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(54) **Title**: OPHTHALMIC FORMULATION OF RHO KINASE INHIBITOR COMPOUND

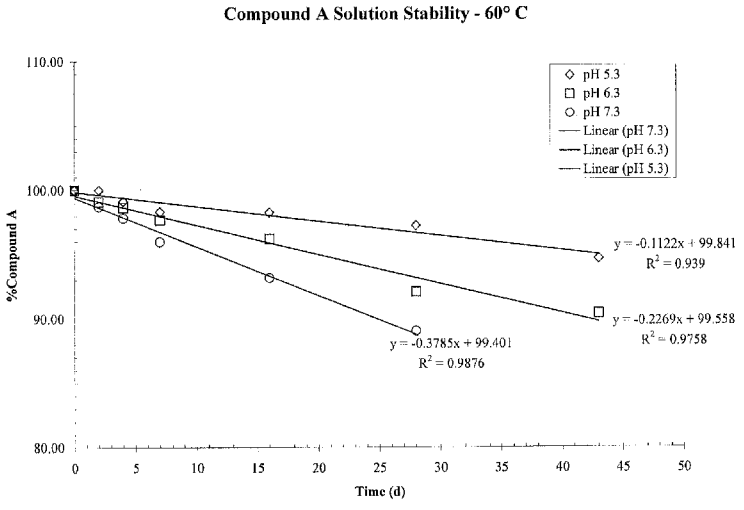

FIGURE 1

(57) **Abstract**: The present invention relates to an aqueous pharmaceutical formulation comprising at least one inhibitor of Rho-associated protein kinase (ROCK). The aqueous pharmaceutical formulation comprises 0.01-0.4% w/v of ROCK inhibitor(s), a non-ionic surfactant in an amount of 0.01-2% w/v, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG, at a pH between 6.3 to 7.8, wherein the ROCK inhibitor, the surfactant, and the tonicity agent are compatible in the formulation. The aqueous ophthalmic formulations of this invention have an increased ocular bioavailability and/or aqueous humor concentrations without a concomitant increase in systemic concentrations. The present invention further provides a method of reducing intraocular pressure, particularly a method of treating glaucoma, by administering the aqueous pharmaceutical formulation to a subject.

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OPHTHALMIC FORMULATION OF RHO KINASE INHIBITOR COMPOUND

TECHNICAL FIELD

This invention relates to pharmaceutical formulations, particularly aqueous ophthalmic formulations, of Rho Kinase (ROCK) inhibitor compounds and their related analogs. The invention also relates to using such formulations for treating diseases or disorders by altering the integrity or rearrangement of the cytoskeleton, particularly, for treating disorders in which intraocular pressure (IOP) is elevated, such as primary open-angle glaucoma.

BACKGROUND OF THE INVENTION

The Rho family of small GTP binding proteins can be activated by several extracellular stimuli such as growth factors, hormones and mechanic stress and function as a molecular signaling switch by cycling between an inactive GDP-bound form and an active GTP-bound form to elicit cellular responses. Rho-kinase (ROCK) functions as a key downstream mediator of Rho and exists as two isoforms (ROCK 1 and ROCK 2) that are ubiquitously expressed. ROCKs are serine/threonine kinases that regulate the function of a number of substrates including cytoskeletal proteins such as adducing, moesin, Na^+-H^+ exchanger 1 (NHE1), LIM-kinase and vimentin, contractile proteins such as the myosin light chain phosphatase binding subunit (MYPT-1), CPI-17, myosin light chain and calponin, microtubule associated proteins such as Tau and MAP-2, neuronal growth cone associate proteins such as CRMP-2, signaling proteins such as PTEN and transcription factors such as serum response factor (Loirand et al, Circ Res 98:322-334 (2006)). ROCK is also required for cellular transformation induced by RhoA. As a key intermediary of multiple signaling pathways, ROCK regulates a diverse array of cellular phenomena including cytoskeletal rearrangement, actin stress fiber formation, proliferation, chemotaxis, cytokinesis, cytokine and chemokine secretion, endothelial or epithelial cell junction integrity, apoptosis, transcriptional activation and smooth muscle contraction. As a result of these cellular actions, ROCK regulates physiologic processes such as vasoconstriction, bronchoconstriction, tissue remodeling, inflammation, edema, platelet aggregation and proliferative disorders.

One well documented example of ROCK activity is in smooth muscle contraction. In smooth muscle cells ROCK mediates calcium sensitization and smooth muscle contraction. Agonists (noradrenaline, acetylcholine, endothelin, etc.) that bind to G protein coupled receptors produce contraction by increasing both the cytosolic Ca^{2+} concentration and the Ca^{2+} sensitivity of the contractile apparatus. The Ca^{2+}-sensitizing effect of smooth muscle constricting agents is ascribed to ROCK-mediated phosphorylation of MYPT-1, the regulatory subunit of myosin light chain phosphatase (MLCP), which inhibits the activity of MLCP resulting in enhanced phosphorylation of the myosin light chain and smooth muscle contraction (WO 2005/003101A2, WO 2005/034866A2).

Glaucoma is an ophthalmic disease that leads to irreversible visual impairment. It is the fourth most common cause of blindness and the second most common cause of visual loss in the United States, and the most common cause of irreversible visual loss among African-Americans. Generally speaking, the disease is characterized by a progressive optic neuropathy caused at least in part by deleterious effects resulting from increased intraocular pressure. In normal individuals, intraocular pressures ranges from 12 to 20 mm Hg, averaging approximately 16 mm Hg. However, in individuals suffering from primary open angle glaucoma, intraocular pressures generally rise above 22 to 30 mm Hg. In angle closure or acute glaucoma intraocular pressure can reach as high as 70 mm Hg leading to blindness within only a few days. Interestingly, the loss of vision can result from statistically normal intraocular pressures in individuals with unusually pressure-sensitive eyes; a condition known as normotensive glaucoma. [See, e.g., P. L. Kaufman and T. W. Mittag, "Medical Therapy Of Glaucoma," Ch. 9, Sec. II (pp. 9.7-9.30) In P. L. Kaufman and T. W. Mittag (eds.): Glaucoma (Vol. 7 of S. M. Podos and M. Yanoff (eds): Textbook of Ophthalmology Series). London, Mosby-Year Book Europe Ltd. (1994); A. C. Guyton, Textbook of Medical Physiology (W. B. Saunders Co., Sixth Ed.), pp. 386-89 (1981)].

Open-angle glaucoma constitutes approximately 90% of all primary glaucomas and is characterized by abnormally high resistance to fluid (aqueous humor) drainage from the eye. Normal resistance is required to maintain an intraocular pressure sufficient to maintain the shape of the eye for optical integrity. This resistance is provided by the trabecular meshwork, a complex, multilaminar tissue consisting of specialized cells with a dense actomyosin cytoskeleton network, collagenous beams and extracellular matrix. The resistance of the trabecular meshwork normally is such that intraocular pressure is ~16 mm Hg, a pressure at which aqueous humor leaves the eye at the same rate at which it is produced (2.5 μL/minute). In

the glaucomatous eye, the rate of aqueous humor production remains constant, while it is the increased resistance to outflow that is responsible for the elevated intraocular pressure.

Typical treatments for glaucoma comprise a variety of pharmaceutical approaches for reducing intraocular pressure (IOP), each with their drawbacks. Beta-blockers and carbonic anhydrase inhibitors reduce aqueous humor production, which is needed to nourish the avascular lens and corneal endothelial cells, and the prostaglandins effect the uvealscleral outflow pathway, which only accounts for 10% of the total outflow facility. There are currently no commercially approved therapeutic agents which act directly upon the trabecular meshwork, the site of aqueous humor drainage where increased resistance to aqueous humor outflow is responsible for elevated IOP. Therefore, a medical need remains for improved IOP-lowering medications that target this structure. Pharmacological agents which target the trabecular meshwork may provide relief to the significant numbers of patients that do not respond adequately to current IOP-lowering medications and/or cannot tolerate the side effects associated with these agents. Additionally, these molecules may prove beneficial as adjunctive therapy in combination with other classes of IOP-lowering medications.

U.S. Patent Nos 6,586,425, 6,110,912, and 5,798,380 disclose a method for the treatment of glaucoma using compounds that affect the actin filament integrity of the eye to enhance aqueous humor outflow. These patents specifically disclose latrunculin-A, -latrunculin-B, swinholide-A, and jasplakinolide, which cause a perturbation of the actin cytoskeleton and tight junctional complexes in the trabecular meshwork or the modulation of its interactions with the underlying membrane.

U.S. Patent Nos 6,649,625 and 6,673,812 disclose the pharmaceutical use of certain compounds having a Rho kinase inhibitory activity for the treatment of glaucoma.

It has long been recognized that systemic absorption of topically applied glaucoma drugs via the conjuctival and nasal mucosae during ocular drug therapy may elicit significant side effects [eg., Nelson, W.L., Fraundfelder, F.T., Sills, J.M., Arrowsmith J.B., Kuritsky, J.N., "Adverse respiratory cardiac events attributed to timolol ophthalmic solution," Am. J. Ophthalmol. 1986, 102, pp606-11; Saxena, R.; Prakash, J., Mathur, P., Gupta, S. K. "Pharmacotherapy of Glaucoma," Ind. J. Pharmacol, 2002, 34, pp71-85].

There is a need for improved IOP-lowering drug formulations that have increased drug bioavailability but without a concomitant increase of the drug concentration in systemic circulation, which would therefore reduce or eliminate the unwanted drug-associated side effects.

SUMMARY OF THE INVENTION

The present invention is directed to an aqueous pharmaceutical formulation comprising at least one ROCK inhibitor of Formula II in an amount of 0.01-0.4% w/v, a non-ionic surfactant in an amount of 0.01-2% w/v, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG, at a pH between 6.3 to 7.8, wherein the ROCK inhibitor, the surfactant, and the tonicity agent are compatible in the formulation.

A preferred surfactant of the formulation is a polysorbate, a polaxamer, or a combination thereof. Preferred pH of the formulation is 6.3-7.5. More preferred pH of the formulation is 6.3-7.3. The formulation optionally comprises a chelating agent and/or a preservative. The tonicity agent can be non-ionic such as glycerol, mannitol, or dextrose. The tonicity agent can also be ionic such as sodium chloride.

The aqueous ophthalmic formulations of this invention have an increased ocular bioavailability and/or aqueous humor concentrations without a concomitant increase in systemic concentrations.

The present invention further provides a method of reducing intraocular pressure, particularly a method of treating glaucoma, by identifying a subject in need of treatement and administering the aqueous pharmaceutical formulation to the subject.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the stability of Compound A at pH 5.3, 6.3 and 7.3 at 60°C. After the formulations were stored at 60°C for a period of time, percent of Compound A remaining were determined and shown in Figure 1.

Figure 2A shows the aqueous humor (AH) Cmax after a 0.12% dose of Compound A at pH 5.3, 6.3 and 7.3. Figure 2B shows the aqueous humor AUC after a 0.12% dose of Compound A at pH 5.3, 6.3 and 7.3. Data represents mean ± SEM, N = 4 eyes.

Figure 3A shows the Plasma Cmax after a 0.12% dose of Compound A at pH 5.3, 6.3 and 7.3. Figure 3B shows the plasma AUC after a 0.12% dose of Compound A at pH 5.3, 6.3 and 7.3. Data represents mean ± SEM, N = 2 animals.

Figure 4 shows the ocular surface concentration over time after a 0.12% (3 mM) dose of Compound A at pH 5.3, 6.3 and 7.3. Data represents mean ± SEM, N = 4 eyes.

Figure 5 shows ocular comfort scores of different formulations.

Figure 6 shows ocular comfort scores of different concentrations of Compound 2.039, in comparison with other drugs.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

When present, unless otherwise specified, the following terms are generally defined as, but are not limited to, the following:

Halo substituents are taken from fluorine, chlorine, bromine, and iodine.

"Alkyl" refers to groups of from 1 to 12 carbon atoms inclusively, either straight chained or branched, more preferably from 1 to 8 carbon atoms inclusively, and most preferably 1 to 6 carbon atoms inclusively.

"Alkenyl" refers to groups of from 2 to 12 carbon atoms inclusively, either straight or branched containing at least one double bond but optionally containing more than one double bond.

"Alkynyl" refers to groups of from 2 to 12 carbon atoms inclusively, either straight or branched containing at least one triple bond but optionally containing more than one triple bond, and additionally optionally containing one or more double bonded moieties.

"Alkoxy" refers to the group alkyl-O- wherein the alkyl group is as defined above including optionally substituted alkyl groups as also defined above.

"Alkenoxy" refers to the group alkenyl-O- wherein the alkenyl group is as defined above including optionally substituted alkenyl groups as also defined above.

"Alkynoxy" refers to the group alkynyl-O- wherein the alkynyl group is as defined above including optionally substituted alkynyl groups as also defined above.

"Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 14 carbon atoms inclusively having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like.

"Arylalkyl" refers to aryl-alkyl- groups preferably having from 1 to 6 carbon atoms inclusively in the alkyl moiety and from 6 to 10 carbon atoms inclusively in the aryl moiety. Such arylalkyl groups are exemplified by benzyl, phenethyl and the like.

"Arylalkenyl" refers to aryl-alkenyl- groups preferably having from 2 to 6 carbon atoms in the alkenyl moiety and from 6 to 10 carbon atoms inclusively in the aryl moiety.

"Arylalkynyl" refers to aryl-alkynyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkynyl moiety and from 6 to 10 carbon atoms inclusively in the aryl moiety.

"Cycloalkyl" refers to cyclic alkyl groups of from 3 to 12 carbon atoms inclusively having a single cyclic ring or multiple condensed rings which can be optionally substituted with from 1 to 3 alkyl groups. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, 1-methylcyclopropyl, 2-methylcyclopentyl, 2-methylcyclooctyl, and the like, or multiple ring structures such as adamantyl, and the like.

"Cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 12 carbon atoms inclusively having a single cyclic ring or multiple condensed rings and at least one point of internal unsaturation, which can be optionally substituted with from 1 to 3 alkyl groups. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl and the like.

"Cycloalkylalkyl" refers to cycloalkyl-alkyl- groups preferably having from 1 to 6 carbon atoms inclusively in the alkyl moiety and from 6 to 10 carbon atoms inclusively in the cycloalkyl moiety. Such cycloalkylalkyl groups are exemplified by cyclopropylmethyl, cyclohexylethyl and the like.

"Cycloalkylalkenyl" refers to cycloalkyl-alkenyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkenyl moiety and from 6 to 10 carbon atoms inclusively in the cycloalkyl moiety. Such cycloalkylalkenyl groups are exemplified by cyclohexylethenyl and the like.

"Cycloalkylalkynyl" refers to cycloalkyl-alkynyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkynyl moiety and from 6 to 10 carbon atoms inclusively in the cycloalkyl moiety. Such cycloalkylalkynyl groups are exemplified by cyclopropylethynyl and the like.

"Heteroaryl" refers to a monovalent aromatic heterocyclic group of from 1 to 10 carbon atoms inclusively and 1 to 4 heteroatoms inclusively selected from oxygen, nitrogen and sulfur within the ring. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl).

"Heteroarylalkyl" refers to heteroaryl-alkyl- groups preferably having from 1 to 6 carbon atoms inclusively in the alkyl moiety and from 6 to 10 atoms inclusively in the

heteroaryl moiety. Such heteroarylalkyl groups are exemplified by pyridylmethyl and the like.

"Heteroarylalkenyl" refers to heteroaryl -alkenyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkenyl moiety and from 6 to 10 atoms inclusively in the heteroaryl moiety.

"Heteroarylalkynyl" refers to heteroaryl -alkynyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkynyl moiety and from 6 to 10 atoms inclusively in the heteroaryl moiety.

"Heterocycle" refers to a saturated or unsaturated group having a single ring or multiple condensed rings, from 1 to 8 carbon atoms inclusively and from 1 to 4 hetero atoms inclusively selected from nitrogen, sulfur or oxygen within the ring. Such heterocyclic groups can have a single ring (e.g., piperidinyl or tetrahydrofuryl) or multiple condensed rings (e.g., indolinyl, dihydrobenzofuran or quinuclidinyl). Preferred heterocycles include piperidinyl, pyrrolidinyl and tetrahydrofuryl.

"Heterocycle-alkyl" refers to heterocycle -alkyl- groups preferably having from 1 to 6 carbon atoms inclusively in the alkyl moiety and from 6 to 10 atoms inclusively in the heterocycle moiety. Such heterocycle-alkyl groups are exemplified by morpholino-ethyl, pyrrolidinylmethyl, and the like.

"Heterocycle-alkenyl" refers to heterocycle -alkenyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkenyl moiety and from 6 to 10 atoms inclusively in the heterocycle moiety.

"Heterocycle-alkynyl" refers to heterocycle -alkynyl- groups preferably having from 2 to 6 carbon atoms inclusively in the alkynyl moiety and from 6 to 10 atoms inclusively in the heterocycle moiety.

Examples of heterocycles and heteroaryls include, but are not limited to, furan, thiophene, thiazole, oxazole, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, piperidine, piperazine, pyrrolidine, indoline and the like.

Unless otherwise specified, positions occupied by hydrogen in the foregoing groups can be further substituted with substituents exemplified by, but not limited to, hydroxy, oxo,

nitro, methoxy, ethoxy, alkoxy, substituted alkoxy, trifluoromethoxy, haloalkoxy, fluoro, chloro, bromo, iodo, halo, methyl, ethyl, propyl, butyl, alkyl, alkenyl, alkynyl, substituted alkyl, trifluoromethyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, thio, alkylthio, acyl carboxy, alkoxycarbonyl, carboxamido, substituted carboxamido, alkylsulfonyl, alkylsulfinyl, alkylsulfonylamino, sulfonamido, substituted sulfonamido, cyano, amino, substituted amino, alkylamino, dialkylamino, aminoalkyl, acylamino, amidino, amidoximo, hydroxamoyl, phenyl, aryl, substituted aryl, aryloxy, arylalkyl, arylalkenyl, arylalkynyl, pyridyl, imidazolyl, heteroaryl, substituted heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, substituted cycloalkyl, cycloalkyloxy, pyrrolidinyl, piperidinyl, morpholino, heterocycle, (heterocycle)oxy, and (heterocycle)alkyl; and preferred heteroatoms are oxygen, nitrogen, and sulfur. It is understood that where open valences exist on these substituents they can be further substituted with alkyl, cycloalkyl, aryl, heteroaryl, and/or heterocycle groups, that where these open valences exist on carbon they can be further substituted by halogen and by oxygen-, nitrogen-, or sulfur-bonded substituents, and where multiple such open valences exist, these groups can be joined to form a ring, either by direct formation of a bond or by formation of bonds to a new heteroatom, preferably oxygen, nitrogen, or sulfur. It is further understood that the above subtitutions can be made provided that replacing the hydrogen with the substituent does not introduce unacceptable instability to the molecules of the present invention, and is otherwise chemically reasonable.

The term "heteroatom-containing substituent" refers to substituents containing at least one non-halogen heteroatom. Examples of such substituents include, but are not limited to, hydroxy, oxo, nitro, methoxy, ethoxy, alkoxy, substituted alkoxy, trifluoromethoxy, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thio, alkylthio, acyl, carboxy, alkoxycarbonyl, carboxamido, substituted carboxamido, alkylsulfonyl, alkylsulfinyl, alkylsulfonylamino, sulfonamido, substituted sulfonamido, cyano, amino, substituted amino, alkylamino, dialkylamino, aminoalkyl, acylamino, amidino, amidoximo, hydroxamoyl, aryloxy, pyridyl, imidazolyl, heteroaryl, substituted heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyloxy, pyrrolidinyl, piperidinyl, morpholino, heterocycle, (heterocycle)oxy, and (heterocycle)alkyl; and preferred heteroatoms are oxygen, nitrogen, and sulfur. It is understood that where open valences exist on these substituents they can be further substituted with alkyl, cycloalkyl,

aryl, heteroaryl, and/or heterocycle groups, that where these open valences exist on carbon they can be further substituted by halogen and by oxygen-, nitrogen-, or sulfur-bonded substituents, and where multiple such open valences exist, these groups can be joined to form a ring, either by direct formation of a bond or by formation of bonds to a new heteroatom, preferably oxygen, nitrogen, or sulfur. It is further understood that the above subtitutions can be made provided that replacing the hydrogen with the substituent does not introduce unacceptable instability to the molecules of the present invention, and is otherwise chemically reasonable.

"Pharmaceutically acceptable salts" are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Pharmaceutically acceptable salt forms include various polymorphs as well as the amorphous form of the different salts derived from acid or base additions. The acid addition salts can be formed with inorganic or organic acids. Illustrative but not restrictive examples of such acids include hydrochloric, hydrobromic, sulfuric, phosphoric, citric, acetic, propionic, benzoic, napthoic, oxalic, succinic, gentisic, maleic, fumaric, malic, adipic, lactic, tartaric, salicylic, methanesulfonic, 2-hydroxyethanesulfonic, toluenesulfonic, benzenesulfonic, camphorsulfonic, and ethanesulfonic acids. The pharmaceutically acceptable base addition salts can be formed with metal or organic counterions and include, but are not limited to, alkali metal salts such as sodium or potassium; alkaline earth metal salts such as magnesium or calcium; and ammonium or tetraalkyl ammonium salts, i.e., NX_4^+ (wherein X is C_{1-4}).

"Tautomers" are compounds that can exist in one or more forms, called tautomeric forms, which can interconvert by way of a migration of one or more hydrogen atoms in the compound accompanied by a rearrangement in the position of adjacent double bonds. These tautomeric forms are in equilibrium with each other, and the position of this equilibrium will depend on the exact nature of the physical state of the compound. It is understood that where tautomeric forms are possible, the current invention relates to all possible tautomeric forms.

"Solvates" are addition complexes in which a compound of Formula I or Formula II is combined with a pharmaceutically acceptable cosolvent in some fixed proportion. Cosolvents include, but are not limited to, water, methanol, ethanol, 1-propanol, isopropanol, 1-butanol, isobutanol, tert-butanol, acetone, methyl ethyl ketone, acetonitrile, ethyl acetate, benzene, toulene, xylene(s), ethylene glycol, dichloromethane, 1,2-

dichloroethane, N-methylformamide, N,N-dimethylformamide, N-methylacetamide, pyridine, dioxane, and diethyl ether. Hydrates are solvates in which the cosolvent is water. It is to be understood that the definitions of compounds in Formula I and Formula II encompass all possible hydrates and solvates, in any proportion, which possess the stated activity.

This invention is directed to a pharmaceutical formulation comprising ROCK inhibitor compounds and their related analogs.

There are five key constraints to develop a successful topical formulation for treating glaucoma: solubility, formulation stability, ocular surface tolerability, systemic exposure, and aqueous humor exposure. Ocular surface relates to the surface of the cornea and conjunctiva. Ocular surface residence time is the average time that a drug resides on the ocular surface. Aqueous humor is the fluid within the anterior chamber of the eye and has the closest correlation to the concentration at the site of action, the trabecular meshwork. Rarely do the physicochemical properties of any drug allow for all five constraints to be simultaneously optimal under one condition. The ideal ophthalmic formulation for treating glaucoma is: (1) sufficiently soluble to deliver a therapeutic dose of drug; (2) sufficiently stable to have a commercial product shelf-life as a glaucoma medication; (3) well-tolerated on the ocular surface at the therapeutic dose; and (4) achieves therapeutic level of drug in the aqueous humor (the site of action) with minimal systemic exposure, thereby minimizing systemic side effects.

For ROCK inhibitor compounds of the present invention, the inventors have discovered that pH of the formulation can influence three of the five constraints. Lower pH improves the solubility and stability of ROCK inhibitor compounds in an aqueous formulation. However, the inventors have discovered that higher pH of the formulation increases residence time of the compound on the ocular surface, thus allowing more drugs to penetrate into the anterior chamber and resulting in higher compound concentration in aqueous humor. The inventors have discovered that pH of the formulation (from pH 5.3-7.3) does not have an effect on systemic exposure. The inventors do not find evidence that pH of the formulation affects ocular comfort up to pH 7.3. However, the ocular surface is in general more tolerable in an acidic formulation than in a basic formulation.

The inventors have identified and selected a pH range of pH 6.3-7.8 that allows for acceptable sacrifices or trade-offs between solubility, stability, ocular tolerability, systemic

exposure, and aqueous humor exposure (for example, poorer solubility may be acceptable at a certain pH if greater tolerability or exposure is achieved).

The concentrations of the ROCK inhibitor compounds affect the ocular comfort; i.e., lower concentrations are more comfortable. The inventors have identified and selected a concentration range of 0.01-0.4% (w/v) of ROCK inhibitor compounds in the formulation; such concentration is effective to provide a therapeutic effect and does not cause ocular discomfort.

The inventors have unexpectedly discovered that certain ROCK-inhibiting compounds, whose aqueous solubilities decrease with increasing pH, exhibit significant increase in anterior chamber bioavailability as the formulation pH is adjusted from acidic pH to physiologic pH over a pharmaceutically acceptable pH range for topical ophthalmic formulations (pH 4.5 to pH 7.8). The inventors have also unexpectedly discovered that ROCK-inhibiting compounds of the present invention increase residence time on the ocular surface and increase concentrations in aqueous humor when the pH of the ophthalmic formulations increases. The increase in residence time on the ocular surface and anterior chamber bioavailability allows lower concentrations of drugs to be used to treat diseases and disorders associated with cytoskeleton disruption, such as primary open-angle glaucoma.

The inventors have discovered that systemic exposure, as measured by the plasma concentration, is only related to the ROCK inhibitor concentration and volume of the ophthalmic formulation, and is not related to pH or composition of the formulation. Therefore, by providing an ophthalmic formulation with a pH of 6.3-7.8, which is closer to a neutral pH but is higher than that of commonly used ophthalmic formulations, the formulation increases the anterior chamber bioavailability through an increase in membrane penetration, but does not concomitantly increase the systemic exposure; thereby increasing the potential ocular to systemic therapeutic margin.

Thus, despite the limitations that this pH of 6.3-7.8 poses for solubility and stability, the exposure in the aqueous humor is sufficiently increased to counterbalance the limitations. The present invention provides optimal therapeutic benefit-risk without having to expose the ocular surface with a high concentration of drug.

Rho Kinase Inhibitor Compounds

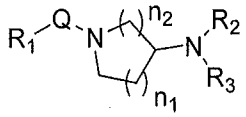
The Rho kinase inhibitor compounds useful for this invention include compounds of general Formula I and Formula II, and/or tautomers thereof, and/or pharmaceutically-acceptable salts, and/or solvates, and/or hydrates thereof.

A compound according to Formula I or Formula II can exist in several diastereomeric forms. The general structures of Formula I and Formula II include all diastereomeric forms of such materials, when not specified otherwise. Formula I and Formula II also include mixtures of compounds of these Formulae, including mixtures of enantiomers, diastereomers and/or other isomers in any proportion.

A. Formula I

Compounds of Formula I are as follows:

Formula I



wherein: R_1 is aryl or heteroaryl, optionally substituted;

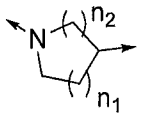
Q is C=O, SO_2, or $(CR_4R_5)_{n3}$;

n_1 is 1, 2, or 3;

n_2 is 1or 2;

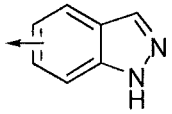
n_3 is 0, 1, 2, or 3;

wherein the ring represented by

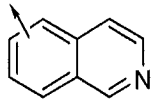


is optionally substituted by alkyl, halo, oxo, OR_6, NR_6R_7, or SR_6;

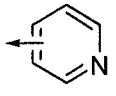
R_2 is selected from the following heteroaryl systems, optionally substituted:



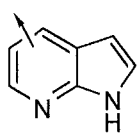
R_2 - 1



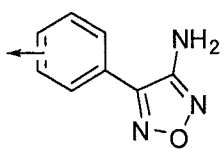
R_2 - 2



R_2 - 3



R_2 - 4



R_2 - 5

R_3 –R_7 are independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, or cycloalkylalkynyl optionally substituted.
In Formula I, the preferred R_1 is substituted aryl, the more preferred R_1 is substituted phenyl, the preferred Q is $(CR_4R_5)_{n3}$, the more preferred Q is CH_2, the preferred n_1 is 1 or 2, the preferred n_2 is 1, the preferred n_3 is 1 or 2, and the preferred R_3 – R_7 are H.

[1] One embodiment of the invention is represented by Formula I, in which R_2 is 5-indazolyl or 6-indazolyl (R_2-1), optionally substituted.
[1a] In embodiment 1, R_2-1 is substituted by one or more alkyl or halo substituents.
[1b] In embodiment 1, R_2-1 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.
[1c] In embodiment 1, R_2-1 is unsubstituted.

[2] In another embodiment, the invention is represented by Formula I in which R_2 is 5-isoquinolinyl or 6-isoquinolinyl (R_2-2), optionally substituted.
[2a] In embodiment 2, R_2-2 is substituted by one or more alkyl or halo substituents.
[2b] In embodiment 2, R_2-2 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.
[2c] In embodiment 2, R_2-2 is unsubstituted.

[3] In another embodiment, the invention is represented by Formula I in which R_2 is 4-pyridyl or 3-pyridyl (R_2-3), optionally substituted.
[3a] In embodiment 3, R_2-3 is substituted by one or more alkyl or halo substituents.
[3b] In embodiment 3, R_2-3 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.
[3c] In embodiment 3, R_2-3 is unsubstituted.

[4] In another embodiment, the invention is represented by Formula I in which R_2 is 7-azaindol-4-yl or 7-azaindol-5-yl (R_2-4), optionally substituted.
[4a] In embodiment 4, R_2-4 is substituted by one or more alkyl or halo substituents.
[4b] In embodiment 4, R_2-4 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.
[4c] In embodiment 4, R_2-4 is is unsubstituted.

[5] In another embodiment, the invention is represented by Formula I in which R_2 is 4-(3-amino-1,2,5-oxadiazol-4-yl)phenyl or 3-(3-amino-1,2,5-oxadiazol-4-yl)phenyl (R_2-5), optionally substituted.

[5a] In embodiment 5, R_2-5 is unsubstituted.

[6] In another embodiment, the invention is represented by Formula I in which R_2 is one of the groups R_2-1 - R_2-5, substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[6a] In embodiment 6, R_2 is substituted by one or more alkyl or halo substituents.

[6b] In embodiment 6, R_2 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.

[7] In another embodiment, the invention is represented by Formula I in which R_2 is one of the groups R_2-1 - R_2-5, and is unsubstituted.

[8] In another embodiment, the invention is represented by Formula I in which R_3 is H.

[9] In another embodiment, the invention is represented by Formula I in which Q is $(CR_4R_5)_{n3}$, and n_3 is 1 or 2.

[10] In another embodiment, the invention is represented by Formula I in which Q is $(CH_2)_{n3}$, and n_3 is 1.

[11] In another embodiment, the invention is represented by Formula I in which R_1 is aryl or heteroaryl substituted with one or more alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl,heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl substituents, optionally further substituted.

Compounds exemplifying embodiment 11 include compounds 1.009, 1.010, 1.011, 1.012, 1.020, 1.021, 1.030, 1.034, 1.037, 1.044, 1.047, 1.076, 1.077, 1.083, 2.010, 2.011, 2.019, 2.020, 2.022, 2.023, and 2.031, shown below in Table I.

[12] In another embodiment, the invention is represented by Formula I in which R_1 is aryl or heteroaryl substituted with one or more heteroatom-containing substituents, with the proviso that if the R_1 substituent is acyclic and is connected to R_1 by a carbon atom, then this substituent contains at least one nitrogen or sulfur atom, with the second proviso that if the substituent is acyclic and is connected to R_1 by an oxygen or nitrogen atom, then this substituent contains at least one additional oxygen, nitrogen or sulfur atom, and with the third proviso that if the substituent is connected to R_1 by a sulfone linkage "$-SO_2-$", then R_2 is not nitrogen- or oxygen-substituted R_2-2.

[12a] In embodiment 12, the heteroatom-containing substituent is connected to R_1 by an oxygen or nitrogen atom.

[12b] In embodiment 12, the heteroatom-containing substituent is connected to R_1 by a sulfide linkage, "-S-".

Compounds exemplifying embodiment 12 include compounds 1.001, 1.002, 1.004, 1.005, 1.038, 1.048, 1.055, 1.056, 2.002, 2.003, 2.005, 2.007, 1.003, 1.006, 1.007, 1.018, 1.039, 1.051, 1.058, 1.060, 1.084, 1.085, 1.086, 1.087, 1.088, 1.090, 1.091, 1.092, 1.093, 1.094, 1.095, 1.096, 1.097, 1.098, 1.102, 1.111, 1.113, 1.115, 1.116, 1.117, 1.118, 1.120, 1.121, 1.123, 1.124, 1.125, 1.126, 1.127, 1.128, 1.129, 1.130, 2.004, 2.008, 2.032, 2.033, 2.034, 2.035, 2.036, 2.037, 2.038, 2.039, 2.040, 2.041, 2.042, 2.043, 2.044, 1.008, 1.017, 1.026, 1.040, 1.074, 1.075, 2.009, 2.012, 2.021, 2.024, 2.026, and 2.029, shown below in Table I.

[13] In another embodiment, the invention is represented by Formula I in which R_1 is aryl or heteroaryl substituted with one or more alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl substituents, which are further substituted with one or more heteroatom-containing substituents, with the proviso that if the R_1 substituent is acyclic and its heteroatom-containing substituent falls on the

carbon by which it is attached to R_1, then the heteroatom-containing substituent contains at least one nitrogen or sulfur atom.

Compounds exemplifying embodiment 13 include compounds 1.019, 1.027, 1.028, 1.029, 1.035, 1.041, 1.042, 1.043, 1.057, 1.061, 1.099, 1.101, 1.103, 1.104, 1.105, 1.106, 1.107, 1.108, 1.109, 1.112, 1.114, 1.119, and 1.122, shown below in Table I.

[14] In another embodiment, the invention is represented by Formula I in which R_1 is aryl or heteroaryl substituted with one or more alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynylsubstituents, optionally further substituted, and R_2 is 5-indazolyl (R_2-1) or 5-isoquinolinyl (R_2-2), optionally substituted.

[14a] In embodiment 14, R_2 is 5-indazolyl (R_2-1), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[14b] In embodiment 14, R_2 is 5-isoquinolinyl (R_2-2), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[14c] In embodiment 14, R_2 is unsubstitued.

Compounds exemplifying embodiment 14 include compounds 1.009, 1.010, 1.011, 1.012, 1.020, 1.021, 1.030, 1.034, 1.037, 1.044, 1.047, 1.076, 1.077, 1.083, 2.010, 2.011, 2.019, 2.020, 2.022, 2.023, and 2.031, shown below in Table I.

[15] In another embodiment, the invention is represented by Formula I in which R_1 is aryl or heteroaryl substituted with one or more heteroatom-containing substituents, and R_2 is 5-indazolyl (R_2-1) or 5-isoquinolinyl (R_2-2), optionally substituted, with the proviso that if the R_1 substituent is acyclic and is connected to R_1 by a carbon atom, then this substituent contains at least one nitrogen or sulfur atom, with the second proviso that if the substituent is acyclic and is connected to R_1 by an oxygen or nitrogen atom, then this substituent contains at least one additional oxygen, nitrogen or sulfur atom, and with the third proviso that if the substituent is connected to R_1 by a sulfone linkage "-SO_2-", then R_2 is not nitrogen- or oxygen-substituted R_2-2.

[15a] In embodiment 15, R_2 is 5-indazolyl (R_2-1), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[15b] In embodiment 15, R_2 is 5-isoquinolinyl (R_2-2), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[15c] In embodiment 15, R_2 is unsubstituted.

[15d] In embodiment 15, the heteroatom-containing substituent is connected to R_1 by an oxygen or nitrogen atom.

[15e] In embodiment 15, the heteroatom-containing substituent is connected to R_1 by a sulfide linkage, "-S-".

Compounds exemplifying embodiment 15 include compounds 1.001, 1.002, 1.004, 1.005, 1.038, 1.048, 1.055, 1.056, 2.002, 2.003, 2.005, 2.007, 1.003, 1.006, 1.007, 1.018, 1.039, 1.051, 1.058, 1.060, 1.084, 1.085, 1.086, 1.087, 1.088, 1.090, 1.091, 1.092, 1.093, 1.094, 1.095, 1.096, 1.097, 1.098, 1.102, 1.111, 1.113, 1.115, 1.116, 1.117, 1.118, 1.120, 1.121, 1.123, 1.124, 1.125, 1.126, 1.127, 1.128, 1.129, 1.130, 2.004, 2.008, 2.032, 2.033, 2.034, 2.035, 2.036, 2.037, 2.038, 2.039, 2.040, 2.041, 2.042, 2.043, 2.044, 1.008, 1.017, 1.026, 1.040, 1.074, 1.075, 2.009, 2.012, 2.021, 2.024, 2.026, and 2.029, shown below in Table I.

[16] In another embodiment, the invention is represented by Formula I in which R_1 is aryl or heteroaryl substituted with one or more alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl substituents, at least one of which is further substituted with one or more heteroatom-containing substituents, and R_2 is 5-indazolyl (R_2-1) or 5-isoquinolinyl (R_2-2), optionally substituted, with the proviso that if the R_1 substituent is acyclic and its heteroatom-containing substituent falls on the carbon by which it is attached to R_1, then the heteroatom-containing substituent contains at least one nitrogen or sulfur atom.

[16a] In embodiment 16, R_2 is 5-indazolyl (R_2-1), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[16b] In embodiment 16, R_2 is 5-isoquinolinyl (R_2-2), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

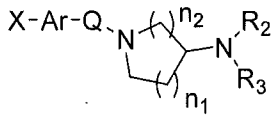
[16c] In embodiment 16, R_2 is unsubstituted.

Compounds exemplifying embodiment 16 include compounds 1.019, 1.027, 1.028, 1.029, 1.035, 1.041, 1.042, 1.043, 1.057, 1.061, 1.099, 1.101, 1.103, 1.104, 1.105, 1.106, 1.107, 1.108, 1.109, 1.112, 1.114, 1.119, and 1.122, shown below in Table I.

B. Formula II

A preferred compound of Formula I is where R_1 = Ar-X, shown below as Formula II:

Formula II



wherein:

Ar is a monocyclic or bicyclic aryl or heteroaryl ring, such as phenyl;

X is from 1 to 3 substituents on Ar, each independently in the form Y-Z, in which Z is attached to Ar;

Y is one or more substituents on Z, and each is chosen independently from H, halogen, or the heteroatom-containing substituents, including but not limited to OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$;

Each instance of Z is chosen independently from alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or is absent;

R_8 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents, including but not limited to OR_{11}, $NR_{11}R_{12}$, NO_2, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $NR_{11}SO_2R_{12}$, OCF_3, $CONR_{11}R_{12}$, $NR_{11}C(=O)R_{12}$, $NR_{11}C(=O)OR_{12}$, $OC(=O)NR_{11}R_{12}$, or $NR_{11}C(=O)NR_{12}R_{13}$;

R_9 and R_{10} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl,

heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents, including but not limited to OR_{14}, $NR_{14}R_{15}$, NO_2, SR_{14}, SOR_{14}, SO_2R_{14}, $SO_2NR_{14}R_{15}$, $NR_{14}SO_2R_{15}$, OCF_3, $CONR_{14}R_{15}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $OC(=O)NR_{14}R_{15}$, or $NR_{14}C(=O)NR_{15}R_{16}$;
any two of the groups R_8, R_9 and R_{10} are optionally joined with a link selected from the group consisting of bond, -O-, -S-, -SO-, $-SO_2-$, and $-NR_{17}-$ to form a ring;
R_{11}-R_{17} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle.

In Formula II, the preferred Y is H, halogen, OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$, the more preferred Y is H, halogen, OR_8, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, $CONR_8R_9$, or $NR_8C(=O)NR_9R_{10}$, the preferred Z is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, or is absent; the more preferred Z is alkyl, alkenyl, alkynyl, cycloalkyl, or is absent, the preferred Q is $(CR_4R_5)_{n3}$, the more preferred Q is CH_2, the preferred n_1 is 1 or 2, the preferred n_2 is 1, the preferred n_3 is 1 or 2, the preferred $R_3 - R_7$ are H, the preferred R_8 is H, alkyl, arylalkyl, cycloalkyl, cycloalkylalkyl, or heterocycle, the preferred R_8 substituents are H, halogen, OR_{11}, $NR_{11}R_{12}$, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $NR_{11}SO_2R_{12}$, $CONR_{11}R_{12}$, $NR_{11}C(=O)R_{12}$, and the preferred $R_9 - R_{17}$ are H or alkyl.

[1] One embodiment of the invention is represented by Formula II in which R_2 is 5-indazolyl or 6-indazolyl (R_2-1), optionally substituted.
[1a] In embodiment 1, R_2-1 is substituted by one or more alkyl or halo substituents.
[1b] In embodiment 1, R_2-1 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.
[1c] In embodiment 1, R_2-1 is unsubstituted.

[2] In another embodiment, the invention is represented by Formula II in which R_2 is 5-isoquinolinyl or 6-isoquinolinyl (R_2-2), optionally substituted.

[2a] In embodiment 2, R_2-2 is substituted by one or more alkyl or halo substituents.

[2b] In embodiment 2, R_2-2 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.

[2c] In embodiment 2, R_2-2 is unsubstituted.

[3] In another embodiment, the invention is represented by Formula II in which R_2 is 4-pyridyl or 3-pyridyl (R_2-3), optionally substituted.

[3a] In embodiment 3, R_2-3 is substituted by one or more alkyl or halo substituents.

[3b] In embodiment 3, R_2-3 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.

[3c] In embodiment 3, R_2-3 is unsubstituted.

[4] In another embodiment, the invention is represented by Formula II in which R_2 is 7-azaindol-4-yl or 7-azaindol-5-yl (R_2-4), optionally substituted.

[4a] In embodiment 4, R_2-4 is substituted by one or more alkyl or halo substituents.

[4b] In embodiment 4, R_2-4 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.

[4c] In embodiment 4, R_2-4 is unsubstituted.

[5] In another embodiment, the invention is represented by Formula II in which R_2 is 4-(3-amino-1,2,5-oxadiazol-4-yl)phenyl or 3-(3-amino-1,2,5-oxadiazol-4-yl)phenyl (R_2-5), optionally substituted.

[5a] In embodiment 5, R_2-5 is unsubstituted.

[6] In another embodiment, the invention is represented by Formula II in which R_2 is one of the groups R_2-1 - R_2-5, substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[6a] In embodiment 6, R_2 is substituted by one or more alkyl or halo substituents.

[6b] In embodiment 6, R_2 is substituted by one or more amino, alkylamino, hydroxyl, or alkoxy substituents.

[7] In another embodiment, the invention is represented by Formula II in which R_2 is one of the groups R_2-1 - R_2-5, and is unsubstituted.

[8] In another embodiment, the invention is represented by Formula II in which R_3 is H.

[9] In another embodiment, the invention is represented by Formula II in which Q is $(CR_4R_5)_{n3}$, and n_3 is 1 or 2.

[10] In another embodiment, the invention is represented by Formula II in which Q is $(CH_2)_{n3}$, and n_3 is 1.

[11] In another embodiment, the invention is represented by Formula II in which Z is alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkylalkenyl, cycloalkylalkynyl, cycloalkenyl, cycloalkylalkyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl.

Compounds exemplifying embodiment 11 include compounds 1.009, 1.010, 1.011, 1.012, 1.020, 1.021, 1.030, 1.034, 1.037, 1.044, 1.047, 1.076, 1.077, 1.083, 2.010, 2.011, 2.019, 2.020, 2.022, 2.023, and 2.031, shown below in Table I.

[12] In another embodiment, the invention is represented by Formula II in which Z is absent, Y is a heteroatom-containing substituent, including but not limited to OR_8, NR_8R_9, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$, with the proviso that if the substituent Y is acyclic and is connected to Ar by a carbon atom, then this substituent contains at least one nitrogen or sulfur atom, with the second proviso that if the substituent Y is acyclic and is connected to Ar by an oxygen or nitrogen atom, then this substituent contains at least one additional oxygen, nitrogen or sulfur atom, and with the third proviso that if the substituent Y is connected to Ar by a sulfone linkage "$-SO_2-$", then R_2 is not nitrogen- or oxygen-substituted R_2-2.

[12a] In embodiment 12, the heteroatom-containing substituent is connected to R_1 by an oxygen or nitrogen atom.

[12b] In embodiment 12, the heteroatom-containing substituent is connected to R_1 by a sulfide linkage, "-S-".

Compounds exemplifying embodiment 12 include compounds 1.001, 1.002, 1.004, 1.005, 1.038, 1.048, 1.055, 1.056, 2.002, 2.003, 2.005, 2.007, 1.003, 1.006, 1.007, 1.018, 1.039, 1.051, 1.058, 1.060, 1.084, 1.085, 1.086, 1.087, 1.088, 1.090, 1.091, 1.092, 1.093, 1.094, 1.095, 1.096, 1.097, 1.098, 1.102, 1.111, 1.113, 1.115, 1.116, 1.117, 1.118, 1.120, 1.121, 1.123, 1.124, 1.125, 1.126, 1.127, 1.128, 1.129, 1.130, 2.004, 2.008, 2.032, 2.033, 2.034, 2.035, 2.036, 2.037, 2.038, 2.039, 2.040, 2.041, 2.042, 2.043, 2.044, 1.008, 1.017, 1.026, 1.040, 1.074, 1.075, 2.009, 2.012, 2.021, 2.024, 2.026, and 2.029, shown below in Table I.

[13] In another embodiment, the invention is represented by Formula II in which Z is alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl, and Y is a heteroatom-containing substituent, including but not limited to OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$, with the proviso that if Z is acyclic and Y falls on the carbon by which Z is attached to Ar, then Y contains at least one nitrogen or sulfur atom.

Compounds exemplifying embodiment 13 include compounds 1.019, 1.027, 1.028, 1.029, 1.035, 1.041, 1.042, 1.043, 1.057, 1.061, 1.099, 1.101, 1.103, 1.104, 1.105, 1.106, 1.107, 1.108, 1.109, 1.112, 1.114, 1.119, and 1.122, shown below in Table I.

[14] In another embodiment, the invention is represented by Formula II in which Z is alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl, and R_2 is 5-indazolyl (R_2-1) or 5-isoquinolinyl (R_2-2), optionally substituted.

[14a] In embodiment 14, R_2 is 5-indazolyl (R_2-1), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[14b] In embodiment 14, R_2 is 5-isoquinolinyl (R_2-2), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[14c] In embodiment 14, R_2 is unsubstituted.

Compounds exemplifying embodiment 14 include compounds 1.009, 1.010, 1.011, 1.012, 1.020, 1.021, 1.030, 1.034, 1.037, 1.044, 1.047, 1.076, 1.077, 1.083, 2.010, 2.011, 2.019, 2.020, 2.022, 2.023, and 2.031, shown below in Table I.

[15] In another embodiment, the invention is represented by Formula II in which Z is absent, Y is a heteroatom-containing substituent, including but not limited to OR_8, NR_8R_9, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$, and R_2 is 5-indazolyl (R_2-1) or 5-isoquinolinyl (R_2-2), optionally substituted, with the proviso that if the substituent Y is acyclic and is connected to Ar by a carbon atom, then this substituent contains at least one nitrogen or sulfur atom, with the second proviso that if the substituent Y is acyclic and is connected to Ar by an oxygen or nitrogen atom, then this substituent contains at least one additional oxygen, nitrogen or sulfur atom, and with the third proviso that if the substituent Y is connected to Ar by a sulfone linkage "-SO_2-", then R_2 is not nitrogen- or oxygen-substituted R_2-2.

[15a] In embodiment 15, R_2 is 5-indazolyl (R_2-1), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[15b] In embodiment 15, R_2 is 5-isoquinolinyl (R_2-2), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[15c] In embodiment 15, R_2 is unsubstituted.

[15d] In embodiment 15, the heteroatom-containing substituent is connected to R_1 by an oxygen or nitrogen atom.

[15e] In embodiment 15, the heteroatom-containing substituent is connected to R_1 by a sulfide linkage, "-S-".

Compounds exemplifying embodiment 15 include compounds 1.001, 1.002, 1.004, 1.005, 1.038, 1.048, 1.055, 1.056, 2.002, 2.003, 2.005, 2.007, 1.003, 1.006, 1.007, 1.018, 1.039, 1.051, 1.058, 1.060, 1.084, 1.085, 1.086, 1.087, 1.088, 1.090, 1.091, 1.092, 1.093, 1.094, 1.095, 1.096, 1.097, 1.098, 1.102, 1.111, 1.113, 1.115, 1.116, 1.117, 1.118, 1.120, 1.121, 1.123, 1.124, 1.125, 1.126, 1.127, 1.128, 1.129, 1.130, 2.004, 2.008, 2.032, 2.033, 2.034,

2.035, 2.036, 2.037, 2.038, 2.039, 2.040, 2.041, 2.042, 2.043, 2.044, 1.008, 1.017, 1.026, 1.040, 1.074, 1.075, 2.009, 2.012, 2.021, 2.024, 2.026, and 2.029, shown below in Table I.

[16] In another embodiment, the invention is represented by Formula II in which Z is alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycbalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl, and Y is a heteroatom-containing substituent, including but not limited to OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$, and R_2 is 5-indazolyl (R_2-1) or 5-isoquinolinyl (R_2-2), optionally substituted, with the proviso that if Z is acyclic and Y falls on the carbon by which Z is attached to Ar, then Y contains at least one nitrogen or sulfur atom.

[16a] In embodiment 16, R_2 is 5-indazolyl (R_2-1), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[16b] In embodiment 16, R_2 is 5-isoquinolinyl (R_2-2), optionally substituted by one or more alkyl, halo, amino, alkylamino, hydroxyl, or alkoxy substituents.

[16c] In embodiment 16, R_2 is unsubstituted.

Compounds exemplifying embodiment 16 include compounds 1.019, 1.027, 1.028, 1.029, 1.035, 1.041, 1.042, 1.043, 1.057, 1.061, 1.099, 1.101, 1.103, 1.104, 1.105, 1.106, 1.107, 1.108, 1.109, 1.112, 1.114, 1.119, and 1.122, shown below in Table I.

In Embodiments 11-16 of Formula II, the preferred Q is $(CR_4R_5)_{n3}$, the more preferred Q is CH_2, the preferred n_1 is 1 or 2, the preferred n_2 is 1, the preferred n_3 is 1 or 2, and the preferred R_3 is H.

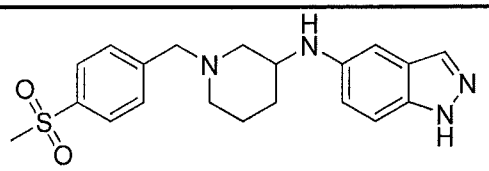
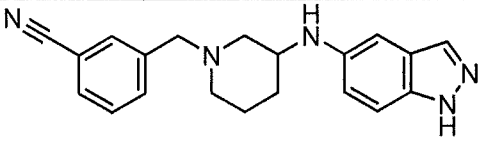
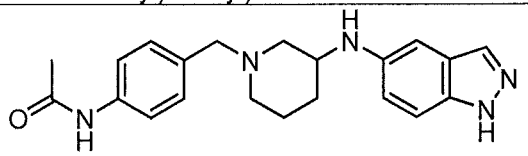
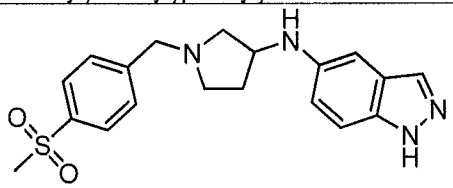
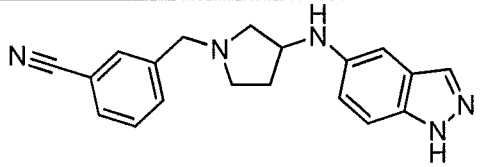
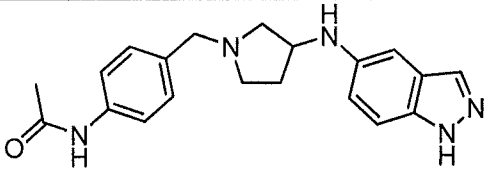
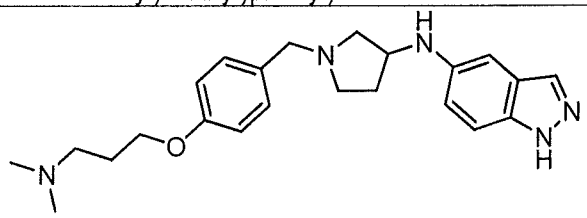
The present compounds are useful for ophthalmic use, particularly in reducing intraocular pressure or treating glaucoma. To be therapeutically effective in ophthalmic use, the compounds must have both adequate potency and proper pharmacokinetic properties such as good permeability across the ocular surface. In general, compounds bearing polar functionality have preferred absorption properties and are particularly suitable

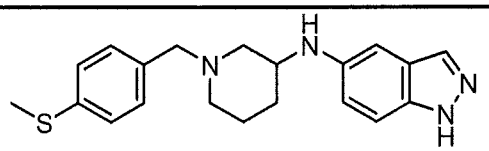
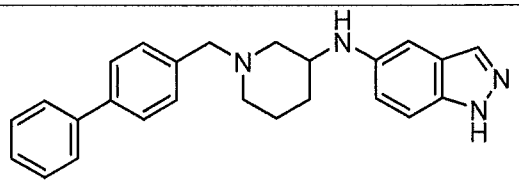
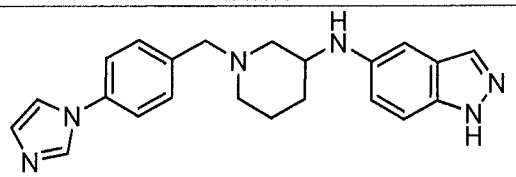
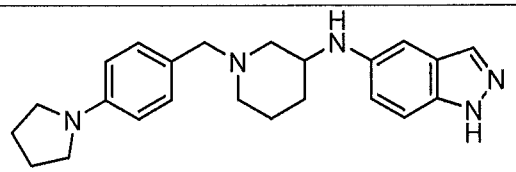
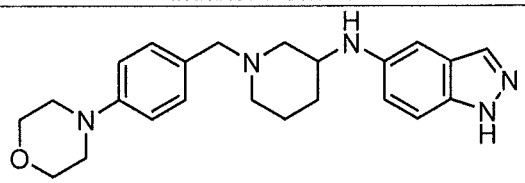
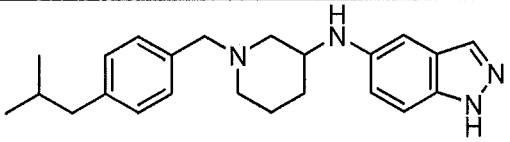
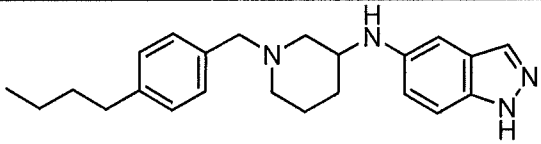
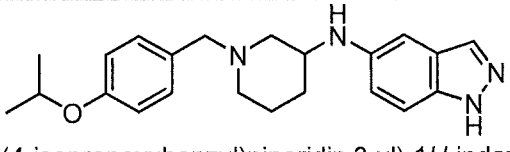
for topical optical use. In general, compounds bearing small lipophilic functional groups have good ROCK inhibitory potency.

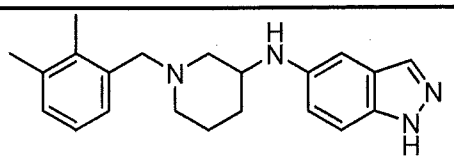
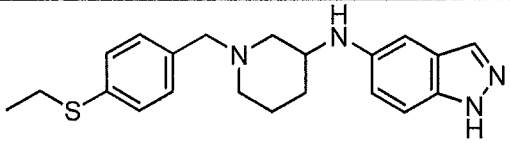
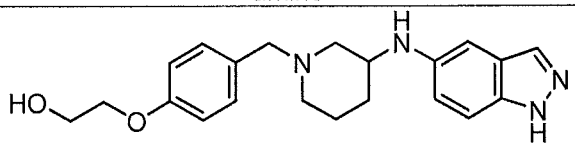
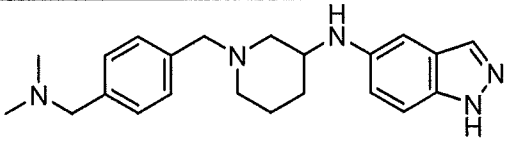
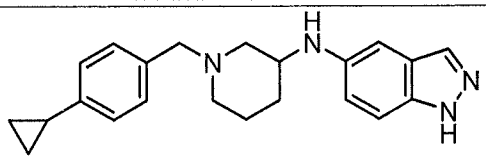
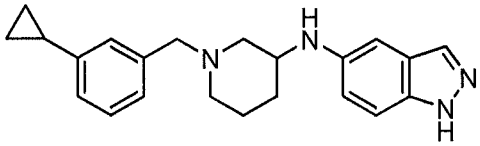
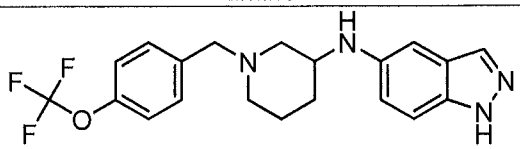
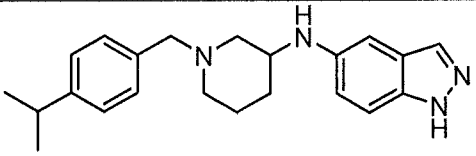
R_1 substitution in Formula I and X in Formula II are important factors for pharmacokinetic properties and ROCK inhibitory potency. Specifically, compounds bearing polar functionality, especially those specified in the embodiments 11, 12, 13, 14, 15, and 16 in Formulae I and II, above, are particularly suitable for topical optical use with adequate ROCK inhibiting activity. Compounds bearing small lipophilic functional groups, as specified in the embodiments 11, 12, 13, 14, 15, and 16 in Formulae I and II, above, display ROCK inhibition with adequate ocular permeability.

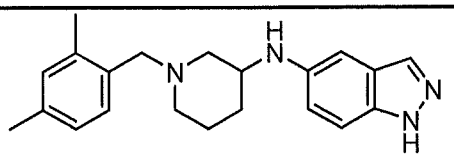
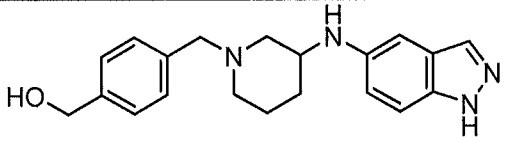
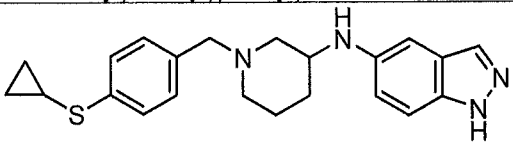
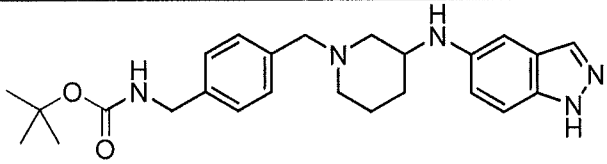
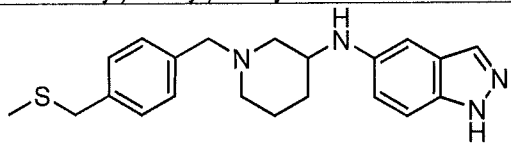
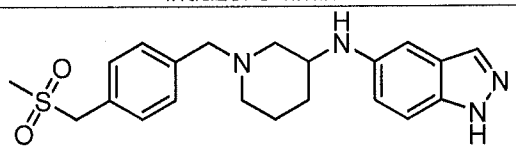
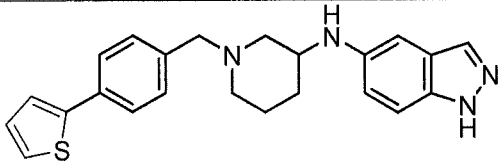
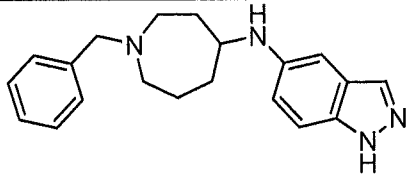
Specific compounds illustrative of Formula I and Formula II are shown in the following Table I. The example compounds have been numbered in such a way that numbers of the form 1.nnn indicate compounds in which R_2 is R_2-1, numbers of the form 2.nnn indicate compounds in which R_2 is R_2-2, and so on in a similar fashion for the remaining compound numbers and groups R_2. In the following structures, hydrogens are omitted from the drawings for the sake of simplicity. Tautomers drawn represent all tautomers possible. Structures are drawn to indicate the preferred stereochemistry; where stereoisomers may be generated in these compounds, structures are taken to mean any of the possible stereoisomers alone or a mixture of stereoisomers in any ratio.

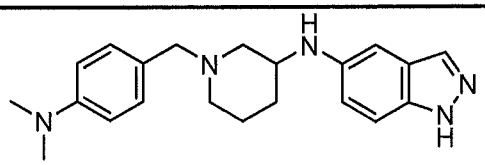
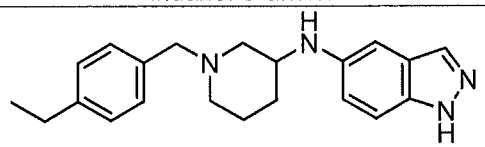
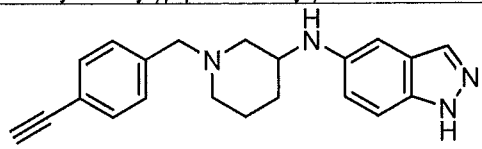
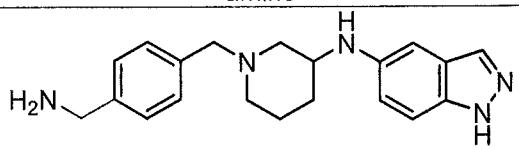
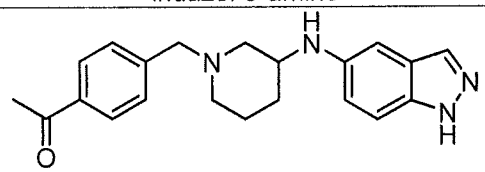
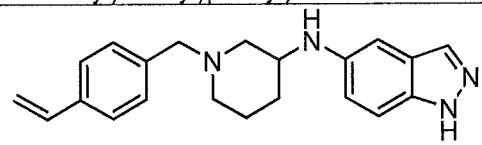
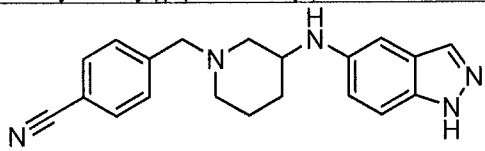
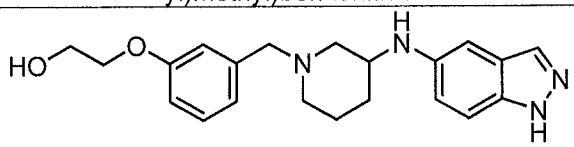
Table I. Example Compounds.

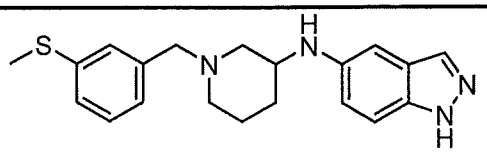
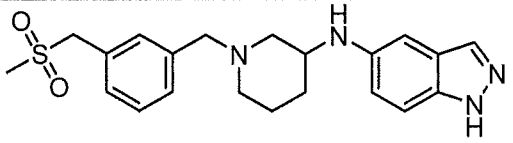
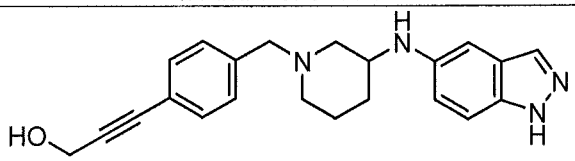
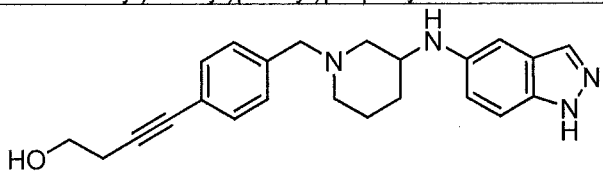
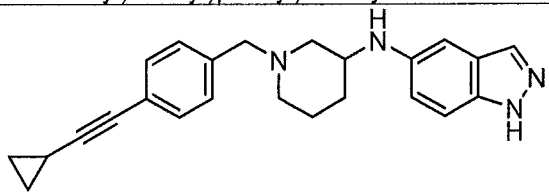
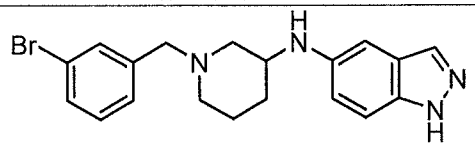
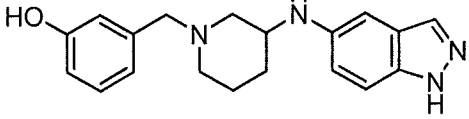
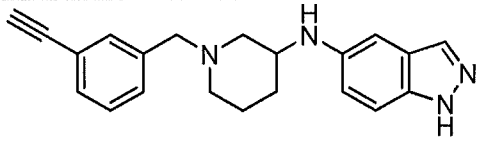
Compound	Structure	Embodiments
1.001	 *N*-(1-(4-(methylsulfonyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c
1.002	 3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzonitrile	1c, 7, 8, 9, 10, 12, 15c
1.003	 *N*-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.004	 *N*-(1-(4-(methylsulfonyl)benzyl)pyrrolidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c
1.005	 3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)benzonitrile	1c, 7, 8, 9, 10, 12, 15c
1.006	 *N*-(4-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.007	 *N*-(1-(4-(3-(dimethylamino)propoxy)benzyl)pyrrolidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12a, 15c, 15d

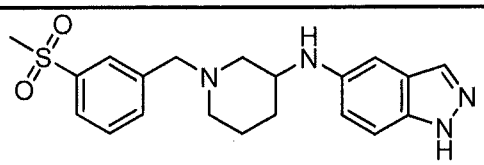
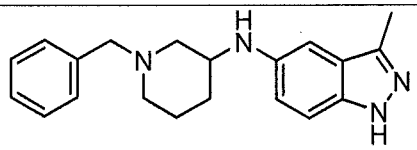
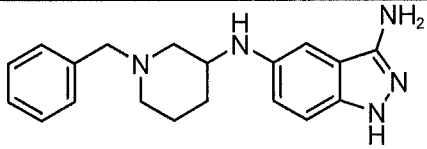
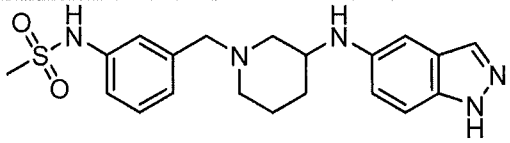
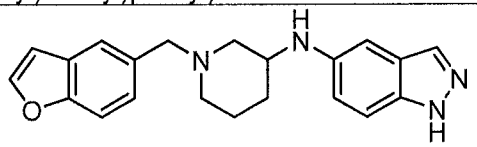
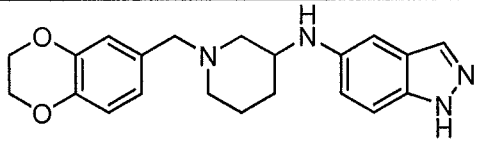
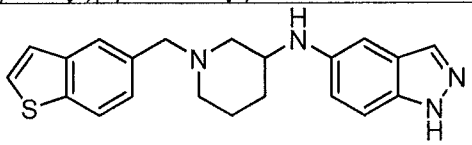
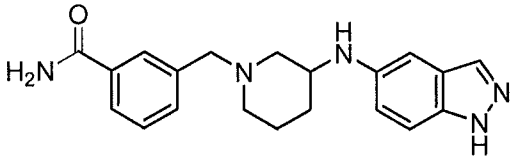
Compound	Structure	Embodiments
1.008	 *N*-(1-(4-(methylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.009	 *N*-(1-(biphenyl-4-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.010	 *N*-(1-(1*H*-imidazol-1-yl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.011	 *N*-(1-(4-(pyrrolidin-1-yl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.012	 *N*-(1-(4-morpholinobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.013	 *N*-(1-(4-isobutylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.014	 *N*-(1-(4-butylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.015	 *N*-(1-(4-isopropoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

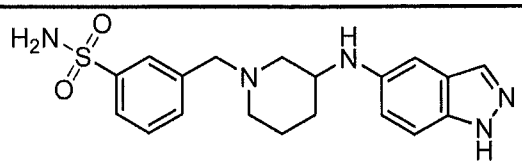
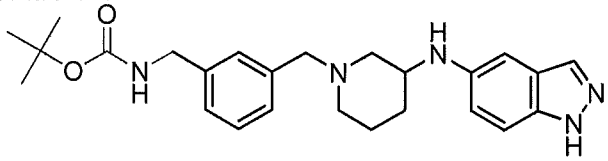
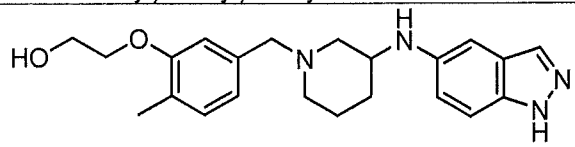
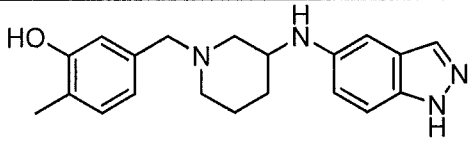
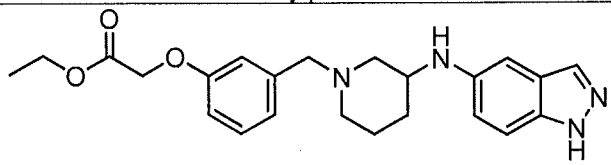
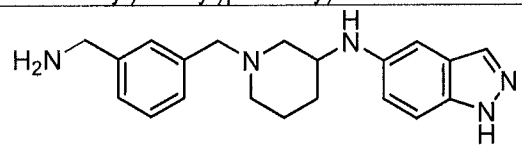
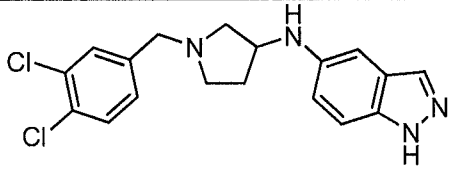
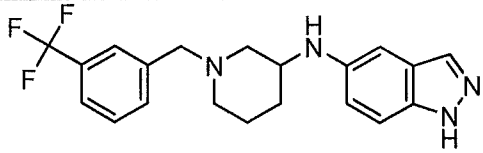
Compound	Structure	Embodiments
1.016	 *N*-(1-(2,3-dimethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.017	 *N*-(1-(4-(ethylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.018	 2-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl) phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.019	 *N*-(1-(4-((dimethylamino)methyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.020	 *N*-(1-(4-cyclopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.021	 *N*-(1-(3-cyclopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.022	 *N*-(1-(4-(trifluoromethoxy)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.023	 *N*-(1-(4-isopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

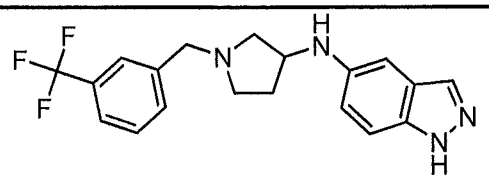
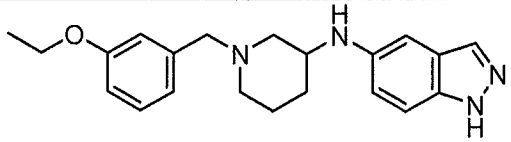
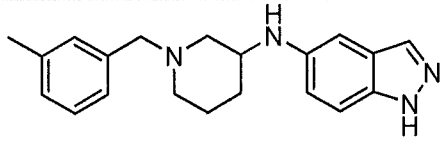
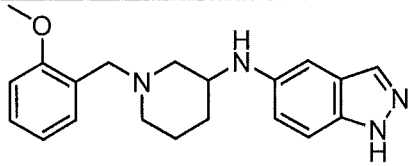
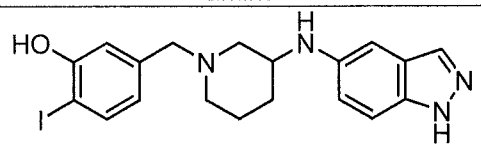
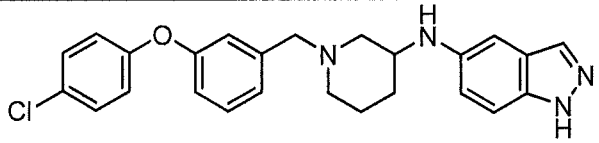
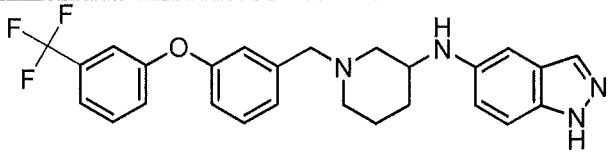
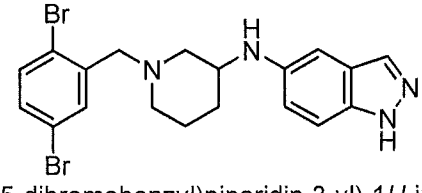
Compound	Structure	Embodiments
1.024	 *N*-(1-(2,4-dimethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.025	 (4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)methanol	1c, 7, 8, 9, 10
1.026	 *N*-(1-(4-(cyclopropylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.027	 *tert*-butyl 4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzylcarbamate	1c, 7, 8, 9, 10, 13, 16c
1.028	 *N*-(1-(4-(methylthiomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.029	 *N*-(1-(4-(methylsulfonylmethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.030	 *N*-(1-(4-(thiophen-2-yl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.031	 *N*-(1-benzylazepan-4-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

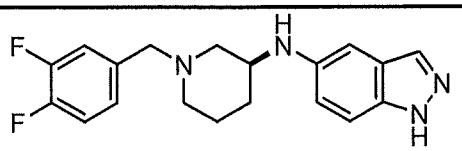
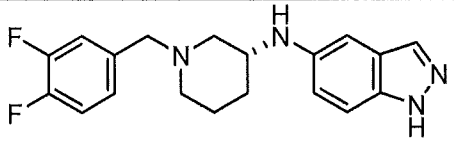
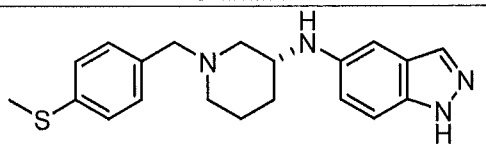
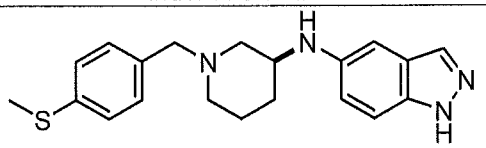
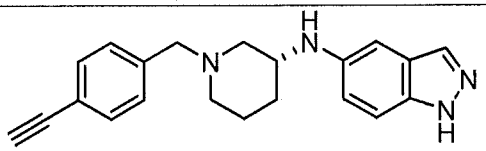
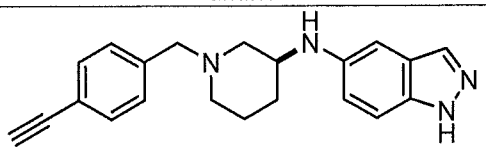
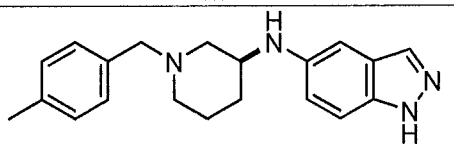
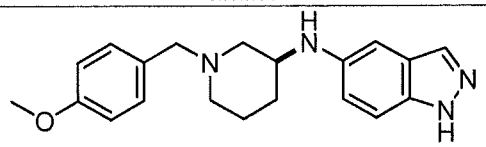
Compound	Structure	Embodiments
1.032	 *N*-(1-(4-(dimethylamino)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.033	 *N*-(1-(4-ethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.034	 *N*-(1-(4-ethynylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.035	 *N*-(1-(4-(aminomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.036	 1-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)ethanone	1c, 7, 8, 9, 10
1.037	 *N*-(1-(4-vinylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.038	 4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzonitrile	1c, 7, 8, 9, 10, 12, 15c
1.039	 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl) phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d

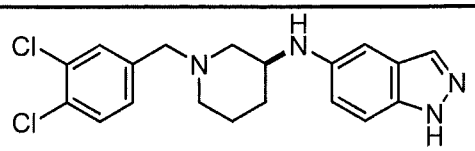
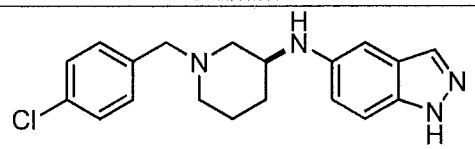
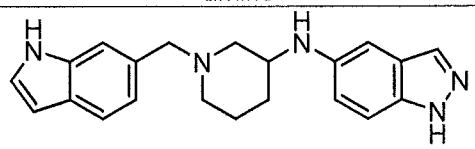
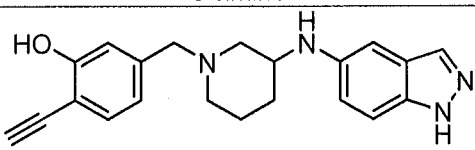
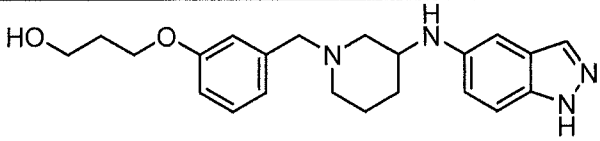
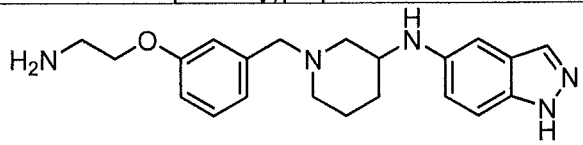
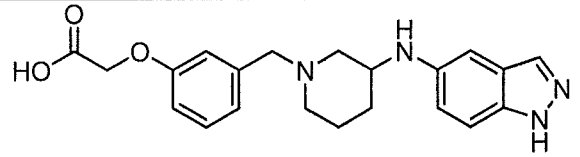
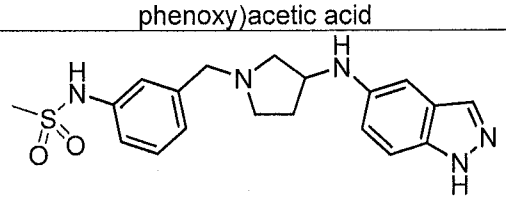
Compound	Structure	Embodiments
1.040	 *N*-(1-(3-(methylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.041	 *N*-(1-(3-(methylsulfonylmethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.042	 3-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)prop-2-yn-1-ol	1c, 7, 8, 9, 10, 13, 16c
1.043	 4-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)but-3-yn-1-ol	1c, 7, 8, 9, 10, 13, 16c
1.044	 *N*-(1-(4-(cyclopropylethynyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.045	 *N*-(1-(3-bromobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.046	 3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenol	1c, 7, 8, 9, 10
1.047	 *N*-(1-(3-ethynylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c

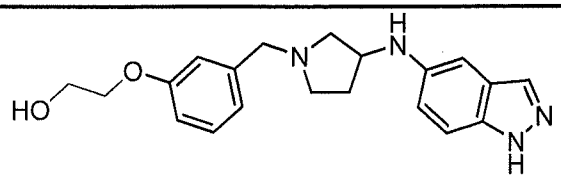
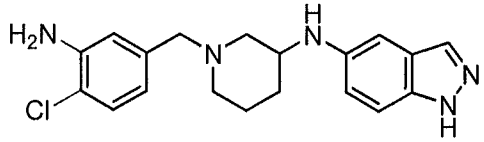
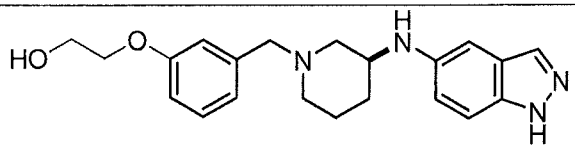
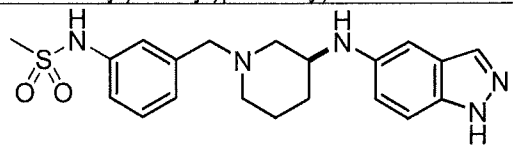
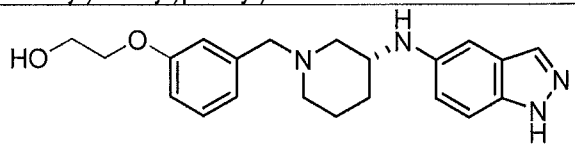
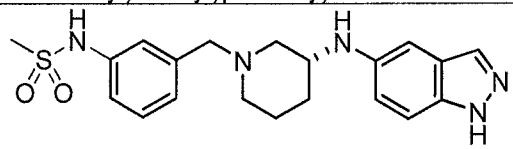
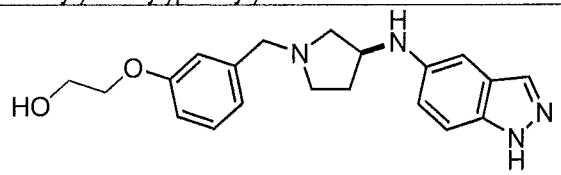
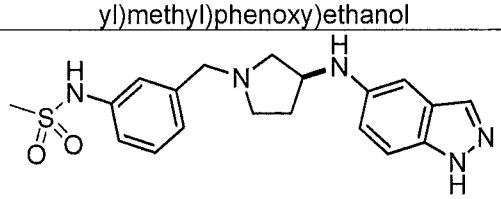
Compound	Structure	Embodiments
1.048	 *N*-(1-(3-(methylsulfonyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c
1.049	 *N*-(1-benzylpiperidin-3-yl)-3-methyl-1*H*-indazol-5-amine	1a, 6a, 8, 9, 10
1.050	 *N*5-(1-benzylpiperidin-3-yl)-1*H*-indazole-3,5-diamine	1b, 6b, 8, 9, 10
1.051	 *N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.052	 *N*-(1-(benzofuran-5-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.053	 *N*-(1-((2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.054	 *N*-(1-(benzo[*b*]thiophen-5-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.055	 3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzamide	1c, 7, 8, 9, 10, 12, 15c

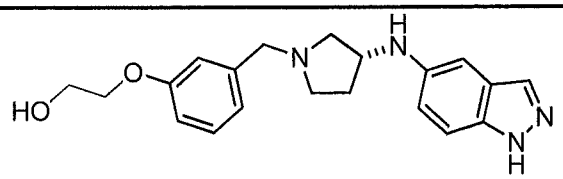
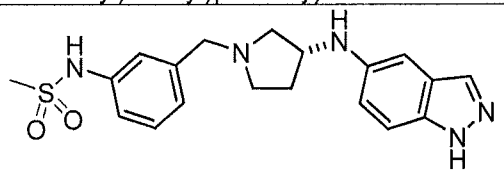
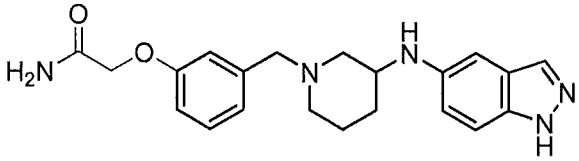
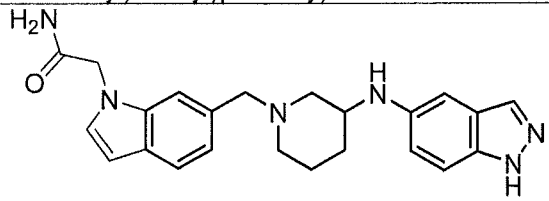
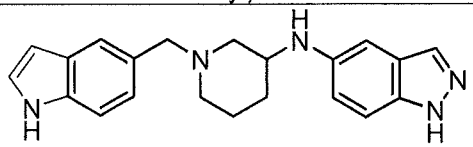
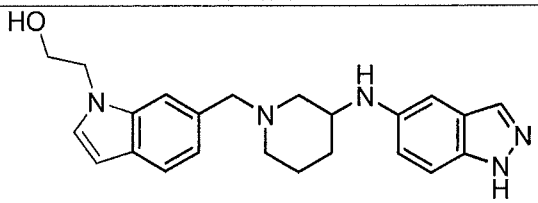
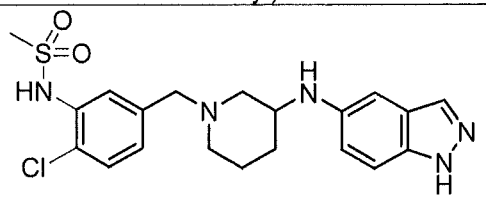
Compound	Structure	Embodiments
1.056	 3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzenesulfonamide	1c, 7, 8, 9, 10, 12, 15c
1.057	 *tert*-butyl 3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzylcarbamate	1c, 7, 8, 9, 10, 13, 16c
1.058	 2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.059	 5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenol	1c, 7, 8, 9, 10
1.060	 ethyl 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetate	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.061	 *N*-(1-(3-(aminomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.062	 *N*-(1-(3,4-dichlorobenzyl)pyrrolidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.063	 *N*-(1-(3-(trifluoromethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

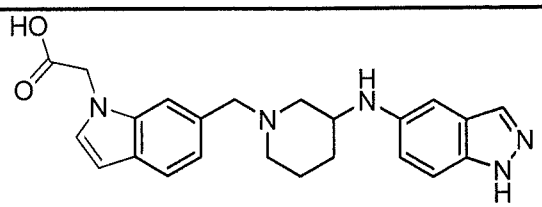
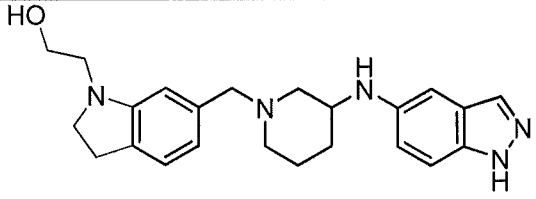
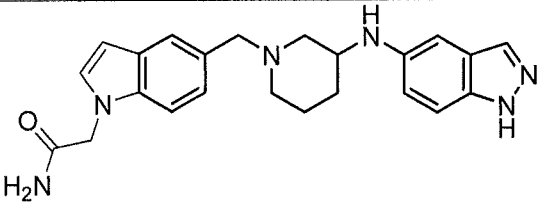
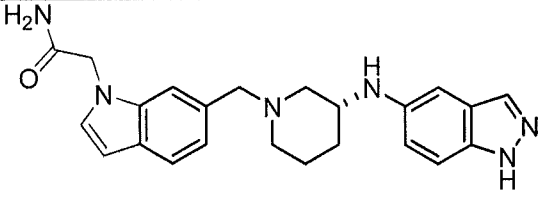
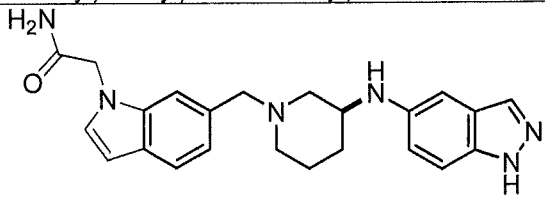
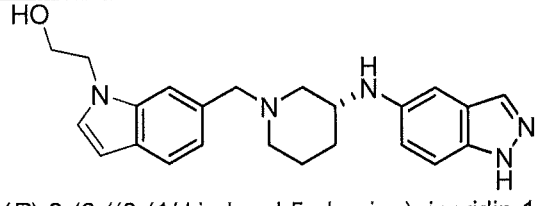
Compound	Structure	Embodiments
1.064	 *N*-(1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.065	 *N*-(1-(3-ethoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.066	 *N*-(1-(3-methylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.067	 *N*-(1-(2-methoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.068	 5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-iodophenol	1c, 7, 8, 9, 10
1.069	 *N*-(1-(3-(4-chlorophenoxy)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.070	 *N*-(1-(3-(3-(trifluoromethyl)phenoxy)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.071	 *N*-(1-(2,5-dibromobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

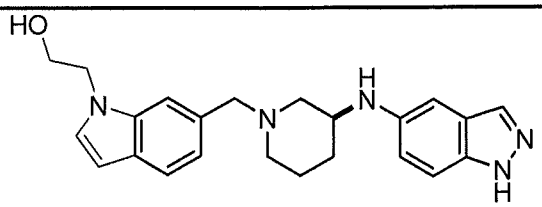
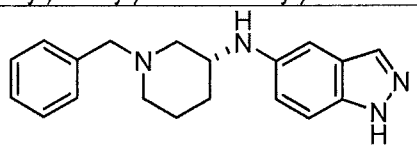
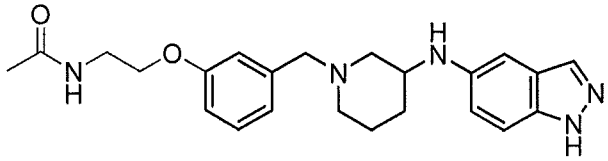
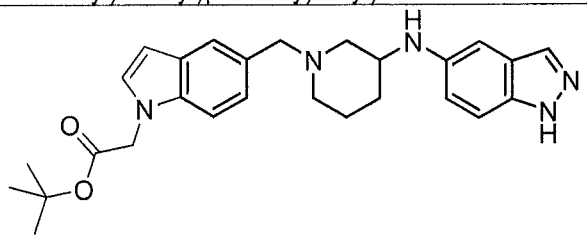
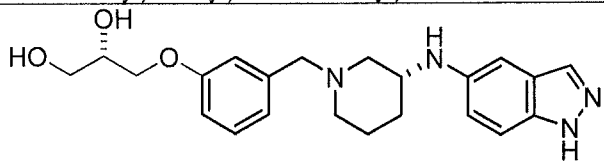
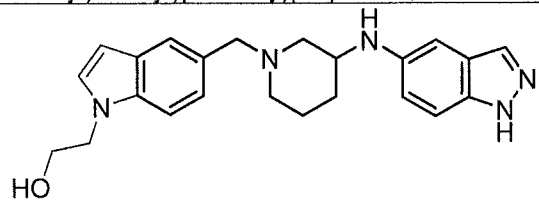
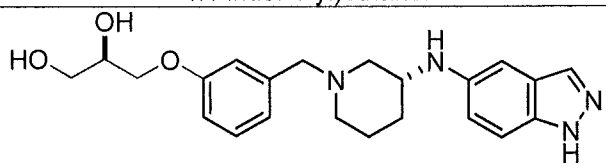
Compound	Structure	Embodiments
1.072	 (*S*)-*N*-(1-(3,4-difluorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.073	 (*R*)-*N*-(1-(3,4-difluorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.074	 (*R*)-*N*-(1-(4-(methylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.075	 (*S*)-*N*-(1-(4-(methylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.076	 (*R*)-*N*-(1-(4-ethynylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.077	 (*S*)-*N*-(1-(4-ethynylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.078	 (*S*)-*N*-(1-(4-methylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.079	 (*S*)-*N*-(1-(4-methoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

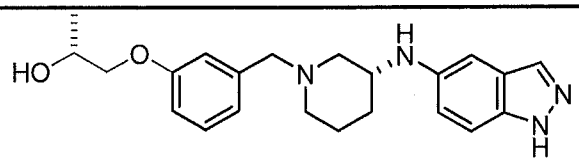
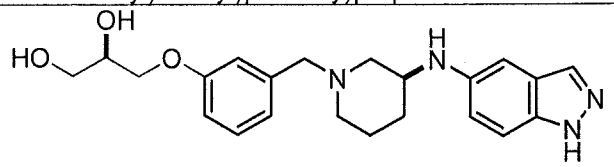
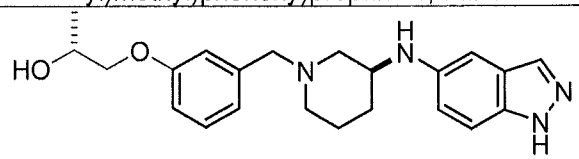
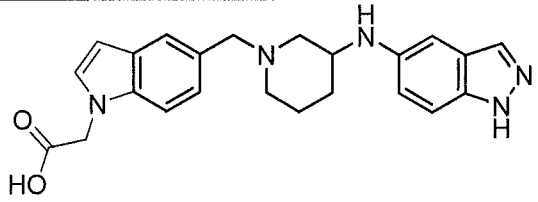
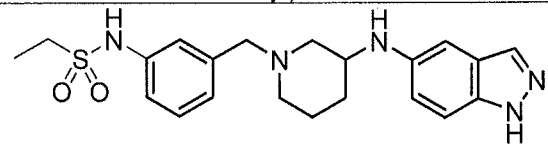
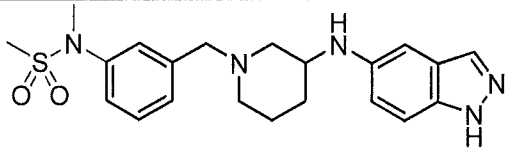
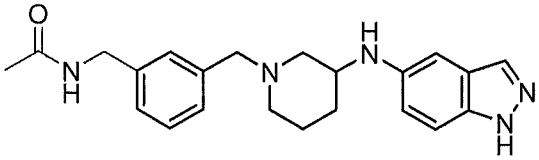
Compound	Structure	Embodiments
1.080	 (*S*)-*N*-(1-(3,4-dichlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.081	 (*S*)-*N*-(1-(4-chlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.082	 *N*-(1-((1*H*-indol-6-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.083	 5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-ethynylphenol	1c, 7, 8, 9, 10, 11, 14c
1.084	 3-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl) phenoxy)propan-1-ol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.085	 *N*-(1-(3-(2-aminoethoxy)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.086	 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl) phenoxy)acetic acid	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.087	 *N*-(3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

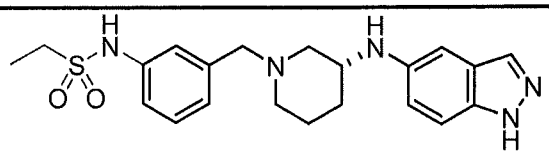
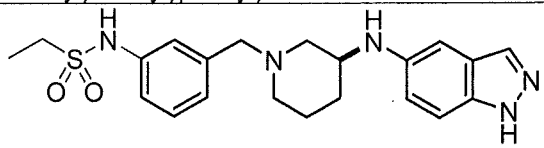
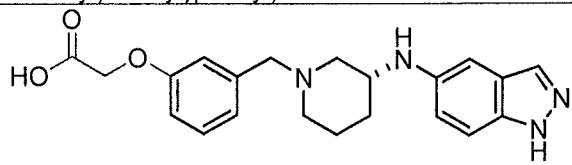
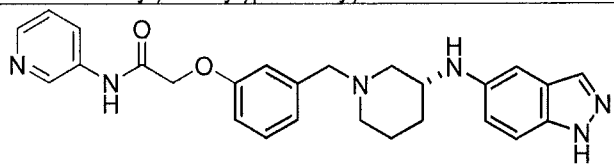
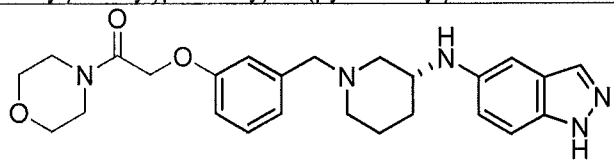
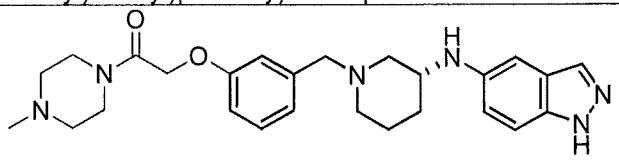
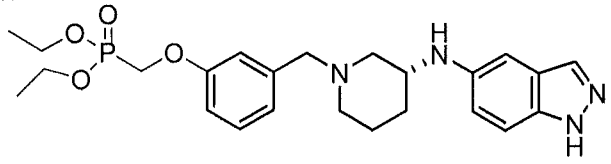
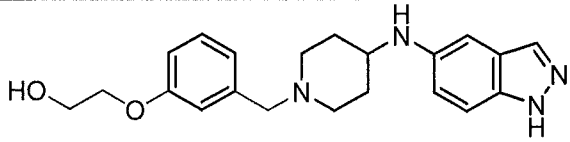
Compound	Structure	Embodiments
1.088	 2-(3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl) phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.089	 *N*-(1-(3-amino-4-chlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.090	 (*S*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.091	 (*S*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.092	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.093	 (*R*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.094	 (*S*)-2-(3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.095	 (*S*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

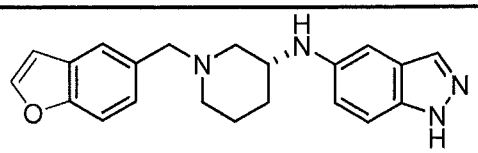
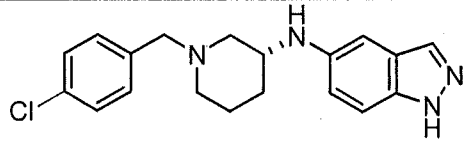
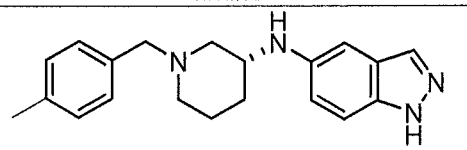
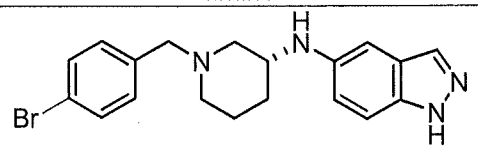
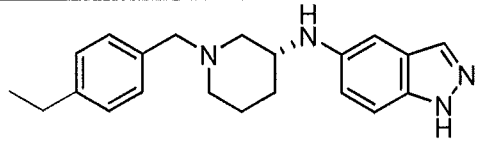
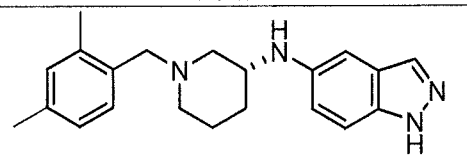
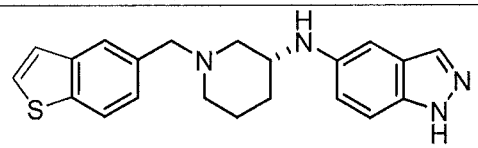
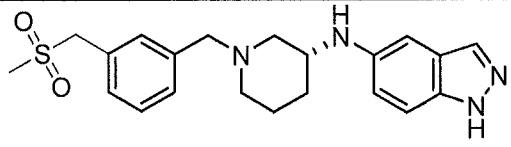
Compound	Structure	Embodiments
1.096	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.097	 (*R*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.098	 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.099	 2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.100	 *N*-(1-((1*H*-indol-5-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.101	 2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)ethanol	1c, 7, 8, 9, 10, 13, 16c
1.102	 *N*-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-chlorophenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

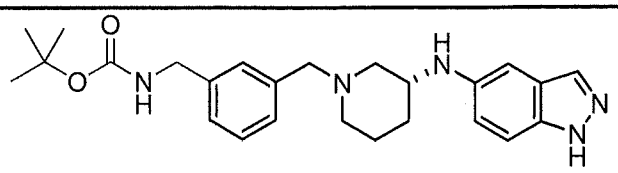
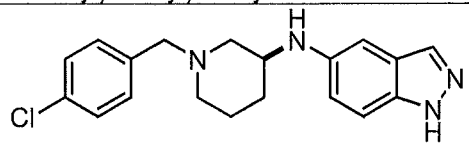
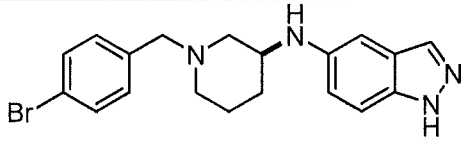
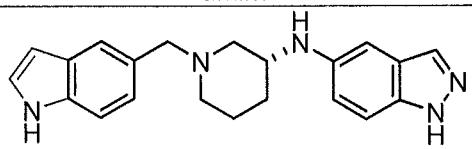
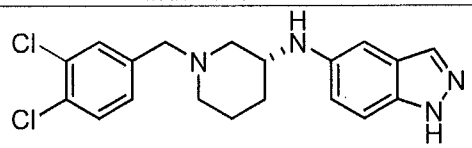
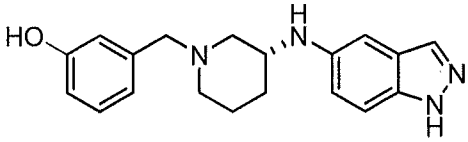
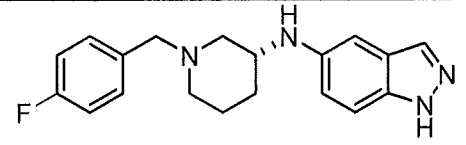
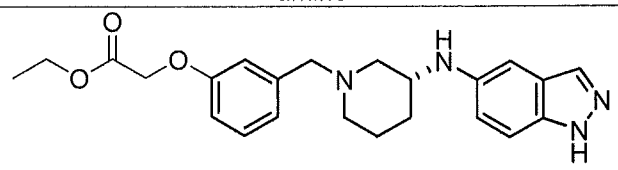
Compound	Structure	Embodiments
1.103	 2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetic acid	1c, 7, 8, 9, 10, 13, 16c
1.104	 2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)indolin-1-yl)ethanol	1c, 7, 8, 9, 10, 13, 16c
1.105	 2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.106	 (*R*)-2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.107	 (*S*)-2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.108	 (*R*)-2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)ethanol	1c, 7, 8, 9, 10, 13, 16c

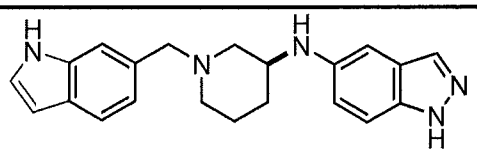
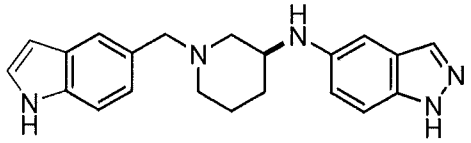
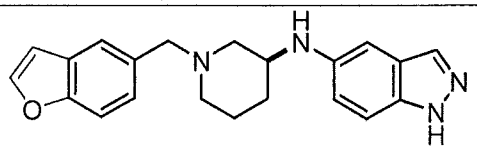
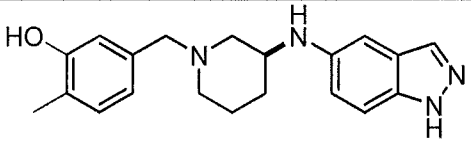
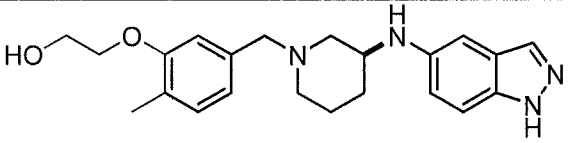
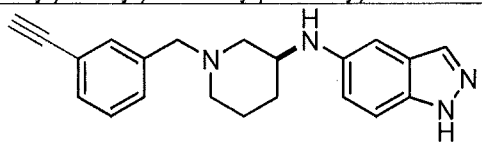
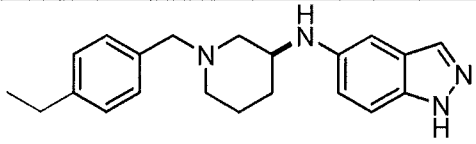
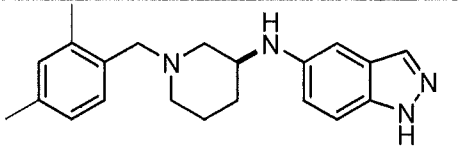
Compound	Structure	Embodiments
1.109	 (*S*)-2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)ethanol	1c, 7, 8, 9, 10, 13, 16c
1.110	 (*R*)-*N*-(1-benzylpiperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.111	 *N*-(2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethyl)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.112	 *tert*-butyl 2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetate	1c, 7, 8, 9, 10, 13, 16c
1.113	 (*S*)-3-(3-(((*R*)-3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propane-1,2-diol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.114	 2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)ethanol	1c, 7, 8, 9, 10, 13, 16c
1.115	 (*R*)-3-(3-(((*R*)-3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propane-1,2-diol	1c, 7, 8, 9, 10, 12a, 15c, 15d

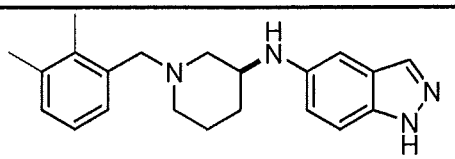
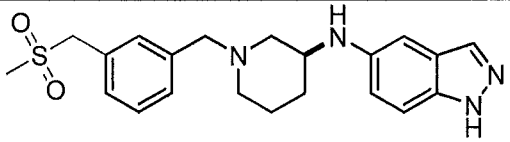
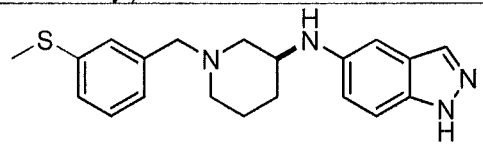
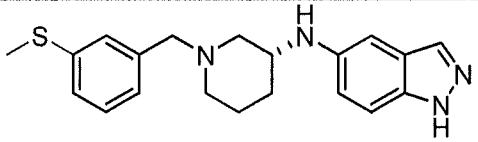
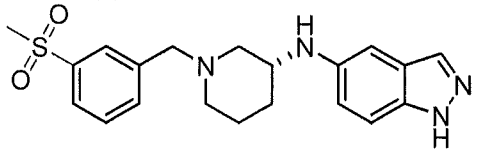
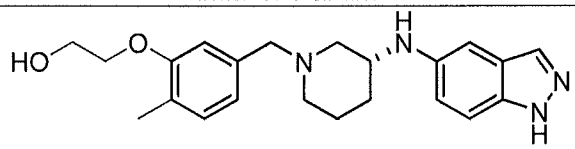
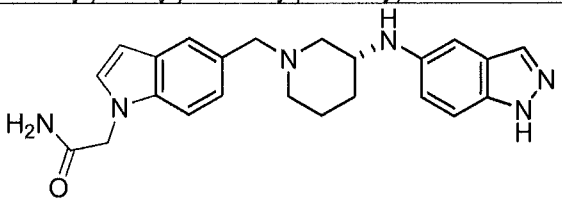
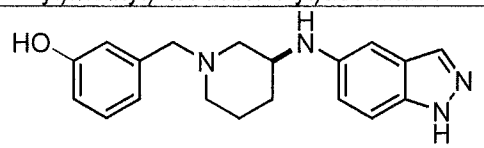
Compound	Structure	Embodiments
1.116	 (*R*)-1-(3-(((*R*)-3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propan-2-ol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.117	 (*R*)-3-(3-(((*S*)-3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propane-1,2-diol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.118	 (*R*)-1-(3-(((*S*)-3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propan-2-ol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.119	 2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetic acid	1c, 7, 8, 9, 10, 13, 16c
1.120	 *N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)ethanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.121	 *N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)-*N*-methylmethanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.122	 *N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzyl)acetamide	1c, 7, 8, 9, 10, 13, 16c

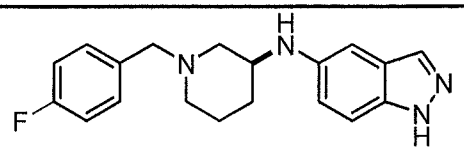
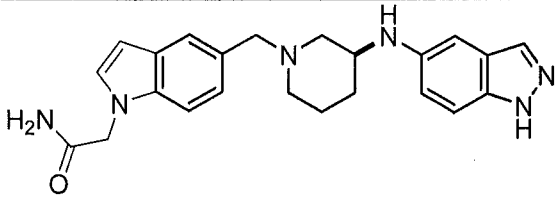
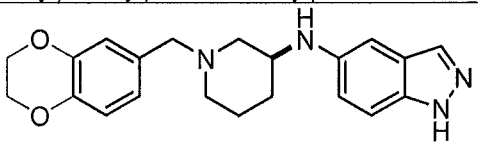
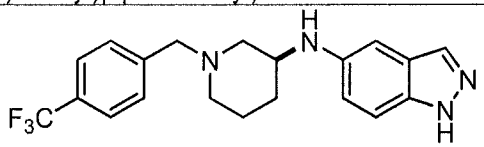
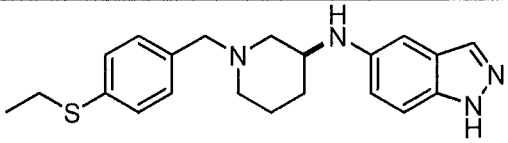
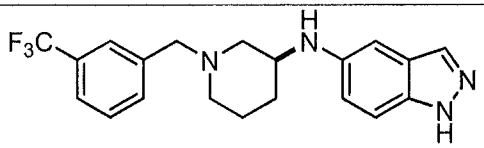
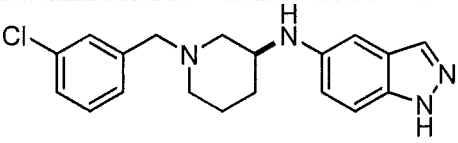
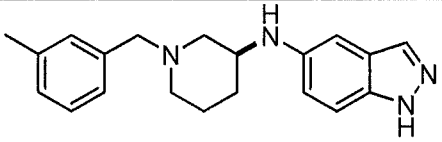
Compound	Structure	Embodiments
1.123	 (*R*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)ethanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.124	 (*S*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)ethanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.125	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetic acid	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.126	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)-*N*-(pyridin-3-yl)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.127	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)-1-morpholinoethanone	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.128	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)-1-(4-methylpiperazin-1-yl)ethanone	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.129	 (*R*)-diethyl (3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)methylphosphonate	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.130	 2-(3-((4-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d

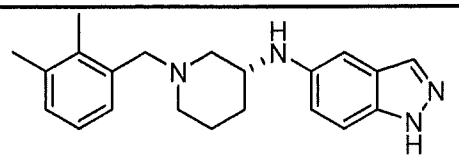
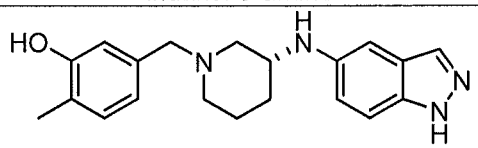
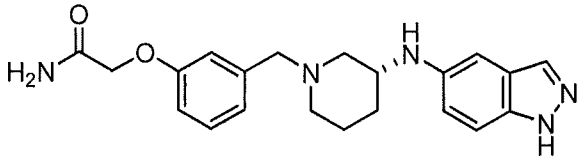
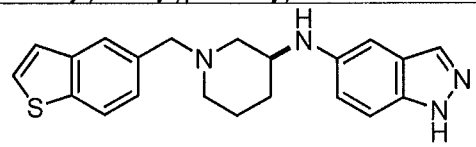
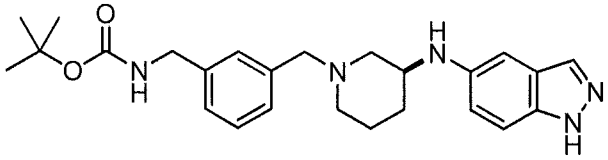
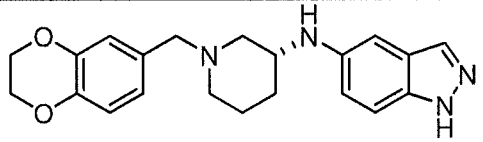
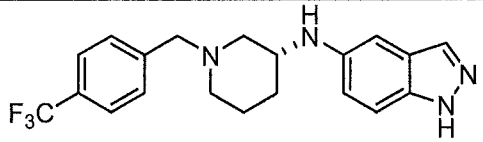
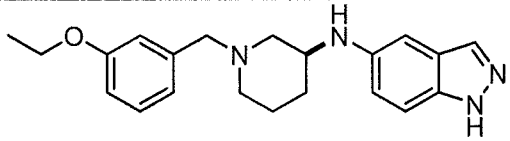
Compound	Structure	Embodiments
1.131	 (*R*)-*N*-(1-(benzofuran-5-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.132	 (*R*)-*N*-(1-(4-chlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.133	 (*R*)-*N*-(1-(4-methylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.134	 (*R*)-*N*-(1-(4-bromobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.136	 (*R*)-*N*-(1-(4-ethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.137	 (*R*)-*N*-(1-(2,4-dimethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.138	 (*R*)-*N*-(1-(benzo[*b*]thiophen-5-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.139	 (*R*)-*N*-(1-(3-(methylsulfonylmethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c

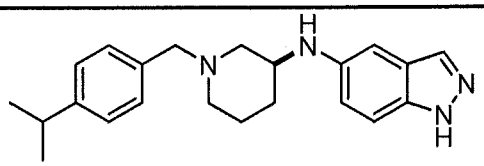
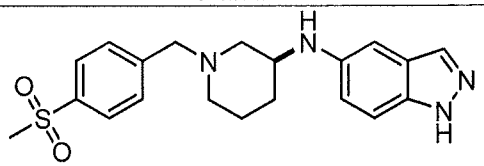
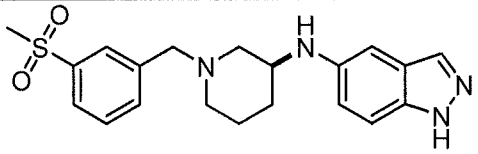
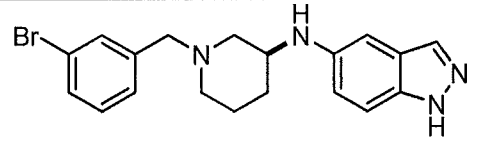
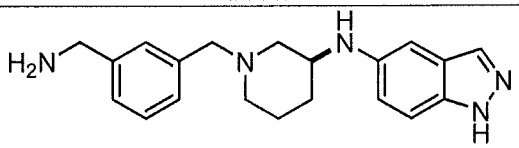
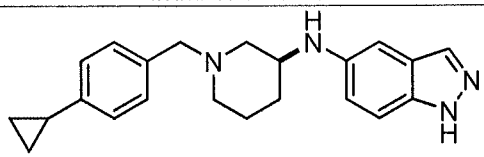
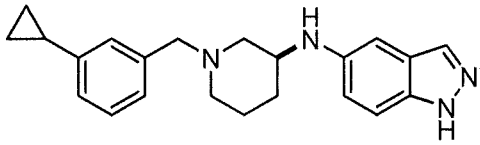
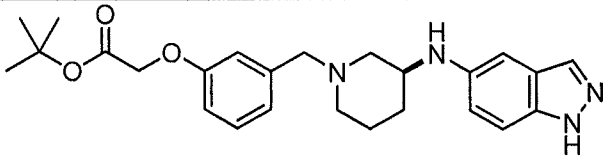
Compound	Structure	Embodiments
1.140	 (*R*)-*tert*-butyl 1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzylcarbamate	1c, 7, 8, 9, 10, 13, 16c
1.141	 (*S*)-*N*-(1-(4-chlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.142	 (*S*)-*N*-(1-(4-bromobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.143	 (*R*)-*N*-(1-((1*H*-indol-5-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.144	 (*R*)-*N*-(1-(3,4-dichlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.145	 (*R*)-3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenol	1c, 7, 8, 9, 10
1.146	 (*R*)-*N*-(1-(4-fluorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.147	 (*R*)-ethyl 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetate	1c, 7, 8, 9, 10, 12a, 15c, 15d

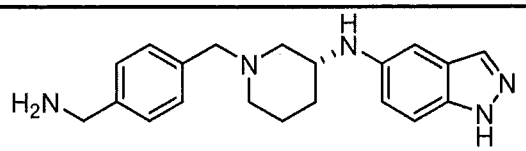
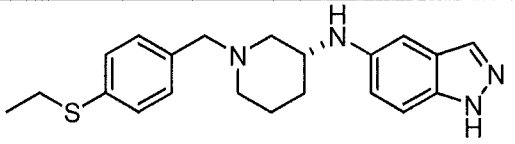
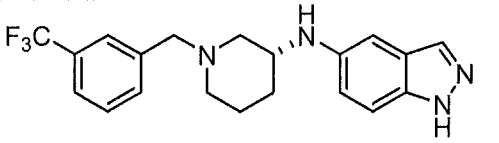
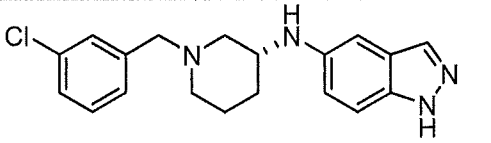
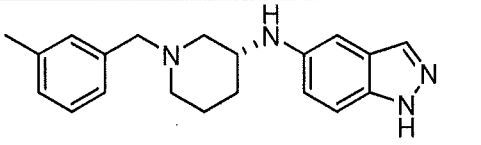
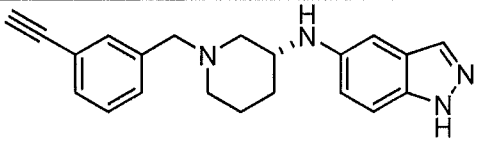
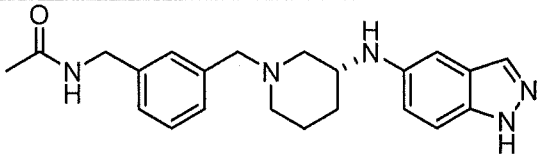
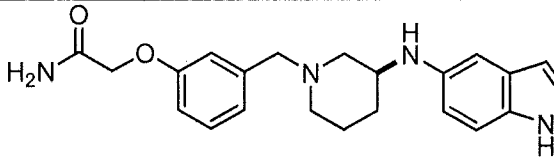
Compound	Structure	Embodiments
1.148	 (*S*)-*N*-(1-((1*H*-indol-6-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.149	 (*S*)-*N*-(1-((1*H*-indol-5-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.150	 (*S*)-*N*-(1-(benzofuran-5-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.151	 (*S*)-5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenol	1c, 7, 8, 9, 10
1.152	 (*S*)-2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.153	 (*S*)-*N*-(1-(3-ethynylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.154	 (*S*)-*N*-(1-(4-ethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.155	 (*S*)-*N*-(1-(2,4-dimethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

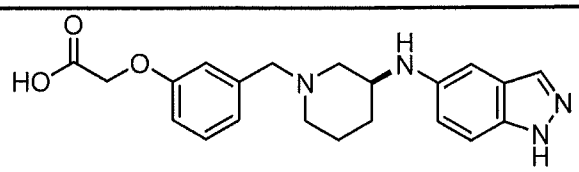
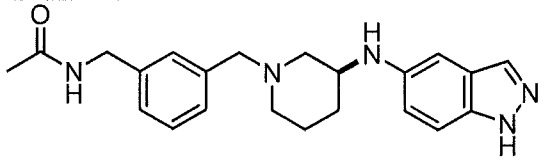
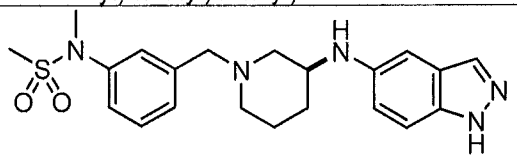
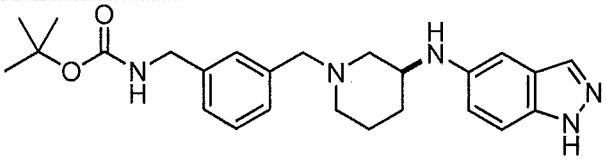
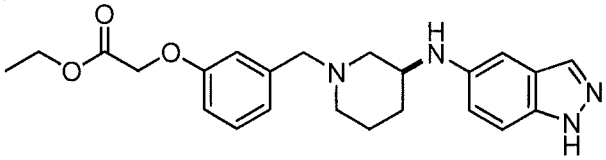
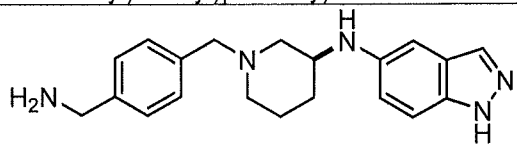
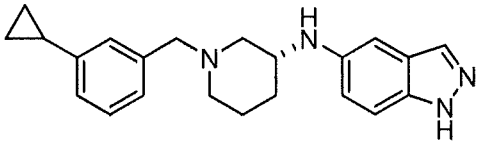
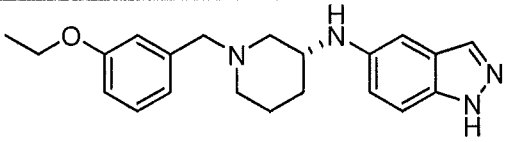
Compound	Structure	Embodiments
1.156	 (*S*)-*N*-(1-(2,3-dimethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.157	 (*S*)-*N*-(1-(3-(methylsulfonylmethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c
1.158	 (*S*)-*N*-(1-(3-(methylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.159	 (*R*)-*N*-(1-(3-(methylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.160	 (*R*)-*N*-(1-(3-(methylsulfonyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c
1.161	 (*R*)-2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.162	 (*R*)-2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.163	 (*S*)-3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenol	1c, 7, 8, 9, 10

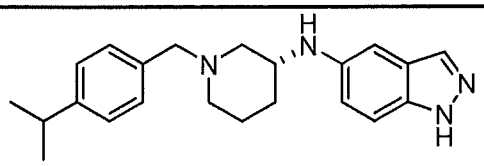
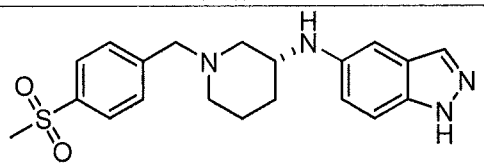
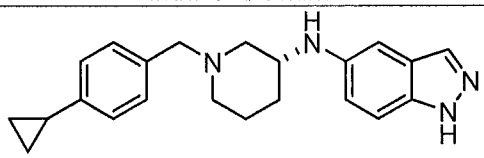
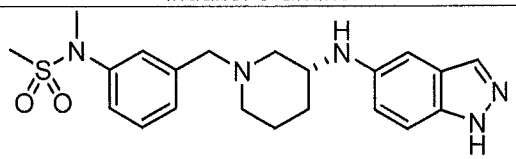
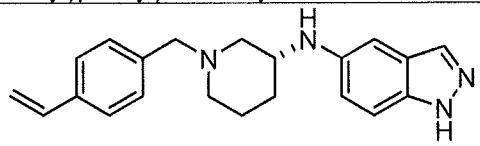
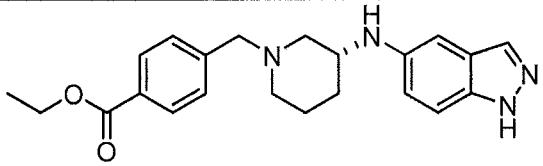
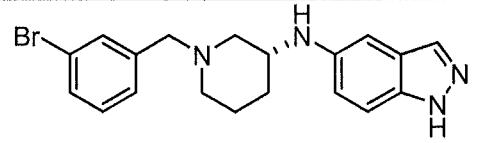
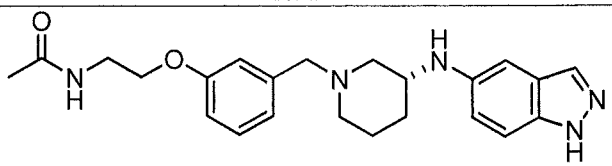
Compound	Structure	Embodiments
1.164	 (*S*)-*N*-(1-(4-fluorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.165	 (*S*)-2-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-1*H*-indol-1-yl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.166	 (*S*)-*N*-(1-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.167	 (*S*)-*N*-(1-(4-(trifluoromethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.168	 (*S*)-*N*-(1-(4-(ethylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12b, 15c, 15e
1.169	 (*S*)-*N*-(1-(3-(trifluoromethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.170	 (*S*)-*N*-(1-(3-chlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.171	 (*S*)-*N*-(1-(3-methylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.171

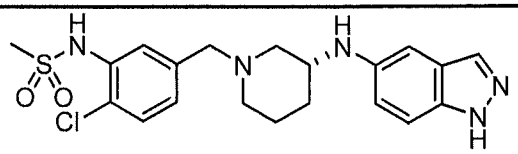
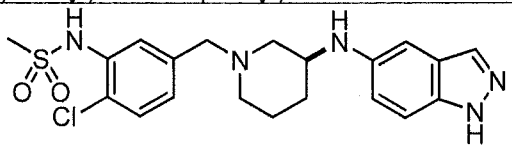
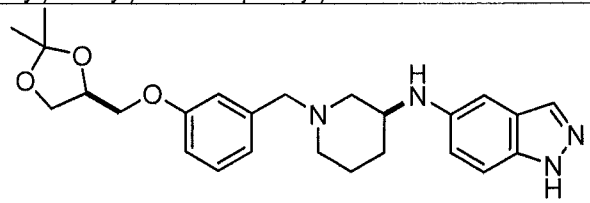
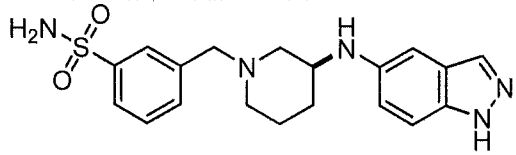
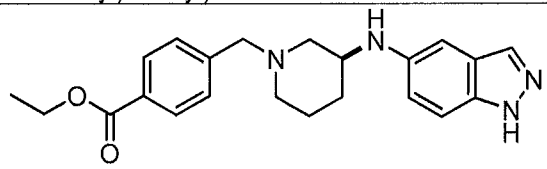
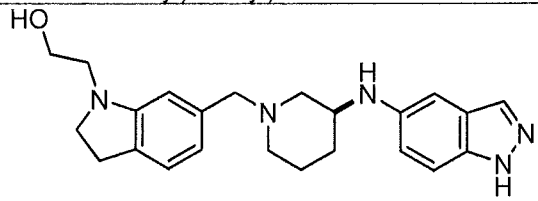
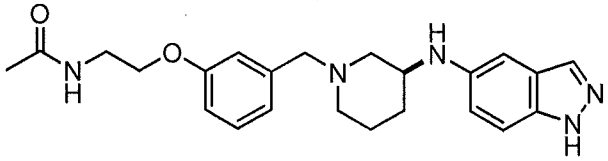
Compound	Structure	Embodiments
1.172	 (*R*)-*N*-(1-(2,3-dimethylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.172
1.173	 (*R*)-5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenol	1.173
1.174	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetamide	1.174
1.175	 (*S*)-*N*-(1-(benzo[b]thiophen-5-ylmethyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.175
1.176	 (*S*)-*tert*-butyl 1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzylcarbamate	1.176
1.177	 (*R*)-*N*-(1-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.177
1.178	 (*R*)-*N*-(1-(4-(trifluoromethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.178
1.179	 (*S*)-*N*-(1-(3-ethoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.179

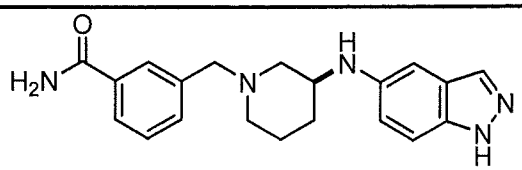
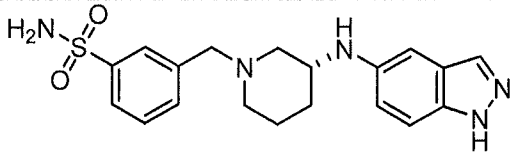
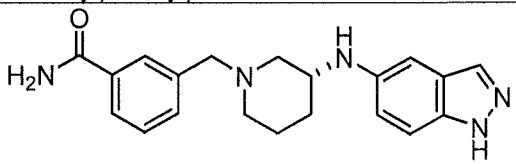
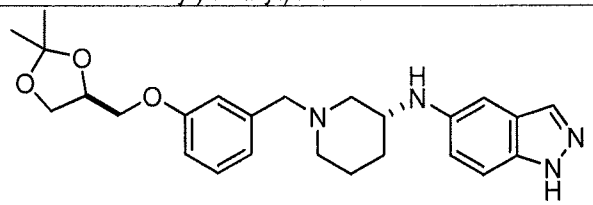
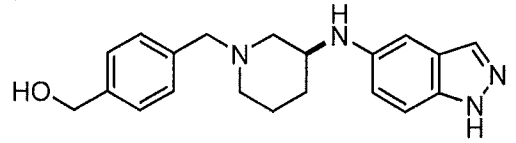
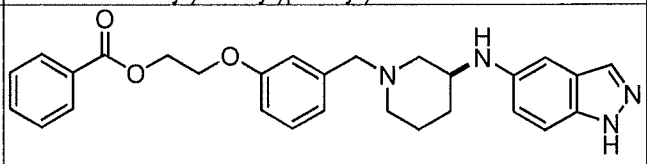
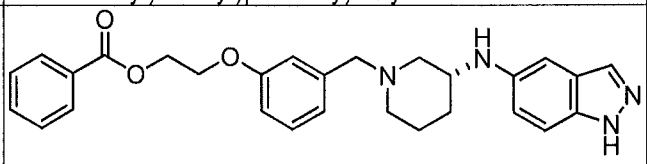
Compound	Structure	Embodiments
1.180	 (*S*)-*N*-(1-(4-isopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.180
1.181	 (*S*)-*N*-(1-(4-(methylsulfonyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.181
1.182	 (*S*)-*N*-(1-(3-(methylsulfonyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.182
1.183	 (*S*)-*N*-(1-(3-bromobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.183
1.184	 (*S*)-*N*-(1-(3-(aminomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.184
1.185	 (*S*)-*N*-(1-(4-cyclopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.185
1.186	 (*S*)-*N*-(1-(3-cyclopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.186
1.187	 (*S*)-*tert*-butyl 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetate	1.187

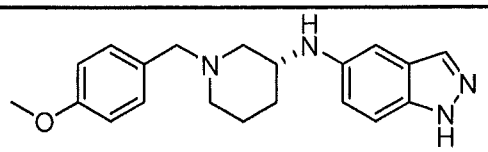
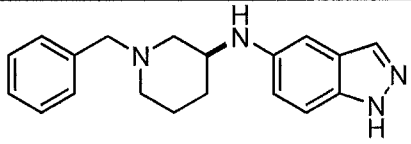
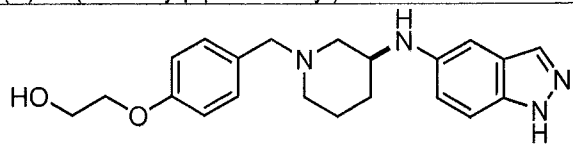
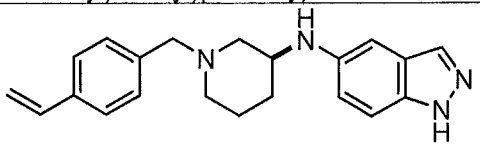
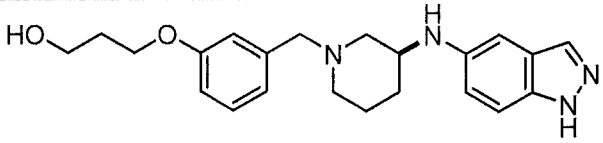
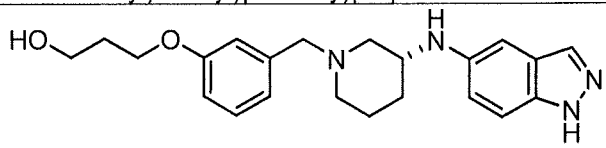
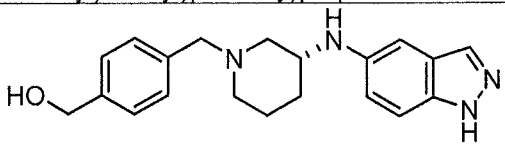
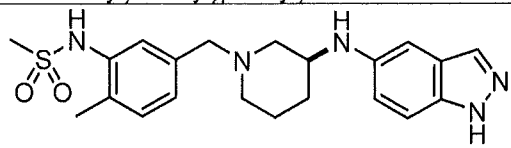
Compound	Structure	Embodiments
1.188	 (*R*)-*N*-(1-(4-(aminomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.188
1.189	 (*R*)-*N*-(1-(4-(ethylthio)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.189
1.190	 (*R*)-*N*-(1-(3-(trifluoromethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1.190
1.191	 (*R*)-*N*-(1-(3-chlorobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.192	 (*R*)-*N*-(1-(3-methylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.193	 (*R*)-*N*-(1-(3-ethynylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.194	 (*R*)-*N*-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzyl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.195	 (*S*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

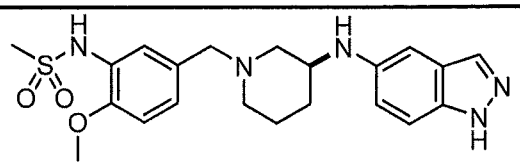
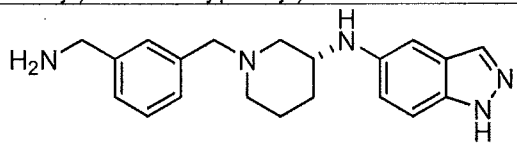
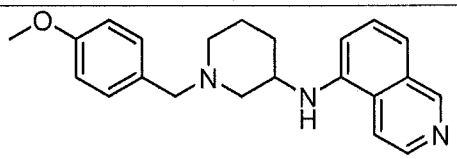
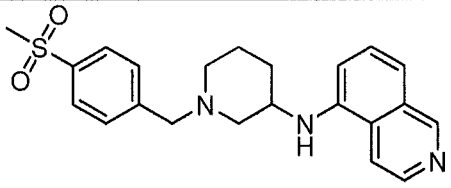
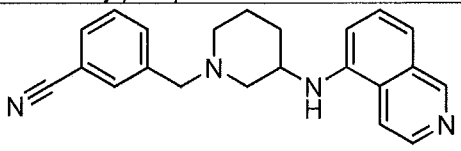
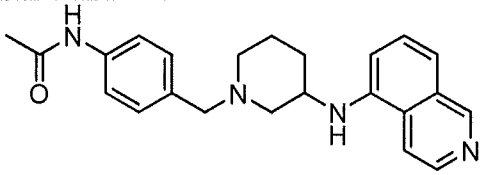
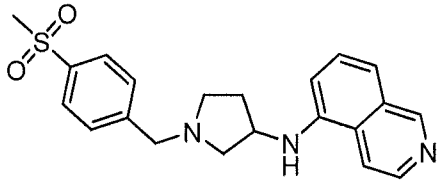
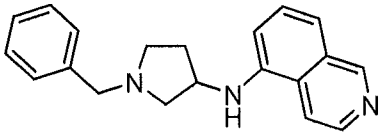
Compound	Structure	Embodiments
1.196	 (*S*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetic acid	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.197	 (*S*)-*N*-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzyl)acetamide	1c, 7, 8, 9, 10, 13, 16c
1.198	 (*S*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)-*N*-methylmethanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.199	 (*S*)-*tert*-butyl 1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzylcarbamate	1c, 7, 8, 9, 10, 13, 16c
1.200	 (*S*)-ethyl 2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)acetate	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.201	 (*S*)-*N*-(1-(4-(aminomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
1.202	 (*R*)-*N*-(1-(3-cyclopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.203	 (*R*)-*N*-(1-(3-ethoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10

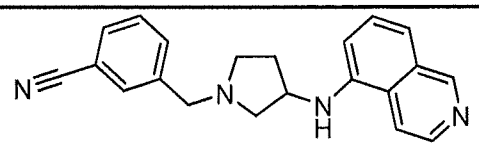
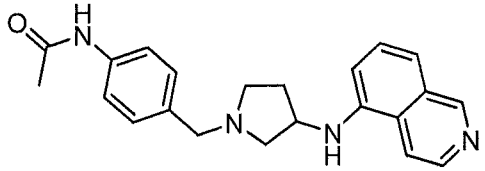
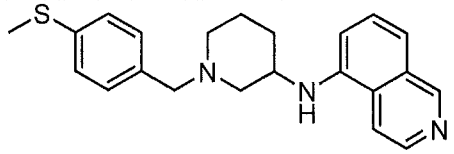
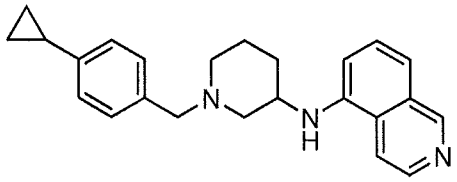
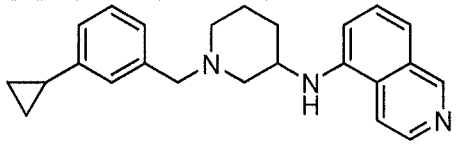
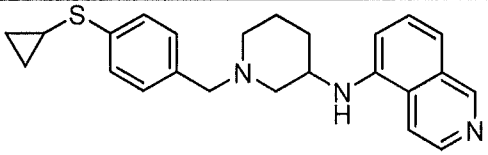
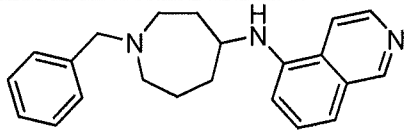
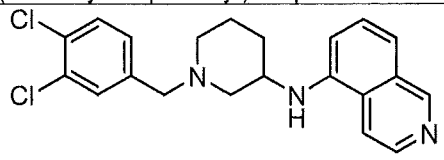
Compound	Structure	Embodiments
1.204	 (*R*)-*N*-(1-(4-isopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.205	 (*R*)-*N*-(1-(4-(methylsulfonyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12, 15c
1.206	 (*R*)-*N*-(1-(4-cyclopropylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.207	 (*R*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)-*N*-methylmethanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.208	 (*R*)-*N*-(1-(4-vinylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.209	 (*R*)-ethyl 4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzoate	1c, 7, 8, 9, 10
1.210	 (*R*)-*N*-(1-(3-bromobenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.211	 (*R*)-*N*-(2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethyl)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

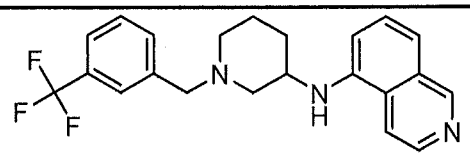
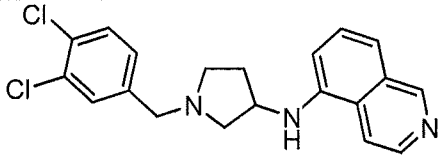
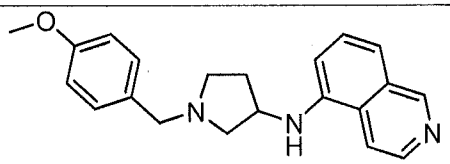
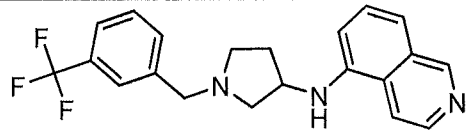
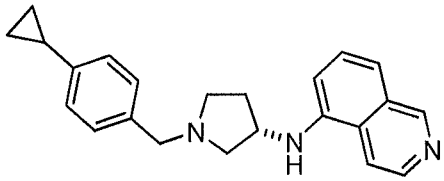
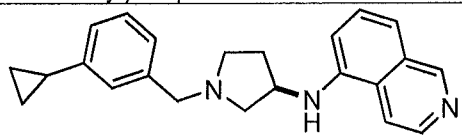
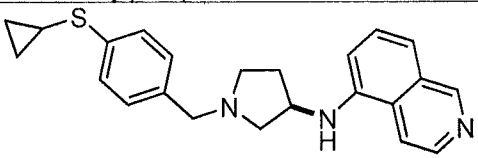
Compound	Structure	Embodiments
1.212	 (*R*)-*N*-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-chlorophenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.213	 (*S*)-*N*-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-chlorophenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.214	 *N*-((*S*)-1-(3-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.215	 (*S*)-3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzenesulfonamide	1c, 7, 8, 9, 10, 12, 15c
1.216	 (*S*)-ethyl 4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzoate	1c, 7, 8, 9, 10
1.217	 (*S*)-2-(6-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)indolin-1-yl)ethanol	1c, 7, 8, 9, 10, 13, 16c
1.218	 (*S*)-*N*-(2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethyl)acetamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

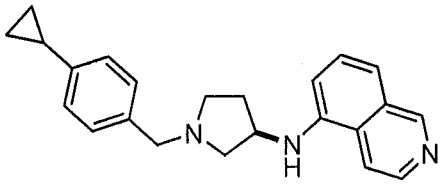
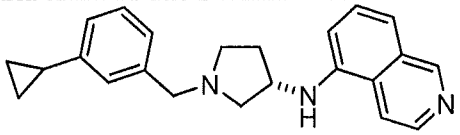
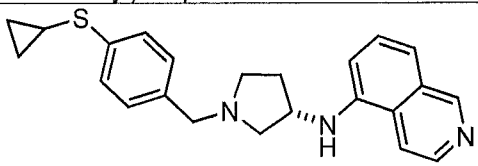
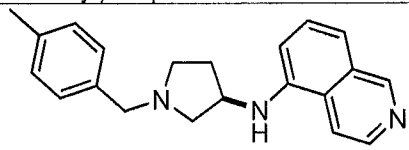
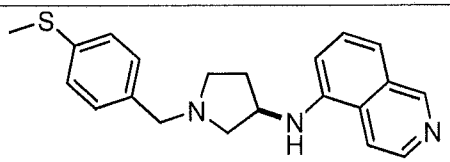
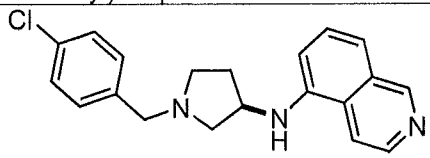
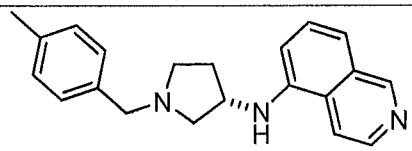
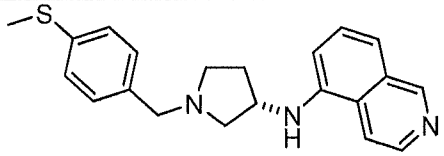
Compound	Structure	Embodiments
1.219	 (*S*)-3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzamide	1c, 7, 8, 9, 10, 12, 15c
1.220	 (*R*)-3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzenesulfonamide	1c, 7, 8, 9, 10, 12, 15c
1.221	 (*R*)-3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)benzamide	1c, 7, 8, 9, 10, 12, 15c
1.222	 *N*-((*R*)-1-(3-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.223	 (*S*)-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)methanol	1c, 7, 8, 9, 10
1.224	 (*S*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethyl benzoate	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.225	 (*R*)-2-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethyl benzoate	1c, 7, 8, 9, 10, 12a, 15c, 15d

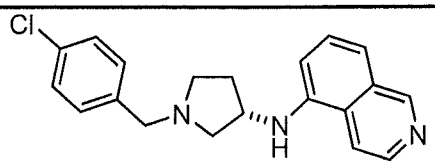
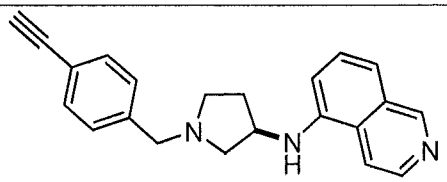
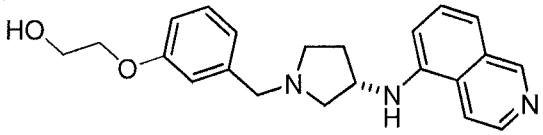
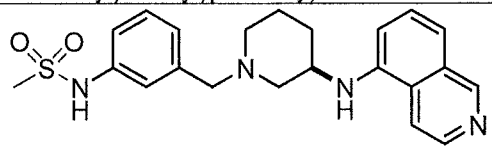
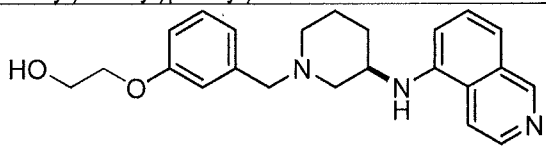
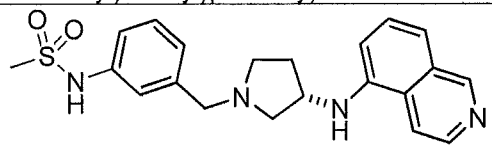
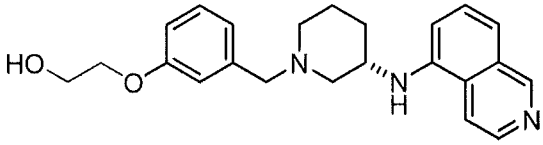
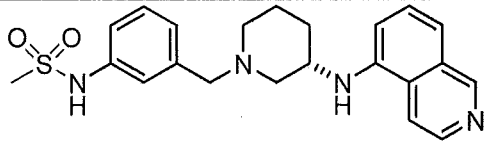
Compound	Structure	Embodiments
1.226	 (*R*)-*N*-(1-(4-methoxybenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.227	 (*S*)-*N*-(1-benzylpiperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10
1.228	 (*S*)-2-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethanol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.229	 (*S*)-*N*-(1-(4-vinylbenzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 11, 14c
1.230	 (*S*)-3-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propan-1-ol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.231	 (*R*)-3-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenoxy)propan-1-ol	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.232	 (*R*)-(4-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)methanol	1c, 7, 8, 9, 10
1.233	 (*S*)-*N*-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methylphenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d

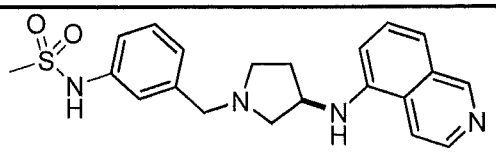
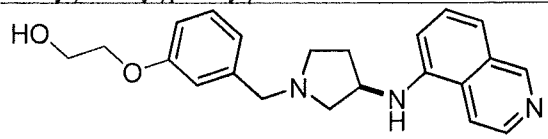
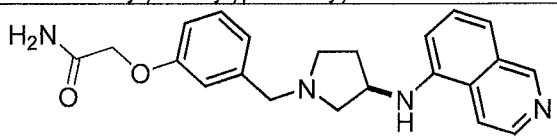
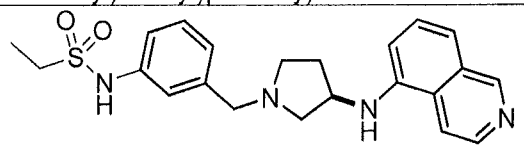
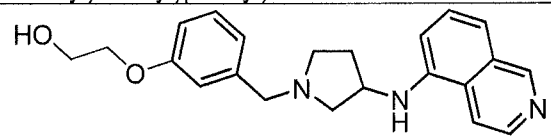
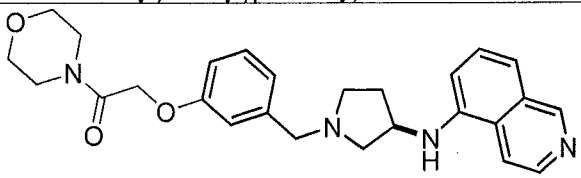
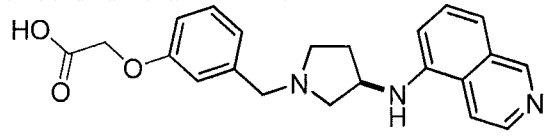
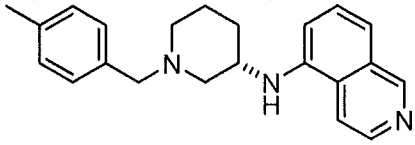
Compound	Structure	Embodiments
1.234	 (*S*)-*N*-(5-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)-2-methoxyphenyl)methanesulfonamide	1c, 7, 8, 9, 10, 12a, 15c, 15d
1.235	 (*R*)-*N*-(1-(3-(aminomethyl)benzyl)piperidin-3-yl)-1*H*-indazol-5-amine	1c, 7, 8, 9, 10, 13, 16c
2.001	 *N*-(1-(4-methoxybenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.002	 *N*-(1-(4-(methylsulfonyl)benzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12, 15c
2.003	 3-((3-(isoquinolin-5-ylamino)piperidin-1-yl)methyl)benzonitrile	2c, 7, 8, 9, 10, 12, 15c
2.004	 *N*-(4-((3-(isoquinolin-5-ylamino)piperidin-1-yl)methyl)phenyl)acetamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.005	 *N*-(1-(4-(methylsulfonyl)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12, 15c
2.006	 *N*-(1-benzylpyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10

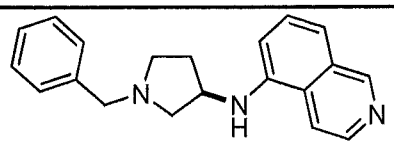
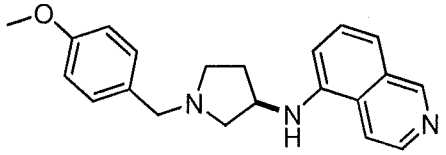
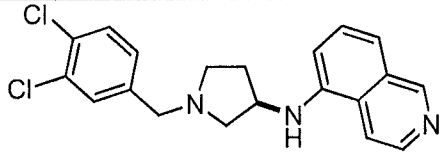
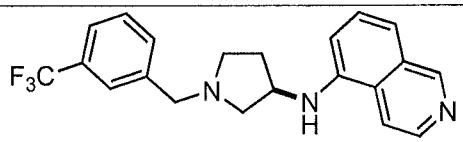
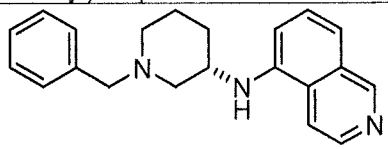
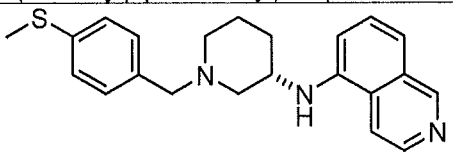
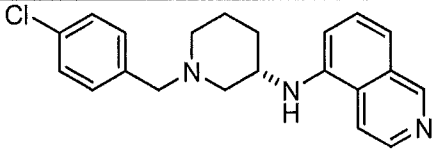
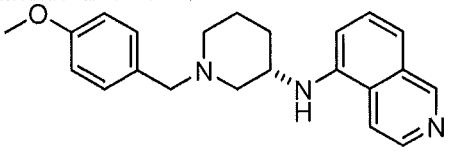
Compound	Structure	Embodiments
2.007	 3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)benzonitrile	2c, 7, 8, 9, 10, 12, 15c
2.008	 *N*-(4-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)acetamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.009	 *N*-(1-(4-(methylthio)benzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e
2.010	 *N*-(1-(4-cyclopropylbenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.011	 *N*-(1-(3-cyclopropylbenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.012	 *N*-(1-(4-(cyclopropylthio)benzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e
2.013	 *N*-(1-benzylazepan-4-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.014	 *N*-(1-(3,4-dichlorobenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10

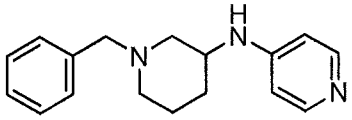
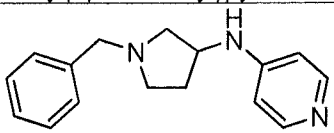
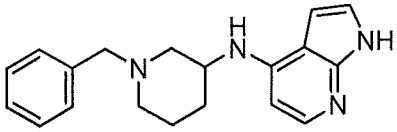
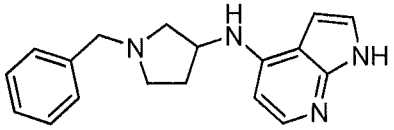
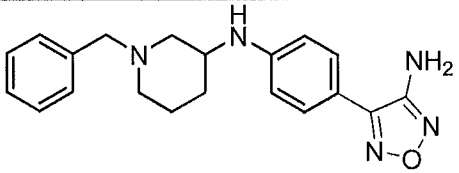
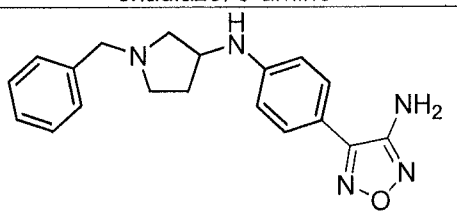
Compound	Structure	Embodiments
2.015	 *N*-(1-(3-(trifluoromethyl)benzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.016	 *N*-(1-(3,4-dichlorobenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.017	 *N*-(1-(4-methoxybenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.018	 *N*-(1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.019	 (*S*)-*N*-(1-(4-cyclopropylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.020	 (*R*)-*N*-(1-(3-cyclopropylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.021	 (*R*)-*N*-(1-(4-(cyclopropylthio)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e

Compound	Structure	Embodiments
2.022	 (*R*)-*N*-(1-(4-cyclopropylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.023	 (*S*)-*N*-(1-(3-cyclopropylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.024	 (*S*)-*N*-(1-(4-(cyclopropylthio)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e
2.025	 (*R*)-*N*-(1-(4-methylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.026	 (*R*)-*N*-(1-(4-(methylthio)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e
2.027	 (*R*)-*N*-(1-(4-chlorobenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.028	 (*S*)-*N*-(1-(4-methylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.029	 (*S*)-*N*-(1-(4-(methylthio)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e

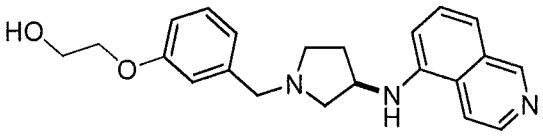
Compound	Structure	Embodiments
2.030	 (*S*)-*N*-(1-(4-chlorobenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.031	 (*R*)-*N*-(1-(4-ethynylbenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 11, 14c
2.032	 (*S*)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.033	 (*R*)-*N*-(3-((3-(isoquinolin-5-ylamino)piperidin-1-yl)methyl)phenyl)methanesulfonamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.034	 (*R*)-2-(3-((3-(isoquinolin-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethanol	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.035	 (*S*)-*N*-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)methanesulfonamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.036	 (*S*)-2-(3-((3-(isoquinolin-5-ylamino)piperidin-1-yl)methyl)phenoxy)ethanol	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.037	 (*S*)-*N*-(3-((3-(isoquinolin-5-ylamino)piperidin-1-yl)methyl)phenyl)methanesulfonamide	2c, 7, 8, 9, 10, 12a, 15c, 15d

Compound	Structure	Embodiments
2.038	 (*R*)-*N*-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)methanesulfonamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.039	 (*R*)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.040	 (*R*)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)acetamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.041	 (*R*)-*N*-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenyl)ethanesulfonamide	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.042	 2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.043	 (*R*)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)-1-morpholinoethanone	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.044	 (*R*)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)acetic acid	2c, 7, 8, 9, 10, 12a, 15c, 15d
2.045	 (*S*)-*N*-(1-(4-methylbenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10

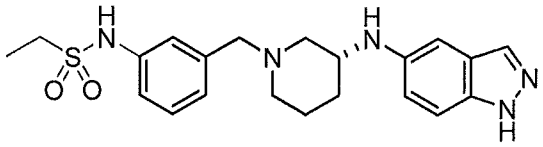
Compound	Structure	Embodiments
2.046	 (*R*)-*N*-(1-benzylpyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.047	 (*R*)-*N*-(1-(4-methoxybenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.048	 (*R*)-*N*-(1-(3,4-dichlorobenzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.049	 (*R*)-*N*-(1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.050	 (*S*)-*N*-(1-benzylpiperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.051	 (*S*)-*N*-(1-(4-(methylthio)benzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10, 12b, 15c, 15e
2.052	 (*S*)-*N*-(1-(4-chlorobenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10
2.053	 (*S*)-*N*-(1-(4-methoxybenzyl)piperidin-3-yl)isoquinolin-5-amine	2c, 7, 8, 9, 10

Compound	Structure	Embodiments
3.001	 *N*-(1-benzylpiperidin-3-yl)pyridin-4-amine	3c, 7, 8, 9, 10
3.002	 *N*-(1-benzylpyrrolidin-3-yl)pyridin-4-amine	3c, 7, 8, 9, 10
4.001	 *N*-(1-benzylpiperidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine	4c, 7, 8, 9, 10
4.002	 *N*-(1-benzylpyrrolidin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-4-amine	4c, 7, 8, 9, 10
5.001	 4-(4-(1-benzylpiperidin-3-ylamino)phenyl)-1,2,5-oxadiazol-3-amine	5a, 7, 8, 9, 10
5.002	 4-(4-(1-benzylpyrrolidin-3-ylamino)phenyl)-1,2,5-oxadiazol-3-amine	5a, 7, 8, 9, 10

Prefered ROCK inhibitor compounds of this invention include, but are not limited to the ROCK inhibitor compounds of embodiments 5, 14, 15, and 16 as described above, and and their associated salts, tautomers, solvates, or hydrates. Compound 2.039 and Compound 1.123 are particularly preferred.



(R)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol (Compound 2.039)



(*R*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl)ethanesulfonamide (Compound 1.123)

Pharmaceutical Formulation

This invention provides a formulation containing one or more agents that enhance the ophthalmic properties of ROCK inhibitor compounds formulated in an aqueous medium whose pH is adjusted to enhance ocular surface residence time and the bioavailability in the aqueous humor of the anterior chamber, and to reduce systemic exposure.

The invention provides an aqueous formulation of ROCK inhibitor compound(s) that is suitable for therapeutic use and remains stable under normal use storage conditions for an extended period of time. The formulation is useful on lowering intraocular pressure in mammals. For topical administration, one to two drops of these formulations are delivered to the surface of the eye one to four times per day.

The aqueous ophthalmic formulations of this invention have an increased residence time on the ocular surface and/or aqueous humor concentrations without a concomitant increase in systemic concentrations.

The present invention is directed to an aqueous pharmaceutical formulation comprising 0.001-2% ROCK inhibitor compound, 1-100 mM buffer suitable to maintain the pH about 6.3-7.8, 0.01-2 % surfactant, and a tonicity agent to maintain a tonicity about 220-360 mOsm/kG. "About" as used herein, refers to ±15%. Preferred pH is about 6.3-7.5, and more preferred pH is about 6.3-7.3,

The concentration of ROCK inhibitor compound in the aqueous formulation is in general 0.001-2%, preferably 0.01-0.5%, more preferably 0.01-0.4%, more preferably 0.03-0.2%, and more prefereably 0.03-0.15, or 0.03-0.1% (w/v).

Buffers suitable to maintain the pH between 6.3 and 7.8 include citrate, phosphate, maleate, or combination thereof. Suitable concentration of the buffer is 1-100mM, preferably 5-50mM, more preferably 5-25 mM, and most preferably 10-20mM.

Surfactants (surface active agents) or solubilizing agents suitable for the present invention are those acceptable for use in ophthalmic preparations. The surfactants can be ionic or non-ionic. Preferably, this surfactant is non-ionic. Useful surfactants include but are not limited to polysorbate 80, tyloxapol, polyoxyl stearates, polyethoxylated castor oils, poloxamers, polaxamines, medium and long chain fatty acids and phospholipids. The concentration of the surfactant in the formulation is about 0.01-3%, preferably 0.01-2%, more preferably 0.1-1% w/v.

The tonicity agent is present in an amount to achieve a final formulation tonicity between 220-360 mOsm/kG, preferably 250-340 mOsm/kG, and most preferably between 260 and 320. The tonicity agent can be non-ionic or ionic. Non-ionic tonicity agents include diols, such as glycerol, mannitol, erythritol; and sugars such as dextrose. Other non-ionic tonicity agents such as polyethylene glycol, propylene glycol, which also function as cosolvents, can also be used. The non-ionic tonicity agent is in general in an amount of 0-20 %, preferably 0-10%, more preferably 0-5%. Preferred non-ionic agents are glycerol, mannitol and dextrose, in an amount 2-6%.

The tonicity agent can also be ionic agents such as sodium chloride, potassium chloride, a balanced salt solution, sodium phosphate, or sodium citrate. The ionic tonicity agents can be present in an amount of 0.3-1.5%, preferably 0.6-0.9%.

The surfactants, the tonicity agent, the buffer and any other ingredients introduced into the formulation must have good solubility in water, and have compatibility with other components in the formulation. Health regulations in various countries require that multi-dose ophthalmic preparations shall include a preservative. Many well known preservatives that have been used in some other ophthalmic preparations cannot be used in the present invention, since those preservatives are not considered safe for repeated ocular use, or they interact with the surfactant employed herein to form a complex that reduces the bactericidal activity of the preservative. In one embodiment, benzalkonium chloride is employed as a safe preservative; benzalkonium chloride may be used with disodium edetate (EDTA), a chelating agent, to enhance its antimicrobial activity. Other suitable preservatives included benzyl alcohol, methyl parabens, propyl parabens, chlorobutanol, borate and benzethonium

chlorides. Typically, such preservatives are employed at a level of from 0.001-1%, preferably, 0.001-0.25%, and most preferably 0.001-0.2%.

Optionally, the formulation can include a viscosity enhancer to increase the resident time of the formulation on the ocular surface. The viscosity enhancer must not cause ocular discomfort. Hydroxypropyl methyl cellulose, for example, is an acceptable viscosity enhancer for the present invention.

In one embodiment, the pharmaceutical formulation comprises 0.5-0.9 % ionic tonicity modifier such as sodium chloride; the formulation contains additional buffering agents (such as sodium phosphates) at 5-100mM, a surfactant within a range of 0.01-3%, a preservative in a range of 0.001 – 0.1%, a chelating agent in a range of 0.01 – 0.5% w/v, and pH adjusters. Such an aqueous composition has a tonicity of 220-360 mOsm/kG and is formulated at pH 6.3 – 7.8.

In another embodiment, the pharmaceutical formulation comprises 1-3 % non-ionic tonicity agent such as glycerol; the formulation contains buffering agents (such as sodium phosphates and/or sodium citrate and citric acid) within a range of 5-50 mM, a surfactant within a range of 0.01-2%, a chelating agent in a range of 0.005-0.5% w/v, and pH adjusters. Such an aqueous composition has a tonicity of 220-360 mOsm/kG and is formulated at pH 6.3-7.8. The formulation optionally contains a preservative in a range of 0.001-0.1% w/v.

The present invention is also directed to an aqueous pharmaceutical formulation comprising 0.001-2% ROCK inhibitor compound, 0.02-0.25% polaxamer, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG. The formulation optionally comprises 1-100 mM buffer to maintain the pH between 6.3-7.8. Suitable buffers include phosphate, citrate, maleate, or a combination thereof. Phosphate buffer is preferred.

In one embodiment, the pharmaceutical formulation of the present invention is administered topically to the eye in the form of ophthalmic drops. The pharmaceutical formulations of the present invention are made by aseptic technique or are terminally sterilized. The solutions of the invention are prepared by thoroughly mixing the ROCK inhibitor compound, buffer, tonicity modifier, surfactant, chelating agent; optionally, non-ionic polymers, complexing agents, solubilizing agents, preservatives and antioxidant agent.

A discovery towards this invention relates to the aqueous solubility and formulation stability in relation to pH. Inventors have unexpectedly found that a more soluble and stable formulation is at the lower pH range of acceptable topical ophaltimc formulations (pH 4.5), rather than the higher pH range. The stability and solubility of the formulation decrease with

increasing pH. However, at pH 6.3-7.8, the stability and solubility of the pharmaceutical formulation of the present invention is acceptable. Thus, the current formulation has improved therapeutic properties with acceptable aqueous solubility and long term stability. At pH higher than 7.8, the stability of the compounds is not acceptable and the ocular tolerability decreases.

The pharmaceutical formulation can be sterilized by filtering the formulation through a sterilizing grade filter, preferably of a 0.22 micron nominal pore size. The pharmaceutical formulation can also be sterilized by terminal sterilization using one or more sterilization techniques, including but not limited to a thermal process, such as an autoclaving process.

The pharmaceutical formulations of the present invention are useful as agents for modulation of wound healing after trabeculectomy. The pharmaceutical formulations in general are less toxic to corneal endothelial cells than the antimetabolites such as 5-fluorouracil or mitomycin C. The pharmaceutical formulations inhibit actomyosin-driven contractility, leading to deterioration of the actin microfilament system and perturbation of its membrane anchorage, which weakens the cell-extracellular matrix adhesions. These properties inhibit wound healing and thereby reduce bleb failure following the surgery.

The pharmaceutical formulation of the present invention is useful as agents for lowering intraocular pressure, and is thus useful in the treatment or prevention of glaucoma or associated ophthalmic conditions.

The pharmaceutical formulation of the present invention is useful in the treatment or prevention of neurodegenerative diseases as a consequence of increased intraocular pressure and damage to the ocular neurons.

The present invention provides a method of reducing intraocular pressure, a method of treating glaucoma, and a method of inhibiting wound healing after trabeculectomy. The method comprises the step of administering to a subject in need of treatment the pharmaceutical formulation of the present invention, in an amount effective to alter the actin cytoskeleton, such as by inhibiting actin polymerization.

The pharmaceutical formulation disclosed herein can be administered to the eyes of a patient by any suitable means, but are preferably administered in the form of drops, spray or gel-forming aqueous solution. Alternatively, the pharmaceutical formulation can be applied to the eye via aqueous formulations of liposomes, micelles, emulsions, and/or microemulsions. Further, the pharmaceutical formulation can be infused onto the tear film via a pump catheter system. In another embodiment, the pharmaceutical formulation is

contained within a continuous or selective release device, for example, membranes such as, but not limited to, those employed in the Ocusert® System (Alza Corp., Palo Alto, CA) or Retisert (Bausch & Lomb, Rochester, NY). As an additional embodiment, the pharmaceutical formulation can be contained within, carried by, or attached to contact lenses that are placed on the eye. Another embodiment of the present invention involves the pharmaceutical formulation contained within a swab or sponge that can be applied to the ocular surface. Another embodiment of the present invention involves the pharmaceutical formulation contained within a liquid spray that can be applied to the ocular surface. Another embodiment of the present invention involves an injection of the pharmaceutical formulation directly into the lacrimal tissues or onto the eye surface.

The invention is illustrated further by the following examples that are not to be construed as limiting the invention in scope to the specific procedures described in them. It is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments therefore are to be construed as merely illustrative, and not limiting the disclosure in any way whatsoever.

The invention is illustrated further by the following examples that are not to be construed as limiting the invention in scope to the specific procedures described in them.

EXAMPLES

Example 1: Impact of pH on Solubility of Compounds

Solubility was determined within a target pH range of 4.0-9.0 using a buffered cosolvent system (plON pSOL Evolution). The results in Table 1 show that Compound 2.039 (A) had solubility > 20 mg/mL at pH 4-5.8, Compound 1.123 (B) had maximum solubility of 5 mg/mL at pH 5.6. These results indicate that as the pH increases, the solubility of the compounds decreases.

Table 1. Impact of pH on Solubility of Compound A and B.

Compound	pH	Avg. Sol (μg/mL)
A	4.0	>20000
	5.8	>20000
	7.7	2312
B	5.6	5001
	7.2	948
	8.5	282

Another study was performed in which Compound A was prepared in a vehicle which contained a tonicity agent (NaCl) and a non-ionic surfactant, to determine the solubility of the compound at a target pH of 7.3. Concentrations of the surfactant used were at the maximum allowable concentration for excipients Generally Regarded As Safe (GRAS). A 20mM concentration of the compound was prepared in 0.85% NaCl, then filtered and analyzed by UV to determine the concentration of Compound A. The results show that formulations containing polysorbate 80 and poloxamer 407 gave the highest solubility of Compound A. Therefore, polysorbate 80 and poloxamer 407 can counteract some of the loss of solubility at neutral pH about 7.3.

Table 2. List of Surfactants and Resulting Compound A Concentrations

Excipient (surfactant or chelating agent)	Concentration of Surfactant	pH of Solution	Concentration (mg/mL) Compound A
EDTA	0.3%	7.39	1.38
Poloxamer 407	0.16%	7.28	6.02
Polysorbate 80	1%	7.49	3.85
Poloxamer 188	0.1%	7.30	1.49
HCO-40 (hydrogenated castor oil)	0.5%	7.39	2.54

Example 2: Stability of Compound A (Accelerated)

Compound A was formulated in a 0.9% saline solution containing 0.1% EDTA, 0.01% Benzalkonium Chloride and 0.8% Polysorbate 80 at three levels of pH; 5.3, 6.3 and 7.3. In order to determine the effects of pH on the stability of the compound, the solutions were stored at 60°C and analyzed by HPLC using UV detection. Figure 1 shows that an increase in pH from pH 5.3 to pH 6.3 and 7.3 caused a decrease in stability of Compound A due to chemical degradation.

Example 3: Effect of pH on ocular surface, aqueous humor and systemic bioavailability

Dose Formulation and Administration. Compound A was formulated at 0.12 % w/v (the equivalent millimolar concentration is 3 mM) in 10mM phosphate, 0.8 % polysorbate 80, 0.85% NaCl, 0.01% BAC, 0.1% EDTA at three different pH's, 5.3, 6.3 and 7.3. Compound A was administered as a 30µl drop to both eyes of each animal within a dosing group and the influence of pH on ocular and systemic exposure was examined.

S*tudy sampling.* Plasma, aqueous humor, and ocular samples were obtained from 2 animals (4 eyes) per dosing group at times of 0.25, 0.5, 1, and 2 hours post dosing.

Figure 2A shows the aqueous humor Cmax vs. pH. Figure 2B shows the aqueous humor AUC vs. pH. Aqueous humor is the fluid within the anterior chamber of the eye and has the closest correlation to the concentration at the site of action, the trabecular meshwork. Cmax indicates the peak concentration of drug found within aqueous humor. AUC indicates total concentration of the drug within the aqueous humor over time. The results of figures 2A and 2B indicate that increasing pH in the formulation enhances the exposure within the aqueous humor.

Figure 3A shows the plasma humor Cmax vs. pH. Figure 3B shows the plasma AUC vs. pH. Plasma concentration analysis indicates systemic exposure. Systemic exposure is the exposure of the drug to the entire body. Cmax and AUC describe the peak concentration and total concentration of the drug over time, respectively, for Compound A in plasma. The results of figures 3A and 3B indicate that increasing pH of the formulation has no effect on the plasma concentration of the compounds.

Figure 4 shows the ocular surface concentration of Compound A over time. 40μL of saline was applied to the eyes at 0.25h, 0.5h, 1h, and 2 h after administration of Compound A, and the lavage fluids were collected as samples. Ocular surface relates to the surface of the cornea and conjunctiva. Ocular surface residence time is the average time Compound A resides on the ocular surface. Figure 4 shows an increase in residence time when the pH of the Compound A formulation was increased from 5.3, 6.3 to 7.3. At 0.25 h, the ocular concentration of Compound A increased only slightly between pH 5.3 and 6.3, with no change from 6.3 to 7.3. The later time points had a greater separation in the ocular concentration of Compound A between pH 5.3-7.3. The ocular concentration of Compound A remained consistent between 1 and 2 hours for pH 7.3. This data indicates higher pH increased residence time over the 2 hour period, thus allowing more drugs to penetrate into the anterior chamber.

These studies demonstrate that when pH of the formulation increases, ROCK-inhibiting compounds exhibit an increase in residence time on the ocular surface and exhibit

an increase in concentration within the aqueous humor of the anterior chamber, while exhibit no effect on systemic exposure.

Example 4: Effect of Concentration and Formulation on Ocular Comfort

Dose Formulation and Administration. Compound 2.039 was formulated at 0.16 % w/v in four different formulations A-D as follows.

Formulation A: 10mM phosphate, 1 % polysorbate 80, 0.85% NaCl, 0.02% BAC, 0.2% EDTA pH 7.0.

Formulation B: 10mM phosphate, 1% polysorbate 80, 2.36% Glycerol, 0.02% BAC, 0.2% EDTA pH 7.1.

Formulation C: 10mM phosphate, 1% polysorbate 80, 2.36% Glycerol, 0.02% BAC, 0.2% EDTA, 0.5% hydroxypropyl methyl cellulose, pH 7.1.

Formulation D: 10mM phosphate, 1% polysorbate 80, 2.36% Glycerol, 0.02% BAC, 0.2% EDTA, 1% 1,2 dimyristoyl-sn-glycero-3-phosphocholine, pH 7.1.

Pharmacodynamic Analysis. Formulations A-D were administered as two 30µl drops to the right eye of each rabbit within a dosing group. The rabbits were evaluated for 15 minutes after ocular instillation and their changes in behavior were recorded. A composite score for each rabbit within each treatment group was created based upon the number of times they demonstrated a unilateral blink, bilateral blink, front pay wipe of the face, scratch and head shake. The higher the score, the more discomfort an animal is. A mean ± SE was generated for each group.

Figure 5 shows ocular comfort scores vs. formulations. Figure 5 shows that the addition of certain adjuvant such as 1,2 dimyristoyl-sn-glycero-3-phosphocholine, which is a viscosity enhancer and increased ocular surface residence, increased ocular discomfort.

Compound 2.039 was then formulated at 0.03%, 0.1% and 0.32% w/v in formulation A above and the effect of concentration on ocular surface comfort was examined in comparison to other approved glaucoma medications. The results are shown in Figure 6.

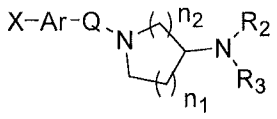
Figure 6 shows ocular comfort scores vs. concentrations of Compound A. Figure 6 indicates that increasing concentrations of a ROCK-inhibiting compound increased ocular discomfort. However, the ocular comfort at the lower concentrations (0.03 and 0.1% w/v) is

comparable to those of the approved glaucoma medications such as ALPHAGAN®, RESTASIS®, pilocarpine, and LUMIGAN®.

WHAT IS CLAIMED:

1. An aqueous pharmaceutical formulation comprising at least one ROCK inhibitor having Formula II in an amount of 0.01-0.4% w/v, a non-ionic surfactant in an amount of 0.01-2% w/v, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG, at a pH between 6.3 to 7.8, wherein the ROCK inhibitor, the surfactant, and the tonicity agent are compatible in the formulation;

Formula II



wherein:

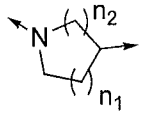
Q is C=O, SO_2, or $(CR_4R_5)_{n3}$;

n_1 is 1, 2, or 3;

n_2 is 1or 2;

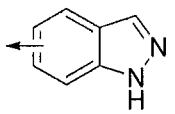
n_3 is 0, 1, 2, or 3;

wherein the ring represented by

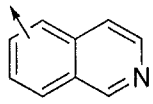


is optionally substituted by alkyl, halo, oxo, OR_6, NR_6R_7, or SR_6;

R_2 is R_2-1or R_2-2, optionally substituted:



R_2 - 1



R_2 - 2

Ar is a monocyclic or bicyclic aryl or heteroaryl ring;

X is from 1 to 3 substituents on Ar, and each is independently selected from the group consisting of OR_8, NR_8R_9, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, and $NR_8C(=O)NR_9R_{10}$,

R_3-R_7 are independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, or cycloalkylalkynyl, optionally substituted;

R_8 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl,

(heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of OR_{11}, $NR_{11}R_{12}$, NO_2, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $NR_{11}SO_2R_{12}$, OCF_3, $CONR_{11}R_{12}$, $NR_{11}C(=O)R_{12}$, $NR_{11}C(=O)OR_{12}$, $OC(=O)NR_{11}R_{12}$, and $NR_{11}C(=O)NR_{12}R_{13}$;

R_9 and R_{10} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of OR_{14}, $NR_{14}R_{15}$, NO_2, SR_{14}, SOR_{14}, SO_2R_{14}, $SO_2NR_{14}R_{15}$, $NR_{14}SO_2R_{15}$, OCF_3, $CONR_{14}R_{15}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $OC(=O)NR_{14}R_{15}$, and $NR_{14}C(=O)NR_{15}R_{16}$;

wherein any two of the groups R_8, R_9 and R_{10} are optionally joined with a link selected from the group consisting of bond, -O-, -S-, -SO-, $-SO_2-$, and $-NR_{17}-$ to form a ring;

R_{11}-R_{17} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle;

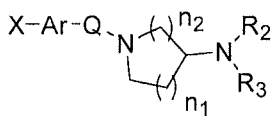
with the first proviso that if X is acyclic and is connected to Ar by a carbon atom, then X contains at least one nitrogen or sulfur atom,

with the second proviso that if X is acyclic and is connected to Ar by an oxygen or nitrogen atom, then X contains at least one additional oxygen, nitrogen or sulfur atom, and

with the third proviso that if X is connected to Ar by a $-SO_2-$ linkage, then R_2 is not nitrogen- or oxygen-substituted R_2-2.

2. An aqueous pharmaceutical formulation comprising at least one ROCK inhibitor having Formula II in an amount of 0.01-0.4% w/v, a non-ionic surfactant in an amount of 0.01-2% w/v, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG, at a pH between 6.3 to 7.8, wherein the ROCK inhibitor, the surfactant, and the tonicity agent are compatible in the formulation;

Formula II



wherein:

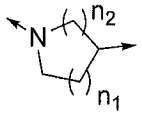
Q is C=O, SO_2, or $(CR_4R_5)_{n3}$;

n_1 is 1, 2, or 3;

n_2 is 1or 2;

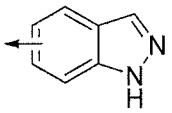
n_3 is 0, 1, 2, or 3;

wherein the ring represented by

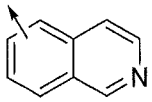


is optionally substituted by alkyl, halo, oxo, OR_6, NR_6R_7, or SR_6;

R_2 is R_2-1or R_2-2, optionally substituted:



R_2 - 1



R_2 - 2

Ar is a monocyclic or bicyclic aryl or heteroaryl ring;

X is from 1 to 3 substituents on Ar, each independently in the form Y-Z, in which Z is attached to Ar;

Y is one or more substituents on Z, and each is independently selected from the group consisting of H, halogen, OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, and $NR_8C(=O)NR_9R_{10}$;

Z is alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, and (heterocycle)alkynyl;

R_3-R_7 are independently H, alkyl, alkenyl, alkynyl,cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, or cycloalkylalkynyl, optionally substituted;

R_8 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of

OR_{11}, $NR_{11}R_{12}$, NO_2, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $NR_{11}SO_2R_{12}$, OCF_3, $CONR_{11}R_{12}$, $NR_{11}C(=O)R_{12}$, $NR_{11}C(=O)OR_{12}$, $OC(=O)NR_{11}R_{12}$, and $NR_{11}C(=O)NR_{12}R_{13}$;

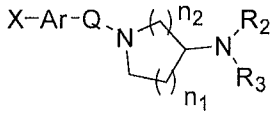
R_9 and R_{10} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of OR_{14}, $NR_{14}R_{15}$, NO_2, SR_{14}, SOR_{14}, SO_2R_{14}, $SO_2NR_{14}R_{15}$, $NR_{14}SO_2R_{15}$, OCF_3, $CONR_{14}R_{15}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $OC(=O)NR_{14}R_{15}$, and $NR_{14}C(=O)NR_{15}R_{16}$;

wherein any two of the groups R_8, R_9 and R_{10} are optionally joined with a link selected from the group consisting of bond, -O-, -S-, -SO-, $-SO_2-$, and $-NR_{17}-$ to form a ring; and

R_{11}-R_{17} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle.

3. An aqueous pharmaceutical formulation comprising at least one ROCK inhibitor having Formula II in an amount of 0.01-0.4% w/v, a non-ionic surfactant in an amount of 0.01-2% w/v, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG, at a pH between 6.3 to 7.8, wherein the ROCK inhibitor, the surfactant, and the tonicity agent are compatible in the formulation;

Formula II



wherein:

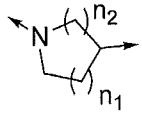
Q is C=O, SO_2, or $(CR_4R_5)_{n3}$;

n_1 is 1, 2, or 3;

n_2 is 1or 2;

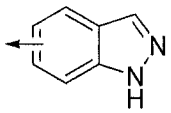
n_3 is 0, 1, 2, or 3;

wherein the ring represented by

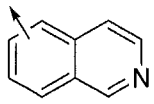


is optionally substituted by alkyl, halo, oxo, OR_6, NR_6R_7, or SR_6;

R_2 is R_2-1or R_2-2, optionally substituted:



R_2 - 1



R_2 - 2

Ar is a monocyclic or bicyclic aryl or heteroaryl ring;

X is from 1 to 3 substituents on Ar, each independently in the form Y-Z, in which Z is attached to Ar;

Y is one or more substituents on Z, and each is independently OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, or $NR_8C(=O)NR_9R_{10}$,

Z is alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, or (heterocycle)alkynyl;

R_3-R_7 are independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, or cycloalkylalkynyl, optionally substituted;

R_8 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of OR_{11}, $NR_{11}R_{12}$, NO_2, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $NR_{11}SO_2R_{12}$, OCF_3, $CONR_{11}R_{12}$, $NR_{11}C(=O)R_{12}$, $NR_{11}C(=O)OR_{12}$, $OC(=O)NR_{11}R_{12}$, and $NR_{11}C(=O)NR_{12}R_{13}$;

R_9 and R_{10} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of

OR_{14}, $NR_{14}R_{15}$, NO_2, SR_{14}, SOR_{14}, SO_2R_{14}, $SO_2NR_{14}R_{15}$, $NR_{14}SO_2R_{15}$, OCF_3, $CONR_{14}R_{15}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $OC(=O)NR_{14}R_{15}$, or $NR_{14}C(=O)NR_{15}R_{16}$;

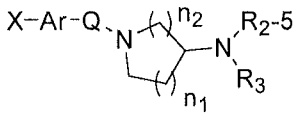
wherein any two of the groups R_8, R_9 and R_{10} are optionally joined with a link selected from the group consisting of bond, -O-, -S-, -SO-, $-SO_2-$, and $-NR_{17}-$ to form a ring; and

R_{11}-R_{17} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle;

with the proviso that when Z is selected from the group consisting of alkyl, alkenyl, and alkynyl, and Y falls on the carbon by which Z is attached to Ar, then Y contains at least one nitrogen or sulfur atom.

4. An aqueous pharmaceutical formulation comprising at least one ROCK inhibitor having Formula II in an amount of 0.01-0.4% w/v, a non-ionic surfactant in an amount of 0.01-2% w/v, and a tonicity agent to maintain a tonicity between 220-360 mOsm/kG, at a pH between 6.3 to 7.8, wherein the ROCK inhibitor, the surfactant, and the tonicity agent are compatible in the formulation;

Formula II



wherein:

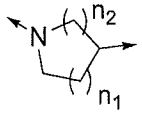
Q is C=O, SO_2, or $(CR_4R_5)_{n3}$;

n_1 is 1, 2, or 3;

n_2 is 1or 2;

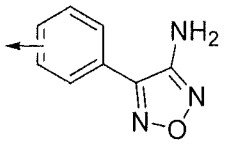
n_3 is 0, 1, 2, or 3;

wherein the ring represented by



is optionally substituted by alkyl, halo, oxo, OR_6, NR_6R_7, or SR_6;

R_2-5 is



R_2 - 5 , optionally substituted;

Ar is a monocyclic or bicyclic aryl or heteroaryl ring;

X is from 1 to 3 substituents on Ar, each independently in the form Y-Z, in which Z is attached to Ar;

Y is one or more substituents on Z, and each is independently selected from the group consisting of H, halogen, OR_8, NR_8R_9, NO_2, SR_8, SOR_8, SO_2R_8, $SO_2NR_8R_9$, $NR_8SO_2R_9$, OCF_3, $CONR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)NR_8R_9$, and $NR_8C(=O)NR_9R_{10}$;

Z is independently selected from the group consisting of absent, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heterocycle, (heterocycle)alkyl, (heterocycle)alkenyl, and (heterocycle)alkynyl;

R_3-R_7 are independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, or cycloalkylalkynyl, optionally substituted;

R_8 is H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of OR_{11}, $NR_{11}R_{12}$, NO_2, SR_{11}, SOR_{11}, SO_2R_{11}, $SO_2NR_{11}R_{12}$, $NR_{11}SO_2R_{12}$, OCF_3, $CONR_{11}R_{12}$, $NR_{11}C(=O)R_{12}$, $NR_{11}C(=O)OR_{12}$, $OC(=O)NR_{11}R_{12}$, and $NR_{11}C(=O)NR_{12}R_{13}$;

R_9 and R_{10} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle; optionally substituted by one or more halogen or heteroatom-containing substituents selected from the group consisting of OR_{14}, $NR_{14}R_{15}$, NO_2, SR_{14}, SOR_{14}, SO_2R_{14}, $SO_2NR_{14}R_{15}$, $NR_{14}SO_2R_{15}$, OCF_3, $CONR_{14}R_{15}$, $NR_{14}C(=O)R_{15}$, $NR_{14}C(=O)OR_{15}$, $OC(=O)NR_{14}R_{15}$, and $NR_{14}C(=O)NR_{15}R_{16}$;

wherein any two of the groups R_8, R_9 and R_{10} are optionally joined with a link selected from the group consisting of bond, -O-, -S-, -SO-, $-SO_2-$, and $-NR_{17}-$ to form a ring; and R_{11}-R_{17} are independently H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroaryl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, (heterocycle)alkyl, (heterocycle)alkenyl, (heterocycle)alkynyl, or heterocycle.

5. The aqueous pharmaceutical formulation according to any one of Claims 1-4, wherein said non-ionic surfactant is selected from the group consisting of: polysorbates, tyloxapol, polyoxyl castor oil, polaxamers, polyethylene glycol, caprylic triglyceride, polyoxyl stearates, glyceryl monostearate, and combination thereof.

6. The aqueous pharmaceutical formulation according to Claim 5, wherein said non-ionic surfactant is a polysorbate, a polaxamer, or a combination thereof.

7. The aqueous pharmaceutical formulation according to any one of Claims 1-4, further comprising 1-100 mM buffer suitable to maintain the pH between 6.3-7.8.

8. The aqueous pharmaceutical formulation according to Claim 7, wherein said buffer is citrate buffer, phosphate buffer, maleate buffer, or combination thereof.

9. The aqueous pharmaceutical formulation according to any one of Claims 1-4, further comprising a chelating agent and/or a preservative.

10. The aqueous pharmaceutical formulation according to any one of Claims 1-4, wherein said tonicity agent is a non-ionic tonicity agent.

11. The aqueous pharmaceutical formulation according to Claim 10, wherein said non-ionic tonicity agent is glycerol, mannitol or dextrose.

12. The aqueous pharmaceutical formulation according to any one of Claims 1-4, wherein said tonicity agent is an ionic tonicity agent.

13. The aqueous pharmaceutical formulation according to Claim 1, wherein said ROCK inhibitor is (R)-2-(3-((3-(isoquinolin-5-ylamino)pyrrolidin-1-yl)methyl)phenoxy)ethanol.

14. The aqueous pharmaceutical formulation according to Claim 1, wherein said ROCK inhibitor is (*R*)-*N*-(3-((3-(1*H*-indazol-5-ylamino)piperidin-1-yl)methyl)phenyl) ethane-sulfonamide.

15. The aqueous pharmaceutical formulation according to any one of Claims 1-4, wherein said ROCK inhibitor is in an amount of 0.03-0.2% (w/v).

16. The aqueous pharmaceutical formulation according to any one of Claims 1-4, wherein said pH is 6.3-7.3.

17. A method for reducing intraocular pressure in a subject in need thereof, comprising the steps of:

identifying a subject in need thereof, and

administering to the subject the aqueous pharmaceutical formulation according to anyone of Claims 1-4, in an amount effective to inhibit actomyosin interactions.

18. The method according to Claim 17, wherein said method treats glaucoma.

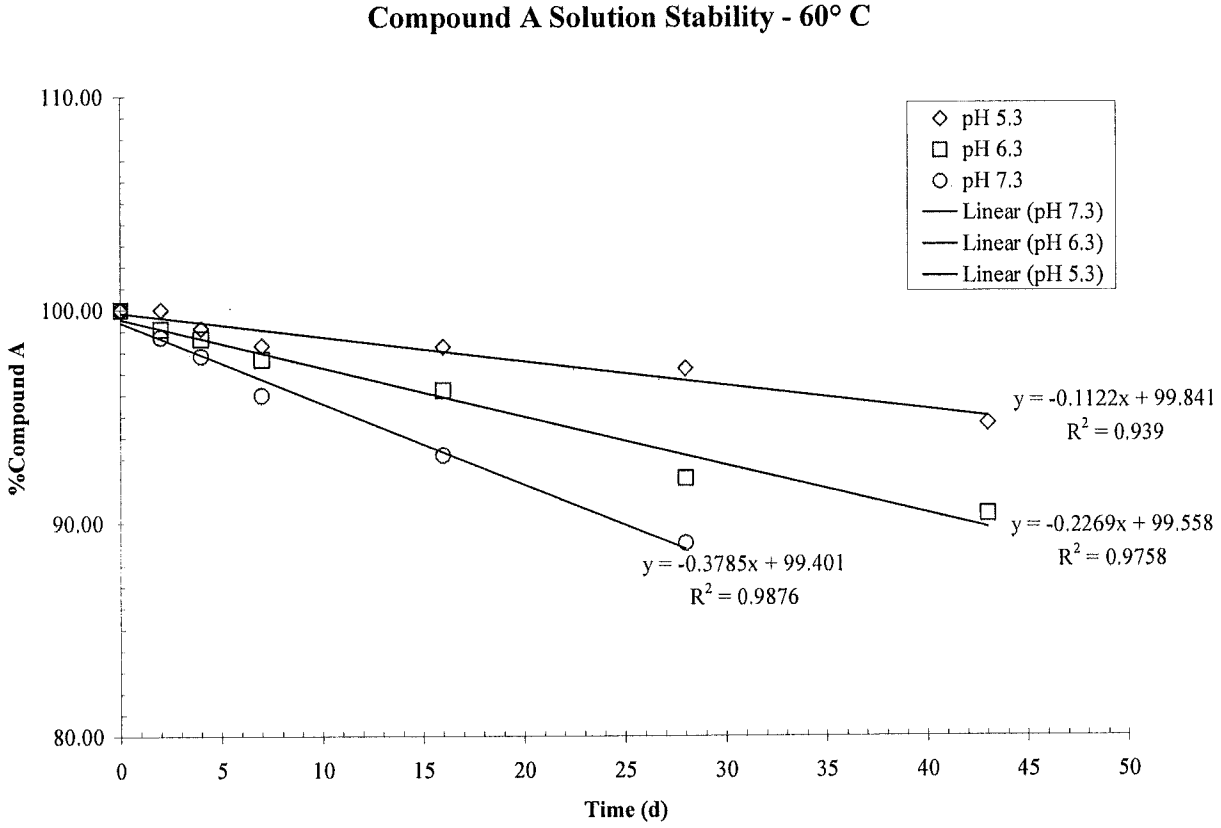

Compound A Solution Stability - 60° C
110.00
100.00
90.00
80.00
%Compound A
0
5
10
15
20
25
30
35
40
45
50
Time (d)
pH 5.3
pH 6.3
pH 7.3
Linear (pH 7.3)
Linear (pH 6.3)
Linear (pH 5.3)
y = -0.1122x + 99.841
R2 = 0.939
y = -0.2269x + 99.558
R2 = 0.9758
y = -0.3785x + 99.401
R2 = 0.9876

FIGURE 1

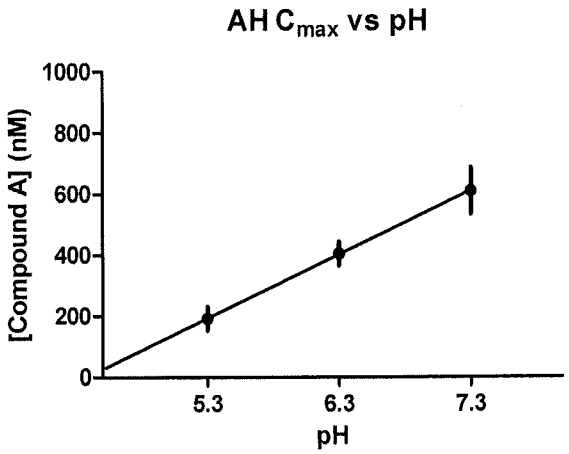


FIGURE 2A

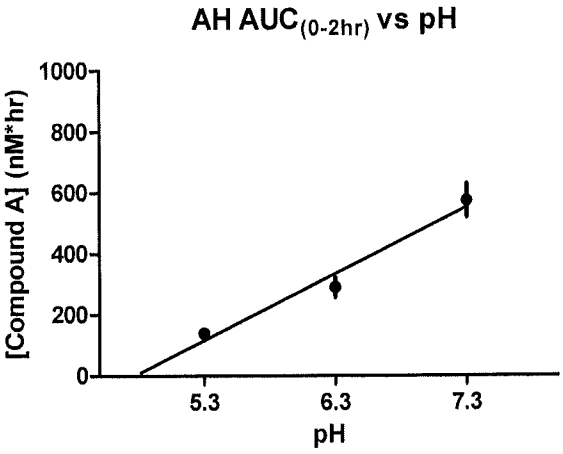


FIGURE 2B

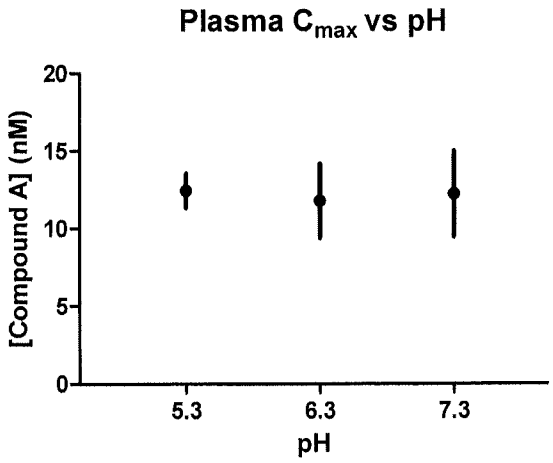


FIGURE 3A

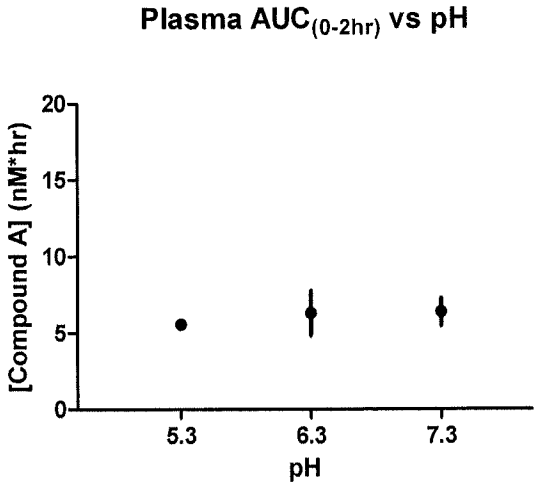


FIGURE 3B

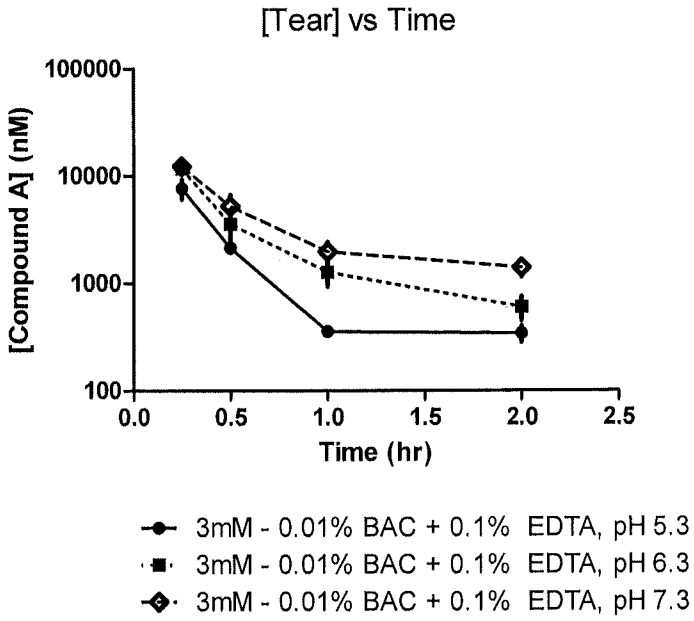

[Tear] vs Time
[Compound A] (nM)
100000
10000
1000
100
0.0
0.5
1.0
1.5
2.0
2.5
Time (hr)
3mM - 0.01% BAC + 0.1% EDTA, pH 5.3
3mM - 0.01% BAC + 0.1% EDTA, pH 6.3
3mM - 0.01% BAC + 0.1% EDTA, pH 7.3

FIGURE 4

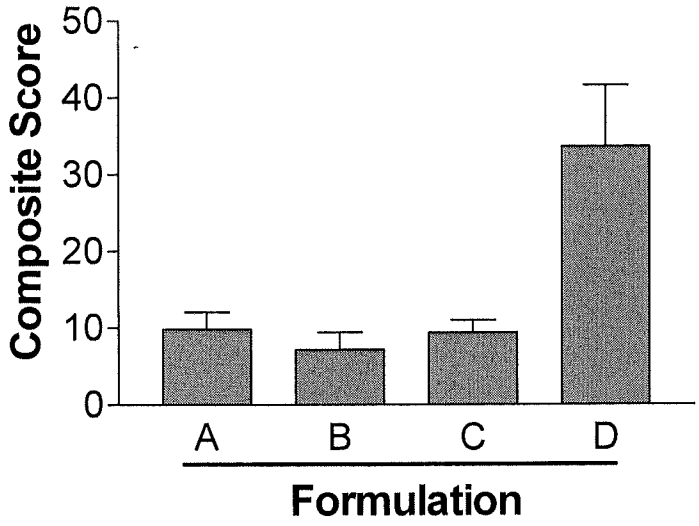


FIGURE 5

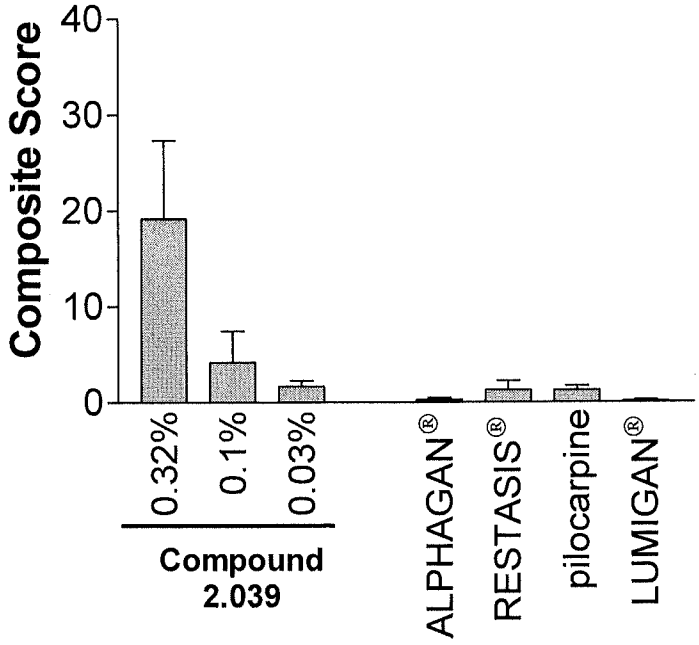


FIGURE 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/47108

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40 (2009.01)
USPC - 514/322
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/322

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/322,403;546/199;548/361.1

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB); Google Scholar
Search terms: RHO, ROCK, pyrrolidin, piperidin, sulfonamide, indazol, isoquinolin, glaucoma, buffer, chelating, noticity, mannitol, glycerol, surfactant, ionic, non-ionic, buffer, phospate, maleate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	US 2006/0167043 A1 (IWAKUBO et al) 27 July 2006 (27.07.2006); entire document, especially para [0019]	1-3,5,7-12,15-18 ---------- 4,6,13,14
Y	US 2005/0272851 A1 (MCKERRACHER et al) 08 December 2005 (08.12.2005); entire document, especially para [0082]	4, 13, 14
Y	US 2007/0129404 A1 (HAGIHARA et al) 07 June 2007 (07.06.2007); entire document, especially para [0024]	6

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2009 (23.07.2009)	31 JUL 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)