	455.9	$[M+H]^+$	Method 2
	4-30	0.826	453.469	453.9	$[M+H]^+$	Method 2
	4-31	0.783	512.577	513	$[M+H]^+$	Method 2
	4-32	0.865	511.468	512.1	$[M+H]^+$	Method 2
	4-33	0.743	510.561	511.1	$[M+H]^+$	Method 2

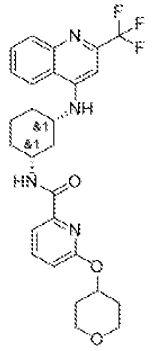
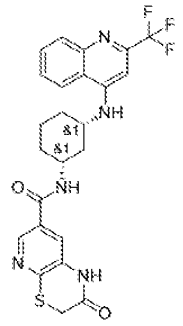
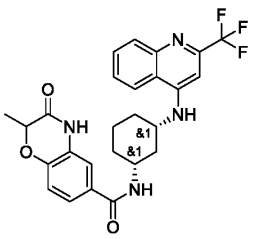
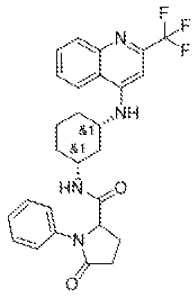
	4-34	0.751	478.479	479.1	[M+H]$^+$	Method 2
	4-35	0.897	540.543	541.2	[M+H]$^+$	Method 2
	4-36	0.890	521.544	522	[M+H]$^+$	Method 2
	4-37	0.824	558.605	559.2	[M+H]$^+$	Method 2
	4-38	0.893	575.633	576.1	[M+H]$^+$	Method 2

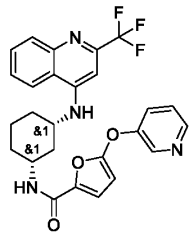
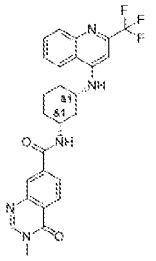
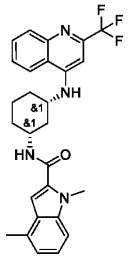
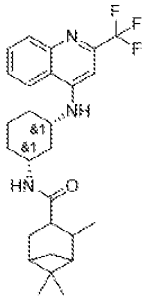
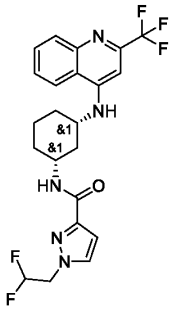
	4-39	0.815	468.484	468.9	[M+H]$^+$	Method 2
	4-40	0.865	463.52	463.9	[M+H]$^+$	Method 2
	4-41	0.912	588.69	589.1	[M+H]$^+$	Method 2
	4-42	0.877	570.616	571.1	[M+H]$^+$	Method 2

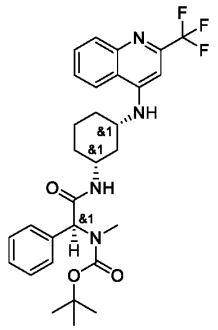
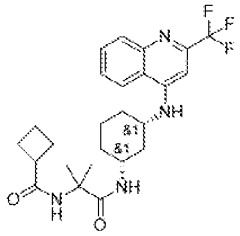
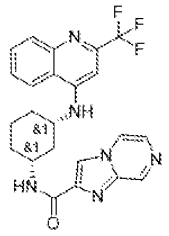
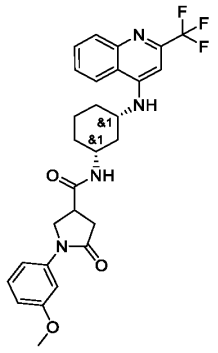
	4-43	0.750	570.58	571.1	[M+H]$^+$	Method 2
	4-44	0.882	546.594	547.1	[M+H]$^+$	Method 2
	4-45	0.885	525.33	525.9	[M+H]$^+$	Method 2
	4-46	0.85	523.56	524	[M+H]$^+$	Method 2

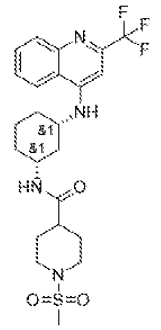
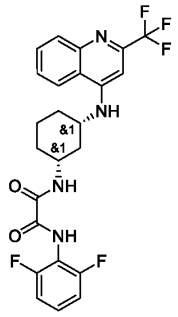
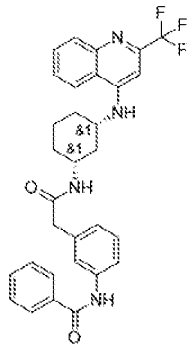
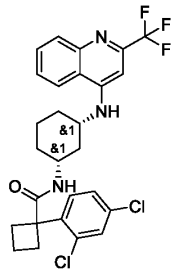
	4-47	0.788	546.95	547	$[M+H]^+$	Method 2
	4-48	0.699	544.622	545.2	$[M+H]^+$	Method 2
	4-49	0.738	463.501	464.1	$[M+H]^+$	Method 2
	4-50	0.718	431.463	432.1	$[M+H]^+$	Method 2
	4-51	0.723	450.413	451	$[M+H]^+$	Method 2

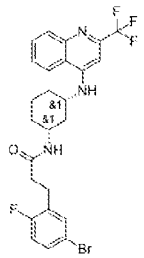
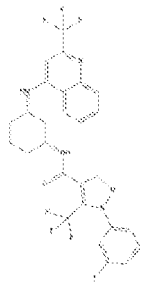
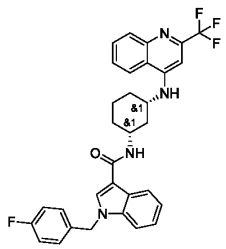
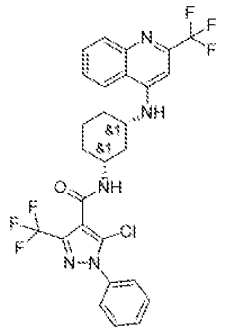
	4-52	0.731	481.475	482.1	[M+H]$^+$	Method 2
	4-53	0.771	511.57	512.3	[M+H]$^+$	Method 2
	4-54	0.863	521.467	521.9	[M+H]$^+$	Method 2
	4-55	0.819	520.556	521	[M+H]$^+$	Method 2
	4-56	0.861	518.48	518.9	[M+H]$^+$	Method 2

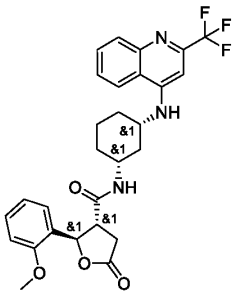
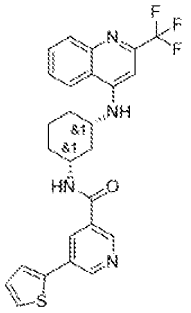
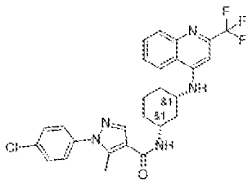
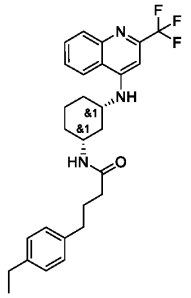
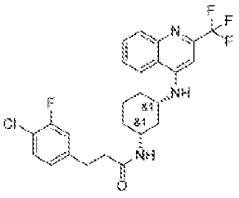
	4-57	0.87	514.549	515	[M+H]$^+$	Method 2
	4-58	0.793	501.53	501.9	[M+H]$^+$	Method 2
	4-59	0.817	498.506	499	[M+H]$^+$	Method 2
	4-60	0.722	496.534	497.3	[M+H]$^+$	Method 2

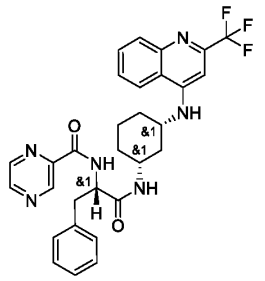
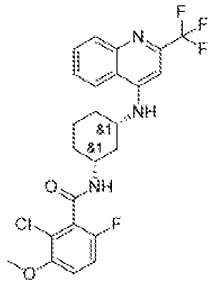
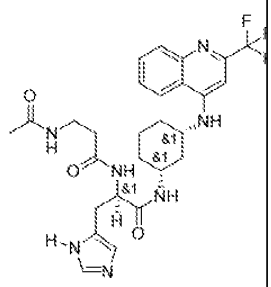
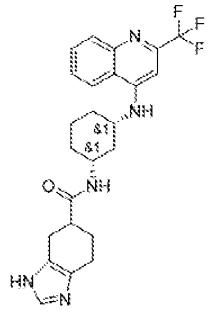
	4-61	0.727	496.49	497.2	[M+H]$^+$	Method 2
	4-62	0.714	495.506	496.2	[M+H]$^+$	Method 2
	4-63	0.841	480.535	481.3	[M+H]$^+$	Method 2
	4-64	0.933	473.584	474	[M+H]$^+$	Method 2
	4-65	0.812	467.444	467.9	[M+H]$^+$	Method 2

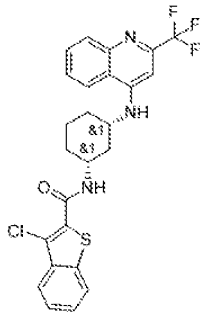
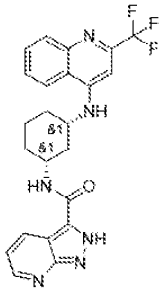
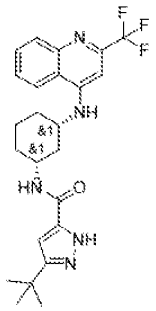
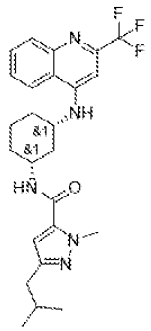
	4-66	0.822	556.63	557.1	$[M+H]^+$	Method 2
	4-67	0.700	476.544	477.1	$[M+H]^+$	Method 2
	4-68	0.685	454.457	455.1	$[M+H]^+$	Method 2
	4-69	0.832	526.56	527.1	$[M+H]^+$	Method 2

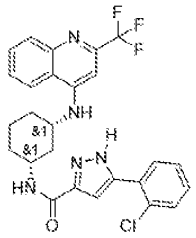
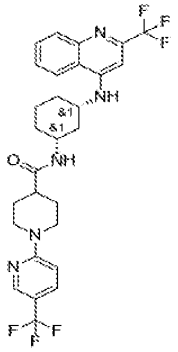
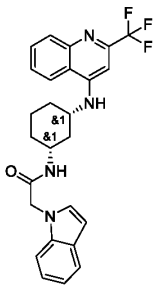
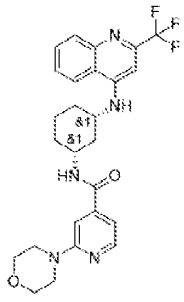
	4-70	0.782	498.57	499	$[M+H]^+$	Method 2
	4-71	0.762	492.45	493.1	$[M+H]^+$	Method 2
	4-72	0.756	546.594	547.3	$[M+H]^+$	Method 2
	4-73	0.868	536.42	537.2	$[M+H]^+$	Method 2

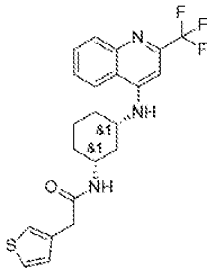
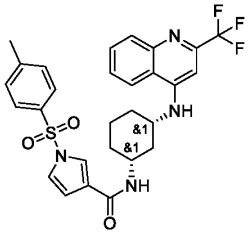
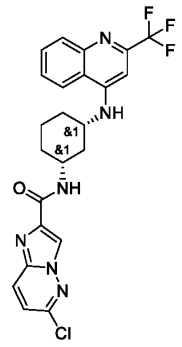
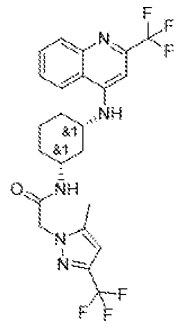
	4-74	0.797	538.385	540.2	[M+H]$^+$	Method 2
	4-75	0.826	565.496	566.2	[M+H]$^+$	Method 2
	4-76	0.847	560.597	561.2	[M+H]$^+$	Method 2
	4-77	0.854	581.95	582.1	[M+H]$^+$	Method 2

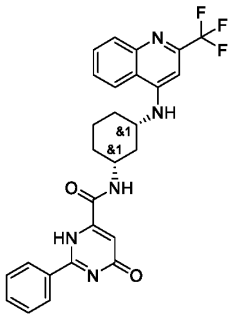
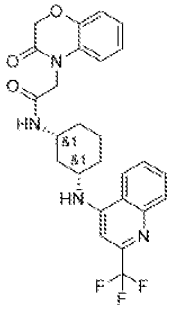
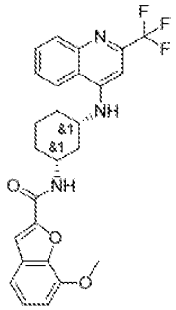
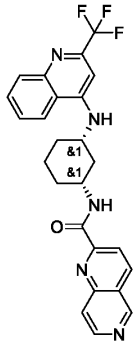
	4-78	0.771	527.544	528.3	[M+H]$^+$	Method 2
	4-79	0.832	496.55	497.1	[M+H]$^+$	Method 2
	4-80	0.883	527.98	528	[M+H]$^+$	Method 2
	4-81	0.905	483.579	484	[M+H]$^+$	Method 2
	4-82	0.875	493.93	494	[M+H]$^+$	Method 2

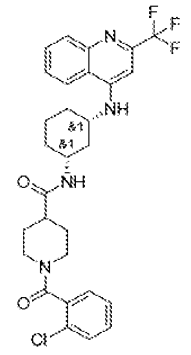
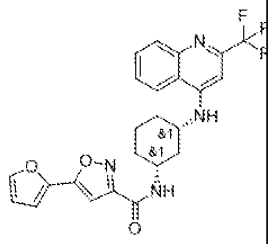
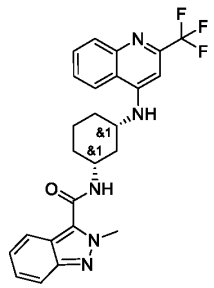
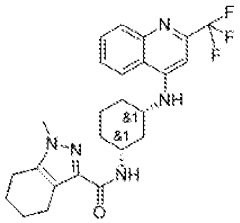
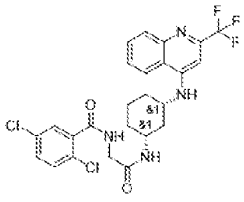
	4-83	0.858	562.597	563.2	$[M+H]^+$	Method 2
	4-84	0.848	495.9	496.1	$[M+H]^+$	Method 2
	4-85	0.694	559.594	560.1	$[M+H]^+$	Method 2
	4-86	0.717	457.501	458	$[M+H]^+$	Method 2

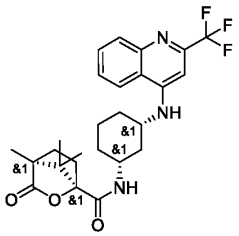
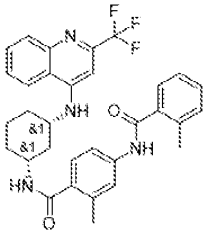
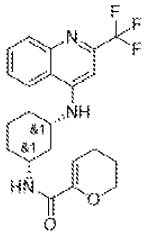
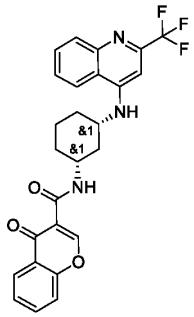
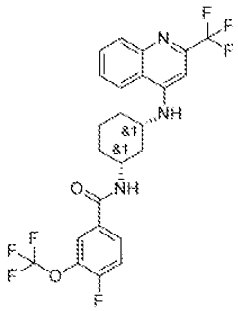
	4-87	0.944	503.97	503.9	$[M+H]^+$	Method 2
	4-88	0.804	454.457	454.9	$[M+H]^+$	Method 2
	4-89	0.849	459.517	460	$[M+H]^+$	Method 2
	4-90	0.801	473.544	474.3	$[M+H]^+$	Method 2

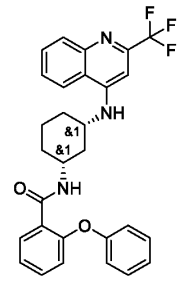
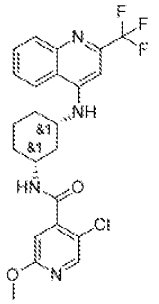
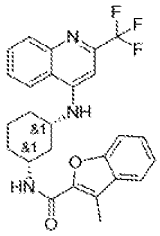
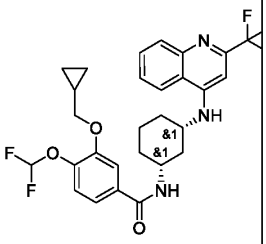
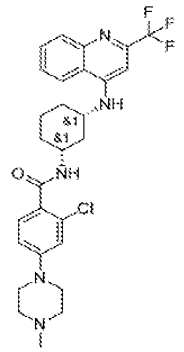
	4-91	0.796	513.95	514.2	[M+H]$^+$	Method 2
	4-92	0.797	565.564	566.2	[M+H]$^+$	Method 2
	4-93	0.794	466.508	467.3	[M+H]$^+$	Method 2
	4-94	0.652	499.538	500.2	[M+H]$^+$	Method 2

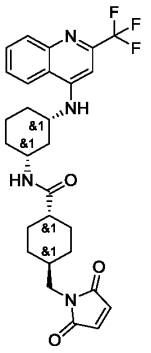
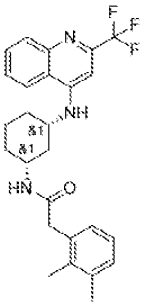
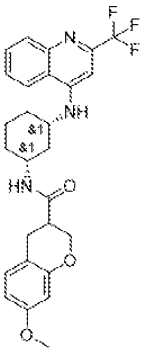
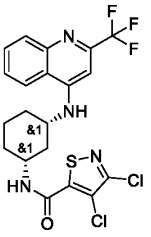
	4-95	0.718	433.49	434.1	[M+H]$^+$	Method 2
	4-96	0.900	556.6	557	[M+H]$^+$	Method 2
	4-97	0.746	488.9	489.2	[M+H]$^+$	Method 2
	4-98	0.767	499.461	500.2	[M+H]$^+$	Method 2

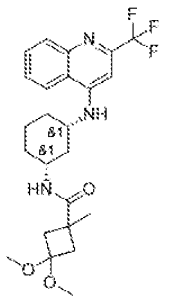
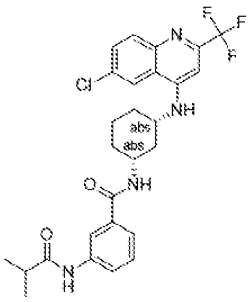
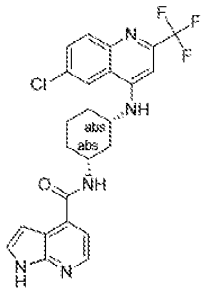
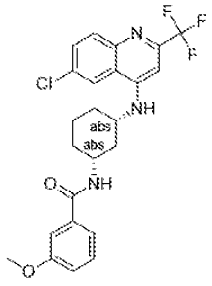
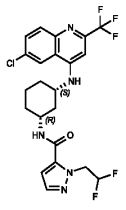
	4-99	0.755	507.517	508.3	$[M+H]^+$	Method 2
	4-100	0.735	498.506	499.2	$[M+H]^+$	Method 2
	4-101	0.702	483.491	484.1	$[M+H]^+$	Method 2
	4-102	0.613	465.48	466.1	$[M+H]^+$	Method 2

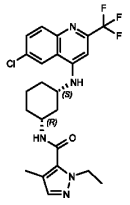
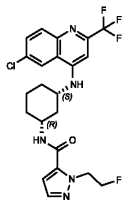
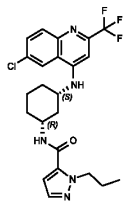
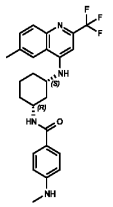
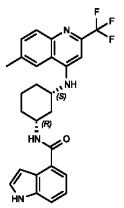
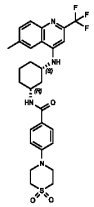
	4-103	0.668	559.03	559.2	[M+H]$^+$	Method 2
	4-104	0.793	470.452	471.1	[M+H]$^+$	Method 2
	4-105	0.844	467.496	468	[M+H]$^+$	Method 2
	4-106	0.779	471.528	472.1	[M+H]$^+$	Method 2
	4-107	0.716	539.38	539	[M+H]$^+$	Method 2

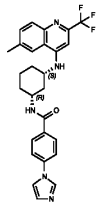
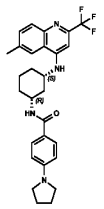
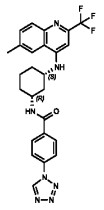
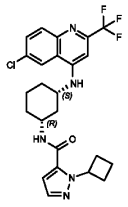
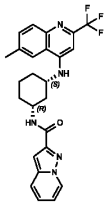
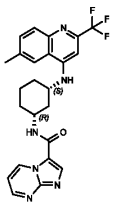
	4-108	0.773	489.539	490.1	[M+H]$^+$	Method 2
	4-109	0.878	560.621	561.4	[M+H]$^+$	Method 2
	4-110	0.733	419.448	420.1	[M+H]$^+$	Method 2
	4-111	0.802	481.475	482.1	[M+H]$^+$	Method 2
	4-112	0.908	515.432	516.3	[M+H]$^+$	Method 2

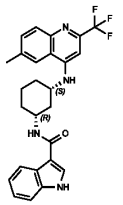
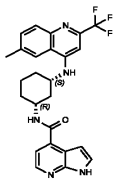
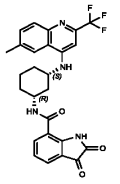
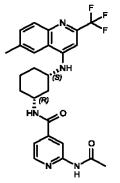
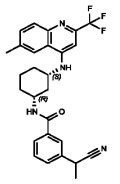
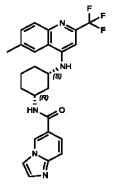
	4-113	0.811	505.541	506.1	[M+H]$^+$	Method 2
	4-114	0.769	478.9	479.2	[M+H]$^+$	Method 2
	4-115	0.846	467.492	468.3	[M+H]$^+$	Method 2
	4-116	0.754	549.542	550.2	[M+H]$^+$	Method 2
	4-117	0.76	546.04	546	[M+H]$^+$	Method 5

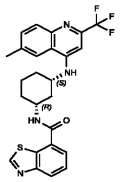
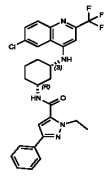
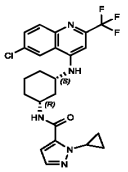
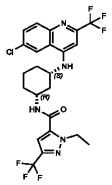
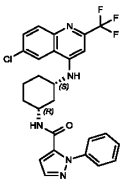
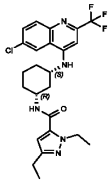
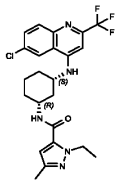
	4-118	0.834	528.576	529	$[M+H]^+$	Method 2
	4-119	0.865	455.525	456.4	$[M+H]^+$	Method 2
	4-120	0.788	499.534	500.2	$[M+H]^+$	Method 2
	4-121	0.905	489.34	489.2	$[M+H]^+$	Method 2

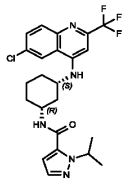
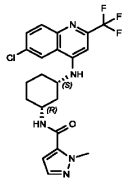
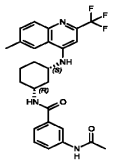
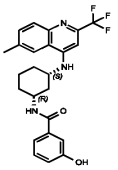
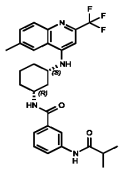
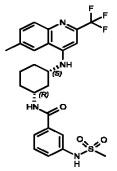
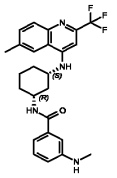
	4-122	0.801	465.517	466.4	[M+H]$^+$	Method 2
	4-123	9.396	532.99	533.2	[M+H]$^+$	Method 1
	4-124	8.317	487.91	488.1	[M+H]$^+$	Method 1
	4-125	9.895	477.91	478.1	[M+H]$^+$	Method 1
	4-126	9.759	501.89	502.2	[M+H]$^+$	Method 1

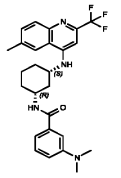
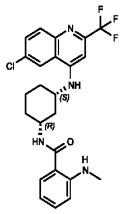
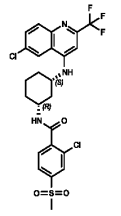
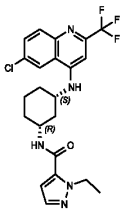
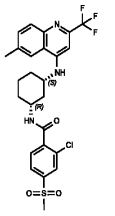
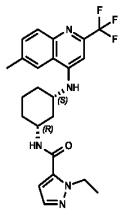
	4-127	9.443	479.93	480.2	[M+H]$^+$	Method 1
	4-128	9.201	483.90	484.2	[M+H]$^+$	Method 1
	4-129	9.959	479.93	480.2	[M+H]$^+$	Method 1
	4-130	7.085	456.51	457.3	[M+H]$^+$	Method 1
	4-131	12.792	466.51	467.2	[M+H]$^+$	Method 1
	4-132	6.772	560.64	561.3	[M+H]$^+$	Method 1

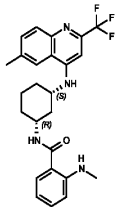
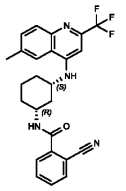
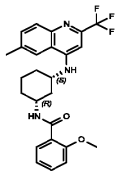
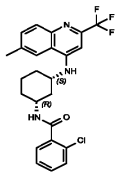
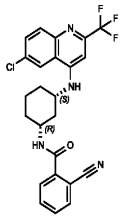
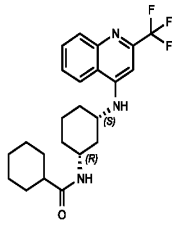
	4-133	4.935	493.53	494.2	$[M+H]^+$	Method 1
	4-134	9.020	496.58	497.3	$[M+H]^+$	Method 1
	4-135	7.015	495.51	496.3	$[M+H]^+$	Method 1
	4-136	10.466	491.94	492.2	$[M+H]^+$	Method 1
	4-137	7.577	467.50	468.2	$[M+H]^+$	Method 1
	4-138	5.990	468.48	469.2	$[M+H]^+$	Method 1

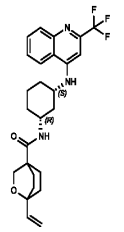
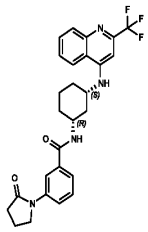
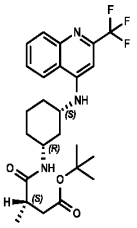
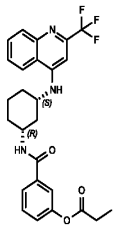
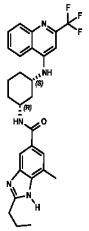
	4-139	7.303	466.51	467.3	$[M+H]^+$	Method 1
	4-140	6.332	467.50	468.2	$[M+H]^+$	Method 1
	4-141	7.298	496.49	497.2	$[M+H]^+$	Method 1
	4-142	6.076	485.51	486.3	$[M+H]^+$	Method 1
	4-143	8.013	480.54	481.3	$[M+H]^+$	Method 1
	4-144	4.631	467.50	468.2	$[M+H]^+$	Method 1

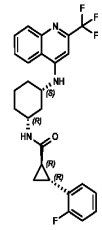
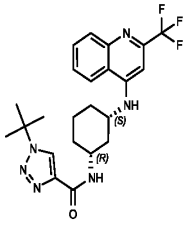
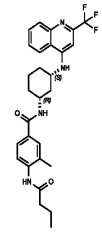
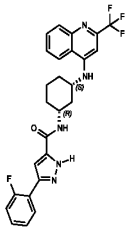
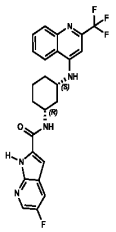
	4-145	7.617	484.54	485.2	[M+H]$^+$	Method 1
	4-146	11.650	542.00	542.2	[M+H]$^+$	Method 1
	4-147	9.473	477.92	478.2	[M+H]$^+$	Method 1
	4-148	10.958	533.90	534.2	[M+H]$^+$	Method 1
	4-149	9.798	513.95	514.2	[M+H]$^+$	Method 1
	4-150	10.244	493.96	494.2	[M+H]$^+$	Method 1
	4-151	9.599	479.93	480.2	[M+H]$^+$	Method 1

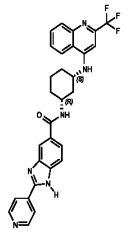
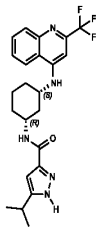
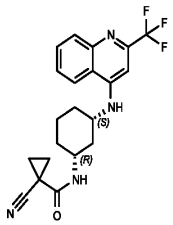
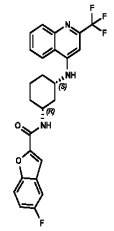
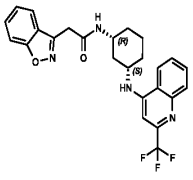
	4-152	10.030	479.93	480.2	[M+H]$^+$	Method 1
	4-153	8.080	451.88	452.2	[M+H]$^+$	Method 1
	4-154	6.356	484.52	485.3	[M+H]$^+$	Method 1
	4-155	6.621	443.47	444.3	[M+H]$^+$	Method 1
	4-156	7.506	512.58	513.3	[M+H]$^+$	Method 1
	4-157	6.812	520.57	521.2	[M+H]$^+$	Method 1
	4-158	6.743	456.51	457.3	[M+H]$^+$	Method 1

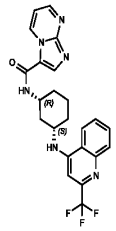
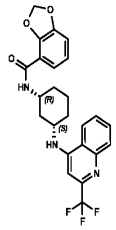
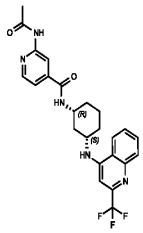
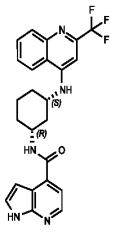
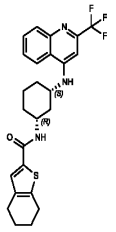
	4-159	7.532	470.54	471.3	$[M+H]^+$	Method 1
	4-160	10.883	476.93	477.2	$[M+H]^+$	Method 1
	4-161	9.303	560.41	560.1	$[M+H]^+$	Method 1
	4-162	9.412	465.91	466.2	$[M+H]^+$	Method 1
	4-163	7.416	540.00	540.2	$[M+H]^+$	Method 1
	4-164	7.340	445.49	446.3	$[M+H]^+$	Method 1

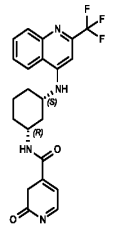
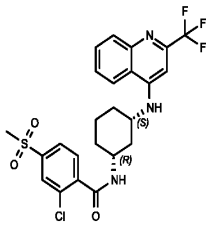
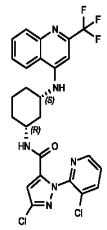
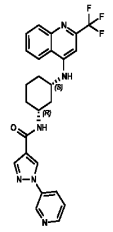
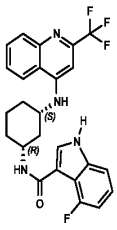
	4-165	9.021	456.51	457.2	[M+H]$^+$	Method 1
	4-166	7.319	452.48	453.3	[M+H]$^+$	Method 1
	4-167	8.330	457.50	458.2	[M+H]$^+$	Method 1
	4-168	8.110	461.91	462.2	[M+H]$^+$	Method 1
	4-169	9.292	472.90	473.2	[M+H]$^+$	Method 1
	4-170	.813	419.483	420.2	[M+H]$^+$	Method 6

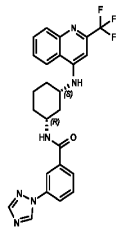
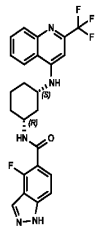
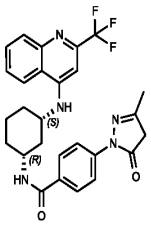
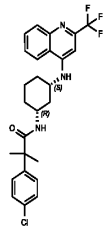
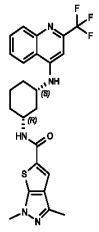
	4-171	0.841	473.531	474	$[M+H]^+$	Method 2
	4-172	0.823	496.524	497	$[M+H]^+$	Method 2
	4-173	0.766	479.544	480.2	$[M+H]^+$	Method 2
	4-174	0.764	485.507	486.1	$[M+H]^+$	Method 2
	4-175	0.778	509.577	510	$[M+H]^+$	Method 2

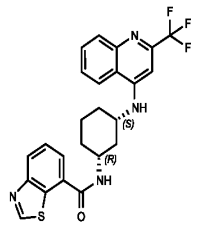
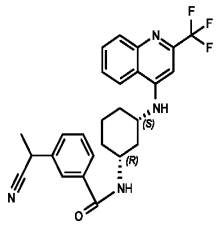
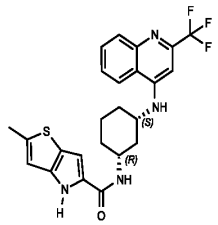
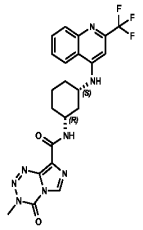
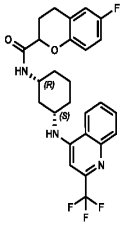
	4-176	0.851	471.500	472.1	$[M+H]^+$	Method 2
	4-177	0.756	460.505	461.3	$[M+H]^+$	Method 2
	4-178	0.744	512.577	513.3	$[M+H]^+$	Method 2
	4-179	0.864	497.498	498	$[M+H]^+$	Method 2
	4-180	0.843	471.460	472	$[M+H]^+$	Method 2

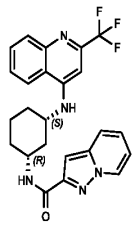
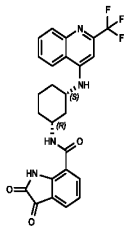
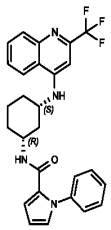
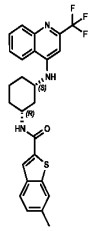
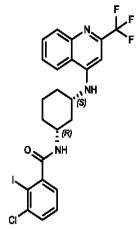
	4-181	0.772	530.555	531	$[M+H]^+$	Method 2
	4-182	0.747	445.490	446.3	$[M+H]^+$	Method 2
	4-183	0.619	402.421	403	$[M+H]^+$	Method 2
	4-184	0.707	471.456	472	$[M+H]^+$	Method 2
	4-185	0.744	468.480	469.1	$[M+H]^+$	Method 2

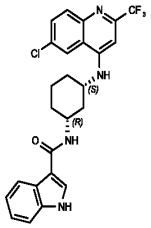
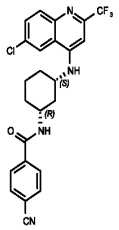
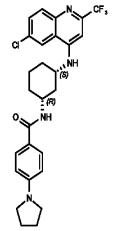
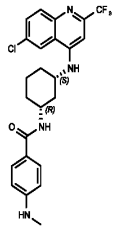
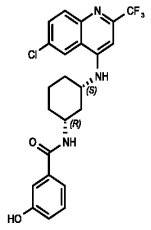
	4-186	0.693	454.457	455.2	$[M+H]^+$	Method 2
	4-187	0.773	457.453	458.3	$[M+H]^+$	Method 2
	4-188	0.692	471.484	472.3	$[M+H]^+$	Method 2
	4-189	0.677	453.469	454.3	$[M+H]^+$	Method 2
	4-190	0.902	473.560	474	$[M+H]^+$	Method 2

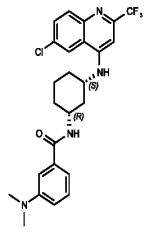
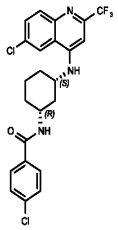
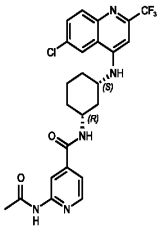
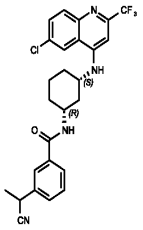
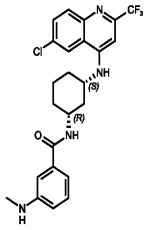
	4-191	0.657	430.431	431.1	[M+H]$^+$	Method 2
	4-192	0.817	525.970	526.1	[M+H]$^+$	Method 2
	4-193	0.862	549.380	549.3	[M+H]$^+$	Method 2
	4-194	0.705	480.495	481.1	[M+H]$^+$	Method 2
	4-195	0.866	470.472	471.3	[M+H]$^+$	Method 2

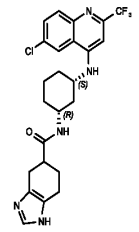
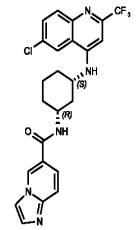
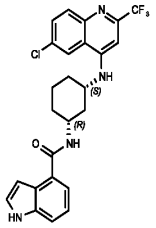
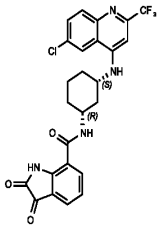
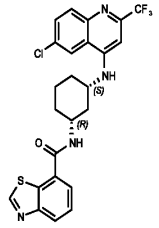
	4-196	0.82	480.495	481.3	$[M+H]^+$	Method 2
	4-197	0.829	471.460	472	$[M+H]^+$	Method 2
	4-198	0.825	509.533	510	$[M+H]^+$	Method 2
	4-199	0.808	489.970	490.1	$[M+H]^+$	Method 2
	4-200	0.842	487.550	488.3	$[M+H]^+$	Method 2

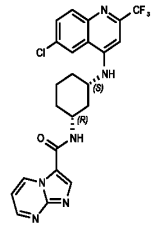
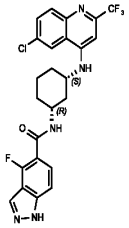
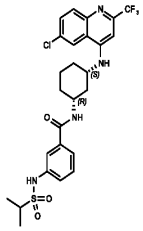
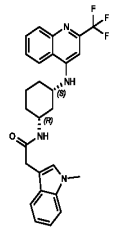
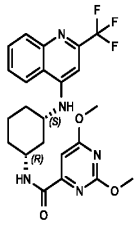
	4-201	0.848	470.510	470.9	$[M+H]^+$	Method 2
	4-202	0.852	466.508	467	$[M+H]^+$	Method 2
	4-203	0.869	472.530	472.9	$[M+H]^+$	Method 2
	4-204	0.638	486.459	487.3	$[M+H]^+$	Method 2
	4-205	0.812	487.499	488	$[M+H]^+$	Method 2

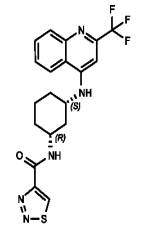
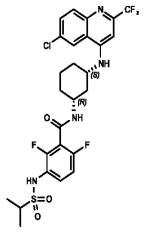
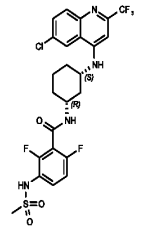
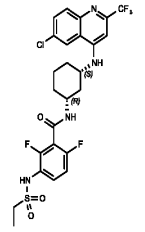
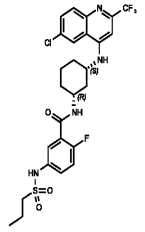
	4-206	0.841	453.469	453.9	$[M+H]^+$	Method 2
	4-207	0.933	482.463	483	$[M+H]^+$	Method 2
	4-208	0.812	478.519	479.2	$[M+H]^+$	Method 2
	4-209	0.843	483.550	484.2	$[M+H]^+$	Method 2
	4-210	0.794	573.780	574	$[M+H]^+$	Method 2

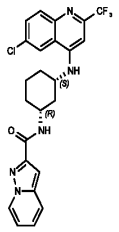
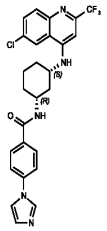
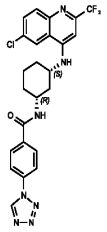
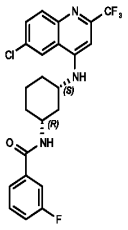
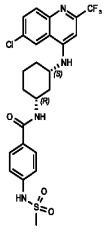
	4-211	9.298	486.92	487.1	$[M+H]^+$	Method 1
	4-212	9.706	472.90	473.2	$[M+H]^+$	Method 1
	4-213	10.821	516.99	517.2	$[M+H]^+$	Method 1
	4-214	9.147	476.93	477.2	$[M+H]^+$	Method 1
	4-215	8.614	463.89	464.1	$[M+H]^+$	Method 1

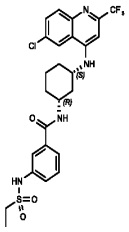
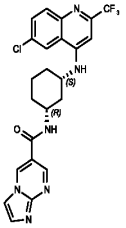
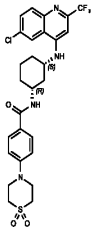
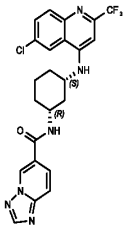
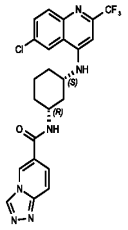
	4-216	9.64	490.96	491.2	$[M+H]^+$	Method 1
	4-217	10.582	482.33	482.1	$[M+H]^+$	Method 1
	4-218	8.086	505.93	506.1	$[M+H]^+$	Method 1
	4-219	9.841	500.95	501.2	$[M+H]^+$	Method 1
	4-220	8.886	476.93	477.2	$[M+H]^+$	Method 1

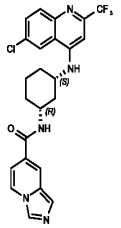
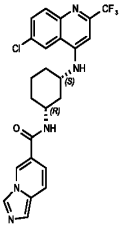
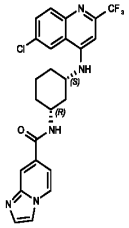
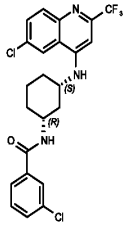
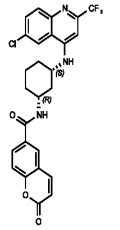
	4-221	6.036	491.94	492.2	$[M+H]^+$	Method 1
	4-222	10.389	487.91	488.1	$[M+H]^+$	Method 1
	4-223	9.278	486.92	487.2	$[M+H]^+$	Method 1
	4-224	9.275	516.91	517.1	$[M+H]^+$	Method 1
	4-225	9.646	504.96	505.1	$[M+H]^+$	Method 1

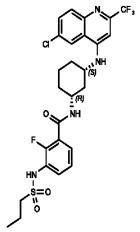
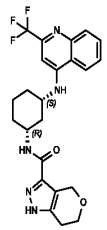
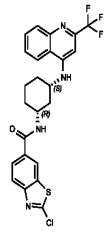
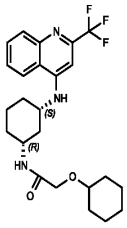
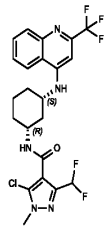
	4-226	7.979	488.90	489.1	$[M+H]^+$	Method 1
	4-227	9.005	505.90	506.2	$[M+H]^+$	Method 1
	4-228	9.364	569.04	570.2	$[M+H]^+$	Method 1
	4-229	0.861	480.535	481.3	$[M+H]^+$	Method 8
	4-230	0.875	475.472	476.2	$[M+H]^+$	Method 4

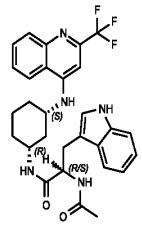
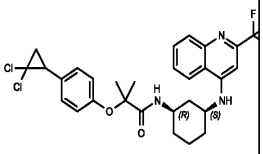
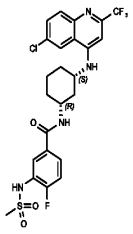
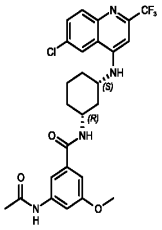
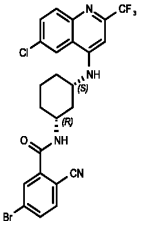
	4-231	0.766	421.440	422.1	[M+H]$^+$	Method 6
	4-232	9.588	605.02	605.2	[M+H]$^+$	Method 1
	4-233	8.967	576.97	577.2	[M+H]$^+$	Method 1
	4-234	9.270	590.99	591.2	[M+H]$^+$	Method 1
	4-235	9.879	587.03	587.2	[M+H]$^+$	Method 1

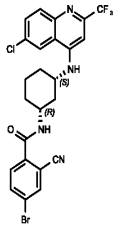
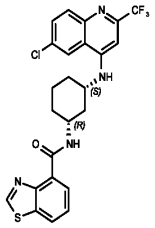
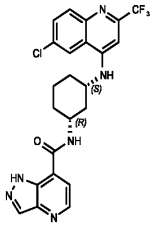
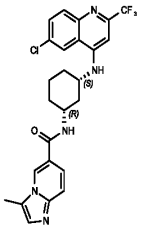
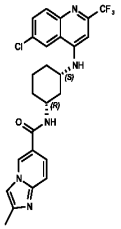
	4-236	9.641	487.91	488.2	$[M+H]^+$	Method 1
	4-237	6.626	513.95	514.1	$[M+H]^+$	Method 1
	4-238	8.026	515.93	516.2	$[M+H]^+$	Method 1
	4-239	10.094	465.88	466.1	$[M+H]^+$	Method 1
	4-240	8.628	540.99	541.1	$[M+H]^+$	Method 1

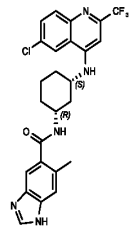
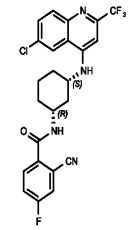
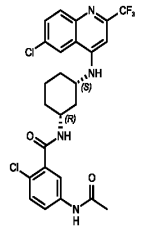
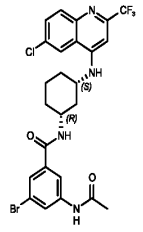
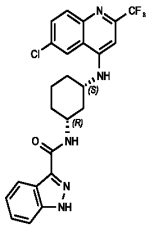
	4-241	9.044	555.01	555.2	$[M+H]^+$	Method 1
	4-242	6.912	488.90	489.1	$[M+H]^+$	Method 1
	4-243	8.659	581.05	581.2	$[M+H]^+$	Method 1
	4-244	8.089	488.90	489.1	$[M+H]^+$	Method 1
	4-245	7.351	488.90	489.1	$[M+H]^+$	Method 1

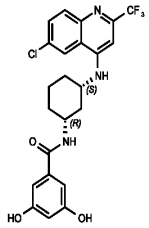
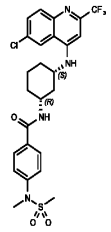
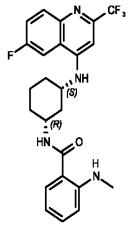
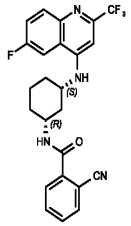
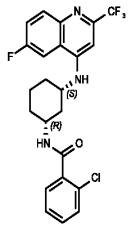
	4-246	6.843	487.91	488.1	$[M+H]^+$	Method 1
	4-247	6.983	487.91	488.1	$[M+H]^+$	Method 1
	4-248	6.240	487.91	488.1	$[M+H]^+$	Method 1
	4-249	10.689	482.33	482.1	$[M+H]^+$	Method 1
	4-250	9.273	515.92	516.2	$[M+H]^+$	Method 1

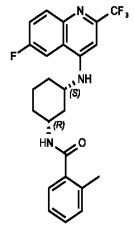
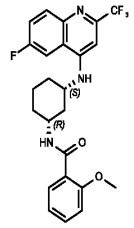
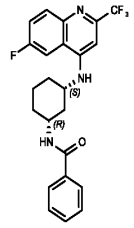
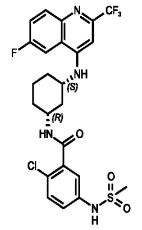
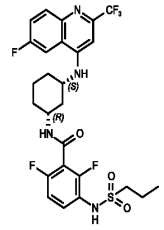
	4-251	9.623	587.03	587.2	$[M+H]^+$	Method 1
	4-252	0.757	459.473	460.1	$[M+H]^+$	Method 6
	4-253	0.876	504.960	505.2	$[M+H]^+$	Method 8
	4-254	0.899	449.518	450.2	$[M+H]^+$	Method 4
	4-255	0.860	501.890	502.1	$[M+H]^+$	Method 4

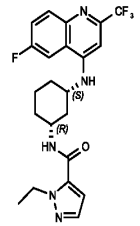
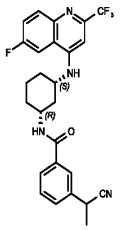
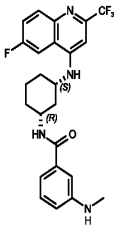
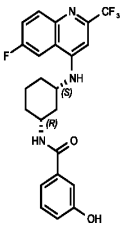
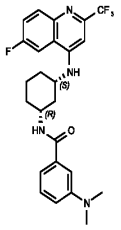
	4-256	0.824	537.587	538.2	$[M+H]^+$	Method 4
	4-257	0.979	580.470	579.17	$[M+H]^+$	Method 4
	4-258	8.809	558.98	559.1	$[M+H]^+$	Method 1
	4-259	8.604	534.96	535.2	$[M+H]^+$	Method 1
	4-260	10.357	551.79	551.1, 553.1	$[M+H]^+$	Method 1

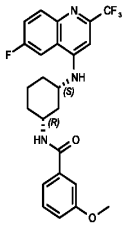
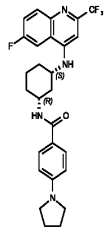
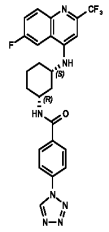
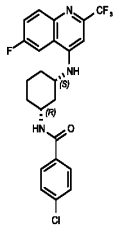
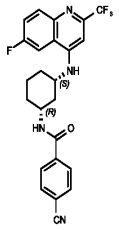
	4-261	10.251	551.79	551.1, 553.0	$[M+H]^+$	Method 1
	4-262	10.953	504.96	505.1	$[M+H]^+$	Method 1
	4-263	8.061	488.90	489.2	$[M+H]^+$	Method 1
	4-264	6.518	501.94	502.1	$[M+H]^+$	Method 1
	4-265	6.403	501.94	502.2	$[M+H]^+$	Method 1

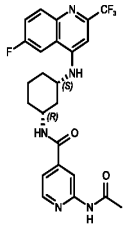
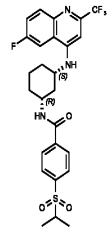
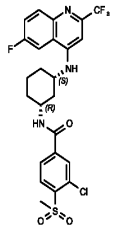
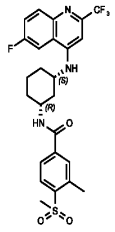
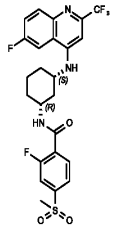
	4-266	6.454	501.94	502.1	$[M+H]^+$	Method 1
	4-267	9.622	490.89	491.1	$[M+H]^+$	Method 1
	4-268	8.839	539.38	539.1	$[M+H]^+$	Method 1
	4-269	9.557	583.83	583.1, 585.1	$[M+H]^+$	Method 1
	4-270	9.737	487.91	488.1	$[M+H]^+$	Method 1

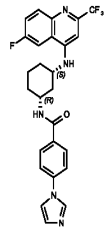
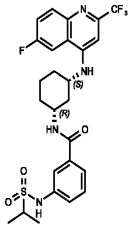
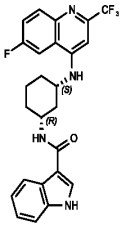
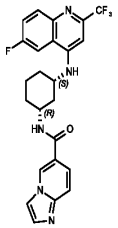
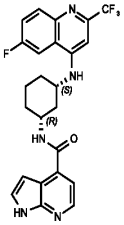
	4-271	13.426	479.88	480.2	$[M+H]^+$	Method 1
	4-272	9.158	555.01	555.2	$[M+H]^+$	Method 1
	4-273	10.200	460.48	461.2	$[M+H]^+$	Method 1
	4-274	8.603	456.44	457.2	$[M+H]^+$	Method 1
	4-275	9.269	466.42	467.2	$[M+H]^+$	Method 1

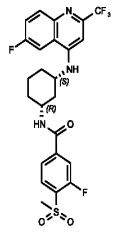
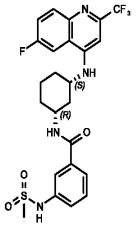
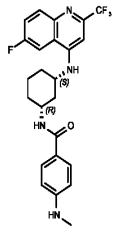
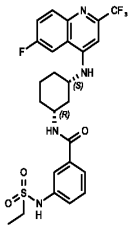
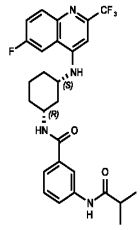
	4-276	9.625	445.46	446.2	$[M+H]^+$	Method 1
	4-277	9.538	461.46	462.2	$[M+H]^+$	Method 1
	4-278	4.924	431.43	432.2	$[M+H]^+$	Method 1
	4-279	8.618	558.98	559.2	$[M+H]^+$	Method 1
	4-280	6.773	588.57	589.2	$[M+H]^+$	Method 1

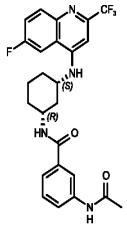
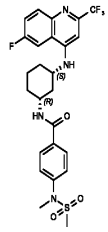
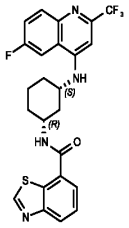
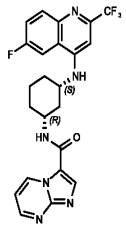
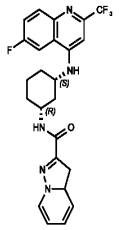
	4-281	8.683	449.45	450.2	$[M+H]^+$	Method 1
	4-282	9.176	484.50	485.2	$[M+H]^+$	Method 1
	4-283	8.06	460.48	461.2	$[M+H]^+$	Method 1
	4-284	7.905	447.43	448.2	$[M+H]^+$	Method 1
	4-285	8.839	474.50	475.2	$[M+H]^+$	Method 1

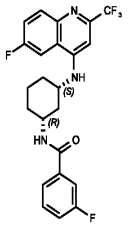
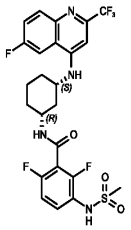
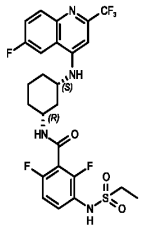
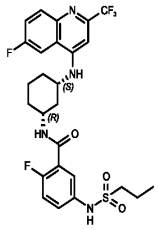
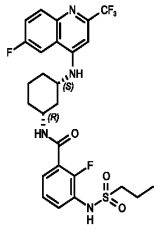
	4-286	9.196	461.46	462.2	$[M+H]^+$	Method 1
	4-287	10.16	500.54	501.2	$[M+H]^+$	Method 1
	4-288	8.239	499.47	500.2	$[M+H]^+$	Method 1
	4-289	9.923	465.88	466.2	$[M+H]^+$	Method 1
	4-290	9.006	456.44	457.2	$[M+H]^+$	Method 1

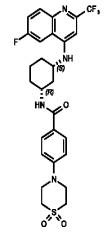
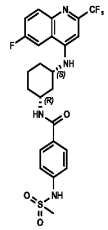
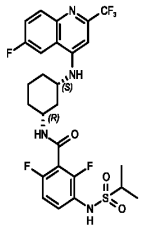
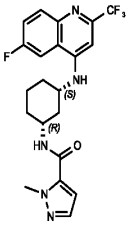
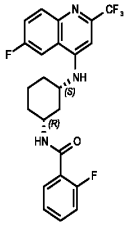
	4-291	7.339	489.47	490.2	$[M+H]^+$	Method 1
	4-292	8.962	537.57	538.2	$[M+H]^+$	Method 1
	4-293	8.903	543.96	544.2	$[M+H]^+$	Method 1
	4-294	8.593	523.55	524.2	$[M+H]^+$	Method 1
	4-295	8.324	527.51	528.2	$[M+H]^+$	Method 1

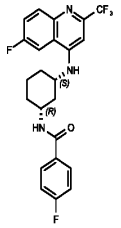
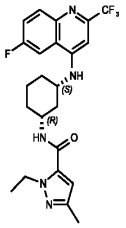
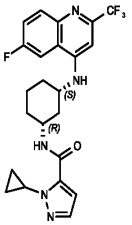
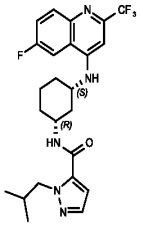
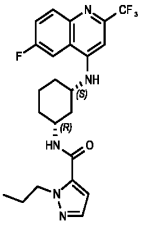
	4-296	5.968	497.50	498.2	$[M+H]^+$	Method 1
	4-297	8.723	552.59	554.2	$[M+H]^+$	Method 1
	4-298	8.597	470.47	471.2	$[M+H]^+$	Method 1
	4-299	5.724	471.46	472.2	$[M+H]^+$	Method 1
	4-300	8.561	471.46	472.2	$[M+H]^+$	Method 1

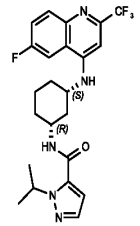
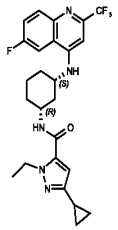
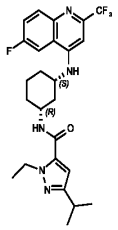
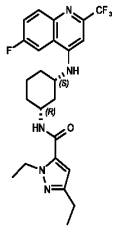
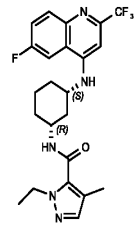
	4-301	8.563	527.51	528.2	$[M+H]^+$	Method 1
	4-302	8.048	524.53	525.2	$[M+H]^+$	Method 1
	4-303	8.43	460.48	461.2	$[M+H]^+$	Method 1
	4-304	8.363	538.56	539.2	$[M+H]^+$	Method 1
	4-305	8.725	516.54	517.2	$[M+H]^+$	Method 1

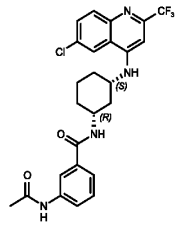
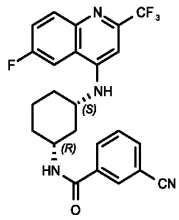
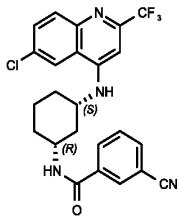
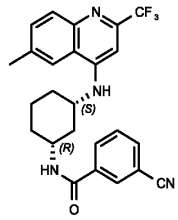
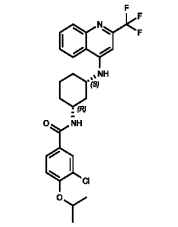
	4-306	7.594	488.49	489.3	$[M+H]^+$	Method 1
	4-307	8.91	538.56	539.2	$[M+H]^+$	Method 1
	4-308	8.91	488.50	489.2	$[M+H]^+$	Method 1
	4-309	7.245	472.45	473.2	$[M+H]^+$	Method 1
	4-310	8.886	473.48	474.2	$[M+H]^+$	Method 1

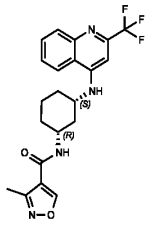
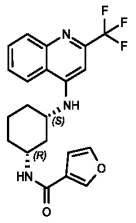
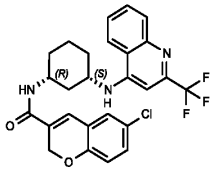
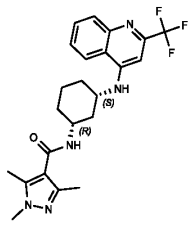
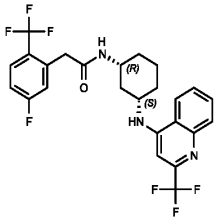
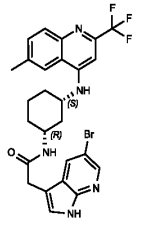
	4-311	9.412	449.43	450.2	$[M+H]^+$	Method 1
	4-312	8.298	560.52	561.2	$[M+H]^+$	Method 1
	4-313	8.613	574.54	575.2	$[M+H]^+$	Method 1
	4-314	9.223	570.58	571.2	$[M+H]^+$	Method 1
	4-315	8.988	570.58	571.2	$[M+H]^+$	Method 1

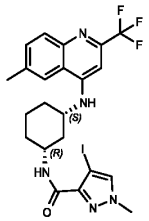
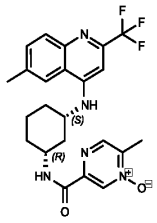
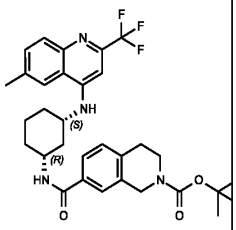
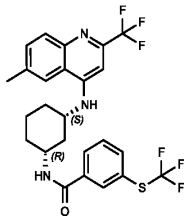
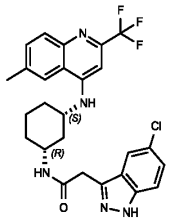
	4-316	7.982	564.60	565.2	$[M+H]^+$	Method 1
	4-317	7.956	524.53	525.2	$[M+H]^+$	Method 1
	4-318	8.361	588.57	589.2	$[M+H]^+$	Method 1
	4-319	8.035	435.43	436.2	$[M+H]^+$	Method 1
	4-320	9.385	449.43	450.2	$[M+H]^+$	Method 1

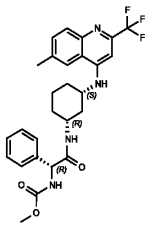
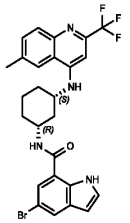
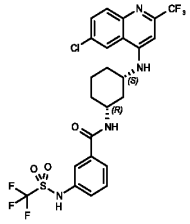
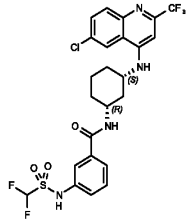
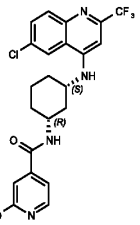
	4-321	11.588	449.43	450.2	$[M+H]^+$	Method 1
	4-322	8.877	463.48	464.3	$[M+H]^+$	Method 1
	4-323	8.687	461.46	462.2	$[M+H]^+$	Method 1
	4-324	9.782	477.51	478.2	$[M+H]^+$	Method 1
	4-325	9.241	463.48	464.2	$[M+H]^+$	Method 1

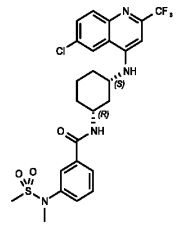
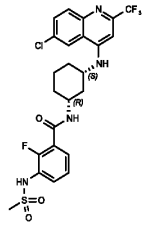
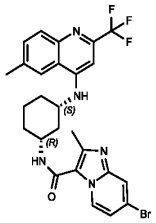
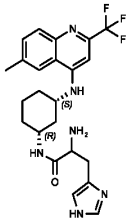
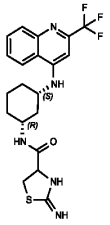
	4-326	9.309	463.48	464.2	$[M+H]^+$	Method 1
	4-327	9.733	489.52	490.3	$[M+H]^+$	Method 1
	4-328	10.186	491.53	492.3	$[M+H]^+$	Method 1
	4-329	9.525	477.51	478.8	$[M+H]^+$	Method 1
	4-330	8.679	463.48	464.2	$[M+H]^+$	Method 1

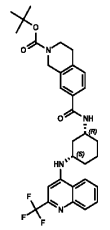
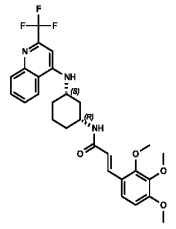
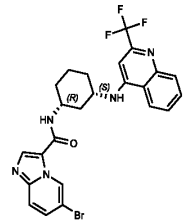
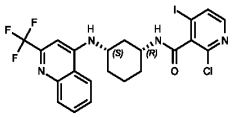
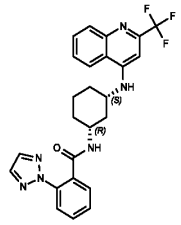
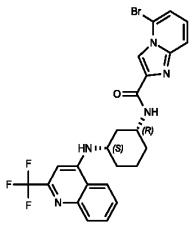
	4-331	8.339	504.94	505.2	$[M+H]^+$	Method 1
	4-332	9.097	456.45	457.8	$[M+H]^+$	Method 1
	4-333	9.84	472.9	473.2	$[M+H]^+$	Method 1
	4-334	7.896	452.48	453.3	$[M+H]^+$	Method 1
	4-335	0.87	505.97	506.2	$[M+H]^+$	Method 2

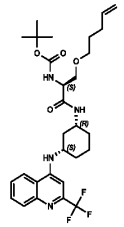
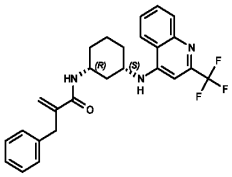
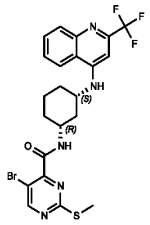
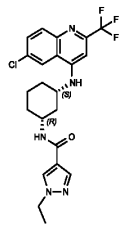
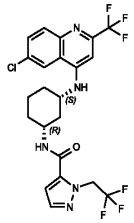
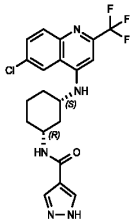
	4-336	0.764	418.42	419.1	$[M+H]^+$	Method 2
	4-337	0.812	403.41	404.1	$[M+H]^+$	Method 2
	4-338	0.907	501.93	502.3	$[M+H]^+$	Method 2
	4-339	0.76	445.49	446.1	$[M+H]^+$	Method 2
	4-340	0.881	513.46	514.3	$[M+H]^+$	Method 2
	4-341	0.777	560.42	560	$[M+H]^+$	Method 2

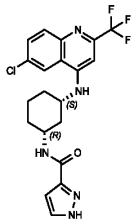
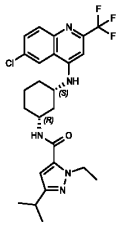
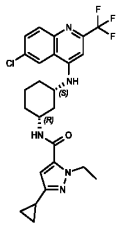
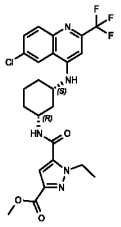
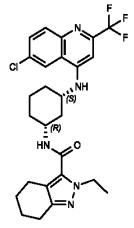
	4-342	0.771	557.36	558	$[M+H]^+$	Method 2
	4-343	0.784	459.47	460.1	$[M+H]^+$	Method 2
	4-344	0.843	582.67	583.1	$[M+H]^+$	Method 2
	4-345	0.856	527.53	528	$[M+H]^+$	Method 2
	4-346	0.827	515.97	516.1	$[M+H]^+$	Method 2

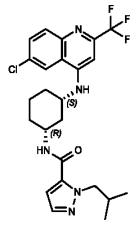
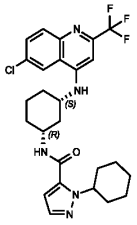
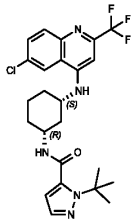
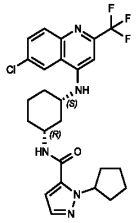
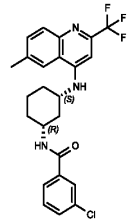
	4-347	0.81	514.55	515.2	$[M+H]^+$	Method 2
	4-348	0.898	545.4	545.1	$[M+H]^+$	Method 2
	4-349	10.15	594.96	595.1	$[M+H]^+$	Method 1
	4-350	9.509	576.97	577.1	$[M+H]^+$	Method 1
	4-351	7.06	464.87	465.2	$[M+H]^+$	Method 1

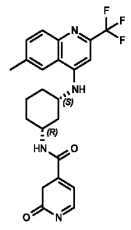
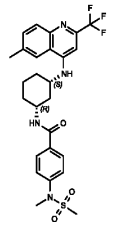
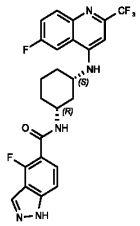
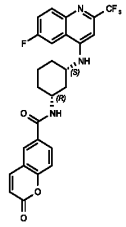
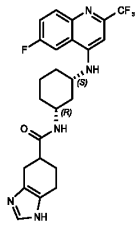
	4-352	9.249	555.01	555.2	$[M+H]^+$	Method 1
	4-353	8.814	558.98	559.1	$[M+H]^+$	Method 1
	4-354	0.822	560.42	562	$[M+H]^+$	Method 2
	4-355	0.676	460.51	461	$[M+H]^+$	Method 2
	4-356	0.873	437.49	438.2	$[M+H]^+$	Method 5

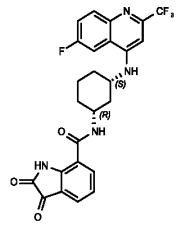
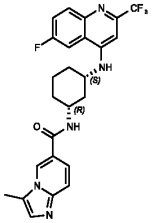
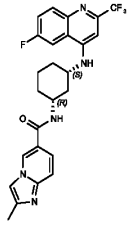
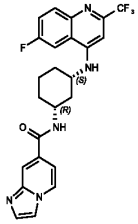
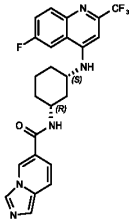
	4-357	0.875	568.64	569.3	[M+H]$^+$	Method 2
	4-358	0.829	529.56	530.2	[M+H]$^+$	Method 2
	4-359	0.796	532.37	532.2	[M+H]$^+$	Method 2
	4-360	0.788	574.77	575.1	[M+H]$^+$	Method 2
	4-361	0.824	480.5	481.3	[M+H]$^+$	Method 2
	4-362	0.664	532.37	532	[M+H]$^+$	Method 2

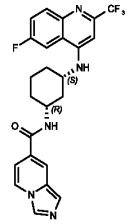
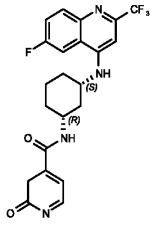
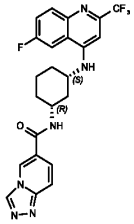
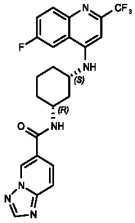
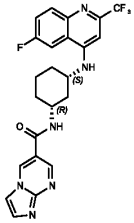
	4-363	0.743	564.65	565.2	$[M+H]^+$	Method 2
	4-364	0.693	453.51	454	$[M+H]^+$	Method 2
	4-365	0.695	540.4	540	$[M+H]^+$	Method 2
	4-366	8.168	465.91	466.2	$[M+H]^+$	Method 1
	4-367	10.196	519.88	520.2	$[M+H]^+$	Method 1
	4-368	7.305	437.85	438.2	$[M+H]^+$	Method 1

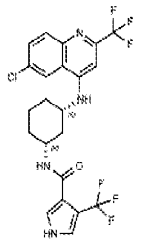
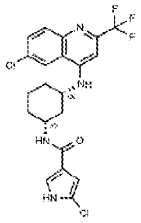
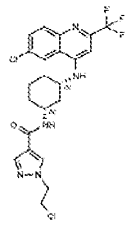
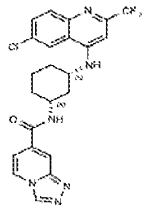
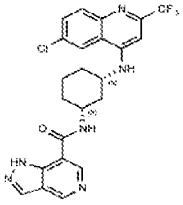
	4-369	7.891	437.85	438.2	$[M+H]^+$	Method 1
	4-370	10.866	507.99	508.2	$[M+H]^+$	Method 1
	4-371	10.415	505.97	506.2	$[M+H]^+$	Method 1
	4-372	9.886	523.94	524.2	$[M+H]^+$	Method 1
	4-373	11.080	520	520.2	$[M+H]^+$	Method 1

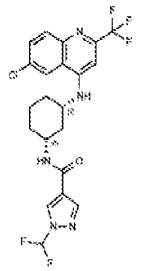
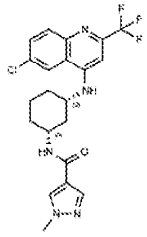
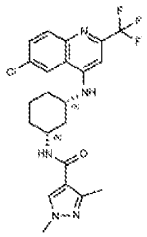
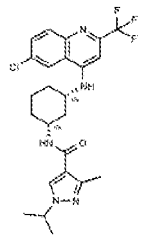
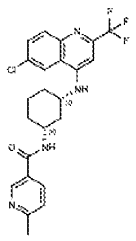
	4-374	10.481	493.96	494.2	$[M+H]^+$	Method 1
	4-375	11.372	520	520.2	$[M+H]^+$	Method 1
	4-376	10.227	493.96	494.2	$[M+H]^+$	Method 1
	4-377	11.009	505.97	506.2	$[M+H]^+$	Method 1
	4-378	8.925	461.91	462.2	$[M+H]^+$	Method 1

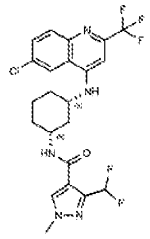
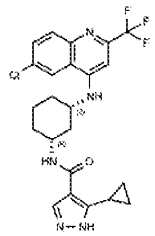
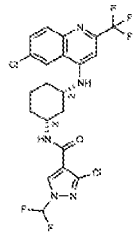
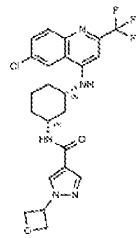
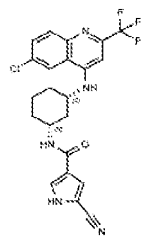
	4-379	5.260	444.46	445.3	$[M+H]^+$	Method 1
	4-380	7.266	534.6	535.3	$[M+H]^+$	Method 1
	4-381	8.256	489.45	490.2	$[M+H]^+$	Method 1
	4-382	8.571	499.47	500.2	$[M+H]^+$	Method 1
	4-383	8.559	475.49	476.2	$[M+H]^+$	Method 1

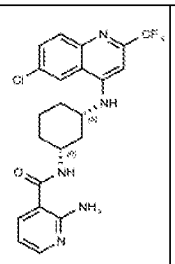
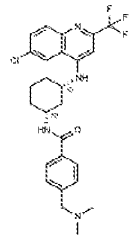
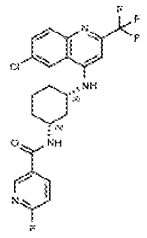
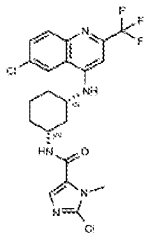
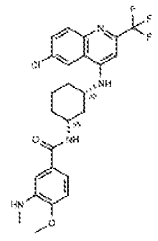
	4-384	8.558	500.45	501.2	$[M+H]^+$	Method 1
	4-385	5.886	485.49	486.2	$[M+H]^+$	Method 1
	4-386	5.812	485.49	486.2	$[M+H]^+$	Method 1
	4-387	5.605	471.46	472.2	$[M+H]^+$	Method 1
	4-388	6.272	471.46	472.2	$[M+H]^+$	Method 1

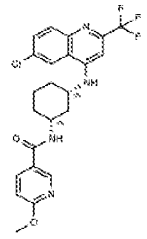
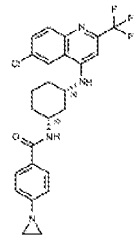
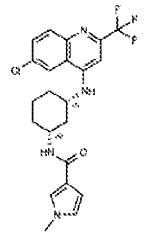
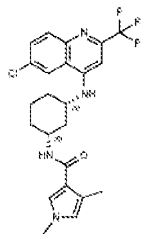
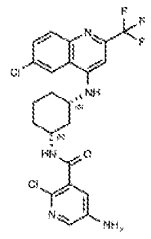
	4-389	6.154	471.46	472.2	$[M+H]^+$	Method 1
	4-390	6.671	448.42	449.2	$[M+H]^+$	Method 1
	4-391	7.366	472.45	473.2	$[M+H]^+$	Method 1
	4-392	7.366	472.45	473.2	$[M+H]^+$	Method 1
	4-393	6.204	472.45	473.2	$[M+H]^+$	Method 1

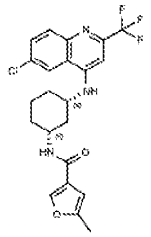
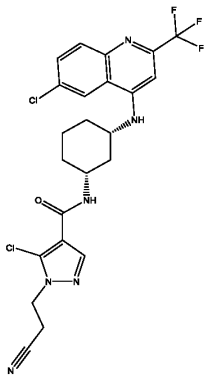
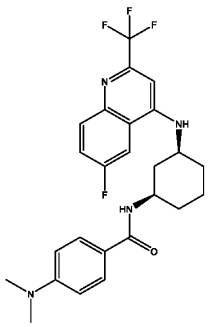
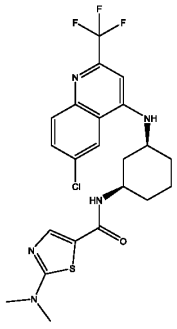
	4-394	9.290	504.86	505.2	$[M+H]^+$	Method 1
	4-395	8.740	471.31	471.1	$[M+H]^+$	Method 1
	4-396	8.589	500.35	500.2	$[M+H]^+$	Method 1
	4-397	7.469	488.9	489.2, 245.2	$[M+H]^+$	Method 1
	4-398	6.429	488.9	489.2, 245.2	$[M+H]^+$	Method 1

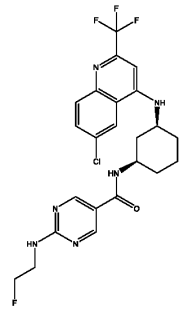
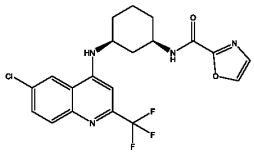
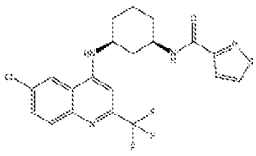
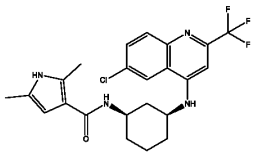
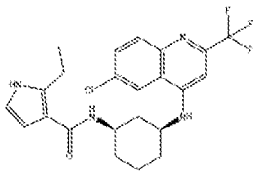
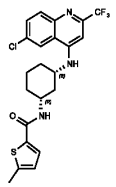
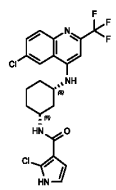
	4-399	9.295	487.86	488.2	$[M+H]^+$	Method 1
	4-400	7.739	451.88	452.2	$[M+H]^+$	Method 1
	4-401	7.981	465.91	466.2	$[M+H]^+$	Method 1
	4-402	9.045	493.96	494.2	$[M+H]^+$	Method 1
	4-403	7.345	462.9	463.2	$[M+H]^+$	Method 1

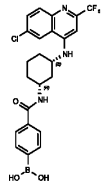
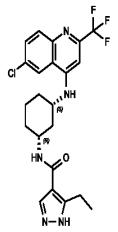
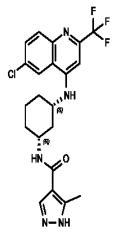
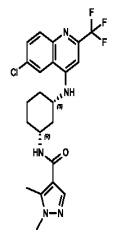
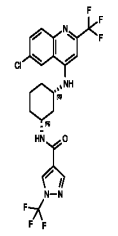
	4-404	9.123	501.89	502.2	$[M+H]^+$	Method 1
	4-405	8.418	477.92	478.2	$[M+H]^+$	Method 1
	4-406	9.897	522.3	522.1	$[M+H]^+$	Method 1
	4-407	7.717	493.92	494.2	$[M+H]^+$	Method 1
	4-408	8.455	461.87	462.2	$[M+H]^+$	Method 1

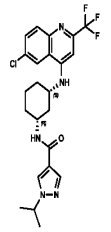
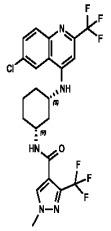
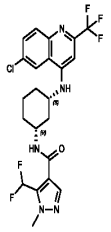
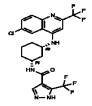
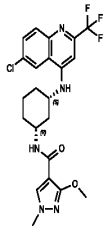
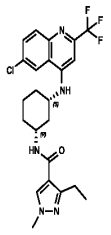
	4-409	6.460	463.89	464.2, 232.7	$[M+H]^+$	Method 1
	4-410	5.896	504.98	505.2	$[M+H]^+$	Method 1
	4-411	9.245	466.86	467.2	$[M+H]^+$	Method 1
	4-412	9.057	486.32	486.2	$[M+H]^+$	Method 1
	4-413	0.539	506.95	507.3	$[M+H]^+$	Method 2

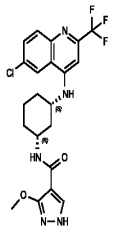
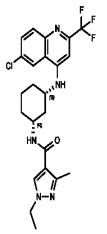
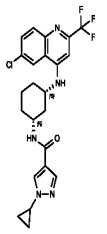
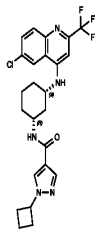
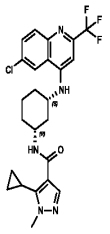
	4-414	0.731	478.9	479	$[M+H]^+$	Method 2
	4-415	0.882	488.94	489.1	$[M+H]^+$	Method 2
	4-416	8.533	450.89	451.2	$[M+H]^+$	Method 1
	4-417	9.279	464.92	465.2	$[M+H]^+$	Method 1
	4-418	0.506	498.33	498.1	$[M+H]^+$	Method 2

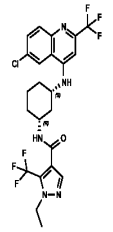
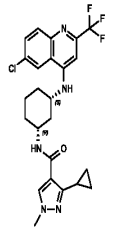
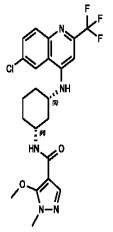
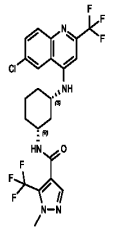
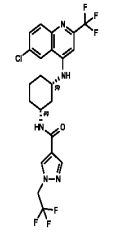
	4-419	9.408	451.87	452.2	$[M+H]^+$	Method 1
	4-420	0.551	525.36	525	$[M+H]^+$	Method 2
	4-421	9.307	474.504	475.2	$[M+H]^+$	Method 1
	4-422	8.614	497.97	498.2	$[M+H]^+$	Method 1

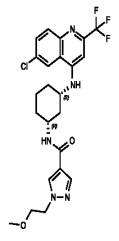
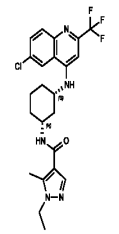
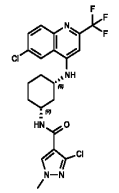
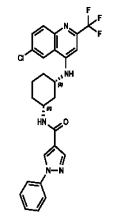
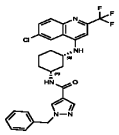
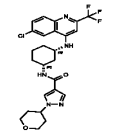
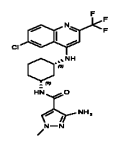
	4-423	8.489	510.92	511.2	$[M+H]^+$	Method 1
	4-424	8.608	438.84	439.2, 440.1, 441.2	$[M+H]^+$	Method 1
	4-425	9.673	454.9	455.2, 456.1, 457.1	$[M+H]^+$	Method 1
	4-426	8.929	464.92	465.2	$[M+H]^+$	Method 1
	4-427	9.113	464.92	465.2	$[M+H]^+$	Method 1
	4-428	10.116	467.94	468.1, 469.4, 470.1	$[M+H]^+$	Method 1
	4-429	8.738	471.31	471.1	$[M+H]^+$	Method 1

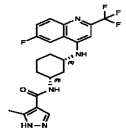
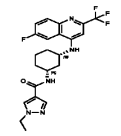
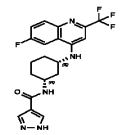
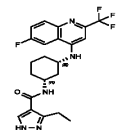
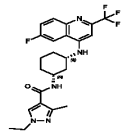
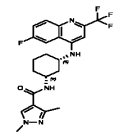
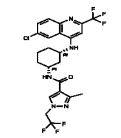
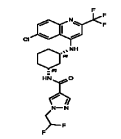
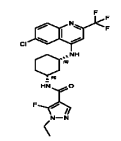
	4-430	8.19	491.7	492.2	$[M+H]^+$	Method 1
	4-431	8.26	465.91	466.2	$[M+H]^+$	Method 1
	4-432	7.74	451.88	452.2	$[M+H]^+$	Method 1
	4-433	8.34	465.91	466.2	$[M+H]^+$	Method 1
	4-434	9.91	505.85	506.2	$[M+H]^+$	Method 1

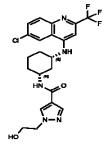
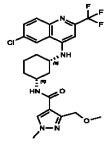
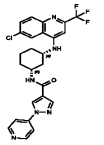
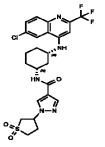
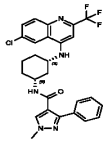
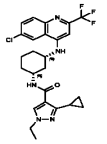
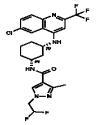
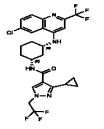
	4-435	8.83	479.93	480.2	$[M+H]^+$	Method 1
	4-436	9.59	519.88	520.2	$[M+H]^+$	Method 1
	4-437	10.03	501.89	502.2	$[M+H]^+$	Method 1
	4-438	9.00	505.85	506.2	$[M+H]^+$	Method 1
	4-439	8.93	481.9	482.2	$[M+H]^+$	Method 1
	4-440	8.74	479.93	480.2	$[M+H]^+$	Method 1

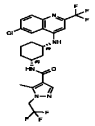
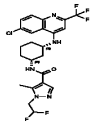
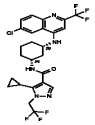
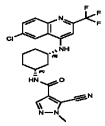
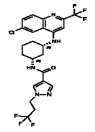
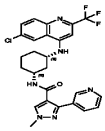
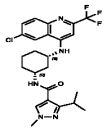
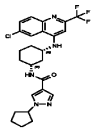
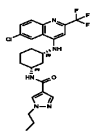
	4-441	8.33	467.88	468.2	$[M+H]^+$	Method 1
	4-442	8.68	479.93	480.2	$[M+H]^+$	Method 1
	4-443	8.65	477.92	478.2	$[M+H]^+$	Method 1
	4-444	9.25	491.94	492.2	$[M+H]^+$	Method 1
	4-445	8.52	491.94	492.2	$[M+H]^+$	Method 1

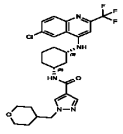
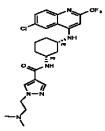
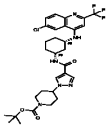
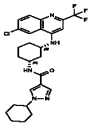
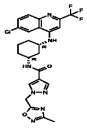
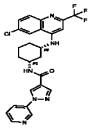
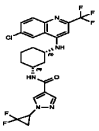
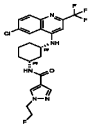
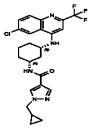
	4-446	9.91	533.9	534.2	$[M+H]^+$	Method 1
	4-447	8.85	491.94	492.3	$[M+H]^+$	Method 1
	4-448	8.33	481.9	482.2	$[M+H]^+$	Method 1
	4-449	9.43	519.88	520.2	$[M+H]^+$	Method 1
	4-450	9.01	519.88	520.2	$[M+H]^+$	Method 1

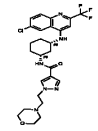
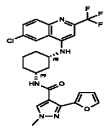
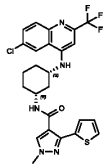
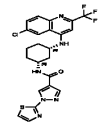
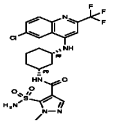
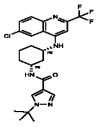
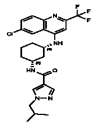
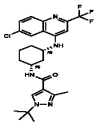
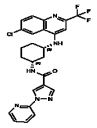
	4-451	7.96	495.93	496.2	$[M+H]^+$	Method 1
	4-452	6.73	479.93	480	$[M+H]^+$	Method 1
	4-453	9.00	486.32	486.1	$[M+H]^+$	Method 1
	4-454	9.90	513.95	514.2	$[M+H]^+$	Method 1
	4-455	9.45	527.98	528.2	$[M+H]^+$	Method 1
	4-456	8.10	521.97	522.2	$[M+H]^+$	Method 1
	4-457	7.45	466.89	467.2	$[M+H]^+$	Method 1

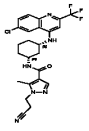
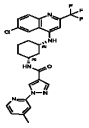
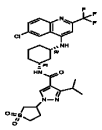
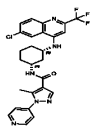
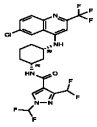
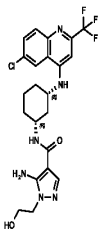
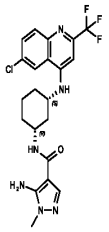
	4-458	6.90	435.427	436.2	$[M+H]^+$	Method 1
	4-459	7.41	449.454	450.2	$[M+H]^+$	Method 1
	4-460	6.57	421.4	422.2	$[M+H]^+$	Method 1
	4-461	7.36	449.454	450.2	$[M+H]^+$	Method 1
	4-462	7.72	463.481	464.2	$[M+H]^+$	Method 1
	4-463	7.23	449.454	450.2	$[M+H]^+$	Method 1
	4-464	9.36	533.9	534.2	$[M+H]^+$	Method 1
	4-465	8.52	501.89	502.2	$[M+H]^+$	Method 1
	4-466	8.86	483.9	484.2	$[M+H]^+$	Method 1

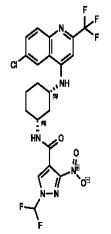
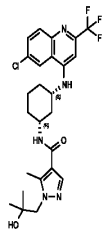
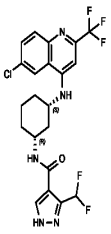
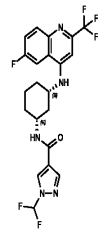
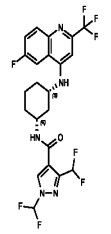
	4-467	7.08	481.9	482.2	$[M+H]^+$	Method 1
	4-468	8.47	495.93	496.2	$[M+H]^+$	Method 1
	4-469	7.09	514.94	515.2	$[M+H]^+$	Method 1
	4-470	8.00	556	556.2	$[M+H]^+$	Method 1
	4-471	9.50	527.98	528.2	$[M+H]^+$	Method 1
	4-472	9.47	505.97	506.2	$[M+H]^+$	Method 1
	4-473	8.86	515.91	516.2	$[M+H]^+$	Method 1
	4-474	10.23	559.94	560.2	$[M+H]^+$	Method 1

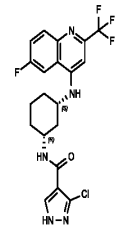
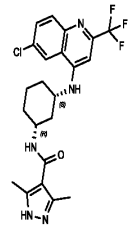
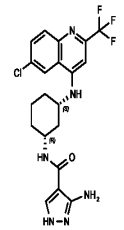
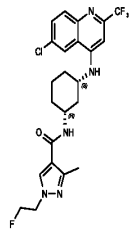
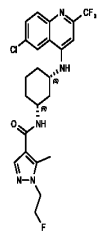
	4-475	9.49	533.9	534.2	$[M+H]^+$	Method 1
	4-476	8.97	515.91	516.2	$[M+H]^+$	Method 1
	4-477	9.71	559.94	560.2	$[M+H]^+$	Method 1
	4-478	0.58	476.89	477	$[M+H]^+$	Method 13
	4-479	9.10	533.9	534.2	$[M+H]^+$	Method 1
	4-480	6.34	528.96	529.2	$[M+H]^+$	Method 1
	4-481	9.19	493.96	494.2	$[M+H]^+$	Method 1
	4-482	9.45	505.97	506.3	$[M+H]^+$	Method 1
	4-483	8.70	479.93	480.2	$[M+H]^+$	Method 1

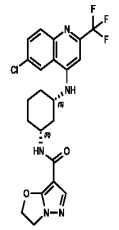
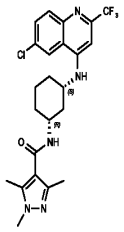
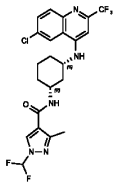
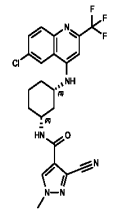
	4-484	8.17	536	536.3	$[M+H]^+$	Method 1
	4-485	5.96	508.97	509.2	$[M+H]^+$	Method 1
	4-486	9.94	621.1	621.3	$[M+H]^+$	Method 1
	4-487	9.92	520	520.2	$[M+H]^+$	Method 1
	4-488	8.25	533.94	534.2	$[M+H]^+$	Method 1
	4-489	8.30	514.94	515.2	$[M+H]^+$	Method 1
	4-490	8.89	513.9	514.2	$[M+H]^+$	Method 1
	4-491	8.16	483.9	484.2	$[M+H]^+$	Method 1
	4-492	8.87	491.94	492.2	$[M+H]^+$	Method 1

	4-493	5.90	551.01	551.3	$[M+H]^+$	Method 1
	4-494	9.04	517.94	518.2	$[M+H]^+$	Method 1
	4-495	9.63	534	534.2	$[M+H]^+$	Method 1
	4-496	9.51	520.96	521.2	$[M+H]^+$	Method 1
	4-497	8.71	530.95	531.2	$[M+H]^+$	Method 1
	4-498	9.28	493.96	494.2	$[M+H]^+$	Method 1
	4-499	9.27	493.96	494.2	$[M+H]^+$	Method 1
	4-500	9.72	507.99	508.3	$[M+H]^+$	Method 1
	4-501	9.55	514.94	515.2	$[M+H]^+$	Method 1

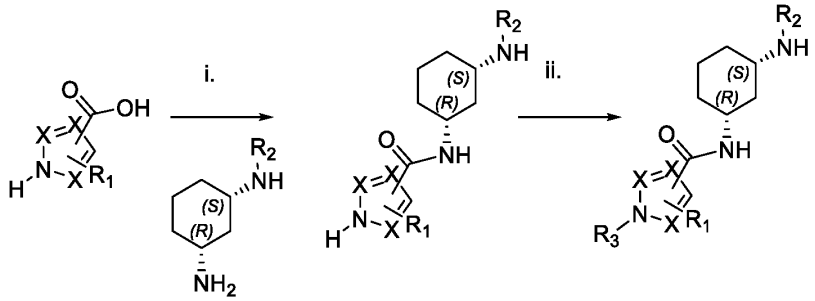
	4-502	8.40	504.94	505.2	$[M+H]^+$	Method 1
	4-503	10.02	528.96	529.3	$[M+H]^+$	Method 1
	4-504	9.48	598.08	598.3	$[M+H]^+$	Method 1
	4-505	7.77	528.96	529.2	$[M+H]^+$	Method 1
	4-506	10.02	537.87	538.2	$[M+H]^+$	Method 1
	4-507	7.17	496.92	497.3	$[M+H]^+$	Method 1
	4-508	7.64	466.89	467.3	$[M+H]^+$	Method 1

	4-509	9.62	532.86	533.2	$[M+H]^+$	Method 1
	4-510	8.12	523.99	524.3	$[M+H]^+$	Method 1
	4-511	8.52	487.86	488.2	$[M+H]^+$	Method 1
	4-512	8.19	471.407	472.3	$[M+H]^+$	Method 1
	4-513	9.36	521.415	522.2	$[M+H]^+$	Method 1

	4-514	7.54	455.84	456.2	$[M+H]^+$	Method 1
	4-515	0.44	465.91	466.1	$[M+H]^+$	Method 14
	4-516	0.43	452.87	453.2	$[M+H]^+$	Method 14
	4-517	8.48	497.92	498.2, 499.2, 500.2	$[M+H]^+$	Method 1
	4-518	8.70	497.92	498.2, 499.2, 500.2	$[M+H]^+$	Method 1

	4-519	7.76	479.89	480.2	$[M+H]^+$	Method 1
	4-520	8.11	479.93	479.9	$[M+H]^+$	Method 1
	4-521	10.69	501.89	502.8	$[M+H]^+$	Method 1
	4-522	0.644	476.89	477.1	$[M+H]^+$	Method 15

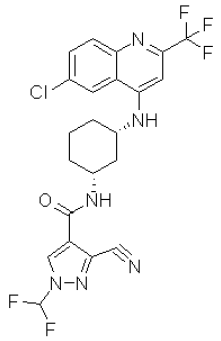
Scheme 5



Reagents: i. coupling conditions described in schemes 3 or 4; ii. R_3X, X is a halogen, mesyl tosyl or any other activating group

EXAMPLE 21

SYNTHESIS OF EXAMPLE 21



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-cyano-1-(difluoromethyl)-1H-pyrazole-4-carboxamide

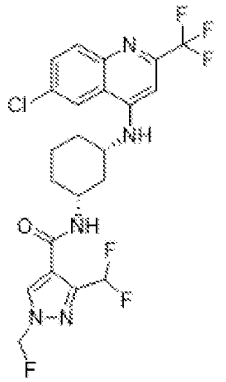
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1H-pyrazole-4-carboxamide (60 mg, 1 Eq, 130 umol), (2-chloro-2,2-difluoro-acetyl)oxysodium (39.5 mg, 2 Eq, 259 umol) and Cs_2CO_3 (85 mg, 2 Eq, 259 umol) in DMF (1 mL). The resulting solution was heated at 100 °C for 1 hour. The reaction mixture was cooled to room temperature and was directly purified by prep HPLC to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(difluoromethyl)pyrazole-4-carboxamide (2.3 mg, 4.45 umol, 3.44% yield).

LCMS-ESI (m/z) calculated: 512.87, found 513.2 $[M+H]^+$, RT = 0.575 min (Method 2)

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.46 (s, 1 H) 8.03 (br d, J=8.88 Hz, 1 H) 7.71 (s, 1 H) 7.65 (br d, J=8.76 Hz, 1H) 7.04 - 7.26 (m, 1 H) 6.78 (s, 1 H) 6.24 (br d, J=6.88 Hz, 1 H) 5.01 (br d, J=6.88 Hz, 1 H) 4.16 - 4.25 (m, 1 H) 3.73 (br d, J=7.00 Hz, 1 H) 2.63 (br d, J=11.13 Hz, 1 H) 2.18 - 2.31 (m, 2 H) 2.01 - 2.06 (m, 1 H) 1.29 - 1.45 (m, 4 H).

EXAMPLE 22

SYNTHESIS OF EXAMPLE 22



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-(difluoromethyl)-1-(fluoromethyl)-1H-pyrazole-4-carboxamide

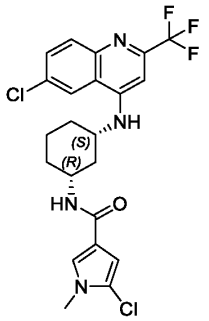
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-(difluoromethyl)-1H-pyrazole-4-carboxamide (100 mg, 1 Eq, 188.58 umol in MeCN (2 mL) were added fluoro(iodo)methane (33.18 mg, 1.1 Eq, 207.44 umol) and K_2CO_3 (52.13 mg, 2 Eq, 377 umol). After heating for 2 hours at 50°C, the reaction mixture was cooled to room temperature and was directly purified by prep-HPLC to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-(difluoromethyl)-1-(fluoromethyl)pyrazole-4-carboxamide (11.7 mg, 22.2 umol, 12% yield).

LCMS-ESI (m/z) calculated: 519.2 found 520.2 $[M+H]^+$, RT = 0.517 min (Method 2)

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.60 (d, *J* = 2.1 Hz, 1H), 8.49 (d, *J* = 7.9 Hz, 1H), 8.27 (s, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.88 - 7.60 (m, 2H), 7.50 (br d, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 6.33 (s, 1H), 6.20 (s, 1H), 4.11 - 3.83.

EXAMPLE 23

SYNTHESIS OF EXAMPLE 23



Synthesis of 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl)-1-methyl-1H-pyrrole-3-carboxamide

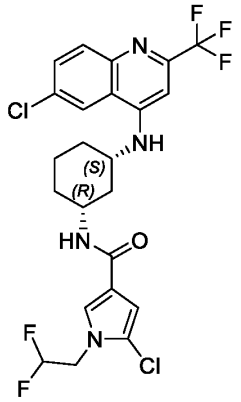
To a solution of 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrrole-3-carboxamide (50 mg, 1 Eq, 0.11 mmol) in DMF (2 mL) at 0°C was added sodium hydride (5.1 mg, 60% Wt, 1.2 Eq, 0.13 mmol). After stirring for 30 minutes, iodomethane (23 mg, 9.9 µL, 1.5 Eq, 0.16 mmol) was added, and the resulting mixture was stirred at room temperature for 18 hours. The crude mixture was directly purified by prep HPLC to afford 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-methyl-1H-pyrrole-3-carboxamide (23.8 mg, 49.0 µmol, 46 %).

LCMS-ESI (m/z) calculated: 485.33 found 485.2 $[M+H]^+$, RT = 9.522 min (Method 1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.73 (d, J = 9.2 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.36 (s, 1H), 6.92 (s, 1H), 6.54 (s, 1H), 3.99 – 3.80 (m, 2H), 3.56 (s, 3H), 2.12 (d, J = 12.1 Hz, 1H), 1.95 (d, J = 12.4 Hz, 1H), 1.87 – 1.76 (m, 2H), 1.59 – 1.42 (m, 2H), 1.39 – 1.23 (m, 2H).

EXAMPLE 24

SYNTHESIS OF EXAMPLE 24



Synthesis of 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2,2-difluoroethyl)-1H-pyrrole-3-carboxamide

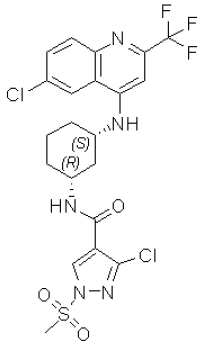
To a solution of 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrrole-3-carboxamide (88 mg, 1 Eq, 0.19 mmol) in DMF (2 mL) at 0°C was added sodium hydride (9.0 mg, 60% Wt, 1.2 Eq, 0.22 mmol). After stirring for 30 minutes, 2,2-difluoroethyl trifluoromethanesulfonate (60 mg, 37 µL, 1.5 Eq, 0.28 mmol) was added, and the resulting mixture was stirred at room temperature for 18 hours. The crude mixture was directly purified by prep HPLC to afford 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2,2-difluoroethyl)-1H-pyrrole-3-carboxamide (53.7 mg, 100 µmol, 54 %).

LCMS-ESI (m/z) calculated: 535.34 found 535.2 $[M+H]^+$, RT = 9.755 min (Method 1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.89 (d, *J* = 9.1 Hz, 1H), 7.75 (dd, *J* = 14.6, 8.8 Hz, 2H), 7.52 – 7.41 (m, 2H), 6.92 (s, 1H), 6.62 (s, 1H), 6.31 (t, *J* = 54.6 Hz, 1H), 4.45 (t, *J* = 15.6 Hz, 2H), 4.02 – 3.81 (m, 2H), 2.12 (d, *J* = 11.9 Hz, 1H), 1.96 (d, *J* = 12.4 Hz, 1H), 1.88 – 1.77 (m, 2H), 1.60 – 1.43 (m, 2H), 1.40 – 1.23 (m, 2H).

EXAMPLE 25

SYNTHESIS OF EXAMPLE 25



Synthesis of 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(methylsulfonyl)-1H-pyrazole-4-carboxamide

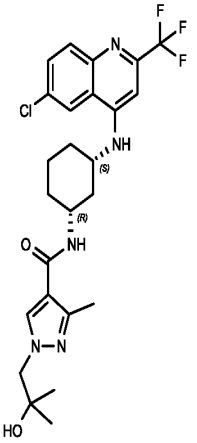
To a suspension of 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrazole-4-carboxamide (100 mg, 1 Eq, 212 µmol) in DCM (3 mL) was added triethylamine (85.7 mg, 118 µL, 4 Eq, 847 µmol), followed by DMAP (5.17 mg, 0.2 Eq, 42.3 µmol) and methanesulfonic anhydride (73.8 mg, 2 Eq, 423 µmol). The resulting mixture was stirred at room temperature for 1 hour, then heated at 50 °C for 1 hour. The reaction mixture was cooled to room temperature and was directly purified by prep HPLC to afford 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(methylsulfonyl)-1H-pyrazole-4-carboxamide (19.4 mg, 35.2 µmol, 17 % yield).

LCMS-ESI (m/z) calculated: 550.38 found 550.1 $[M+H]^+$, RT = 9.645 min (Method 1)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.59 (s, 1H), 8.29 (d, J = 7.7 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 4.01 – 3.83 (m, 2H), 3.68 (s, 3H), 2.17 (d, J = 11.8 Hz, 1H), 2.01 – 1.78 (m, 3H), 1.60 – 1.34 (m, 3H), 1.29 – 1.19 (m, 1H).

EXAMPLE 26

SYNTHESIS OF EXAMPLE 26



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2-hydroxy-2-methylpropyl)-3-methyl-1H-pyrazole-4-carboxamide

To a solution of 3-methyl-1H-pyrazole-4-carboxylic acid (33 mg, 263 umol, 1 eq) and (1S,3R)-N1-[6-chloro-2-(trifluoromethyl)-4-quinolyl]cyclohexane-1,3-diamine hydrochloride salt (100 mg, 263 umol, 1 eq) in DMF (4 mL) were added DIEA (102 mg, 789 umol, 137 uL, 3 eq) and HATU (120 mg, 316 umol, 1.2 eq). After stirring for 2 hr at room temperature, the solvent was removed in vacuo. To the crude residue was added water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL), washed with water (3 x 25 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-methyl-1H-pyrazole-4-carboxamide (109 mg, 241 umol) that was used without further purification.

To a solution of crude N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-methyl-1H-pyrazole-4- carboxamide (109 mg, 241 umol, 1 eq) in DMF (2 mL) were added 2,2-dimethyloxirane (61 mg, 844 umol, 74.97 uL, 3.5 eq) and K_2CO_3 (67 mg, 482 umol, 2 eq). The reaction mixture was heated at 100 °C for 12 hr, then the reaction mixture was cooled to room temperature and concentrated in vacuo to afford a crude solid. The crude solid was purified by prep-HPLC [(FA):column: Phenomenex luna C18 150x25mm 10um;mobile phase: [water(0.225%FA)-ACN];B%: 38%-68%,10min] and lyophilized to give N-((1R,3S)-3-((6-chloro-2-

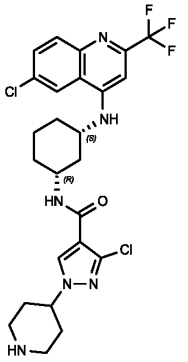
(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2-hydroxy-2-methylpropyl)-3-methyl-1H-pyrazole-4-carboxamide (2.5 mg, 4.6 umol, 2% yield).

LCMS-ESI (m/z) calculated: 523.2 found 524.2 $[M+H]^+$, RT = 0.461 min (Method 11)

^{1}H NMR (400 MHZ, DMSO-D_6) δ = 8.60 (D, J = 2.0 HZ, 1H), 8.10 (S, 1H), 7.89 (D, J = 9.0 HZ, 1H), 7.79 - 7.69 (M, 2H), 7.48 (BR D, J = 7.9 HZ, 1H), 6.92 (S, 1H), 6.96 - 6.89 (M, 1H), 4.00 - 3.79 (M, 1H), 2.30 (S, 1H), 2.32 - 2.24 (M, 1H), 2.19 - 2.09 (M, 1H), 1.96 (BR D, J = 11.6 HZ, 1H), 1.91 - 1.74 (M, 2H), 1.59 - 1.43 (M, 2H), 1.39 - 1.19 (M, 2H), 1.10 - 1.00 (M, 6H)

EXAMPLE 27

SYNTHESIS OF EXAMPLE 27



Synthesis of 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl)-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide

To a stirred solution of 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrazole-4-carboxamide (50 mg, 1 Eq, 0.11 mmol) were added tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (44 mg, 1.5 Eq, 0.16 mmol) and cesium carbonate (86 mg, 2.5 Eq, 0.26 mmol). The resulting suspension was heated and stirred at 90 °C for 18 hours. The reaction mixture was directly purified by prep-HPLC to yield tert-butyl 4-(3-chloro-4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl) carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (35.7 mg, 54.5 µmol, 51 % yield) as a solid.

LCMS-ESI (m/z) calculated: 654.21 found 655.1 $[M+H]^+$, RT = 1.140 min (Method 11)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.31 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.81 – 7.70 (m, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 6.93 (s, 1H), 4.39 – 4.28 (m, 1H), 4.10 – 3.81 (m, 4H), 2.91 (s, 2H), 2.19 – 2.11 (m, 1H), 2.04 – 1.93 (m, 2H), 1.93 – 1.74 (m, 4H), 1.73 – 1.63 (m, 1H), 1.55 – 1.22 (m, 13H).

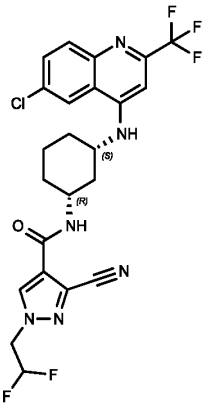
To a stirred solution of tert-butyl 4-(3-chloro-4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (32.2 mg, 1 Eq, 49.1 µmol) in 1,4-dioxane (2 mL) was added 4M HCl in 1,4-dioxane (123 µL, 10 Eq, 491 µmol). The resulting suspension was heated at 50 °C for 18 hours. The reaction mixture was cooled to room temperature and dissolved in MeOH and directly purified by prep-HPLC to yield 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide (8.9 mg, 16 µmol, 33 %) as a solid.

LCMS-ESI (m/z) calculated: 554.16 found 554.9 [M+H]+, RT = 6.170 min (Method 1)

^{1}H NMR (400 MHz, DMSO-d6) δ 8.60 (d, J = 2.3 Hz, 1H), 8.31 (s, 1H), 8.23 (s, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.74 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 4.38 – 4.24 (m, 1H), 3.99 – 3.83 (m, 2H), 3.27 – 3.15 (m, 3H), 2.82 – 2.74 (m, 2H), 2.16 (d, *J* = 11.9 Hz, 1H), 2.09 – 2.01 (m, 2H), 1.96 (d, *J* = 11.3 Hz, 1H), 1.92 – 1.78 (m, 4H), 1.59 – 1.42 (m, 2H), 1.40 – 1.22 (m, 2H).

EXAMPLE 28

SYNTHESIS OF EXAMPLE 28



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-cyano-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide

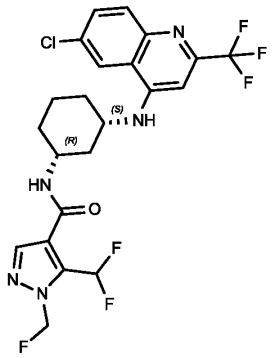
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-cyano-1H-pyrazole-4- carboxamide (50 mg, 1 eq) 108 umol) in DMF (3 mL) were added K_2CO_3 (44.8 mg, 3 eq , 324 umol) and 2,2-difluoroethyl trifluoromethanesulfonate (30.0 mg, 1.3 eq, 140 umol). The resulting mixture was heated at 60 °C for 1 hr. The mixture was cooled to room temperature, directly filtered and the filtrate was collected. The residue was purified by prep-HPLC to afford -(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(2,2-difluoroethyl)pyrazole4-carboxamide (11 mg, 21 umol, 19% yield) as a solid.

LCMS-ESI (m/z) calculated: 526.2 found 527.3 $[M+H]^+$, RT = 0.594 min (Method 11).

^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.37 (d, J = 2.3 Hz, 1H), 8.32 (s, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.69 (dd, J = 2.3, 9.0 Hz, 1H), 6.91 (s, 1H), 6.42 - 6.12 (m, 1H), 4.72 (dt, J = 3.5, 14.6 Hz, 2H), 4.09 - 4.00 (m, 1H), 3.87 - 3.77 (m, 1H), 2.43 - 2.36 (m, 1H), 2.17 - 1.92 (m, 3H), 1.70 - 1.58 (m, 1H), 1.55 - 1.36 (m, 3H).

EXAMPLE 29

SYNTHESIS OF EXAMPLE 29



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-5-(difluoromethyl)-1-(fluoromethyl)-1H-pyrazole-4-carboxamide

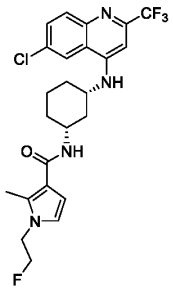
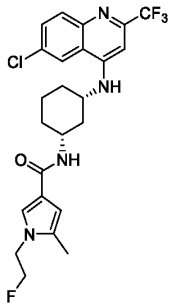
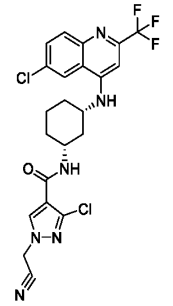
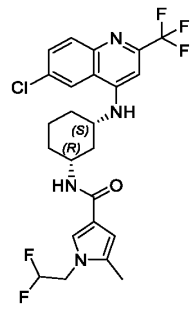
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino] cyclohexyl]-3-(difluoromethyl)-1H-pyrazole-4- carboxamide (100 mg, 189 umol, 92% purity, 1 eq) in MeCN (2 mL) were added fluoro(iodo)methane (33 mg, 207umol, 1.1 eq) and K_2CO_3 (52 mg, 377 umol, 2 eq). The resulting mixture was heated for 2 h at 50 °C. The mixture was cooled to room temperature, filtered, and the crude product was purified by reversed-phase HPLC:Column (Phenomenex luna C18 150*25mm* 10um) Condition water((0.225%FA)-ACN) to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-(difluoromethyl)-1- (fluoromethyl)pyrazole-4-carboxamide 33% yield).

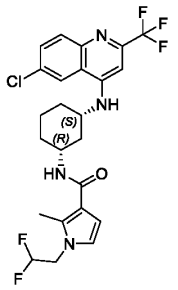
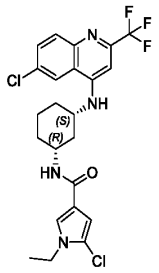
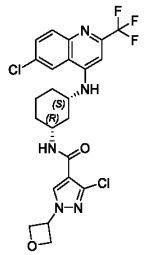
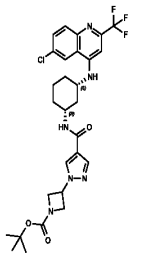
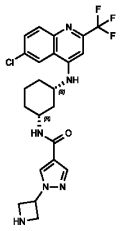
LCMS-ESI (m/z) calculated: 519.1 found 520.1 $[M+H]^+$, RT = 0.517 min (Method 11)

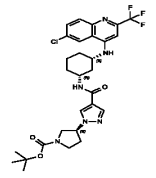
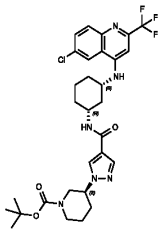
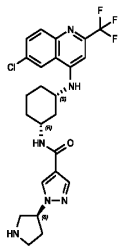
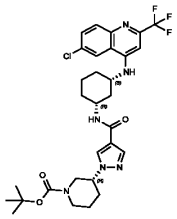
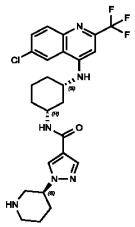
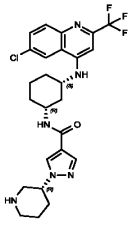
^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.60 (d, J = 2.1 Hz, 1H), 8.49 (d, J = 7.9 Hz, 1H), 8.27 (s, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.88 - 7.60 (m, 2H), 7.50 (br d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.33 (s, 1H), 6.20 (s, 1H), 4.11 - 3.83 (m, 2H), 2.18 (br d, J = 12.0 Hz, 1H), 2.03 - 1.88 (m, 2H), 1.84 (br d, J = 13.1 Hz, 1H), 1.59 - 1.49 (m, 2H), 1.44 - 1.27 (m, 2H).

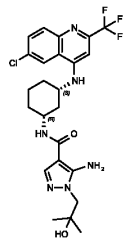
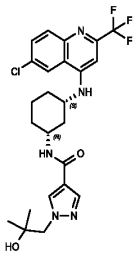
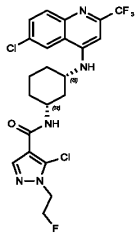
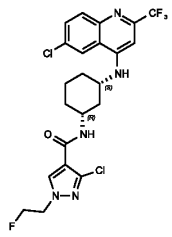
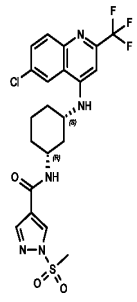
The compounds listed in Table 5 were made using the procedures of Scheme 5.

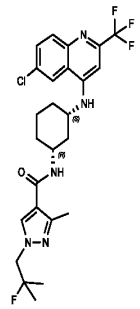
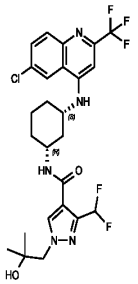
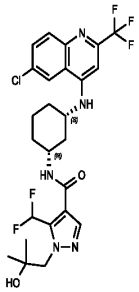
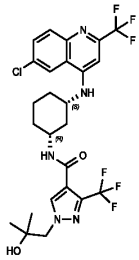
Table 5

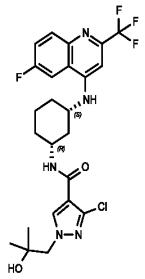
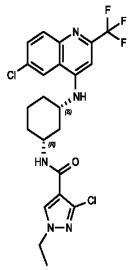
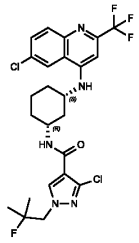
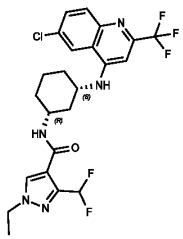
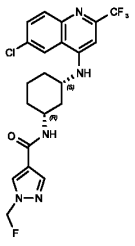
Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	5-1	9.353	496.17	497.2	$[M+H]^+$	Method 1
	5-2	9.058	496.17	497.2	$[M+H]^+$	Method 1
	5-3	0.565	525.36	526.9	$[M+H]^+$	Method 2
	5-4	9.28	514.93	515.2	$[M+H]^+$	Method 1

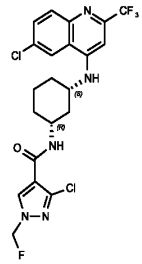
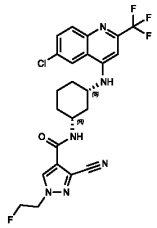
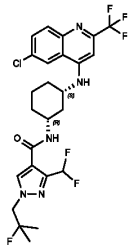
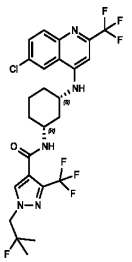
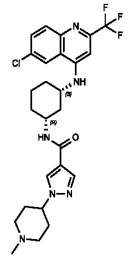
	5-5	9.573	514.93	515.2	$[M+H]^+$	Method 1
	5-6	10.067	499.36	499.2	$[M+H]^+$	Method 1
	5-7	8.912	528.36	528.1	$[M+H]^+$	Method 1
	5-8	9.57	593.05	593.3	$[M+H]^+$	Method 1
	5-9	5.83	492.93	493.2	$[M+H]^+$	Method 1

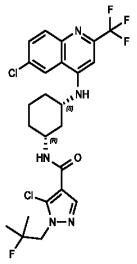
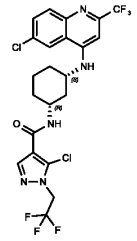
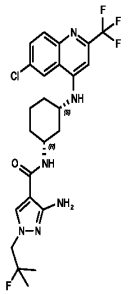
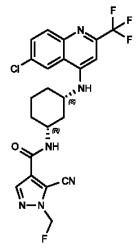
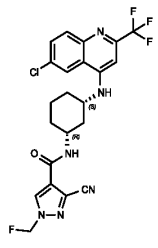
	5-10	9.71	607.08	607.3	$[M+H]^+$	Method 1
	5-11	10.14	621.1	621.3	$[M+H]^+$	Method 1
	5-12	5.78	506.96	507.2	$[M+H]^+$	Method 1
	5-13	10.13	621.1	621.3	$[M+H]^+$	Method 1
	5-14	5.87	520.99	521.3	$[M+H]^+$	Method 1
	5-15	5.83	520.99	521.3	$[M+H]^+$	Method 1

	5-16	0.60	524.97	525.1	$[M+H]^+$	Method 12
	5-17	7.63	509.96	510.3	$[M+H]^+$	Method 1
	5-18	9.03	518.34	518.2, 519.2, 520.1, 521.1	$[M+H]^+$	Method 1
	5-19	9.33	518.34	518.2, 519.2, 520.1, 521.1	$[M+H]^+$	Method 1
	5-20	0.899	515.94	515.9	$[M+H]^+$	Method 16

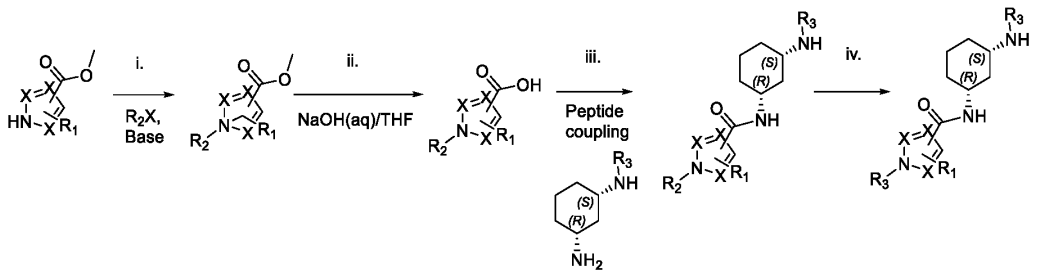
	5-21	0.539	525.98	526.3	$[M+H]^+$	Method 14
	5-22	8.956	559.97	560.3	$[M+H]^+$	Method 1
	5-23	9.676	559.97	560.3	$[M+H]^+$	Method 2
	5-24	9.297	577.8	578.2	$[M+H]^+$	Method 1

	5-25	8.14	527.9	528.2	$[M+H]^+$	Method 1
	5-26	9.625	500.3	500.1	$[M+H]^+$	Method 1
	5-27	10.133	546.39	546.2	$[M+H]^+$	Method 1
	5-28	0.605	515.91	516.1	$[M+H]^+$	LCMS-Q 5-95AB_1min.lcm
	5-29	8.359	469.87	469.9	$[M+H]^+$	Method 1

	5-30	9.332	504.3	503.9	$[M+H]^+$	Method 1
	5-31	0.552	508.9	509.1	$[M+H]^+$	Method 1
	5-32	0.572	561.96	562.3	$[M+H]^+$	Method 14
	5-33	0.61	579.95	580.1	$[M+H]^+$	Method 14
	5-34	5.958	535.01	535.3	$[M+H]^+$	Method 1

	5-35	9.830	546.39	546.2	$[M+H]^+$	Method 1
	5-36	9.900	554.32	554.1, 555.1, 556.1	$[M+H]^+$	Method 1
	5-37	0.513	526.96	527.3	$[M+H]^+$	Method 14
	5-38	9.41	494.88	495	$[M+H]^+$	Method 1
	5-39	9.279	494.88	495	$[M+H]^+$	Method 1

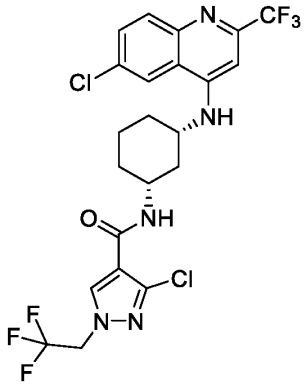
Scheme 6



Reagents: i. R_2-Mesylate or R_2-Triflate, base (K_2CO_3); ii. NaOH or LiOH aqueous/THF; iii. Peptide coupling conditions (HATU), base (DIPEA), solvent (DMF); iv. Includes R_2 deprotection or further modifications

EXAMPLE 30

SYNTHESIS OF EXAMPLE 30



Synthesis of 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide

To a stirring solution of ethyl 3-chloro-1H-pyrazole-4-carboxylate (200 mg, 1 Eq, 1.15 mmol) in DMF (5 mL) at room temperature was added cesium carbonate (1.12 g, 3 Eq, 3.44 mmol) portionwise over 2 minutes. After stirring for 30 minutes, 2,2,2-Trifluoroethyl trifluoromethanesulfonate (798 mg, 3 Eq, 3.44 mmol) was added dropwise over 2 minutes. The reaction mixture was stirred for 14 h. Water (5 mL) was added and the mixture wasextracted with EtOAc (3 x 5 mL), dried over sodium sulfate,

filtered through Celite, and concentrated in vacuo to afford an 87:13 mixture of ethyl 3-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate and ethyl 5-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate that was used without further purification.

To a stirring solution of the crude ethyl 3-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate and 5-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate mixture (294 mg, 1 Eq, 1.15 mmol) in THF (6 mL) was added an aqueous solution of 1M sodium hydroxide (5.7 mL, 5 Eq, 5.73 mmol). The reaction mixture was heated at 50 °C for 14 h. 10 mL of 3 M HCl was added. The aqueous layer was extracted with EtOAc (3 x 10 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo to afford a mixture of 3-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylic acid and 5-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylic acid (276 mg, 1.21 mmol, 105 %) that was used without further purification.

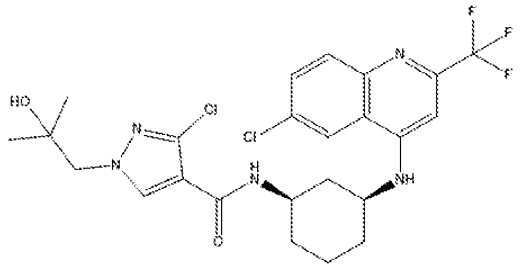
To a stirring solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (100 mg, 1 Eq, 0.264 mmol) in DMF (1.5 mL) were added a crude mixture of 3-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylic acid and 5-chloro-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylic acid (60 mg, 1 Eq, 0.264 mmol), N-ethyl-N-isopropylpropan-2-amine (DIPEA) (0.138 mL, 3 Eq, 0.793 mmol) and HATU (111 mg, 1.1 Eq, 0.291 mmol). The reaction mixture was stirred at room temperature for 2 h. Purification by reversed phase HPLC (35□55% 0.1% formic acid in MeCN and 0.1% formic acid in H_2O) afforded 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxamide (69 mg, 47% yield).

LCMS-ESI (m/z) calculated: 553.09 found 553.8 $[M+H]^+$, RT = 10.114 min (Method 1)

^{1}H NMR (400 MHz, DMSO-d6) δ 8.60 (d, *J* = 10.9 Hz, 1H), 8.35 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.74 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 5.21 (q, *J* = 9.0 Hz, 1H), 4.01-3.83 (m, 2H), 2.17 (d, *J* = 12.0 Hz, 1H), 2.00-1.78 (m, 3H), 1.61-1.21 (m, 4H).

EXAMPLE 31

SYNTHESIS OF EXAMPLE 31



Synthesis of 3-chloro-N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino] cyclohexyl]-1-(2-hydroxy-2-methylpropyl)pyrazole-4-carboxamide

To a solution of ethyl 3-chloro-1H-pyrazole-4-carboxylate (9.0 g, 52 mmol, 1 eq) and 2,2-dimethyloxirane (11.2 g, 155 mmol, 13.7 mL, 3 eq) in DMF (100 mL) was added K_2CO_3 (14.3 g, 103 mmol, 2 eq) and the resulting mixture was heated at 60°C for 2 h. The reaction was cooled to room temperature, diluted with water, and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue. The residue was purified by flash chromatography on silica gel eluting with [ethyl acetate in petroleum ether] (25%) to afford ethyl 3-chloro-1-(2-hydroxy-2-methyl-propyl)pyrazole-4-carboxylate (60% yield) as an oil.

LCMS-ESI (m/z) calculated: 246.1 found 247 [M+H]+, RT = 0.478 min (Method 14).

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.22 (s, 1H), 4.77 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.01 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.07 (s, 6H).

To a solution of ethyl 3-chloro-1-(2-hydroxy-2-methyl-propyl)pyrazole-4-carboxylate (6.6 g, 27 mmol, 1 eq) in MeOH (25 mL) and H_2O (25 mL) was added LiOH.H_2O (3.37 g, 80.3 mmol, 3 eq) and the resulting mixture was stirred at 25°C for 1.5 h. The reaction mixture pH was adjusted using 1 M HCl to pH 5~6. The mixture was concentrated in vacuo to give a crude residue. The residue was purified by reversed phase flash (0.1% FA condition in H_2O/CH_3CN, 0%). The crude product was obtained by lyophilization. The crude product was diluted with 20 mL H_2O and adjusted with 6 HCl to pH 1~2. The reaction solution was extracted with ethyl acetate. The combined organic

layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give 3-chloro-1-(2-hydroxy-2-methyl-propyl)pyrazole-4-carboxylic acid (74% yield).

LCMS (m/z) calculated: 218.1; found 201.2 [M18+H]+, t_R = 0.272 min (Method 14).

^{1}H NMR (400 MHz, DMSOd_6) δ = 12.62 (s, 1H), 8.16 (s, 1H), 4.77 (s, 1H), 4.00 (s, 2H), 1.07 (s, 6H)

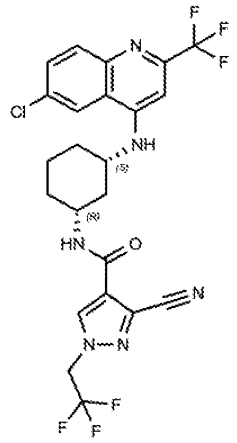
To a solution of 3-chloro-1-(2-hydroxy-2-methyl-propyl)pyrazole-4-carboxylic acid (3.7 g, 16.92 mmol, 1 eq) in DCM (40 mL) were added TEA (5.14 g, 50.8 mmol, 7.07 mL, 3 eq), HOBt (2.29 g, 16.9 mmol, 1 eq), EDCI (3.89 g, 20.3 mmol, 1.2 eq) and (1S,3R)-N1-[6-chloro-2-(trifluoromethyl)-4-quinolyl]cyclohexane-1,3-diamine (5.53 g, 16.08 mmol, 0.95 eq). The reaction was stirred at 25°C for 12 h. The reaction solution was diluted with water (200 mL) and then extracted with DCM (2 x 200 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give a crude residue. The residue was triturated with CH_3CN (40 mL). The mixture was filtered and the filter cake was collected and concentrated in vacuo to give a crude residue. The crude residue was purified by reversed phase flash column chromatography([water(NH_4HCO_3)-ACN];B%: 38%-68%) to afford 3-chloro-N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-1-(2-hydroxy-2-methylpropyl)pyrazole-4-carboxamide as a solid.

LCMS (m/z) calculated: 543.1; found 544.2 $[M+H]^+$, t_R = 0.529 min (Method 14).

^{1}H NMR (400 MHz, DMSO-d6) δ = 8.59 (s, 1H), 8.19 (s, 1H), 7.91 - 7.84 (m, 2H), 7.72 (br d, J = 8.5 Hz, 1H), 7.48 (br d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 4.80 (s, 1H), 3.96 (s, 2H), 3.95 - 3.79 (m, 2H), 2.16 (br d, J = 11.1 Hz, 1H), 2.07 (s, 1H), 2.00 - 1.77 (m, 3H), 1.58 - 1.44 (m, 2H), 1.40 - 1.22 (m, 2H), 1.07 (s, 6H).

EXAMPLE 32

SYNTHESIS OF EXAMPLE 32



Synthesis of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(2,2,2- trifluoroethyl)pyrazole-4-carboxamide

To a solution of ethyl 1H-pyrazole-4-carboxylate (10 g, 71.36 mmol, 1 eq) in THF (50 mL) was added NaH (3.42 g, 85.6 mmol, 60% purity, 1.2 eq) and stirred for 1 h at 0 °C under N_2. SEM-Cl (14.3 g, 85.6 mmol, 15.2 mL, 1.2 eq) was added and the mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched with saturated NH_4Cl aqueous (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give crude material. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 80/20) to afford ethyl 1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (15.8 g, 58.4 mmol, 82% yield) as an oil.

To a solution of ethyl 1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (15.5 g, 57.3 mmol, 1 eq) in THF (200 mL) was added dropwise of LDA (2 M, 43.0 mL, 1.5 eq) at -70 °C over 10 min. After stirring for 30 min, DMF (25.1 g, 344 mmol, 26.5 mL, 6 eq) was added. The resulting mixture was stirred at -70 °C for an additional 20 min. The reaction was quenched with saturated NH_4Cl aqueous (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 85/15) to afford ethyl 5-formyl-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (6.1 g, 20.4 mmol, 36% yield) as an oil.

To a solution of ethyl 5-formyl-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (6.0 g, 20.1 mmol, 1 eq) in EtOH (20 mL) were added NaOAc (4.95 g, 60.3

mmol, 3 eq) and $NH_5OH.HCl$ (1.68 g, 24.1 mmol, 1.2 eq). After stirring for 3 h at 70 °C, the reaction mixture was cooled to room temperature and was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organics were dried over $MgSO_4$ and concentrated in vacuo to afford ethyl 5-(hydroxyiminomethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (8.1 g, crude) as a solid that was used without further purification.

Ethyl 5-(hydroxyiminomethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (7.5 g, 23.9 mmol, 1 eq) was dissolved in Ac_2O (20 mL) and heated for 12 h at 145 °C. TLC indicated 70% of starting material remained. To the reaction mixture was added additional Ac_2O (20 mL) and the mixture was heated for an additional 12h at 145°C. The reaction mixture was cooled to room temperature and was partitioned between EtOAc (25 mL) and water (25 mL). The aqueous phase was extraced with EtOAc (2 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated in vacuo to afford ethyl 5-cyano-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate.

To a solution of ethyl 5-cyano-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (350 mg, 1.18 mmol, 1 eq) in MeOH (2 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (149 mg, 3.55 mmol, 3 eq). After stirring for 1h at 25°C, the reaction mixture was concentrated in vacuo to give afford 5-cyano-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylic acid (300 mg, 1.12 mmol, 95% yield) as a solid.

To a solution of 5-cyano-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylic acid (300 mg, 1.12 mmol, 1 eq) (1S,3R)-N1- [6-chloro-2-(trifluoromethyl)-4-quinolyl]cyclohexane-1,3-diamine (427 mg, 1.12 mmol, 1 eq, HCl) in DMF (6 mL) were added DIPEA (435 mg, 3.37 mmol, 586 uL, 3 eq) and HATU (640 mg, 1.68 mmol, 1.5 eq). The resulting mixture was stirred for 12 h at 25 °C. The mixture was partitioned between EtOAc (25 mL) and water (25 mL). The aqueous phase was extraced with EtOAc (2x 20 mL). The combined organics were dried over $MgSO_4$ and concentrated in vacuo to give a crude residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 63/37) to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-cyano-1-(2- trimethylsilylethoxymethyl)pyrazole-4-carboxamide (500 mg, 843 umol, 75% yield) as a solid.

N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)pyrazole4-carboxamide (500 mg, 843 umol, 1 eq) was dissolved in TBAF (1.0 M, 10 mL, 11.9 eq) (in THF) and heated for 2 h at 50 °C. The mixture was filtered and the residue was purified by prep-TLC (SiO_2, PE: EtOAc =1:1 , TLC, PE: EtOAc =1:1 , Rf=0) and concentrated in vacuo to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-cyano-1H-pyrazole-4-carboxamide (170 mg, 367 umol, 44% yield) as a solid.

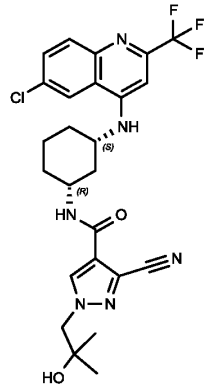
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl] amino]cyclohexyl]-3-cyano-1H-pyrazole-4- carboxamide (100 mg, 216 umol, 1 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (100 mg, 432 umol, 2 eq) in MeCN (3 mL) was added Cs_2CO_3 (211 mg, 648 umol, 3 eq). The reaction mixture was heated for 12 h at 60 °C. The reaction mixture was cooled to room temperature and concentrated in vacuo to give a residue. The crude product was purified by reversed-phase HPLC:Column (Phenomenex luna C18 150*25mm* 10um) Condition water((0.225%FA)-ACN) Begin B (50) End B (80) Gradient Time(min) (10) to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(2,2,2-trifluoroethyl)pyrazole-4-carboxamide (19.5 mg, 35.8 umol, 16% yield, 100% purity).

LCMS (m/z) calculated for $C_{23}H_{19}ClF_6N_6O$: 544.1; found 545.1 $[M+H]^+$, t_R = 0.602 min (Method 11)).

^1H NMR (400 MHz, DMSO-d_6) δ = 8.60 - 8.56 (m, 2H), 8.46 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 2.3, 9.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 5.43 (q, J = 9.1 Hz, 2H), 4.02 - 3.85 (m, 2H), 2.18 (br d, J = 11.6 Hz, 1H), 2.00 - 1.89 (m, 2H), 1.87 - 1.78 (m, 1H), 1.57 - 1.22 (m, 4H).

EXAMPLE 33

SYNTHESIS OF EXAMPLE 33



Synthesis of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(2-hydroxy-2-methylpropyl)pyrazole-4-carboxamide

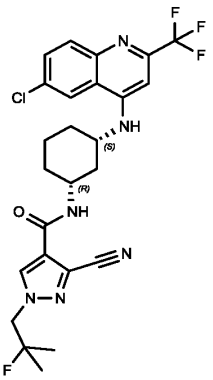
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-cyano-1H-pyrazole-4- carboxamide (45 mg, 97 umol, 1 eq) and 2,2-dimethyloxirane (10.5 mg, 146 umol, 13 uL, 1.5 eq) in DMF (2 mL) was added K_2CO_3 (27 mg, 194.45 umol, 2 eq). The mixture was heated for 12 h at 100 °C. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC:Column (Welch Xtimate C18 150*25mm*5um) Condition water((0.05%HCl)-ACN) to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(2-hydroxy-2-methylpropyl)pyrazole-4-carboxamide (30% yield) as a solid.

LCMS-ESI (m/z) calculated: 534.2 found 535.2 $[M+H]^+$, RT = 0.582 min (Method 14)

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.49 (s, 1H), 8.04 - 7.95 (m, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.17 - 7.09 (m, 2H), 6.91 - 6.84 (m, 1H), 3.92 - 3.76 (m, 1H), 3.65 - 3.51 (m, 1H), 1.77 - 1.64 (m, 8H).

EXAMPLE 34

SYNTHESIS OF EXAMPLE 34



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-cyano-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide

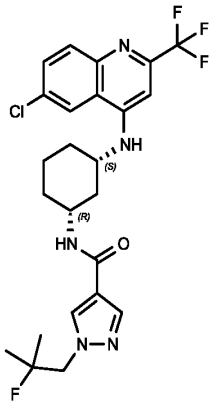
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino] cyclohexyl]-3-cyano-1-(2-hydroxy-2-methylpropyl)pyrazole-4-carboxamide (140 mg, 1 eq, 262 umol) in DCM (2 mL) was added DAST (127 mg, 1 eq, 785 umol, 104 uL). The reaction mixture was stirred at 25°C for 1 hr. The solvent was filtered and filtrate was collected. The crude product was purified by prep-HPLC to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-cyano-1-(2-fluoro-2-methylpropyl)pyrazole-4-carboxamide (23 mg, 42 umol, 15% yield) as a solid.

LCMS-ESI (m/z) calculated: 536.95 found 537.3 $[M+H]^+$, RT = 0.479 min (Method 11).

^{1}H NMR (400 MHz, METHANOL-d_4) δ = 8.37 (d, J = 2.1 Hz, 1H), 8.27 (d, J = 1.3 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.69 (dd, J = 2.3, 9.0 Hz, 1H), 6.91 (s, 1H), 4.52 - 4.34 (m, 2H), 4.10 - 3.99 (m, 1H), 3.86 - 3.76 (m, 1H), 2.39 (br d, J = 12.0 Hz, 1H), 2.16 - 1.93 (m, 3H), 1.71 - 1.38 (m, 4H), 1.37 - 1.28 (m, 6H).

EXAMPLE 35

SYNTHESIS OF EXAMPLE 35



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrazole-4-carboxamide

To a stirred suspension of tert-butyl 4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazole-1-carboxylate (1.014 g, 1 Eq, 1.885 mmol) in 1,4-Dioxane (15 mL) was added HCl in 1,4-dioxane (687.2 mg, 4.712 mL, 4.00 molar, 10 Eq, 18.85 mmol). The resulting mixture was heated at 50 °C for 2 hours, and then concentrated under reduced pressure to yield N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrazole-4-carboxamide hydrochloride (1128 mg, 2.378 mmol, 126 %) as a solid. The product was used in the next step without further purification.

LCMS-ESI (m/z) calculated: 437.12 found 438.0 $[M+H]^+$, RT = 0.825 min (Method 11)

To a stirred solution of 1-(tert-butoxycarbonyl)-1H-pyrazole-4-carboxylic acid (960 mg, 1 Eq, 4.52 mmol) and DIPEA (2.34 g, 3.2 mL, 4 Eq, 18.1 mmol) in DMF (10 mL) was added HATU (1.72 g, 1 Eq, 4.52 mmol).After stirring for 10 minutes at room temperature, (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (1.72 g, 1 Eq, 4.52 mmol) was added in one portion. The resulting mixture (brown solution) was allowed to stir at room temperature for 18 hours. The reaction mixture was diluted with EtOAc and washed with H_2O. The organic layer was collected, and the aqueous layer was back-extracted 2x with EtOAc. The

organic layers were combined, washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL) and purified by reverse-phase flash column chromatography to yield tert-butyl 4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazole-1-carboxylate (1.042 g, 1.937 mmol, 43 %) as a solid.

LCMS-ESI (m/z) calculated: 537.17 found 538.0 $[M+H]^+$, RT = 5.264 min (Method 10)

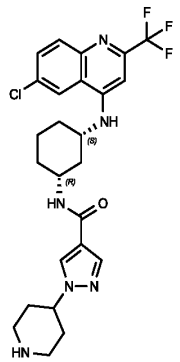
To a stirred solution of 1-bromo-2-fluoro-2-methylpropane (64 mg, 3 Eq, 0.41 mmol), followed in DMF (2 mL) were added N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-pyrazole-4-carboxamide hydrochloride (60 mg, 1 Eq, 0.14 mmol) and potassium carbonate (28 mg, 1.5 Eq, 0.21 mmol). The resulting white suspension was heated and stirred at 80 °C for 2 days. The reaction mixture was cooled to room temperature and directly purified by prep-HPLC to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2-fluoro-2-methylpropyl)-1H-pyrazole-4-carboxamide (12 mg, 23 µmol, 17 %) as a solid.

LCMS-ESI (m/z) calculated: 511.18 found 512.3 $[M+H]^+$, RT = 8.865 min (Method 1)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.13 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.76 – 7.71 (m, 1H), 7.48 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 4.33 (d, J = 19.9 Hz, 2H), 4.03 – 3.94 (m, 1H), 3.91 – 3.83 (m, 1H), 2.15 (d, J = 11.9 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.90 – 1.78 (m, 2H), 1.60 – 1.44 (m, 2H), 1.42 – 1.34 (m, 1H), 1.27 (d, J = 21.5 Hz, 7H).

EXAMPLE 36

SYNTHESIS OF EXAMPLE 36



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide

To a stirring solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (40 mg, 1 Eq, 0.11 mmol) in DMF (2 mL) were added 1-(1-(tert-butoxycarbonyl)piperidin-4-yl)-1H-pyrazole-4-carboxylic acid (31 mg, 1 Eq, 0.11 mmol), HATU (40 mg, 1 Eq, 0.11 mmol) and DIPEA (54 mg, 73 µL, 4 Eq, 0.42 mmol). The resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was directly purified by prep-HPLC to yield tert-butyl 4-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (36.6 mg, 58.9 µmol, 56 %) as a solid.

LCMS-ESI (m/z) calculated: 620.25 found 621.3 [M+H]+, RT = 9.935 (Method 1)

^{1}H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.23 (s, 1H), 7.94 – 7.82 (m, 3H), 7.74 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 4.36 (t, J = 11.8 Hz, 1H), 4.00 (s, 3H), 3.87 (d, J = 9.5 Hz, 1H), 2.90 (s, 2H), 2.15 (d, J = 11.9 Hz, 1H), 2.00 (d, J = 12.9 Hz, 3H), 1.89 – 1.69 (m, 4H), 1.60 – 1.44 (m, 2H), 1.44 – 1.34 (m, 10H), 1.29 – 1.22 (m, 1H).

To a stirring solution of tert-butyl 4-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (30.4 mg, 1 Eq, 48.9 µmol) in 1,4-dioxane (1.5 mL) was added 4M HCl in 1,4-dioxane (122 µL, 10 Eq, 489 µmol). The resulting white cloudy suspension was stirred for 2 hours at 50 °C. The reaction mixture was subsequently purified by prep-HPLC to yield N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-

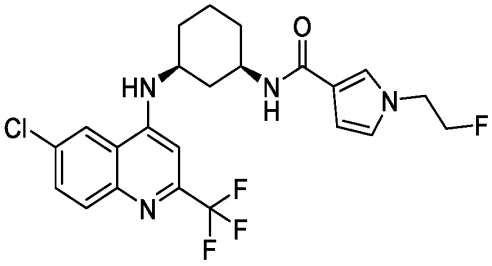
yl)amino)cyclohexyl)-1-(piperidin-4-yl)-1H-pyrazole-4-carboxamide (11.7 mg, 22.5 µmol, 46 %) as a solid.

LCMS-ESI (m/z) calculated: 520.20 found 521.2 [M+H]+, RT = 5.861 min (Method 1).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.59 (s, 1H), 8.20 (s, 1H), 7.95 – 7.80 (m, 3H), 7.74 (d, J = 9.0 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 6.93 (s, 1H), 4.25 (t, J = 11.9 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.91 – 3.82 (m, 1H), 3.10 (d, J = 12.5 Hz, 2H), 2.68 (t, J = 12.2 Hz, 2H), 2.15 (d, J = 11.9 Hz, 1H), 1.99 (d, J = 12.6 Hz, 3H), 1.90 – 1.76 (m, 4H), 1.57 – 1.35 (m, 3H), 1.29 – 1.22 (m, 1H).

EXAMPLE 37

SYNTHESIS OF EXAMPLE 37



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2-fluoroethyl)-1H-pyrrole-3-carboxamide

To a stirring solution of methyl 1H-pyrrole-3-carboxylate (250 mg, 1 Eq, 2.00 mmol) in DMF (4 mL) at 0 °C was added sodium hydride (95.9 mg, 60% Wt, 1.2 Eq, 2.40 mmol). The reaction mixture was stirred for 10 minutes. 1-bromo-2-fluoroethane (380 mg, 1.5 Eq, 3.00 mmol) was added and the reaction mixture was warmed to room temperature. After stirring overnight at room temperature, H_2O (5 mL) was added. The aqueous layer was extracted with EtOAc (3 x 5 mL), washed with H_2O (3 x 5 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo to afford crude material. The crude material was purified by silica gel chromatography (0-->50% EtOAc and hexanes) to afford methyl 1-(2-fluoroethyl)-1H-pyrrole-3-carboxylate (205.3 mg, 1.199 mmol, 60.0 % yield).

LCMS-ESI (m/z) calculated: 171.07 found 172.0 $[M+H]^+$, RT = 0.660 min (Method 11)

To a stirring solution of methyl 1-(2-fluoroethyl)-1H-pyrrole-3-carboxylate (205 mg, 1 Eq, 1.19 mmol) in THF (6 mL) was added sodium hydroxide (240 mg, 5.99 mL, 1 molar, 5 Eq, 5.99 mmol). The reaction mixture was heated at 50 °C for 12h. Additional sodium hydroxide (240 mg, 5.99 mL, 1 molar, 5 Eq, 5.99 mmol) and heated at 70 °C overnight. The reaction mixture was cooled to room temperature, 3M HCl was added (10 mL), extracted with EtOAc (3 x 10 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo to afford 1-(2-fluoroethyl)-1H-pyrrole-3-carboxylic acid (169 mg, 1.08 mmol, 90 % yield).

LCMS-ESI (m/z) calculated: 157.05 found 158.0 $[M+H]^+$, RT = 0.487 min (Method 11)

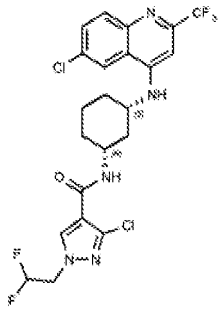
N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2-fluoroethyl)-1H-pyrrole-3-carboxamide was synthesized using scheme 4 and starting from 1-(2-fluoroethyl)-1H-pyrrole-3-carboxylic acid and (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride.

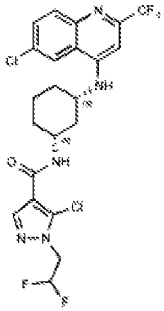
LCMS-ESI (m/z) calculated: 482.15 found 483.2 $[M+H]^+$, RT = 9.764 min (Method 1)

^{1}H NMR (400 MHz, DMSO) δ 8.61 (s, 1H), 7.93-7.88 (m, 1H), 7.77-7.14 (m, 1H), 7.64-7.59 (m, 1H), 7.52-7.47 (m, 1H), 7.35 (s, 1H), 6.93 (s, 1H), 6.79-6.75 (m, 1H), 6.51-6.47 (m, 1H), 4.75-4.69 (m, 1H), 4.62-4.58 (m, 1H), 4.28-4.21 (m, 1H), 4.20-4.14 (m, 1H), 4.04-3.93 (m, 1H), 3.91-3.79 (m, 1H), 2.17-2.09 (m, 1H), 2.01-1.91 (m, 1H), 1.90-1.78 (m, 2H), 1.58-1.23 (m, 5H).

EXAMPLES 38 AND 39

SYNTHESIS OF EXAMPLE 38 AND 39





Synthesis of 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino) cyclohexyl)-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide and 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide

To a stirring solution of ethyl 3-chloro-1H-pyrazole-4-carboxylate (200 mg, 1 Eq, 1.15 mmol) in MeCN (15 mL) were added cesium carbonate (1.49 g, 4 Eq, 4.58 mmol) and 2-bromo-1,1-difluoroethane (498 mg, 3 Eq, 3.44 mmol). The vial was capped, heated at 60 °C overnight, and concentrated in vacuo. The reaction mixture was cooled to room temperature, Water (20 mL) was added, and the mixture was extracted with EtOAc (2 x 20 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo to afford a mixture of ethyl 3-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylate and ethyl 5-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylate (335.3 mg, 1.405 mmol, 123 %) that was used without further purification.

To a stirring solution of crude ethyl 3-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylate and ethyl 5-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylate (273 mg, 1 Eq, 1.14 mmol) in THF (8 mL) was added sodium hydroxide (229 mg, 5.72 mL, 1 molar, 5 Eq, 5.72 mmol). The reaction mixture was heated at 50 °C for 4h. The reaction mixture was concentrated in vacuo, 3M HCl was added (10 mL), and the mixture was extracted with EtOAc (3 x 10 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo to afford 3-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylic acid and 5-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylic acid (289 mg, 1.37 mmol, 120 %) as a crude mixture that was used without further purification.

To a stirring solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (100 mg, 1 Eq, 264 µmol) in DMF (1.5 mL) were added crude 3/5-chloro-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxylic acid (55.7 mg, 1 Eq, 264 µmol), N-ethyl-N-isopropylpropan-2-amine (DIPEA) (103 mg, 138 µL, 3

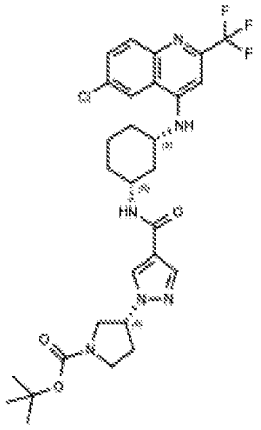
Eq, 793 µmol) and HATU (111 mg, 1.1 Eq, 291 µmol). The reaction mixture was stirred at room temperature for 2h. The crude mixture was purified by reversed phase HPLC (35-55% 0.1% formic acid in MeCN and 0.1% formic acid in H_2O) to afford 3-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide (70 mg, 131 µmol, 50 %) and 5-chloro-N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-(2,2-difluoroethyl)-1H-pyrazole-4-carboxamide (26 mg, 48 µmol, 18 %).

Example 38: LCMS-ESI (m/z) calculated: 535.1 found 536.1 $[M+H]^+$, RT = 9.368 min (Method 1)

Example 39: LCMS-ESI (m/z) calculated: 535.1 found 536.1 $[M+H]^+$, RT = 9.622 min (Method 1)

EXAMPLE 40

SYNTHESIS OF EXAMPLE 40



Synthesis of tert-butyl (R)-3-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate

A solution of (S)-tert-butyl 3-bromopyrrolidine-1-carboxylate (500 mg, 1.2 Eq, 2.00 mmol) in DMF (5 mL) was charged with ethyl 4-pyrazolecarboxylate (233 mg, 1 Eq, 1.67 mmol) and cesium carbonate (1.36 g, 2.5 Eq, 4.16 mmol). The resulting suspension was heated and stirred at 90 °C. After stirring for 19 hours, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with cold water and extracted with EtOAc (3x100mL). The organic layers were combined, washed with

brine, and concentrated under reduced pressure to yield the expected product. The crude product was used without further purification or characterization.

A solution of ethyl (R)-1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazole-4-carboxylate (515 mg, 1 Eq, 1.66 mmol) in THF (20 mL) was added 1M sodium hydroxide (666 mg, 16.6 mL, 1.00 molar, 10 Eq, 16.6 mmol). The resulting solution was heated and stirred overnight at 50 °C. After heating at 50 °C for 18 hours, the reaction mixture was concentrated under reduced pressure. The aqueous residue was acidified to pH 3-4 using 3N HCl. The mixture was extracted with EtOAc (3x30mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield (R)-1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazole-4-carboxylic acid (351 mg, 1.25 mmol, 75 %).

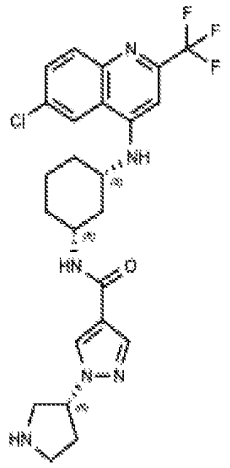
A solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (40 mg, 1 Eq, 0.11 mmol) in DMF (2 mL) was added HATU (40 mg, 1 Eq, 0.11 mmol), (R)-1-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)-1H-pyrazole-4-carboxylic acid (30 mg, 1 Eq, 0.11 mmol), and DIPEA (73 µL, 4 Eq, 0.42 mmol). The resulting solution was allowed to stir at room temperature for 18 hours. The crude was directly purified by prep-HPLC to afford tert-butyl (R)-3-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (13.5 mg, 22.2 µmol, 21 %).

LCMS-ESI (m/z) calculated: 606.23 found 607.3 $[M+H]^+$, RT = 9.718 min (Method 1)

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.23 (s, 1H), 7.96 – 7.83 (m, 3H), 7.74 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 6.93 (s, 1H), 5.00 – 4.92 (m, 1H), 4.02 – 3.83 (m, 2H), 3.74 – 3.67 (m, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 3.46 – 3.35 (m, 2H), 2.29 (d, *J* = 25.7 Hz, 2H), 2.15 (d, *J* = 11.8 Hz, 1H), 1.96 (d, *J* = 12.3 Hz, 1H), 1.90 – 1.78 (m, 2H), 1.59 – 1.44 (m, 2H), 1.42 – 1.24 (m, 11H).

EXAMPLE 41

SYNTHESIS OF EXAMPLE 41



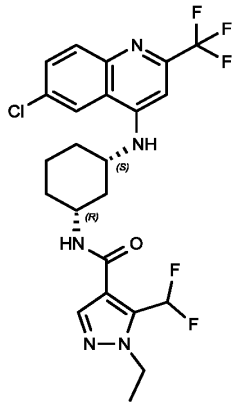
Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazole-4-carboxamide

To a solution of tert-butyl (R)-3-(4-(((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)carbamoyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (9.2 mg, 1 Eq, 15 µmol) in 1,4-Dioxane (1.5 mL) was added hydrogen chloride in 1,4-dioxane (5.5 mg, 38 µL, 4.00 molar, 10 Eq, 0.15 mmol). The resulting mixture was heated at 50 °C for 2 hours. The reaction mixture was diluted in MeOH and directly purified by prep-HPLC to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1-((R)-pyrrolidin-3-yl)-1H-pyrazole-4-carboxamide (2.2 mg, 4.3 µmol, 29 % yield).

LCMS-ESI (m/z) calculated: 506.18 found 507.2 $[M+H]^+$, RT = 5.834 min (Method 1)

EXAMPLE 42

SYNTHESIS OF EXAMPLE 42



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-5-(difluoromethyl)-1-ethyl-1H-pyrazole-4-carboxamide

A solution of ethyl 5-(difluoromethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylate (200 mg, 624 umol, 1 eq) in THF (1.5 mL) and H_2O (1.5 mL) was added $LiOH.H_2O$ (79 mg, 1.9 mmol, 3 eq) and heated for 2 h at 50 °C. The reaction mixture was cooled to room temperature and neutralized with 5% HCl to pH 7. The reaction mixture was concentrated in vacuo to afford 5-(difluoromethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylic acid (180 mg, 617 umol, 99% yield) as a solid that was used without further purification

To a solution of 5-(difluoromethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxylic acid (175 mg, 599 umol, 1 eq) and (1S,3R)-N1-[6-chloro-2-(trifluoromethyl)-4-quinolyl]cyclohexane-1,3-diamine (206 mg, 599 umol, 1 eq) in DMF (4 mL) were added HATU (341 mg, 898 umol, 1.5 eq) and DIEA (232 mg, 1.80 mmol, 313 uL, 3 eq). The mixture was stirred for 12 h at 25 °C. The mixture was partitioned between EtOAc (15 mL) and water (15 mL). The aqueous phase was back extraced with EtOAc (2 x 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo to give crude material. The crude residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 0/1) to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-(difluoromethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxamide (280 mg, 453 umol, 76% yield) as an oil.

To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino] cyclohexyl]-5-(difluoromethyl)-1-(2-trimethylsilylethoxymethyl)pyrazole-4-carboxamide (280 mg, 453 umol, 1 eq) in DCM (3 mL) was added TFA (924 mg, 8.10 mmol, 600 uL, 17.9 eq). The reaction mixture was stirred for 1h at 25°C. The reaction mixture was concentrated under reduced pressure to give a residue. MeOH (3 mL) and K_2CO_3 (313 mg, 2.26 mmol, 5 eq) were added and heated for 1h at 50 °C. The mixture was cooled to room tempearature and partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organics were dried over $MgSO_4$ and concentrated in vacuo to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-(difluoromethyl)-1H-pyrazole-4- carboxamide (210 mg, 396 umol, 87% yield, 92% purity) as an oil that was used without further purification.

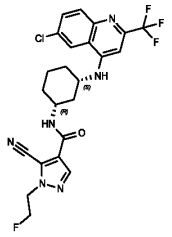
To a solution of N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-3-(difluoromethyl)-1H-pyrazole-4- carboxamide (60 mg, 113 umol, 92% purity, 1 eq) and iodoethane (53 mg, 340 umol, 27 uL, 3 eq) in MeCN (1.5 mL) was added K_2CO_3 (47 mg, 340 umol, 3 eq) and the mixture was heated for 14h at 50 °C. The mixture was cooled to room temperature and filtered to remove insoluble material. The crude product was purified by reversed-phase HPLC:Column (Phenomenex luna C18 150*25mm* 10um) Condition water((0.225%FA)-ACN) Begin B (46) End B (76) Gradient Time(min) (10.5) to afford N-[(1R,3S)-3-[[6-chloro-2-(trifluoromethyl)-4-quinolyl]amino]cyclohexyl]-5-(difluoromethyl)-1-ethyl-pyrazole-4- carboxamide (9.3 mg, 17.4 umol, 15% yield, 97% purity) as a solid.

LCMS-ESI (m/z) calculated: 515.1 found 516.1 $[M+H]^+$, RT = 0.625 min (Method 14)

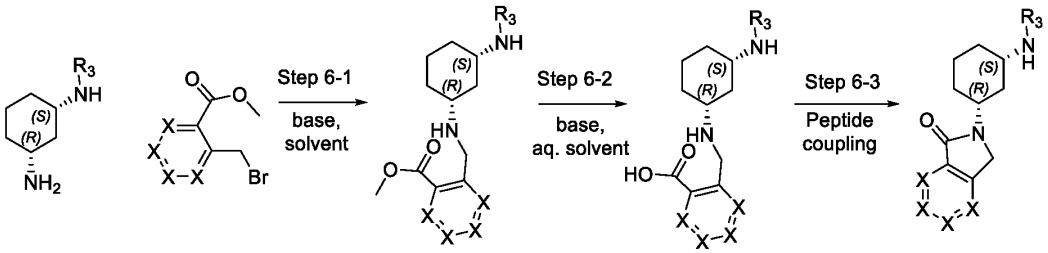
^1H NMR (400 MHz, DMSO-d_6) δ = 8.59 (d, J = 2.0 Hz, 1H), 8.30 - 8.30 (m, 1H), 8.29 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.87 - 7.58 (m, 2H), 7.48 (br d, J = 8.0 Hz, 1H), 6.93 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.06 - 3.81 (m, 2H), 2.15 (br d, J = 12.1 Hz, 1H), 1.97 (br d, J = 11.3 Hz, 1H), 1.92 - 1.78 (m, 2H), 1.59 - 1.46 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.34 - 1.20 (m, 2H).

The compounds listed in Table 6 were made using the procedures of Scheme 6.

Table 6

Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	6-1	0.572	508.9	509.1	$[M+H]^+$	Method 11

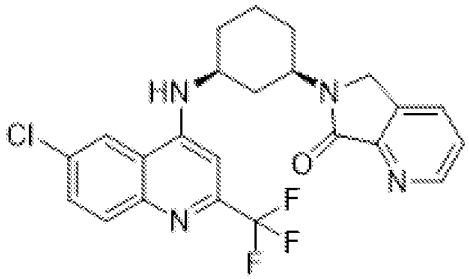
Scheme 7



Reagents: X is C or N independtly. Step 6-1. base (DIPEA), solvent (DMF); Step 6-2. NaOH aqueous/THF; Step 5-3. Peptide coupling conditions (HATU), base (DIPEA), solvent (DMF)

EXAMPLE 43

SYNTHESIS OF EXAMPLE 43



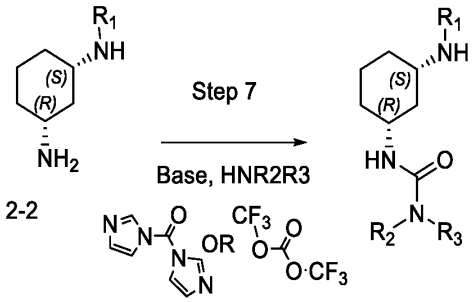
Synthesis of 6-[(1R,3S)-3-{[6-chloro-2-(trifluoromethyl)quinolin-4-yl]amino}cyclohexyl]-5H,6H,7H-pyrrolo[3,4-b]pyridin-7-one

To a stirring solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (50 mg, 1 Eq, 0.13 mmol) in DMF (1.5 mL) were added N-ethyl-N-isopropylpropan-2-amine (DIPEA) (85 mg, 0.12 mL, 5 Eq, 0.66 mmol) and methyl 3-(bromomethyl)picolinate (46 mg, 1.5 Eq, 0.20 mmol). The vial was capped and heated at 40 °C over the weekend. The crude product was purified by reversed phase HPLC (35-->55% 0.1% formic acid in H_2O and 0.1% formic acid in MeCN) to afford 6-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-5,6-dihydro-7H-pyrrolo[3,4-b]pyridin-7-one (37.1 mg, 80.5 µmol, 61 % yield).

LCMS-ESI (m/z) calculated: 460.13 found 461.2 $[M+H]^+$, RT = 8.116 min (Method 1)

^{1}H NMR (400 MHz, DMSO) δ 8.72 (s, 1H), 8.61 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.60-7.51 (m, 2H), 7.00 (s, 1H), 4.52 (app q, *J* = 13.0 Hz, 2H), 4.43-4.29 (m, 1H), 4.09-3.98 (m, 1H), 2.20-2.12 (m, 1H), 2.04-1.98 (m, 1H), 1.94-1.76 (m, 3H), 1.69-1.56 (m, 2H), 1.52-1.40 (m, 1H).

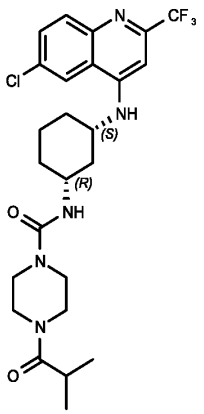
Scheme 8



Reagents: R_2R_3NH, di(1H-imidazol-1-yl)methanone or triphosgene, base (TEA), solvent (DCM)

EXAMPLE 44

SYNTHESIS OF EXAMPLE 44



Step 7. N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-4-isobutyrylpiperazine-1-carboxamide

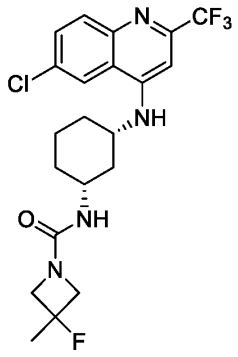
To a stirring solution of di(1H-imidazol-1-yl)methanone (2.14 g, 5 Eq, 13.2 mmol) and triethylamine (348 mg, 479 µL, 1.3 Eq, 3.44 mmol) in DCM (20 mL) at 0 °C was added (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine hydrochloride (1.00 g, 1 Eq, 2.64 mmol) in two portions,separated by 10 minutes. The reaction mixture was stirred at 0 °C for 1h and then 30 minutes at room temperature. The reaction mixture was concentrated in vacuo to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-imidazole-1-carboxamide that was dried under high vacuum and used without further purification.

To a stirring solution of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-1H-imidazole-1-carboxamide (100 mg, 50% Wt, 1 Eq, 114 µmol) in DCM (1.5 mL) were added 2-methyl-1-(piperazin-1-yl)propan-1-one (89.2 mg, 5 Eq, 571 µmol) and N-ethyl-N-isopropylpropan-2-amine (DIPEA) (73.8 mg, 99.5 µL, 5 Eq, 571 µmol). The reaction mixture was stirred at room temperature overnight. The crude mixture was purified by reversed phase prep HPLC to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-4-isobutyrylpiperazine-1-carboxamide (29.1 mg, 55.3 µmol).

LCMS-ESI (m/z) calculated: 526 found 526.3 $[M+H]^+$, RT = 8.141 min (Method 1).

EXAMPLE 45

SYNTHESIS OF EXAMPLE 45



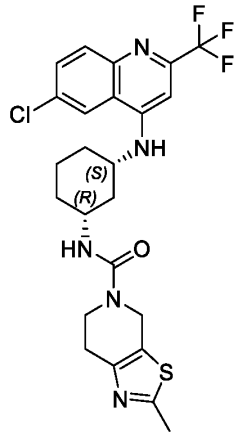
Step 5. Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-fluoro-3-methylazetidine-1-carboxamide

To a stirring solution of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-hydroxy-3-methylazetidine-1-carboxamide (40 mg, 1.0 Eq, 0.088 mmol) in DCM (0.5 mL) at room temperature was added a solution of Deoxo-Fluor (29 mg, 1.5 Eq, 0.13 mmol). The reaction mixture was stirred at room temperature for 5 min. Sat. ammonium chloride solution (2 mL) was added dropwise. The aqueous layer was extracted with EtOAc/MeOH (5:1) (2 x 5 mL), dried over sodium sulfate, filtered through Celite, and concentrated in vacuo. The crude mixture was purified by prep HPLC to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-3-fluoro-3-methylazetidine-1-carboxamide (23.5 mg, 51.2 μmol, 58 %).

LCMS-ESI (m/z) calculated: 458.15 found 459.2 [M+H]+, RT = 8.638 min (Method 1)

EXAMPLE 46

SYNTHESIS OF EXAMPLE 46



Synthesis of N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxamide

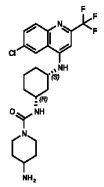
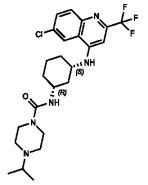
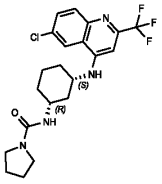
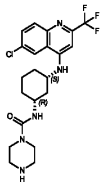
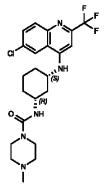
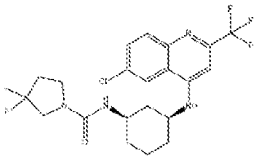
To an ice-cold solution of (1S,3R)-N1-(6-chloro-2-(trifluoromethyl)quinolin-4-yl)cyclohexane-1,3-diamine 60 mg, 1 Eq, 0.16 mmol) and DIPEA (0.10 g, 0.14 mL, 5 Eq, 0.79 mmol) in MeCN (2 mL) was added triphosgene (47 mg, 1 Eq, 0.16 mmol) in one portion. The resulting mixture was stirred at 0°C for 10 minutes. To the mixture was subsequently added 4,5,6,7-tetrahydro-2-methylthiazolo[5,4-c]pyridine (61 mg, 2.5 Eq, 0.39 mmol), followed by DIPEA (50 mg, 70 µL, 2.5 eq.). The resulting mixture was stirred at 50°C for 18 hours. The crude mixture was directly purified by prep HPLC to afford N-((1R,3S)-3-((6-chloro-2-(trifluoromethyl)quinolin-4-yl)amino)cyclohexyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxamide (52.6 mg, 100 µmol, 64 % yield).

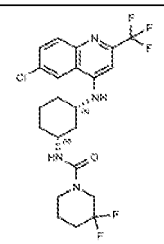
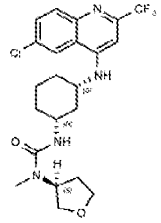
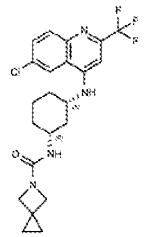
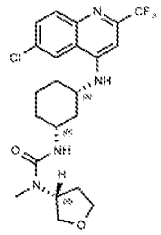
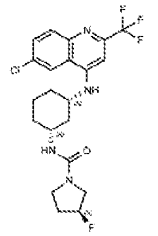
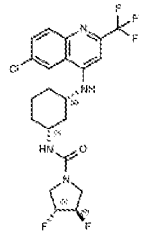
LCMS-ESI (m/z) calculated: 524.00 found 524.2 [M+H]+, RT = 8.534 min (Method 1)

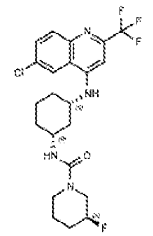
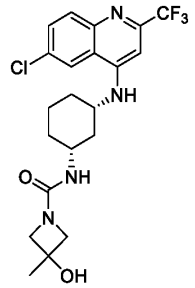
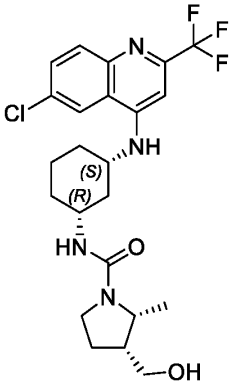
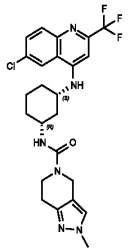
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.73 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 6.88 (s, 1H), 6.51 (d, J = 7.6 Hz, 1H), 4.51 (s, 2H), 3.82 – 3.60 (m, 4H), 2.67 (s, 2H), 2.58 (s, 3H), 2.11 (d, J = 11.7 Hz, 1H), 1.94 (d, J = 12.2 Hz, 1H), 1.79 (t, J = 15.3 Hz, 2H), 1.53 – 1.37 (m, 2H), 1.35 – 1.19 (m, 2H).

The compounds listed in Table 8 were made using the procedures of Scheme 8.

Table 8

Structure	Cpd No.	Purity RT (min)	MW	Observed m/z	Ion	Purity Method
	8-1	0.406	469.94	470.1	$[M+H]^+$	Method 6
	8-2	0.427	497.99	498.3	$[M+H]^+$	Method 6
	8-3	0.556	440.9	441.3	$[M+H]^+$	Method 6
	8-4	0.409	455.91	456.2	$[M+H]^+$	Method 6
	8-5	0.783	469.94	470	$[M+H]^+$	Method 6
	8-6	8.762	472.91	473.3, 474.2, 475.1	$[M+H]^+$	Method 1

	8-7	9.340	490.9	491.3	$[M+H]^+$	Method 1
	8-8	8.059	470.92	471.2, 472.2, 473.3	$[M+H]^+$	Method 1
	8-9	0.495	452.91	453.3	$[M+H]^+$	Method 2
	8-10	8.056	470.92	471.2, 472.2, 473.2	$[M+H]^+$	Method 1
	8-11	8.254	458.89	459.2	$[M+H]^+$	Method 1
	8-12	8.564	476.88	477.2	$[M+H]^+$	Method 1

	8-13	8.902	472.91	473.3	$[M+H]^+$	Method 1
	8-14	7.041	456.89	457.3, 458.2, 459.2	$[M+H]^+$	Method 1
	8-15	7.485	484.95	485.3	$[M+H]^+$	Method 1
	8-16	7.755	506.96	507.2	$[M+H]^+$	Method 1

EXAMPLE 47

MRGPRX2 ACTIVITY

CHO cells stably transfected to express human MRGPRX2 were maintained in an incubator at 37° C with 5% CO_2 and grown in F12 (HAM) media with 10% fetal bovine serum (FBS), 1% Glutamax, 1% penicillin /streptomycin, 800 µg/mL Geneticin (G418), and 300 µg/mL Hygromycin B.

Cells were plated in a 384-well assay plate at 20,000 cells per well in 12 µL of Opti-MEM and kept in an incubator overnight. On the day of the assay, compounds solubilized at 10 mM in DMSO were added as a 10-point curve (30 uM final top concentration with 1:3 serial dilutions) using a Tecan D300E digital dispenser. Agonists were diluted in assay buffer (final concentrations of 5.7 mM Tris-HCl, 43 mM NaCl, 50 mM LiCl, pH= 8) and 2 µL of the agonist Cortistatin-14 (CPC Scientific, catalog CORT-002) are added to each well. Final concentrations of agonists were 0.3 µM Cortistatin. Final concentrations of DMSO were kept consistent across the plate. Plates were incubated in the dark for 1 h at 37 °C and then for 1 h at room temperature. IP-1 standards and HTRF detection reagents were added according to the IP-One – Gq Kit purchased from Cisbio (part number 62IPAPEJ) and incubated in the dark for 1 h at room temperature. The plate was read on a Molecular Devices SpectraMax iD5 plate reader. The HTRF ratio was calculated from the raw data and graphed using GraphPad Prism to calculate an IC50 value for each compound.

Activity data for selected MRGPRX2 antagonists (versus 0.3 uM Cortistatin-14 agonist) are displayed in Table 9. The activity ranges are denoted as follows: "+++++" denotes antagonist activity <100 nM; "++++" denotes antagonist activity between 100 and 500 nM; "+++" denotes activity between 501 and 1000 nM; "++" denotes activity between 1001 and 2500 nM; and "+" denotes activity >2500 nM

Table 9

Cpd No.	MRGPRX2 Antagonist Activity
Example 1	+++++
Example 3	+++
Example 14	+++++
Example 15	+++++
Example 19	+++++
Example 30	+++++

Cpd No.	MRGPRX2 Antagonist Activity
Example 31	+++++
Example 32	+++++
Example 40	+++++
Example 46	+++++
1-3	+++++
1-8	++++

Cpd No.	MRGPRX2 Antagonist Activity
3-5	++++
3-6	++++
3-19	+++++
3-20	+++++
4-18	++++
4-22	++
4-29	++
4-31	+
4-35	++
4-40	++
4-64	+
4-74	+
4-82	+
4-90	++
4-100	++
4-111	+
4-113	+
4-130	+++++
4-159	++++
4-165	+++
4-171	+++
4-172	++
4-181	++++
4-183	++
4-216	++++
4-223	+++++
4-225	+++++
4-228	+++++

Cpd No.	MRGPRX2 Antagonist Activity
4-239	++++
4-240	+++++
4-241	+++++
4-245	+++++
4-249	++++
4-258	+++++
4-263	+++++
4-265	+++++
4-271	+++++
4-282	+++++
4-284	+++++
4-297	+++++
4-302	+++++
4-303	+++++
4-304	+++++
4-317	+++++
4-325	++++
4-394	+++++
4-396	+++++
4-397	+++++
4-398	+++++
4-399	+++++
4-400	+++++
4-401	+++++
4-402	+++++
4-403	+++++
4-404	+++++
4-405	+++++

Cpd No.	MRGPRX2 Antagonist Activity
4-406	+++++
4-407	+++++
4-408	+++++
4-409	+++++
4-410	+++++
4-411	+++++
4-412	+++++
4-413	+++++
4-414	+++++
4-415	+++++
4-416	+++++
4-417	+++++
4-418	+++++
4-419	+++++
4-420	+++++
4-421	+++++
4-422	+++++
4-423	+++++

Cpd No.	MRGPRX2 Antagonist Activity
4-424	+++++
4-425	+++++
4-426	+++++
4-427	+++++
4-430	+++++
4-452	+++++
4-464	+++++
4-487	+++++
4-511	+++++
5-1	+++++
5-5	+++++
5-13	+++++
5-31	+++++
8-3	+++++
8-9	+++++
8-16	+++++

EXAMPLE 48

MAST CELL BETA-HEXOSAMINIDASE RELEASE ASSAY

Human LAD2 cells (NIH) were maintained in an incubator at 37°C with 5% CO_2 and cultured in StemPro-34 serum-free media (Gibco 10639011) supplemented with 2 mM L-glutamine, 100 U/ml penicillin, 50 mg/ml streptomycin and 100 ng/ml SCF (Invitrogen PEP0860), at a concentration of 2-5 x 10^5 cells/mL, with hemidepletion every 1-2 weeks.

Cells were transferred to SCF-Free medium at 2.5 x 10^5 cells/mL and kept in an incubator overnight. On the day of the assay, cells were washed twice in Assay Buffer

(final concentrations 10 mM HEPES, 137 mM NaCl, 5.6 mM D-glucose, 2.7 mM KCl, 1 mM MgCl, 1.8 mM $CalCl_2$, 0.4 mM $Na_2HPO_4.7H_2O$, 0.04% BSA, pH = 7.4) and plated in a 96-well v-bottom plate at 20,000 cells per well in 80 µL Assay Buffer. Antagonist compounds solubilized at 10 mM in DMSO were diluted in Assay Buffer to 10X final desired concentrations as a 10-point curve (10 µM final top concentration with 1:3 serial dilutions) and 10 µL added per well. Plates were then incubated for 1 hour at 37°C. Agonists were diluted in Assay Buffer to 10X desired concentrations and 10 µL of the appropriate agonist added to each well. The final concentration of Cortistatin-14 (Tocris 3374) used in antagonist assays was 500 nM. Final concentrations of DMSO were kept consistent across the plate. Plates were then incubated in a warm air oven for 30 minutes at 37°C, followed by centrifugation at 4°C for 5 minutes at 450 x g. 50 µL supernatant from each well was then transferred to a 96-well flat bottom plate containing 100 µL substrate solution per well (3.5 mg/mL *p*-Nitrophenyl-N-acetyl-β-D-glucosaminide (Sigma 487052) in Citrate Buffer containing a final concentration of 40 mM Citric Acid, 20 mM $Na_2HPO_4.7H_2O$, pH = 4.5). To the cell pellets left in the remaining assay buffer, 150 µL 0.1% Triton-X-100 was then added to each well, resuspended by pipetting up and down, and 50 µL cell lysates transferred to a second 96-well flat bottom plate containing 100 µL substrate solution per well. Plates containing transferred supernatant and cell lysates were then incubated in a warm air oven for 90 minutes at 37°C. After incubation, 50 µL of 400 mM Glycine buffer (pH 10.7) was added into each well and the plate was read on a Molecular Devices SpectraMax iD5 plate reader (absorbance at 405 nm with reference filter at 620 nm). After background subtraction, the percentage degranulation (percent beta-hexosaminidase release) was calculated as 100 x (supernatant values)/(supernatant + lysate values), followed by analysis using GraphPad Prism software to calculate an IC_{50} value for each compound.

Activity data for selected MRGPRX2 antagonists in the Mast Cell Beta-Hexosaminidase Release Assay are displayed in Table 10. The activity ranges are denoted as follows: "+++++" denotes antagonist activity <100 nM; "++++" denotes antagonist activity between 100 and 500 nM; "+++" denotes activity between 501 and 1000 nM; "++" denotes activity between 1001 and 2500 nM; and "+" denotes activity >2500 nM.

Table 10

Cpd No.	MRGPRX2 Antagonist Activity
Example 1	+++++
Example 14	+++++
Example 15	+++++
Example 30	+++++
Example 31	+++++
Example 32	+++++
Example 44	+++++
Example 45	++++
1-3	++++
1-8	+
3-4	++
4-225	+++++
4-241	+++++
4-303	+++++
4-304	+++++
4-306	+++++
4-318	+++
4-400	+++++
4-411	+++++
4-414	+++++
4-420	+++++
4-430	+++++
5-2	+++++
5-3	+++++
8-9	++++

EXAMPLE 49

MOUSE PHARMACOKINETICS STUDIES

Compounds were formulated in 5% DMSO, 5% Solutol, and 90% PBS without Ca and Mg (pH 7.4) at a concentration of 5 mg/mL. Male C57BL/6 mice (n=3 / compound) were administered a 50 mg/kg dose of each compound by oral gavage under a non-fasted condition. Blood samples were collected via the saphenous vein onto K2-EDTA at 0.25, 0.5, 1, 2, 4, 8 and 24 hours after dosing, and plasma was prepared and stored at -80°C until analysis. Plasma sample preparation for analysis was done by protein precipitation using acetonitrile (including Verapamil as an internal standard) followed by centrifugation. Compound concentrations were determined in extracted plasma using LC-MS/MS relative to a 12-point standard curve covering the 1 to 4000 nM range. Non-compartmental analysis using Phoenix WinNonlin was used to estimate pharmacokinetic parameters including area under the curve, clearance, and half-life. The administered dose was confirmed by analysis of residual dosing material by UPLC-UV relative to a single point calibration sample. The results of these studies are presented in Table 11.

Table 11

Compound Name	Cmax (uM)	AUC 0-last (uM X hr)	AUC 0-24 (uM X hr)	PK: Tmax (hr)
Example 1	6.1	78	78	8
Example 15	36	140	140	1
Example 30	13	150	150	0.5
Example 31	74	740	740	1.7
Example 32	39	390	390	4.7
1-3	13	83	83	0.83
1-4	8.6	120	120	6.7
1-8	48	650	650	8
3-4	30	230	230	3.3
3-19	46	220	220	0.83

4-366	44	290	290	1
4-399	19	230	230	3.7
4-400	61	640	640	1.3
4-402	14	150	150	2
4-403	15	130	130	2.3
4-409	25	280	280	2.7
4-414	11	140	140	4

EXAMPLE 50

EVANS BLUE VASCULAR PERMEABILITY ASSAY

8–10-week-old C57BL/6J (strain 000664; Jackson Laboratories) or MrgprX2 knockin (Mrgb2KI; Escient Pharmaceuticals Inc.) mice were anesthetized with isoflurane and shaved on the back 5-6 days prior to the beginning of the study. On the day of the study, mice were dosed either with vehicle or EP8615 at 100, 30, 20, 10 or 3 mg/kg 3 hours prior to Evans blue injection. Animals were restrained and injected intravenously (IV) with 200 □l of 1% Evans Blue (cat. no.314-13-6; Fisher Chemical) in 0.9% saline, before being placed under isoflurane. Ten minutes after IV injections animals were maintained under anesthesia and injected intradermally with 25 □l of vehicle PBS, cortistatin-14 (C-14; 300 nM; cat. no. 3374; Tocris Bioscience); Icatibant (HOE-140; 38 □M; Cat no.3014; Tocris Bioscience) or goat anti-mouse IgE (50 □g/ml; ab9162; Abcam). Ten minutes after intradermal injection animals were photographed and sacrificed. The skin around the injection site was punctured with an 8 mm circular dermal punch and weighed and placed in 1.5ml Eppendorf tubes. Evans blue dye was extracted from the tissue by adding 1 ml of Formamide (BP227-500; Fisher Scientific) in the tube which was then vortexed covered in foil and placed at 55°C overnight. 200 □l of extracted dye in formamide was then placed into a 96 well plate in duplicate along with a standard curve of known Evans blue concentration standards. The plate was read at 620 nM on a plate reader and the results were expressed as □g of dye per mg tissue. Statistical tests were performed with the software Graphpad Prism 8 (Graphpad Software). Data is expressed as mean and standard error of mean. Unpaired t-Tests were used to compare the statistical difference between groups.

The various embodiments described above can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary, to employ concepts of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. A compound having one of the following structures, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof:

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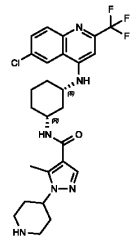
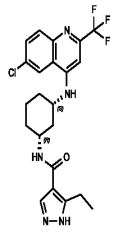
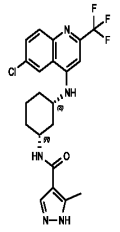
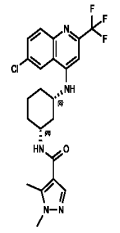
	Ex. 19
	4-431
	4-432
	4-433

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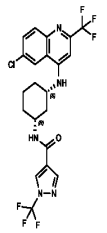
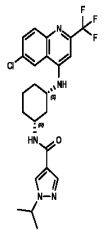
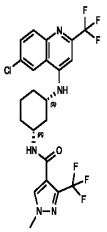
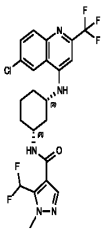
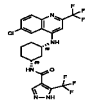
	4-434
	4-435
	4-436
	4-437
	4-438

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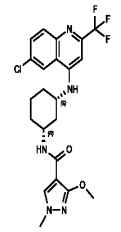
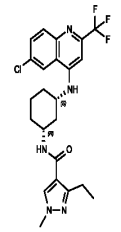
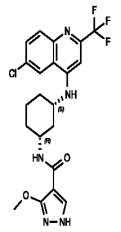
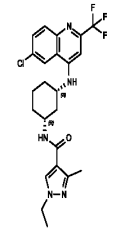
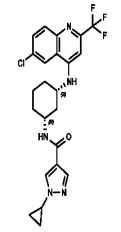
	4-439
	4-440
	4-441
	4-442
	4-443

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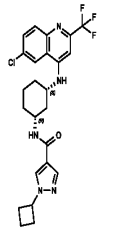
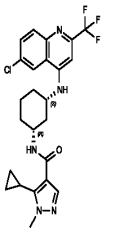
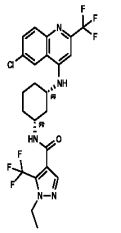
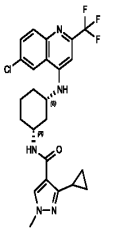
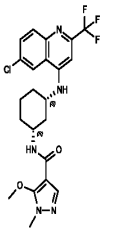
	4-444
	4-445
	4-446
	4-447
	4-448

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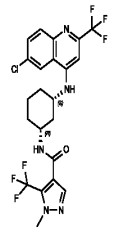
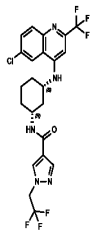
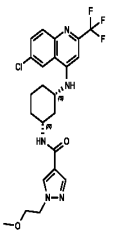
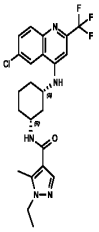
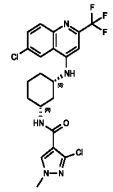
	4-449
	4-450
	4-451
	4-452
	4-453

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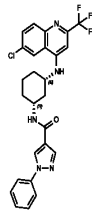
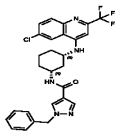
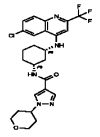
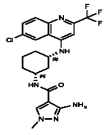
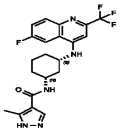
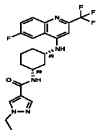
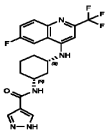
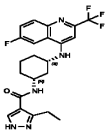
	4-454
	4-455
	4-456
	4-457
	4-458
	4-459
	4-460
	4-461

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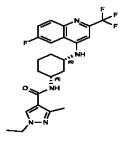
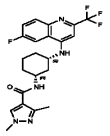
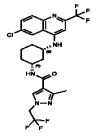
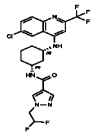
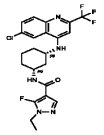
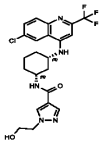
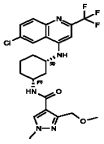
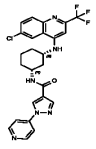
	4-462
	4-463
	4-464
	4-465
	4-466
	4-467
	4-468
	4-469

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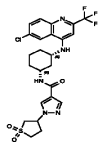
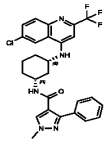
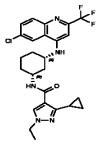
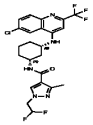
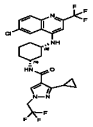
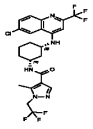
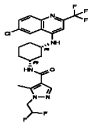
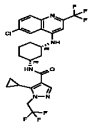
	4-470
	4-471
	4-472
	4-473
	4-474
	4-475
	4-476
	4-477

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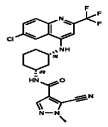
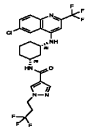
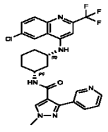
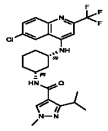
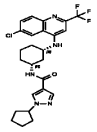
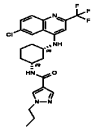
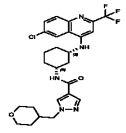
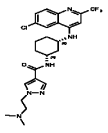
	4-478
	4-479
	4-480
	4-481
	4-482
	4-483
	4-484
	4-485

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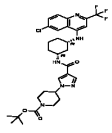
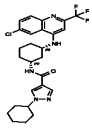
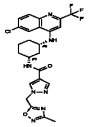
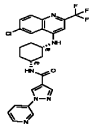
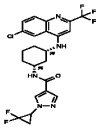
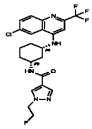
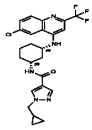
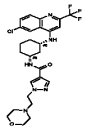
	4-486
	4-487
	4-488
	4-489
	4-490
	4-491
	4-492
	4-493

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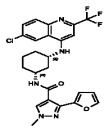
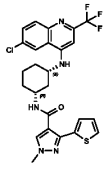
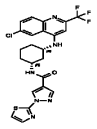
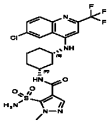
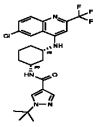
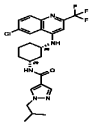
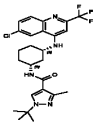
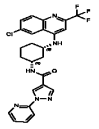
	4-494
	4-495
	4-496
	4-497
	4-498
	4-499
	4-500
	4-501

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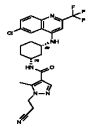
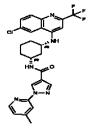
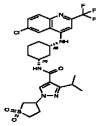
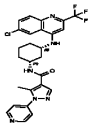
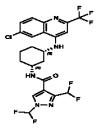
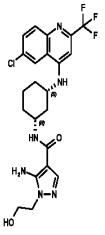
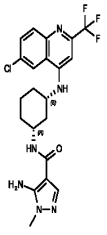
	4-502
	4-503
	4-504
	4-505
	4-506
	4-507
	4-508

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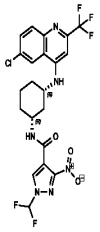
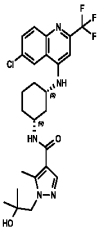
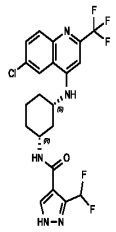
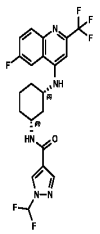
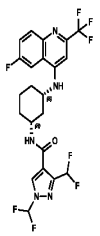
	4-509
	4-510
	4-511
	4-512
	4-513

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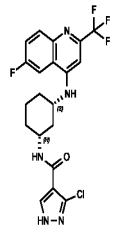
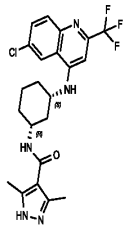
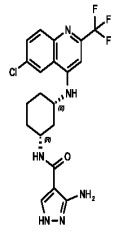
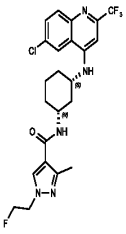
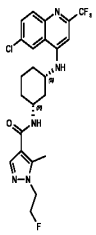
	4-514
	4-515
	4-516
	4-517
	4-518

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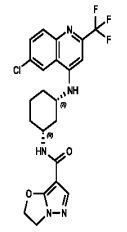
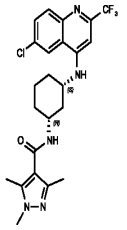
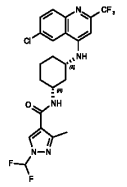
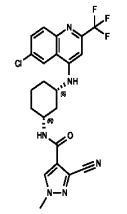
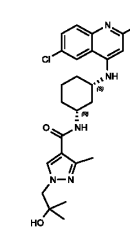
	4-519
	4-520
	4-521
	4-522
	Ex. 26

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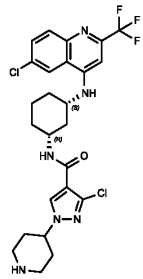
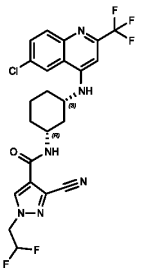
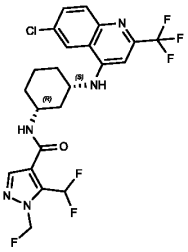
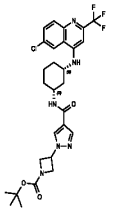
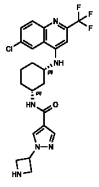
	Ex. 27
	Ex. 28
	Ex. 29
	5-8
	5-9

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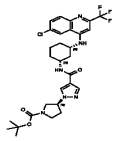
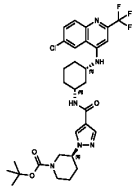
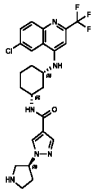
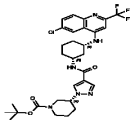
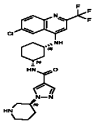
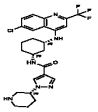
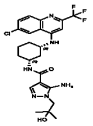
	5-10
	5-11
	5-12
	5-13
	5-14
	5-15
	5-16

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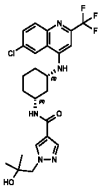
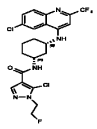
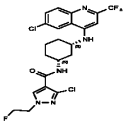
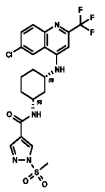
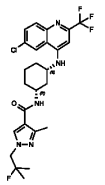
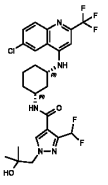
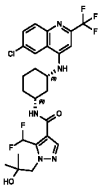
	5-17
	5-18
	5-19
	5-20
	5-21
	5-22
	5-23

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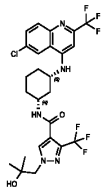
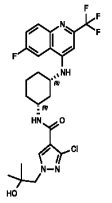
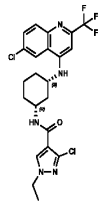
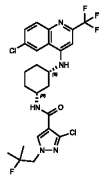
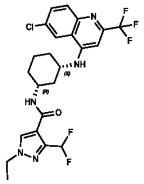
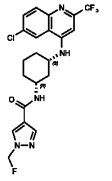
	5-24
	5-25
	5-26
	5-27
	5-28
	5-29

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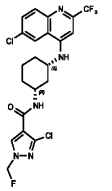
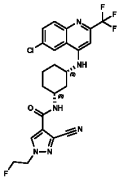
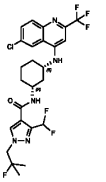
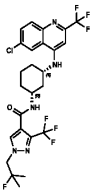
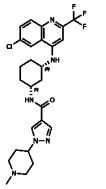
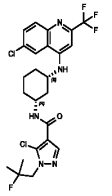
	5-30
	5-31
	5-32
	5-33
	5-34
	5-35

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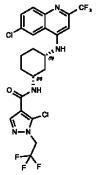
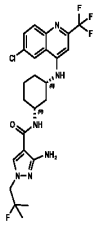
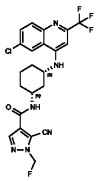
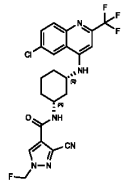
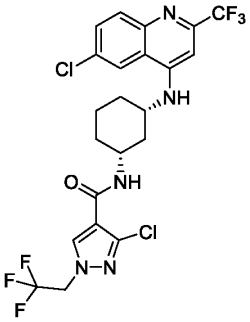
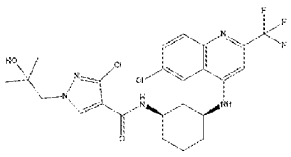
	5-36
	5-37
	5-38
	5-39
	Ex. 30
	Ex. 31

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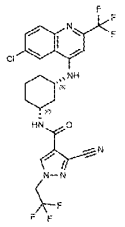
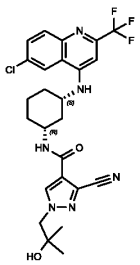
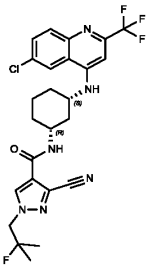
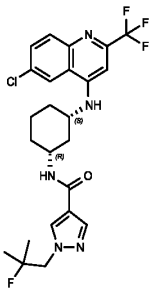
	Ex. 32
	Ex. 33
	Ex. 34
	Ex. 35

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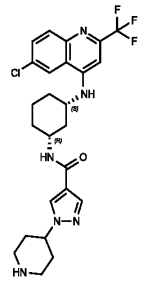
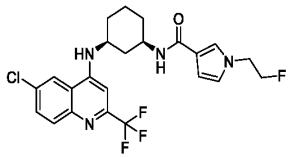
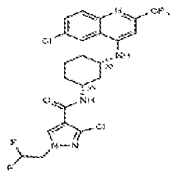
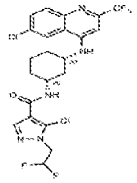
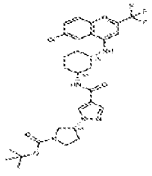
	Ex. 36
	Ex. 37
	Ex. 38
	Ex. 39
	Ex. 40

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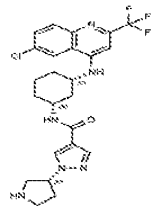
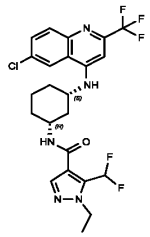
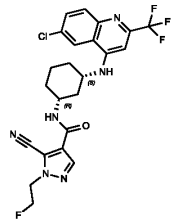
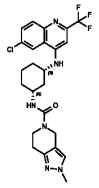
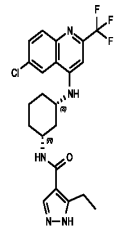
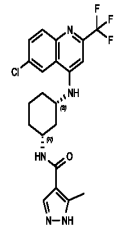
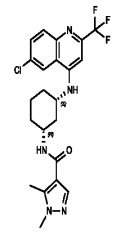
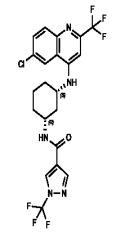
	Ex. 41
	Ex. 42
	6-1
	8-16

2. The compound of claim 1, wherein the compound has the structure of Ex. 19, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

3. The compound of claim 1, wherein the compound has one of the following structures, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof:

Structure	Cpd No.
	4-431
	4-432
	4-433
	4-434

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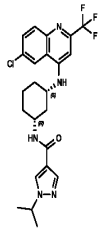
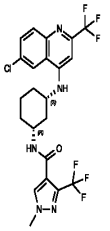
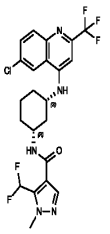
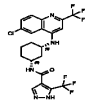
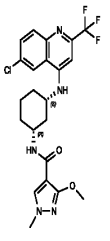
	4-435
	4-436
	4-437
	4-438
	4-439

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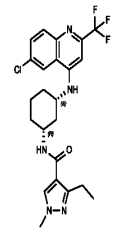
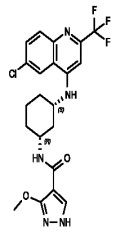
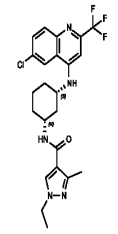
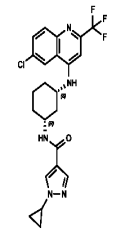
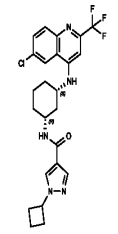
	4-440
	4-441
	4-442
	4-443
	4-444

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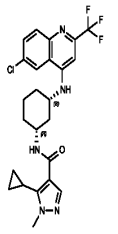
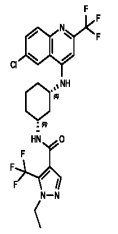
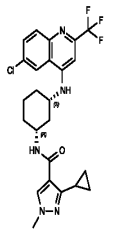
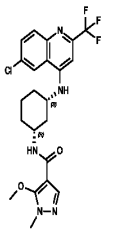
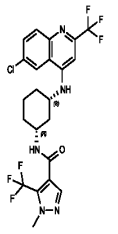
	4-445
	4-446
	4-447
	4-448
	4-449

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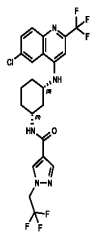
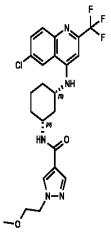
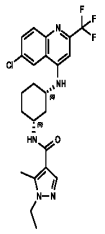
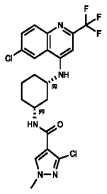
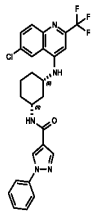
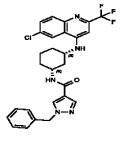
	4-450
	4-451
	4-452
	4-453
	4-454
	4-455

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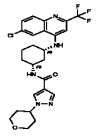
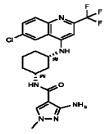
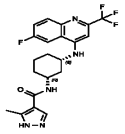
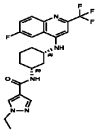
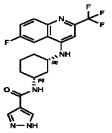
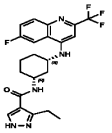
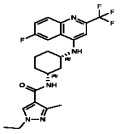
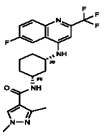
	4-456
	4-457
	4-458
	4-459
	4-460
	4-461
	4-462
	4-463

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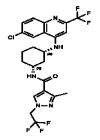
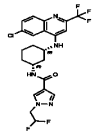
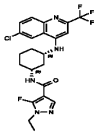
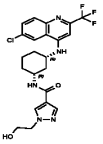
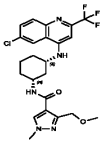
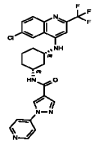
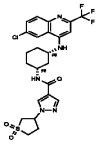
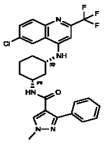
	4-464
	4-465
	4-466
	4-467
	4-468
	4-469
	4-470
	4-471

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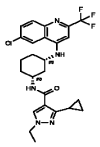
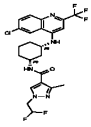
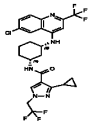
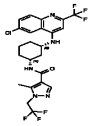
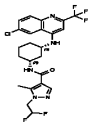
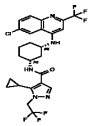
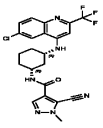
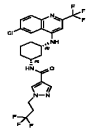
	4-472
	4-473
	4-474
	4-475
	4-476
	4-477
	4-478
	4-479

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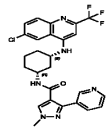
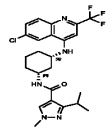
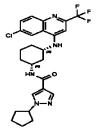
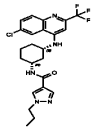
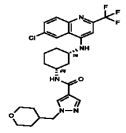
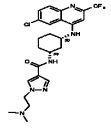
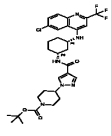
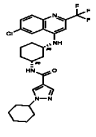
	4-480
	4-481
	4-482
	4-483
	4-484
	4-485
	4-486
	4-487

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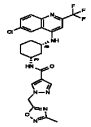
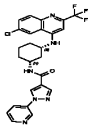
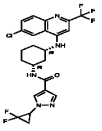
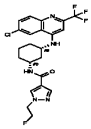
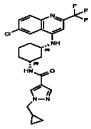
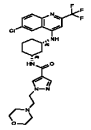
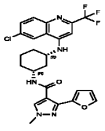
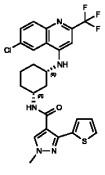
	4-488
	4-489
	4-490
	4-491
	4-492
	4-493
	4-494
	4-495

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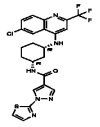
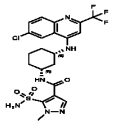
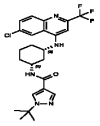
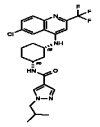
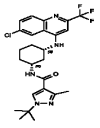
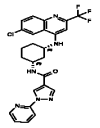
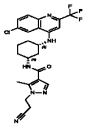
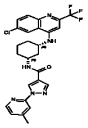
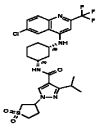
	4-496
	4-497
	4-498
	4-499
	4-500
	4-501
	4-502
	4-503
	4-504

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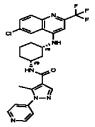
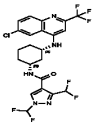
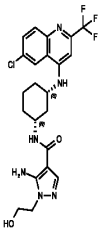
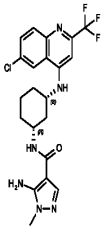
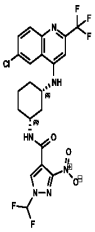
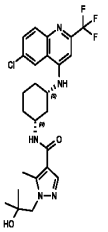
	4-505
	4-506
	4-507
	4-508
	4-509
	4-510

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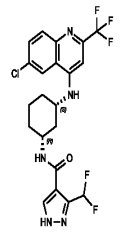
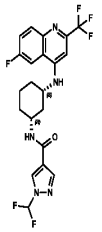
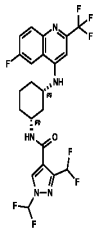
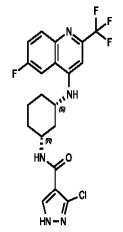
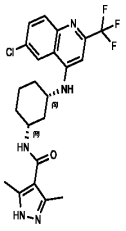
	4-511
	4-512
	4-513
	4-514
	4-515

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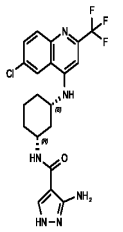
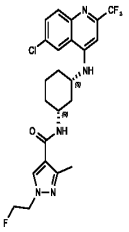
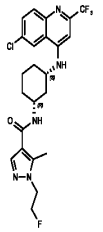
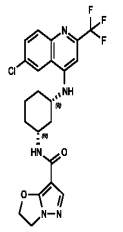
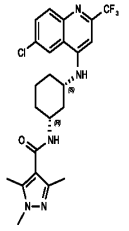
	4-516
	4-517
	4-518
	4-519
	4-520

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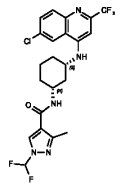	4-521

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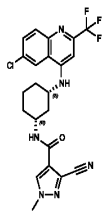
	4-522

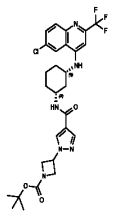
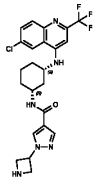
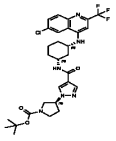
4. The compound of claim 1, wherein the compound has the structure of Ex. 26, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

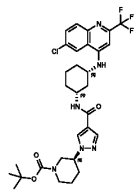
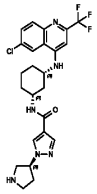
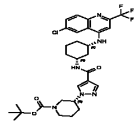
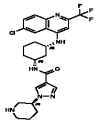
5. The compound of claim 1, wherein the compound has the structure of Ex. 27, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

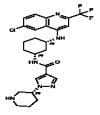
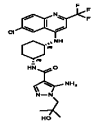
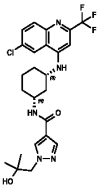
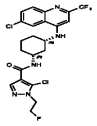
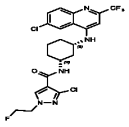
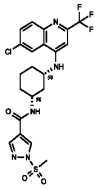
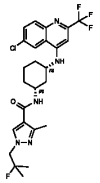
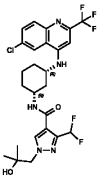
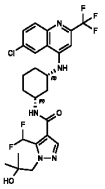
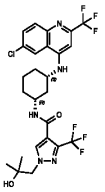
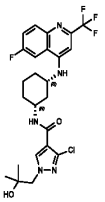
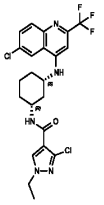
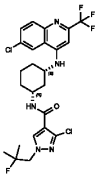
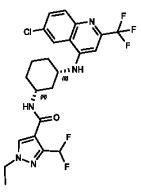
6 The compound of claim 1, wherein the compound has the structure of Ex. 28, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

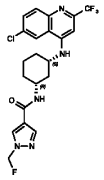
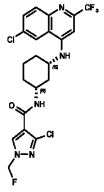
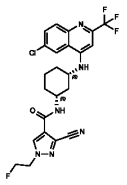
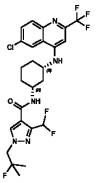
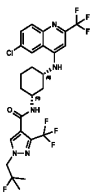
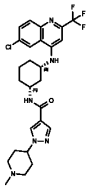
7. The compound of claim 1, wherein the compound has the structure of Ex. 29, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

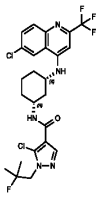
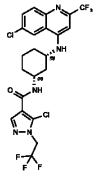
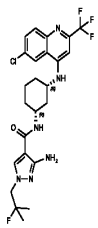
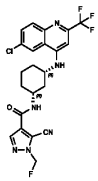
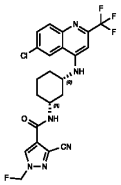
8. The compound of claim 1, wherein the compound has one of the following structures, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof:

	5-8
	5-9
	5-10

	5-11
	5-12
	5-13
	5-14

	5-15
	5-16
	5-17
	5-18
	5-19
	5-20
	5-21
	5-22
	5-23
	5-24
	5-25
	5-26
	5-27
	5-28

	5-29
	5-30
	5-31
	5-32
	5-33
	5-34

	5-35
	5-36
	5-37
	5-38
	5-39

9. The compound of claim 1, wherein the compound has the structure of Ex. 30, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

10. The compound of claim 1, wherein the compound has the structure of Ex. 31, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

11. The compound of claim 1, wherein the compound has the structure of Ex. 32, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

12. The compound of claim 1, wherein the compound has the structure of Ex. 33, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

13. The compound of claim 1, wherein the compound has the structure of Ex. 34, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

14. The compound of claim 1, wherein the compound has the structure of Ex. 35, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

15. The compound of claim 1, wherein the compound has the structure of Ex. 36, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

16. The compound of claim 1, wherein the compound has the structure of Ex. 37, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

17. The compound of claim 1, wherein the compound has the structure of Ex. 38, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

18. The compound of claim 1, wherein the compound has the structure of Ex. 39, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

19. The compound of claim 1, wherein the compound has the structure of Ex. 40, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

20. The compound of claim 1, wherein the compound has the structure of Ex. 41, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

21. The compound of claim 1, wherein the compound has the structure of Ex. 42.

22. The compound of claim 1, wherein the compound has the structure of Cpd. 6-1, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

23. The compound of claim 1, wherein the compound has the structure of Cpd. 8-16, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof.

24. A pharmaceutical composition comprising the compound of any one of claims 1-23, or a pharmaceutically acceptable salt, hydrate, solvate or isotope thereof and at least one pharmaceutically acceptable excipient.

25. A method of modulating a Mas-Related G-Protein Receptor (MRGPR) X2 or a MRGPRX2 ortholog by contacting MRGPRX2 or MRGPRX2 ortholog with an effective amount of the pharmaceutical composition of claim 24.

26. A method of treating a MRGPRX2 or a MRGPRX2 ortholog dependent condition by administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 24.

27. A method of treating a pseudo-allergic reaction, an itch associated condition, a pain associated condition, a cancer associated condition, an inflammatory or autoimmune disorder by administering to a subject in need thereof an effective amount of the pharmaceutical composition of claim 24.

28. The method of claim 27, wherein the pseudo-allergic reaction is caused by secretagogues, cationic peptidergic drugs, anionic peptidergic drugs, neutral peptidergic drugs, non-steroidal antagonist drugs, neuropeptides, antimicrobial peptides, MCD peptide, Substance P, VIP, PACAP, dynorphin, somatostatin, Compound 48/80, cortistatin-14, mastoparan, melettin, cathelicidin peptides, ciprofloxacin, vancomycin, leuprolide, goserelin, histrelin, triptorelin, cetrorelix, ganirelix, degarelix,

octreotide, lanreotide, pasireotide, sermorelin, tesamorelin, icatibant, glatiramer acetate, teriparatide, pramlintide, bleomycin, exenatide, glucagon, liraglutide, enfuvirtide, colistimethate, succinylcholine, tubocurarine, atracurium, mivacurium, and rocuronium.

29. The method of claim 27, wherein the itch associated condition is chronic itch; contact dermatitis; Allergic blepharitis; Anemia; Atopic dermatitis; Bullous pemphigoid; Candidiasis; Chicken pox; end-stage renal failure; hemodialysis; Chronic urticaria; Contact dermatitis, Atopic Dermatitis; Dermatitis herpetiformis; Diabetes; Drug allergy, Dry skin; Dyshidrotic dermatitis; Ectopic eczema; Eosinophilic fasciitis; Epidermolysis bullosa; Erythrasma; Food allergy; Folliculitis; Fungal skin infection; Hemorrhoids; Herpes; HIV infection; Hodgkin's disease; Hyperthyroidism; Iodinated contrast dye allergy; Iron deficiency anemia; Kidney disease; Leukemia, porphyrias; Lymphoma; Malignancy; Mastocystosis; Multiple myeloma; Neurodermatitis; Onchocerciasis; Paget's disease; Pediculosis; Polycythemia rubra vera; Prurigo nodularis; Lichen Planus; Lichen Sclerosis; Pruritus ani; Pseudorabies; Psoriasis; Rectal prolapse; Sarcoidosis granulomas; Scabies; Schistosomiasis; Scleroderma, Severe stress, Stasia dermatitis; Swimmer's itch; Thyroid disease; Tinea cruris; Rosacea; Cutaneous amyloidosis; Scleroderma; Acne; wound healing; burn healing; ocular itch; or Urticaria.

30. The method of claim 28, wherein the itch associated condition is urticaria, pruritus, atopic dermatitis, dry skin, psoriasis, contact dermatitis, or eczema.

31. The method of claim 27, wherein the pain associated condition is Acute Pain, Advanced Prostate Cancer, AIDS-Related Pain, Ankylosing Spondylitis, Arachnoiditis, Arthritis, Arthrofibrosis, Ataxic Cerebral Palsy, Autoimmune Atrophic Gastritis, Avascular Necrosis, Back Pain, Behcet’s Disease (Syndrome), Burning Mouth Syndrome, Bursitis, Cancer Pain, Carpal Tunnel, Cauda Equina Syndrome, Central Pain Syndrome, Cerebral Palsy, Cervical Stenosis, Charcot-Marie-Tooth (CMT) Disease, Chronic Fatigue Syndrome (CFS), Chronic Functional Abdominal Pain (CFAP), Chronic Pain, Chronic Pancreatitis, Chronic Pelvic Pain Syndrome, Collapsed Lung (Pneumothorax), Complex Regional Pain Syndrome (RSD), Corneal Neuropathic Pain,

Crohn's Disease, Degenerative Disc Disease, Dental Pain, Dercum's Disease, Dermatomyositis, Diabetic Peripheral Neuropathy (DPN), Dystonia, Ehlers-Danlos Syndrome (EDS), Endometriosis, Eosinophilia-Myalgia Syndrome (EMS), Erythromelalgia, Fibromyalgia, Gout, Headaches, Herniated disc, Hydrocephalus, Intercostal Neuraligia, Interstitial Cystitis, Irritable Bowel syndrome (IBS), Juvenile Dermatositis (Dermatomyositis), Knee Injury, Leg Pain, Loin Pain-Haematuria Syndrome, Lupus, Lyme Disease, Medullary Sponge Kidney (MSK), Meralgia Paresthetica, Mesothelioma, Migraine, Musculoskeletal pain, Myofascial Pain, Myositis, Neck Pain, Neuropathic Pain, Occipital Neuralgia, Osteoarthritis, Paget's Disease, Parsonage Turner Syndrome, Pelvic Pain, Periodontitis Pain, Peripheral Neuropathy, Phantom Limb Pain, Pinched Nerve, Polycystic Kidney Disease, Polymyalgia Rhuematica, Polymyositis, Porphyria, Post Herniorraphy Pain Syndrome, Post Mastectomy, Postoperative Pain, Pain Syndrome, Post Stroke Pain, Post Thorocotomy Pain Syndrome, Postherpetic Neuralgia (Shingles), Post-Polio Syndrome, Primary Lateral Sclerosis, Psoriatic Arthritis, Pudendal Neuralgia, Radiculopathy, Raynaud's Disease, Rheumatoid Arthritis (RA), Sacroiliac Joint Dysfunction, Sarcoidosi, Scheuemann's Kyphosis Disease, Sciatica, Scoliosis, Shingles (Herpes Zoster), Sjogren's Syndrome, Spasmodic Torticollis, Sphincter of Oddi Dysfunction, Spinal Cerebellum Ataxia (SCA Ataxia), Spinal Cord Injury, Spinal Stenosis, Syringomyelia, Tarlov Cysts, Transverse Myelitis, Trigeminal Neuralgia, Neuropathic Pain, Ulcerative Colitis, Vascular Pain or Vulvodynia.

32. The method of claim 27, wherein the inflammatory or autoimmune disorder is chronic inflammation, mast cell activation syndrome, Multiple Sclerosis, Steven Johnson's Syndrome, Toxic Epidermal Necrolysis, appendicitis, bursitis, cutaneous lupus, colitis, cystitis, dermatitis, phlebitis, reflex sympathetic dystrophy/complex regional pain syndrome (rsd/crps), rhinitis, tendonitis, tonsillitis, acne vulgaris, sinusitis, rosacea, psoriasis, graft-versus-host disease, reactive airway disorder, asthma, airway infection, allergic rhinitis, autoinflammatory disease, celiac disease, chronic prostatitis, diverticulitis, glomerulonephritis, hidradenitis suppurativa, hypersensitivities, intestinal disorder, epithelial intestinal disorder, inflammatory bowel disease, irritable bowel syndrome, Crohn's Disease, ulcerative colitis, lupus erythematous, interstitial cystitis, otitis, pelvic inflammatory disease, endometrial pain,

reperfusion injury, rheumatic fever, rheumatoid arthritis, sarcoidosis, transplant rejection, psoriasis, lung inflammation, chronic obstructive pulmonary disease, permanent sputum eosiniophilia, eosinophilic leukemia, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic duodenitis, eosinophilic gastroenteritis, mast cell gastrointestinal disease, hypereosinophilic syndrome, aspirin-exacerbated respiratory disease, nasal polyposis, chronic rhinosinusitis, antibody-dependent cell-mediated cytotoxicity, neurofibromatosis, swannamatoisis, tubulointerstitial nephritis, glomerulonephritis, diabetic nephropathy, allograft rejection, amyloidosis, renovascular ischemia, reflux nephropathy, polycystic kidney disease, liver fibrosis/cirrhosis, autoimmune liver disease, Biliary atresia, acute and chronic Hepatitis B and C virus, Liver tumors and cancer, Alcoholic liver disease, Polycystic liver disease, Liver cholangiocarcinoma, neuromyelitis optica spectum disorder, cardiovascular disease, inflammation induced by bacterial or viral infection, inflammation associated with SARS-CoV-2 infection or its variants and Coronavirus Disease 2019 (COVID-19), acute respiratory distress syndrome, pneumonia, Long/Long-Term/Chronic COVID, Post-Acute Sequelae of COVID-19 (PASC), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS "Brain Fog") and vasculitis.

33. The method of claim 27, wherein the cancer associated condition is adenoid cystic carcinoma, adrenal gland tumor, amyloidosis, anal cancer, appendix cancer, astrocytoma, ataxia-telangiectasia, beckwith-wiedemann syndrome, cholangiocarcinoma, birt-hogg-dube syndrome, bone cancer, brain stem glioma, brain tumor, breast cancer (inflammatory, metastatic, male), prostrate, basal cell, melanoma, colon, colorectal, bladder, kidney cancer, lacrimal gland cancer, laryngeal and hypopharyngeal cancer, lung cancer (non-small cell, small cell), leukemia (acute lymphoblastic, acute lymphocytic, acute myeloid, B cell prolymphocytic, chronic lymphocytic, chronic myeloid, chronic T cell lymphocytic, eosinophilic), Liver Cancer, Li-Fraumei syndrome, lymphoma (Hodgkin and non-hodgkin), lynch syndrome, mastocytosis, medulloblastoma, meningioma, mesothelioma, multiple endocrine neoplasia, multiple myeloma, MUTYH-associated polyposis, myelodyspastic syndrome, nasal cavity and paranasal sinus cancer, neurobastoma, neuroendocrine tyymors, neurofibromatosis, penile cancer, parathyroid cancer, ovarian fallopian tube and

peritoneal cancer, osteosarcoma, pituitary gland tumor, pleupulmonary blastoma, oral and oropharyngeal , thyroid, uterine, pancreatic, carney complex, brain and spinal cord cancer, cervical cancer, cowden syndrome, craniopharyngioma, desmoid tumor, desmoplatic infantile ganglioglioma, ependymoma, esophageal cancer, ewing sarcoma, eye cancer, eyelid cancer, familial adenomatous polyposis, familial GIST, familial malignant melanoma, familial pancreatic cancer, gallbladder cancer, gastrointestinal stromal tumor, germ cell tumor, gestational trophoblastic disease, head and neck cancer, hereditary breast and ovarian cancer, hereditary diffuse gastric cancer, hereditary, leiomyomastosis and renal cell cancer, hereditary pancreatitis, herediatary papillary renal carcinoma, hereditary mixed polyposis syndrome, HIV/AIDS related cancers, retinoblastoma, rhabdomyosarcoma, salivary glanc cancer, Kaposi sarcoma, small bowel cancer, stomach cancer, testicular cancer, thymoma and thymic carcinoma, thyroid cancer, vaginal cancer, culver cancer, werner syndrome and Xeroderma pigmentosum.