



(12) **DEMANDE DE BREVET CANADIEN**
CANADIAN PATENT APPLICATION
(13) **A1**

(86) **Date de dépôt PCT/PCT Filing Date:** 2017/03/31
(87) **Date publication PCT/PCT Publication Date:** 2018/02/22
(85) **Entrée phase nationale/National Entry:** 2019/02/06
(86) **N° demande PCT/PCT Application No.:** US 2017/025609
(87) **N° publication PCT/PCT Publication No.:** 2018/034702
(30) **Priorité/Priority:** 2016/08/19 (US62/377,219)

(51) **Cl.Int./Int.Cl.** **A61K 31/16** (2006.01),
C07C 237/48 (2006.01), **C07D 333/22** (2006.01)
(71) **Demandeur/Applicant:**
AERIE PHARMACEUTICALS, INC., US
(72) **Inventeurs/Inventors:**
STURDIVANT, JILL M., US;
DELONG, MITCHELL A., US;
ROYALTY, SUSAN M., US
(74) **Agent:** SMART & BIGGAR

(54) **Titre :** COMPOSES AMIDES BETA-AMINO-ISOQUINOLEINE
(54) **Title:** BETA-AMINO-ISOQUINOLINYL AMIDE COMPOUNDS

(57) **Abrégé/Abstract:**

Disclosed are alpha-axyl-beta-axmno isoquinoline amide compounds and substituted benzamide compounds. In particular, the invention provides compounds that affect the function of kinases in a cell and that are useful as therapeutic agents or with therapeutic agents. The compounds of the invention are useful in the treatment of a variety of diseases and conditions including eye diseases such as glaucoma, cardiovascular diseases, and diseases characterized by abnormal growth, such as cancers. The invention further provides compositions containing isoquinoline amide compounds.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(10) International Publication Number
WO 2018/034702 A1

(43) International Publication Date
22 February 2018 (22.02.2018)

(51) International Patent Classification:

A61K 31/16 (2006.01) *C07C 237/48* (2006.01)
C07D 333/22 (2006.01)

Published:

— with international search report (Art. 21(3))

(21) International Application Number:

PCT/US2017/025609

(22) International Filing Date:

31 March 2017 (31.03.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/377,219 19 August 2016 (19.08.2016) US

(71) Applicant: **AERIE PHARMACEUTICALS, INC.**
[US/US]; 135 US Highway 206, Suite 15, Bedminster, NJ
07921 (US).

(72) Inventors: **STURDIVANT, Jill, M.**; 3930 Crawford Dairy
Road, Chapel Hill, NC 27516 (US). **DELONG, Mitchell,**
A.; 212 Hillcrest Circle, Chapel Hill, NC 27514 (US).
ROYALTY, Susan, M.; 1920 El Dorado Place, Davis, CA
95616 (US).

(74) Agent: **YAGER, Charlene, L.**; Michael Best & Friedrich
LLP, 100 East Wisconsin Avenue, Suite 3300, Milwaukee,
WI 53202-4108 (US).

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR,
KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,
TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

(54) Title: BETA-AMINO-ISOQUINOLINYL AMIDE COMPOUNDS

(57) Abstract: Disclosed are *alpha*-axyl-*beta*-axmno isoquinoline amide compounds and substituted benzamide compounds. In particular, the invention provides compounds that affect the function of kinases in a cell and that are useful as therapeutic agents or with therapeutic agents. The compounds of the invention are useful in the treatment of a variety of diseases and conditions including eye diseases such as glaucoma, cardiovascular diseases, and diseases characterized by abnormal growth, such as cancers. The invention further provides compositions containing isoquinoline amide compounds.

WO 2018/034702 A1

- 1 -

BETA-AMINO-ISOQUINOLINYL AMIDE COMPOUNDS**CROSS-REFERENCE TO RELATED APPLICATION**

[0001] The application claims priority to U.S. Provisional Patent Application No. 62/377,219, filed August 19, 2016, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to *beta*-amino isoquinoliny1 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, for the treatment of cardiovascular diseases, and for diseases characterized by abnormal growth, such as cancers.

BACKGROUND

[0003] 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 only recently been recognized and investigated as potential intervention points in disease states. One of the most important classes of these downstream effectors is the “kinase” class.

[0004] The various kinases thus 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

- 2 -

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*).

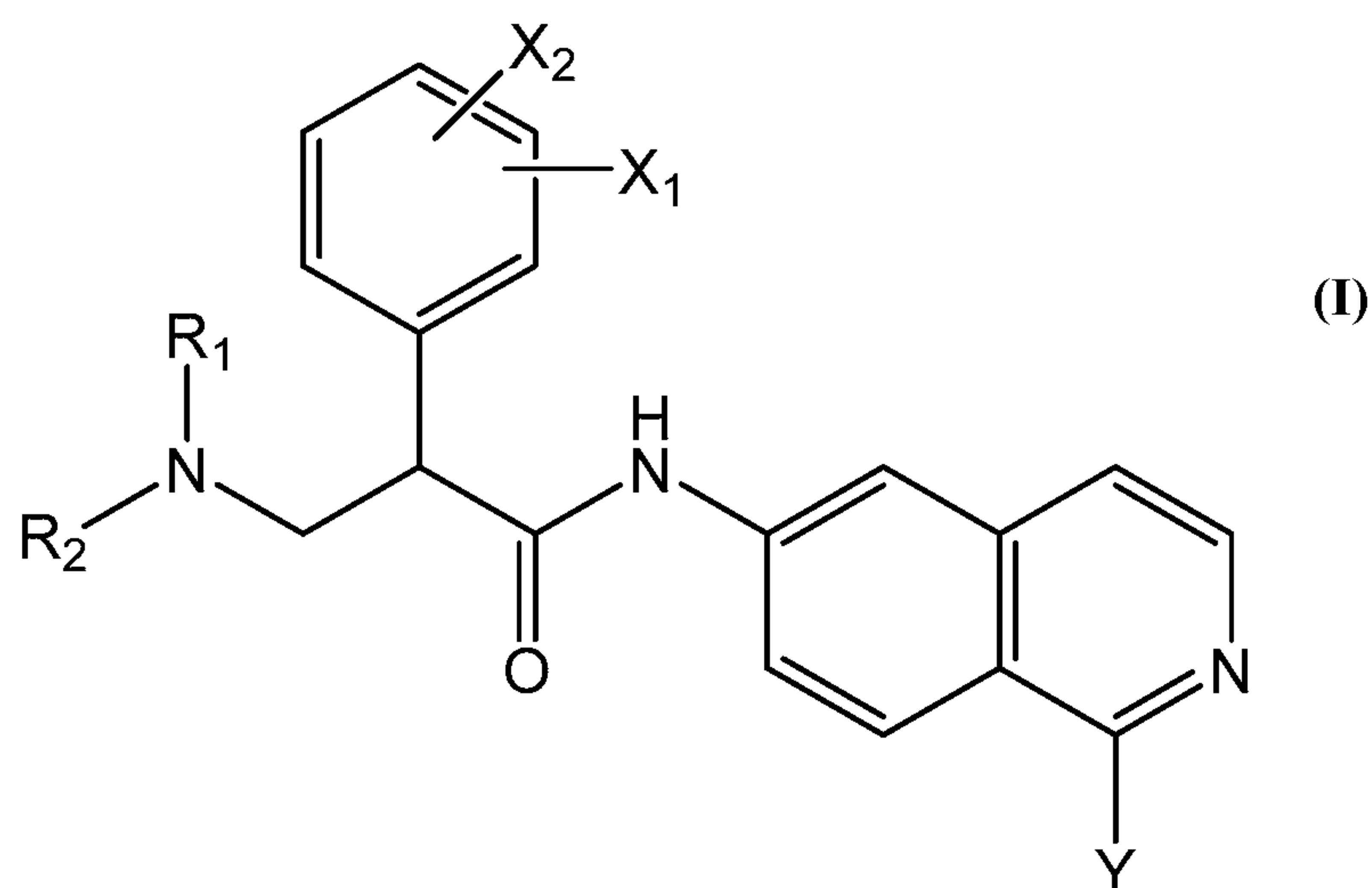
[0005] The success of the tyrosine-kinase inhibitor STI571 (Gleevec) in the treatment of chronic myelogenous leukaemia (*Nature Reviews Drug Discovery 2003, 2: 296-313*) has spurred considerable efforts to develop other kinase inhibitors for the treatment of a wide range of other cancers (*Nature Reviews 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.

- 3 -

[0006] In view of the role that kinases have 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 by the compounds of the present invention is, at least in part, responsible for their beneficial effects.

SUMMARY

[0007] In an aspect of the invention, a compound is provided according to Formula I:



and enantiomers, diastereomers, and salts thereof;

wherein R_1 and R_2 are, independently, H or C_1 - C_4 alkyl; and

wherein X_1 and X_2 are, independently, H, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, or halogen; or together X_1 and X_2 may form, along with the phenyl ring to which they are attached, a naphthyl ring; and

wherein Y is H or OH;

wherein C_1 - C_4 alkyl and C_1 - C_4 alkoxy may be optionally substituted.

[0008] In another aspect of the invention, a composition is provided, comprising a compound according to Formula I, II, or III as described above, and a carrier.

[0009] In yet a further aspect of the invention, a method of treating a disease is provided, comprising administering to a subject in need of treatment effective amount of a compound

- 4 -

according to Formula I, II, or III as described above, wherein the disease is selected from the group consisting of eye disease, bone disorder, obesity, heart disease, hepatic disease, renal disease, pancreatitis, cancer, myocardial infarct, gastric disturbance, hypertension, fertility control, disorders of hair growth, nasal congestion, neurogenic bladder disorder, gastrointestinal disorder, and dermatological disorder.

[0010] In another aspect of the invention, a method of modulating kinase activity is provided, comprising contacting a cell with a compound according to the Formula I, II or III in an amount effective to modulate kinase activity

DETAILED DESCRIPTION

[0011] 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.

[0012] *Beta*-amino isoquinolinyl amides are provided.

[0013] "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 C₁-C₄ alkyl, aryl, heteroaryl, amino, imino, cyano, halogen, alkoxy or hydroxyl. "C₁-C₄ alkyl" refers to alkyl groups containing one to four carbon atoms.

[0014] "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. "C₂-C₄ alkenyl" refers to alkenyl groups containing two to four carbon atoms.

[0015] "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.

- 5 -

Alkynyl groups may be substituted or unsubstituted. More than one substituent may be present. When substituted, the substituent group is preferably alkyl, amino, cyano, halogen, alkoxy or hydroxyl. Substituents may also be themselves substituted. Substituents are not on the alkyne itself but on the adjacent member atoms of the alkynyl moiety. "C₂-C₄ alkynyl" refers to alkynyl groups containing two to four carbon atoms.

[0016] "Acyl" or "carbonyl" refers to the group -C(O)R wherein R is alkyl, alkenyl, alkynyl, aryl, heteroaryl, carbocyclic, heterocarbocyclic, C₁-C₄ alkyl aryl or C₁-C₄ alkyl heteroaryl. C₁-C₄ alkylcarbonyl refers to a group wherein the carbonyl moiety is preceded by an alkyl chain of 1-4 carbon atoms.

[0017] "Alkoxy" refers to the group -O-R wherein R is alkyl, alkenyl, acyl, alkyl alkenyl, alkyl alkynyl, aryl, carbocyclic, heterocarbocyclic, heteroaryl, C₁-C₄ alkyl aryl or C₁-C₄ alkyl heteroaryl.

[0018] "Amino" refers to the group -NR'R' wherein each R' is, independently, hydrogen, amino, hydroxyl, alkoxy, alkyl, alkenyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, C₁-C₄ alkyl aryl or C₁-C₄ 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 guanidinyll is specifically contemplated under the term "amino".

[0019] "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, carbonylamino, nitro, amino, cyano, halogen, or hydroxyl.

[0020] "Carboxyl" refers to the group -C(=O)O-C₁-C₄ alkyl.

[0021] "Carbonyl" refers to the group -C(O)R wherein each R is, independently, hydrogen, alkyl, aryl, cycloalkyl; heterocycloalkyl; heteroaryl, C₁-C₄ alkyl aryl or C₁-C₄ alkyl heteroaryl.

[0022] "Carbonylamino" refers to the group -C(O)NR'R' wherein each R' is, independently, hydrogen, alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, C₁-C₄ alkyl aryl or C₁-C₄ alkyl heteroaryl. The two R' groups may themselves be linked to form a ring.

- 6 -

[0023] "C₁-C₄ alkyl aryl" refers to C₁-C₄ alkyl groups having an aryl substituent such that the aryl substituent is bonded through an alkyl group. "C₁-C₄ alkyl aryl" may be exemplified by benzyl.

[0024] "C₁-C₄ alkyl heteroaryl" refers to C₁-C₄ alkyl groups having a heteroaryl substituent such that the heteroaryl substituent is bonded through an alkyl group.

[0025] "Carbocyclic group" or "cycloalkyl" means a monovalent 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.

[0026] "Halogen" refers to fluoro, chloro, bromo or iodo moieties. Preferably, the halogen is fluoro, chloro, or bromo.

[0027] "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, C₁-C₄ alkylaryl, hydroxyl, carboxyl, carbonylamino, or C₁-C₄ alkyl. Preferred heteroaromatic groups include benzo[b]thiophenyl, pyrrolidyl, benzofuranyl, isoquinoliny, quinoliny, cinnoliny, tetrazoyl, triazolyl, thienyl, thiazolyl, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic groups include isoquinoliny, benzo[b]thiophenyl; thienyl, furanyl, tetrazoyl, triazolyl, and pyridyl.

[0028] "Heteroatom" means an 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

- 7 -

selected from the group consisting of nitrogen, sulfur, and oxygen atoms. Groups containing more than one heteroatom may contain different heteroatoms.

[0029] “Heterocarboyclic group” or “heterocycloalkyl” or “heterocyclic” means a monovalent saturated or unsaturated hydrocarbon ring containing at least one heteroatom. Heterocarboyclic groups are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic heterocarboyclic 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 heterocarboyclic groups contain 8 to 12 carbon atoms, preferably 9 to 10 carbon atoms in the ring. Heterocarboyclic 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, alkoxy, amino, trifluoromethyl, and trifluoromethoxy. Preferred heterocarboyclic groups include epoxy, tetrahydrofuranyl, azacyclopentyl (or pyrrolidyl), azacyclohexyl, piperidyl, and homopiperidyl. More preferred heterocarboyclic groups include pyrrolidyl, piperidyl, and homopiperidyl. The most preferred heterocarboyclic group is piperidyl. Heterocarboyclic groups are not aromatic.

[0030] “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.

[0031] “Linker” means a linear chain of n member atoms where n is an integer from 1 to 4.

[0032] “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.

[0033] “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.

- 8 -

[0034] "Thioalkyl" refers to the group –S–alkyl.

[0035] "Sulfonyl" refers to the –S(O)₂R' group wherein R' is alkoxy, alkyl, aryl, carbocyclic, heterocarbocyclic; heteroaryl, C₁-C₄ alkyl aryl or C₁-C₄ alkyl heteroaryl.

[0036] "Sulfonylamino" refers to the –S(O)₂NR'R' group wherein each R' is independently alkyl, aryl, heteroaryl, C₁-C₄ alkyl aryl or C₁-C₄ alkyl heteroaryl.

[0037] "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.

[0038] "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.

[0039] "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.

[0040] "Administering" as used herein refers to administration of the compounds as needed to achieve the desired effect.

[0041] "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.

[0042] 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.

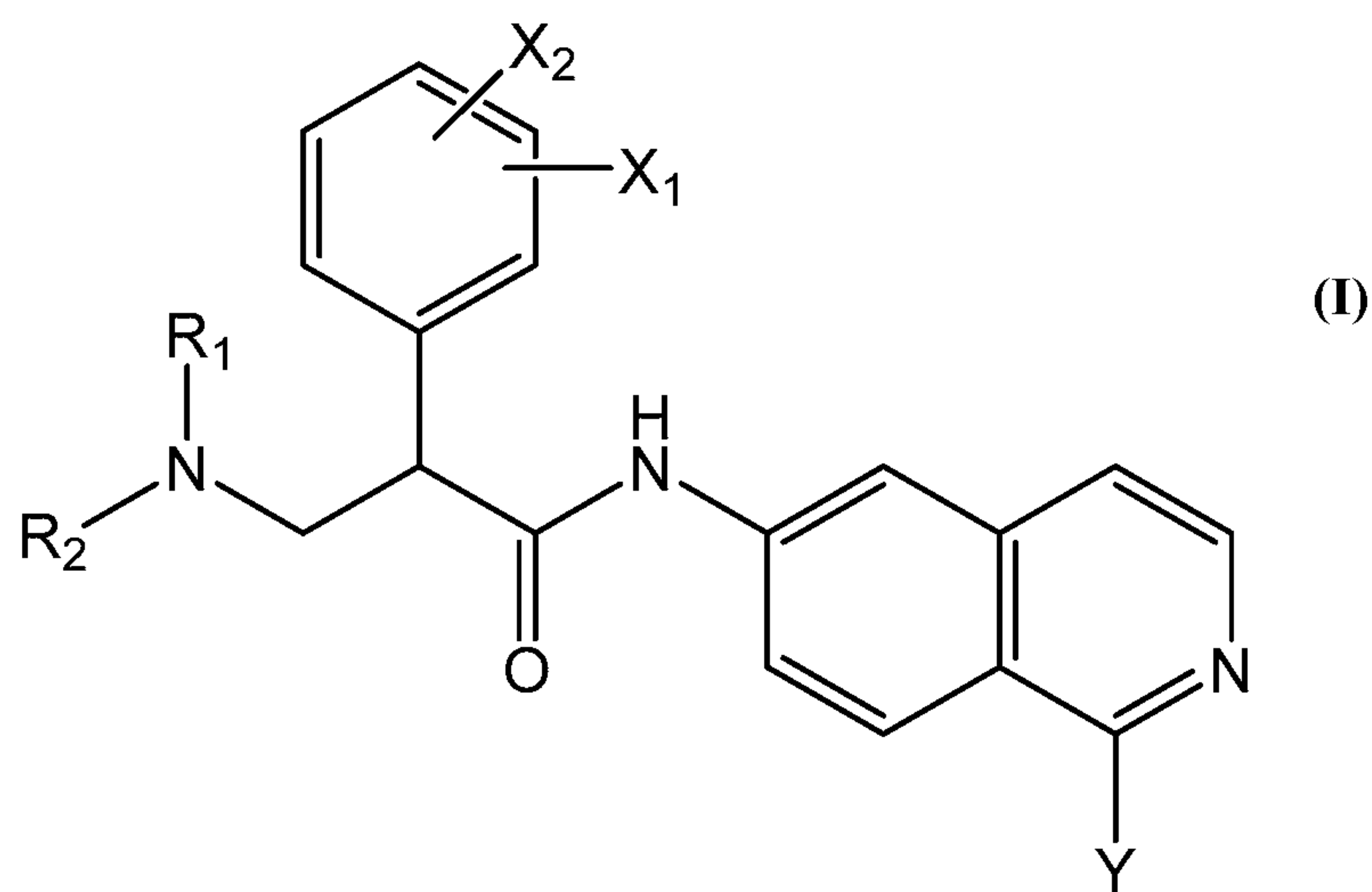
- 9 -

[0043] 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.

[0044] 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

[0045] The *beta*-amino isoquinoline amide according to Formula I is provided:



and enantiomers, diastereomers, and salts thereof;

wherein R₁ and R₂ are, independently, H or C₁-C₄ alkyl; and

wherein X₁ and X₂ are, independently, H, C₁-C₄ alkyl, C₁-C₄ alkoxy, or halogen; or together X₁ and X₂ may form, along with the phenyl ring to which they are attached, a naphthyl ring; and

wherein Y is H or OH;

wherein C₁-C₄ alkyl and C₁-C₄ alkoxy may be optionally substituted.

[0046] In an embodiment of Formula I, R₁ and R₂ are methyl groups or H, and Y is H. Suitably, X₁ and X₂ may be arylalkoxy, haloalkyl, or hydroxyalkyl. Suitably, X₁ and X₂ are selected from -F, -Cl, -OMe, -OH, -CF₃, and -CH₂OH. Suitably, X₁ and X₂ may be at the 2-, 3-, and/or 4-positions.

- 10 -

Isomers

[0047] 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").

[0048] 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.

[0049] 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%.

[0050] 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.

[0051] 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.

- 11 -

[0052] 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.

[0053] 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, $-\text{OCH}_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-\text{CH}_2\text{OH}$. 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).

[0054] 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.

[0055] 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 ^1H , ^2H (D), and ^3H (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

[0056] 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

- 12 -

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.

[0057] 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.

[0058] 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.

[0059] Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetoxybenzoic, 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, pantoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, p-toluenesulfonic, and valeric. Examples of suitable

- 13 -

polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

[0060] Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Chemically Protected Forms

[0061] 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.

[0062] 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.

[0063] A hydroxy 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

- 14 -

(triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(O)CH₃, -OAc).

[0064] An aldehyde or ketone group may be protected as an acetal (RCH(OR)₂) or ketal (R₂C(OR)₂), respectively, in which the carbonyl group (R₂C=O) is converted to a diether (R₂C(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.

[0065] 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)CH₃); a benzyloxy amide (-NHC(O)OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHC(O)OC(CH₃)₃, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO(O)C(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethoxy amide (-NH-Teoc), as a 2,2,2-trichloroethoxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2-(phenylsulphonyl)ethoxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O $\cdot$).

[0066] 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.

[0067] A thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(O)CH₃)

Prodrugs and Other Modifications

[0068] In addition to salt forms, the present invention 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 invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with or without a suitable enzyme or chemical reagent.

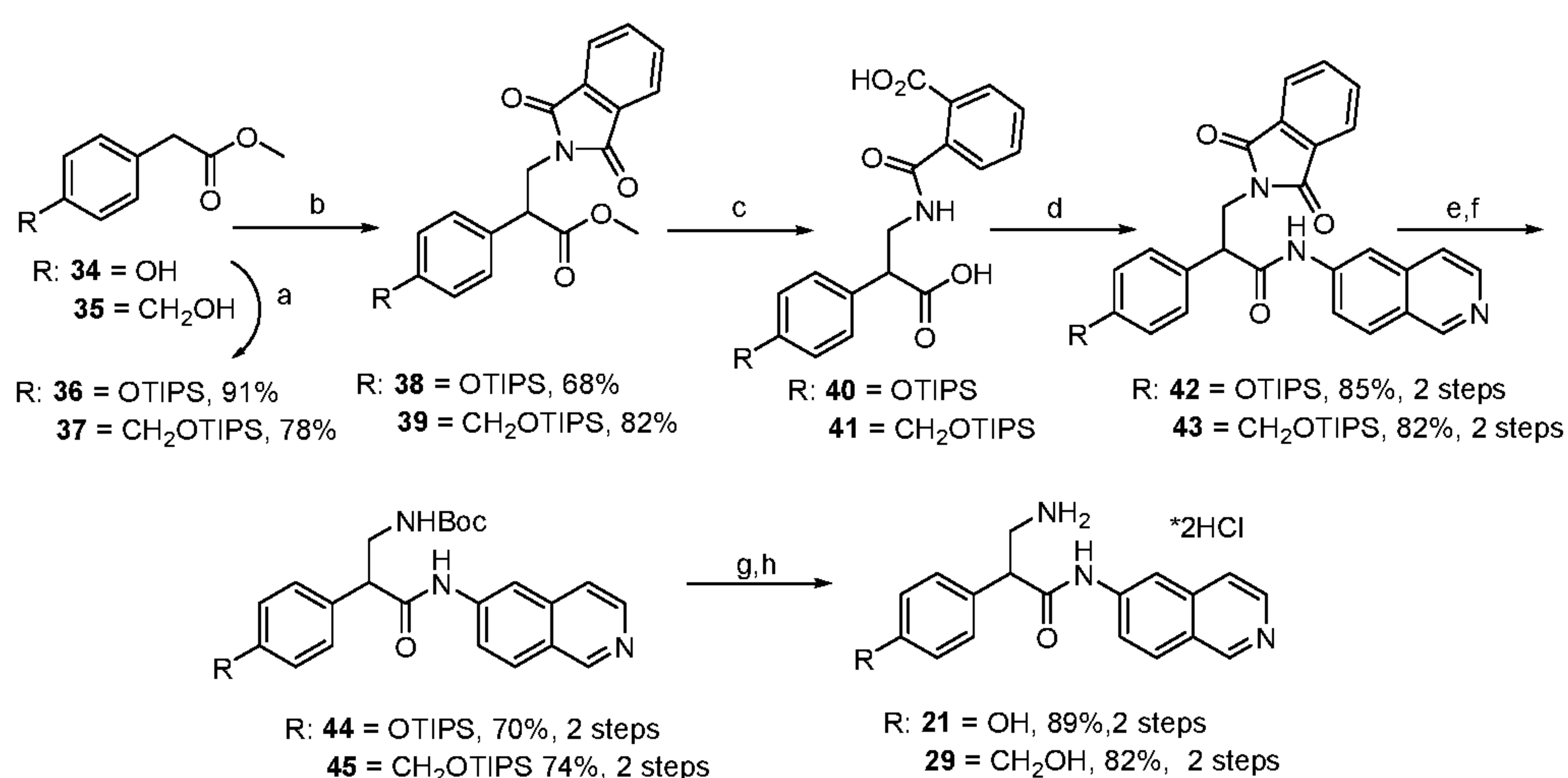
[0069] A compound described herein can also be modified by appending appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those that increase biological penetration into a given biological system

- 15 -

(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 pivalates or fatty acid substituents, conversion to carbamates, hydroxylation of aromatic rings, and heteroatom substitution in aromatic rings.

Synthesis

[0070] The compounds may be synthesized by the general Scheme set forth below:



(a) TIPS-OTf, 2,6-lutidine, CH₂Cl₂; (b) LiHMDS, N-bromomethylphthalimide⁵, THF, -78 °C to 0 °C; (c) LiOH·H₂O, THF-H₂O (d) EDC, DMAP, 6-aminoisoquinoline; (e) NH₂NH₂, MeOH, reflux; (f) Boc₂O, NEt₃, CH₂Cl₂ (g) TBAF, THF; (h) 4 N HCl- dioxane, CH₂Cl₂ (or CH₂Cl₂-H₂O), rt.

[0071] Other suitable synthetic routes would be known to those of ordinary skill in the art.

Methods of Use and Activity

[0072] 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

- 16 -

body *in vivo* an effective inhibitory amount of a compound as disclosed herein. In a preferred embodiment, the kinase inhibited is a *rho* kinase.

[0073] The compounds of the present invention 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 invention 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.

[0074] In another embodiment, the compounds of the present invention 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 invention effective to modulate the action of a kinase in a cell. In one embodiment, the compounds of the present invention are administered in a pharmaceutically acceptable composition, such as in or with a pharmaceutically acceptable carrier.

[0075] Treatment or prevention of diseases or conditions for which the compounds of the present invention 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 retinal degradation, glaucoma, cardiovascular diseases and cancer.

[0076] In some embodiments, the compounds of the present invention will be administered in conjunction with one or more additional therapeutic agents. Suitable 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 compounds.

[0077] **Beta blockers.** These reduce the production of aqueous humor. Examples include levobunolol (Betagan), timolol (Betimol, Timoptic), betaxolol (Betoptic) and metipranolol (OptiPranolol).

[0078] **Alpha-agonists.** These reduce the production of aqueous humor and increase drainage. Examples include apraclonidine (Iopidine) and brimonidine (Alphagan).

[0079] **Carbonic anhydrase inhibitors.** These also reduce the production of aqueous humor. Examples include dorzolamide (Trusopt) and brinzolamide (Azopt).

- 17 -

[0080] **Prostaglandin-like compounds.** These eyedrops increase the outflow of aqueous humor. Examples include latanoprost (Xalatan), bimatoprost (Lumigan) and travoprost (Travatan).

[0081] **Miotic or cholinergic agents.** These also increase the outflow of aqueous humor. Examples include pilocarpine (Isopto Carpine, Pilopine) and carbachol (Isopto Carbachol).

[0082] **Epinephrine compounds.** These compounds, such as dipivefrin (Propine), also increase the outflow of aqueous humor.

[0083] **Neuroprotective compounds.** These compounds, such as Aflibercept (Eylea) are treatments for conditions of the retina such as Macular Degeneration, are anti-VEGF treatments or have similar types of anti-growth or anti-inflammatory activity.

Compositions and Administration

[0084] The additional therapeutic agent or agents can be administered simultaneously or sequentially with the compounds of the present invention. Sequential administration includes administration before or after the compounds of the present invention. In some embodiments, the additional therapeutic agent or agents can be administered in the same composition as the compounds of the present invention. In other embodiments, there can be an interval of time between administration of the additional therapeutic agent and the compounds of the present invention.

[0085] In some embodiments, the administration of an additional therapeutic agent with a compound of the present invention will enable lower doses of the other therapeutic agents to be administered for a longer period of time.

[0086] Pharmaceutical compositions for use in accordance with the present invention 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, 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.).

[0087] The route by which the compounds of the present invention (component A) will be administered and the form of the composition will dictate the type of carrier (component

- 18 -

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).

[0088] 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.

[0089] 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%.

[0090] 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%.

[0091] 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%.

[0092] Ingredient d) is a disintegrant. Suitable disintegrants for solid dosage forms include agar, alginic acid and the sodium salt thereof, effervescent mixtures, croscarmellose, crospovidone, sodium carboxymethyl starch, sodium starch glycolate, clays, and ion

- 19 -

exchange resins. The amount of ingredient d) in the systemic or topical composition is typically about 0.1 to about 10%.

[0093] 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%.

[0094] 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%.

[0095] 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%.

[0096] 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%.

[0097] 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%.

[0098] 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%.

[0099] 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%.

[00100] 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%.

[00101] Ingredient o) is a surfactant such as lecithin, Polysorbate 80, and sodium lauryl sulfate, and the TWEENS® from Atlas Powder Company of Wilmington, Delaware.

- 20 -

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%.

[00102] 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.

[00103] Compositions for parenteral administration typically comprise A) 0.1 to 10% of the compounds of the present invention 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.

[00104] 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%.

[00105] 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 croscarmellose. 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.

- 21 -

[00106] 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.

[00107] 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 invention. One skilled in the art would know how to select appropriate ingredients without undue experimentation.

[00108] 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.

[00109] 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.

[00110] 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

- 22 -

further comprise b) lubricants, e) colorants, f) flavors, g) sweeteners, h) antioxidants, and k) glidants.

[00111] In one embodiment of the invention, the compounds of the present invention 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-de-sac of the eye or another appropriate location.

[00112] 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.

[00113] An effective amount of a compound according to the present invention 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 invention for systemic administration is from about 0.01 to about 1000 $\mu\text{g/kg}$ body weight, preferably from about 0.1 to about 100 $\mu\text{g/kg}$ per body weight, most preferably from about 1 to about 50 $\mu\text{g/kg}$ 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 invention 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.

[00114] The compounds of the present invention are useful in a method of reducing or decreasing intraocular pressure. The compounds of the present invention may be

- 23 -

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.

[00115] 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 IC_{50} of the medicament is 1000 nM, the amount of component A will be 1 to 100%, preferably 5% to 50%. 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.

[00116] 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 invention 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).

[00117] 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.

[00118] 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.

- 24 -

[00119] 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.

[00120] 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.

[00121] 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.

[00122] 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.

[00123] Ingredient u) is a thickener. The amount of ingredient u) in the topical composition is typically about 0 to about 95%.

[00124] 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

- 25 -

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.

[00125] 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.

[00126] 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 invention 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.

[00127] The organic pigments and lakes useful in this invention 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.

[00128] The pearlescent pigments useful in this invention 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.

[00129] In a particularly preferred embodiment of the invention, topical pharmaceutical compositions for ocular administration are prepared typically comprising component A and B

- 26 -

(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.

[00130] 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.

[00131] 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.

[00132] 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 5.0-7.5.

[00133] Component A may be included in kits comprising component A, 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).

[00134] The invention will be further explained by the following illustrative Examples that are to be considered to be non-limiting.

Examples

[00135] All temperatures are in degrees Centigrade. Reagents and starting materials were purchased from commercial sources or prepared following published literature procedures.

[00136] Unless otherwise noted, HPLC purification, when appropriate, was performed by redissolving the compound in a small volume of DMSO and filtering through a 0.45 micron (nylon disc) syringe filter. The solution was then purified using, for example, a 50 mm Varian Dynamax HPLC 21.4 mm Microsorb Guard-8 C₈ column. A typical initial eluting

- 27 -

mixture of 40-80% MeOH:H₂O was selected as appropriate for the target compound. This initial gradient was maintained for 0.5 minutes then increased to 100% MeOH:0% H₂O over 5 minutes. 100% MeOH was maintained for 2 more minutes before re-equilibration back to the initial starting gradient. A typical total run time was 8 minutes. The resulting fractions were analyzed, combined as appropriate, and then evaporated to provide purified material.

[00137] Proton magnetic resonance (¹H NMR) spectra were recorded on either a Varian INOVA 600 MHz (¹H) NMR spectrometer, Varian INOVA 500 MHz (¹H) NMR spectrometer, Varian Mercury 300 MHz (¹H) NMR spectrometer, or a Varian Mercury 200 MHz (¹H) NMR spectrometer. All spectra were determined in the solvents indicated. Although chemical shifts are reported in ppm downfield of tetramethylsilane, they are referenced to the residual proton peak of the respective solvent peak for ¹H NMR. Interproton coupling constants are reported in Hertz (Hz).

[00138] Analytical LCMS spectra were obtained using a Waters ZQ MS ESI instrument with an Alliance 2695 HPLC and a 2487 dual wavelength UV detector. Spectra were analyzed at 254 and 230 nm. Samples were passed through a Waters Symmetry C18 4.6x75 mm 3.5 μ column with or without a guard column (3.9x20 mm 5 μ). Gradients were run with mobile phase A: 0.1% formic acid in H₂O and mobile phase B: ACN with a flow rate of 0.8 mL/min. Two gradients will illustrate:

Gradient A			Gradient B		
Time	A%	B%	Time	A%	B%
0.00	80.0	20.0	0.00	80.0	20.0
1.00	80.0	20.0	1.00	80.0	20.0
6.00	25.0	75.0	6.00	25.0	75.0
7.00	5.0	95.0	7.00	5.0	95.0
8.00	5.0	95.0	8.00	5.0	95.0
9.00	80.0	20.0	9.00	80.0	20.0
12.00	80.0	20.0	12.00	80.0	20.0

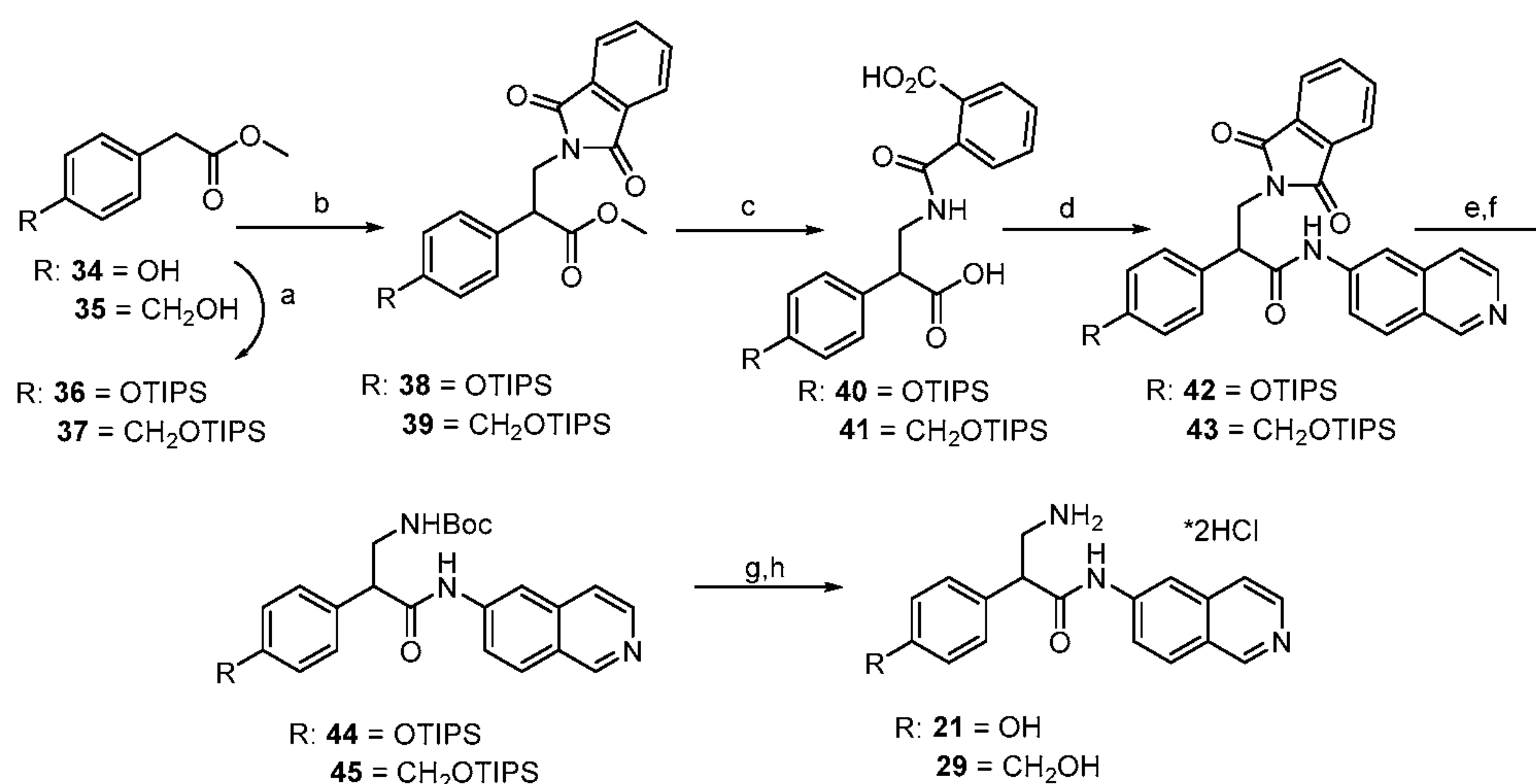
[00139] The settings for the MS probe were a cone voltage at 38 mV and a desolvation temperature at 250°C. Any variations in these methods are noted below.

- 28 -

[00140] The following preparations illustrate procedures for the preparation of intermediates and methods for the preparation of a *beta*-amino isoquinoliny amide derivative.

EXAMPLES

Examples 1-32.



(a) TIPS-OTf, 2,6-lutidine, CH₂Cl₂; (b) LiHMDS, N-bromomethylphthalimide⁵, THF, -78 °C to 0 °C; (c) LiOH·H₂O, THF-H₂O (d) EDC, DMAP, 6-aminoisoquinoline; (e) NH₂NH₂, MeOH, reflux; (f) Boc₂O, NEt₃, CH₂Cl₂ (g) TBAF, THF; (h) 4 N HCl- dioxane, CH₂Cl₂ (or CH₂Cl₂-H₂O), rt.

[00141] Using commercially available compounds and largely the procedures set forth in Scheme 1 herein and substituting the appropriate starting materials, the compounds **2-32** were made.

Compound	X ₁ , X ₂	Y
2	H	H

- 29 -

3(S)	H	H
4(R)	H	H
5	H	OH
6	2-fluoro	H
7	3-fluoro	H
8	4-fluoro	H
9	2-chloro	H
10	3-chloro	H
11	4-chloro	H
12	2,4-dichloro	H
13	2-methyl	H
14	3-methyl	H
15	4-methyl	H
16	3-OH	H
17	4-OH	H
18	3,4-OH	H
19	3-OCH ₃	H
20	4-OCH ₃	H
21	3-CF ₃	H
22	4-CF ₃	H
23	3-CH ₂ OH	H
24	4-CH ₂ OH	H
25	3,4-difluoro	H
26	2,4-dichloro	H
27	4-fluoro	OH

- 30 -

28	3-CH ₃ , 4-OH	H
29	3-OCH ₃ , 4-OH	H
30	4-OCH ₂ C ₆ H ₅	H
31	α -naphthyl	H
32	β -naphthyl	H

Example 33. ROCK Kinase Assay.

[00142] All compounds were initially prepared as 10 mM stocks in anhydrous dimethylsulfoxide (DMSO). A 20 μ l 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 1:3 in DMSO for a 10-point concentration response and further diluted in the assay buffer bringing all compound concentrations to 4X final concentration in 10% DMSO. The assay was performed in 96-well half white, flat-bottom, half-area, non-binding assay plate (Corning #3642) in assay buffer consisting of 50 mM HEPES (pH 7.5), 10 mM MgCl₂*6H₂O, 100 μ M sodium orthovanadate, 0.01% CHAPS and 0.1% bovine serum albumin. A 10 μ L aliquot of compound from each well of the intermediate dilution plate and 10 μ L of a 4x stock solution containing ATP (5 μ M) and acceptor substrate (20 μ M RSK2 peptide KKRNRRTLTK) were added to all wells. The reaction was initiated by the addition of 20 μ L of 2x stock solution containing ROCK2 (1nM). Reactions were thoroughly mixed manually, covered and allowed to incubate at room temperature for 180 min. Protein kinase activity was quantitated using Promega's Kinase-GloTM 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:

- 31 -

$$\text{POC} = ((\text{Test well value} - \text{BKG}) / (\text{CTRL} - \text{BKG})) * 100$$

[00143] IC₅₀ values were calculated using the following 4-parameter logistic curve-fitting algorithm:

$$f(x) = (A + ((B - A) / (1 + ((x / C)^D))))$$

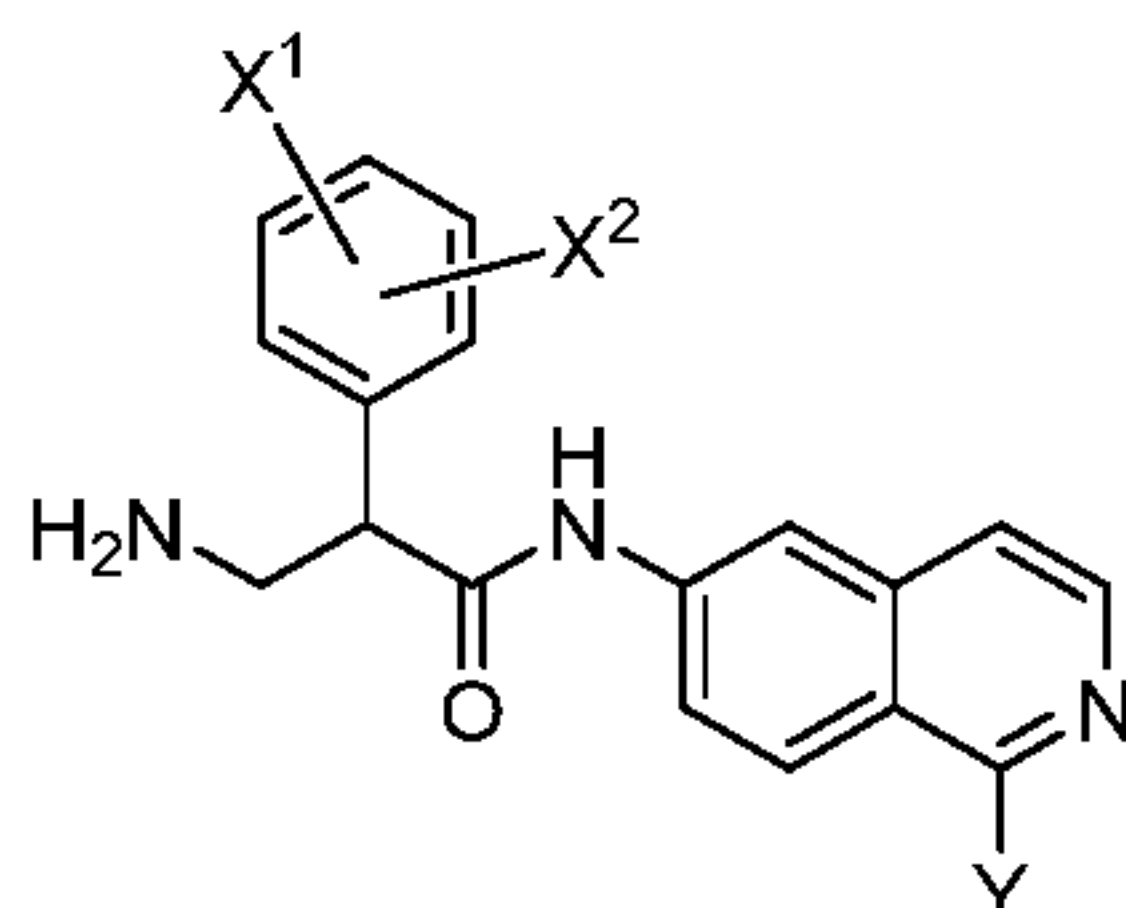
[00144] IC₅₀ values were converted to K_i values using the Cheng-Prusoff Equation: $K_i = IC_{50} / (1 + ([ATP]/K_m ATP))$.

[00145] Results are shown below in Table 1.

Example 34. PTM-HTM assay

[00146] Porcine Trabecular Meshwork cells (PTM) were isolated from freshly obtained enucleated porcine eyes following a procedure by Rao *et al.*¹ 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 Prism4 using sigmoidal dose-response and constraining top and bottom to 100% and 0%, respectively. Results are shown below in Table 1.

TABLE 1.



- 32 -

Compd	X1,X2	Y	ROCK2 ^a K _i nM	HTM ^b IC ₅₀ nM	PTM ^c IC ₅₀ nM
1/SNJ ^d	n.a.	n.a.	2.3	278	243
2	H	H	0.8	123	137
3 (S)	H	H	0.4	41	179
4 (R)	H	H	16	1216	1816
5	H	OH	2.2	266	45
6	2-Fluoro	H	1.0	139	260
7	3-Fluoro	H	1.0	201	298
8	4-Fluoro	H	1.0	102	175
9	2-Chloro	H	1.3	192	245
10	3-Chloro	H	0.9	383	455
11	4-Chloro	H	0.4	64	129
12	2,4-Dichloro	H	0.8	208	214
13	2-Methyl	H	1.0	90	200
14	3-Methyl	H	3.3	324	511
15	4-Methyl	H	0.4	39	84
16	3-OH	H	1.3	1721	459
17	4-OH	H	0.6	193	1015
18	3,4-OH	H	5.5	11002	5147
19	3-OCH ₃	H	2.0	214	448
20	4-OCH ₃	H	1.3	111	670
21	3-CF ₃	H	2.7	475	596
22	4-CF ₃	H	1.8	493	152
23	3-CH ₂ OH	H	3.0	248	1376
24	4-CH ₂ OH	H	0.2	48	485

- 33 -

Example 35.

[00147] Topical pharmaceutical compositions for lowering intraocular pressure are prepared by conventional methods and formulated as follows:

<u>Ingredient</u>	<u>Amount (wt %)</u>
<i>beta</i> 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 5.5-6.5
Purified water	q.s. to 100%

[00148] A compound according to this invention is used as the *beta* 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.

Reference Example One. Pharmacological Activity for Glaucoma Assay.

[00149] 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.

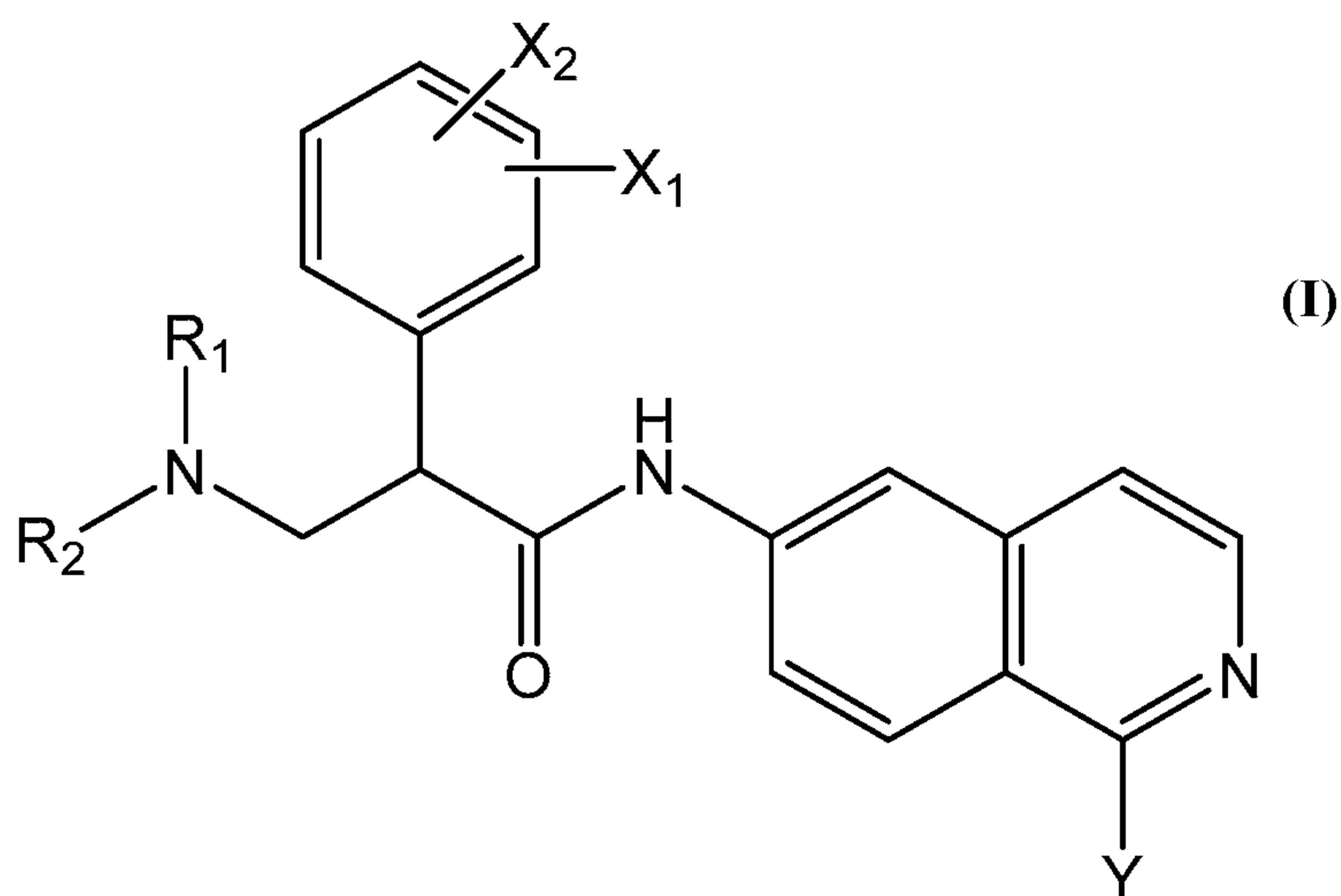
[00150] While the invention has been described in detail and with reference to specific embodiments thereof, it will be apparent to one skilled in the art that various changes and modifications can be made without departing from the spirit and scope of the invention.

- 34 -

CLAIMS

What is claimed is:

1. A compound of formula (I):



and enantiomers, diastereomers, and salts thereof;

wherein R_1 and R_2 are, independently, H or C_1 - C_4 alkyl; and

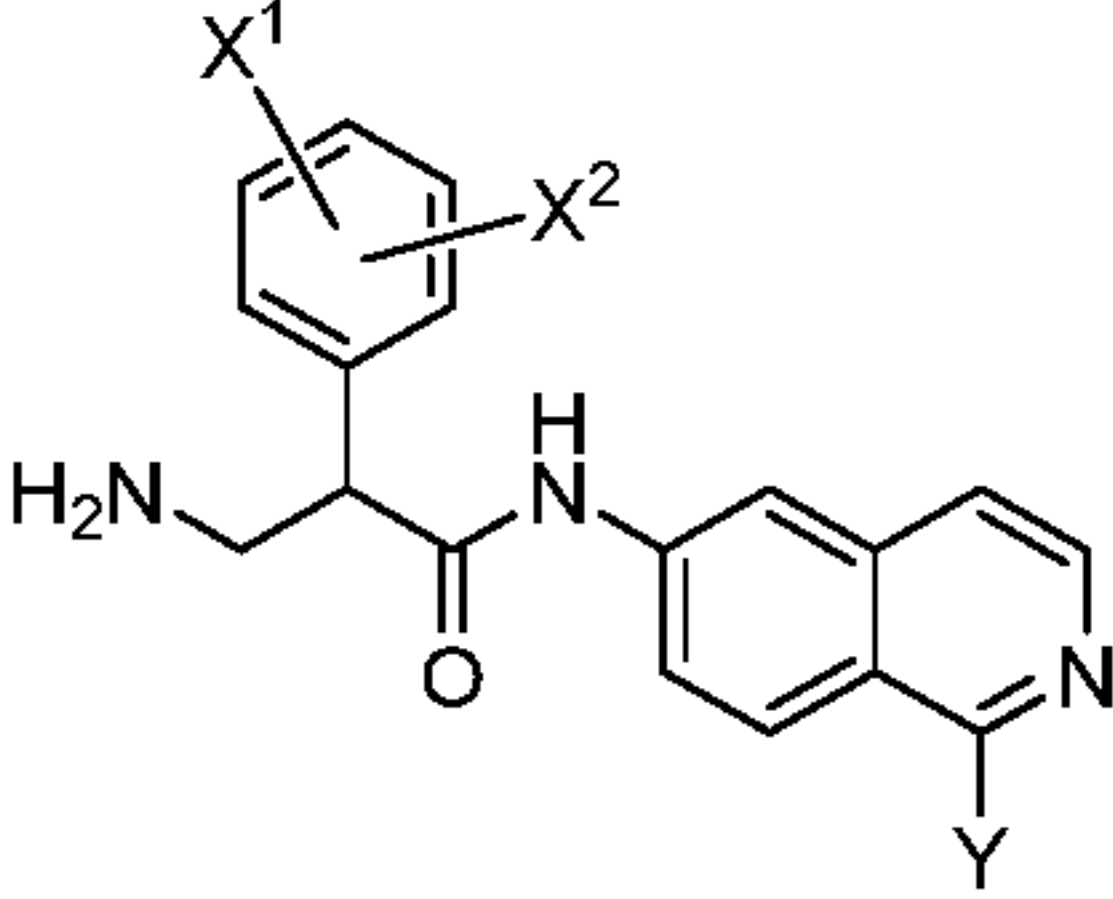
wherein X_1 and X_2 are, independently, H, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, or halogen; or together X_1 and X_2 may form, along with the phenyl ring to which they are attached, a naphthyl ring; and

wherein Y is H or OH;

wherein C_1 - C_4 alkyl and C_1 - C_4 alkoxy may be optionally substituted.

2. A compound according to claim 1, wherein R_1 and R_2 are both hydrogen.
3. A compound according to any one of the preceding claims, wherein Y is H.
4. A compound according to any one of the preceding claims, wherein X_1 and X_2 are haloalkyl or hydroxyalkyl.
5. A compound according to any one of the preceding claims, wherein X_1 and X_2 are selected from -F, -Cl, -OMe, -OH, -CF₃, and -CH₂OH.

6. A compound selected from:

		
Compound	X ₁ , X ₂	Y
2	H	H
3(S)	H	H
4(R)	H	H
5	H	OH
6	2-fluoro	H
7	3-fluoro	H
8	4-fluoro	H
9	2-chloro	H
10	3-chloro	H
11	4-chloro	H
12	2,4-dichloro	H
13	2-methyl	H
14	3-methyl	H
15	4-methyl	H
16	3-OH	H
17	4-OH	H
18	3,4-OH	H
19	3-OCH ₃	H
20	4-OCH ₃	H

- 36 -

21	3-CF ₃	H
22	4-CF ₃	H
23	3-CH ₂ OH	H
24	4-CH ₂ OH	H
25	3,4-difluoro	H
26	2,4-dichloro	H
27	4-fluoro	OH
28	3-CH ₃ , 4-OH	H
29	3-OCH ₃ , 4-OH	H
30	4-OCH ₂ C ₆ H ₅	H
31	α -naphthyl	H
32	β -naphthyl	H

7. A composition comprising a compound according to any one of the preceding claims and a carrier.

8. The composition of claim 7, wherein the carrier is saline buffered to a pH of about 5.5 to about 6.5.

9. A method for treating a disease in a subject comprising:

administering to a subject an effective amount of a compound according to any one of claims 1-6,

wherein the disease comprises at least one of eye disease, bone disorder, obesity, heart disease, hepatic disease, renal disease, pancreatitis, cancer, myocardial infarct, gastric disturbance, hypertension, fertility control, disorders of hair growth, nasal congestion, neurogenic bladder disorder, gastrointestinal disorder, dermatological disorder, and respiratory indications.

10. The method of claim 9, wherein the disease comprises an eye disease.

- 37 -

11. The method of claim 10, wherein the eye disease comprises glaucoma or a neurodegenerative eye disease.
12. The method of claim 9, wherein the disease comprises a respiratory indication selected from asthma, chronic bronchitis, bronchospasm, emphysema, and airway obstruction.
13. The method of claim 12, wherein the respiratory indication comprises asthma.
14. A method of modulating kinase activity comprising:

 contacting a cell with a compound according to any one of claims 1-6 in an amount effective to modulate kinase activity.
15. The method of claim 14, wherein the cell is in a subject.