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(54) Title: THIENYL CYCLOPROPYL-AMINO-ISOQUINOLINYL AMIDE COMPOUNDS

(57) Abstract: Provided herein are thienyl cyclopropyl-amino-isoquinoline amide compounds. In particular, provided herein are compounds that affect the function of kinases in a cell and that are useful as therapeutic agents or with therapeutic agents. The compounds provided herein are useful in the treatment of a variety of diseases and conditions including eye diseases such as glaucoma, cardiovascular diseases, diseases characterized by abnormal growth, such as cancers, and inflammatory diseases. Also provided herein are compositions comprising thienyl cyclopropyl-amino-isoquinoline amide compounds.

THIENYL CYCLOPROPYL-AMINO-ISOQUINOLINYL AMIDE COMPOUNDS

RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Patent Application No. 62/810,783, filed February 26, 2019, the entire content of which is herein incorporated by reference.

SEQUENCE LISTING

[0002] This application contains a sequence listing having the filename 1959002-00199_PCT_ST25.txt, which is 666 bytes in size, and was created on February 24, 2020. The entire content of this sequence listing is herein incorporated by reference.

FIELD OF THE INVENTION

[0003] The present disclosure relates to amino isoquinolinyl amide compounds that affect the function of kinases and other proteins in a cell and that are useful as therapeutic agents or with therapeutic agents. In particular, these compounds are useful in the treatment of eye diseases such as glaucoma and retinal diseases, as anti-inflammatory agents, for the treatment of cardiovascular diseases, and for diseases characterized by abnormal growth, such as cancers.

BACKGROUND

[0004] A variety of hormones, neurotransmitters and biologically active substances control, regulate or adjust the functions of living bodies *via* specific receptors located in cell membranes. Many of these receptors mediate the transmission of intracellular signals by activating guanine nucleotide-binding proteins (G proteins) to which the receptor is coupled. Such receptors are generically referred to as G-protein coupled receptors (GPCRs) and include, among others, α-adrenergic receptors, β-adrenergic receptors, opioid receptors, cannabinoid receptors and prostaglandin receptors. The biological effects of activating or inhibiting these receptors is not direct, but is mediated by a host of intracellular proteins. The importance of these secondary proteins has been recognized and modulation of this class is now being investigated as intervention points in disease states. One of the most important classes of these downstream effectors is the "kinase" class.

[0005] The various kinases play important roles in the regulation of various physiological functions. For example, kinases have been implicated in a number of disease states, including, but not limited to: cardiac indications such as angina pectoris, essential hypertension, myocardial infarction, supraventricular and ventricular arrhythmias, congestive heart failure, atherosclerosis, renal failure, diabetes, respiratory indications such as asthma, chronic bronchitis, bronchospasm, emphysema, airway obstruction, upper respiratory indications such as rhinitis, seasonal allergies, inflammatory disease, inflammation in response to injury, rheumatoid arthritis. The importance of p38 MAPK inhibitors in particular as new drugs for rheumatoid arthritis is reflected by the large number of compounds that has been developed over the last years (*J. Westra and P.C. Limburg* Mini-Reviews in Medicinal Chemistry Volume 6,

Number 8, August 2006). Other conditions include chronic inflammatory bowel disease, glaucoma, hypergastrinemia, gastrointestinal indications such as acid/peptic disorder, erosive esophagitis, gastrointestinal hypersecretion, mastocytosis, gastrointestinal reflux, peptic ulcer, Zollinger-Ellison syndrome, pain, obesity, bulimia nervosa, depression, obsessive-compulsive disorder, organ malformations (*e.g.*, cardiac malformations), neurodegenerative diseases such as Parkinson's Disease and Alzheimer's Disease, multiple sclerosis, Epstein-Barr infection and cancer (*Nature Reviews Drug Discovery* 2002, 1: 493-502). In other disease states, the role of kinases is only now becoming clear. The retina is a complex tissue composed of multiple interconnected cell layers, highly specialized for transforming light and color into electrical signals that are perceived by the brain. Damage or death of the primary light-sensing cells, the photoreceptors, results in devastating effects on vision. Despite the identification of numerous mutations that cause inherited retinal degenerations, the cellular and molecular mechanisms leading from the primary mutations to photoreceptor apoptosis are not well understood, but may involve the wnt pathway (AS Hackam "The Wnt Signaling Pathway in Retinal Degeneration" *IUBMB Life* Volume 57, Number 6 / June 2005).

[0006] The success of the tyrosine-kinase inhibitor STI571 (Gleevec) in the treatment of chronic myelogenous leukemia (*Nature Reviews Drug Discovery* 2003, 2: 296-313) has spurred considerable efforts to develop other kinase inhibitors for the treatment of a wide range of other cancers (*Nature Reviews Cancer* 2003, 3: 650-665). The balance between the initiation and the inactivation of intracellular signals determines the intensity and duration of the response of the receptors to stimuli such as agonists. When desensitization occurs, the mediation or regulation of the physiological function mediated or regulated by the G proteins to which the receptors are coupled is reduced or prevented. For example, when agonists are administered to treat a disease or condition by activation of certain receptors, the receptors relatively quickly become desensitized from the action of the GRKs such that agonist administration may no longer result in therapeutic activation of the appropriate receptors. At that point, administration of the agonist no longer enables sufficient or effective control of or influence on the disease or condition intended to be treated.

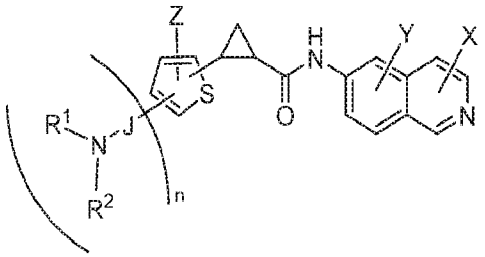
[0007] Janus Kinases (or JAK) are a family of cytoplasmic protein tyrosine kinases. The JAK family plays a role in the cytokine-dependent regulation of proliferation and function of cells involved in immune response. Currently, there are four JAK family members are known JAK1, JAK2, JAK3, and TYK2. The JAKs usually associate with cytokine receptors in pairs as homodimers or heterodimers. Specific cytokines are associated with specific JAK pairings. Each of the four members of the JAK family is implicated in the signaling of at least one of the cytokines associated with inflammation. Binding of cytokine to a JAK-dependent cytokine receptor induces receptor dimerization which results in phosphorylation of tyrosine residues on the JAK kinase, effecting JAK activation. Phosphorylated JAKs, in turn, bind and phosphorylate

various STAT proteins which dimerize, internalize in the cell nucleus and directly modulate gene transcription, leading, among other effects, to the downstream effects associated with inflammatory disease.

[0008] In view of the role that kinases play in many disease states, there is an urgent and continuing need for small molecule ligands which inhibit or modulate the activity of kinases. Without wishing to be bound by theory, it is thought that modulation of the activity of kinases, in particular ROCK and JAK kinases, by the compounds of the present disclosure is, at least in part, responsible for their beneficial effects.

SUMMARY

[0009] In one aspect, provided herein are compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein,

n is 0 or 1;

J is $-S(O_2)-$ or $-C(O)-$;

R^1 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, $-C_{1-6}$ alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, $-C_{1-6}$ alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a -heterocycle;

R^3 is H, C_{1-6} alkyl or $-C_{1-6}$ haloalkyl;

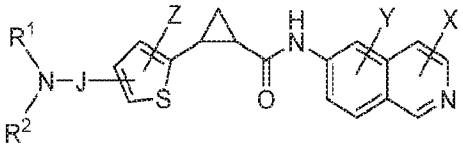
R^4 is H, C_{1-6} alkyl or $-C_{1-6}$ haloalkyl;

X is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl;

Y is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl; and

Z is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen, hydroxyl, -(C_{1-6} alkyl)-N-[(C_{1-6} alkyl)]-(C_{1-6} alkyl), $-C_{1-6}$ alkyl-CN, $-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl-O(CO)-C_{1-6} alkyl, $-C_{1-6}$ alkyl-(CO)O-C_{1-6} alkyl, -(CO)OH, or -(CO)O-C_{1-6} alkyl.

[0010] In one aspect, provided herein are compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein,

J is $-S(O_2)-$ or $-C(O)-$;

R^1 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, $-C_{1-6}$ alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, $-C_{1-6}$ alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a -heterocycle;

R^3 is H, C_{1-6} alkyl or $-C_{1-6}$ haloalkyl;

R^4 is H, C_{1-6} alkyl or $-C_{1-6}$ haloalkyl;

X is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl;

Y is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl; and

Z is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl.

[0011] In an aspect, the present disclosure provides a pharmaceutical composition comprising a compound according to the present disclosure and a pharmaceutically acceptable excipient.

[0012] In an aspect, the present disclosure provides a method of treating an ocular disorder in a subject in need of treatment, comprising administering to the subject a compound or composition according to the present disclosure.

[0013] In an aspect, the present disclosure provides a method of reducing intraocular pressure in a subject in need thereof, comprising administering to an eye of the subject a compound or composition according to the present disclosure.

[0014] In an aspect, the present disclosure provides a kit comprising a compound or composition of according to the present disclosure and instructions for use.

DETAILED DESCRIPTION

[0015] Publications and patents are referred to throughout this disclosure. All U.S. Patents cited herein are hereby incorporated by reference. All percentages, ratios, and proportions used herein are percent by weight unless otherwise specified.

[0016] Arylcyclopropyl amino-isoquinolinyl amides are provided.

[0017] "Alkyl" refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. "Alkyl" may be exemplified by groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and the like. Alkyl groups may be substituted or unsubstituted. More than one substituent may be present. Substituents may also be themselves substituted. When substituted, the substituent group is preferably but not limited to C_1-C_4 alkyl, aryl, heteroaryl, amino, thioalkyl, cyano, halogen, alkoxy or hydroxyl. "C_1-C_4 alkyl" refers to alkyl groups containing one to four carbon atoms.

[0018] "Alkenyl" refers to an unsaturated aliphatic hydrocarbon moiety including straight chain and branched chain groups. Alkenyl moieties must contain at least one alkene. "Alkenyl" may be exemplified by groups such as ethenyl, *n*-propenyl, isopropenyl, *n*-butenyl and the like. Alkenyl groups may be substituted or unsubstituted. More than one substituent may be present. When substituted, the substituent group is preferably alkyl, halogen or alkoxy. Substituents may also be themselves substituted. Substituents can be placed on the alkene itself and also on the adjacent member atoms or the alkynyl moiety. "C_2-C_4 alkenyl" refers to alkenyl groups containing two to four carbon atoms.

[0019] "Alkynyl" refers to an unsaturated aliphatic hydrocarbon moiety including straight chain and branched chain groups. Alkynyl moieties must contain at least one alkyne. "Alkynyl" may be exemplified by groups such as ethynyl, propynyl, *n*-butynyl and the like. Alkynyl groups may be substituted or unsubstituted. More than one substituent may be present. Substituents are not on the alkyne itself but on the adjacent member atoms of the alkynyl moiety. When substituted, the substituent group is preferably alkyl, amino, cyano, halogen, alkoxyl or hydroxyl. Substituents may also be themselves substituted. "C_2-C_4 alkynyl" refers to alkynyl groups containing two to four carbon atoms.

[0020] "Acyl" or "carbonyl" refers to the group –C(O)R wherein R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclic, heterocarbocyclic, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl. C_1-C_4 alkylcarbonyl refers to a group wherein the carbonyl moiety is preceded by an alkyl chain of 1-4 carbon atoms.

[0021] "Alkoxy" refers to the group –O–R wherein R is alkyl, alkenyl, acyl, alkyl alkenyl, alkyl alkynyl, aryl, carbocyclic, heterocarbocyclic, heteroaryl, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl.

[0022] "Amino" refers to the group –NR'R' wherein each R' is, independently, hydrogen, amino, hydroxyl, alkoxyl, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl. The two R' groups may themselves be linked to form a ring. The R' groups may themselves be further substituted, in which case the group also known as guanidinyl is specifically contemplated under the term 'amino".

[0023] "Aryl" refers to an aromatic carbocyclic group. "Aryl" may be exemplified by phenyl. The aryl group may be substituted or unsubstituted. More than one substituent may be present.

Substituents may also be themselves substituted. When substituted, the substituent group is preferably but not limited to alkyl, alkenyl, heteroaryl, acyl, carboxyl, sulfonyl, sulfonylamino, thioalkyl, trifluoromethyl, carbonylamino, amino, cyano, halogen, or hydroxyl.

[0024] "Carboxyl" refers to the group –C(=O)O–C_1-C_4 alkyl.

[0025] "Carbonyl" refers to the group –C(O)R wherein each R is, independently, hydrogen, alkyl, aryl, cycloalkyl; heterocycloalkyl; heteroaryl, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl.

[0026] "Carbonylamino" refers to the group –C(O)NR'R' wherein each R' is, independently, hydrogen, alkyl, aryl, cycloalkyl; heterocycloalkyl; heteroaryl, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl. The two R' groups may themselves be linked to form a ring.

[0027] "C_1-C_4 alkyl aryl" refers to C_1-C_4 alkyl groups having an aryl substituent such that the aryl substituent is bonded through an alkyl group. "C_1-C_4 alkyl aryl" may be exemplified by benzyl.

[0028] "C_1-C_4 alkyl heteroaryl" refers to C_1-C_4 alkyl groups having a heteroaryl substituent such that the heteroaryl substituent is bonded through an alkyl group.

[0029] "Carbocyclic group" or "cycloalkyl" means a saturated or unsaturated hydrocarbon ring. Carbocyclic groups are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic groups contain 3 to 10 carbon atoms, preferably 4 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic groups contain 8 to 12 carbon atoms, preferably 9 to 10 carbon atoms in the ring. Carbocyclic groups may be substituted or unsubstituted. More than one substituent may be present. Substituents may also be themselves substituted. Suitable substituents include halogen, cyano, alkoxyl, amino, trifluoromethyl, and trifluoromethoxyl. Preferred carbocyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, and cycloheptyl. The most preferred carbocyclic groups are cyclohexyl and cyclopentyl. Carbocyclic groups are not aromatic.

[0030] "Halogen" refers to fluoro, chloro, bromo or iodo moieties. Preferably, the halogen is fluoro, chloro, or bromo.

[0031] "Heteroaryl" or "heteroaromatic" refers to a monocyclic or bicyclic aromatic carbocyclic radical having one or more heteroatoms in the carbocyclic ring. Heteroaryl may be substituted or unsubstituted. More than one substituent may be present. When substituted, the substituents may themselves be substituted. Preferred but non limiting substituents are halogen, cyano, alkoxyl, amino, trifluoromethyl, trifluoromethoxyl, aryl, C_1-C_4 alkylaryl, hydroxyl, carboxyl, carbonylamino, or C_1-C_4 alkyl. Preferred heteroaromatic groups include benzo[b]thiophenyl, pyrrolidyl, benzofuranyl, isoquinolinyl, imidazolyl, quinolinyl, cinnolinyl, tetrazoyl, triazolyl, thienyl, thiazolyl, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic groups include isoquinolinyl, benzo[b]thiophenyl; thienyl, furanyl, tetrazoyl, triazolyl, and pyridyl.

[0032] "Heteroatom" means a polyvalent atom other than carbon in the ring of a heterocyclic group or a heteroaromatic group or the chain of a heterogeneous group. Preferably, heteroatoms are selected from the group consisting of nitrogen, sulfur, and oxygen atoms.

Groups containing more than one heteroatom may contain different heteroatoms. Halogens are monovalent and thus are not considered heteroatoms in this sense, but have their own category.

[0033] "Heterocarbocyclic group" or "heterocycloalkyl" or "heterocyclic" means a saturated or unsaturated hydrocarbon ring containing at least one heteroatom. Heterocarbocyclic groups are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic heterocarbocyclic groups contain 3 to 10 carbon atoms, preferably 4 to 7 carbon atoms, and more preferably 5 to 6 carbon atoms in the ring. Bicyclic heterocarbocyclic groups contain 8 to 12 carbon atoms, preferably 9 to 10 carbon atoms in the ring. Heterocarbocyclic groups may be substituted or unsubstituted. More than one substituent may be present. Substituents may also be themselves substituted. Suitable substituents include halogen, nitrile, hydroxyl, alkoxyl, amino, trifluoromethyl, and trifluoromethoxyl. Preferred heterocarbocyclic groups include epoxy, tetrahydrofuranyl, azacyclopentyl (or pyrrolidyl), azacyclohexyl, piperidyl, and homopiperidyl. More preferred heterocarbocyclic groups include pyrrolidyl, piperidyl, and homopiperidyl. The most preferred heterocarbocyclic group is piperidyl. Heterocarbocyclic groups are not aromatic.

[0034] "Hydroxy" or "hydroxyl" means a chemical entity that consists of –OH. Alcohols contain hydroxy groups. Hydroxy groups may be free or protected. An alternative name for hydroxy is hydroxyl.

[0035] "Linker" means a linear chain of n member atoms where n is an integer from 1 to 4.

[0036] "Member atom" means a carbon, nitrogen, oxygen or sulfur atom. Member atoms may be substituted up to their normal valence. If more than one stable valence is available for a member atom, *e.g.*, sulfur, then all stable valences are contemplated. If substitution is not completely specified, the unspecified substituents required for valency are hydrogen.

[0037] "Ring" means a collection of member atoms that are cyclic. Rings may be carbocyclic, aromatic, or heterocyclic or heteroaromatic, and may be substituted or unsubstituted, and may be saturated or unsaturated. More than one substituent may be present. Ring junctions with the main chain may be fused or spirocyclic. Rings may be monocyclic or bicyclic. Rings contain at least 3 member atoms and at most 10 member atoms. Monocyclic rings may contain 3 to 7 member atoms and bicyclic rings may contain from 8 to 12 member atoms. Bicyclic rings themselves may be fused or spirocyclic.

[0038] "Thioalkyl" refers to the group –S–alkyl.

[0039] "Sulfonyl" refers to the $-S(O)_2R'$ group wherein R' is alkoxy, alkyl, aryl, carbocyclic, heterocarbocyclic; heteroaryl, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl.

[0040] "Sulfonylamino" refers to the $-S(O)_2NR'R'$ group wherein each R' is independently alkyl, aryl, heteroaryl, C_1-C_4 alkyl aryl or C_1-C_4 alkyl heteroaryl.

[0041] "Pharmaceutically acceptable carrier" means a carrier that is useful for the preparation of a pharmaceutical composition that is: generally compatible with the other ingredients of the composition, not deleterious to the recipient, and neither biologically nor otherwise undesirable.

"A pharmaceutically acceptable carrier" includes both one and more than one carrier. Embodiments include carriers for topical, ocular, parenteral, intravenous, intraperitoneal intramuscular, sublingual, nasal and oral administration. "Pharmaceutically acceptable carrier" also includes agents for preparation of aqueous dispersions and sterile powders for injection or dispersions.

[0042] "Excipient" as used herein includes physiologically compatible additives useful in preparation of a pharmaceutical composition. Examples of pharmaceutically acceptable carriers and excipients can for example be found in Remington Pharmaceutical Science, 16th Ed.

[0043] "Therapeutically effective amount" as used herein refers to a dosage of the compounds or compositions effective for influencing, reducing or inhibiting the activity of or preventing activation of a kinase. This term as used herein may also refer to an amount effective at bringing about a desired *in vivo* effect in an animal, preferably, a human, such as reduction in intraocular pressure.

[0044] "Eye disease" as used herein includes, but is not limited to, glaucoma, allergy, cancers of the eye, neurodegenerative diseases of the eye, such as diabetic eye disease, macular degeneration (AMD), inflammation, and dry eye.

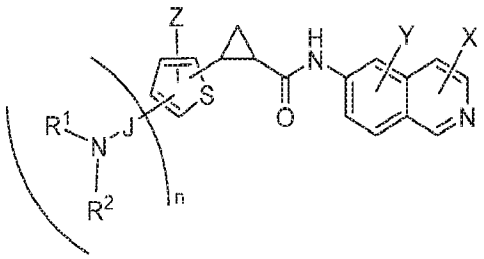
[0045] The term "disease or condition associated with kinase activity" is used to mean a disease or condition treatable, in whole or in part, by inhibition of one or more kinases.

[0046] The term "controlling the disease or condition" is used to mean changing the activity of one or more kinases to affect the disease or condition.

[0047] The term "contacting a cell" is used to mean contacting a cell *in vitro* or *in vivo* i.e. in a subject, such as a mammal, including humans, rabbits, cats and dogs.

Compounds

[0048] In one aspect, provided herein are compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein,

n is 0 or 1;

J is $-S(O_2)-$ or $-C(O)-$;

R^1 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6}

alkyl), -NH-heteroaryl, -NH-aryl, -C_{1-6} alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-N(R^3)R^4, -heteroaryl-(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, -C_{1-6} alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a -heterocycle;

R^3 is H, C_{1-6} alkyl or -C_{1-6} haloalkyl;

R^4 is H, C_{1-6} alkyl or -C_{1-6} haloalkyl;

X is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen or hydroxyl;

Y is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen or hydroxyl; and

Z is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen, hydroxyl, -(C_{1-6} alkyl)-N-[(C_{1-6} alkyl)]-(C_{1-6} alkyl), -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O(CO)-C_{1-6} alkyl, -C_{1-6} alkyl-(CO)O-C_{1-6} alkyl, -(CO)OH, or -(CO)O-C_{1-6} alkyl.

[0049] In an embodiment of the Formulae provided herein, Z is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen or hydroxyl.

[0050] In an embodiment of the Formulae provided herein, n is 1, and Z is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen or hydroxyl.

[0051] In an embodiment of the Formulae provided herein, n is 1.

[0052] In an embodiment of the Formulae provided herein, n is 0.

[0053] In an embodiment of the Formulae provided herein:

R^1 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl; and

R^2 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

[0054] In an embodiment of the Formulae provided herein:

R^1 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

[0055] In an embodiment of the Formulae provided herein:

n is 0; and

Z is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen, hydroxyl, -(C_{1-6} alkyl)-N-[(C_{1-6} alkyl)]-(C_{1-6} alkyl), -C_{1-6} alkyl-CN, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O(CO)-C_{1-6} alkyl, -(CO)OH, or -(CO)O-C_{1-6} alkyl.

[0056] In an embodiment of the Formulae provided herein;

n is 0; and

Z is hydroxyl, -C_{1-6} alkyl-OH, -C_{1-6} alkyl-O(CO)-C_{1-6} alkyl, -(CO)OH, or -(CO)O-C_{1-6} alkyl.

[0057] In an embodiment of the Formulae provided herein:

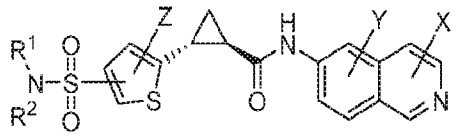
n is 0; and

Z is H, C_{1-6} alkyl, -C_{1-6} haloalkyl, halogen,-(C_{1-6} alkyl)-N-[(C_{1-6} alkyl)]-(C_{1-6} alkyl), or -C_{1-6} alkyl-CN.

[0058] In an embodiment of the Formulae provided herein, -C_{1-6} alkyl is methyl or ethyl.

[0059] In an embodiment of the Formulae provided herein, -C_{1-6} haloalkyl is trihalomethanyl or trihaloethanyl.

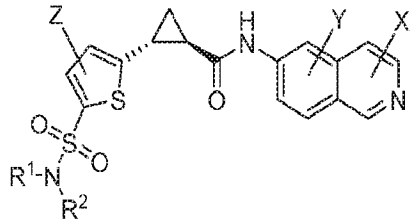
[0060] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A):



(I-A),

or a pharmaceutically acceptable salt thereof.

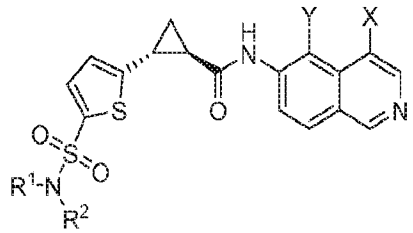
[0061] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A1):



(I-A1),

or a pharmaceutically acceptable salt thereof.

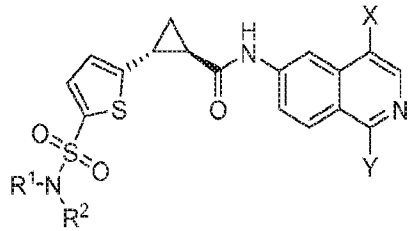
[0062] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A1-a):



(I-A1-a),

or a pharmaceutically acceptable salt thereof.

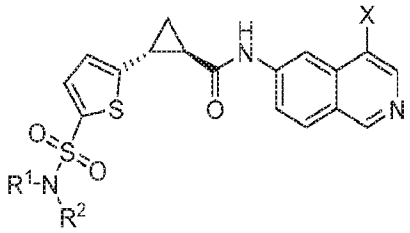
[0063] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A1-b):



(I-A1-b),

or a pharmaceutically acceptable salt thereof.

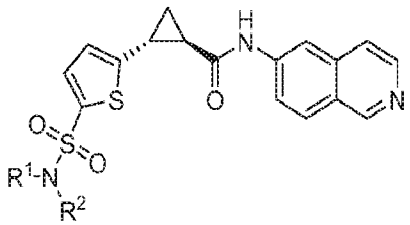
[0064] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A1-c):



(I-A1-c),

or a pharmaceutically acceptable salt thereof.

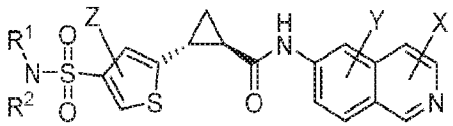
[0065] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A1-d):



(I-A1-d),

or a pharmaceutically acceptable salt thereof.

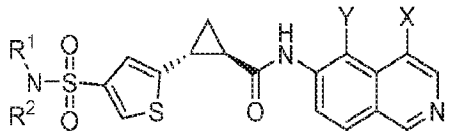
[0066] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A2):



(I-A2),

or a pharmaceutically acceptable salt thereof.

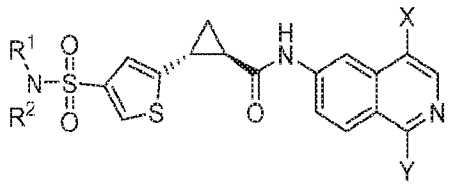
[0067] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A2-a):



(I-A2-a),

or a pharmaceutically acceptable salt thereof.

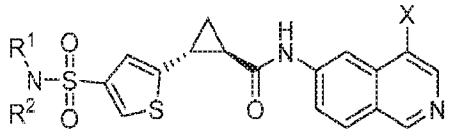
[0068] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A2-b):



(I-A2-b),

or a pharmaceutically acceptable salt thereof.

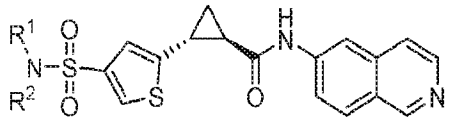
[0069] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A2-c):



(I-A2-c),

or a pharmaceutically acceptable salt thereof.

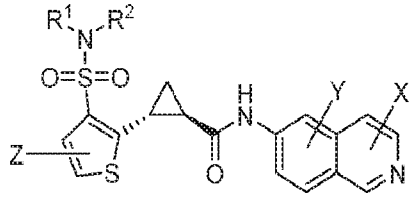
[0070] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A2-d):



(I-A2-d),

or a pharmaceutically acceptable salt thereof.

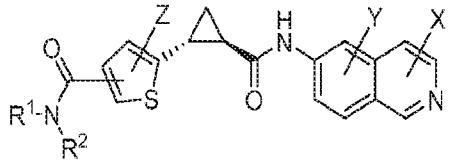
[0071] In an embodiment, the compound of Formula (I) is a compound of Formula (I-A3):



(I-A3),

or a pharmaceutically acceptable salt thereof.

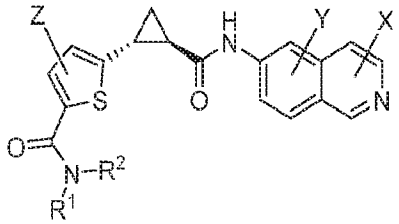
[0072] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B):



(I-B),

or a pharmaceutically acceptable salt thereof.

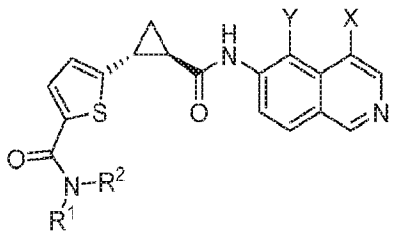
[0073] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B1):



(I-B1),

or a pharmaceutically acceptable salt thereof.

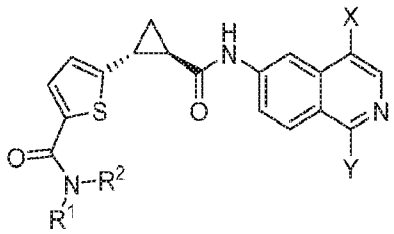
[0074] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B1-a):



(I-B1-a),

or a pharmaceutically acceptable salt thereof.

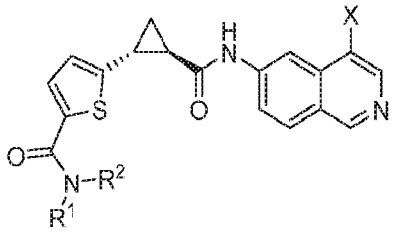
[0075] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B1-b):



(I-B1-b),

or a pharmaceutically acceptable salt thereof.

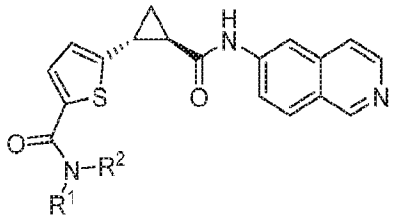
[0076] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B1-c):



(I-B1-c),

or a pharmaceutically acceptable salt thereof.

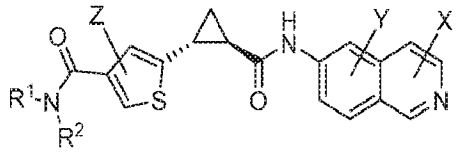
[0077] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B1-d):



(I-B1-d),

or a pharmaceutically acceptable salt thereof.

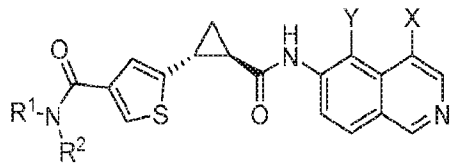
[0078] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B2):



(I-B2),

or a pharmaceutically acceptable salt thereof.

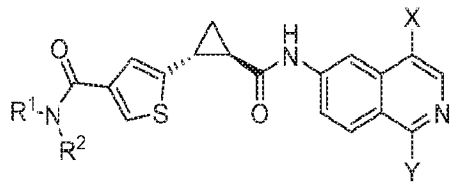
[0079] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B2-a):



(I-B2-a),

or a pharmaceutically acceptable salt thereof.

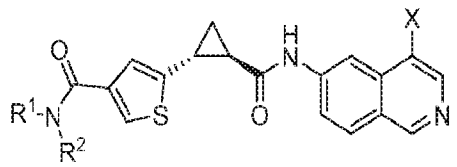
[0080] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B2-b):



(I-B2-b),

or a pharmaceutically acceptable salt thereof.

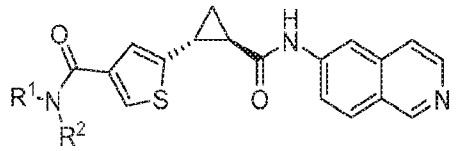
[0081] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B2-c):



(I-B2-c),

or a pharmaceutically acceptable salt thereof.

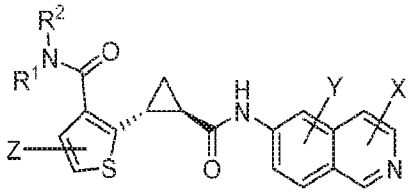
[0082] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B2-d):



(I-B2-d),

or a pharmaceutically acceptable salt thereof.

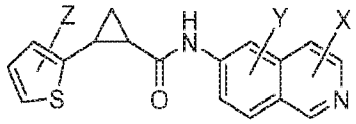
[0083] In an embodiment, the compound of Formula (I) is a compound of Formula (I-B3):



(I-B3),

or a pharmaceutically acceptable salt thereof.

[0084] In an embodiment, the compound of Formula (I) is a compound of Formula (I-C):



(I-C),

or a pharmaceutically acceptable salt thereof.

[0085] In some embodiments of the Formulae provided herein, Z is .

[0086] In some embodiments of the Formulae provided herein, X, Y and Z are H.

[0087] In some embodiments of the Formulae provided herein, X and Z are H.

[0088] In some embodiments of the Formulae provided herein, Y and Z are H.

[0089] In some embodiments of the Formulae provided herein, X is H.

[0090] In some embodiments of the Formulae provided herein:

R^1 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl; and

R^2 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

[0091] In some embodiments of the Formulae provided herein:

R^1 is H, -C_{1-6} alkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, -C_{1-6} alkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a heterocycle;

R^3 is H or C_{1-6} alkyl;

R^4 is H or C_{1-6} alkyl;

X is H, C_{1-6} alkyl, halogen or hydroxyl;

Y is H, C_{1-6} alkyl, halogen or hydroxyl; and

Z is H, C_{1-6} alkyl, halogen or hydroxyl.

[0092] In some embodiments of the Formulae provided herein:

R^1 is H, -C_{1-4} alkyl, aryl, heteroaryl, -(C_{1-4} alkyl)-pyridinyl, -(C_{1-4} alkyl)-N(R^3)R^4, -(C_{1-4} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, -C_{1-4} alkyl, aryl, heteroaryl, -(C_{1-4} alkyl)-pyridinyl, -(C_{1-4} alkyl)-N(R^3)R^4, -(C_{1-4}

alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a heterocycle;

R^3 is H or C_{1-4} alkyl;

R^4 is H or C_{1-4} alkyl;

X is H, C_{1-4} alkyl, halogen or hydroxyl;

Y is H, C_{1-4} alkyl, halogen or hydroxyl; and

Z is H, C_{1-4} alkyl, halogen or hydroxyl.

[0093] In some embodiments of the Formulae provided herein:

R^1 is H, phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl; and

R^2 is H, phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

[0094] In some embodiments of the Formulae provided herein:

R^1 is H; and

R^2 is H, phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

[0095] In some embodiments of the Formulae provided herein, R^1 is H or -C_{1-6} alkyl.

[0096] In some embodiments of the Formulae provided herein, R^1 is -C_{1-6} alkyl.

[0097] In some embodiments of the Formulae provided herein, R^1 is H.

[0098] In some embodiments of the Formulae provided herein, R^2 is phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

[0099] In some embodiments of the Formulae provided herein, pyridinyl is 2-pyridinyl.

[0100] In some embodiments of the Formulae provided herein, pyridinyl is 3-pyridinyl.

[0101] In some embodiments of the Formulae provided herein, pyridinyl is 4-pyridinyl.

[0102] In some embodiments of the Formulae provided herein, R^2 is phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

[0103] In some embodiments of the Formulae provided herein, R^2 is -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

[0104] In some embodiments of the Formulae provided herein, R^2 is phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl.

[0105] In some embodiments of the Formulae provided herein, R^2 is pyridinyl.

[0106] In some embodiments of the Formulae provided herein, R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl containing six ring atoms.

[0107] In some embodiments of the Formulae provided herein, R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl containing six ring atoms, wherein one or two of the ring atoms are, independently, O, S or N.

[0108] In some embodiments of the Formulae provided herein, R^1 and R^2, together with the

nitrogen to which they are attached, form a heterocyclyl containing six ring atoms, wherein one or two of the ring atoms are N.

[0109] In some embodiments of the Formulae provided herein, R^3 and R^4 are H.

[0110] In some embodiments of the Formulae provided herein, R^3 and R^4 are, independently, C_{1-6} alkyl.

[0111] In some embodiments of the Formulae provided herein, R^3 is H, and R^4 is C_{1-6} alkyl.

[0112] In some embodiments of the Formulae provided herein:

X is C_{1-6} alkyl, halogen or hydroxyl; and

Y and Z are H.

[0113] In some embodiments of the Formulae provided herein:

X is halogen; and

Y and Z are H.

[0114] In some embodiments of the Formulae provided herein, X is C_{1-6} alkyl, halogen or hydroxyl.

[0115] In some embodiments of the Formulae provided herein, X is methyl, ethyl, CF_3, CHF_2 or CH_2F.

[0116] In some embodiments of the Formulae provided herein, Y is methyl, ethyl, CF_3, CHF_2 or CH_2F.

[0117] In some embodiments of the Formulae provided herein, Z is methyl, ethyl, CF_3, CHF_2 or CH_2F.

[0118] In some embodiments of the Formulae provided herein, X is halogen.

[0119] In some embodiments of the Formulae provided herein, X is F or Cl.

[0120] In some embodiments of the Formulae provided herein, X is Cl.

[0121] In some embodiments of the Formulae provided herein:

X is methyl or halogen;

Y is methyl or halogen; and

Z is methyl or halogen.

[0122] In some embodiments of the Formulae provided herein:

X is methyl, F or Cl;

Y is methyl, F or Cl; and

Z is methyl, F or Cl.

[0123] In some embodiments of the Formulae provided herein:

X is halogen; and

Y is hydroxyl.

[0124] In some embodiments of the Formulae provided herein, Y is hydroxyl.

[0125] In some embodiments of the Formulae provided herein, Z is H or F.

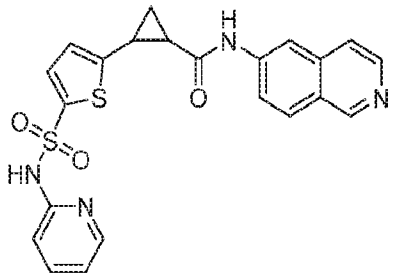
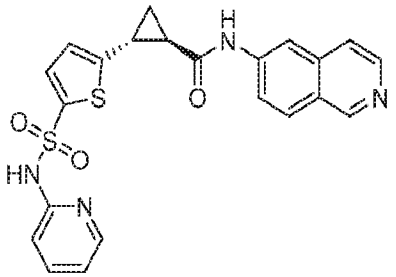
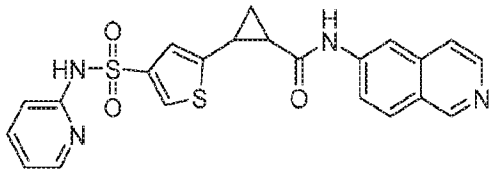
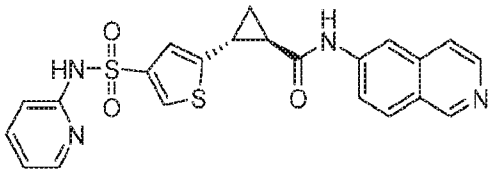
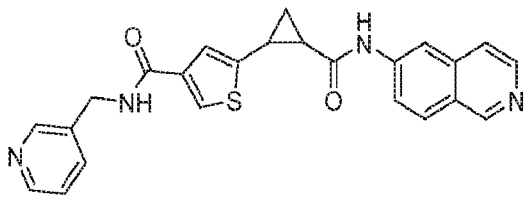
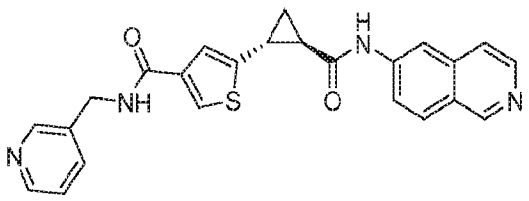
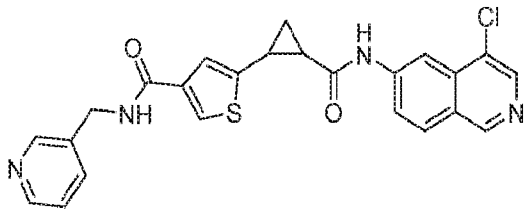
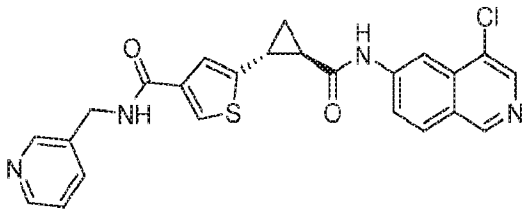
[0126] In some embodiments of the Formulae provided herein, aryl is phenyl.

[0127] In some embodiments of the Formulae provided herein, heteroaryl is pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, pyrazolyl, or imidazolyl.

[0128] In some embodiments of the Formulae provided herein,

[0129] In some embodiments of the Formulae provided herein, the compound is a compound provided in Table 1, or a pharmaceutically acceptable salt thereof.

Table 1.

Compound 1 	Compound 2 
Compound 3 	Compound 4 
Compound 5 	Compound 6 
Compound 7 	Compound 8 

[0130] In some embodiments of the Formulae provided herein, the compound is a compound provided in Table 2, below, or a pharmaceutically acceptable salt thereof.

[0131] In some embodiments of the Formulae provided herein, the compound is a compound provided in Table 3, below, or a pharmaceutically acceptable salt thereof.

Isomers

[0132] Compounds described herein may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, atropic, stereoisomer, tautomeric, conformational, or anomeric forms, including but not limited to, *cis*- and *trans*-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and half chair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

[0133] In one embodiment, a compound described herein may be an enantiomerically enriched isomer of a stereoisomer described herein. For example, the compound may have an enantiomeric excess of at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%. Enantiomer, when used herein, refers to either of a pair of chemical compounds whose molecular structures have a mirror-image relationship to each other.

[0134] In one embodiment, a preparation of a compound disclosed herein is enriched for an isomer of the compound having a selected stereochemistry, e.g., R or S, corresponding to a selected stereocenter. For example, the compound has a purity corresponding to a compound having a selected stereochemistry of a selected stereocenter of at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%.

[0135] In one embodiment, a composition described herein includes a preparation of a compound disclosed herein that is enriched for a structure or structures having a selected stereochemistry, e.g., R or S, at a selected stereocenter. Exemplary R/S configurations can be those provided in an example described herein.

[0136] An "enriched preparation," as used herein, is enriched for a selected stereoconfiguration of one, two, three or more selected stereocenters within the subject compound. Exemplary selected stereocenters and exemplary stereoconfigurations thereof can be selected from those provided herein, e.g., in an example described herein. By enriched is meant at least 60%, e.g., of the molecules of compound in the preparation have a selected stereochemistry of a selected stereocenter. In an embodiment it is at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%. Enriched refers to the level of a subject molecule(s) and does not connote a process limitation unless specified.

[0137] Compounds may be prepared in racemic form or as individual enantiomers or diastereomers by either stereospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers or diastereomers by standard techniques, such as the formation of stereoisomeric pairs by salt formation with an optically active base, followed by fractional crystallization and regeneration of the free acid. The

compounds may also be resolved by formation of stereoisomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral chromatography column. The enantiomers also may be obtained from kinetic resolution of the racemate of corresponding esters using lipase enzymes.

[0138] Except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_3-alkyl or propyl includes n-propyl and iso-propyl; C_4-alkyl or butyl includes n-, iso-, sec-, and *tert*-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

[0139] The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol, imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.

[0140] Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Salts

[0141] A compound described herein can be in the form of a salt, e.g., a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" includes salts of the active compounds that are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. Neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in a conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of this disclosure. Examples of pharmaceutically acceptable salts are discussed in Berge et al, 1977, "Pharmaceutically Acceptable Salts." *J. Pharm. Sci.* Vol. 66, pp. 1-19. In an embodiment, the compound is present in mono-salt form. In embodiments, the compound is present in di-salt form.

[0142] For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^-$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+,

alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., $NH_3R_1^+$, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as dibasic amino acids, such as lysine and arginine.

[0143] If the compound is cationic, or has a functional group that may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

[0144] Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, p-toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

[0145] Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Chemically Protected Forms

[0146] It may be convenient or desirable to prepare, purify, and/or handle an active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999). Unless otherwise specified, a reference to a particular compound also includes chemically

protected forms thereof.

[0147] A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

[0148] A hydroxyl group may be protected as an ether (-OR) or an ester (-OC(O)R), for example, as: a *t*-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(O)CH_3, -OAc).

[0149] An aldehyde or ketone group may be protected as an acetal ($RCH(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group ($R_2C=O$) is converted to a diether ($R_2C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

[0150] An amine group may be protected, for example, as an amide (-NRC(O)R) or a urethane (-NRC(O)OR), for example, as: a methyl amide (-NHC(O)CH_3); a benzyloxy amide (-NHC(O)$OCH_2C_6H_5$, -NH-Cbz); as a *tert*-butoxy amide (-NHC(O)$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO(O)$C(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9- fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH- Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH- Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O«).

[0151] A carboxylic acid group may be protected as an ester, for example, as: an alkyl ester (e.g., a methyl ester; a t-butyl ester); a haloalkyl ester (e.g., a haloalkyl ester); a trialkylsilylalkyl ester; or an arylalkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

[0152] A thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(O)CH_3$)

Prodrugs and Other Modifications

[0153] In addition to salt forms, the present disclosure may also provide compounds that are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds described herein. Prodrugs can be converted to the compounds of the present disclosure by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present disclosure when placed in a transdermal patch reservoir with or

without a suitable enzyme or chemical reagent.

[0154] A compound described herein can also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those that increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism, and/or alter rate of excretion. Examples of these modifications include, but are not limited to, esterification with polyethylene glycols, derivatization with pivolates or fatty acid substituents, conversion to carbamates, hydroxylation of aromatic rings, and heteroatom substitution in aromatic rings.

Synthesis

[0155] Methods of synthesizing the herein described compounds will be evident to those of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), and subsequent editions thereof.

Methods of Use and Activity

[0156] The compounds as disclosed herein and compositions including them have kinase inhibitory activity and are thus useful in modulating the action of kinases, and in treatment and/or prevention of diseases or conditions influenced by kinases. The above compounds and compositions may be used to modulate (e.g., influence or inhibit) the action of kinases either in a cell *in vitro* or in a cell in a living body *in vivo*. Specifically, in one embodiment, a method is provided of inhibiting the action of a kinase comprising applying to a medium such as an assay medium or contacting with a cell either in a cell *in vitro* or in a cell in a living body *in vivo* an effective inhibitory amount of a compound as disclosed herein. In one embodiment, the kinase inhibited is a *rho* kinase (e.g., ROCK1 or ROCK2). In another embodiment, the kinase inhibited is a JAK (e.g., JAK2) kinase.

[0157] JAK inhibitors are useful in treating various JAK-associated diseases or disorders. Examples of JAK-associated diseases include diseases involving the immune system including, for example, organ transplant rejection (e.g., allograft rejection and graft versus host disease). Further examples of JAK-associated diseases include autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, autoimmune thyroid disorders, chronic obstructive

pulmonary disease (COPD), and the like. In some embodiments, the autoimmune disease is arthritis.

[0158] Further examples of JAK-associated diseases include allergic conditions such as asthma, food allergies, eczematous dermatitis, contact dermatitis, atopic dermatitis (atropic eczema), and rhinitis. Further examples of JAK-associated diseases include viral diseases such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV) and Human Papilloma Virus (HPV).

[0159] Further examples of JAK-associated diseases or conditions include those characterized by solid tumors (e.g., prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, uterine leiomyosarcoma, melanoma etc.), hematological cancers (e.g., lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and cutaneous B-cell lymphoma. Example CTCLs include Sezary syndrome and mycosis fungoides. Other examples of JAK-associated diseases or conditions include pulmonary arterial hypertension.

[0160] Other examples of JAK-associated diseases or conditions include inflammation-associated cancers. In some embodiments, the cancer is associated with inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is ulcerative colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the inflammation-associated cancer is colitis-associated cancer. In some embodiments, the inflammation-associated cancer is colon cancer or colorectal cancer. In some embodiments, the cancer is gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), adenocarcinoma, small intestine cancer, or rectal cancer.

[0161] The compounds of the present disclosure are used in methods of inhibiting kinases in a cell, a tissue or a subject such as a human comprising contacting the cell with an amount of one or more of the compounds of the present disclosure effective to inhibit the kinase. In one embodiment, the compounds are administered in a pharmaceutically acceptable composition, such as in or with a pharmaceutically acceptable carrier.

[0162] In another embodiment, the compounds of the present disclosure are used in methods for modulating the action of a kinase in a cell comprising contacting the cell with amount of one or more compounds of the present disclosure effective to modulate the action of a kinase in a cell. In one embodiment, the compounds of the present disclosure are administered in a pharmaceutically acceptable composition, such as in or with a pharmaceutically acceptable carrier.

[0163] Treatment or prevention of diseases or conditions for which the compounds of the present disclosure may be useful includes any of the diseases or conditions associated with

kinase activity or diseases or conditions affected by kinases. Examples of these types of diseases include neurodegenerative diseases, such as Alzheimer's; ocular diseases, such as diabetic eye diseases, wet age-related macular degeneration, or dry age-related macular degeneration, inflammatory eye diseases, retinal degradation and glaucoma; cardiovascular diseases; and cancer. Additional examples include bone disorder, obesity, hepatic disease, renal disease, pancreatitis, gastric disturbance, hypertension, fertility control, disorders of hair growth, nasal congestion, neurogenic bladder disorder, gastrointestinal disorder, dermatological disorder, and respiratory indications.

[0164] In some embodiments, the compounds of the present disclosure will be administered in conjunction with one or more additional therapeutic agents. Suitable classes of additional therapeutic agents include, but are not limited to, beta blockers, alpha-agonists, carbonic anhydrase inhibitors, prostaglandin-like compounds, miotic or cholinergic agents, epinephrine compounds, or neuroprotective or anti-inflammatory compounds.

[0165] Beta blockers. These compounds are thought to lower intraocular pressure (IOP) by reducing the production of aqueous humor. Examples include levobunolol (BETAGAN™), timolol (BETIMOL™, TIMOPTIC™), betaxolol (BETOPTIC™) and metipranolol (OPTIPRANOLOL™).

[0166] Alpha-agonists. These compounds are thought to lower IOP by reducing the production of aqueous humor and increasing drainage. Examples include apraclonidine (IOPIDINE™) and brimonidine (ALPHAGAN™).

[0167] Carbonic anhydrase inhibitors. These compounds are thought to lower IOP by also reducing the production of aqueous humor. Examples include dorzolamide (TRUSOPT™) and brinzolamide (AZOPT™).

[0168] Prostaglandin-like compounds. These compounds are thought to lower IOP by increasing the outflow of aqueous humor by the uveoscleral pathway. Examples include AR-102, latanoprost (XALATAN™), bimatoprost (LUMIGAN™), tafluprost (ZIOPTAN™), and travoprost (TRAVATAN™).

[0169] Miotic or cholinergic agents. These agents are thought to function by causing the pupil to constrict, which opens drainage channels in the eye. Examples include pilocarpine (ISOPTO CARPINE™, PILOPINE™) and carbachol (ISOPTO CARBACHOL™).

[0170] Epinephrine compounds. These compounds, such as dipivefrin (PROPINE™), are thought to function by both decreasing the outflow of aqueous humor, as well as increasing fluid drainage.

[0171] Neuroprotective or anti-inflammatory compounds. These compounds, such as Aflibercept (EYLEA™) are treatments for conditions of the retina such as Macular Degeneration, and are designed as anti-VEGF treatments or have similar types of anti-growth or anti-inflammatory activity.

[0172] Thus, provided herein are methods of treating an ocular disorder in a subject in need thereof, comprising administering to the subject a compound, a composition, or a pharmaceutical composition provided herein.

[0173] Also provided herein are methods of reducing intraocular pressure in a subject in need thereof, comprising administering to the subject a compound, a composition, or a pharmaceutical composition provided herein.

[0174] In one aspect, provided herein are methods of treating an ocular disorder in a subject in need thereof, comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, provided herein.

[0175] In some embodiments, the ocular disorder is glaucoma.

[0176] In another aspect, provided herein are methods of reducing intraocular pressure in a subject in need thereof, comprising administering to the subject a compound, or a pharmaceutically acceptable salt thereof, provided herein.

[0177] In some embodiments of these aspects, the compound is administered topically to an eye of the subject.

[0178] In some embodiments, provided herein are methods of treating an ocular disorder in a subject in need thereof, comprising administering to the subject a compound of one of the Formulae provided herein, or a pharmaceutically acceptable salt thereof.

[0179] In some embodiments, provided herein are methods of treating an ocular disorder in a subject in need thereof, comprising administering to the subject a compound provided in Table 1, or a pharmaceutically acceptable salt thereof.

[0180] In some embodiments, provided herein are methods of reducing intraocular pressure in a subject in need thereof, comprising administering to the subject a compound of one of the Formulae provided herein, or a pharmaceutically acceptable salt thereof.

[0181] In some embodiments, provided herein are methods of reducing intraocular pressure in a subject in need thereof, comprising administering to the subject a compound provided in Table 1, or a pharmaceutically acceptable salt thereof.

[0182] In some embodiments of these methods, the method further comprises administering one or more additional therapeutic agents. In some embodiments, the one or more additional therapeutic agents is a beta blocker, an alpha-agonist, a carbonic anhydrase inhibitor, a prostaglandin or a prostaglandin-like compound, a miotic or cholinergic agent, an epinephrine compound, or a neuroprotective or anti-inflammatory compound. In some embodiments, the one or more additional therapeutic agents is a prostaglandin or a prostaglandin-like compound. In some embodiment, the prostaglandin-like compound is AR-102, latanoprost, bimatoprost, tafluprost, or travoprost.

[0183] Also provided herein are methods of treating an autoimmune disease in a subject in need thereof, comprising administering to the subject a compound, a composition, or a

pharmaceutical composition provided herein.

[0184] In some embodiments, provided herein are methods of treating an autoimmune disease in a subject in need thereof, comprising administering to the subject a compound of one of the Formulae provided herein, or a pharmaceutically acceptable salt thereof.

[0185] In some embodiments, provided herein are methods of treating an autoimmune disease in a subject in need thereof, comprising administering to the subject a compound provided in Table 1, or a pharmaceutically acceptable salt thereof.

[0186] In some embodiments, the autoimmune disease is multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, autoimmune thyroid disorders, or chronic obstructive pulmonary disease.

Compositions and Administration

[0187] The additional therapeutic agent or agents can be administered simultaneously or sequentially with the compounds of the present disclosure. Sequential administration includes administration before or after the compounds of the present disclosure. In some embodiments, the additional therapeutic agent or agents can be administered in the same composition as the compounds of the present disclosure. In other embodiments, there can be an interval of time between administration of the additional therapeutic agent and the compounds of the present disclosure.

[0188] In some embodiments, the administration of an additional therapeutic agent with a compound of the present disclosure will enable lower doses of the other therapeutic agents to be administered for a longer period of time.

[0189] Also provided herein are compositions comprising a compound provided herein, or a pharmaceutically acceptable salt thereof. In one embodiment, the compositions provided herein are pharmaceutical compositions comprising a pharmaceutically acceptable carrier.

[0190] Pharmaceutical compositions for use in accordance with the present disclosure may be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. Thus, the compounds and their physiologically acceptable salts and solvates may be formulated for administration by, for example, solid dosing, eyedrop, in a topical oil-based formulation, injection (including injection of a drug-eluting device either into the body as a whole, or into specific tissues of the eye), inhalation (either through the mouth or the nose), implants, or oral, buccal, parenteral or rectal administration. Techniques and formulations may generally be found in "Remington's Pharmaceutical Sciences," (Meade Publishing Co., Easton, PA).

[0191] The route by which the compounds of the present disclosure (component A) will be administered and the form of the composition will dictate the type of carrier (component B) to be used. The composition may be in a variety of forms, suitable, for example, for systemic administration (*e.g.*, oral, rectal, nasal, sublingual, buccal, implants, or parenteral, or by

ocular injection into one of the chambers of the eye, such as intravitreal injection, intracameral injection, or injection into the aqueous humour.) or topical administration (*e.g.*, local application on the skin, ocular, liposome delivery systems, or iontophoresis).

[0192] Carriers for systemic administration typically comprise at least one of a) diluents, b) lubricants, c) binders, d) disintegrants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, j) preservatives, k) glidants, m) solvents, n) suspending agents, o) wetting agents, p) surfactants, combinations thereof, and others. All carriers are optional in the systemic compositions.

[0193] Ingredient a) is a diluent. Suitable diluents for solid dosage forms include sugars such as glucose, lactose, dextrose, and sucrose; diols such as propylene glycol; calcium carbonate; sodium carbonate; sugar alcohols, such as glycerin; mannitol; and sorbitol. The amount of ingredient a) in the systemic or topical composition is typically about 50 to about 90%.

[0194] Ingredient b) is a lubricant. Suitable lubricants for solid dosage forms are exemplified by solid lubricants including silica, talc, stearic acid and its magnesium salts and calcium salts, calcium sulfate; and liquid lubricants such as polyethylene glycol and vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of Theobroma. The amount of ingredient b) in the systemic or topical composition is typically about 5 to about 10%.

[0195] Ingredient c) is a binder. Suitable binders for solid dosage forms include polyvinyl pyrrolidone; magnesium aluminum silicate; starches such as corn starch and potato starch; gelatin; tragacanth; and cellulose and its derivatives, such as sodium carboxymethylcellulose, ethyl cellulose, methylcellulose, microcrystalline cellulose, and sodium carboxymethylcellulose. The amount of ingredient c) in the systemic composition is typically about 5 to about 50%, and in ocular solid dosing forms up to 99%.

[0196] Ingredient d) is a disintegrant. Suitable disintegrants for solid dosage forms include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmelose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion exchange resins. The amount of ingredient d) in the systemic or topical composition is typically about 0.1 to about 10%.

[0197] Ingredient e) for solid dosage forms is a colorant such as an FD&C dye. When used, the amount of ingredient e) in the systemic or topical composition is typically about 0.005 to about 0.1%.

[0198] Ingredient f) for solid dosage forms is a flavor such as menthol, peppermint, and fruit flavors. The amount of ingredient f), when used, in the systemic or topical composition is typically about 0.1 to about 1.0%.

[0199] Ingredient g) for solid dosage forms is a sweetener such as aspartame and saccharin. The amount of ingredient g) in the systemic or topical composition is typically about 0.001 to about 1%.

[0200] Ingredient h) is an antioxidant such as butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), and vitamin E. The amount of ingredient h) in the systemic or topical composition is typically about 0.1 to about 5%.

[0201] Ingredient j) is a preservative such as benzalkonium chloride, methyl paraben and sodium benzoate. The amount of ingredient j) in the systemic or topical composition is typically about 0.01 to about 5%.

[0202] Ingredient k) for solid dosage forms is a glidant such as silicon dioxide. The amount of ingredient k) in the systemic or topical composition is typically about 1 to about 5%.

[0203] Ingredient m) is a solvent, such as water, isotonic saline, ethyl oleate, glycerine, hydroxylated castor oils, alcohols such as ethanol, and phosphate buffer solutions. The amount of ingredient m) in the systemic or topical composition is typically from about 0 to about 100%.

[0204] Ingredient n) is a suspending agent. Suitable suspending agents include AVICEL® RC-591 (from FMC Corporation of Philadelphia, PA) and sodium alginate. The amount of ingredient n) in the systemic or topical composition is typically about 1 to about 8%.

[0205] Ingredient o) is a surfactant such as lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS® from Atlas Powder Company of Wilmington, Delaware. Suitable surfactants include those disclosed in the C.T.F.A. Cosmetic Ingredient Handbook, 1992, pp.587-592; Remington's Pharmaceutical Sciences, 15th Ed. 1975, pp. 335-337; and McCutcheon's Volume 1, Emulsifiers & Detergents, 1994, North American Edition, pp. 236-239. The amount of ingredient o) in the systemic or topical composition is typically about 0.1% to about 5%.

[0206] Although the amounts of components A and B in the systemic compositions will vary depending on the type of systemic composition prepared, the specific derivative selected for component A and the ingredients of component B, in general, system compositions comprise 0.01% to 50% of component A and 50 to 99.99% of component B.

[0207] Compositions for parenteral administration typically comprise A) 0.1 to 10% of the compounds of the present disclosure and B) 90 to 99.9% of a carrier comprising a) a diluent and m) a solvent. In one embodiment, component a) comprises propylene glycol and m) comprises ethanol or ethyl oleate.

[0208] Compositions for oral administration can have various dosage forms. For example, solid forms include tablets, capsules, granules, and bulk powders. These oral dosage forms comprise a safe and effective amount, usually at least about 5%, and more particularly from about 25% to about 50% of component A). The oral dosage compositions further comprise about 50 to about 95% of component B), and more particularly, from about 50 to about 75%.

[0209] Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed. Tablets typically comprise component A, and component B a carrier comprising ingredients selected from the group consisting of a) diluents, b) lubricants, c) binders,

d) disintegrants, e) colorants, f) flavors, g) sweeteners, k) glidants, and combinations thereof. Specific diluents include calcium carbonate, sodium carbonate, mannitol, lactose and cellulose. Specific binders include starch, gelatin, and sucrose. Specific disintegrants include alginic acid and croscarmelose. Specific lubricants include magnesium stearate, stearic acid, and talc. Specific colorants are the FD&C dyes, which can be added for appearance. Chewable tablets preferably contain g) sweeteners such as aspartame and saccharin, or f) flavors such as menthol, peppermint, fruit flavors, or a combination thereof.

[0210] Capsules (including implants, time release and sustained release formulations) typically comprise component A, and a carrier comprising one or more a) diluents disclosed above in a capsule comprising gelatin. Granules typically comprise component A, and preferably further comprise k) glidants such as silicon dioxide to improve flow characteristics. Implants can be of the biodegradable or the non-biodegradable type. Implants may be prepared using any known biocompatible formulation.

[0211] The selection of ingredients in the carrier for oral compositions depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of this disclosure. One skilled in the art would know how to select appropriate ingredients without undue experimentation.

[0212] The solid compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that component A is released in the gastrointestinal tract in the vicinity of the desired application, or at various points and times to extend the desired action. The coatings typically comprise one or more components selected from the group consisting of cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, EUDRAGIT® coatings (available from Rohm & Haas G.M.B.H. of Darmstadt, Germany), waxes and shellac.

[0213] Compositions for oral administration can also have liquid forms. For example, suitable liquid forms include aqueous solutions, emulsions, suspensions, solutions reconstituted from non-effervescent granules, suspensions reconstituted from non-effervescent granules, effervescent preparations reconstituted from effervescent granules, elixirs, tinctures, syrups, and the like. Liquid orally administered compositions typically comprise component A and component B, namely, a carrier comprising ingredients selected from the group consisting of a) diluents, e) colorants, f) flavors, g) sweeteners, j) preservatives, m) solvents, n) suspending agents, and o) surfactants. *Peroral* liquid compositions preferably comprise one or more ingredients selected from the group consisting of e) colorants, f) flavors, and g) sweeteners.

[0214] Other compositions useful for attaining systemic delivery of the subject compounds include injection, sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as a) diluents including sucrose, sorbitol and mannitol; and c) binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose,

and hydroxypropyl methylcellulose. Such compositions may further comprise b) lubricants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, and k) glidants.

[0215] In one embodiment of the disclosure, the compounds of the present disclosure are topically administered. Topical compositions that can be applied locally to the eye may be in any form known in the art, non-limiting Examples of which include solids, gelable drops, sprays, ointments, or a sustained or non-sustained release unit placed in the conjunctival cul-du-sac of the eye or another appropriate location.

[0216] Topical compositions that can be applied locally to the skin may be in any form including solids, solutions, oils, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like. Topical compositions comprise: component A, the compounds described above, and component B, a carrier. The carrier of the topical composition preferably aids penetration of the compounds into the eye. Component B may further comprise one or more optional components.

[0217] An effective amount of a compound according to the present disclosure will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of treatment, the nature of concurrent therapy, the route of administration, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician. For example, an effective amount of the compounds of the present disclosure for systemic administration is from about 0.01 to about 1000 µg/kg body weight, preferably from about 0.1 to about 100 µg/kg per body weight, most preferably form about 1 to about 50 µg/kg body weight per day. The transdermal dosages will be designed to attain similar serum or plasma levels, based upon techniques known to those skilled in the art of pharmacokinetics and transdermal formulations. Plasma levels for systemic administration are expected to be in the range of 0.01 to 100 ng/mL, more preferably from 0.05 to 50 ng/mL and most preferably from 0.1 to 10 ng/mL. While these dosages are based upon a daily administration rate, the compounds of the present disclosure may also be administered at other intervals, such as twice per day, twice weekly, once weekly, or once a month. One of ordinary skill in the art would be able to calculate suitable effective amounts for other intervals of administration.

[0218] The compounds of the present disclosure are useful in a method of reducing or decreasing intraocular pressure. The compounds of the present disclosure may be administered to a subject in need of treatment in an amount effective to reduce intraocular pressure. Thus, these compounds are useful in the treatment of glaucoma. The preferred route of administration for treating glaucoma is topically.

[0219] The exact amounts of each component in the topical composition depend on various factors. The amount of component A added to the topical composition is dependent on the IC_{50} of component A, typically expressed in nanomolar (nM) units. For example, if the IC_{50} of the

medicament is 1 nM, the amount of component A will be from about 0.001 to about 0.3%. If the IC_{50} of the medicament is 10 nM, the amount of component A) will be from about 0.01 to about 1%. If the IC_{50} of the medicament is 100 nM, the amount of component A will be from about 0.1 to about 10%. If the amount of component A is outside the ranges specified above (*i.e.*, lower), efficacy of the treatment may be reduced. One skilled in the art understands how to calculate and understand an IC_{50}. The remainder of the composition, up to 100%, is component B.

[0220] The amount of the carrier employed in conjunction with component A is sufficient to provide a practical quantity of composition for administration per unit dose of the medicament. Techniques and compositions for making dosage forms useful in the methods of this disclosure are described in the following references: *Modern Pharmaceutics*, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman *et al.*, *Pharmaceutical Dosage Forms: Tablets* (1981); and Ansel, *Introduction to Pharmaceutical Dosage Forms*, 2nd Ed., (1976).

[0221] Component B may comprise a single ingredient or a combination of two or more ingredients. In the topical compositions, component B comprises a topical carrier. Suitable topical carriers comprise one or more ingredients selected from the group consisting of phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols, symmetrical alcohols, *aloe vera* gel, allantoin, glycerin, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, dimethyl isosorbide, castor oil, combinations thereof, and the like. More particularly, carriers for skin applications include propylene glycol, dimethyl isosorbide, and water, and even more particularly, phosphate buffered saline, isotonic water, deionized water, monofunctional alcohols and symmetrical alcohols.

[0222] The carrier of the topical composition may further comprise one or more ingredients selected from the group consisting of q) emollients, r) propellants, s) solvents, t) humectants, u) thickeners, v) powders, w) fragrances, x) pigments, and y) preservatives.

[0223] Ingredient q) is an emollient. The amount of ingredient q) in a skin-based topical composition is typically about 5 to about 95%. Suitable emollients include stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, di-*n*-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate, and combinations thereof. Specific emollients for skin include stearyl alcohol and polydimethylsiloxane.

[0224] Ingredient r) is a propellant. The amount of ingredient r) in the topical composition is typically about 0 to about 95%. Suitable propellants include propane, butane, isobutane,

dimethyl ether, carbon dioxide, nitrous oxide, and combinations thereof.

[0225] Ingredient s) is a solvent. The amount of ingredient s) in the topical composition is typically about 0 to about 95%. Suitable solvents include water, ethyl alcohol, methylene chloride, isopropanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethylsulfoxide, dimethyl formamide, tetrahydrofuran, and combinations thereof. Specific solvents include ethyl alcohol and homotopic alcohols.

[0226] Ingredient t) is a humectant. The amount of ingredient t) in the topical composition is typically 0 to 95%. Suitable humectants include glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin, and combinations thereof. Specific humectants include glycerin.

[0227] Ingredient u) is a thickener. The amount of ingredient u) in the topical composition is typically about 0 to about 95%.

[0228] Ingredient v) is a powder. The amount of ingredient v) in the topical composition is typically 0 to 95%. Suitable powders include *beta*-cyclodextrins, hydroxypropyl cyclodextrins, chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically-modified magnesium aluminum silicate, organically-modified Montmorillonite clay, hydrated aluminum silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, and combinations thereof. For ocular applications, specific powders include *beta*-cyclodextrin, hydroxypropyl cyclodextrin, and sodium polyacrylate. For gel dosing ocular formulations, sodium polyacrylate may be used.

[0229] Ingredient w) is a fragrance. The amount of ingredient w) in the topical composition is typically about 0 to about 0.5%, particularly, about 0.001 to about 0.1%. For ocular applications a fragrance is not typically used.

[0230] Ingredient x) is a pigment. Suitable pigments for skin applications include inorganic pigments, organic lake pigments, pearlescent pigments, and mixtures thereof. Inorganic pigments useful in this disclosure include those selected from the group consisting of rutile or anatase titanium dioxide, coded in the Color Index under the reference CI 77,891; black, yellow, red and brown iron oxides, coded under references CI 77,499, 77,492 and, 77,491; manganese violet (CI 77,742); ultramarine blue (CI 77,007); chromium oxide (CI 77,288); chromium hydrate (CI 77,289); and ferric blue (CI 77,510) and mixtures thereof.

[0231] The organic pigments and lakes useful in this disclosure include those selected from the group consisting of D&C Red No. 19 (CI 45,170), D&C Red No. 9 (CI 15,585), D&C Red No. 21 (CI 45,380), D&C Orange No. 4 (CI 15,510), D&C Orange No. 5 (CI 45,370), D&C Red No. 27 (CI 45,410), D&C Red No. 13 (CI 15,630), D&C Red No. 7 (CI 15,850), D&C Red No. 6 (CI 15,850), D&C Yellow No. 5 (CI 19,140), D&C Red No. 36 (CI 12,085), D&C Orange No. 10 (CI

45,425), D&C Yellow No. 6 (CI 15,985), D&C Red No. 30 (CI 73,360), D&C Red No. 3 (CI 45,430), the dye or lakes based on Cochineal Carmine (CI 75,570) and mixtures thereof.

[0232] The pearlescent pigments useful in this disclosure include those selected from the group consisting of the white pearlescent pigments such as mica coated with titanium oxide, bismuth oxychloride, colored pearlescent pigments such as titanium mica with iron oxides, titanium mica with ferric blue, chromium oxide and the like, titanium mica with an organic pigment of the above-mentioned type as well as those based on bismuth oxychloride and mixtures thereof. The amount of pigment in the topical composition is typically about 0 to about 10%. For ocular applications a pigment is generally not used.

[0233] In a particularly preferred embodiment of the disclosure, topical pharmaceutical compositions for ocular administration are prepared typically comprising component A and B (a carrier), such as purified water, and one or more ingredients selected from the group consisting of y) sugars or sugar alcohols such as dextrans, particularly mannitol and dextran 70, z) cellulose or a derivative thereof, aa) a salt, bb) disodium EDTA (Edetate disodium), and cc) a pH adjusting additive.

[0234] Examples of z) cellulose derivatives suitable for use in the topical pharmaceutical composition for ocular administration include sodium carboxymethylcellulose, ethylcellulose, methylcellulose, and hydroxypropyl-methylcellulose, particularly, hydroxypropyl-methylcellulose.

[0235] Examples of aa) salts suitable for use in the topical pharmaceutical composition for ocular administration include mono-, di- and trisodium phosphate, sodium chloride, potassium chloride, and combinations thereof.

[0236] Examples of cc) pH adjusting additives include HCl or NaOH in amounts sufficient to adjust the pH of the topical pharmaceutical composition for ocular administration to the range of 4.5-7.5 pH units.

[0237] Component A may be included in kits comprising a compound as described herein, a systemic or topical composition described above, or both; and information, instructions, or both that use of the kit will provide treatment for cosmetic and medical conditions in mammals (particularly humans). The information and instructions may be in the form of words, pictures, or both, and the like. In addition or in the alternative, the kit may comprise the medicament, a composition, or both; and information, instructions, or both, regarding methods of application of medicament, or of composition, preferably with the benefit of treating or preventing cosmetic and medical conditions in mammals (*e.g.*, humans).

[0238] The disclosure will be further explained by the following illustrative Examples that are to be considered to be non-limiting.

Examples

Example 1: ROCK and JAK assays.

ROCK Kinase Inhibition Assays.

[0239] All compounds were initially prepared as 10 mM stocks in anhydrous dimethylsulfoxide (DMSO). A 20 µL aliquot of the 10 mM solutions was transferred to individual wells in column 1 of a 96-well polypropylene microtiter plate (Corning #3363) and diluted with DMSO to give a final compound concentration of 4 mM. Test compounds were then serially diluted 1:5 in DMSO for an 11-point concentration response and further diluted in the assay buffer bringing all compound concentrations to a final range of 100 µM to 10 pM in 2.5% DMSO. The assay was performed in white 96-well, flat-bottom, half-area, non-binding assay plate (Corning #3642) in assay buffer consisting of 20 mM HEPES (pH 7.5), 10 mM $MgCl_2$*$6H_2O$, 100 µM sodium orthovanadate, 0.05% CHAPS and 0.1% bovine serum albumin. A 10 µL aliquot of compound from each well of the intermediate dilution plate and 20 µL of a 2X substrate/enzyme solution containing acceptor substrate (800nM RSK2 peptide KRRRLSSLRA (SEQ ID NO: 1)), ROCK2 enzyme (10 nM), or ROCK1 enzyme, and 1,4-Dithiothreitol (DTT, 2uM) were added to all wells. The reaction was initiated by the addition of 10 µL of 4x stock solution ATP (2 µM). Reactions were thoroughly mixed manually, covered and allowed to incubate at room temperature for 75 min. Protein kinase activity was quantitated using Promega's KINASE-GLO™ luminescent Kinase Assay Kit according to the manufacturer's directions. ATP concentrations remaining in Test wells following the termination of the enzymatic reaction were compared against control wells containing equivalent amounts of DMSO containing no inhibitor (CTRL). ATP concentrations in both Test wells and CTRL wells were normalized against background (BKG) ATP concentrations in wells containing concentrations of inhibitor that completely inhibited the protein kinase under investigation (i.e. a concentration that prevented any consumption of ATP over the course of the incubation). Percent of Control (POC) values were determined for each concentration of compound tested according to the equation: POC = ((Test well value – BKG)/ (CTRL – BKG))*100

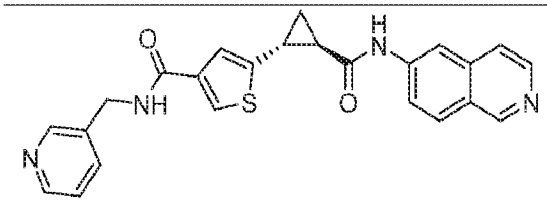
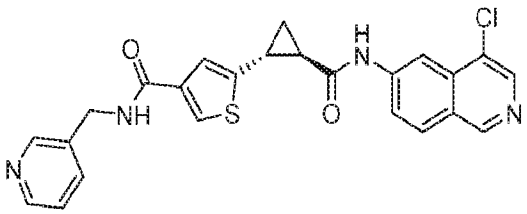
[0240] IC_{50} values were calculated using the following 4-parameter logistic curve-fitting algorithm: f(x) = (A+((B-A)/(1+((x/C)^D))))

[0241] IC_{50} values were converted to K_i values using the Cheng-Prusoff Equation: $K_i = IC_{50} / (1 + ([ATP]/Km\ ATP]))$.

JAK Kinase Assays.

[0242] Compounds were prepared in the exact same manner as described in the ROCK Kinase Assay with the exception to the substrate and enzyme. The JAK 2X substrate/enzyme solution consisted of acceptor substrate (800nM Abl peptide EAIYAAPFAKKK (SEQ ID NO:2)), JAK2 or JAK3 enzyme (10nM) and DTT (2uM). All other steps and solutions remain identical to the ROCK Kinase Assay above. Results are shown below in Table 2 and Table 3.

Table 2.

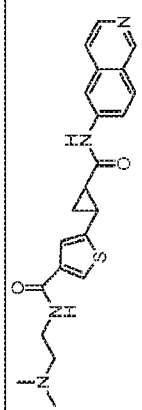
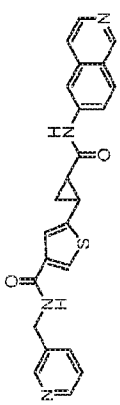
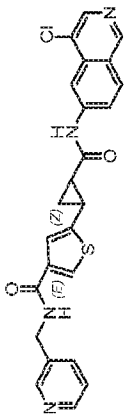
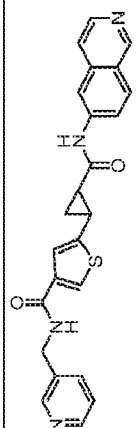
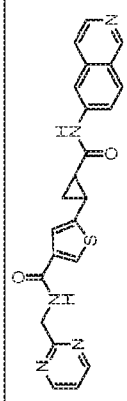
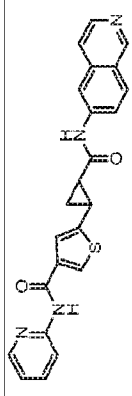
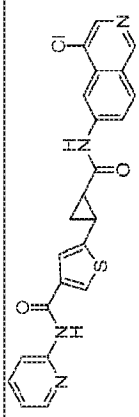
	IC_{50} (nM)
 Compound 6	3.5 nM (ROCK2) 3.9 nM (ROCK1) 109.2 nM (JAK2) 33.5 nM (PKCh) 43.8 nM (PKCd)
 Compound 8	6.9 nM (ROCK2) 7.7 nM (ROCK1) 12.8 nM (JAK2) 31.5 nM (PKCh) 45.9 nM (JAK3) 90.5 nM (PKCd)

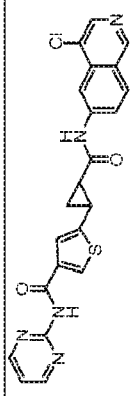
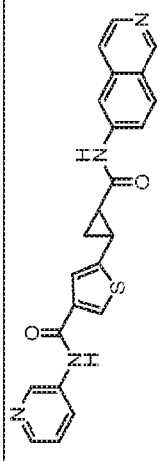
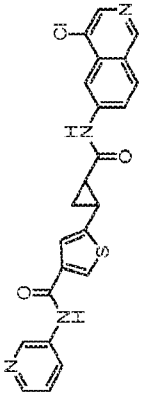
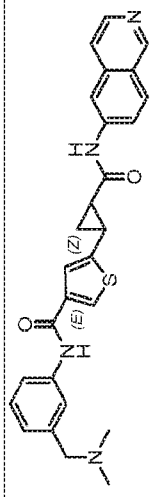
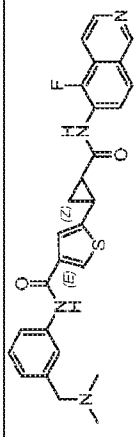
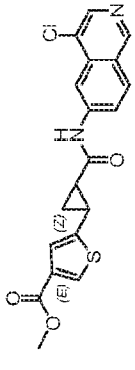
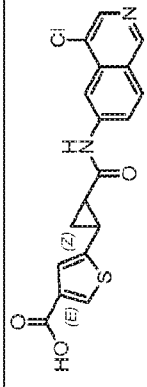
Example 2. PTM-HTM assay

[0243] Porcine Trabecular Meshwork cells (PTM) were isolated from freshly obtained enucleated porcine eyes. Immortalized Human Trabecular Meshwork cells (TM-1) were obtained through a kind gift from Donna Peters in the Department of Ophthalmology and Visual Sciences at the University of Wisconsin. Cells were plated onto fibronectin coated glass-bottom 96-well plates and allowed to attach overnight. Media was removed and replaced with test compound in media with 1% fetal bovine serum and incubated for various times. After incubation, cells were formaldehyde fixed, triton solubilized, and stained. PTM cells were stained with Alexa Fluor® 488 phalloidin (F-actin) and Hoechst 33342 (nuclei). TM-1 cells were stained with anti-paxillin followed by Alexa Fluor® 488 goat-anti-mouse IgG (focal adhesions) and Hoechst 33342 (nuclei). All staining reagents were obtained through Invitrogen. Images were collected on an INCell 2200 imager with a 20X objective. The actin fiber length and total area of focal adhesions were analyzed using custom algorithms developed in the INCell Developer Toolbox, v1.9.3. Data collected were converted to percent of control (untreated cells). Curves were fit to data in GraphPad Prizm using sigmoidal dose-response and constraining top and bottom to 100% and 0%, respectively. Results are shown below in Table 3.

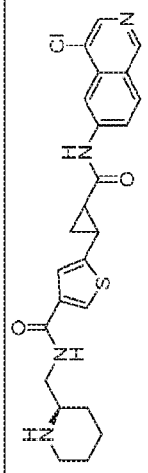
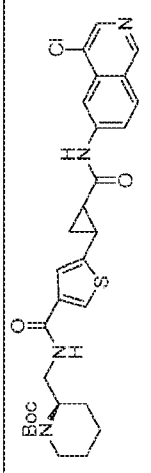
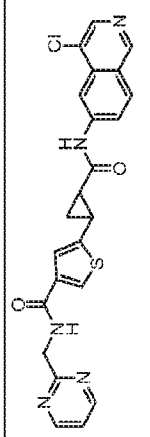
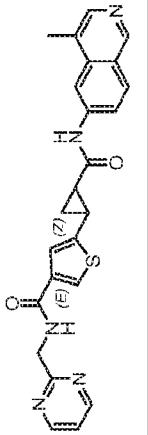
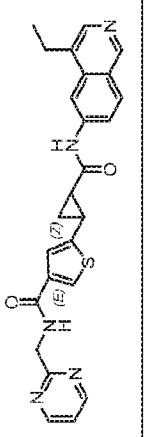
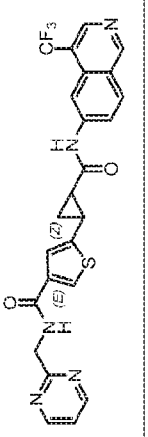
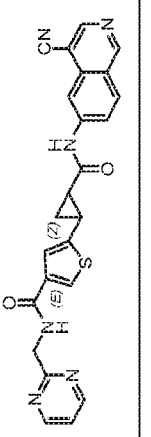
Table 3.

Compound	ROCK1 Ki nM	ROCK2 Ki nM	JAK1 Ki nM	JAK2 Ki nM	JAK3 Ki nM	TyK Ki nM	IKKb Ki nM	PTM IC50 nM	STAT5 XC50 nM	STAT3 XC50 nM	NfkB XC50 nM
	5.0	4.0	89	30	1.9	173	41	49	3000	531	1359
	6.0	5.0	19	2.5	0.65	24	25	79	150	64	187
	7	4	7	2	1.0	4.9	55	125	111	18	ND
	2.5	6.0	5	2.0	1.9	8	204	ND	ND	ND	ND
	7.0	5.0	12	2.0	1.9	10	83	71	93	79	83
	8	4.0	34	4.4	9.0	91	460	ND	ND	ND	ND

	4.7	4.0	ND	677	2799	ND	2255	96	ND	ND	ND
	3.5	3.9	ND	112	266	ND	943	71	ND	ND	ND
	8.0	7.0	86	13	46	41	1490	337	ND	ND	ND
	3.9	3.5	ND	112	266	ND	943	71	ND	ND	ND
	4.7	4.0	78	7.0	4.4	69	95	40	3000	440	1013
	6	3	ND	90	269	ND	386	9	ND	ND	ND
	6.0	7.0	39	14	45	77	441	11	ND	ND	ND

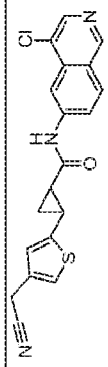
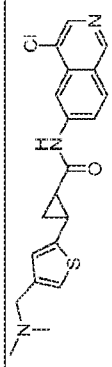
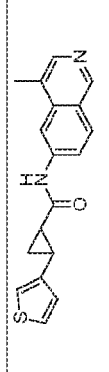
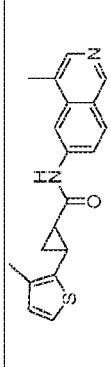
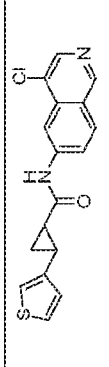
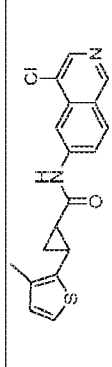
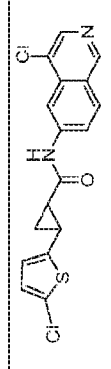
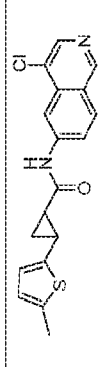
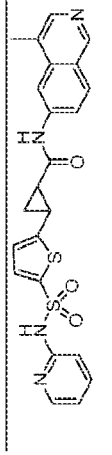
	5.0	3.5	30	3.9	27	34	102	50	634	331	1612
	3.9	2.0	ND	160	463	ND	ND	65	ND	ND	ND
	6.0	4.5	175	17	129	140	857	48	ND	ND	ND
	2.6	1.0	ND	116	957	ND	626	24	ND	ND	ND
	3.5	2.5	ND	1272	4872	ND	3240	8	ND	ND	ND
	19	10	135	25	120	698	1304	952	ND	ND	ND
	171	79	267	50	267	284	1961	ND	ND	ND	ND

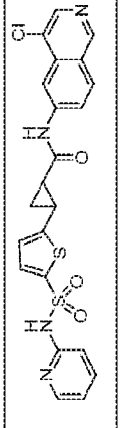
	77	33	199	33	219	659	3613	ND	ND	ND
	10	6.0	42	10	39	198	1581	ND	3000	ND
	23	12	29	7	38	127	925	ND	ND	ND
	49	48	135	10	7	313	409	ND	ND	ND
	26	21	159	3.9	8	289	581	ND	399	3000
	8	4.9	18	2.0	2.4	72	211	64	74	133
	21	17	322	66	234	369	2677	ND	ND	ND

	7	4.9	68	19	96	104	1245	89	ND	ND	ND	ND	ND
	21	13	240	74	248	836	50000	ND	ND	ND	ND	ND	ND
	7.0	5.0	12	2.0	1.9	10	83	71	93	79	83		
	8	7	45	3.9	2.9	38	115	617	467	219	455		
	22	32	194	14	7	183	89	ND	1774	275	990		
	67	77	127	7	4.8	96	556	ND	327	124	105		
	27	28	66	3.9	3.4	47	356	ND	354	443	453		

	48	53	123	7	3.9	103	73	ND	230	289	1154
	7	4.5	603	130	24	902	281	253	ND	ND	ND
	14	10	ND	11	3.4	ND	250	379	643	267	
	6	11	ND	685	2211	ND	2703	882	ND	ND	ND
	12	9	ND	46	222	ND	1660	972	ND	ND	ND
	7	5	ND	325	1406	ND	668	159	ND	ND	ND
	15	10	ND	67	926	ND	5472	180	ND	ND	ND
	2.2	4.0	ND	794	3077	ND	2776	331	ND	ND	ND
	15	16	ND	88	628	ND	2071	305	ND	ND	ND

Compound	ROCK1 Ki nM	ROCK2 Ki nM	JAK1 Ki nM	JAK2 Ki nM	JAK3 Ki nM	TyK Ki nM	IKKb Ki nM	PTM IC50 nM	STAT5 XC50 nM	STAT5-IL2 nM	STAT3 XC50 nM	NfkB XC50 nM
	15	15	38	4.0	6.0	22	246	752	318	597	ND	
	23	12	29	7	38	127	925	ND	3000	2027	281	ND
	20	160	104	20	74	377	738	ND	643		267	
	34	26	50	10	68	214	1390	ND	ND	1092	321	ND
	260	237	408	73	455	1686	6406	ND	ND	ND	ND	ND
	3	2	6	0.98	0.71	8	68	44	ND	98	ND	43
	135	87	461	56	149	130	4881	ND	ND	ND	ND	ND

	108	60	96	16	86	242	3982	ND	ND	ND	ND
	280	194	215	42	228	790	10483	ND	ND	ND	ND
	46	40	166	41	248	733	1500	ND	ND	ND	ND
	619	652	1327	156	1812	3126	10595	ND	ND	ND	ND
	39	35	58	14	99	340	1948	ND	ND	ND	ND
	521	462	501	78	1080	1674	32095	ND	ND	ND	ND
											
											
	8	4	39	3.9	23	121	106	232	3000	2353	2153	ND

	8	4.9	12	3.0	12	48	111	105	3000	1406	110	ND

Example 3. Formulations.

[0244] In some embodiments, topical pharmaceutical compositions for lowering intraocular pressure comprising the compounds provided herein are prepared by conventional methods and formulated as shown in Table 4.

Table 4.

Ingredient	Amount (wt %)
Thienylcyclopropyl amino acid isoquinolyl amide	0.50
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium Chloride	0.77
Potassium chloride	0.12
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 4.5-6.5
Purified water	q.s. to 100%

[0245] A compound according to this disclosure is used as the thienylcyclopropyl amino acid isoquinolyl amide. When the composition is topically administered to the eyes once daily, the above composition decreases intraocular pressure in a subject suffering from glaucoma.

Example 4. Pharmacological Activity for Glaucoma Assay.

[0246] Pharmacological activity for glaucoma can also be demonstrated using assays designed to test the ability of the subject compounds to decrease intraocular pressure. Examples of such assays are described in the following reference, incorporated herein by reference: C. Liljebris, G. Selen, B. Resul, J. Sternschantz, and U. Hacksell, "Derivatives of 17-phenyl-18, 19, 20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester: Potential Anti-glaucoma Agents", *Journal of Medicinal Chemistry* 1995, 38 (2): 289-304.

Example 5. Storage.

[0247] A compound or composition provided herein is prepared and placed in a container for storage at ambient or elevated temperature. When the compound or composition is stored in a polyolefin plastic container as compared to a polyvinyl chloride plastic container, discoloration of the compound or composition is reduced, whether dissolved or suspended in a liquid composition (e.g., an aqueous or organic liquid solution), or as a solid. Without wishing to be bound by theory, the container reduces exposure of the container's contents to electromagnetic radiation, whether visible light (e.g., having a wavelength of about 380–780 nm) or ultraviolet (UV) light (e.g., having a wavelength of about 190–320 nm (UV-B light) or about 320–380 nm (UV-A light)). Some containers also include the capacity to reduce exposure of the container's

contents to infrared light, or a second component with such a capacity. The containers used include those made from a polyolefin such as polyethylene, polypropylene, polyethylene terephthalate, polycarbonate, polymethylpentene, polybutene, or a combination thereof, especially polyethylene, polypropylene, or a combination thereof. The container may further be disposed within a second container, for example, a paper, cardboard, paperboard, metallic film, or foil, or a combination thereof, container to further reduce exposure of the container's contents to UV, visible, or infrared light. Compounds and compositions benefiting from reduced discoloration, decomposition, or both during storage, include eye drop solutions or implants that include a compound or composition thereof provided herein. Eye drop solutions or implants may need storage lasting up to, or longer than, three months; in some cases up to, or longer than one year. The containers described herein may be eye drop or implant containers. The containers may be in any form suitable to contain the contents; for example, a bag, a bottle, or a box.

[0248] Other suitable containers and packaging are described, for example, in International publication numbers WO 2018/159700, WO 2018/159701, and WO 2018/159702, and JP 6236167 B2, the contents of which are incorporated herein by reference.

[0249] Compositions disposed within the containers described may include: boric acid, D-mannitol, benzalkonium chloride, polyoxyl 40 stearate, polyethylene glycol 400, ethylenediamine tetraacetic acid, or a combination thereof; and water or another suitable solvent vehicle or excipient. In some cases, the vehicle is an aqueous vehicle. In other cases, the vehicle is a non-aqueous vehicle.

[0250] The preceding disclosures are illustrative embodiments. It should be appreciated by those of skill in the art that the devices, techniques and methods disclosed herein elucidate representative embodiments that function well in the practice of the present disclosure. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

[0251] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the invention are approximations, the numerical values set forth in the

specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

[0252] The terms "a" and "an" and "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0253] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

[0254] Groupings of alternative elements or embodiments of the invention disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0255] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects those of ordinary skill in the art to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

[0256] Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed or

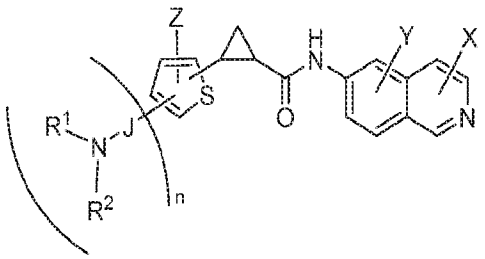
added per amendment, the transition term "consisting of" excludes any element, step, or ingredient not specified in the claims. The transition term "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the invention so claimed are inherently or expressly described and enabled herein.

[0257] Further, it is to be understood that the embodiments of the invention disclosed herein are illustrative of the principles of the present invention. Other modifications that may be employed are within the scope of the invention. Thus, by way of example, but not of limitation, alternative configurations of the present invention may be utilized in accordance with the teachings herein. Accordingly, the present invention is not limited to that precisely as shown and described.

CLAIMS

What is claimed is:

1. A compound according to Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein,

n is 0 or 1;

J is $-S(O_2)-$ or $-C(O)-$;

R^1 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, $-C_{1-6}$ alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ haloalkyl, aryl, -aryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -heteroaryl-(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heteroaryl-(C_{1-6} alkyl), -(C_{1-6} alkyl)-aryl-(C_{1-6} alkyl), -NH-heteroaryl, -NH-aryl, $-C_{1-6}$ alkyl-CN, heteroaryl, -(C_{1-6} alkyl)-heteroaryl, -(C_{1-6} alkyl)-$N(R^3)R^4$, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a -heterocycle;

R^3 is H, C_{1-6} alkyl or $-C_{1-6}$ haloalkyl;

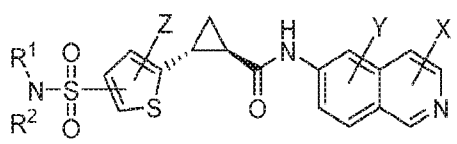
R^4 is H, C_{1-6} alkyl or $-C_{1-6}$ haloalkyl;

X is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl;

Y is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen or hydroxyl; and

Z is H, C_{1-6} alkyl, $-C_{1-6}$ haloalkyl, halogen, hydroxyl, -(C_{1-6} alkyl)-N-[(C_{1-6} alkyl)]-(C_{1-6} alkyl), $-C_{1-6}$ alkyl-CN, $-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl-O(CO)-C_{1-6} alkyl, $-C_{1-6}$ alkyl-(CO)O-C_{1-6} alkyl, -(CO)OH, or -(CO)O-C_{1-6} alkyl.

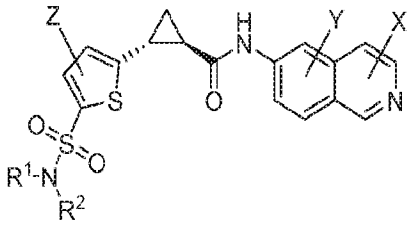
2. The compound of claim 1, having a Formula (I-A):



(I-A),

or a pharmaceutically acceptable salt thereof.

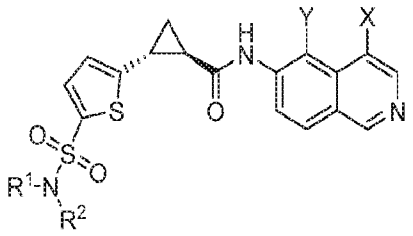
3. The compound of claim 1, having a Formula (I-A1):



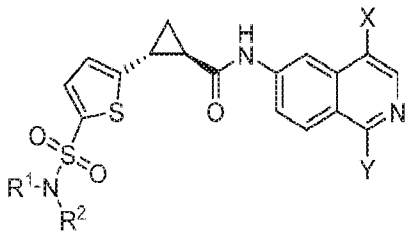
(I-A1),

or a pharmaceutically acceptable salt thereof.

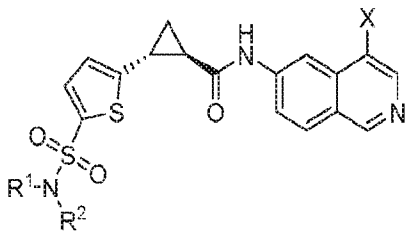
4. The compound of claim 3, wherein the compound of Formula (I) is a compound of



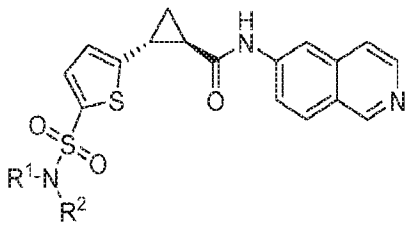
(I-A1-a),



(I-A1-b),



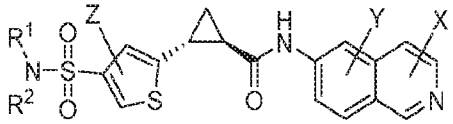
(I-A1-c),



(I-A1-d),

or a pharmaceutically acceptable salt thereof.

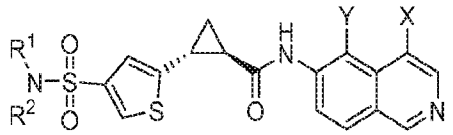
5. The compound of claim 1, having a Formula (I-A2):



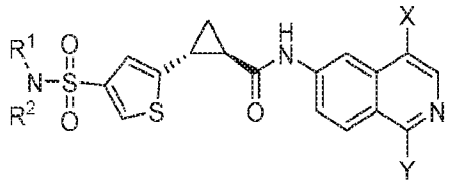
(I-A2),

or a pharmaceutically acceptable salt thereof.

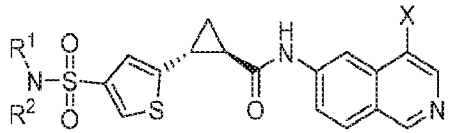
6. The compound of claim 5, wherein the compound of Formula (I) is a compound of



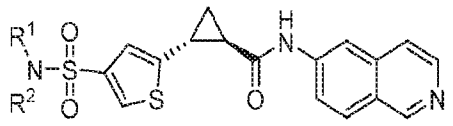
(I-A2-a),



(I-A2-b),



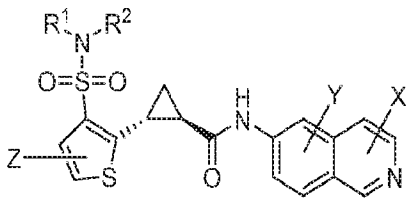
(I-A2-c),



(I-A2-d),

or a pharmaceutically acceptable salt thereof.

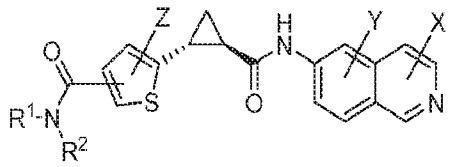
7. The compound of claim 1, having a Formula (I-A3):



(I-A3),

or a pharmaceutically acceptable salt thereof.

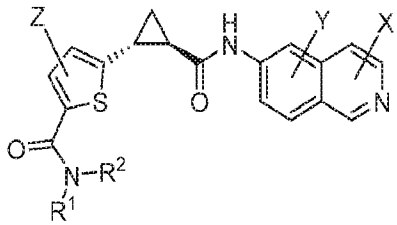
8. The compound of claim 1, having a Formula (I-B):



(I-B),

or a pharmaceutically acceptable salt thereof.

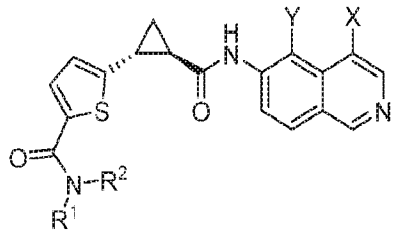
9. The compound of claim 1, having a Formula (I-B1):



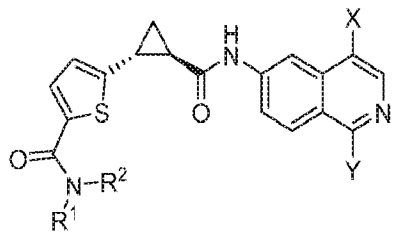
(I-B1),

or a pharmaceutically acceptable salt thereof.

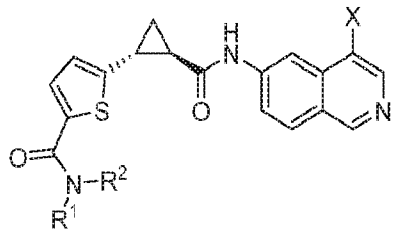
10. The compound of claim 9, wherein the compound of Formula (I) is a compound of:



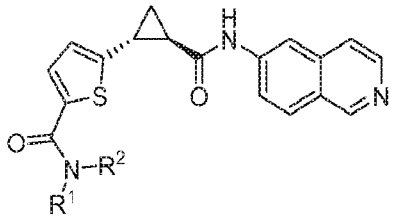
(I-B1-a),



(I-B1-b),



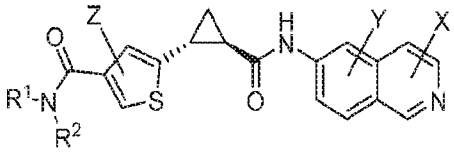
(I-B1-c),



(I-B1-d),

or a pharmaceutically acceptable salt thereof.

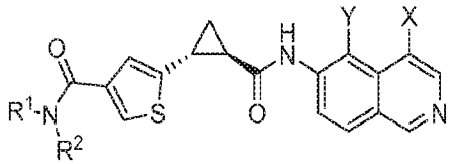
11. The compound of claim 1, having a Formula (I-B2):



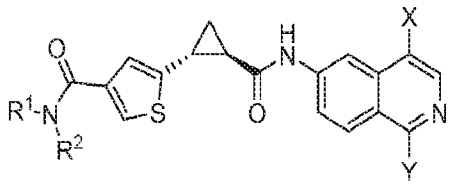
(I-B2),

or a pharmaceutically acceptable salt thereof.

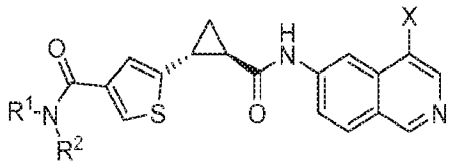
12. The compound of claim 9, wherein the compound of Formula (I) is a compound of:



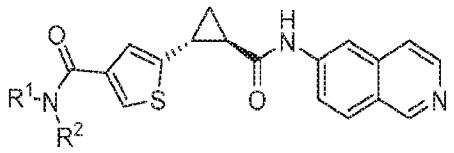
(I-B2-a),



(I-B2-b),



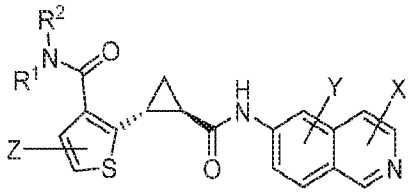
(I-B2-c),



(I-B2-d),

or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, having a Formula (I-B3):



(I-B3),

or a pharmaceutically acceptable salt thereof.

14. The compound of one of claims 1-13,

wherein R^1 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl; and

R^2 is H, -C_{1-6} alkyl, -C_{1-6} haloalkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

15. The compound of one of claims 1-13,

wherein R^1 is H, -C_{1-6} alkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, -C_{1-6} alkyl, aryl, heteroaryl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a heterocycle;

R^3 is H or C_{1-6} alkyl;

R^4 is H or C_{1-6} alkyl;

X is H, C_{1-6} alkyl, halogen or hydroxyl;

Y is H, C_{1-6} alkyl, halogen or hydroxyl; and

Z is H, C_{1-6} alkyl, halogen or hydroxyl.

16. The compound of one of claims 1-13,

wherein R^1 is H, -C_{1-4} alkyl, aryl, heteroaryl, -(C_{1-4} alkyl)-pyridinyl, -(C_{1-4} alkyl)-N(R^3)R^4, -(C_{1-4} alkyl)-heterocyclyl or heterocycloalkyl;

R^2 is H, -C_{1-4} alkyl, aryl, heteroaryl, -(C_{1-4} alkyl)-pyridinyl, -(C_{1-4} alkyl)-N(R^3)R^4, -(C_{1-4} alkyl)-heterocyclyl or heterocycloalkyl;

or R^1 and R^2, together with the nitrogen to which they are attached, form a heterocycle;

R^3 is H or C_{1-4} alkyl;

R^4 is H or C_{1-4} alkyl;

X is H, C_{1-4} alkyl, halogen or hydroxyl;

Y is H, C_{1-4} alkyl, halogen or hydroxyl; and

Z is H, C_{1-4} alkyl, halogen or hydroxyl.

17. The compound of one of claims 1-13,

wherein R^1 is H, phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl; and

R^2 is H, phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

18. The compound of one of claims 1-13,

wherein R^1 is H; and

R^2 is H, phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

19. The compound of one of claims 1-13, wherein R^1 is H or -C_{1-6} alkyl.

20. The compound of one of claims 1-13, wherein R^1 is -C_{1-6} alkyl.

21. The compound of one of claims 1-13, wherein R^1 is H.

22. The compound of one of claims 1-13, wherein R^2 is phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

23. The compound of one of claims 1-13, wherein pyridinyl is 2-pyridinyl.

24. The compound of one of claims 1-13, wherein pyridinyl is 3-pyridinyl.

25. The compound of one of claims 1-13, wherein pyridinyl is 4-pyridinyl.

26. The compound of one of claims 1-13, wherein R^2 is phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl.

27. The compound of one of claims 1-13, wherein R^2 is -(C_{1-6} alkyl)-N(R^3)R^4, -(C_{1-6} alkyl)-heterocyclyl or heterocycloalkyl;

28. The compound of one of claims 1-13, wherein R^2 is phenyl, pyridinyl, -(C_{1-6} alkyl)-pyridinyl.

29. The compound of one of claims 1-13, wherein R^2 is pyridinyl.

30. The compound of one of claims 1-13, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl containing six ring atoms.

31. The compound of one of claims 1-13, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl containing six ring atoms, wherein one or two of the ring atoms are, independently, O, S or N.

32. The compound of one of claims 1-13, wherein R^1 and R^2, together with the nitrogen to which they are attached, form a heterocyclyl containing six ring atoms, wherein one or two of the ring atoms are N.

33. The compound of one of claims 1-13, wherein R^3 and R^4 are H.

34. The compound of one of claims 1-13, wherein R^3 and R^4 are, independently, C_{1-6} alkyl.

35. The compound of one of claims 1-13, wherein R^3 is H, and R^4 is C_{1-6} alkyl.

36. The compound of one of claims 1-13, wherein
X is C_{1-6} alkyl, halogen or hydroxyl; and
Y and Z are H.

37. The compound of one of claims 1-13, wherein
X is halogen; and
Y and Z are H.

38. The compound of one of claims 1-13, wherein X is C_{1-6} alkyl, halogen or hydroxyl.

39. The compound of one of claims 1-13, wherein X is methyl, ethyl, CF_3, CHF_2 or CH_2F.

40. The compound of one of claims 1-13, wherein Y is methyl, ethyl, CF_3, CHF_2 or CH_2F.

41. The compound of one of claims 1-13, wherein Z is methyl, ethyl, CF_3, CHF_2 or CH_2F.

42. The compound of one of claims 1-13, wherein X is halogen.

43. The compound of one of claims 1-13, wherein X is F or Cl.

44. The compound of one of claims 1-13, wherein X is Cl.

45. The compound of one of claims 1-13, wherein
X is methyl or halogen;
Y is methyl or halogen; and
Z is methyl or halogen.

46. The compound of one of claims 1-13, wherein
X is methyl, F or Cl;
Y is methyl, F or Cl; and
Z is methyl, F or Cl.

47. The compound of one of claims 1-13, wherein
X is halogen; and
Y is hydroxyl.

48. The compound of one of claims 1-13, wherein Y is hydroxyl.

49. The compound of one of claims 1-13, wherein Z is H or F.

50. The compound of one of claims 1–13, wherein:
aryl is phenyl; and
heteroaryl is pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, pyrazolyl, or imidazolyl.

51. The compound of one of claims 1–13, wherein the compound is a compound of Table 1 or Table 3, or a pharmaceutically acceptable salt thereof.

52. A composition, comprising the compound of one of claims 1–51.

53. A pharmaceutical composition, comprising the compound of one of claims 1–51, and a pharmaceutically acceptable excipient.

54. A method of treating an ocular disorder in a subject in need thereof, the method comprising administering to the subject a compound of one of claims 1-51.

55. A method of treating an ocular disorder in a subject in need thereof, the method comprising administering to the subject a composition including a compound of one of claims 1-51.

56. The method of claim 54 or 55 wherein the ocular disorder is glaucoma.

57. A method of reducing intraocular pressure in a subject in need thereof, the method comprising administering to the subject a compound of one of claims 1-51.

58. A method of reducing intraocular pressure in a subject in need thereof, the method comprising administering to the subject a composition including a compound of one of claims 1-51.

59. The method of one of claims 54-58 wherein the administering is topically to an eye.

60. A method of treating an autoimmune disease in a subject in need thereof, the method comprising administering to the subject a compound of one of claims 1-51.

61. A method of treating an autoimmune disease in a subject in need thereof, the method comprising administering to the subject a composition including a compound of one of claims 1-51.

62. The method of claim 61, wherein the autoimmune disease is multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, autoimmune thyroid disorders, chronic obstructive pulmonary disease, or a combination thereof.

63. A method of treating a disease or condition associated with kinase activity or diseases or conditions affected by kinases, the method comprising administering to the subject a compound of one of claims 1-51.

64. A method of treating a disease or condition associated with kinase activity or diseases or conditions affected by kinases, the method comprising administering to the subject a composition including a compound of one of claims 1-51.

65. The method of claims 63 or 64, wherein the disease is neurodegenerative disease, ocular disease, cardiovascular disease, or cancer.

66. A kit including a composition including a compound of one of claims 1-51 and instructions for use.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/19822

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/19822

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 52-66
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/19822

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/381; A61K 31/4709; A61P 9/00; 27/02; 35/00 (2020.01)

CPC - C07D 213/56; C07C 237/48; C07D 333/06; C07D 409/12; A61K 31/381; A61K 31/4709

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2018/0327381 A1 (AERIE PHARMACEUTICALS, INC.) 15 November 2018 (15.11.2018) para [0003];[0008];[0164];[0172];[0373];[0382];[0406];[0422];[0424];[0425] pg. 40, Table 2; pg. 42, Table 2; pg 56, Table 6; pg. 60, Table 6.1; pg. 80, Table 10; pg. 91, Table 13.1; pg. 93, Table 14; pg. 102-104, Table 15; pg. 113, Table 16; pg. 115, Table 17; pg. 121, Table 17; pg. 136, Col 1	1-51
Y	US 2018/0186746 A1 (AERIE PHARMACEUTICALS, INC.) 05 July 2018 (05.07.2018) para [0002];[0006]; [0025];[0027]; [0045]	1-51
A	US 2017/0319559 A1 (PLEXXIKON, INC.) 09 November 2017 (09.11.2017) ENTIRE DOCUMENT	1-51
A	US 2010/0168102 A9 (DEFERT et al.) 01 July 2010 (01.07.2010) ENTIRE DOCUMENT	1-51

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
25 APRIL 2020	05 JUN 2020
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. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300