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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2016 (24.11.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/187324 A1

(51) International Patent Classification:
A01N 43/40 (2006.01)

(21) International Application Number:
PCT/US2016/033111

(22) International Filing Date:
18 May 2016 (18.05.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/163,369 18 May 2015 (18.05.2015) US
62/203,070 10 August 2015 (10.08.2015) US

(71) Applicant: **TD2, INC.** [US/US]; 13208 E. Shea Blvd., Suite 100, Scottsdale, Arizona 85259 (US).

(72) Inventors: **WANG, Tong**; 13208 E. Shea Blvd., Suite 100, Scottsdale, Arizona 85259 (US). **GATELY, Stephen**; 13208 E. Shea Blvd., Suite 100, Scottsdale, Arizona 85259 (US).

(74) Agent: **FULLER, Rodney J.**; Booth Udall Fuller, PLC, 1255 West Rio Salado Parkway, Suite 215, Tempe, Arizona 85281 (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, 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, KN, KP, KR, 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).

Published:

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

WO 2016/187324 A1

(54) Title: HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS

(57) Abstract: The present invention is directed to certain amides and heterocyclic compounds. The present invention also relates to uses of these compounds to treat several diseases including autoimmune disorders, cardiovascular disorders, inflammation, central nervous system disorders, arterial thrombotic disorders, fibrotic disorders, glaucoma, and neoplastic disorders.

HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application No. 62/163,369, filed May 18, 2015, and U.S. Provisional Patent Application No. 62/203,070, filed August 10, 2015, the contents of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

The present invention relates to heterocyclic compounds, their compositions and medicaments containing the same, as well as processes for the preparation and use of such compounds, compositions and medicaments. Such compounds are potentially useful in the treatment of diseases associated with inappropriate tyrosine and/or serine/threonine kinase activity.

BACKGROUND OF THE INVENTION

An important large family of enzymes is the protein kinase enzyme family. Currently, there are about 500 different known protein kinases. Protein kinases serve to catalyze the phosphorylation of an amino acid side chain in various proteins by the transfer of the γ-phosphate of the ATP-Mg^{2+} complex to said amino acid side chain. These enzymes control the majority of the signaling processes inside cells, thereby governing cell function, growth, differentiation and destruction (apoptosis) through reversible phosphorylation of the hydroxyl groups of serine, threonine and tyrosine residues in proteins. Studies have shown that protein kinases are key regulators of many cell functions, including signal transduction, transcriptional regulation, cell motility, and cell division. Several oncogenes have also been shown to encode protein kinases, suggesting that kinases play a role in oncogenesis. These processes are highly regulated, often by complex intermeshed pathways where each kinase will itself be regulated by one or more kinases. Consequently, aberrant or inappropriate protein kinase activity can contribute to the rise of disease states associated with such aberrant kinase activity. Due to their physiological relevance, variety and ubiquitousness, protein kinases have become one of the most important and widely studied family of enzymes in biochemical and medical research.

The protein kinase family of enzymes is typically classified into two main subfamilies: Protein Tyrosine Kinases and Protein Serine/Threonine Kinases, based on the amino acid residue they phosphorylate. The serine/threonine kinases (PSTK), includes cyclic AMP- and cyclic GMP-dependent protein kinases, calcium- and phospholipid-dependent protein kinase, calcium- and calmodulin-dependent protein kinases, casein kinases, cell division cycle protein kinases and others. These kinases are usually cytoplasmic or associated with the particulate fractions of cells, possibly by anchoring proteins. Aberrant protein serine/threonine kinase activity has been implicated or is suspected in a number of pathologies such as rheumatoid arthritis, psoriasis, septic shock, bone loss, many cancers and other proliferative diseases. Accordingly, serine/threonine kinases and the signal transduction pathways which they are part of are important targets for drug design. The tyrosine kinases phosphorylate tyrosine residues. Tyrosine kinases play an equally important role in cell regulation. These kinases include several receptors for molecules such as growth factors and hormones, including epidermal growth factor receptor, insulin receptor, platelet derived growth factor receptor and others. Studies have indicated that many tyrosine kinases are transmembrane proteins with their receptor domains located on the outside of the cell and their kinase 5 domains on the inside. Much work is also under progress to identify modulators of tyrosine kinases as well.

A major signal transduction systems utilized by cells is the RhoA- signaling pathways. RhoA is a small GTP binding protein that can be activated by several extracellular stimuli such as growth factor, hormones, mechanic stress, osmotic change as well as high concentration of metabolite like glucose. RhoA activation involves GTP binding, conformation alteration, post- translational modification (geranylgeranyllization and famesylation) and activation of its intrinsic GTPase activity. Activated RhoA is capable of interacting with several effector proteins including ROCKs and transmit signals into cellular cytoplasm and nucleus.

ROCK1 and 2 constitute a family of kinases that can be activated by RhoA-GTP complex via physical association. Activated ROCKs phosphorylate a number of substrates and play important roles in pivotal cellular functions. The substrates for ROCKs include myosin binding subunit of myosin light chain phosphatase (MBS, also named MYPT1), adducin, moesin, myosin light chain (MLC), LIM kinase as well as transcription factor FHL. The phosphorylation of theses

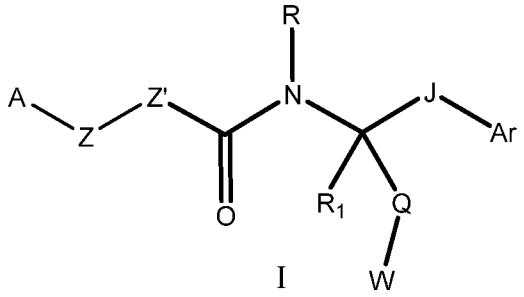
substrates modulate the biological activity of the proteins and thus provide a means to alter cell's response to external stimuli. One well documented example is the participation of ROCK in smooth muscle contraction. Upon stimulation by phenylephrine, smooth muscle from blood vessels contracts. Studies have shown that phenylephrine stimulates alpha-adrenergic receptors and leads to the activation of RhoA. Activated RhoA in turn stimulates kinase activity of ROCK1 and which in turn phosphorylates MBS. Such phosphorylation inhibits the enzyme activity of myosin light chain phosphatase and increases the phosphorylation of myosin light chain itself by a calcium-dependent myosin light chain kinase (MLCK) and consequently increases the contractility of myosin-actin bundle, leading to smooth muscle contraction. This phenomena is also sometimes called calcium sensitization. In addition to smooth muscle contraction, ROCKs have also been shown to be involved in cellular functions including apoptosis, cell migration, transcriptional activation, fibrosis, cytokinesis, inflammation and cell proliferation. Moreover, in neurons ROCK plays a critical role in the inhibition of axonal growth by myelin-associated inhibitory factors such as i myelin-associated glycoprotein (MAG). ROCK-activity also mediates the collapse of growth cones in developing neurons. Both processes are thought to be mediated by ROCK-induced phosphorylation of substrates such as LIM kinase and myosin light chain phosphatase, resulting in increased contractility of the neuronal actin-myosin system. Inhibitors of ROCKs have been suggested for use in the treatments of a variety of diseases. They include cardiovascular diseases such as hypertension, chronic and congestive heart failure, cardiac hypertrophy, restenosis, chronic renal failure and atherosclerosis. In addition, because of its muscle relaxing properties, it is also suitable for asthma, male erectile dysfunctions, female sexual dysfunction and over-active bladder syndrome. ROCK inhibitors have been shown to possess anti-inflammatory properties. Thus they can be used as treatment for neuroinflammatory diseases such as stroke, multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and inflammatory pain, as well as other inflammatory diseases such as rheumatoid arthritis, irritable bowel syndrome, inflammatory bowel disease. In addition, based on their neurite outgrowth inducing effects, ROCK inhibitors could be useful drugs for neuronal regeneration, inducing new axonal growth and axonal rewiring across lesions within the CNS. ROCK inhibitors are therefore likely to be useful for regenerative (recovery) treatment of CNS disorders such as spinal cord injury, acute neuronal injury (stroke, traumatic brain injury), Parkinson’s disease, Alzheimer’s disease and other neurodegenerative disorders.

Since ROCK inhibitors reduce cell proliferation and cell migration, they could be useful in treating cancer and tumor metastasis. Furthermore, there is evidence suggesting that ROCK inhibitors suppress cytoskeletal rearrangement upon virus invasion, thus they also have potential therapeutic value in antiviral and anti-bacterial applications. ROCK inhibitors may also be useful for the treatment of insulin resistance and diabetes.

The inventors have discovered novel heterocyclic compounds, which are inhibitors of ROCK activity. Such derivatives are useful in the treatment of disorders associated with inappropriate ROCK activity.

SUMMARY OF THE INVENTION

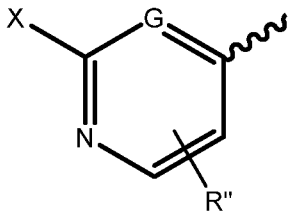
The present invention is directed to a compound of Formula I:



I

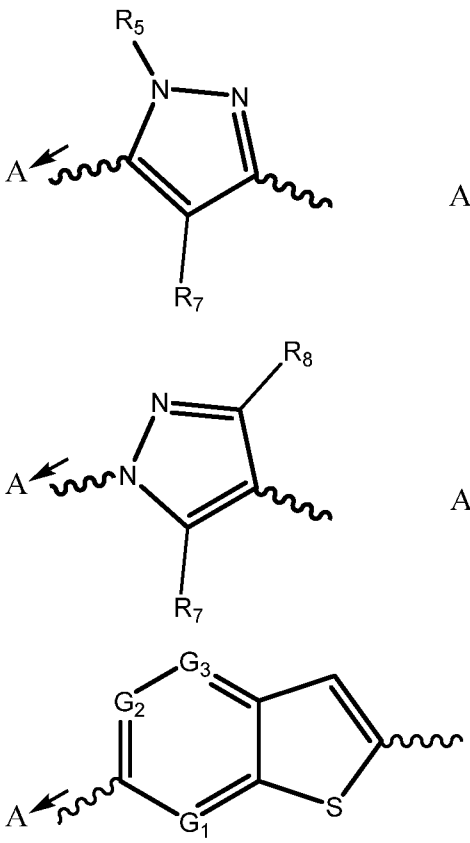
or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate or physiologically functional derivative thereof;

wherein:



A is indazol-3-yl, pyrazol-4-yl, , wherein (i) G is CR' or N; (ii) X is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $-OR_2$ or $-NR_3R_4$; and (iii) R', R", R_2, R_3 and R_4 are independently –H or C_{1-6} alkyl or , C_{3-7} cycloalkyl;

Z is selected from the group consisting of:



wherein (i) R_5 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl; (ii) R_7 and R_8 are independently –H, halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, -O-(C_{1-6} alkyl), -OH, -CN, -COOR', -OC(O)R', NHR', $N(R')_2$, -NHC(O)R', $-NHS(O)_2R'$, -C(O)NHR', or $–S(O)_2R'$ wherein R' is –H, C_{1-6} alkyl, or C_{3-7} cycloalkyl; (iii) G_1, G_2 and G_3 are independently CH or N.

Z' is a bond, O or NR_6, wherein R_6 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R_1 is –H or C_{1-6} alkyl;

Q is a bond or C_{1-6} alkyl;

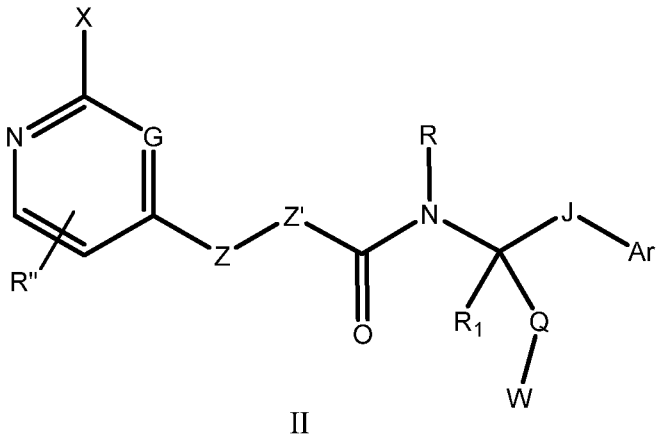
J is a bond or C_{1-6} alkyl;

W is –H , $–OR_9$, $–NR_{10}R_{11}$, or $–S(O)_mR_{12}$, wherein (i) R_9, R_{10} and R_{11} are independently –H, C_{1-6} alkyl, C_{3-7} cycloalkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, or C_{1-6} alkylsulfonyl; (ii) m is an integer from 0 to 2; and (iii) R_{12} is C_{1-6} alkyl or C_{3-7} cycloalkyl; and

Ar is a phenyl, naphthyl, or C_{5-10} heterocycle, each of which is optionally substituted with halo, –OH, –CN, $–COOR_a$, $–OR_a$, $–SR_a$, $–OC(O)R_a$, $–NHR_a$, $–NR_aR_b$, $-NHC(O)R_a$, $-NHC(O)NR_aR_b$, $-C(O)NR_aR_b$, $-NS(O)_2R_a$, $-S(O)_2NR_aR_b$, $-S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle, wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3

to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, –OH, –CN, $–COOR_a$, $–OR_a$, $–SR_a$, $–OC(O)R_a$, $–NHR_a$, $–NR_aR_b$, $–NHC(O)R_a$, $–NHC(O)NR_aR_b$, $–C(O)NR_aR_b$, $–NS(O)_2R_a$, $–S(O)_2NR_aR_b$, $–S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, or C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O form a 4- to 8-membered heterocycle.

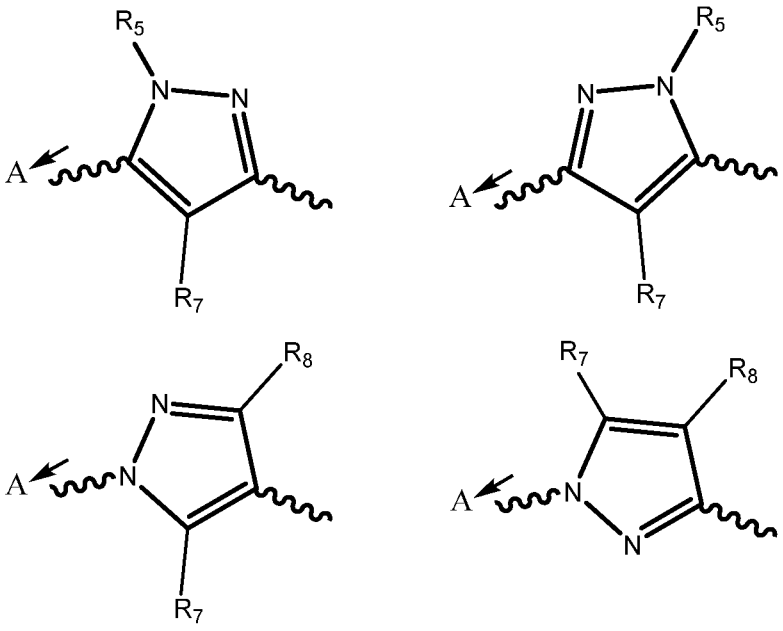
In one embodiment, the present invention is directed to a compound of Formula II:



II

wherein (i) G is CR' or N; (ii) X is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $–OR_2$ or $–NR_3R_4$; and (iii) R', R", R_2, R_3 and R_4 are independently –H or C_{1-6} alkyl or , C_{3-7} cycloalkyl;Z is selected from the group consisting of:

,



wherein (i) R_5 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl; (ii) R_7 and R_8 are independently –H, halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, -O-(C_{1-6} alkyl), -OH, -CN, -COOR', -OC(O)R', NHR', $N(R')_2$, -NHC(O)R', $-NHS(O)_2R'$, -C(O)NHR', or $–S(O)_2R'$ wherein R' is –H, C_{1-6} alkyl, or C_{3-7} cycloalkyl; (iii) G_2, G_3 and G_4 are independently CH or N.

Z' is a bond, O or NR_6, wherein R_6 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R_1 is –H or C_{1-6} alkyl;

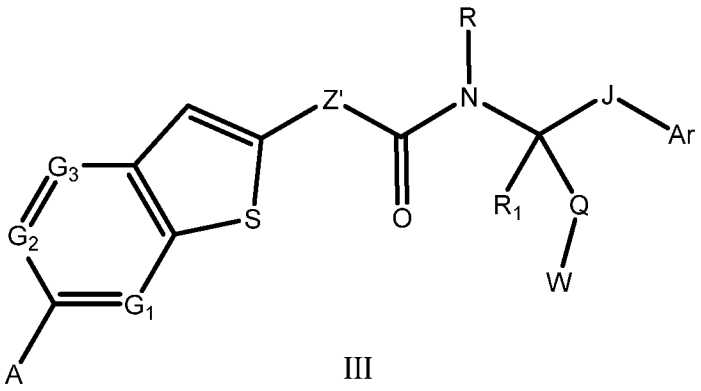
Q is a bond or C_{1-6} alkyl;

J is a bond or C_{1-6} alkyl;

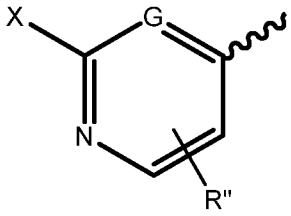
W is –H , $–OR_9$, $–NR_{10}R_{11}$, or $–S(O)_mR_{12}$, wherein (i) R_9, R_{10} and R_{11} are independently –H, C_{1-6} alkyl, C_{3-7} cycloalkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, or C_{1-6} alkylsulfonyl; (ii) m is an integer from 0 to 2; and (iii) R_{12} is C_{1-6} alkyl or C_{3-7} cycloalkyl; and

Ar is a phenyl, naphthyl, or C_{5-10} heterocycle, each of which is optionally substituted with halo, –OH, –CN, $–COOR_a$, $–OR_a$, $–SR_a$, $–OC(O)R_a$, $–NHR_a$, $–NR_aR_b$, $-NHC(O)R_a$, $-NHC(O)NR_aR_b$, $-C(O)NR_aR_b$, $-NS(O)_2R_a$, $-S(O)_2NR_aR_b$, $-S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle, wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, –OH, –CN, $–COOR_a$, $–OR_a$, $–SR_a$, $–OC(O)R_a$, $–NHR_a$, $–NR_aR_b$, $–NHC(O)R_a$, $–NHC(O)NR_aR_b$, $–C(O)NR_aR_b$, $–NS(O)_2R_a$, $–S(O)_2NR_aR_b$, $–S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, or C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O form a 4- to 8-membered heterocycle.

In another embodiment, the present invention is directed to a compound of Formula III:



III



Wherein A is indazol-3-yl, pyrazol-4-yl, , wherein (i) G is CR' or N; (ii) X is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $-OR_2$ or $-NR_3R_4$; and (iii) R', R", R_2, R_3 and R_4 are independently –H or C_{1-6} alkyl or , C_{3-7} cycloalkyl;

G_5, G_6 and G_7 are independently CH or N.

Z' is a bond, O or NR_6, wherein R_6 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R_1 is –H or C_{1-6} alkyl;

Q is a bond or C_{1-6} alkyl;

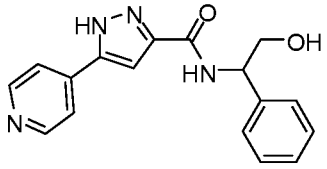
J is a bond or C_{1-6} alkyl;

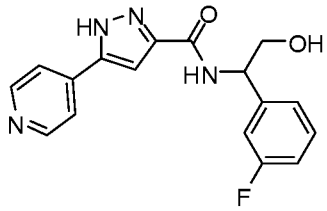
W is –H , $-OR_9$, $-NR_{10}R_{11}$, or $-S(O)_mR_{12}$, wherein (i) R_9, R_{10} and R_{11} are independently –H, C_{1-6} alkyl, C_{3-7} cycloalkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, or C_{1-6} alkylsulfonyl; (ii) m is an integer from 0 to 2; and (iii) R_{12} is C_{1-6} alkyl or C_{3-7} cycloalkyl; and

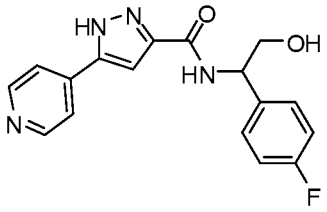
Ar is a phenyl, naphthyl, or C_{5-10} heterocycle, each of which is optionally substituted with halo, –OH, –CN, $-COOR_a$, $-OR_a$, $-SR_a$, $-OC(O)R_a$, $-NHR_a$, $-NR_aR_b$, $-NHC(O)R_a$, $-NHC(O)NR_aR_b$, $-C(O)NR_aR_b$, $-NS(O)_2R_a$, $-S(O)_2NR_aR_b$, $-S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle, wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, –OH, –CN, $-COOR_a$, $-OR_a$, $-SR_a$, $-OC(O)R_a$, $-NHR_a$, $-NR_aR_b$, $-NHC(O)R_a$, $-NHC(O)NR_aR_b$, $-C(O)NR_aR_b$, $-NS(O)_2R_a$, $-S(O)_2NR_aR_b$, $-S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, or

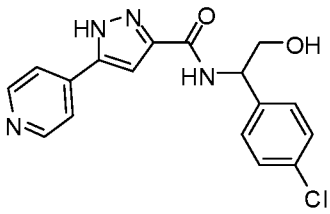
C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O form a 4- to 8-membered heterocycle.

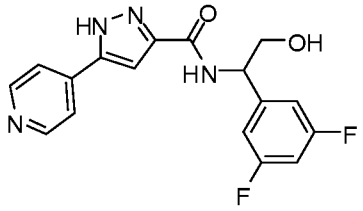
In some embodiments, the present invention is directed to a compound of Formula I, II, and/or III selected from the group consisting of:

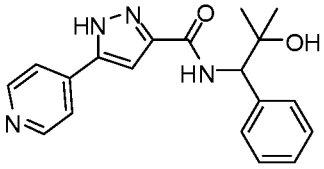


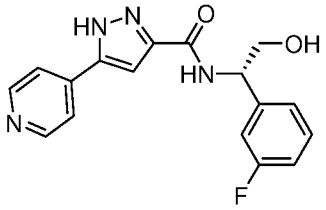


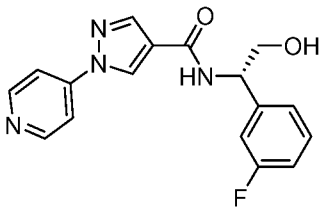


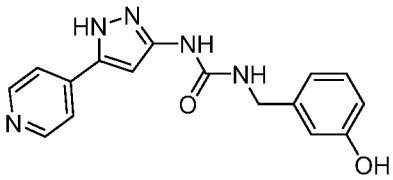


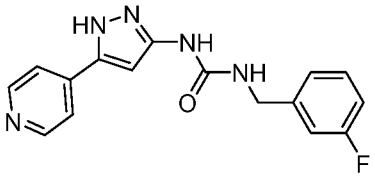


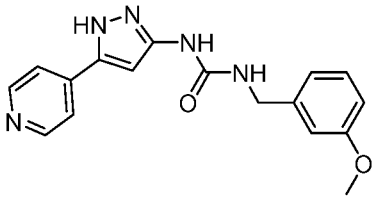


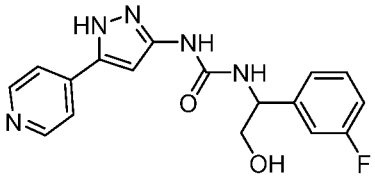


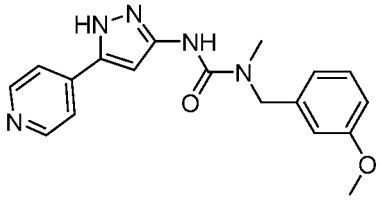


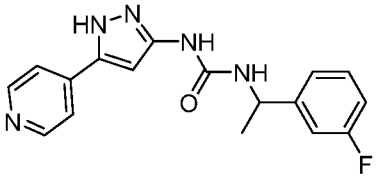


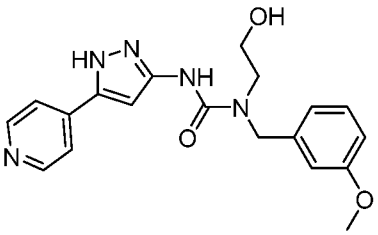


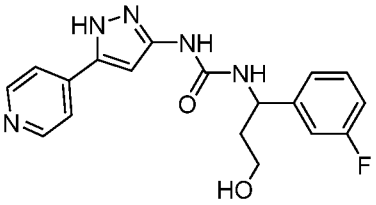


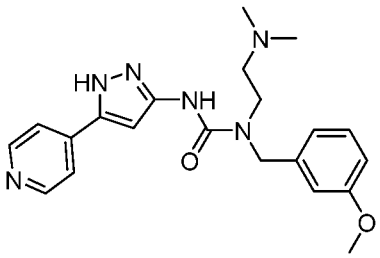


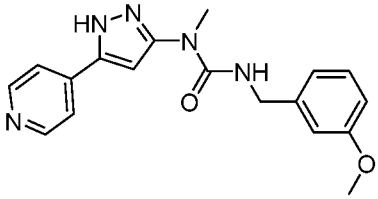


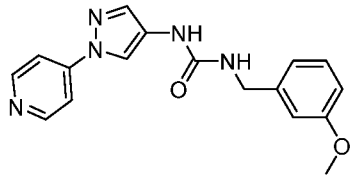


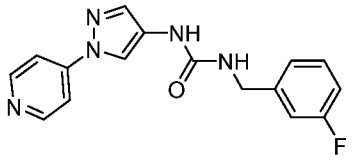


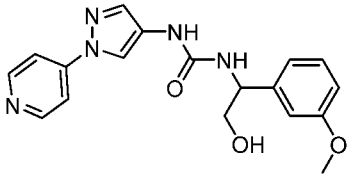


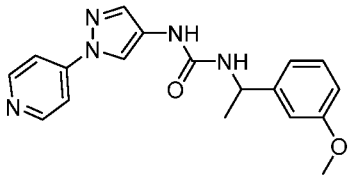


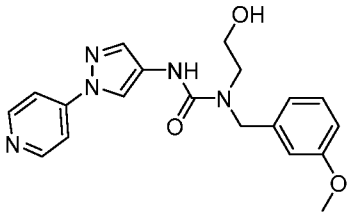


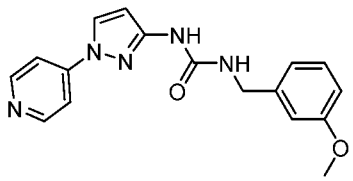


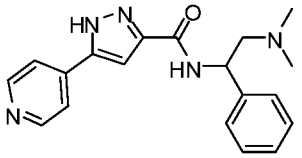


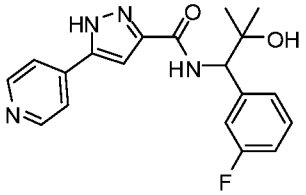


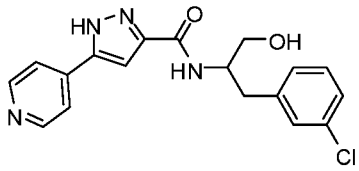


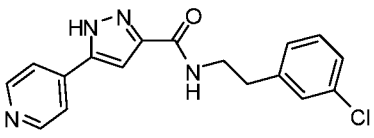


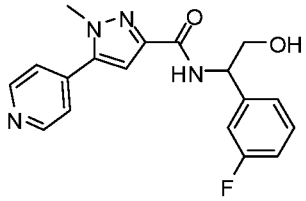


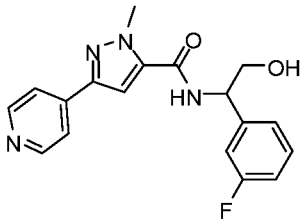


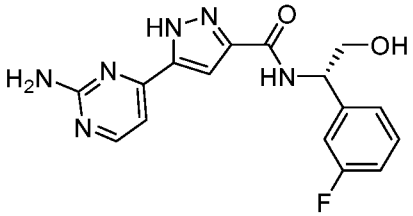


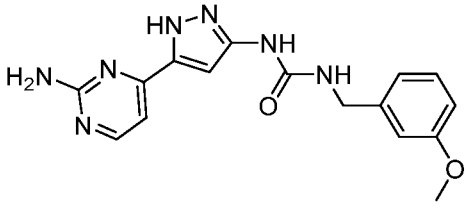


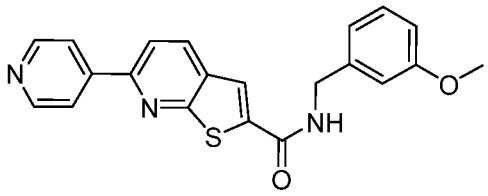


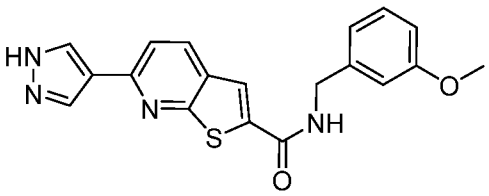


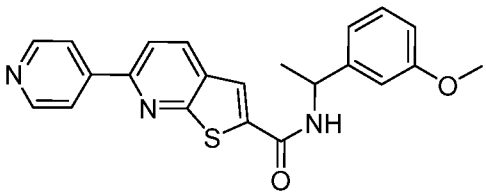


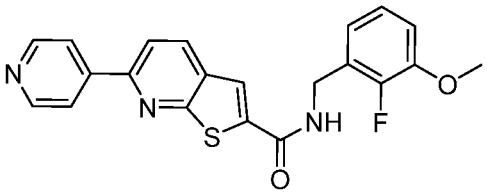


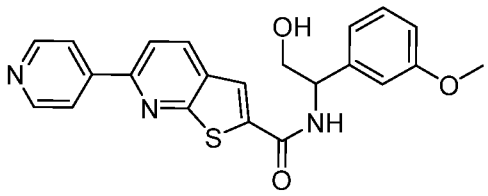


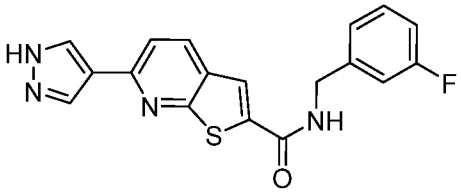


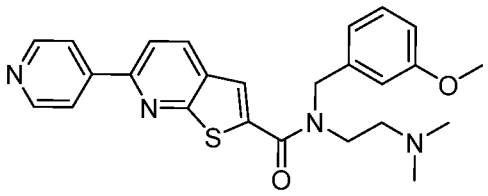


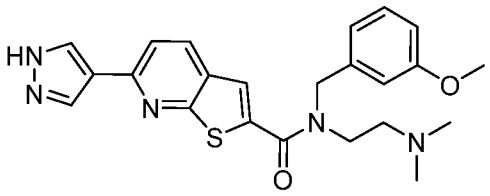


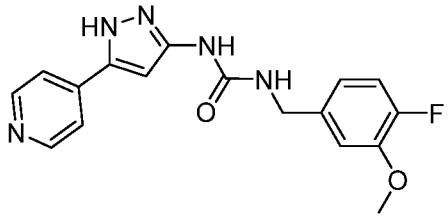


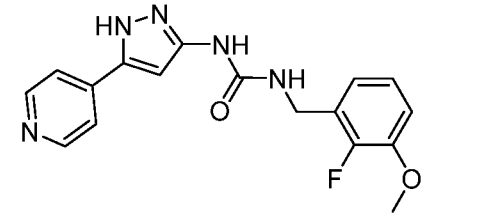


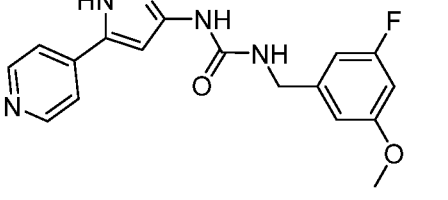


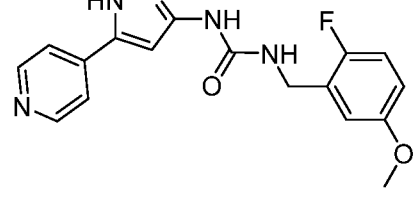


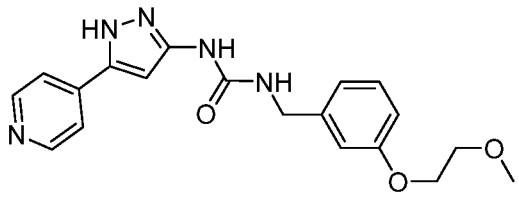


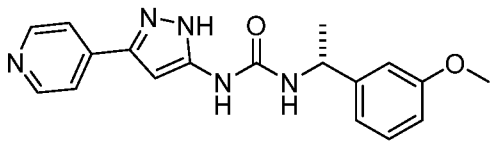


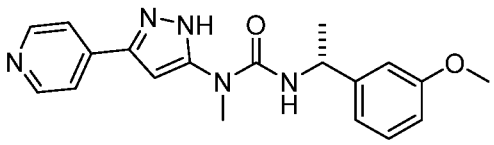


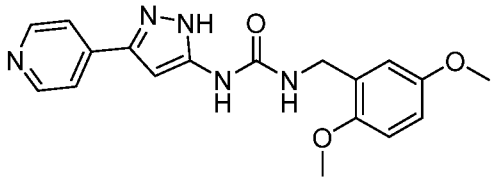


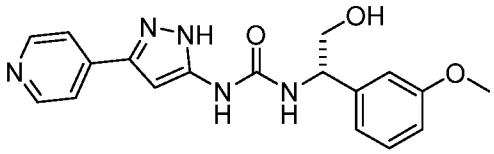


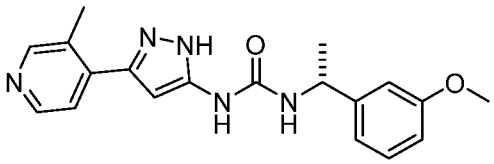


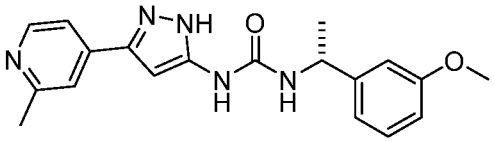




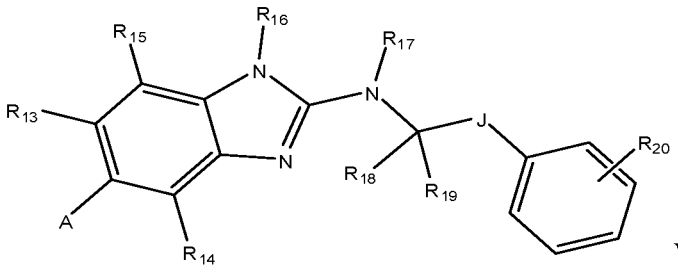








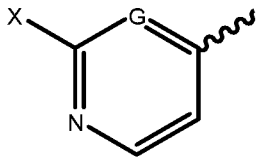
The present invention is also directed to a compound of Formula V:



V

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate or physiologically functional derivative thereof;

wherein:

A is indazol-3-yl, pyrazol-4-yl or 

, wherein (i) G is CH or N; and (ii) X is hydrogen, -OR_2 or –NR_3R_4, wherein each of R_2, R_3 and R4 is independently –H or C_{1-6} alkyl;

each of R_{13} and R_{14} is independently –H, halo, C_{1-6} alkyl, or C_{3-7} cycloalkyl;

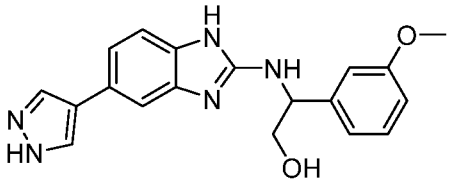
each of R_{15} and R_{20} is independently–H, halo, -OH, -CN, -COOR', -OR', -SR', -OC(O)R', -NHR', -NR'R", -NHC(O)R', -NHC(O)NR'R", -C(O)NR'R", -$NS(O)_2$R', -$S(O)_2$NR'R", -$S(O)_2$R', guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, and 3- to 10-membered heterocycle, wherein each of the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle independently is unsubstituted or substituted with one or more of halo, -OH, -CN, -COOR', -OR', -SR', -OC(O)R', -NHR', -NR'R", -NHC(O)R', -NHC(O)NR'R", -C(O)NR'R", -$NS(O)_2$R', -$S(O)_2$NR'R", -$S(O)_2$R', guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl; wherein each of R' and R" is independently -H or C_{1-6} alkyl; and optionally R' and R" together attaching to N or O form a 4- to 8-membered heterocycle;

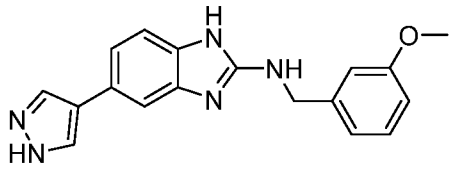
each of R_{16}, R_{17}, R_{18} and R_{19} is independently –H, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle; wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, -OH, -CN, -$COOR_a$, -OR_a, -SR_a, -$OC(O)R_a$, -NHR_a, -NR_aR_b, -$NHC(O)R_a$, -$NHC(O)NR_aR_b$, -$C(O)NR_aR_b$, -$NS(O)_2R_a$, -$S(O)_2NR_aR_b$, -$S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently -H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O forms a 4- to 8-membered heterocycle; and

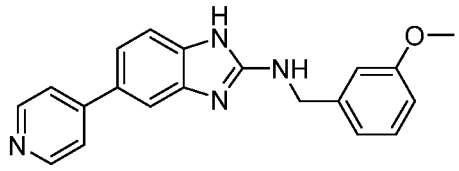
J is a bond or C_{1-6} alkyl.

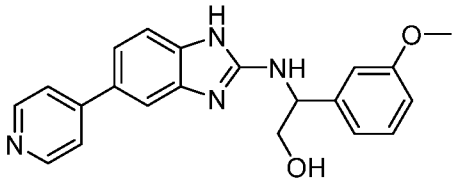
In certain aspects, A is pyrazol-4-yl. In other aspects, A is pyridine-4-yl. In one aspect, the present invention relates to a compound of Formula II wherein both R_{13} and R_{14} are methyl.

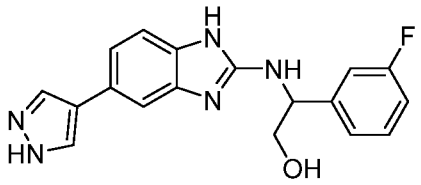
In some embodiments, the present invention is directed to a compound of Formula V is selected from the group consisting of:











In certain aspects, the present invention provides a compound as disclosed herein for use in treating a disease related to upregulation of Rho kinase- signaling pathways.

In other aspects, the present invention is directed to a method of treating an autoimmune disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In one aspect, the autoimmune disorder is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), psoriasis, Crohn's disease, atopic dermatitis, eczema, or graft- versus-host disease (GVHD).

In some embodiments, the present invention provides a method of treating a cardiovascular disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In one embodiment, the cardiovascular disorder is hypertension, atherosclerosis, restenosis, cardiac hypertrophy, ocular hypertension, cerebral ischemia, cerebral vasospasm, or erectile dysfunction.

In other embodiments, the present invention provides a method of treating inflammation in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In certain aspects, the inflammation is asthma, cardiovascular inflammation, renal inflammation or arteriosclerosis.

In certain aspects, the present invention provides a method of treating a central nervous system disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In one aspect, the central nervous system disorder is neuronal degeneration or spinal cord injury. In another aspect, the central nervous system disorder is Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), or multiple sclerosis.

The present invention also provides a method of treating an arterial thrombotic disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In one embodiment, the arterial thrombotic disorder is platelet aggregation, or leukocyte aggregation.

In other aspects, the present invention relates to a method of treating a fibrotic disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In one embodiment, the fibrotic disorder is liver fibrosis, lung fibrosis, or kidney fibrosis.

The present invention also relates to a method of treating glaucoma or regulating intraocular pressure in a subject comprising administering to the subject a therapeutically effective amount of a compound disclosed herein. In one aspect, the glaucoma is primary open-angle glaucoma, acute angle-closure glaucoma, pigmentary glaucoma, congenital glaucoma, normal tension glaucoma, or secondary glaucoma.

In some embodiments, the present invention is directed to a method of treating a neoplastic disease in a subject comprising: administering to the subject a therapeutically effective amount of a compound disclosed herein. In certain aspects, the neoplastic disorder is a lymphoma,

carcinoma, leukemia, sarcoma, or blastoma. In other aspects, the neoplastic disorder is squamous cell cancer, small- cell king cancer, pituitary cancer, esophageal cancer, astrocytoma, soft tissue sarcoma, non- small cell lung cancer, adenocarcinoma of the king, squamous carcinoma of the king, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer, melanoma, or head and neck cancer.

In yet other embodiments, the present invention provides a method of treating metabolic syndrome, insulin resistance, hyperinsulinemia, type 2 diabetes, or glucose intolerance in a subject comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In one embodiment, the present invention relates to a method of treating osteoporosis or promoting bone formation in a subject comprising administering to the subject a therapeutically effective amount of a compound disclosed herein.

In another embodiment, the present invention relates to a method of treating an ocular disorder having an angiogenic component comprising administering to the subject a therapeutically effective amount of a compound disclosed herein and an angiogenesis inhibitor. In certain aspects, the ocular disorder is age related macular degeneration (AMD), choroidal neovascularization (CNV), diabetic macular edema (DME), iris neovascularization, uveitis, neo vascular glaucoma, or retinitis of prematurity (ROP).

DETAILED DESCRIPTION OF THE INVENTION

In the following description, and for the purposes of explanation, numerous specific details are set forth in order to provide a thorough understanding of the various aspects of the invention. It will be understood, however, by those skilled in the relevant arts, that the present invention may be practiced without these specific details. In other instances, known structures and devices are

shown or discussed more generally in order to avoid obscuring the invention. In many cases, a description of the operation is sufficient to enable one to implement the various forms of the invention, particularly when the operation is to be implemented in software. It should be noted that there are many different and alternative configurations, devices and technologies to which the disclosed inventions may be applied. The full scope of the inventions is not limited to the examples that are described below.

It will be understood that "substituted", "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein below.

The term “alkyl,” as used herein unless otherwise defined, refers to a straight or branched saturated group derived from the removal of a hydrogen atom from an alkane. Representative straight chain alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, and n-heptyl. Representative branched alkyl groups include -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl and 1,2-dimethylpropyl.

As used herein, halo groups include any halogen. Examples include but are not limited to –F, -Cl, -Br, or –I.

A C_1-C_6 alkyl group includes any straight or branched, saturated or unsaturated, substituted or unsubstituted hydrocarbon comprised of between one and six carbon atoms. Examples of -C_1-C_6 alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, sec- butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, neohexyl, ethylenyl, propylenyl, 1-

butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, acetylenyl, pentynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl and 3-hexynyl groups. Substituted -C_1-C_6 alkyl groups may include any applicable chemical moieties. Examples of groups that may be substituted onto any of the above listed -C_1-C_6 alkyl groups include but are not limited to the following examples: halo, -C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), C_3-C_7 cycloalkyl, -OH, -CN, -COOR', -OC(O)R', -NHR', $N(R')_2$,-NHC(O)R' or -C(O)NHR' groups. The groups denoted R' above may be –H, any -C_1-C_6 alkyl, or two R' may, optionally with a nitrogen or an oxygen atom which they are bound to, form a 3-, 4-, 5-, 6-, 7- membered ring system when the substitution is $–N(R')_2$;

An aryl group includes any unsubstituted or substituted phenyl or napthyl group. Examples of groups that may be substituted onto ay aryl group include, but are not limited to: halo, -C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), -OH, -CN, -COOR', -OC(O)R', NHR', N (R') 2,- NHC(O), R', or -C(O)NEtR'. The group denoted R' may be -H or any -C_1-C_6 alkyl.

A C_3-C_7 cycloalkyl group includes any 3-, 4-, 5-, 6-, or 7-membered substituted or unsubstituted non-aromatic carbocyclic ring. Examples of C_3-C_7 cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptanyl, 1,3-cyclohexadienyl,-1, 4- cyclohexadienyl,-1, 3-cycloheptadienyl, and-1,3, 5-cycloheptatrienyl groups. Examples of groups that may be substituted onto C_3-C_7 cycloalkyl groups include, but are not limited to: -halo, -C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), -OH, -CN, -COOR', -OC(O) R', NHR', N(R')2, -NHC(O)R' or -C(O)NHR' groups. The groups denoted R' above include an -H or any unsubstituted -C_1-C_6 alkyl, examples of which are listed above. Halo groups include any halogen. Examples include but are not limited to –F, -Cl, -Br, or –I.

A heterocycle may be any optionally substituted saturated, unsaturated or aromatic cyclic moiety wherein said cyclic moiety is interrupted by at least one heteroatom selected from oxygen (O) , sulfur (S) or nitrogen (N) . Heterocycles may be monocyclic or polycyclic rings. For example, suitable substituents include halogen, halogenated C1-6 alkyl, halogenated C1-6 alkoxy, amino, amidino, amido, azido, cyano, guanidino, hydroxyl, nitro, nitroso, urea, $OS(O)_2R$; $OS(O)_2OR$, $S(O)_2OR$ $S(O)_{0\text{-}2}R$, C(O)OR wherein R may be H, C_1-C_6 alkyl, aryl or 3 to 10 membered

heterocycle) $OP(O)OR_1OR_2$, $P(O)OR_1OR_2$, $SO_2NR_1R_2$, $NR_1SO_2R_2$ $C(R_1)NR_2$ $C(R_1)NOR_2$, R1 and R2 may be independently H, C_1-C_6 alkyl, aryl or 3 to 10 membered heterocycle), $NR_1C(O)R_2$, $NR_1C(O)OR_2$, $NR_3C(O)NR_2R_1$, $C(O)NR_1R_2$, $OC(O)NR_1R_2$. For these groups, R_1, R_2 and R_3 are each independently selected from H, C_1-C_6 alkyl, aryl or 3 to 10 membered heterocycle or R_1 and R_2 are taken together with the atoms to which they are attached to form a 3 to 10 membered heterocycle.

Possible substituents of heterocycle groups include halogen (Br, Cl, I or F), cyano, nitro, oxo, amino, C1-4 alkyl (e.g., CH_3, C_2H_5, isopropyl) C_{1-4} alkoxy (e.g., OCH_3, OC_2H_5), halogenated C_{1-4} alkyl (e.g., CF_3, CHF_2), halogenated C_{1-4} alkoxy (e.g., OCF_3, OC_2F_5), COOH, COO-C_{1-4} alkyl, CO-C_{1-4} alkyl, C_{1-4} alkyl -S- (e.g., CH_3S, C_2H_5S), halogenated C_{1-4} alkyl -S- (e.g., CF_3S, C_2F_5S), benzyloxy, and pyrazolyl.

Examples of heterocycles include but are not limited to azepinyl, aziridinyl, azetyl, azetidinyl, diazepinyl, dithiadiazinyl , dioxazepinyl, dioxolanyl, dithiazolyl, furanyl, isooxazolyl, isothiazolyl, imidazolyl, morpholinyl, morpholino, oxetanyl , oxadiazolyl, oxiranyl, oxazinyl, oxazolyl, piperazinyl, pyrazinyl, pyridazinyl, pyrimidinyl, piperidyl, piperidino, pyridyl, pyranyl, pyrazolyl, pyrrolyl, pyrrolidinyl, thiatriazolyl, tetrazolyl, thiadiazolyl, triazolyl, thiazolyl, thienyl, tetrazinyl, thiadiazinyl , triazinyl, thiazinyl, thiopyranyl furoisoxazolyl , imidazothiazolyl, thienoisothiazolyl , thienothiazolyl , imidazopyrazolyl , cyclopentapyrazolyl, pyrrolopyrrolyl, thienothienyl, thiadiazolopyrimidinyl , thiazolothiazinyl , thiazolopyrimidinyl , thiazolopyridinyl, oxazolopyrimidinyl , oxazolopyridyl, benzoxazolyl, benzisothiazolyl, benzothiazolyl, imidazopyrazinyl , purinyl , pyrazolopyrimidinyl , imidazopyridinyl, benzimidazolyl, indazolyl, benzoxathiolyl, benzodioxolyl, benzodithiolyl, indolizinyl, indolinyl, isoindolinyl, furopyrimidinyl, furopyridyl, benzofuranyl , isobenzofuranyl , thienopyrimidinyl , thienσpyridyl, benzothienyl, cyclopentaoxazinyl, cyclopentafuranyl , benzoxazinyl, benzothiazinyl, quinazolinyl, naphthyridinyl, quinolinyl, isoquinolinyl, benzopyranyl , pyridopyridazinyl and pyridopyrimidinyl groups.

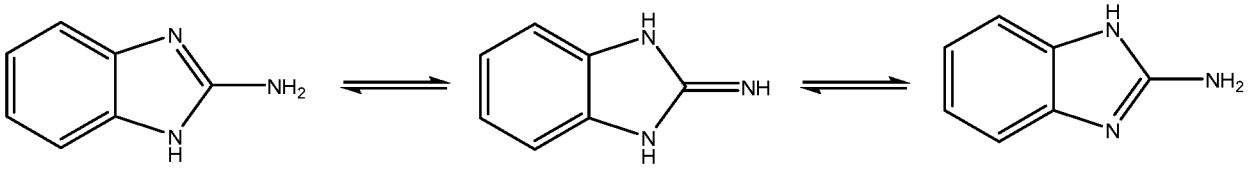
The invention further encompasses any other physiochemical or sterochemical form that the compound may assume. Such forms include diastereomers, racemates, isolated enantiomers,

hydrated forms, solvated forms, any known or yet to be disclosed crystalline or amorphous form including all polymorphic crystalline forms. Amorphous forms lack a distinguishable crystal lattice and therefore lack an orderly arrangement of structural units. Many pharmaceutical compounds have amorphous forms. Methods of generating such chemical forms will be well known by one with skill in the art.

Another aspect of the invention is that the carbon atom bearing R_1 and –QW in Formula I and may have "S" or "R" configuration. All diastereomers, racemates, and isolated enantiomers are within the scope of the invention.

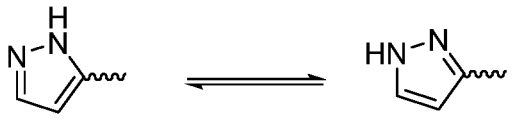
Racemates, individual enantiomers, or diasteromers of the compound may be prepared by specific synthesis or resolution through any method now known or yet to be disclosed. For example, the compound may be resolved into it enantiomers by the formation of diasteromeric pairs through salt formation using an optically active acid. Enantiomers are fractionally crystallized and the free base regenerated. In another example, enantiomers may be separated by chromatography. Such chromatography may be any appropriate method now known or yet to be disclosed that is appropriate to separate enantiomers such as HPLC on a chiral column.

The benzamide and pyrazole moiety and its intermediates may exist in different tautomeric forms. Tautomers include any structural isomers of different energies that have a low energy barrier to interconversion. One example is proton tautomers (prototropic tautomers.) In this example, the interconversions occur via the migration of a proton. Examples of prototropic tautomers include, but are not limited to keto-enol and imine-enamine isomerizations. In another example illustrated graphically below, proton migration between the 1-position, 2-amino and 3-position nitrogen atoms of a 2-aminobenzimidazole ring may occur. As a result, Formulas IIa, IIb and IIc are tautomeric forms of each other:



IIa IIb IIc

Similarly, Formulas IIIa and IIIb are tautomeric forms of each other:



IIIa IIIb

In some aspects of the invention the compound is in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts include any salt derived from an organic or inorganic acid. Examples of such salts include but are not limited to the following: salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2- (4-chlorophenoxy)-2- methylpropionic acid, 1, 2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, N-glycolylarsanilic acid, 4-hexylresorcinol, hippuric acid, 2- (4-hydroxybenzoyl) benzoicacid, 1-hydroxy-2-naphthoicacid, 3-hydroxy- 2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphuric acid, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulpuric acid, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ((4-aminophenyl) phosphonic acid), picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid or any other such acid now known or yet to be disclosed. It will be appreciated that such salts, provided that they are pharmaceutically acceptable, may be used in therapy. Such salts may be prepared by reacting the compound with a suitable acid in a manner known by those skilled in the art.

In some embodiments, the compounds of the present invention cause kinase inhibition *in vitro* and/or *in vivo*. Methods of determining kinase inhibition are well known in the art. For example, kinase activity of an enzyme and the inhibitory capacity of a test compound can be determined by measuring enzyme specific phosphorylation of a substrate. Commercial assays and kits can be employed. For example, kinase inhibition can be determined using an IMAP® assay (Molecular Devices). This assay method involves the use of a fluorescently- tagged peptide substrate. Phosphorylation of the tagged peptide by a kinase of interest promotes binding of the peptide to a trivalent metal-based nanoparticle via the specific, high affinity interaction between the phospho-group and the trivalent metal. Proximity to the nanoparticle results in increased fluorescence

polarization. Inhibition of the kinase by a kinase inhibitor prevents phosphorylation of the substrate and thereby limits binding of the fluorescently-tagged substrate to the nanoparticle. Such an assay can be compatible with a microwell assay format, allowing simultaneous determination of IC_{50} of multiple compounds.

In another aspect of the present invention there is provided a method of treating a patient suffering from a disease comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of the present invention. The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment, e.g., reasonable side effects applicable to any medical treatment.

Compounds of the invention are useful for treatment of patients suffering from cardiovascular and non-cardiovascular diseases, such as hypertension, pulmonary hypertension, atherosclerosis, restenosis, coronary heart disease, cardiac hypertrophy, ocular hypertension, retinopathy, ischemic diseases, cerebral ischemia, cerebral vasospasm, penile erectile dysfunction, peripheral circulatory disorder, peripheral artery occlusive disease, glaucoma, (e.g., regulating intraocular pressure), fibroid lung, fibroid liver, fibroid kidney, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome, central nervous system disorders such as neuronal degeneration and spinal cord injury. Further, the compounds of the invention can be used to treat arterial thrombotic disorders such as platelet aggregation and leukocyte aggregation, and bone resorption.

In an embodiment of the invention, compounds are used to treat cerebral cavernous malformation (CCM). CCMs are vascular lesions consisting of clusters of leaky, dilated capillaries and are associated with central nervous system (CNS) disorders, including seizures and stroke. The loss of vascular integrity is thought to involve activation of RhoA and activation of ROCK, leading to changes in cytoskeletal stability and increased vascular permeability. The compounds of the invention inhibit ROCK activation and restore vascular endothelial function.

The compounds of the invention can also be used to treat glaucoma. There are several types of glaucoma which can be treated, including, without limitation, the following types. The two most common, primary open-angle glaucoma and acute angle-closure glaucoma are characterized by high ocular pressure. Pigmentary glaucoma and congenital glaucoma also are characterized by reduced fluid outflow and high intraocular pressure (IOP). Normal tension glaucoma is thought to be due to another mechanism, in particular poor blood flow to the optic nerve. Secondary glaucoma can result from injury, infection, inflammation, tumor or cataracts, and is also associated with prolonged use of steroids, systemic hypertension, diabetic retinopathy, and central retinal vein occlusion.

In certain embodiments, the compounds of the invention are used to treat inflammation, including, but not limited to asthma, cardiovascular inflammation, renal inflammation, atherosclerosis and arteriosclerosis.

In some embodiments, the compounds of the invention inhibit tumor cell growth and metastasis, and angiogenesis, and are useful for treating neoplastic diseases. Neoplastic diseases include any malignant growth or tumor caused by abnormal or uncontrolled cell division, and may spread to other parts of the body through the lymphatic system or the blood stream Neoplastic disease includes, without limitation, lymphoma (a neoplasm of lymph tissue that is usually malignant), carcinoma (any malignant tumor derived from epithelial tissue), leukemia (malignant neoplasm of blood-forming tissues; characterized by abnormal proliferation of leukocytes), sarcoma (a usually malignant tumor arising from connective tissue (bone or muscle etc.), and blastoma (malignancy in precursor cells). Non-limiting examples include squamous cell cancer, small-cell lung cancer, pituitary cancer, esophageal cancer, astrocytoma, soft tissue sarcoma, non-small cell king cancer, adenocarcinoma of the lung, squamous carcinoma of the king, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer, melanoma, and various types of head and neck cancer.

According to one aspect of the invention, the inventive compounds are used to effect weight loss and/or limit weight gain. In a preferred embodiment, the compound is ROCK2 selective. ROCK-2 inhibitors promote weight loss in normal subjects, and limit weight gain in subjects prone to obesity.

In an embodiment of the invention, the inventive compound is used to reduce or prevent insulin resistance or restore insulin sensitivity. Accordingly, in one embodiment, the compounds of the invention are used to promote or restore insulin- dependent glucose uptake. In another embodiment of the invention, a compound of the invention is used to promote or restore glucose tolerance. In another embodiment of the invention, a compound of the invention is used to treat metabolic syndrome. In another embodiment, a compound of the invention is used to reduce or prevent hyperinsulinemia. In an embodiment of the invention, an inventive compound is used to treat diabetes (particularly type 2 diabetes). Compounds of the invention may also be used to promote or restore insulin-mediated relaxation of vascular smooth muscle cells (VSMCs).

The invention provides methods and compounds for treating diseases and disorders with an angiogenic component. According to the invention, in certain embodiments, such diseases and disorders are treated by administering to a subject an effective amount of a rho kinase inhibitor. In certain embodiments, the inventive compound is a ROCK2 selective inhibitor. According to the invention, such diseases and disorders can also be treated by administering an effective amount of a rho kinase inhibitor that inhibits ROCK2, and may be ROCK2 selective, and an effective amount of an angiogenesis inhibitor. According to the invention, ocular diseases and disorders having an angiogenic component are treated in this manner. In one embodiment, the invention provides a method of treating age related macular degeneration (AMD), which occurs in "dry" and "wet" forms. The "wet" form of AMD causes vision loss due to abnormal blood vessel growth (neovascularization). Bleeding, leaking, and scarring from these retinal blood vessels eventually causes irreversible damage to the photoreceptors. The dry form results from atrophy of the retinal pigment epithelial layer, which causes vision loss through loss of photoreceptors (rods and cones) in the central part of the eye. In another embodiment, the invention provides a method of treating choroidal neovascularization (CNV). Choroidal neovascularization is a process in which new blood vessels grow in the choroid, through the Bruch membrane and invade the subretinal space, and is a symptom of, among other causes, age-

related macular degeneration, myopia and ocular trauma. In another embodiment, the invention provides a method of treating diabetic macular edema (DME). In another embodiment, the invention provides a method of treating macular edema that is secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). In other embodiments, the diseases to be treated include, without limitation, retinal neovascularization, infectious and non-infectious, corneal neovascularization infectious and non-infectious, iris neovascularization, uveitis, neovascular glaucoma, and retinitis of prematurity (ROP). The method of treatment can be prophylactic, such as to stave off corneal neovascularization after corneal transplant, or to modulate the wound healing process in trabeculectomy surgery. These diseases and disorders may be characterized as having an angiogenic component. According to the invention, such disorders are treated by administering an inventive compound and an angiogenesis inhibitor.

Accordingly, in one such embodiment, the disease or disorder is AMD, and a subject in need of treatment for AMD is administered an amount of an inventive compound to treat AMD. In another embodiment, the subject is administered an inventive compound and an angiogenesis inhibitor in amounts effective to treat AMD. In such embodiments, a ROCK2- selective inhibitor may be preferred. In some embodiments, the angiogenesis inhibitor is a VEGFR2 antagonist. In certain such embodiments, the VEGFR2 antagonist binds to VEGF. In other such embodiments, the VEGFR2 antagonist binds to VEGFR2. Such VEGFR2-binding inhibitors include agents that bind to the extracellular domain of VEGFR2, including but not limited to antibodies and VEGFR2-binding fragments thereof and agents that interact with the intracellular domain of VEGFR2 and block activation of VEGFR2- dependent signal transduction. VEGFR2 antagonists further include agents that interact with other cellular components to block VEGFR2- dependent signal transduction. In other embodiments of the invention, other ocular diseases and disorders having an angiogenic component, such as are indicated above, are similarly treated.

According to the invention, an inventive compound and an angiogenesis inhibitor are administered to a subject in amounts effective amount to treat or preventing a pathologic condition characterized by excessive angiogenesis. Such conditions, involving for example, vascularization and/or inflammation, include atherosclerosis, rheumatoid arthritis (RA), hemangiomas, angiofibromas, and psoriasis. Other non-limiting examples of angiogenic disease are retinopathy of prematurity (retrolental fibroplastic), corneal graft rejection, corneal

neovascularization related to complications of refractive surgery, corneal neovascularization related to contact lens complications, corneal neovascularization related to pterygium and recurrent pterygium, corneal ulcer disease, and non-specific ocular surface disease, insulin-dependent diabetes mellitus, multiple sclerosis, myasthenia gravis, Crohn's disease, autoimmune nephritis, primary biliary cirrhosis, acute pancreatitis, allograph rejection, allergic inflammation, contact dermatitis and delayed hypersensitivity reactions, inflammatory bowel disease, septic shock, osteoporosis, osteoarthritis, cognition defects induced by neuronal inflammation, Osier-Weber syndrome, restenosis, and fungal, parasitic and viral infections, including cytomegalovirus infections.

The invention further encompasses pharmaceutical compositions that include the disclosed compound as an ingredient. Such pharmaceutical compositions may take any physical form necessary depending on a number of factors including the desired method of administration and the physicochemical and stereochemical form taken by the disclosed compound or pharmaceutically acceptable salts of the compound. Such physical forms include a solid, liquid, gas, sol, gel, aerosol, or any other physical form now known or yet to be disclosed. The concept of a pharmaceutical composition including the disclosed compound also encompasses the disclosed compound or a pharmaceutically acceptable salt thereof without any other additive. The physical form of the invention may affect the route of administration and one skilled in the art would know to choose a route of administration that takes into consideration both the physical form of the compound and the disorder to be treated. Pharmaceutical compositions that include the disclosed compound may be prepared using methodology well known in the pharmaceutical art. A pharmaceutical composition that includes the disclosed compound may include a second effective compound of a distinct chemical formula from the disclosed compound. This second effective compound may have the same or a similar molecular target as the target or it may act upstream or downstream of the molecular target of the disclosed compound with regard to one or more biochemical pathways.

Pharmaceutical compositions including the disclosed compound include materials capable of modifying the physical form of a dosage unit. In one nonlimiting example, the composition includes a material that forms a coating that holds in the compound. Materials that may be used in such a coating, include, for example, sugar, shellac, gelatin, or any other inert coating agent.

Pharmaceutical compositions including the disclosed compound may be prepared as a gas or aerosol. Aerosols encompass a variety of systems including colloids and pressurized packages. Delivery of a composition in this form may include propulsion of a pharmaceutical composition including the disclosed compound through use of liquefied gas or other compressed gas or by a suitable pump system. Aerosols may be delivered in single phase, bi-phasic, or tri-phasic systems.

In some aspects of the invention, the pharmaceutical composition including the disclosed compound is in the form of a solvate. Such solvates are produced by the dissolution of the disclosed compound in a pharmaceutically acceptable solvent. Pharmaceutically acceptable solvents include any mixtures of more than one solvent. Such solvents may include pyridine, chloroform, propan-1-ol, ethyl oleate, ethyl lactate, ethylene oxide, water, ethanol, and any other solvent that delivers a sufficient quantity of the disclosed compound to treat the affliction without serious complications arising from the use of the solvent in patients.

Pharmaceutical compositions that include the disclosed compound may also include a pharmaceutically acceptable carrier. Carriers include any substance that may be administered with the disclosed compound with the intended purpose of facilitating, assisting, or helping the administration or other delivery of the compound. Carriers include any liquid, solid, semisolid, gel, aerosol or anything else that may be combined with the disclosed compound to aid in its administration. Examples include diluents, adjuvants, excipients, water, oils (including petroleum, animal, vegetable or synthetic oils,) Such carriers include particulates such as a tablet or powder, liquids such as an oral syrup or injectable liquid, and inhalable aerosols. Further examples include saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, and urea. Such carriers may further include binders such as ethyl cellulose, carboxymethylcellulose, microcrystalline cellulose, or gelatin; excipients such as starch, lactose or dextrins; disintegrating agents such as alginic acid, sodium alginate, Primogel, and corn starch; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin, a flavoring agent such as peppermint, methyl salicylate or orange flavoring, or coloring agents. Further examples of carriers include polyethylene glycol, cyclodextrin, oils, or any other similar liquid carrier that may be formulated into a capsule. Still further examples of carriers include sterile diluents such as water for injection, saline solution,

physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides, polyethylene glycols, glycerin, cyclodextrin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose, thickening agents, lubricating agents, and coloring agents.

The pharmaceutical composition including the disclosed compound may take any of a number of formulations depending on the physicochemical form of the composition and the type of administration. Such forms include solutions, suspensions, emulsions, tablets, pills, pellets, capsules, capsules including liquids, powders, sustained-release formulations, directed release formulations, lyophylates, suppositories, emulsions, aerosols, sprays, granules, powders, syrups, elixirs, or any other formulation now known or yet to be disclosed. Additional examples of suitable pharmaceutical carriers are described in “Remington's Pharmaceutical Sciences” by E. W. Martin, hereby incorporated by reference in its entirety.

Methods of administration include, but are not limited to, oral administration and parenteral administration. Parenteral administration includes, but is not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, sublingual, intranasal, intracerebral, intraventricular, intrathecal, intravaginal, transdermal, rectal, by inhalation, or topically to the ears, nose, eyes, or skin. Other methods of administration include but are not limited to infusion techniques including infusion or bolus injection, by absorption through epithelial or mucocutaneous linings such as oral mucosa, rectal and intestinal mucosa. Compositions for parenteral administration may be enclosed in ampoule, a disposable syringe or a multiple-dose vial made of glass, plastic or other material.

Administration may be systemic or local. Local administration is administration of the disclosed compound to the area in need of treatment. Examples include local infusion during surgery; topical application, by local injection; by a catheter; by a suppository; or by an implant. Administration may be by direct injection at the site (or former site) of a cancer, tumor, or precancerous tissue or into the central nervous system by any suitable route, including intraventricular and intrathecal injection. Intraventricular injection may be facilitated by an

intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration may be achieved by any of a number of methods known in the art. Examples include use of an inhaler or nebulizer, formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. The disclosed compound may be delivered in the context of a vesicle such as a liposome or any other natural or synthetic vesicle.

A pharmaceutical composition formulated so as to be administered by injection may be prepared by dissolving the disclosed compound with water so as to form a solution. In addition, a surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants include any complex capable of non-covalent interaction with the disclosed compound so as to facilitate dissolution or homogeneous suspension of the compound.

Pharmaceutical compositions including the disclosed compound may be prepared in a form that facilitates topical or transdermal administration. Such preparations may be in the form of a solution, emulsion, ointment, gel base, transdermal patch or iontophoresis device. Examples of bases used in such compositions include opetrolatum, lanolin, polyethylene glycols, beeswax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers, thickening agents, or any other suitable base now known or yet to be disclosed.

Examples that represent different aspects of the invention follow. Such examples should not be construed as limiting the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention would be apparent to those skilled in the art.

Elements and acts in the examples are intended to illustrate the invention for the sake of simplicity and have not necessarily been rendered according to any particular sequence or embodiment.

EXAMPLES

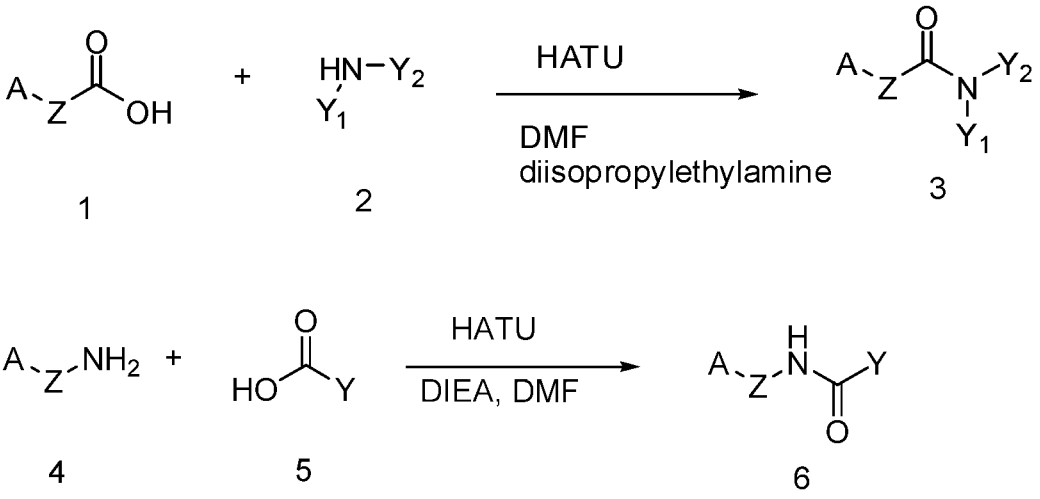
Example 1. Synthesis of Kinase Inhibitors

Different aspects of the invention may be prepared via the general synthetic procedures outlined below. It will be apparent to one skilled in the art how to prepare the other aspects of the

invention by choice of proper and relevant starting materials, synthetic intermediates and reagents.

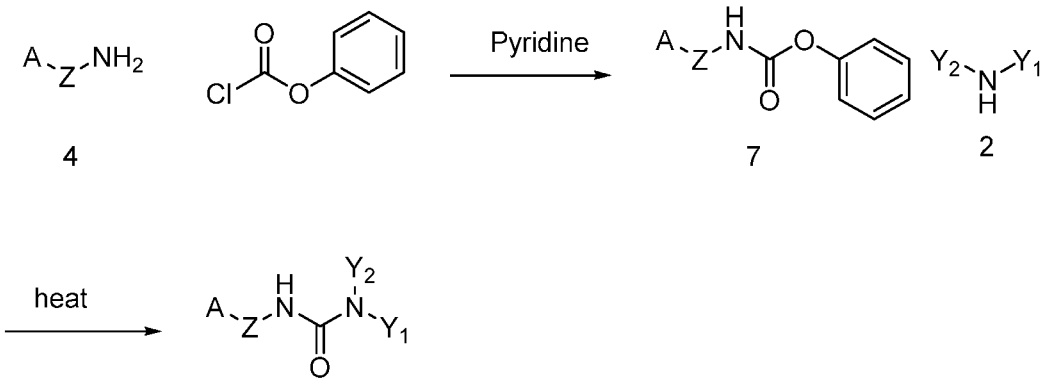
A compound of Formula I can be prepared according to **Scheme 1**. A 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) mediated amide coupling reaction between carboxylic acid **1** and amine **2** in DMF (N,N-dimethylformamide) generates structure **3**. Under the same conditions, amine 4 reacts with 5 to generate structure 6.

Scheme 1



Another compound of Formula I can be prepared according to **Scheme 2**. The coupling of amine 4 and phenyl chloroformate yields structure 7, which is treated with amine 2 to afford urea 9.

Scheme 2

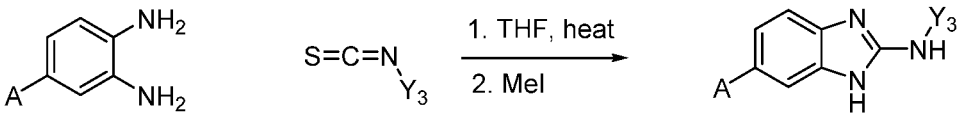


4 7 2

9

A compound of Formula V can be prepared according to **Scheme 3**. Aniline diamine 10 and isothiocyanate 11 are heated in THF and the cyclization of the resulting thiourea with iodomethane yields aminoimidazole 12.

Scheme 3

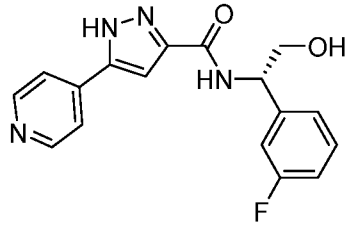
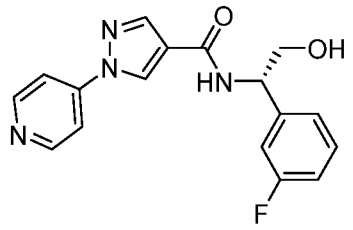
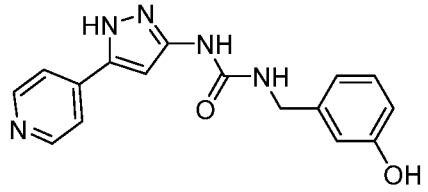
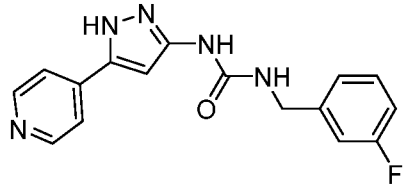
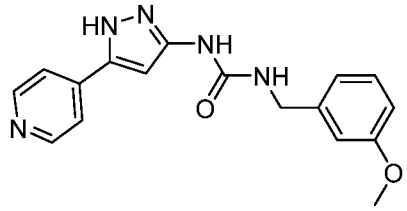
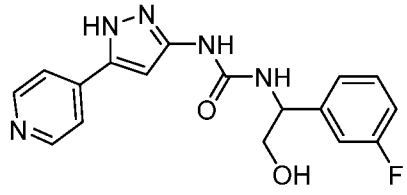


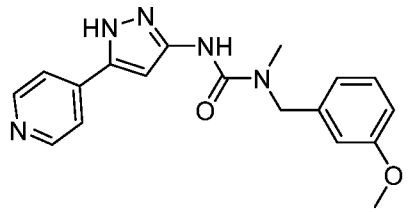
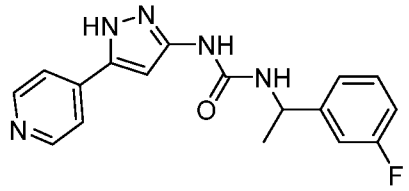
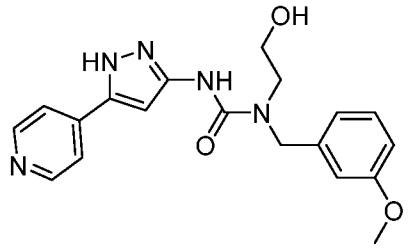
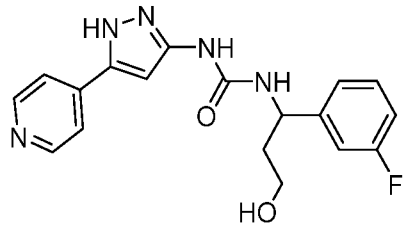
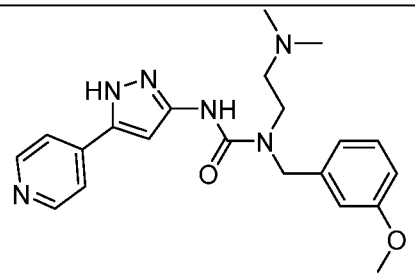
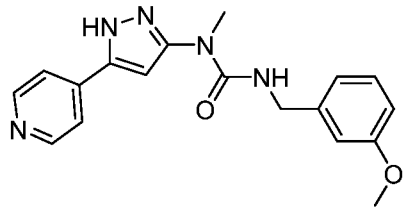
10 11 12

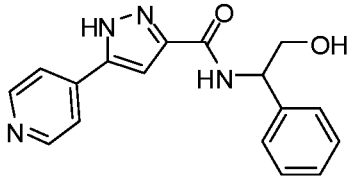
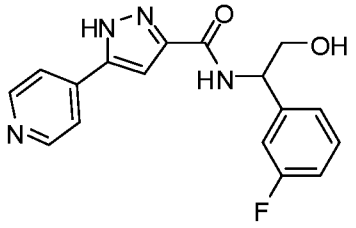
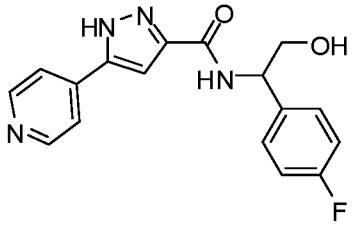
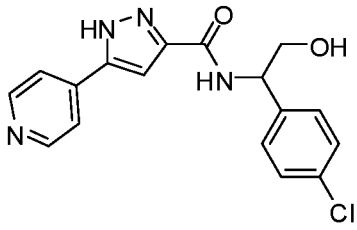
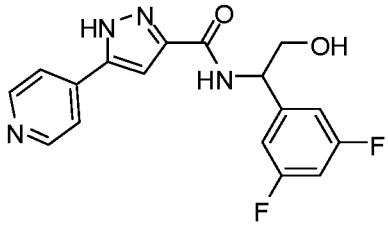
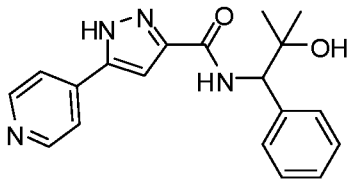
Example 2. Kinase Inhibitor Compounds

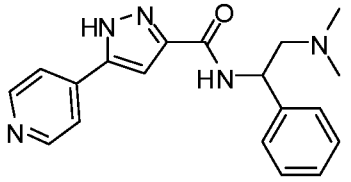
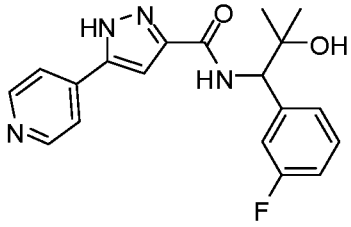
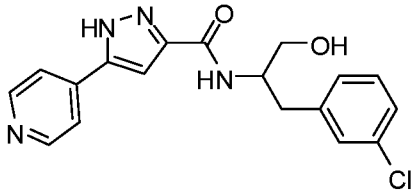
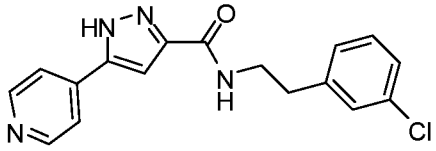
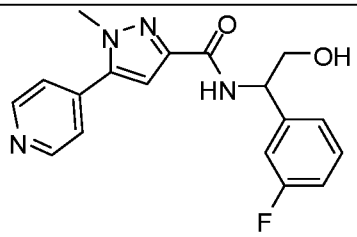
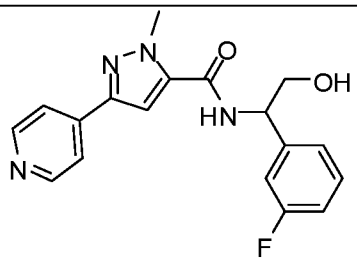
Non-limiting examples illustrative of the invention include those shown in **Table 1**.

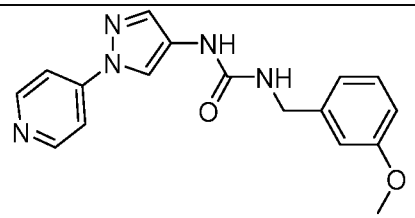
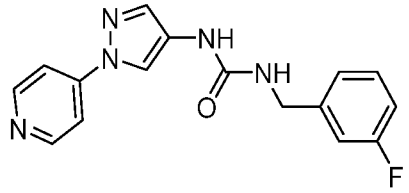
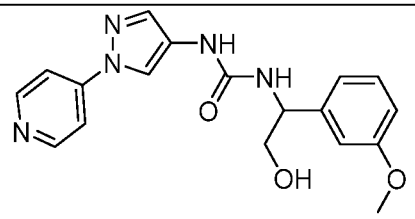
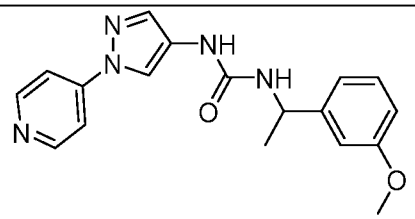
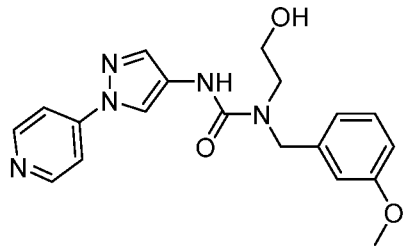
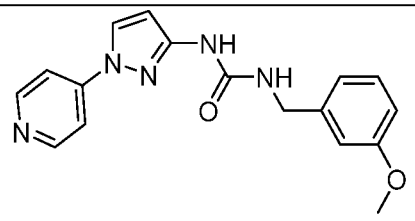
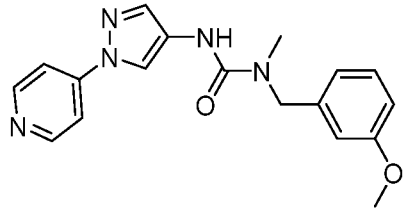
Table 1. Non-limiting examples of kinase inhibitor compounds. Unless specified, example compounds with a chiral center represent racemic mixture of the corresponding *R* and *S* enantiomers and all racemates and isolated enantiomers are within the scope of the invention.

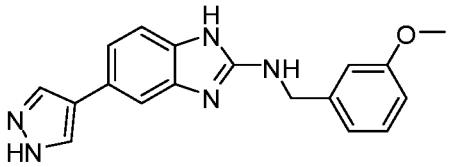
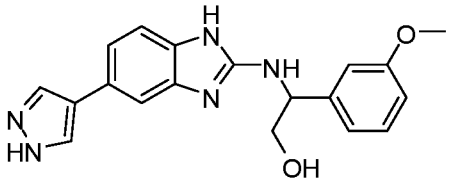
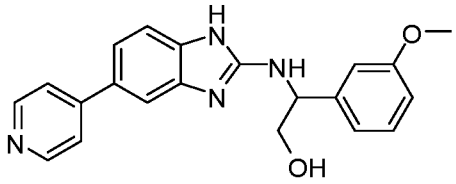
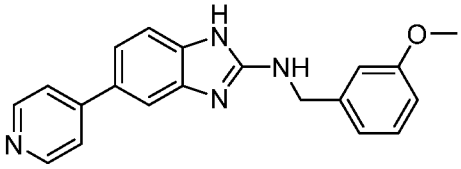
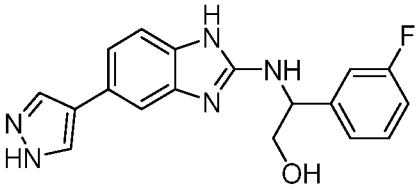
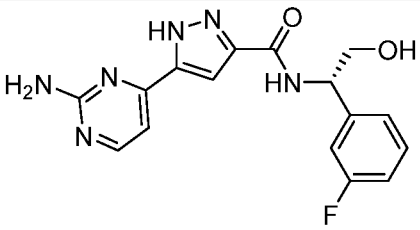
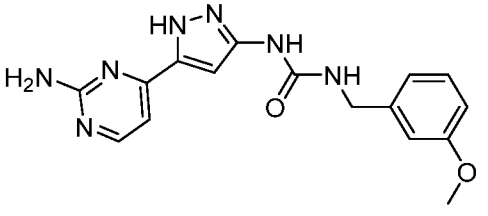
ID	Structure	M+1
1		327
2		327
3		310
4		312
5		324
6		342

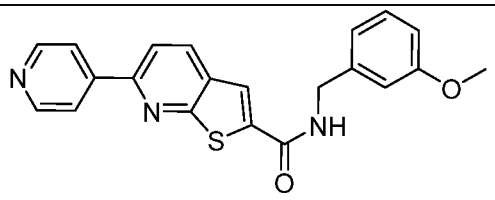
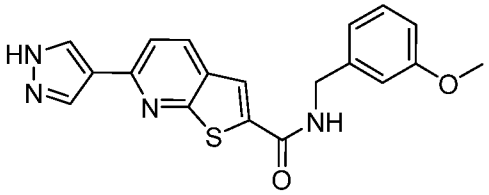
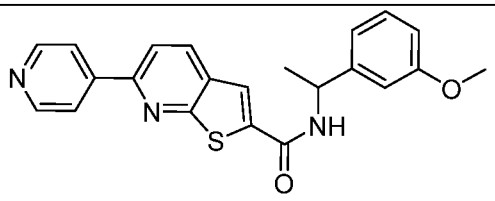
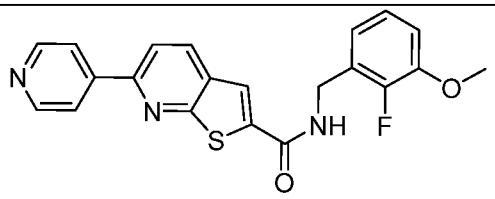
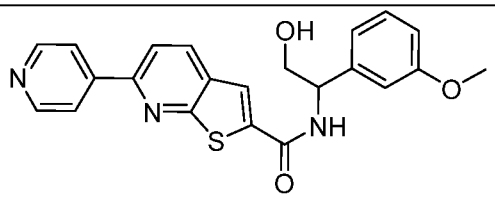
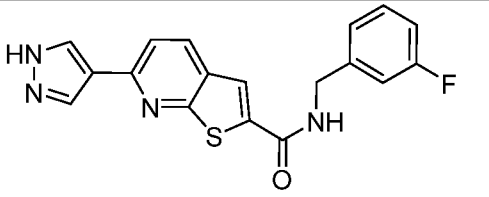
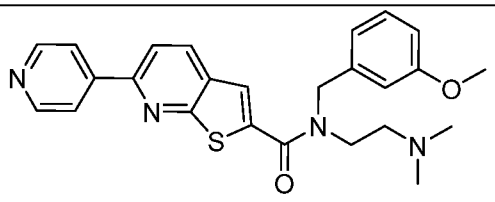
ID	Structure	M+1
7		338
8		326
9		368
10		356
11		395
12		338

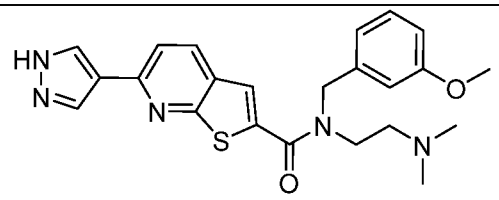
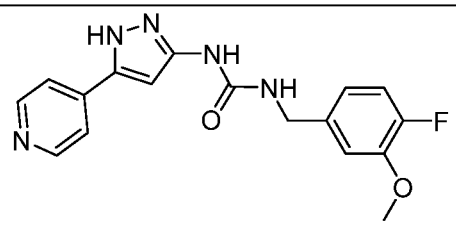
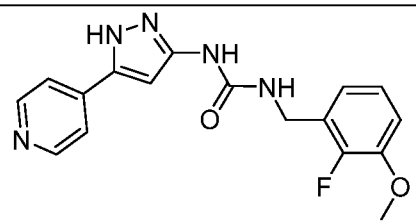
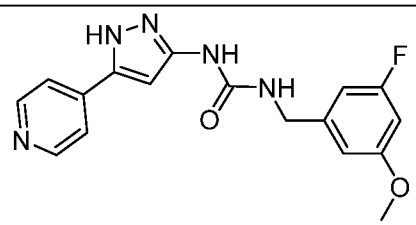
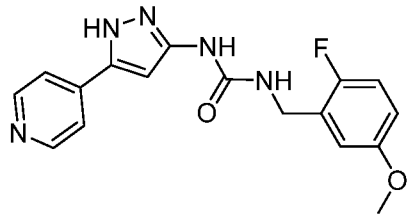
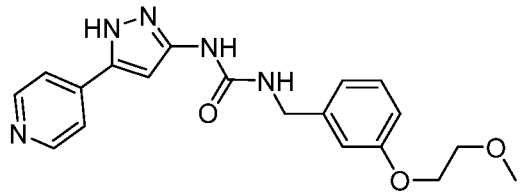
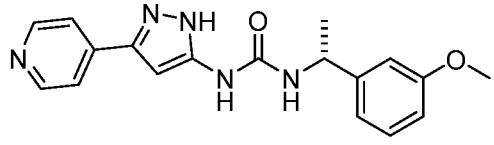
ID	Structure	M+1
13		309
14		327
15		327
16		343
17		345
18		337

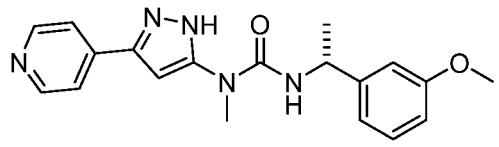
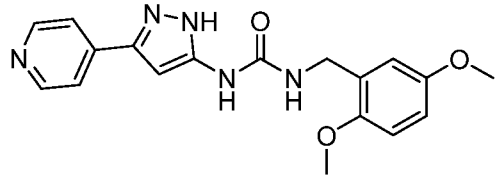
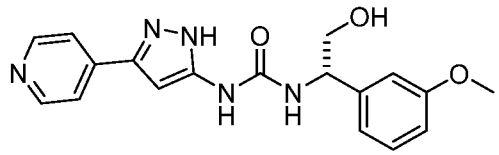
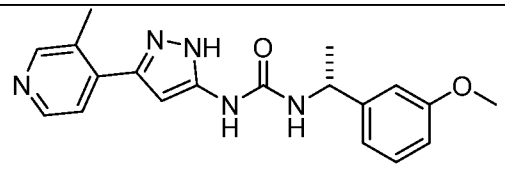
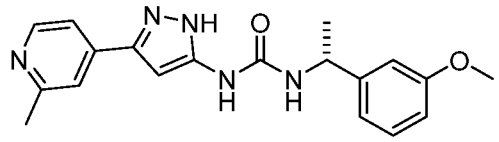
ID	Structure	M+1
19		336
20		355
21		357
22		327
23		341
24		341

ID	Structure	M+1
25		324
26		312
27		354
28		338
29		368
30		324
31		338

ID	Structure	M+1
32		320
33		350
34		361
35		331
36		338
37		343
38		340

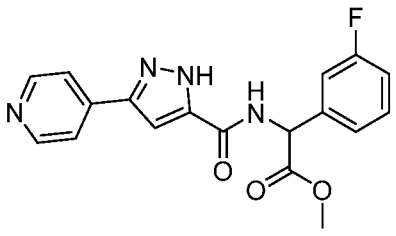
ID	Structure	M+1
39		376
40		365
41		390
42		394
43		406
44		353
45		447

ID	Structure	M+1
46		436
47		342
48		342
49		342
50		342
51		368
52		338

ID	Structure	M+1
53		352
54		354
55		354
56		352
57		352

Example 3. Synthesis of Compound 14

Step 1

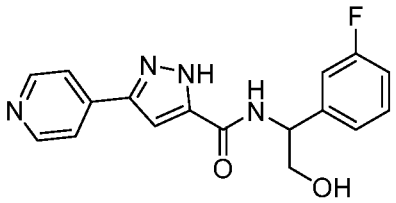


methyl 2-(3-fluorophenyl)-2-(3-(pyridin-4-yl)-1H-pyrazole-5-carboxamido)acetate

To a mixture of 3-(pyridin-4-yl)-1H-pyrazole-5-carboxylic acid (95 mg, 0.50 mmol), methyl 2-amino-2-(3-fluorophenyl)acetate HCl salt (143 mg, 0.65 mmol) and diisopropylethylamine (0.26

mL, 1.5 mmol) in DMF was added HATU (248 mg, 0.65 mmol). The reaction was stirred at room temperature for 3 h, quenched with water and extracted with ethyl acetate. The organic layer was dried, concentrated and purified by BIOTAGE® column chromatography to give methyl 2-(3-fluorophenyl)-2-(3-(pyridin-4-yl)-1H-pyrazole-5-carboxamido)acetate (126 mg).

Step 2

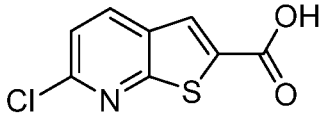


Compound 14

To a solution of methyl 2-(3-fluorophenyl)-2-(3-(pyridin-4-yl)-1H-pyrazole-5-carboxamido) acetate (62 mg, 0.17 mmol) in MeOH was added sodium borohydride (13 mg, 0.34 mmol). The reaction was stirred overnight, quenched with NaOH (1N) and concentrated. The residue was purified by C-18 BIOTAGE® column chromatography to give Compound 14 (29 mg).

Example 4. Synthesis of Compound 39

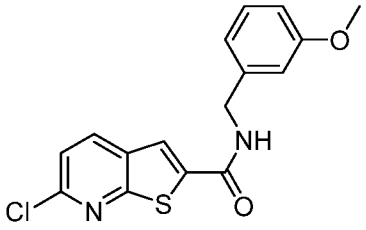
Step 1



6-chlorothieno[2,3-b]pyridine-2-carboxylic acid

To a suspension of 2-bromo-6-chlorothieno[2,3-b]pyridine (100 mg, 0.40 mmol) in ether was added n-butyllithium (0.29 mL, 2.5 M, 0.72 mmol) dropwise at -40 °C. The reaction was stirred for 0.5 h, quenched with excess dry ice and partitioned between water and ethyl acetate. The organic layer was dried, concentrated and purified by C-18 BIOTAGE® column chromatography to give 6-chlorothieno[2,3-b]pyridine-2-carboxylic acid (36 mg).

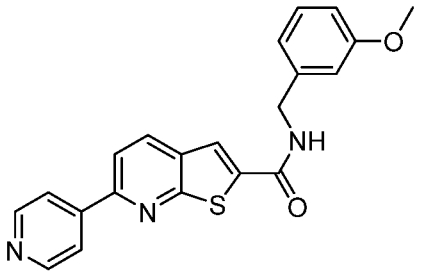
Step 2



6-chloro-N-(3-methoxybenzyl)thieno[2,3-b]pyridine-2-carboxamide

6-chloro-N-(3-methoxybenzyl)thieno[2,3-b]pyridine-2-carboxamide was prepared from 6-chlorothieno[2,3-b]pyridine-2-carboxylic acid by following the synthesis method of Step 2 in Example 3.

Step 3



Compound 39

A mixture of 6-chloro-N-(3-methoxybenzyl)thieno[2,3-b]pyridine-2-carboxamide (25 mg, 0.075 mmol), pyridine-4-boronic acid (30 mg, 0.22 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5 mg, 5%) and cesium carbonate (95 mg, 0.3 mmol) in 1,4-dioxane was heated to 100 °C and stirred under nitrogen atmosphere overnight. The mixture was filtered through a Celite pad. The filtrate was concentrated and purified by BIOTAGE® C-18 column chromatography to give Compound 39 (12 mg).

Example 5. ROCK1 and ROCK2 Kinase Inhibition Assays

The following assay protocol is for measuring the phosphorylation of a peptide substrate (FAM-KKLRRTLSVA-OH wherein FAM is carboxyfluorescein). The peptide is >98% purity by Capillary Electrophoresis. The peptide is phosphorylated by the protein kinase ROCK1 or

ROCK2. The ROCK1 or ROCK2 enzyme, substrate, and cofactors (ATP and Mg^{2+}) are combined in a well of a microtiter plate and incubated for 3 hours at 25°C. At the end of the incubation, the reaction is quenched by the addition of an EDTA-containing buffer. The substrate and product are separated and quantified electrophoretically using the microfluidic-based LABCHIP® 3000 Drug Discovery System from Caliper Life Sciences (Hopkinton, Massachusetts).

The components of the assay mixture are:

100 mM HEPES, pH 7.5
0.1% BSA
0.01% Triton X-100
1 mM DTT
10 mM $MgCl_2$
10 μM Sodium Orthovanadate
10 μM Beta-Glycerophosphate
5 μM ATP (for ROCK1) or 7 μM ATP (for ROCK2)
1% DMSO (from compound)
1.25 μM FAM-KKLRRTLSVA-OH
3 nM ROCK1 or 2.5 nM ROCK2 enzyme

Substrate and product peptides present in each sample are separated electrophoretically using the LABCHIP® 3000 capillary electrophoresis instrument. As substrate and product peptides are separated two peaks of fluorescence are observed. Change in the relative fluorescence intensity of the substrate and product peaks is the parameter measured reflecting enzyme activity. Capillary electrophoregramms (RDA acquisition files) are analyzed using HTS Well Analyzer software (Caliper Life Sciences, Hopkinton, Massachusetts). The kinase activity in each sample is determined as the product to sum ratio (PSR): P/(S+P), where P is the peak height of the product peptide and S is the peak height of the substrate peptide. For each compound, enzyme activity is measured at various concentrations (12 concentrations of compound spaced by 3X dilution intervals). Negative control samples (0%- inhibition in the absence of inhibitor) and positive control samples (100%-inhibition in the presence of 20 mM EDTA) are assembled in

replicates of four and are used to calculate %-inhibition values for each compound at each concentration. Percent inhibition (Pinh) is determined using the following equation:

$$Pinh = (PSR0\% - PSRinh)/(PSR0\% - PSR100\%)*100$$

where PSRinh is the product sum ratio in the presence of inhibitor, PSR0% is the average product sum ratio in the absence of inhibitor, and PSR100% is the average product sum ratio in 100%-inhibition control samples. The IC_{50} values of inhibitors are determined by fitting the inhibition curves (Pinh versus inhibitor concentration) by 4 parameter sigmoidal dose-response model using XLfit 4 software (IBDS).

This assay can be used to test the activity of each of the exemplary compounds identified in **Table 1**. It is expected that each of these compounds will demonstrate inhibition of the protein kinase ROCK1 and/or ROCK2.

Example 6. Cell Viability Assay

Cell viability in the presence of varying concentrations of the above listed compounds at different time points was used to assess cytotoxicity and the effect of the compounds on cell proliferation. IC_{50} (or percent activity) data for the compounds of the present invention in K562 or MV411 cell lines are summarized in **Table 2**.

Cell Viability Assay- Cell viability was measured by the CELLTITER-GlO® cell viability assay from Promega (Madison, WI). The CELLTITER-GlO® Luminescent Cell Viability Assay is a homogeneous method to determine the number of viable cells in culture based on quantitation of the ATP present, which signals the presence of metabolically active cells. Following treatment, CELLTITER-GlO® is added to treatment wells and incubated at 37° C. luminescence values were measured at using a Molecular Devices Spectramax microplate reader.

Experimental Design

Single Agent Studies- Cells were grown to 70% confluency, trypsinized, counted, and seeded in 96 well flat-bottom plates at a final concentration of $2.5x10^3$-$5x10^3$ cells/well (Day 0). Cells were allowed to incubate in growth media for 24 hours. Treatment with the test agents or standard agents began on Day 1 and continued for 72 hours. At the 72-hour time point, treatment

containing media was removed. Viable cell numbers were quantified by the CELLTITER-GLO® cell viability assay as described above. Results from these studies were used to calculate an IC_{50} value (concentration of drug that inhibits cell growth by 50 percent of control) for each compound.

Data Collection- For single agent and combination studies, data from each experiment was collected and expressed as % Cell Growth using the following calculation:

$$\% \text{ Cell Growth} = (f_{test}/f_{vehicle}) \times 100$$

Where f_{test} is the luminescence of the tested sample, and $f_{vehicle}$ is the luminescence of the vehicle in which the drug is dissolved. Dose response graphs and IC_{50} values were generated using Prism 6 software (GraphPad) using the following equation:

$$Y = \underline{(\text{Top-Bottom})}/(1+10^{((\log IC50-X)\text{-HillSlope})})$$

Where X is the logarithm of the concentration and Y is the response. Y starts at the Bottom and goes to the Top with a sigmoid shape.

Example 7. ROCK1 and ROCK2 Kinase Inhibition and Cell Viability Assay Results

The protocols outlined in Examples 5 and 6 were followed to test ROCK1 and ROCK2 kinase inhibition and cancer cell viability with compounds from **Table 1**. As shown in **Table 2**, the compounds demonstrated inhibition of the ROCK1 and ROCK2 kinases and growth of cancer cells.

The experiments also evaluated the selectivity of the compounds for inhibiting growth of cancer cells carrying a mutation in the *Flt3* gene. The MV411 cell line expresses the mutant allele of *Flt3* with internal tandem duplications (ITD) of the gene. *See* Quentmeier *et al.*, "FLT3 Mutations in Acute Myeloid Leukemia Cell Lines," Leukemia 17(1), 2003, 120-124. K562 is a chronic myeloid leukemia cell line that does not express FLT3 protein. *See* Grafone *et al.*, "Monitoring of FLT3 Phosphorylation Status and Its Response to Drugs By Flow Cytometry in

AML Blast Cells," Hematol Oncol. 26(3), 2008, 159-166. Patients with ITD-*FLT3*$^+$ acute myeloid leukemia (AML) experience an extremely poor prognosis. Surprisingly, many of the compounds demonstrated greater efficacy with the MV11 cells than with the K562 cells suggesting that these compounds could be used to effectively treat ITD-*FLT3*$^+$ AML.

5

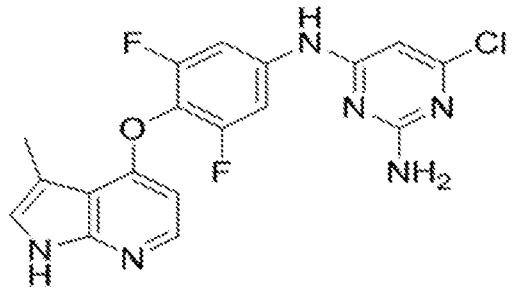
Table 2. ROCK1 and ROCK2 kinase inhibition and cell viability

Compound ID	**ROCK1 IC_{50} (nM)**	**ROCK2 IC_{50} (nM)**	**K562* (μM)**	**MV411* (μM)**	**FLT3-ITD$^+$ Selectivity (K562/MV411)**
1	207	98	>100	67.6	>1
3			>100	43.7	>2
5	73	16.1	43.6	10.2	4
7	102	22.9	89.1	7.6	12
9	237	39.1	97.2	39.8	2
11	63.6	22.1	>100	14.5	>7
25	130	28.7	85	34	3
40	65.1	17.4	>100	7.1	>14
47			17.8	7.8	2
48	6400	1870			
49			17.8	7.8	2
50	1010	239	>100	7.8	>13
51			>100	17.0	>6
52	34	8.7	>100	11.2	>9
53			64.6	93.3	1
54			>100	12.6	>8
Compound A**	3.3	2.8	0.8	0.7	1

* MV411 is ITD-*FLT3*$^+$, and K562 does not express ITD-*FLT3*. Rho-associated kinase may be manipulated for the treatment of ITD-*FLT3*$^+$ AML as reported in Onish *et al.*, "Internal Tandem Duplication Mutations in *FLT3* Gene Augment Chemotaxis to Cxcl12 Protein by Blocking the

Down-regulation of the Rho-associated Kinase via the Cxcl12/Cxcr4 Signaling Axis," J. Biol. Chem. 289 (45), 2014, 31053–31065.

** Compound A is shown below and is described by Schirok et al., "Design and Synthesis of Potent and Selective Azaindole-Based Rho Kinase (ROCK) Inhibitors," ChemMedChem 3, 2008, 1893 – 1904.



Compound A

Unless defined otherwise, all technical and scientific terms herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patents, and patent publications cited are incorporated by reference herein in their entirety for all purposes.

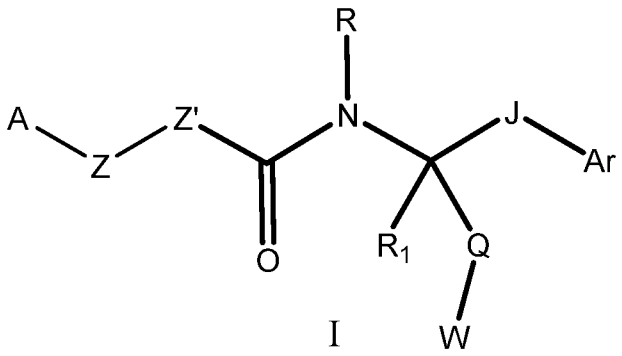
It is understood that the disclosed invention is not limited to the particular methodology, protocols and materials described as these can vary. It is also understood that the terminology used herein is for the purposes of describing particular embodiments only and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

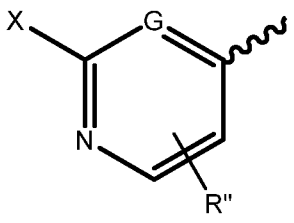
1. A compound of Formula (I):



I

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate or physiologically functional derivative thereof;

wherein:

A is indazol-3-yl, pyrazol-4-yl, 

,

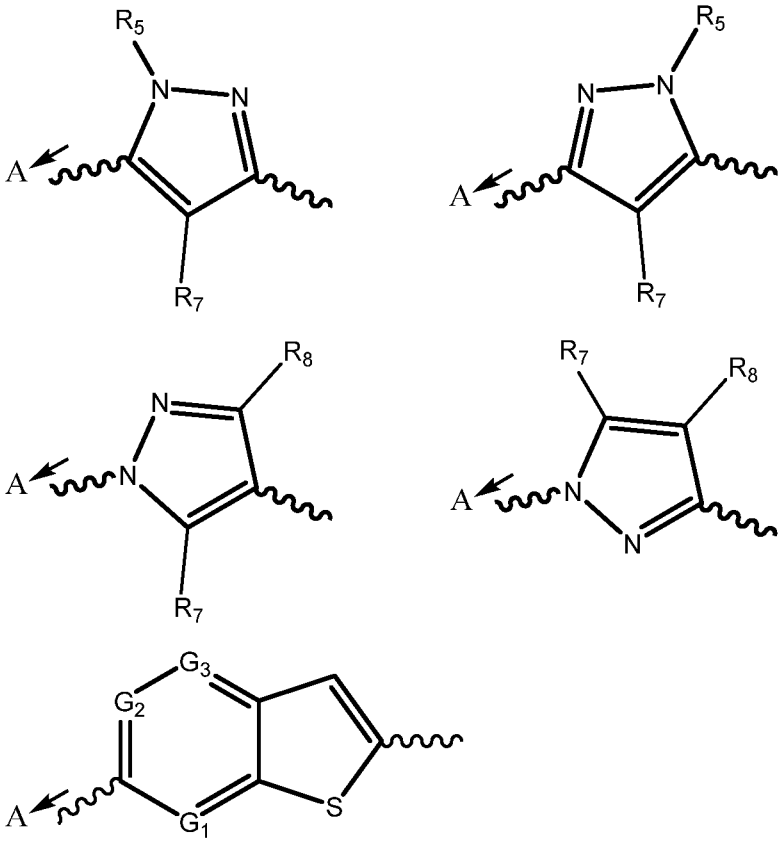
wherein

(i) G is CR' or N;

(ii) X is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $-OR_2$ or $-NR_3R_4$; and

(iii) R', R", R_2, R_3 and R_4 are independently –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

Z is selected from the group consisting of:



wherein

(i) R_5 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

(ii) R_7 and R_8 are independently –H, halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, -O-(C_{1-6} alkyl), -OH, -CN, -COOR', -OC(O)R', NHR', $N(R')_2$, -NHC(O)R', $-NHS(O)_2R'$, -C(O)NHR', or $–S(O)_2R'$ wherein R' is –H, C_{1-6} alkyl, or C_{3-7} cycloalkyl; and

(iii) G_1, G_2 and G_3 are independently CH or N;

Z' is a bond, O or NR_6, wherein R_6 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R_1 is –H or C_{1-6} alkyl;

Q is a bond or C_{1-6} alkyl;

J is a bond or C_{1-6} alkyl;

W is –H , $–OR_9$, $–NR_{10}R_{11}$, or $–S(O)_mR_{12}$,

wherein

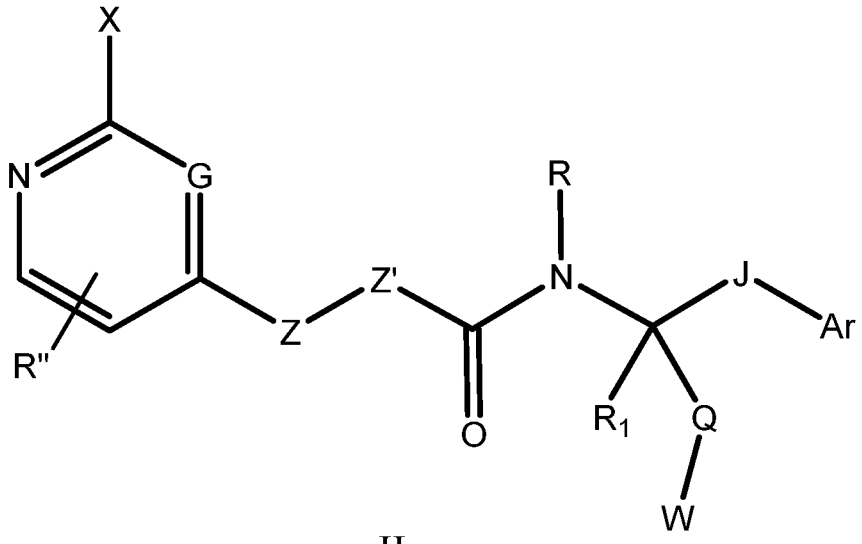
(i) R_9, R_{10} and R_{11} are independently –H, C_{1-6} alkyl, C_{3-7} cycloalkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, or C_{1-6} alkylsulfonyl;

(ii) m is an integer from 0 to 2; and

(iii) R_{12} is C_{1-6} alkyl or C_{3-7} cycloalkyl; and

Ar is a phenyl, naphthyl, or C_{5-10} heterocycle, each of which is optionally substituted with halo, –OH, –CN, –$COOR_a$, –OR_a, –SR_a, –$OC(O)R_a$, –NHR_a, –NR_aR_b, -$NHC(O)R_a$, -$NHC(O)NR_aR_b$, -$C(O)NR_aR_b$, -$NS(O)_2R_a$, -$S(O)_2NR_aR_b$, -$S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle, wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, –OH, –CN, –$COOR_a$, –OR_a, –SR_a, –$OC(O)R_a$, –NHR_a, –NR_aR_b, –$NHC(O)R_a$, –$NHC(O)NR_aR_b$, –$C(O)NR_aR_b$, –$NS(O)_2R_a$, –$S(O)_2NR_aR_b$, –$S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, or C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O form a 4- to 8-membered heterocycle.

2. A compound of Formula II:



II

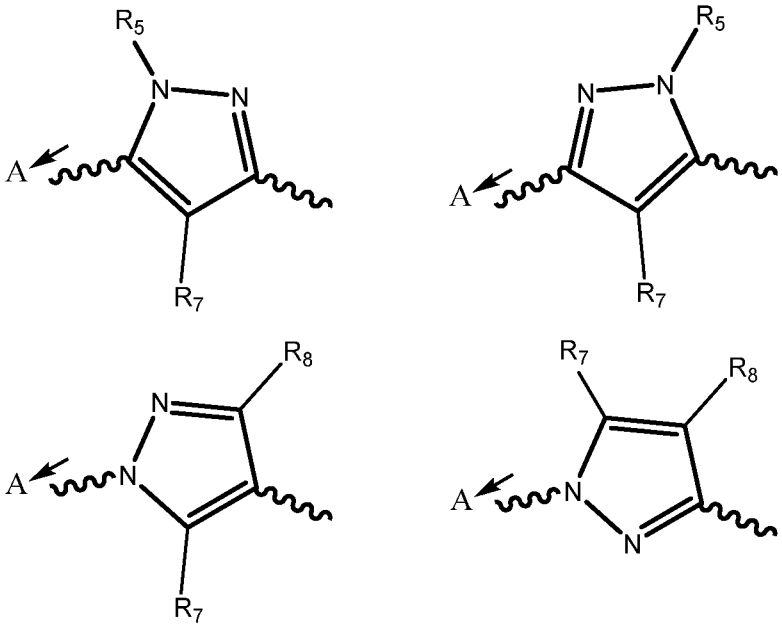
wherein

(i) G is CR' or N;

(ii) X is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, –OR_2 or –NR_3R_4; and

(iii) R', R", R_2, R_3 and R_4 are independently –H or C_{1-6} alkyl or , C_{3-7} cycloalkyl; and

Z is selected from the group consisting of:



wherein

(i) R_5 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

(ii) R_7 and R_8 are independently –H, halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, -O-(C_{1-6} alkyl), -OH, -CN, -COOR', -OC(O)R', NHR', N(R')$_2$, -NHC(O)R', -NHS(O)$_2$R', -C(O)NHR', or –S(O)$_2$R' wherein R' is –H, C_{1-6} alkyl, or C_{3-7} cycloalkyl;

(iii) G_2, G_3 and G_4 are independently CH or N; and

Z' is a bond, O or NR_6, wherein R_6 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R_1 is –H or C_{1-6} alkyl;

Q is a bond or C_{1-6} alkyl;

J is a bond or C_{1-6} alkyl;

W is –H , $–OR_9$, $–NR_{10}R_{11}$, or $–S(O)_mR_{12}$,

wherein

(i) R_9, R_{10} and R_{11} are independently –H, C_{1-6} alkyl, C_{3-7} cycloalkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, or C_{1-6} alkylsulfonyl;

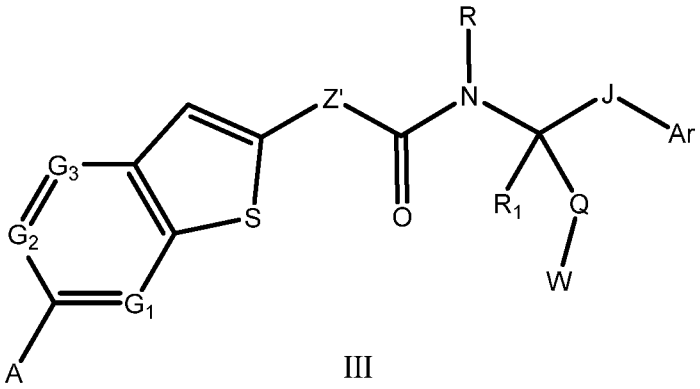
(ii) m is an integer from 0 to 2; and

(iii) R_{12} is C_{1-6} alkyl or C_{3-7} cycloalkyl; and

Ar is a phenyl, naphthyl, or C_{5-10} heterocycle, each of which is optionally substituted with

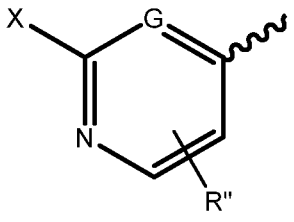
halo, –OH, –CN, –$COOR_a$, –OR_a, –SR_a, –$OC(O)R_a$, –NHR_a, –NR_aR_b, -$NHC(O)R_a$, -$NHC(O)NR_aR_b$, -$C(O)NR_aR_b$, -$NS(O)_2R_a$, -$S(O)_2NR_aR_b$, -$S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle, wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, –OH, –CN, –$COOR_a$, –OR_a, –SR_a, –$OC(O)R_a$, –NHR_a, –NR_aR_b, –$NHC(O)R_a$, –$NHC(O)NR_aR_b$, –$C(O)NR_aR_b$, –$NS(O)_2R_a$, –$S(O)_2NR_aR_b$, –$S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, or C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O form a 4- to 8-membered heterocycle.

3. A compound of Formula III:



III

wherein



A is indazol-3-yl, pyrazol-4-yl, ,

wherein

(i) G is CR' or N;

(ii) X is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $–OR_2$ or $–NR_3R_4$; and

(iii) R', R", R_2, R_3 and R_4 are independently –H or C_{1-6} alkyl or , C_{3-7} cycloalkyl; and

G_1, G_2 and G_3 are independently CH or N.

Z' is a bond, O or NR_6, wherein R_6 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl;

R_1 is –H or C_{1-6} alkyl;

Q is a bond or C_{1-6} alkyl;

J is a bond or C_{1-6} alkyl;

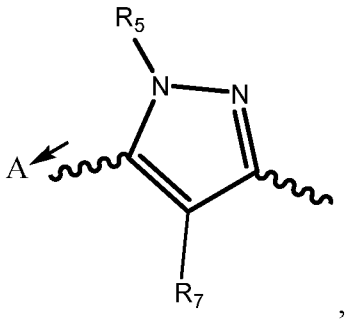
W is –H , $–OR_9$, $–NR_{10}R_{11}$, or $–S(O)_mR_{12}$, wherein (i) R_9, R_{10} and R_{11} are independently –H, C_{1-6} alkyl, C_{3-7} cycloalkyl, formyl, C_{1-6} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, or C_{1-6} alkylsulfonyl; (ii) m is an integer from 0 to 2; and (iii) R_{12} is C_{1-6} alkyl or C_{3-7} cycloalkyl; and

Ar is a phenyl, naphthyl, or C_{5-10} heterocycle, each of which is optionally substituted with halo, –OH, –CN, $–COOR_a$, $–OR_a$, $–SR_a$, $–OC(O)R_a$, $–NHR_a$, $–NR_aR_b$, $-NHC(O)R_a$, $-NHC(O)NR_aR_b$, $-C(O)NR_aR_b$, $-NS(O)_2R_a$, $-S(O)_2NR_aR_b$, $-S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle, wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, –OH, –CN, $–COOR_a$, $–OR_a$, $–SR_a$, $–OC(O)R_a$, $–NHR_a$, $–NR_aR_b$, $–NHC(O)R_a$, $–NHC(O)NR_aR_b$, $–C(O)NR_aR_b$, $–NS(O)_2R_a$, $–S(O)_2NR_aR_b$, $–S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, or C_{3-7} cycloalkyl; wherein each of R_a and R_b is independently H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O form a 4- to 8-membered heterocycle.

4. The compound of any one of Claims 1 to 3, wherein Z' is a bond.

5. The compound of claim 4, wherein Ar is an optionally substituted phenyl.

6. The compound of Claim 1 or 2 wherein Z is



,

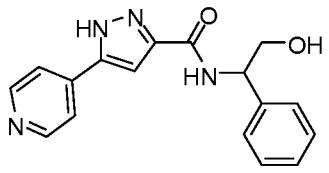
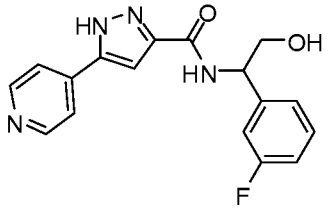
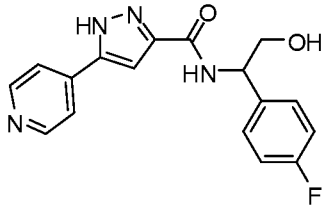
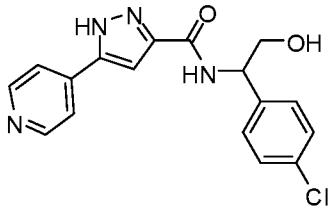
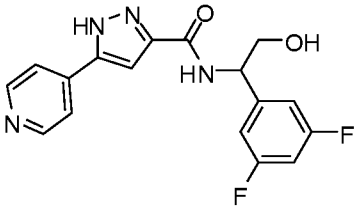
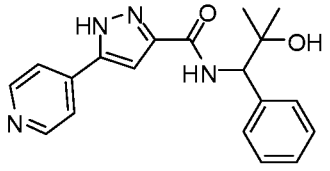
wherein

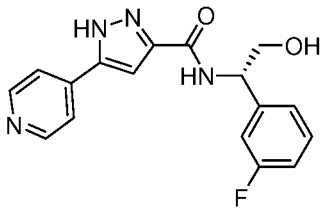
R_5 is –H, C_{1-6} alkyl or C_{3-7} cycloalkyl; and

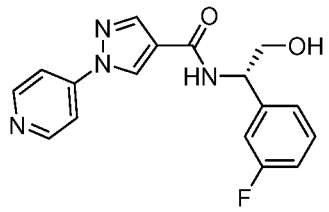
R_7 is –H, halo, C_{1-6} alkyl, C_{3-7} cycloalkyl, -O-(C_{1-6} alkyl), -OH, -CN, -COOR', -OC(O)R', NHR', $N(R')_2$, -NHC(O)R', $-NHS(O)_2R'$, -C(O)NHR', or $–S(O)_2R'$ wherein R' is –H, C_{1-6} alkyl, or C_{3-7} cycloalkyl;

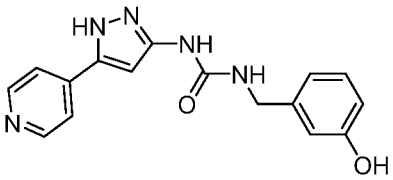
8. The compound according to any one of the preceding claims wherein W is –OH, $-NH_2$, $-NHCH_3$, or $–N(CH_3)_2$.

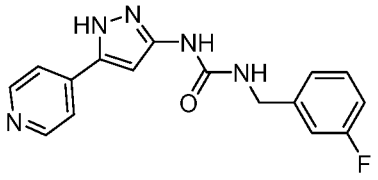
9. The compound of claim 1, wherein the compound is selected from the group consisting of:

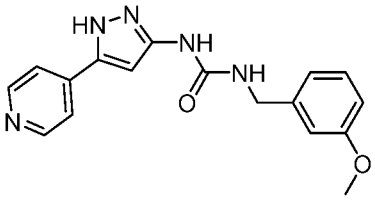







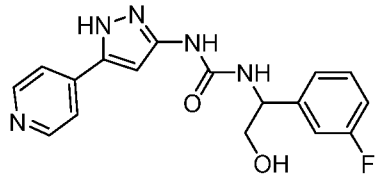


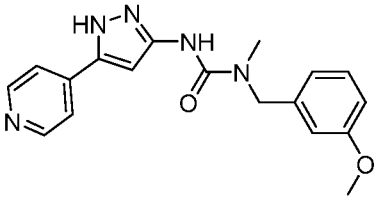


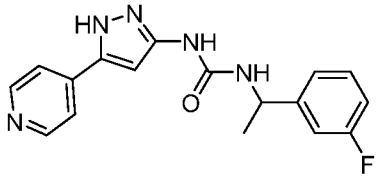


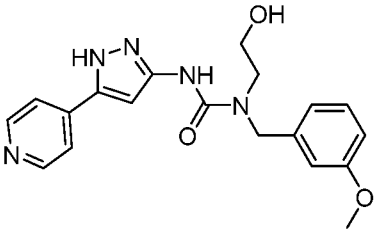


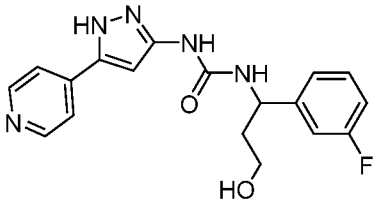


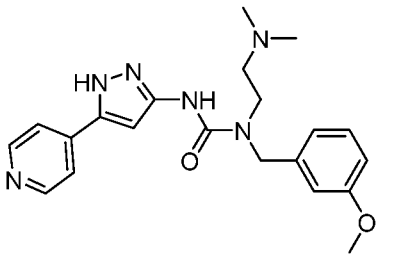


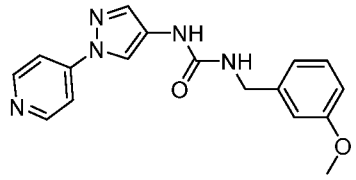


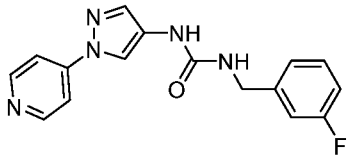


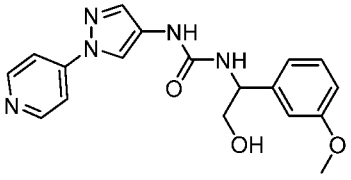


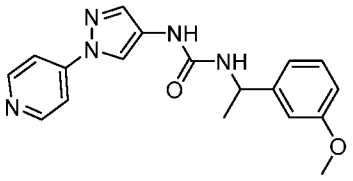


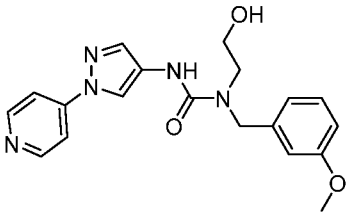


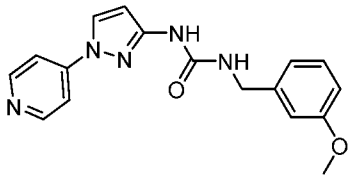


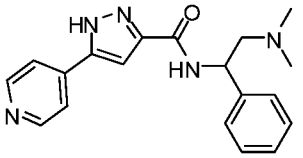


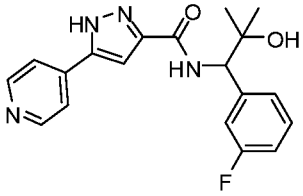


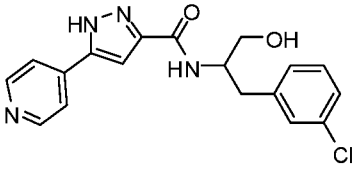


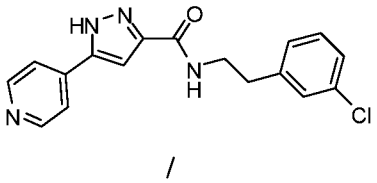


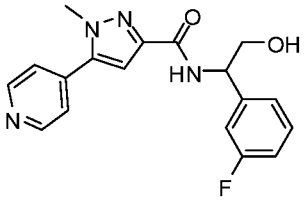


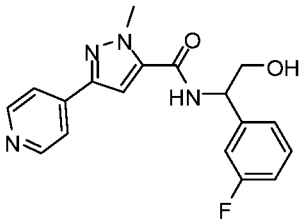


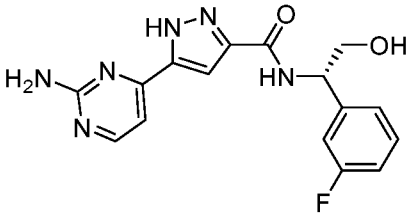


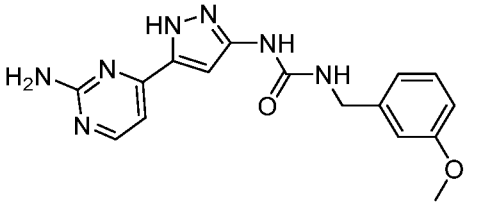


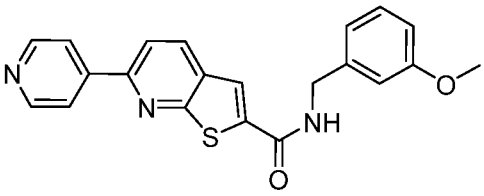


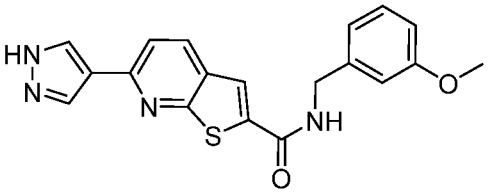


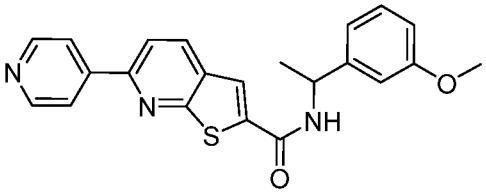


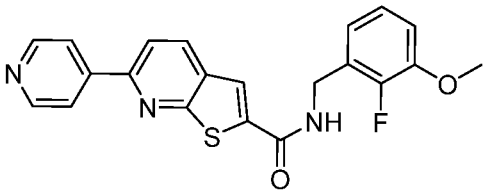


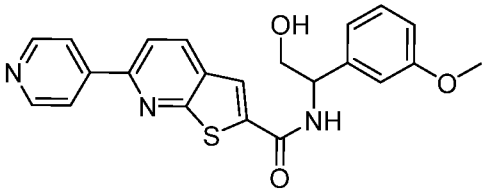


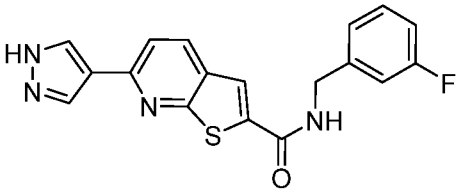


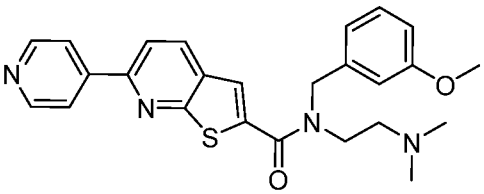


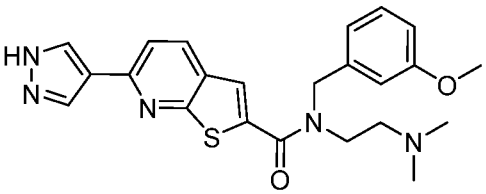


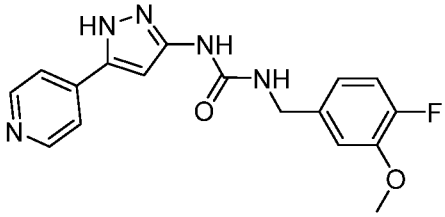


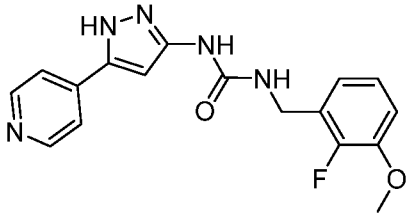


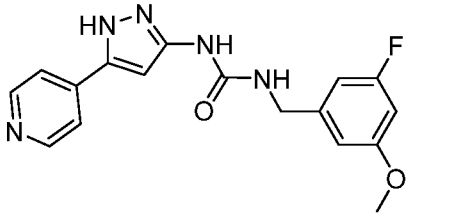


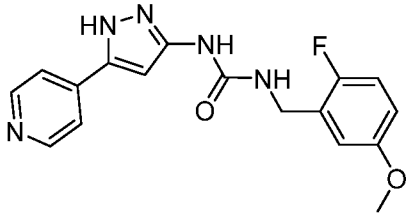


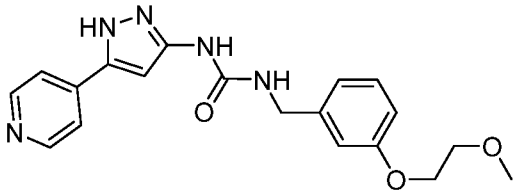


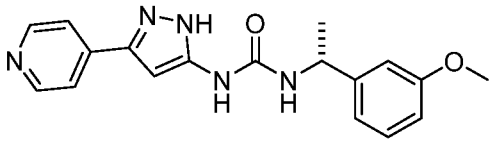


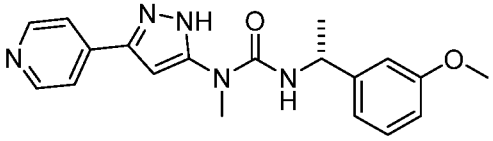


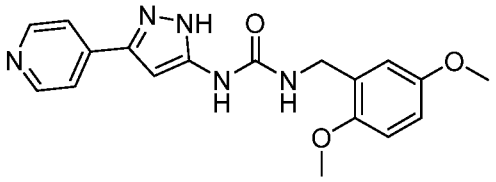


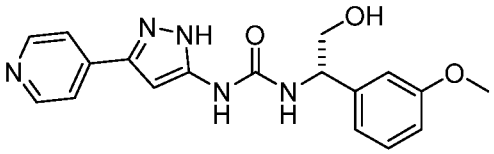


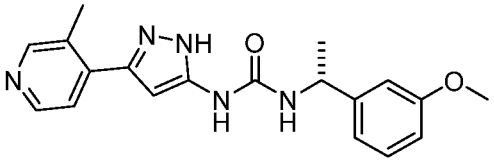


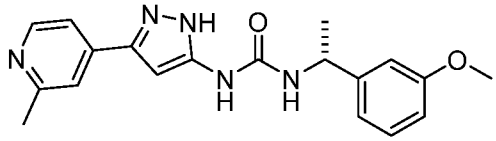






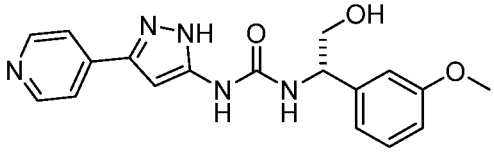




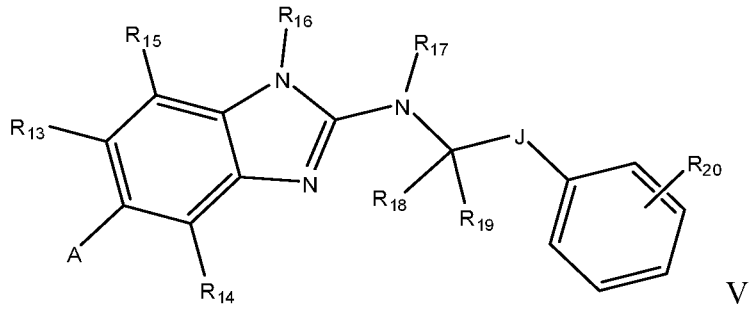


.

10. The compound of claim 1, wherein the compound is

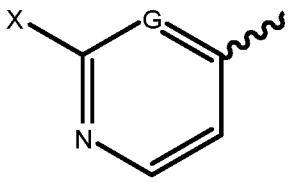


11. A compound of Formula V:



V

wherein:

A is indazol-3-yl, pyrazol-4-yl or 

,

wherein

(i) G is CH or N; and

(ii) X is hydrogen, $-OR_2$ or $-NR_3R_4$, wherein each of R_2, R_3 and R4 is independently –H or C_{1-6} alkyl;

each of R_{13} and R_{14} is independently –H, halo, C_{1-6} alkyl, or C_{3-7} cycloalkyl;

each of R_{15} and R_{20} is independently–H, halo, -OH, -CN, -COOR', -OR', -SR', -OC(O)R', -NHR', -NR'R", -NHC(O)R', -NHC(O)NR'R", -C(O)NR'R", $-NS(O)_2R'$, $-S(O)_2NR'R"$, $-S(O)_2R'$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, and 3- to 10-membered heterocycle, wherein each of the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle independently is unsubstituted or substituted with one or more of halo, -OH, -CN, -COOR', -OR', -SR', -OC(O)R', -NHR', -NR'R", -NHC(O)R', -NHC(O)NR'R", -C(O)NR'R", $-NS(O)_2R'$, $-S(O)_2NR'R"$, $-S(O)_2R'$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl; wherein each of R' and R" is independently -H or C_{1-6} alkyl; and optionally R' and R" together attaching to N or O form a 4- to 8-membered heterocycle;

each of R_{16}, R_{17}, R_{18} and R_{19} is independently –H, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3 to 10-membered heterocycle; wherein the C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl, or 3- to 10-membered heterocycle is unsubstituted or substituted with one or more of halo, -OH, -CN, $-COOR_a$, $-OR_a$, $-SR_a$, $-OC(O)R_a$, $-NHR_a$, $-NR_aR_b$, $-NHC(O)R_a$, $-NHC(O)NR_aR_b$, $-C(O)NR_aR_b$, $-NS(O)_2R_a$, $-S(O)_2NR_aR_b$, $-S(O)_2R_a$, guanidino, nitro, nitroso, C_{1-6} alkyl, aryl, C_{3-7} cycloalkyl; wherein each

of R_a and R_b is independently -H or C_{1-6} alkyl; and optionally R_a and R_b together attaching to N or O forms a 4- to 8-membered heterocycle; and

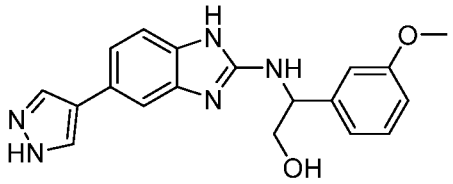
J is a bond or C_{1-6} alkyl.

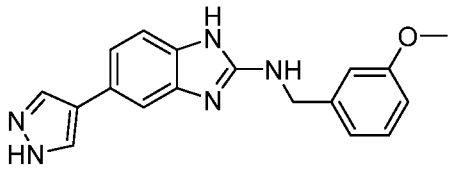
12. The compound of Claim 11, wherein A pyrazol-4-yl.

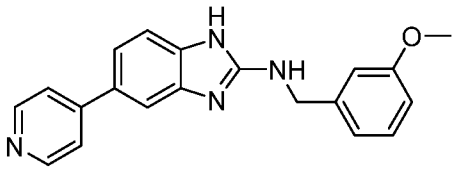
13. The compound of Claim 11, wherein A is pyridine-4-yl.

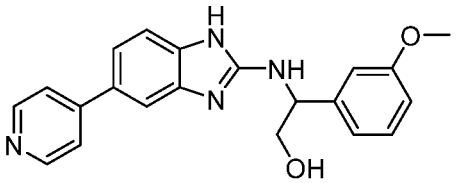
14. The compound of any one of Claims 11 to 13, wherein both R_{13} and R_{14} are methyl.

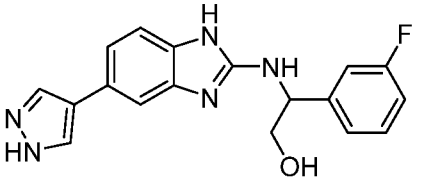
15. The compound of claim 11, wherein the compound is selected from the group consisting of:











15. A compound according to any one of claims 1 to 14 for use in treating a disease related to upregulation of Rho kinase- signaling pathways.

16. A method of treating an autoimmune disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

17. The method of claim 16, wherein the autoimmune disorder is rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus (SLE), psoriasis, Crohn's disease, atopic dermatitis, eczema, or graft-versus-host disease (GVHD).

18. A method of treating a cardiovascular disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

19. The method of claim 18, wherein the cardiovascular disorder is hypertension, atherosclerosis, restenosis, cardiac hypertrophy, ocular hypertension, cerebral ischemia, cerebral vasospasm, or erectile dysfunction.

20. A method of treating inflammation in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

21. The method of claim 20, wherein the inflammation is asthma, cardiovascular inflammation, renal inflammation or arteriosclerosis.

22. A method of treating a central nervous system disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

23. The method of claim 22, wherein the central nervous system disorder is neuronal degeneration or spinal cord injury.

24. The method of claim 22, wherein the central nervous system disorder is Huntington's disease, Parkinson's Disease, Alzheimer's, Amyotrophic lateral sclerosis (ALS), or multiple sclerosis.

25. A method of treating an arterial thrombotic disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

26. The method of claim 25, wherein the arterial thrombotic disorder is platelet aggregation, or leukocyte aggregation

27. A method of treating a fibrotic disorder in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

28. The method of claim 27, wherein the fibrotic disorder is liver fibrosis, lung fibrosis, or kidney fibrosis.

29. A method of treating glaucoma or regulating intraocular pressure in a subject comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

30. The method of claim 29, wherein the glaucoma is primary open-angle glaucoma, acute angle-closure glaucoma, pigmentary glaucoma, congenital glaucoma, normal tension glaucoma, or secondary glaucoma.

31. A method of treating a neoplastic disease in a subject comprising: administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

32. The method of claim 31, wherein the neoplastic disorder is a lymphoma, carcinoma, leukemia, sarcoma, or blastoma.

33. The method of claim 32, wherein the neoplastic disorder is acute myeloid leukemia (AML).

34. The method of claim 33, wherein the AML is ITD-*FLT3*$^{+}$ AML.

35. The method of claim 31, wherein the neoplastic disorder is squamous cell cancer, small- cell king cancer, pituitary cancer, esophageal cancer, astrocytoma, soft tissue sarcoma, non- small cell lung cancer, adenocarcinoma of the king, squamous carcinoma of the king, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, liver cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, brain cancer, endometrial cancer, testis cancer, cholangiocarcinoma, gallbladder carcinoma, gastric cancer, melanoma, or head and neck cancer.

36. A method of treating metabolic syndrome, insulin resistance, hyperinsulinemia, type 2 diabetes, or glucose intolerance in a subject comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

37. A method of treating osteoporosis or promoting bone formation in a subject comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14.

38. A method of treating an ocular disorder having an angiogenic component comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 14 and an angiogenesis inhibitor.

39. The method of claim 38, wherein the ocular disorder is age related macular degeneration (AMD), choroidal neovascularization (CNV), diabetic macular edema (DME), iris neovascularization, uveitis, neo vascular glaucoma, or retinitis of prematurity (ROP).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/33111

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40 (2016.01)
CPC - C07D 405/12; C07D 405/14; C07D 405/04
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)
IPC(8) - A01N 43/40 (2016.01)
CPC - C07D 405/12; C07D 405/14; C07D 405/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/320; 514/321

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Pathase, Google Patent, Google Web
Search terms used - rock inhibitor RhoA indazole td2 pyridine indazol-3-yl pyrazol-4-yl heterocyclic compounds thieno[2,3-b]pyridine
Pubchem substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- A	Pubchem-'042' Date Created: 20 March 2015 (20.03.2015) Date Accessed: 12 July 2016 (12.07.2016); pg. 3, compound	1-2, (4-5)/(1-2), 6, 9 ---------- 10
X	US 2013/0129677 A1 (Dai et al.) 23 May 2013 (23.05.2013); table 6	3, (4-5)/3
X	US 2011/0052562 A1 (Feng et al.) 03 March 2011 (03.03.2011); para [0483], [0529]	11-14, 15a
A	WO 2007/026920 A2 (ASTELLAS PHARMA, INC.) 08 March 2007 (08.03.2007); pg. 115, Table 1: example 4	10
A	Pubchem-'397' Date Created: 25 October 2006 (25.10.2006) Date Accessed: 12 July 2016 (12.07.2016); pg. 3, compound	10
A	WO 2009/126635 A1 (ABBOTT LABORATORIES) 15 October 2009 (15.10.2009); entire document	1-6, 9, 11-14,15a

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

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

Date of the actual completion of the international search	Date of mailing of the international search report
12 July 2016 (12.07.2016)	26 AUG 2016

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/33111

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.: 8, 15b, 16-39
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.

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 107835637 A
(43)申请公布日 2018.03.23

(21)申请号 201680041168.4

(22)申请日 2016.05.18

(30)优先权数据
62/163,369 2015.05.18 US
62/203,070 2015.08.10 US

(85)PCT国际申请进入国家阶段日
2018.01.12

(86)PCT国际申请的申请数据
PCT/US2016/033111 2016.05.18

(87)PCT国际申请的公布数据
WO2016/187324 EN 2016.11.24

(71)申请人 转化药物开发有限责任公司
地址 美国亚利桑那州

(72)发明人 T·王 S·盖特利

(74)专利代理机构 北京戈程知识产权代理有限公司 11314
代理人 程伟 刘彬娜

(51)Int.Cl.
A01N 43/40(2006.01)

权利要求书12页 说明书34页

(54)发明名称

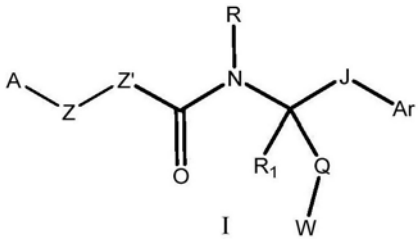
作为激酶抑制剂的杂环化合物

(57)摘要

本发明涉及某些酰胺和杂环化合物。本发明还涉及这些化合物用于治疗多种疾病的用途，所述疾病包括自身免疫性疾病、心血管疾病、炎症、中枢神经系统疾病、动脉血栓性疾病、纤维化疾病、青光眼和肿瘤性疾病。

CN 107835637 A

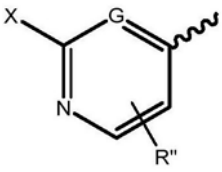
1.一种式(I)的化合物：



I

或其对映异构体、对映异构体的混合物、或两种或多种非对映异构体的混合物；或其药学上可接受的盐、溶剂化物、水合物或生理学功能衍生物；

其中：

A为吲唑-3-基、吡唑-4-基、  ，

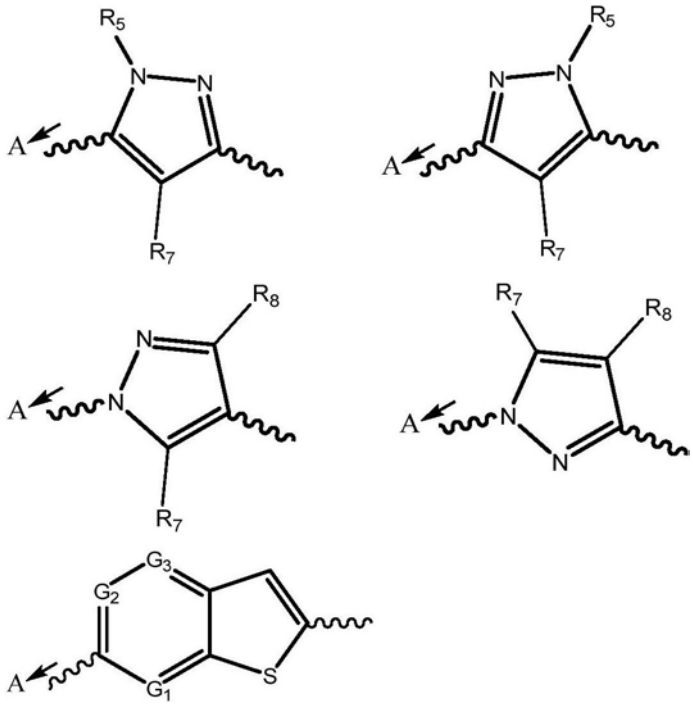
其中

(i)G为CR’或N；

(ii)X为氢、C_{1-6}烷基、C_{3-7}环烷基、-OR_2或-NR_3R_4；和

(iii)R’、R”、R_2、R_3和R_4独立地为-H、C_{1-6}烷基或C_{3-7}环烷基；

Z选自：



其中

(i)R_5为-H、C_{1-6}烷基或C_{3-7}环烷基；

(ii)R_7和R_8独立地为-H、卤素、C_{1-6}烷基、C_{3-7}环烷基、-O-(C_{1-6}烷基)、-OH、-CN、-COOR’、-OC(O)R’、NHR’、N(R’)$_2$、-NHC(O)R’、-NHS(O)$_2$R’、-C(O)NHR’、或-S(O)$_2$R’，其中R’为-H、C_{1-6}烷基或C_{3-7}环烷基；和

(iii)G_1、G_2和G_3独立地为CH或N；

Z'为键、O或NR_6，其中R_6为-H、C_{1-6}烷基或C_{3-7}环烷基；

R为-H、C_{1-6}烷基或C_{3-7}环烷基；

R_1为-H或C_{1-6}烷基；

Q为键或C_{1-6}烷基；

J为键或C_{1-6}烷基；

W为-H、$-OR_9$、$-NR_{10}R_{11}$、或$-S(O)_mR_{12}$，

其中

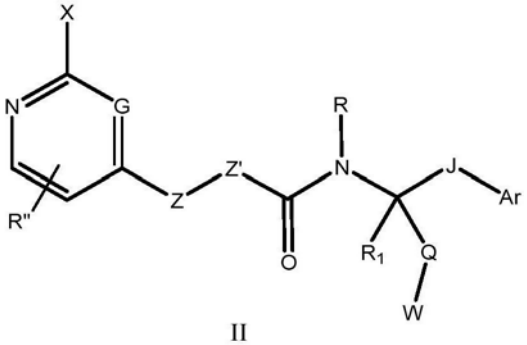
(i)R_9、R_{10}和R_{11}独立地为-H、C_{1-6}烷基、C_{3-7}环烷基、甲酰基、C_{1-6}烷基羰基、C_{3-7}环烷基羰基、或C_{1-6}烷基磺酰基；

(ii)m为0至2的整数；和

(iii)R_{12}为C_{1-6}烷基或C_{3-7}环烷基；和

Ar为苯基、萘基、或C_{5-10}杂环，其每个任选地被卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环取代，其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环为未取代的，或者被一个或多个卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、或C_{3-7}环烷基取代；其中R_a和R_b各自独立地为H或C_{1-6}烷基；和任选地R_a和R_b一起连接至N或O形成4至8元杂环。

2.一种式II的化合物：



II

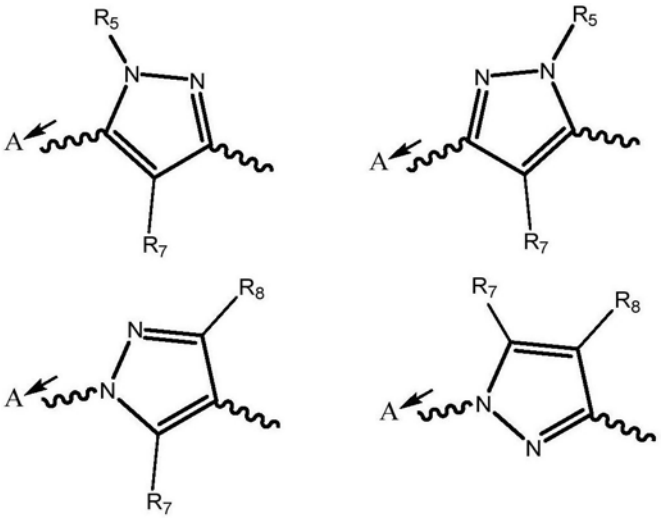
其中

(i)G为CR'或N；

(ii)X为氢、C_{1-6}烷基、C_{3-7}环烷基、$-OR_2$或$-NR_3R_4$；和

(iii)R'、R"、R_2、R_3和R_4独立地为-H或C_{1-6}烷基或C_{3-7}环烷基；和

Z选自：



其中

(i)R_5为-H、C_{1-6}烷基或C_{3-7}环烷基;

(ii)R_7和R_8独立地为-H、卤素、C_{1-6}烷基、C_{3-7}环烷基、-O-(C_{1-6}烷基)、-OH、-CN、-COOR'、-OC(O)R'、NHR'、N(R')$_2$、-NHC(O)R'、-NHS(O)$_2$R'、-C(O)NHR'、或-S(O)$_2$R',其中R'为-H、C_{1-6}烷基或C_{3-7}环烷基;

(iii)G_2、G_3和G_4独立地为CH或N;和

Z'为键、O或NR_6,其中R_6为-H、C_{1-6}烷基或C_{3-7}环烷基;

R为-H、C_{1-6}烷基或C_{3-7}环烷基;

R_1为-H或C_{1-6}烷基;

Q为键或C_{1-6}烷基;

J为键或C_{1-6}烷基;

W为-H、$-OR_9$、$-NR_{10}R_{11}$或$-S(O)_mR_{12}$,

其中

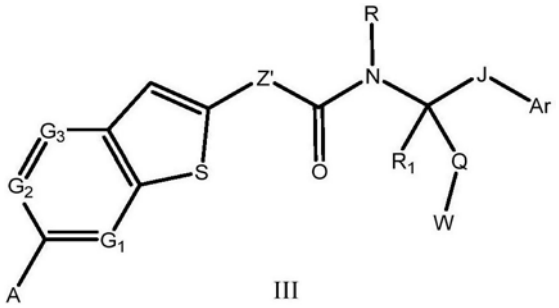
(i)R_9、R_{10}和R_{11}独立地为-H、C_{1-6}烷基、C_{3-7}环烷基、甲酰基、C_{1-6}烷基羰基、C_{3-7}环烷基羰基或C_{1-6}烷基磺酰基;

(ii)m为0至2的整数;和

(iii)R_{12}为C_{1-6}烷基或C_{3-7}环烷基;和

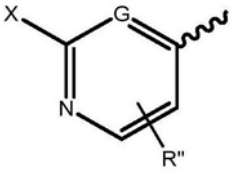
Ar为苯基、萘基、或C_{5-10}杂环,其每个任选地被卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环取代,其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环为未取代的,或者被一个或多个卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基或C_{3-7}环烷基取代;其中R_a和R_b各自独立地为H或C_{1-6}烷基;和任选地R_a和R_b一起连接至N或O形成4至8元杂环。

3.一种式III的化合物:



III

其中

A为吲唑-3-基、吡唑-4-基、 

，

其中

(i)G为CR'或N；

(ii)X为氢、C_{1-6}烷基、C_{3-7}环烷基、$-OR_2$或$-NR_3R_4$；和

(iii)R'、R"、R_2、R_3和R_4独立地为-H或C_{1-6}烷基或C_{3-7}环烷基；和

G_1、G_2和G_3独立地为CH或N；

Z'为键、O或NR_6，其中R_6为-H、C_{1-6}烷基或C_{3-7}环烷基；

R为-H、C_{1-6}烷基或C_{3-7}环烷基；

R_1为-H或C_{1-6}烷基；

Q为键或C_{1-6}烷基；

J为键或C_{1-6}烷基；

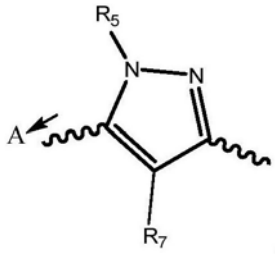
W为-H、$-OR_9$、$-NR_{10}R_{11}$或$-S(O)_mR_{12}$，其中(i)R_9、R_{10}和R_{11}独立地为-H、C_{1-6}烷基、C_{3-7}环烷基、甲酰基、C_{1-6}烷基羰基、C_{3-7}环烷基羰基或C_{1-6}烷基磺酰基；(ii)m为0至2的整数；和(iii)R_{12}为C_{1-6}烷基或C_{3-7}环烷基；和

Ar为苯基、萘基或C_{5-10}杂环，其每个任选地被卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环取代，其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环为未取代的，或者被一个或多个卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、或C_{3-7}环烷基取代；其中R_a和R_b各自独立地为H或C_{1-6}烷基；和任选地R_a和R_b一起连接至N或O形成4至8元杂环。

4.根据权利要求1至3中任一项所述的化合物，其中Z'为键。

5.根据权利要求4所述的化合物，其中Ar为任选被取代的苯基。

6.根据权利要求1或2所述的化合物，其中Z为



，

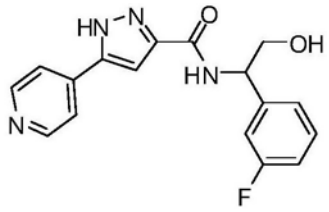
其中

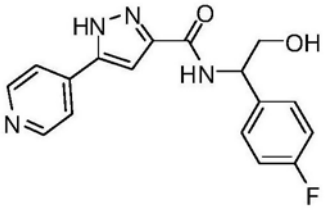
R_5为-H、C_{1-6}烷基或C_{3-7}环烷基；和

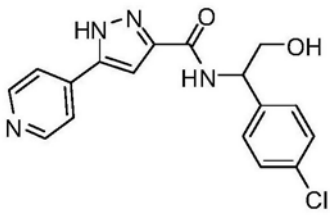
R_7为-H、卤素、C_{1-6}烷基、C_{3-7}环烷基、-O-(C_{1-6}烷基)、-OH、-CN、-COOR'、-OC(O)R'、NHR'、N(R')$_2$、-NHC(O)R'、-NHS(O)$_2$R'、-C(O)NHR'、或-S(O)$_2$R'，其中R'为-H、C_{1-6}烷基或C_{3-7}环烷基。

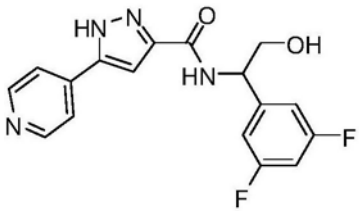
8.根据前述权利要求中任一项所述的化合物，其中W为-OH、-NH_2、-$NHCH_3$或-N(CH_3)$_2$。

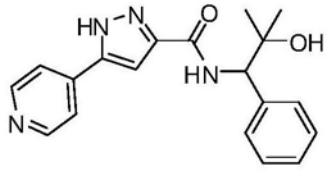
9.根据权利要求1所述的化合物，其中所述化合物选自：

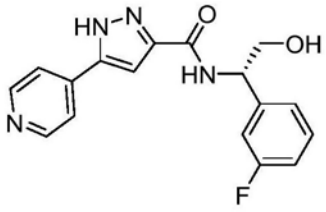


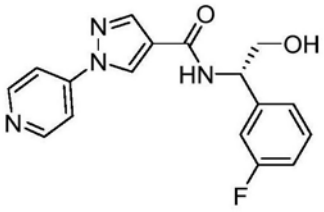


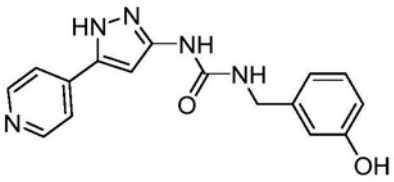


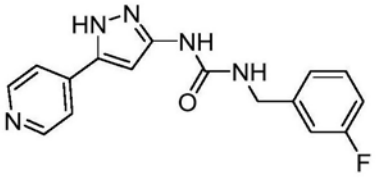


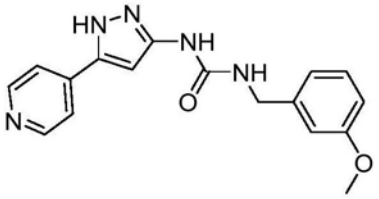


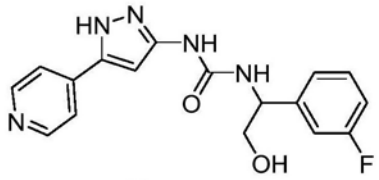


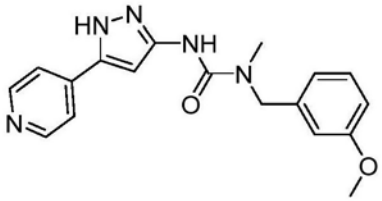


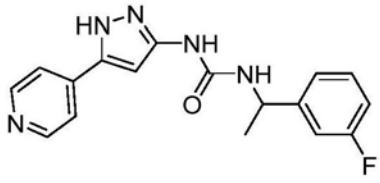


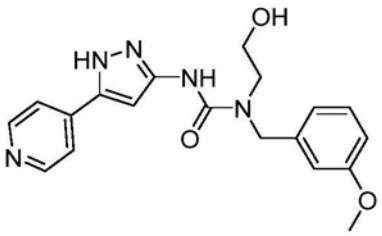


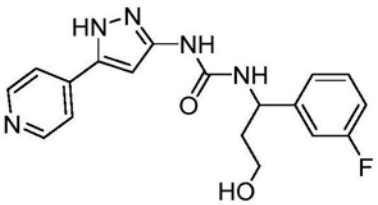


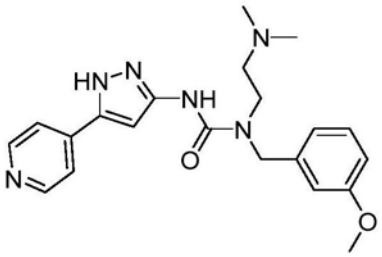


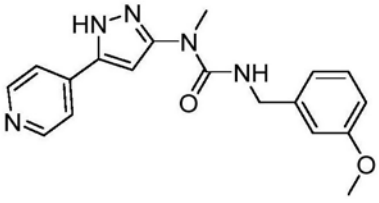


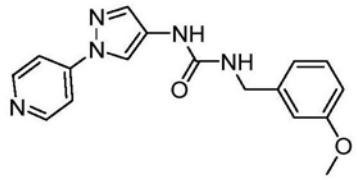


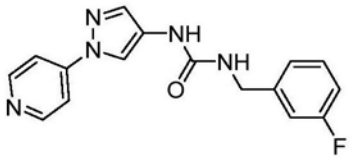


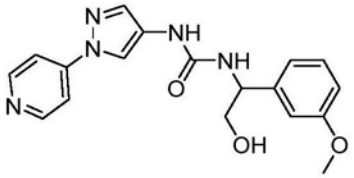


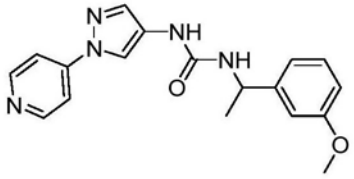


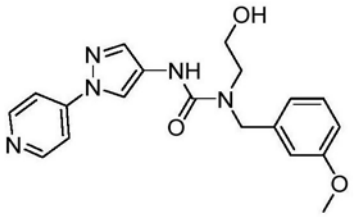


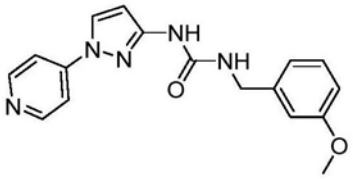


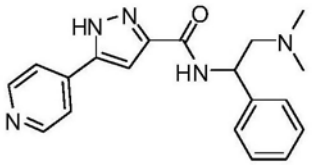


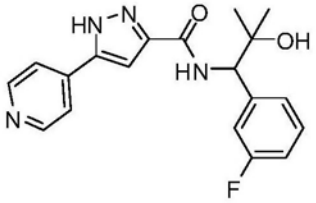


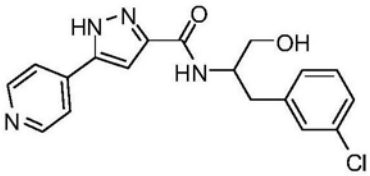


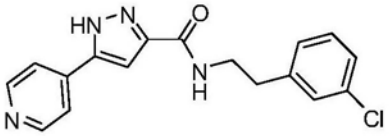


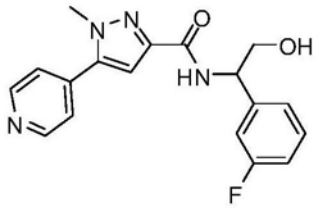


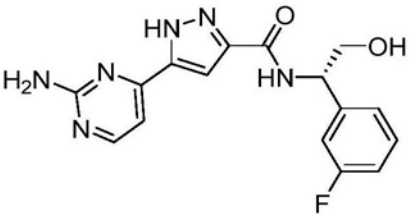


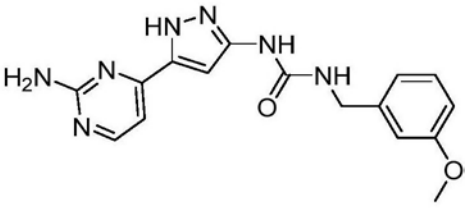


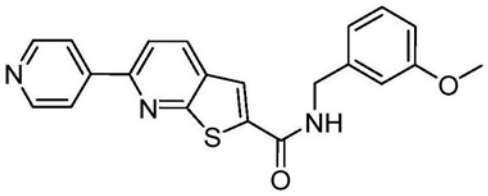


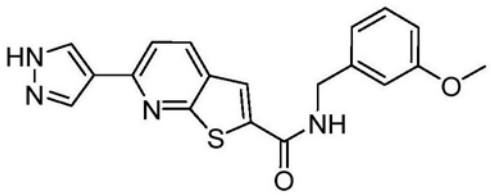


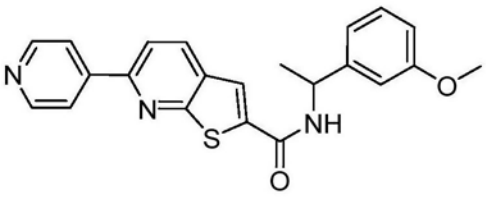


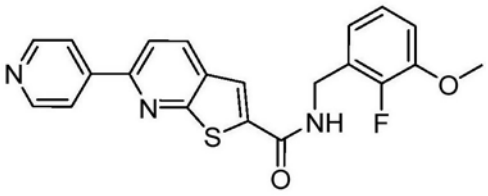


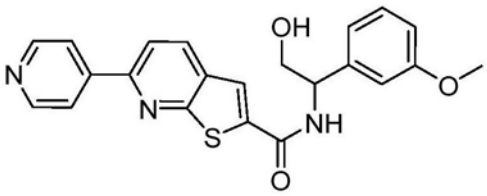


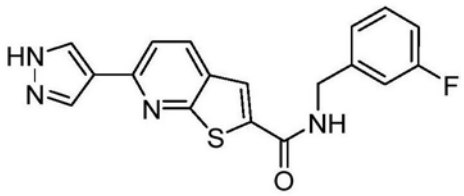


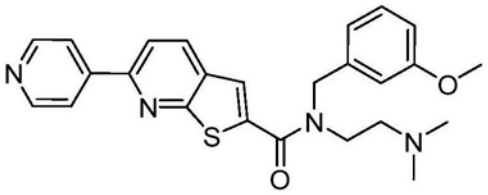


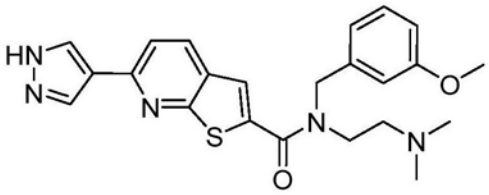


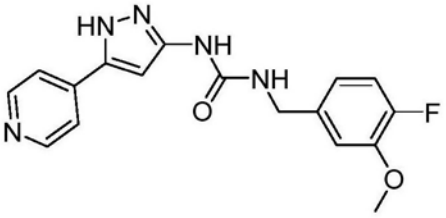


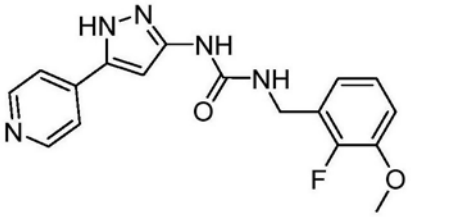


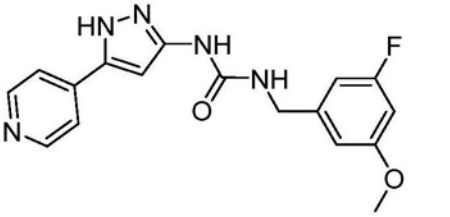


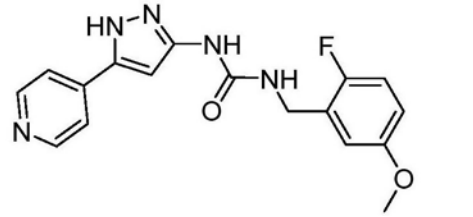


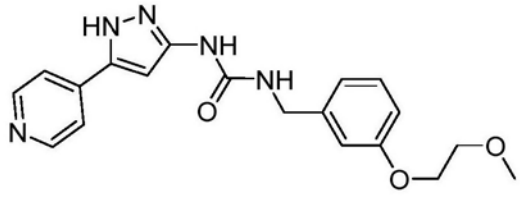


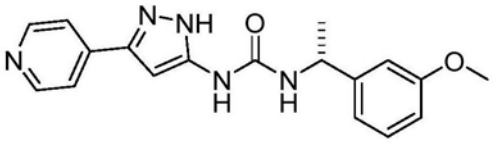


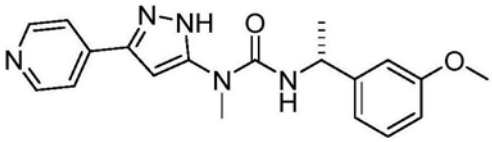


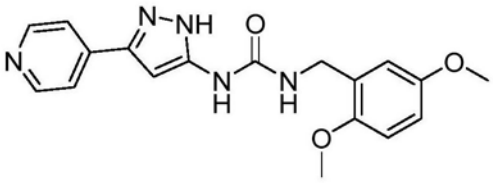


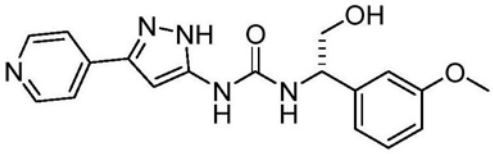


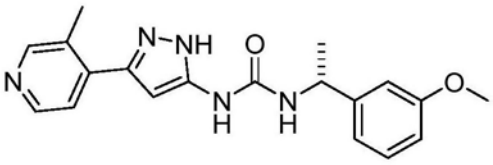


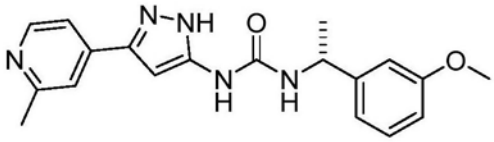






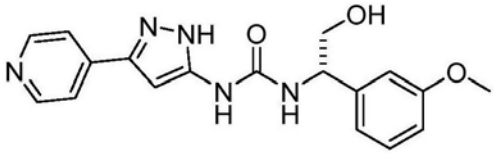






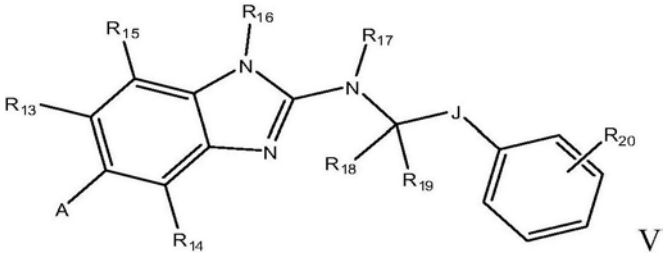
。

10.根据权利要求1所述的化合物,其中所述化合物为



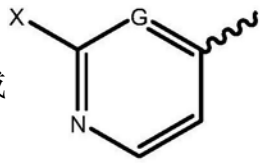
。

11.一种式V的化合物:



V

其中:

A为吲唑-3-基、吡唑-4-基或  ,

其中

(i)G为CH或N;和

(ii)X为氢、-OR_2或-NR_3R_4，其中R_2、R_3和R4每个独立地为-H或C_{1-6}烷基；

R_{13}和R_{14}各自独立地为-H、卤素、C_{1-6}烷基或C_{3-7}环烷基；

R_{15}和R_{20}各自独立地为-H、卤素、-OH、-CN、-COOR'、-OR'、-SR'、-OC(O)R'、-NHR'、-NR'R"、-NHC(O)R'、-NHC(O)NR'R"、-C(O)NR'R"、-NS(O)$_2$R'、-S(O)$_2$NR'R"、-S(O)$_2$R'、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、和3至10元杂环，其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环各自独立地为未取代的，或者被一个或多个卤素、-OH、-CN、-COOR'、-OR'、-SR'、-OC(O)R'、-NHR'、-NR'R"、-NHC(O)R'、-NHC(O)NR'R"、-C(O)NR'R"、-NS(O)$_2$R'、-S(O)$_2$NR'R"、-S(O)$_2$R'、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基取代；其中R'和R"各自独立地为-H或C_{1-6}烷基；和任选地R'和R"一起连接至N或O形成4至8元杂环；

R_{16}、R_{17}、R_{18}和R_{19}各自独立地为-H、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环；其中C_{1-6}烷基、芳基、C_{3-7}环烷基或3至10元杂环为未取代的，或者被一个或多个卤素、-OH、-CN、-$COOR_a$、-OR_a、-SR_a、-OC(O)R_a、-NHR_a、-NR_aR_b、-NHC(O)R_a、-NHC(O)NR_aR_b、-C(O)NR_aR_b、-NS(O)$_2R_a$、-S(O)$_2NR_aR_b$、-S(O)$_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基取代；其中R_a和R_b各自独立地为-H或C_{1-6}烷基；和任选地R_a和R_b一起连接至N或O形成4至8元杂环；和

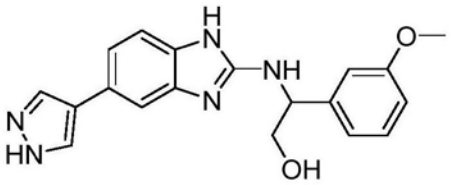
J为键或C_{1-6}烷基。

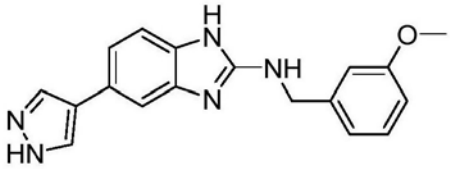
12.根据权利要求11所述的化合物，其中A为吡唑-4-基。

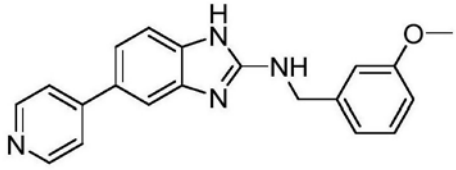
13.根据权利要求11所述的化合物，其中A为吡啶-4-基。

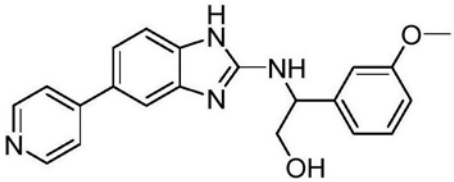
14.根据权利要求11至13中任一项所述的化合物，其中R_{13}和R_{14}均为甲基。

15.根据权利要求11所述的化合物，其中化合物选自：









15.根据权利要求1至14中任一项所述的化合物，其用于治疗与Rho激酶信号传导通路上调有关的疾病的用途。

16.一种治疗受试者中自身免疫性疾病的方法，其包括向受试者施用治疗有效量的根

据权利要求1至14中任一项所述的化合物。

17.根据权利要求16所述的方法，其中所述自身免疫性疾病为类风湿性关节炎、多发性硬化症、系统性红斑狼疮(SLE)、银屑病、克罗恩氏病、特应性皮炎、湿疹、或移植物抗宿主病(GVHD)。

18.一种治疗受试者中心血管疾病的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

19.根据权利要求18所述的方法，其中所述心血管疾病为高血压、动脉粥样硬化、再狭窄、心脏肥大、高眼压、脑缺血、脑血管痉挛、或勃起功能障碍。

20.一种治疗受试者中炎症的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

21.根据权利要求20所述的方法，其中所述炎症为哮喘、心血管炎症、肾脏炎症或动脉硬化。

22.一种治疗受试者中的中枢神经系统疾病的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

23.根据权利要求22所述的方法，其中所述中枢神经系统疾病为神经元变性或脊髓损伤。

24.根据权利要求22所述的方法，其中所述中枢神经系统疾病为亨廷顿氏病、帕金森病、阿尔茨海默病、肌萎缩性侧索硬化症(ALS)或多发性硬化症。

25.一种治疗受试者中动脉血栓性疾病的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

26.根据权利要求25所述的方法，其中所述动脉血栓性疾病为血小板聚集或白细胞聚集。

27.一种治疗受试者中纤维化疾病的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

28.根据权利要求27所述的方法，其中所述纤维化疾病为肝纤维化、肺纤维化或肾纤维化。

29.一种治疗受试者中青光眼或调节眼内压的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

30.根据权利要求29所述的方法，其中所述青光眼为原发性开角型青光眼、急性闭角型青光眼、色素性青光眼、先天性青光眼、正常眼压性青光眼或继发性青光眼。

31.一种治疗受试者中肿瘤性疾病的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

32.根据权利要求31所述的方法，其中所述肿瘤性疾病为淋巴瘤、恶性上皮肿瘤、白血病、肉瘤或胚细胞瘤。

33.根据权利要求32所述的方法，其中所述肿瘤性疾病为急性髓性白血病(AML)。

34.根据权利要求33所述的方法，其中所述AML为ITD-FLT3^{+}AML。

35.根据权利要求31所述的方法，其中所述肿瘤性疾病为鳞状细胞癌、小细胞肺癌、垂体癌、食道癌、星形细胞瘤、软组织肉瘤、非小细胞肺癌、肺腺癌、肺鳞状细胞癌、腹膜癌、肝细胞癌、胃肠癌、胰腺癌、成胶质细胞瘤、宫颈癌、卵巢癌、肝癌、膀胱癌、肝细胞瘤、乳腺癌、

结肠癌、结直肠癌、子宫内膜癌或子宫癌、唾液腺癌、肾癌、肝癌、前列腺癌、外阴癌、甲状腺癌、肝癌、脑癌、子宫内膜癌、睾丸癌、胆管癌、胆囊癌、胃癌、黑素瘤或头颈癌。

36.一种治疗受试者中代谢综合征、胰岛素抵抗、高胰岛素血症、2型糖尿病或葡萄糖耐受不良的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

37.一种治疗受试者中骨质疏松症或促进骨形成的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物。

38.一种治疗具有血管生成组成的眼部疾病的方法，其包括向受试者施用治疗有效量的根据权利要求1至14中任一项所述的化合物和血管生成抑制剂。

39.根据权利要求38所述的方法，其中所述眼部疾病为年龄相关性黄斑变性(AMD)、脉络膜新血管形成(CNV)、糖尿病性黄斑水肿(DME)、虹膜新血管形成、葡萄膜炎、新生血管性青光眼、或早产儿视网膜炎(ROP)。

作为激酶抑制剂的杂环化合物

[0001] 相关申请的交叉引用

[0002] 本申请要求在2015年5月18日提交的美国临时专利申请No.62/163,369和在2015年8月10日提交的美国临时专利申请No.62/203,070的优先权,其内容通过引用整体并入本文。

技术领域

[0003] 本发明涉及杂环化合物,其组合物和含有其的药物,以及这些化合物、组合物和药物的制备方法和用途。这些化合物可能用于治疗与不适当的酪氨酸和/或丝氨酸/苏氨酸激酶活性相关的疾病。

背景技术

[0004] 酶的一个重要的大家族是蛋白激酶家族。目前,已知有大约500种不同的蛋白激酶。蛋白激酶通过将ATP-Mg^{2+}络合物的γ-磷酸酯转移至不同蛋白质中的氨基酸侧链上,来催化所述氨基酸侧链的磷酸化。这些酶控制细胞内的大部分信号传导过程,从而通过蛋白质中丝氨酸、苏氨酸和酪氨酸残基的羟基的可逆磷酸化,来调控细胞功能、生长、分化和破坏(凋亡)。研究已显示,蛋白激酶是许多细胞功能的关键调控因子,所述细胞功能包括信号转导、转录调节、细胞运动性和细胞分裂。已经显示,一些致癌基因编码蛋白激酶,提示激酶在癌形成中发挥作用。这些过程受到高度调节,通常是通过复杂的相互结合的通路,其中每种激酶自身将受到一种或多种激酶的调节。因此,异常的或不适当的蛋白激酶活性可以促成与这种异常的激酶活性相关的疾病状态的产生。由于它们的生理相关性、多样性和普遍存在性,蛋白激酶已经成为生物化学和医学研究中最重要且广泛研究的酶家族之一。

[0005] 酶的蛋白激酶家族基于它们磷酸化的氨基酸残基,通常被分为两个主要的亚家族:蛋白酪氨酸激酶和蛋白丝氨酸/苏氨酸激酶。丝氨酸/苏氨酸激酶(PSTK)包括环AMP和环GMP依赖性蛋白激酶、钙和磷脂依赖性蛋白激酶、钙和钙调蛋白依赖性蛋白激酶、酪蛋白激酶、细胞分裂周期蛋白激酶等。这些激酶通常是细胞质的或者可能通过锚定蛋白与细胞的颗粒部分相关。在许多病理学如类风湿性关节炎、银屑病、脓毒性休克、骨丢失、许多癌症和其他增殖性疾病中,牵涉或怀疑有异常的蛋白质丝氨酸/苏氨酸激酶活性。因此,丝氨酸/苏氨酸激酶和它们所属的信号转导通路是药物设计的重要靶点。酪氨酸激酶使酪氨酸残基磷酸化。酪氨酸激酶在细胞调控中发挥同样重要的作用。这些激酶包括分子(如生长因子和激素)的多种受体,包括表皮生长因子受体、胰岛素受体、血小板衍化生长因子受体等。研究已表明,许多酪氨酸激酶是跨膜蛋白,其中它们的受体结构域位于细胞外部,它们的激酶5结构域位于内部。目前也在进行许多工作,以确认酪氨酸激酶的调节剂。

[0006] 细胞所利用的一种主要的信号转导系统是RhoA-信号传导通路。RhoA是一种小的GTP结合蛋白,其可以被多种细胞外刺激物如生长因子、激素、机械应激、渗透压改变以及高浓度的代谢产物(如葡萄糖)活化。RhoA活化涉及GTP结合、构象改变、翻译后修饰(香叶基香叶酰化(geranylgeranyllization)和法尼基化(famesylation))和其内在的GTP酶活性的

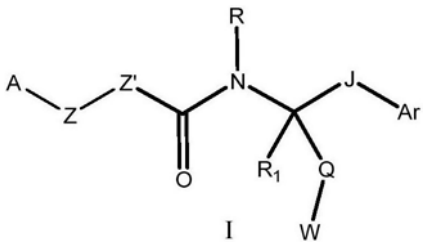
活化。活化的RhoA能够与多种效应蛋白(包括ROCK)相互作用,并将信号传递到细胞质和细胞核中。

[0007] ROCK1和2构成一种激酶家族,其可以经由物理结合被RhoA-GTP络合物活化。活化的ROCK使许多底物磷酸化,并在关键的细胞功能中发挥重要作用。ROCK的底物包括肌球蛋白轻链磷酸酶的肌球蛋白结合亚单位(MBS,也被称为MYPT1)、内收蛋白、膜突蛋白、肌球蛋白轻链(MLC)、LIM激酶以及转录因子FHL。这些底物的磷酸化调节蛋白质的生物活性,从而提供改变细胞对外部刺激物的应答的手段。一个有据可查的示例是ROCK在平滑肌收缩中的参与。经苯肾上腺素刺激后,血管的平滑肌收缩。研究已显示,苯肾上腺素刺激α-肾上腺素能受体,并导致RhoA的活化。活化的RhoA反过来刺激ROCK1的激酶活性,并且其反过来使MBS磷酸化。这种磷酸化抑制肌球蛋白轻链磷酸酶的酶活性,并通过钙依赖性肌球蛋白轻链激酶(MLCK)增加肌球蛋白轻链自身的磷酸化,并因此增加肌球蛋白-肌动蛋白束的收缩性,导致平滑肌收缩。这种现象有时也被称为钙敏感化。除平滑肌收缩以外,还已显示ROCK参与细胞功能,包括细胞凋亡、细胞迁移、转录活化、纤维化、胞质分裂、炎症和细胞增殖。此外,在神经元中,ROCK通过髓磷脂相关抑制因子如i髓磷脂相关糖蛋白(MAG)在轴突生长的抑制中发挥关键作用。ROCK活性还介导了发育中的神经元的生长锥的折叠(collapse)。这两个过程被认为是通过ROCK诱导的底物(如LIM激酶和肌球蛋白轻链磷酸酶)的磷酸化介导的,导致神经元的肌动蛋白-肌球蛋白系统的增加的收缩性。已经提出在各种疾病的治疗中使用ROCK的抑制剂。它们包括心血管疾病如高血压、慢性和充血性心力衰竭、心脏肥大、再狭窄、慢性肾衰竭和动脉粥样硬化。此外,由于其肌肉松弛性质,其也适用于哮喘、男性勃起功能障碍、女性性功能障碍和膀胱过度活跃综合征。已经显示ROCK抑制剂具有抗炎性质。因此,它们可以被用于治疗神经炎性疾病如中风、多发性硬化症、阿尔茨海默病、帕金森病、肌萎缩性侧索硬化症和炎性疼痛,以及其他炎性疾病如类风湿性关节炎、肠易激综合征、炎性肠病。此外,基于ROCK抑制剂的神经突生长诱导作用,它们可以是用于神经元再生的有用药物,诱导新的轴突生长和轴突穿过CNS内病变的重新连接。因此,ROCK抑制剂可能用于CNS疾病的再生(恢复)治疗,如脊髓损伤、急性神经元性损伤(中风、创伤性脑损伤)、帕金森病、阿尔茨海默病和其他神经变性疾病。由于ROCK抑制剂减少细胞增殖和细胞迁移,因此它们可以用于治疗癌症和肿瘤转移。此外,有证据表明,ROCK抑制剂抑制病毒侵袭后的细胞骨架重排,因此它们在抗病毒和抗细菌应用中也具有潜在的治疗价值。ROCK抑制剂也可以用于治疗胰岛素抵抗和糖尿病。

[0008] 本发明人发现了新的杂环化合物,其是ROCK活性的抑制剂。这些衍生物可以用于治疗与不适当的ROCK活性相关的疾病。

发明内容

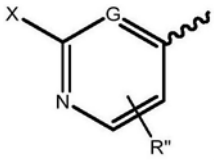
[0009] 本发明涉及一种式I的化合物:

[0010] 

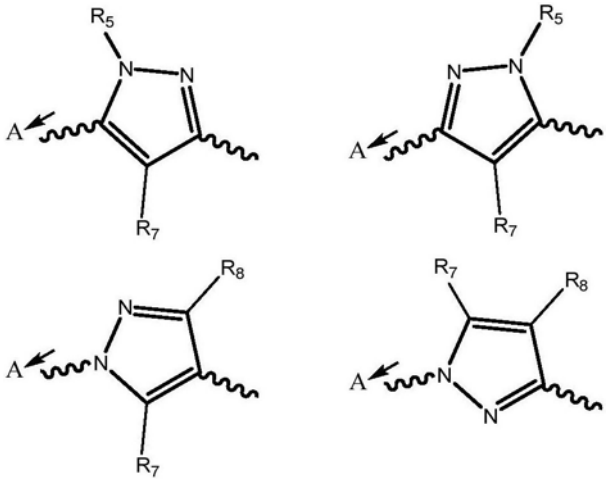
I

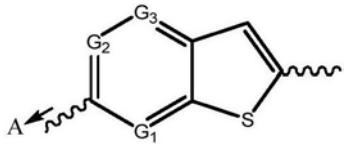
[0011] 或其对映异构体、对映异构体的混合物、或两种或多种非对映异构体的混合物；或其药学上可接受的盐、溶剂化物、水合物或生理学功能衍生物；

[0012] 其中：

[0013] A为吲唑-3-基、吡唑-4-基、  其中(i)G为CR'或N；(ii)X为氢、C_{1-6}烷基、C_{3-7}环烷基、$-OR_2$或$-NR_3R_4$；和(iii)R'、R"、R_2、R_3和R_4独立地为-H或C_{1-6}烷基或C_{3-7}环烷基；

[0014] Z选自：

[0015] 

[0016] 

[0017] 其中(i)R_5为-H、C_{1-6}烷基或C_{3-7}环烷基；(ii)R_7和R_8独立地为-H、卤素、C_{1-6}烷基、C_{3-7}环烷基、-O-(C_{1-6}烷基)、-OH、-CN、-COOR'、-OC(O)R'、NHR'、N(R')$_2$、-NHC(O)R'、-NHS(O)$_2$R'、-C(O)NHR'或-S(O)$_2$R'，其中R'为-H、C_{1-6}烷基或C_{3-7}环烷基；(iii)G_1、G_2和G_3独立地为CH或N。

[0018] Z'为键、O或NR_6，其中R_6为-H、C_{1-6}烷基或C_{3-7}环烷基；

[0019] R为-H、C_{1-6}烷基或C_{3-7}环烷基；

[0020] R_1为-H或C_{1-6}烷基；

[0021] Q为键或C_{1-6}烷基；

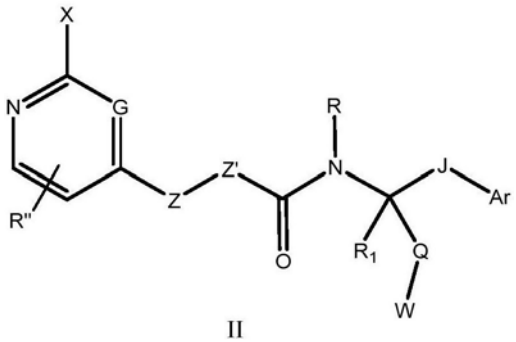
[0022] J为键或C_{1-6}烷基；

[0023] W为-H、$-OR_9$、$-NR_{10}R_{11}$、或$-S(O)_mR_{12}$，其中(i)R_9、R_{10}和R_{11}独立地为-H、C_{1-6}烷基、C_{3-7}环烷基、甲酰基、C_{1-6}烷基羰基、C_{3-7}环烷基羰基、或C_{1-6}烷基磺酰基；(ii)m为0至2的整数；和(iii)R_{12}为C_{1-6}烷基或C_{3-7}环烷基；和

[0024] Ar为苯基、萘基、或C_{5-10}杂环，其每个任选地被卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环取代，其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环为未取代的，或者被一个或多个卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、或C_{3-7}环烷基取代；其中R_a和R_b各自独

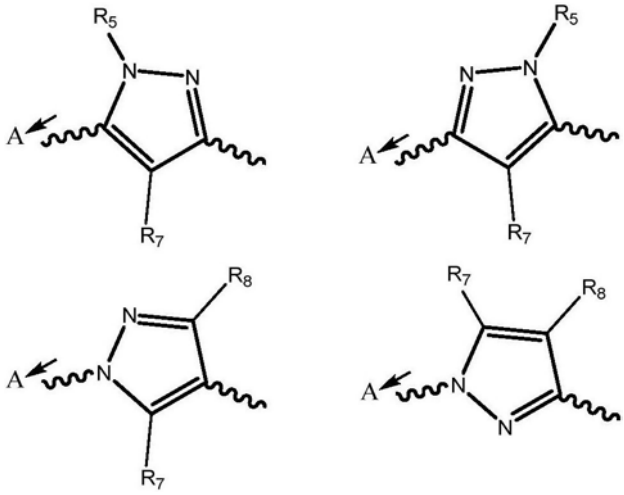
立地为H或C_{1-6}烷基;和任选地R_a和R_b一起连接至N或O形成4至8元杂环。

[0025] 在一个实施方案中,本发明涉及一种式II的化合物:

[0026] 

II

[0027] 其中(i)G为CR'或N;(ii)X为氢、C_{1-6}烷基、C_{3-7}环烷基、$-OR_2$或$-NR_3R_4$;和(iii)R'、R"、R_2、R_3和R_4独立地为-H或C_{1-6}烷基或C_{3-7}环烷基;Z选自:

[0028] 

[0029] 其中(i)R_5为-H、C_{1-6}烷基或C_{3-7}环烷基;(ii)R_7和R_8独立地为-H、卤素、C_{1-6}烷基、C_{3-7}环烷基、$-O-(C_{1-6}$烷基)、-OH、-CN、-COOR'、$-OC(O)R'$、NHR'、$N(R')_2$、$-NHC(O)R'$、$-NHS(O)_2R'$、$-C(O)NHR'$、或$-S(O)_2R'$,其中R'为-H、C_{1-6}烷基或C_{3-7}环烷基;(iii)G_2、G_3和G_4独立地为CH或N;

[0030] Z'为键、O或NR_6,其中R_6为-H、C_{1-6}烷基或C_{3-7}环烷基;

[0031] R为-H、C_{1-6}烷基或C_{3-7}环烷基;

[0032] R_1为-H或C_{1-6}烷基;

[0033] Q为键或C_{1-6}烷基;

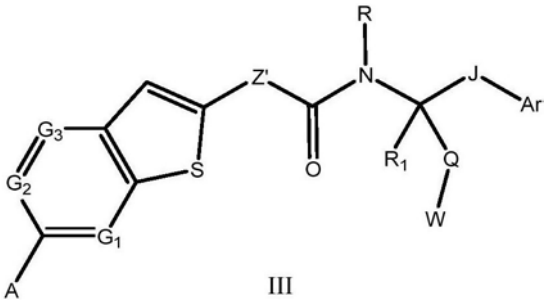
[0034] J为键或C_{1-6}烷基;

[0035] W为-H、$-OR_9$、$-NR_{10}R_{11}$或$-S(O)_mR_{12}$,其中(i)R_9、R_{10}和R_{11}独立地为-H、C_{1-6}烷基、C_{3-7}环烷基、甲酰基、C_{1-6}烷基羰基、C_{3-7}环烷基羰基或C_{1-6}烷基磺酰基;(ii)m为0至2的整数;和(iii)R_{12}为C_{1-6}烷基或C_{3-7}环烷基;和

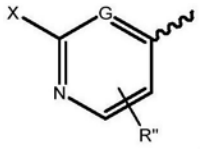
[0036] Ar为苯基、萘基、或C_{5-10}杂环,其每个任选地被卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环取代,其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环为未取代的,或者被一个或多个卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基或C_{3-7}环烷基取代;其中R_a和R_b各自独立

地为H或C_{1-6}烷基;和任选地R_a和R_b一起连接至N或O形成4至8元杂环。

[0037] 在另一个实施方案中,本发明涉及一种式III的化合物:

[0038] 

III

[0039] 其中A为吲唑-3-基、吡唑-4-基、 

,其中(i)G为CR'或N;(ii)X为氢、C_{1-6}烷基、C_{3-7}环烷基、$-OR_2$或$-NR_3R_4$;和(iii)R'、R"、R_2、R_3和R_4独立地为-H或C_{1-6}烷基或C_{3-7}环烷基;

[0040] G_5、G_6和G_7独立地为CH或N;

[0041] Z'为键、O或NR_6,其中R_6为-H、C_{1-6}烷基或C_{3-7}环烷基;

[0042] R为-H、C_{1-6}烷基或C_{3-7}环烷基;

[0043] R_1为-H或C_{1-6}烷基;

[0044] Q为键或C_{1-6}烷基;

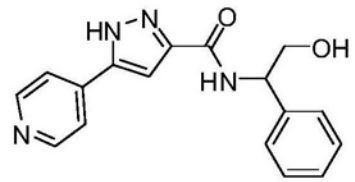
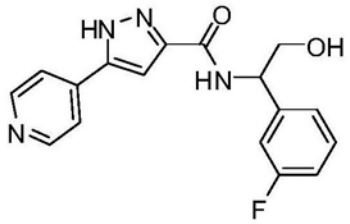
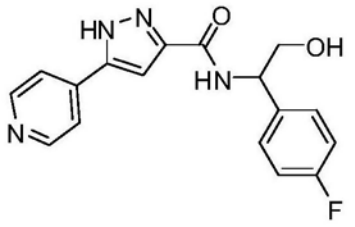
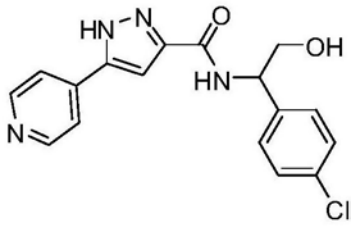
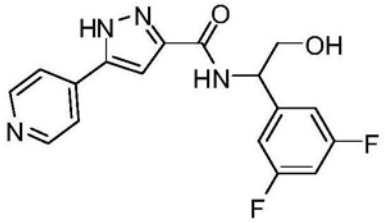
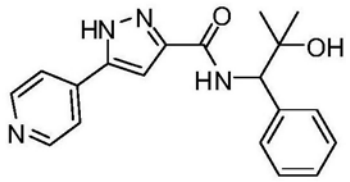
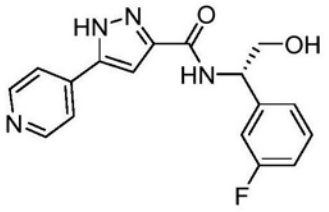
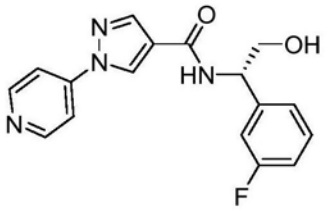
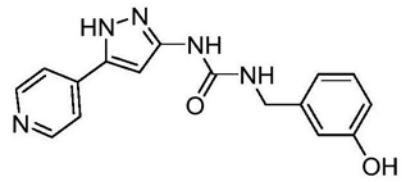
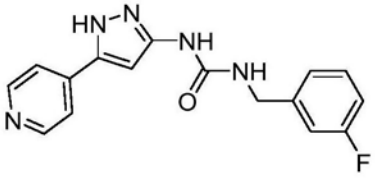
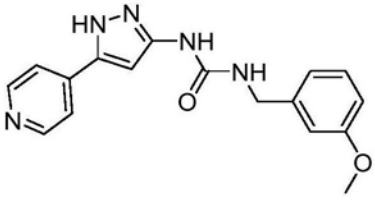
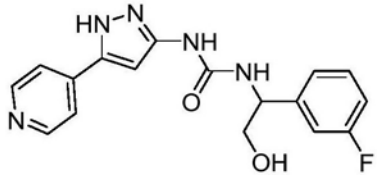
[0045] J为键或C_{1-6}烷基;

[0046] W为-H、$-OR_9$、$-NR_{10}R_{11}$或$-S(O)_mR_{12}$,其中(i)R_9、R_{10}和R_{11}独立地为-H、C_{1-6}烷基、C_{3-7}环烷基、甲酰基、C_{1-6}烷基羰基、C_{3-7}环烷基羰基或C_{1-6}烷基磺酰基;(ii)m为0至2的整数;和(iii)R_{12}为C_{1-6}烷基或C_{3-7}环烷基;和

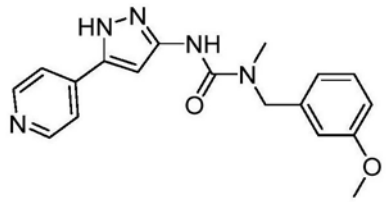
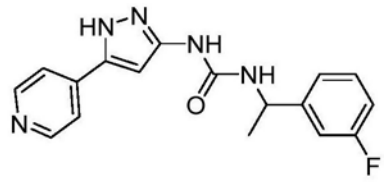
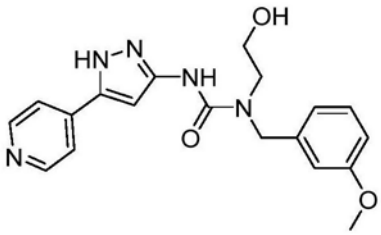
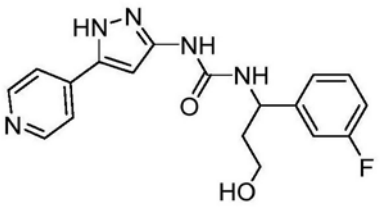
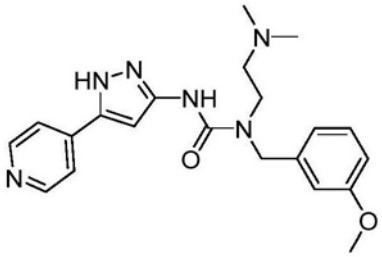
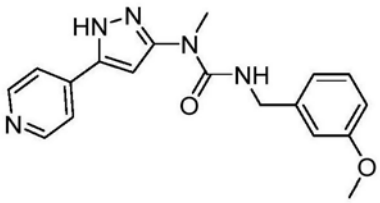
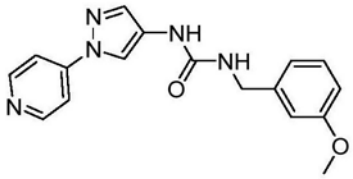
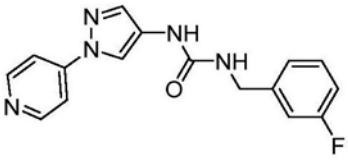
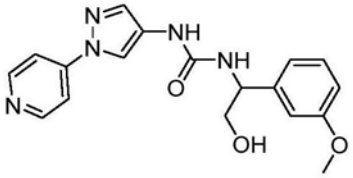
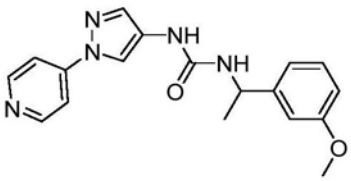
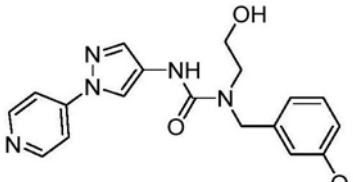
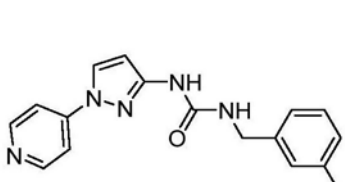
[0047] Ar为苯基、萘基或C_{5-10}杂环,其每个任选地被卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环取代,其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环为未取代的,或者被一个或多个卤素、-OH、-CN、$-COOR_a$、$-OR_a$、$-SR_a$、$-OC(O)R_a$、$-NHR_a$、$-NR_aR_b$、$-NHC(O)R_a$、$-NHC(O)NR_aR_b$、$-C(O)NR_aR_b$、$-NS(O)_2R_a$、$-S(O)_2NR_aR_b$、$-S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、或C_{3-7}环烷基取代;其中R_a和R_b各自独立地为H或C_{1-6}烷基;和任选地R_a和R_b一起连接至N或O形成4至8元杂环。

[0048] 在一些实施方案中,本发明涉及选自以下的式I、II和/或III的化合物:

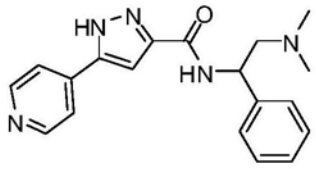
[0049]

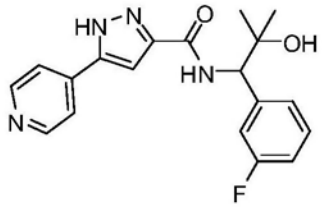













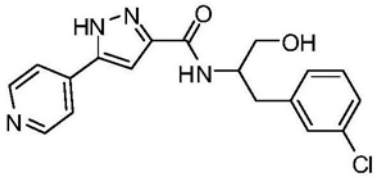
[0050]

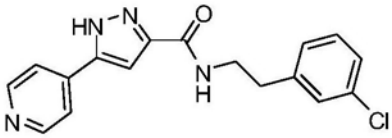













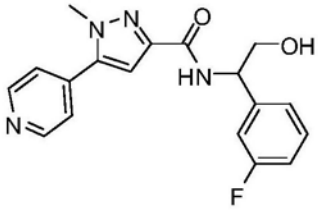
[0051]

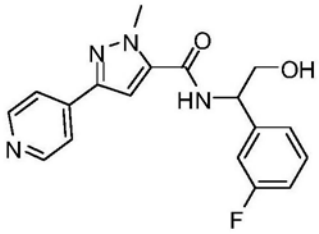


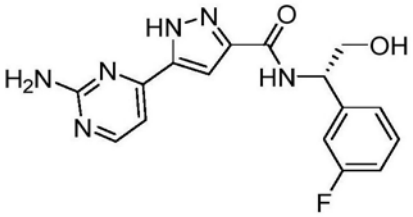


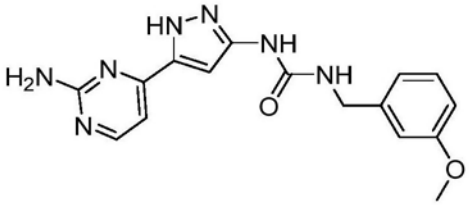


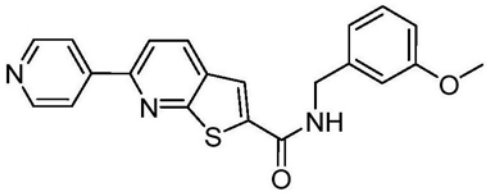


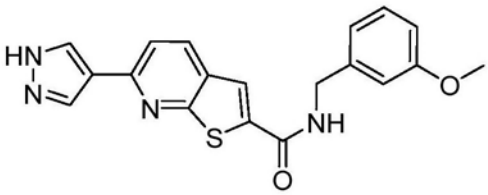


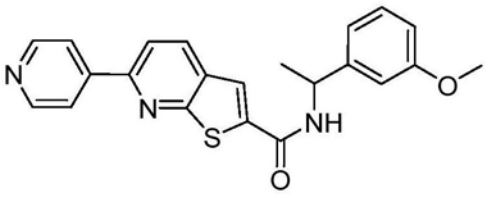


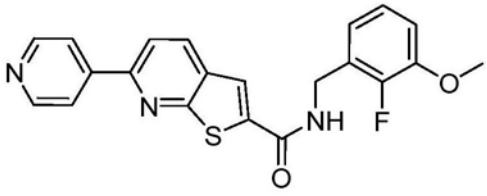


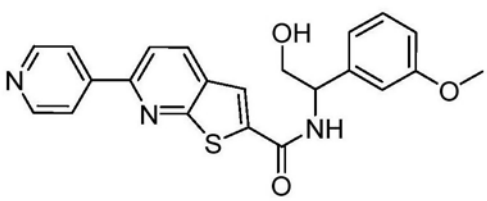


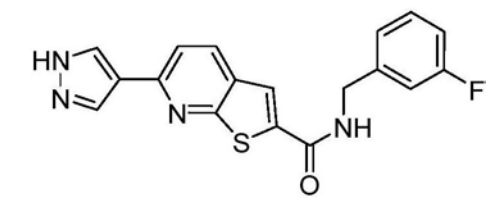




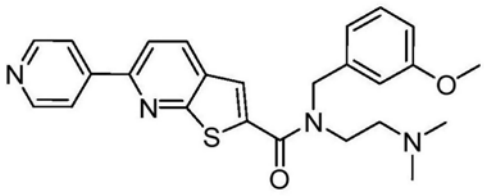
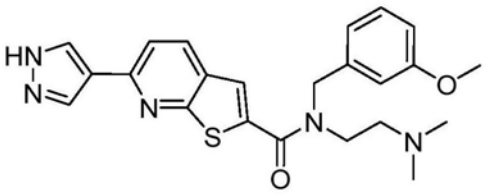
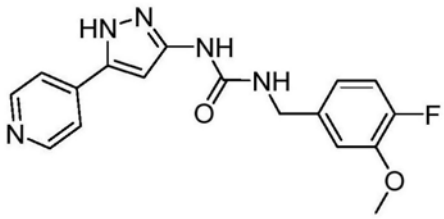
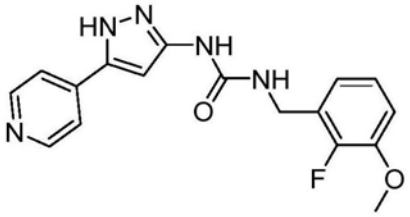
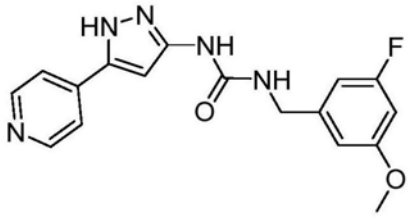
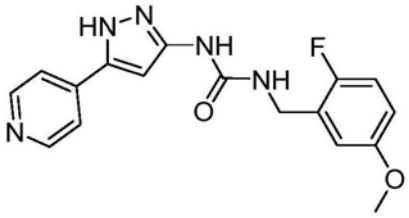
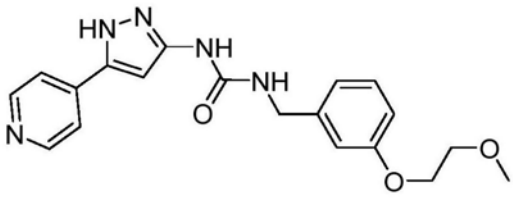
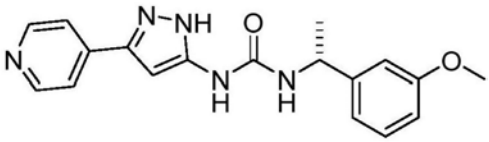
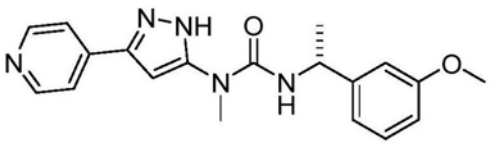
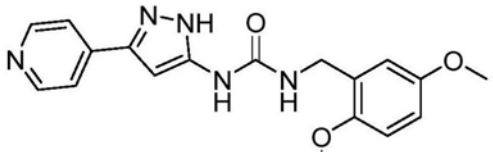
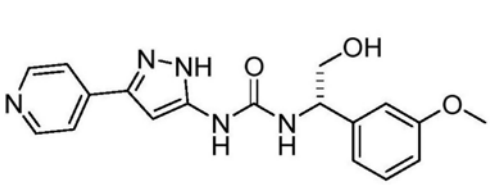
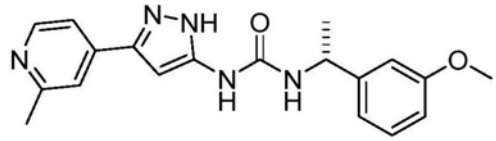






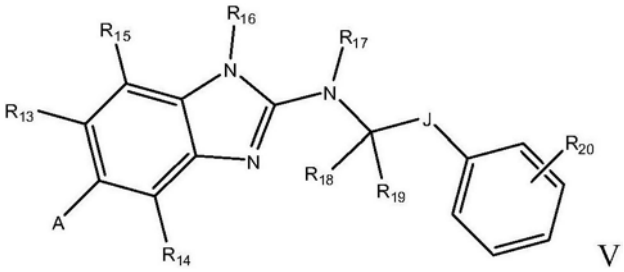


[0052]

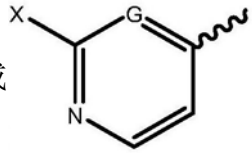
。

[0053] 本发明还涉及一种式V的化合物：

[0054] 

[0055] 或其对映异构体、对映异构体的混合物、或两种或多种非对映异构体的混合物；或其药学上可接受的盐、溶剂化物、水合物或生理学功能衍生物；

[0056] 其中：

[0057] A吲唑-3-基、吡唑-4-基、或  其中(i)G为CH或N；和(ii)X为氢、-OR_2或-NR_3R_4，其中R_2、R_3和R4每个独立地为-H或C_{1-6}烷基；

[0058] R_{13}和R_{14}各自独立地为-H、卤素、C_{1-6}烷基或C_{3-7}环烷基；

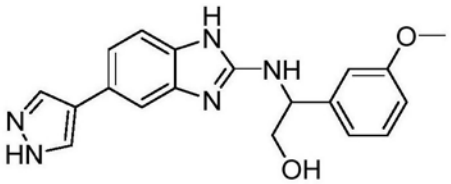
[0059] R_{15}和R_{20}各自独立地为-H、卤素、-OH、-CN、-COOR'、-OR'、-SR'、-OC(O)R'、-NHR'、-NR'R"、-NHC(O)R'、-NHC(O)NR'R"、-C(O)NR'R"、-$NS(O)_2$R'、-$S(O)_2$NR'R"、-$S(O)_2$R'、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基、和3至10元杂环，其中C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环各自独立地为未取代的，或者被一个或多个卤素、-OH、-CN、-COOR'、-OR'、-SR'、-OC(O)R'、-NHR'、-NR'R"、-NHC(O)R'、-NHC(O)NR'R"、-C(O)NR'R"、-$NS(O)_2$R'、-$S(O)_2$NR'R"、-$S(O)_2$R'、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基取代；其中R'和R"各自独立地为-H或C_{1-6}烷基；和任选地R'和R"一起连接至N或O形成4至8元杂环；

[0060] R_{16}、R_{17}、R_{18}和R_{19}各自独立地为-H、C_{1-6}烷基、芳基、C_{3-7}环烷基、或3至10元杂环；其中C_{1-6}烷基、芳基、C_{3-7}环烷基或3至10元杂环为未取代的，或者被一个或多个卤素、-OH、-CN、-$COOR_a$、-OR_a、-SR_a、-$OC(O)R_a$、-NHR_a、-NR_aR_b、-$NHC(O)R_a$、-$NHC(O)NR_aR_b$、-$C(O)NR_aR_b$、-$NS(O)_2R_a$、-$S(O)_2NR_aR_b$、-$S(O)_2R_a$、胍基、硝基、亚硝基、C_{1-6}烷基、芳基、C_{3-7}环烷基取代；其中R_a和R_b各自独立地为-H或C_{1-6}烷基；和任选地R_a和R_b一起连接至N或O形成4至8元杂环；和

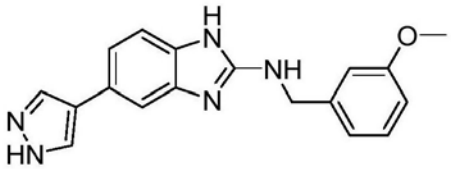
[0061] J为键或C_{1-6}烷基。

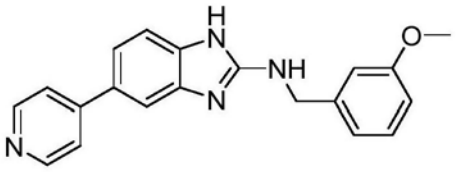
[0062] 在某些方面，A为吡唑-4-基。在其他方面，A为吡啶-4-基。在一个方面，本发明涉及一种式II的化合物，其中R_{13}和R_{14}均为甲基。

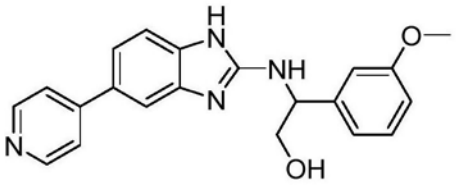
[0063] 在一些实施方案中，本发明涉及选自以下的式V的化合物：

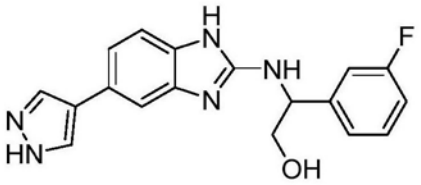


[0064]









[0065] 在某些方面，本发明提供如本文所公开的化合物，其用于治疗与Rho激酶信号传导通路上调相关的疾病。

[0066] 在其他方面，本发明涉及一种治疗受试者中自身免疫性疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在一个方面，所述自身免疫性疾病为类风湿性关节炎、多发性硬化症、系统性红斑狼疮(SLE)、银屑病、克罗恩氏病、特应性皮炎、湿疹、或移植物抗宿主病(GVHD)。

[0067] 在一些实施方案中，本发明提供一种治疗受试者中心血管疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在一个实施方案中，所述心血管疾病为高血压、动脉粥样硬化、再狭窄、心脏肥大、高眼压、脑缺血、脑血管痉挛、或勃起功能障碍。

[0068] 在其他实施方案中，本发明提供一种治疗受试者中炎症的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在某些方面，所述炎症为哮喘、心血管炎症、肾脏炎症或动脉硬化。

[0069] 在某些方面，本发明提供一种治疗受试者中的中枢神经系统疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在一个方面，所述中枢神经系统疾病为神经元变性或脊髓损伤。在另一方面，所述中枢神经系统疾病为亨廷顿氏病、帕金森病、阿尔茨海默病、肌萎缩性侧索硬化症(ALS)或多发性硬化症。

[0070] 本发明还提供一种治疗受试者中动脉血栓性疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在一个实施方案中，所述动脉血栓性疾病为血小板聚集或白细胞聚集。

[0071] 在其他方面，本发明涉及一种治疗受试者中的纤维化疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在一个实施方案中，所述纤维化疾病为肝纤维化、肺纤维化或肾纤维化。

[0072] 本发明还涉及一种治疗受试者中青光眼或调节眼内压的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在一个方面，所述青光眼为原发性开角型青光眼、急性闭角型青光眼、色素性青光眼、先天性青光眼、正常眼压性青光眼或继发性青光眼。

[0073] 在一些实施方案中，本发明涉及一种治疗受试者中肿瘤性疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。在某些方面，所述肿瘤性疾病为淋巴瘤、恶性上皮肿瘤(carcinoma)、白血病、肉瘤或胚细胞瘤。在其他方面，所述肿瘤性疾病为鳞状细胞癌、小细胞肺癌(small-cell king cancer)、垂体癌、食道癌、星形细胞瘤、软组织肉瘤、非小细胞肺癌、肺腺癌(adenocarcinoma of the king)、肺鳞状细胞癌(squamous carcinoma of the king)、腹膜癌、肝细胞癌、胃肠癌、胰腺癌、成胶质细胞瘤、宫颈癌、卵巢癌、肝癌、膀胱癌、肝细胞瘤(hepatoma)、乳腺癌、结肠癌、结直肠癌、子宫内膜癌或子宫癌、唾液腺癌、肾癌、肝癌(liver cancer)、前列腺癌、外阴癌、甲状腺癌、肝癌(hepatic carcinoma)、脑癌、子宫内膜癌、睾丸癌、胆管癌、胆囊癌、胃癌、黑素瘤或头颈癌。

[0074] 在其他实施方案中，本发明提供一种治疗受试者中代谢综合征、胰岛素抵抗、高胰岛素血症、2型糖尿病或葡萄糖耐受不良的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。

[0075] 在一个实施方案中，本发明涉及一种治疗受试者中骨质疏松症或促进骨形成的方法，其包括向受试者施用治疗有效量的本文所公开的化合物。

[0076] 在另一个实施方案中，本发明涉及一种治疗具有血管生成组成的眼部疾病的方法，其包括向受试者施用治疗有效量的本文所公开的化合物和血管生成抑制剂。在某些方面，所述眼部疾病为年龄相关性黄斑变性(AMD)、脉络膜新血管形成(CNV)、糖尿病性黄斑水肿(DME)、虹膜新血管形成、葡萄膜炎、新生血管性青光眼、或早产儿视网膜炎(ROP)。

具体实施方式

[0077] 在以下描述中，为了解释的目的，阐述了许多具体细节以便提供对本发明的各个方面的透彻理解。然而，相关领域的技术人员将理解，可以在没有这些具体的细节时实施本发明。在其他情况下，已知的结构和装置被更一般性地示出或讨论，以避免使本发明不清楚。在许多情况下，对操作的描述足以使得他人能够实现本发明的不同形式，特别是当以软件实现操作时。应当注意的是，有许多所公开的发明可以应用的不同的和可选的配置、装置和技术。本发明的全部范围不限于以下描述的示例。

[0078] 将理解的是，“取代的(substituted)”、“取代(substitution)”或“被……取代(substituted with)”包括隐含的条件，即这种取代符合取代的原子和取代基的允许的化合价，并且取代带来稳定的化合物，例如，所述稳定的化合物不会自发地通过如重排、环化、消除等而经历转化。

[0079] 如本文所使用，术语“取代的”预期包括有机化合物的所有可允许的取代基。在一个广泛的方面，可允许的取代基包括有机化合物的非环的和环状的、支链的和直链的、碳环的和杂环的、芳香的和非芳香的取代基。示例性的取代基包括例如下文所描述的那些。

[0080] 除非另外定义，如本文所使用的术语“烷基”是指直链或支链饱和基团，其来源于从烷烃中去除氢原子。代表性的直链烷基包括甲基、乙基、正丙基、正丁基、正戊基和正庚基。代表性的支链烷基包括异丙基、仲丁基、异丁基、叔丁基、异戊基、新戊基、1-甲基丁基、

2-甲基丁基、3-甲基丁基、1,1-二甲基丙基和1,2-二甲基丙基。

[0081] 如本文所使用，卤素基团包括任何卤素。示例包括但不限于F、Cl、Br或I。

[0082] C_1-C_6烷基包括任何由一至六个碳原子组成的直链或支链、饱和的或不饱和的、取代的或未取代的烃。-C_1-C_6烷基的示例包括但不限于甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基、戊基、异戊基、新戊基、己基、异己基、新己基、乙烯基、丙烯基、1-丁烯基、2-丁烯基、1-戊烯基、2-戊烯基、1-己烯基、2-己烯基、3-己烯基、乙炔基、戊炔基、1-丁炔基、2-丁炔基、1-戊炔基、2-戊炔基、1-己炔基、2-己炔基和3-己炔基。取代的-C_1-C_6烷基可以包括任何合适的化学部分。可以被取代到上面所列的任何-C_1-C_6烷基上的基团的示例包括但不限于以下示例：卤素、-C_1-C_6烷基、-O-(C_1-C_6烷基)、C_3-C_7环烷基、-OH、-CN、-COOR'、-OC(O)R'、-NHR'、N(R')$_2$、-NHC(O)R'或-C(O)NHR'基团。上面的被表示为R'的基团可以为-H、任何-C_1-C_6烷基，或者当取代基为-N(R')$_2$时，两个R'可以任选地与它们所结合的氮或氧原子形成3、4、5、6、7元环系。

[0083] 芳基包括任何未取代的或取代的苯基或萘基。可以被取代到芳基上的基团的示例包括但不限于：卤素、-C_1-C_6烷基、-O-(C_1-C_6烷基)、-OH、-CN、-COOR'、-OC(O)R'、NHR'、N(R')2、-NHC(O)、R'或-C(O)NEtR'。被表示为R'的基团可以为-H或任何-C_1-C_6烷基。

[0084] C_3-C_7环烷基包括任何3、4、5、6或7元取代的或未取代的非芳香碳环。C_3-C_7环烷基的示例包括但不限于环丙基、环丁基、环戊基、环戊二烯基、环己基、环己烯基、环庚基、环庚烯基、1,3-环己二烯基、-1,4-环己二烯基、-1,3-环庚二烯基和-1,3,5-环庚三烯基。可以被取代到C_3-C_7环烷基上的基团的示例包括但不限于：卤素、-C_1-C_6烷基、-O-(C_1-C_6烷基)、-OH、-CN、-COOR'、-OC(O)R'、NHR'、N(R')2、-NHC(O)R'或-C(O)NHR'基团。上面被表示为R'的基团包括-H或任何未取代的-C_1-C_6烷基，其示例如上面所列。卤素基团包括任何卤素。示例包括但不限于F、Cl、Br或I。

[0085] 杂环可以为任何任选取代的饱和的、不饱和的或芳香的环状部分，其中所述环状部分被选自氧(O)、硫(S)或氮(N)的至少一个杂原子隔断。杂环可以为单环或多环。例如，合适的取代基包括卤素、卤代C1-6烷基、卤代C1-6烷氧基、氨基、脒基、酰胺基、叠氮基、氰基、胍基、羟基、硝基、亚硝基、脲、OS(O)$_2$R、OS(O)$_2$OR、S(O)$_2$OR S(O)$_{0-2}$R、C(O)OR(其中R可以为H、C_1-C_6烷基、芳基或3至10元杂环)、OP(O)OR_1OR_2、P(O)OR_1OR_2、$SO_2NR_1R_2$、$NR_1SO_2R_2$C(R_1)NR_2C(R_1)NOR_2(R1和R2可以独立地为H、C_1-C_6烷基、芳基或3至10元杂环)、NR_1C(O)R_2、NR_1C(O)OR_2、NR_3C(O)NR_2R_1、C(O)NR_1R_2、OC(O)NR_1R_2。对于这些基团，R_1、R_2和R_3各自独立地选自H、C_1-C_6烷基、芳基或3至10元杂环，或者R_1和R_2与它们所连接的原子一起形成3至10元杂环。

[0086] 杂环基的可能的取代基包括卤素(Br、Cl、I或F)、氰基、硝基、氧代、氨基、C1-4烷基(例如CH_3、C_2H_5、异丙基)、C_{1-4}烷氧基(例如OCH_3、OC_2H_5)、卤代C_{1-4}烷基(例如CF_3、CHF_2)、卤代C_{1-4}烷氧基(例如OCF_3、OC_2F_5)、COOH、COO-C_{1-4}烷基、CO-C_{1-4}烷基、C_{1-4}烷基-S-(例如CH_3S、C_2H_5S)、卤代C_{1-4}烷基-S-(例如CF_3S、C_2F_5S)、苄氧基和吡唑基。

[0087] 杂环的示例包括但不限于氮杂卓基(azepinyl)、吖丙啶基、氮杂环丁二烯基(azetyl)、氮杂环丁烷基(azetidinyl)、二氮杂卓基(diazepinyl)、二硫二氮杂苯基(dithiadiazinyl)、二氧氮杂卓基(dioxazepinyl)、二氧戊环基(dioxolanyl)、二噻唑基(dithiazolyl)、呋喃基、异噁唑基、异噻唑基、咪唑基、吗啉基、吗啉代、氧杂环丁烷基、噁二唑基、环氧乙烷基、噁嗪基、噁唑基、哌嗪基、吡嗪基、哒嗪基、嘧啶基、哌啶基(piperidyl)、

哌啶基(piperidino)、吡啶基、吡喃基、吡唑基、吡咯基、吡咯烷基、噻三唑基、四唑基、噻二唑基、三唑基、噻唑基、噻吩基、四嗪基、噻二嗪基、三嗪基、噻嗪基、噻喃基(thiopyranyl)、呋喃并异噁唑基、咪唑并噻唑基、噻吩并异噻唑基、噻吩并噻唑基、咪唑并吡唑基、环戊并吡唑基、吡咯并吡咯基、噻吩并噻吩基、噻二唑并嘧啶基、噻唑并噻嗪基、噻唑并嘧啶基、噻唑并吡啶基、噁唑并嘧啶基、噁唑并吡啶基、苯并噁唑基、苯并异噻唑基、苯并噻唑基、咪唑并吡嗪基、嘌呤基、吡唑并嘧啶基、咪唑并吡啶基、苯并咪唑基、吲唑基、苯并噁硫醇基(benzoxathiolyl)、苯并二氧杂环戊烯基(benzodioxolyl)、苯并二硫醇基(benzodithiolyl)、吲嗪基(indolizinyl)、二氢吲哚基、异二氢吲哚基、呋喃并嘧啶基、呋喃并吡啶基、苯并呋喃基、异苯并呋喃基、噻吩并嘧啶基、噻呋并吡啶基(thienσpyridyl)、苯并噻吩基、环戊并噁嗪基(cyclopentaoxazinyl)、环戊并呋喃基、苯并噁嗪基、苯并噻嗪基、喹唑啉基、萘啶基、喹啉基、异喹啉基、苯并吡喃基、吡啶并哒嗪基和吡啶并嘧啶基。

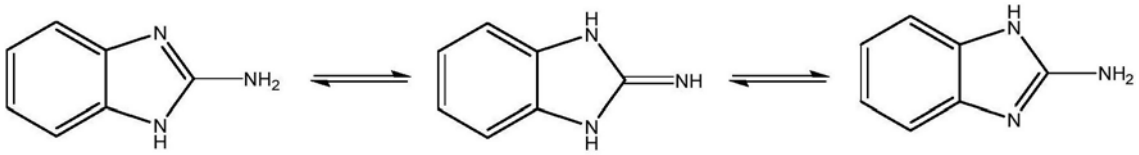
[0088] 本发明进一步涵盖化合物可能呈现的任何其他物理化学或立体化学形式。这些形式包括非对映异构体、外消旋体、分离的对映异构体、水合形式、溶剂化形式、任何已知的或尚未公开的晶体或无定形形式，包括所有多晶型晶体形式。无定形形式缺乏可辨识的晶格，因此缺乏有序排列的结构单元。许多药物化合物具有无定形形式。产生这种化学形式的方法将是本领域技术人员熟知的。

[0089] 本发明的另一个方面在于，式I中带有R_1和-QW的碳原子可以具有“S”或“R”构型。所有非对映异构体、外消旋体和分离的对映异构体均在本发明的范围内。

[0090] 可以经由现在已知的或尚未公开的任何方法通过特定的合成或拆分来制备化合物的外消旋体、单独的对映异构体或非对映异构体。例如，使用光学活性的酸通过成盐形成非对映异构体对，可以将化合物拆分成其对映异构体。对映异构体被分级结晶，并再生为游离碱。在另一个示例中，可以通过色谱法分离对映异构体。这种色谱法可以是现在已知的或尚未公开的任何合适的方法，其适用于分离对映异构体，如在手性柱上的HPLC。

[0091] 苯甲酰胺和吡唑部分及其中间体可以以不同的互变异构形式存在。互变异构体包括任何不同能量的结构异构体，其具有低的互变能垒。一个示例是质子互变异构体(质子移变互变异构体(prototropic tautomer))。在这个示例中，经由质子的迁移发生互变。质子移变互变异构体的示例包括但不限于酮-烯醇和亚胺-烯胺异构化。在下面阐明的另一个示例中，可以发生2-氨基苯并咪唑环的1-位、2-氨基和3-位氮原子之间的质子迁移。因此，式IIa、IIb和IIc是彼此的互变异构形式：

[0092]



IIa IIb IIc

[0093] 类似地，式IIIa和IIIb是彼此的互变异构形式：

[0094]

IIIa IIIb

[0095] 在本发明的一些方面，化合物呈药学上可接受的盐的形式。药学上可接受的盐包括任何来源于有机或无机酸的盐。这些盐的示例包括但不限于以下：氢溴酸、盐酸、硝酸、磷酸和硫酸的盐。有机酸加成盐包括例如乙酸、苯磺酸、苯甲酸、樟脑磺酸、柠檬酸、2-(4-氯苯氧基)-2-甲基丙酸、1,2-乙烷二磺酸、乙烷磺酸、乙二胺四乙酸(EDTA)、富马酸、葡庚糖酸、葡糖酸、谷氨酸、N-羟乙酰基阿散酸(N-glycolylarsanilic acid)、4-己基间苯二酚、马尿酸、2-(4-羟基苯甲酰基)苯甲酸、1-羟基-2-萘甲酸、3-羟基-2-萘甲酸、2-羟基乙磺酸、乳糖酸、正十二烷基硫酸、马来酸、苹果酸、扁桃酸、甲磺酸、甲基硫酸、粘酸、2-萘磺酸、双羟萘酸、泛酸、phosphanilicacid((4-氨基苯基)膦酸)、苦味酸、水杨酸、硬脂酸、琥珀酸、鞣酸、酒石酸、对苯二甲酸、对甲苯磺酸、10-十一碳烯酸或现在已知的或尚未公开的任何其他这样的酸的盐。将理解的是，这些盐，只要它们是药学上可接受的，则可以在治疗中使用。可以通过将化合物与合适的酸以本领域技术人员已知的方式反应来制备这些盐。

[0096] 在一些实施方案中，本发明的化合物在体外和/或体内引起激酶抑制。确定激酶抑制的方法是本领域熟知的。例如，可以通过测量底物的酶特异性磷酸化来确定酶的激酶活性和待测化合物的抑制能力。可以采用市售的试验产品和试剂盒。例如，可以使用IMAP®试验产品(Molecular Devices)来确定激酶抑制。该试验方法涉及使用荧光标记的肽底物。感兴趣的激酶对标记的肽的磷酸化促进了肽与三价金属基纳米颗粒经由磷酸基与三价金属之间的特异性、高亲和力相互作用的结合。向纳米颗粒靠近导致增加的荧光偏振。激酶抑制剂对激酶的抑制阻止了底物的磷酸化，从而限制了荧光标记的底物与纳米颗粒的结合。该试验可以与微孔试验形式相容，允许同时确定多种化合物的IC_{50}。

[0097] 在本发明的另一个方面，提供一种治疗患有疾病的患者的方法，其包括向需要这种治疗的患者施用治疗有效量的本发明的化合物。如本文所使用的短语“治疗有效量”是指包含本发明的化合物的化合物、材料或组合物的量，所述量以适用于任何医学治疗的合理的收益/风险比(例如，适用于任何医学治疗的合理的副作用)，在动物的至少一个细胞亚群中有效地产生一些期望的治疗作用。

[0098] 本发明的化合物可以用于治疗患有心血管和非心血管疾病的患者，如高血压、肺动脉高压、动脉粥样硬化、再狭窄、冠心病、心脏肥大、高眼压、视网膜病变、缺血性疾病、脑缺血、脑血管痉挛、阴茎勃起功能障碍、外周循环障碍、外周动脉闭塞性疾病、青光眼(例如调节眼内压)、肺纤维化、肝纤维化、肾纤维化、慢性阻塞性肺病(COPD)、成人呼吸窘迫综合征、中枢神经系统疾病如神经元变性和脊髓损伤。此外，本发明的化合物可以用于治疗动脉血栓性疾病(如血小板聚集和白细胞聚集)和骨吸收。

[0099] 在本发明的一个实施方案中，化合物用于治疗脑海绵状血管畸形(CCM)。CCM是由漏出的扩张的毛细血管簇组成的血管损伤，并与中枢神经系统(CNS)疾病(包括癫痫和中风)相关。认为血管完整性的丧失涉及RhoA的活化和ROCK的活化，导致细胞骨架稳定性的改变和增加的血管渗透性。本发明的化合物抑制ROCK活化，并恢复血管内皮的功能。

[0100] 本发明的化合物还可以用于治疗青光眼。有多种可以被治疗的青光眼，包括但不限于以下类型。两种最常见的类型，即原发性开角型青光眼和急性闭角型青光眼，其特征在于高眼压。色素性青光眼和先天性青光眼的特征还在于液体流出减少和高的眼内压(IOP)。正常压力型青光眼被认为是由于另一种机制，特别是向视神经不良的血液流动。继发性青光眼可以由损伤、感染、炎症、肿瘤或白内障导致，并且其还与长期使用类固醇、全身性高血

压、糖尿病视网膜病和视网膜中央静脉阻塞有关。

[0101] 在某些实施方案中，本发明的化合物用于治疗炎症，包括但不限于哮喘、心血管炎症、肾脏炎症、动脉粥样硬化和动脉硬化。

[0102] 在一些实施方案中，本发明的化合物抑制肿瘤细胞生长和转移及血管生成，并且可以用于治疗肿瘤性疾病。肿瘤性疾病包括任何由异常的或不受控制的细胞分裂引起的恶性生长或肿瘤，并且其可以通过淋巴系统或血流扩散至身体的其他部位。肿瘤性疾病包括但不限于淋巴瘤(淋巴组织的肿瘤，其通常是恶性的)、恶性上皮肿瘤(任何来源于上皮组织的恶性肿瘤)、白血病(血液形成组织的恶性肿瘤；其特征在于白细胞的异常增殖)、肉瘤(通常是由结缔组织(骨骼或肌肉等)引起的恶性肿瘤)和胚细胞瘤(前体细胞中的恶性肿瘤)。非限制性示例包括鳞状细胞癌、小细胞肺癌、垂体癌、食道癌、星形细胞瘤、软组织肉瘤、非小细胞肺癌、肺腺癌、肺鳞状癌、腹膜癌、肝细胞癌、胃肠癌、胰腺癌、成胶质细胞瘤、宫颈癌、卵巢癌、肝癌、膀胱癌、肝细胞瘤、乳腺癌、结肠癌、结直肠癌、子宫内膜癌或子宫癌、唾液腺癌、肾癌、肝癌、前列腺癌、外阴癌、甲状腺癌、肝癌、脑癌、子宫内膜癌、睾丸癌、胆管癌、胆囊癌、胃癌、黑色素瘤和不同类型的头颈癌。

[0103] 根据本发明的一个方面，本发明的化合物被用于实现体重减轻和/或限制体重增加。在一个优选的实施方案中，所述化合物是ROCK2选择性的。ROCK-2抑制剂促进正常受试者的体重减轻，并限制容易肥胖的受试者的体重增加。

[0104] 在本发明的一个实施方案中，本发明的化合物被用于降低或预防胰岛素抵抗，或恢复胰岛素敏感性。因此，在一个实施方案中，本发明的化合物被用于促进或恢复胰岛素依赖性葡萄糖摄取。在本发明的另一个实施方案中，本发明的化合物被用于促进或恢复葡萄糖耐量。在本发明的另一个实施方案中，本发明的化合物被用于治疗代谢综合征。在另一个实施方案中，本发明的化合物被用于减轻或预防高胰岛素血症。在本发明的一个实施方案中，本发明的化合物被用于治疗糖尿病(特别是2型糖尿病)。本发明化合物还可以用于促进或恢复胰岛素介导的血管平滑肌细胞(VSMC)的松弛。

[0105] 本发明提供用于治疗具有血管生成组成的疾病和病症的方法和化合物。根据本发明，在某些实施方案中，通过向受试者施用有效量的rho激酶抑制剂来治疗这些疾病和病症。在某些实施方案中，本发明的化合物为ROCK2选择性抑制剂。根据本发明，还可以通过施用有效量的rho激酶抑制剂(其抑制ROCK2，并且可以是ROCK2选择性的)和有效量的血管生成抑制剂，来治疗这些疾病和病症。根据本发明，以这种方式治疗具有血管生成组成的眼部疾病和病症。在一个实施方案中，本发明提供一种治疗以“干”和“湿”形式发生的年龄相关性黄斑变性(AMD)的方法。AMD的“湿”形式导致由于血管生长异常(新血管形成)造成的视力丧失。这些视网膜血管的出血、渗漏和疤痕最终导致光感受器的不可逆转的损伤。干形式由视网膜色素上皮层的萎缩导致，其通过眼睛中央部分的光感受器(视杆和视锥)的损失导致视力丧失。在另一个实施方案中，本发明提供一种治疗脉络膜新血管形成(CNV)的方法。脉络膜新血管形成是新的血管在脉络膜内生长，穿过布鲁赫膜并侵入视网膜下间隙的过程，其为(除其他原因之外)老年性黄斑变性，近视和眼外伤的症状之一。在另一个实施方案中，本发明提供一种治疗糖尿病性黄斑水肿(DME)的方法。在另一个实施方案中，本发明提供一种治疗继发于视网膜分支静脉阻塞(BRVO)或视网膜中央静脉阻塞(CRVO)的黄斑水肿的方法。在其他实施方案中，待治疗的疾病包括但不限于感染性和非感染性视网膜新血管形成、

感染性和非感染性角膜新血管形成、虹膜新血管形成、葡萄膜炎、新生血管性青光眼和早产儿视网膜炎(ROP)。治疗的方法可以是预防性的,如在角膜移植后避免角膜新血管形成,或调节小梁切除手术中的伤口愈合过程。这些疾病和病症可以被表征为具有血管生成组成。根据本发明,通过施用本发明的化合物和血管生成抑制剂来治疗这些病症。

[0106] 因此,在一个这样的实施方案中,所述疾病或病症为AMD,并且向需要治疗AMD的受试者施用一定量的本发明的化合物以治疗AMD。在另一个实施方案中,向受试者施用有效治疗AMD的量的本发明的化合物和血管生成抑制剂。在这些实施方案中,ROCK2选择性抑制剂可以是优选的。在一些实施方案中,血管生成抑制剂为VEGFR2拮抗剂。在某些这样的实施方案中,VEGFR2拮抗剂结合至VEGF。在其他这样的实施方案中,VEGFR2拮抗剂结合至VEGFR2。这些VEGFR2结合抑制剂包括结合至VEGFR2的细胞外结构域的试剂,包括但不限于抗体及其VEGFR2结合片段,和与VEGFR2的细胞内结构域相互作用并阻断VEGFR2依赖性信号传导的活化的试剂。VEGFR2拮抗剂进一步包括与其他细胞组分相互作用以阻断VEGFR2依赖性信号传导的试剂。在本发明的其他实施方案中,类似地治疗具有血管生成组成的其他眼部疾病和病症(如上面所说明的)。

[0107] 根据本发明,将有效量的本发明的化合物和血管生成抑制剂施用于受试者,以治疗或预防以过度的血管生成为特征的病理状况。涉及例如血管形成和/或炎症的此类病症包括动脉粥样硬化、类风湿性关节炎(RA)、血管瘤、血管纤维瘤和银屑病。血管形成性疾病的其他非限制性示例为早产儿视网膜病(晶状体后纤维增生(retrolental fibroplastic))、角膜移植排斥、与屈光手术并发症相关的角膜新血管形成、与隐形眼镜并发症有关的角膜新血管形成、与翼状胬肉(pterygium)和复发性翼状胬肉(recurrent pterygium)相关的角膜新血管形成、角膜溃疡病和非特异性眼表疾病、胰岛素依赖型糖尿病、多发性硬化症、重症肌无力、克罗恩氏病、自身免疫性肾炎、原发性胆汁性肝硬化、急性胰腺炎、排异反应、过敏性炎症、接触性皮炎和迟发型超敏反应、炎性肠病、感染性休克、骨质疏松症、骨关节炎、由神经元炎症诱导的认知缺陷、Osier-Weber综合征、再狭窄,和真菌、寄生虫及病毒感染(包括巨细胞病毒感染)。

[0108] 本发明进一步涵盖药物组合物,其包含作为成分的所公开的化合物。这些药物组合物可以采用任何必需的物理形式,这取决于许多因素,包括期望的施用方法,和所公开的化合物或该化合物的药学上可接受的盐所采用的物理化学和立体化学形式。这些物理形式包括固体、液体、气体、溶胶、凝胶、气雾剂或现在已知的或尚未公开的任何其他物理形式。包括所公开的化合物的药物组合物的概念还涵盖所公开的化合物或其药学上可接受的盐且没有任何其他添加剂。本发明的物理形式可以影响施用途径,并且本领域技术人员将知道选择施用途径,所述施用途径考虑了化合物的物理形式和待治疗的疾病。可以使用制药领域熟知的方法制备包含所公开的化合物的药物组合物。包含所公开的化合物的药物组合物可以包含不同于所公开化合物的化学式的第二有效化合物。该第二有效化合物可以具有与靶标相同或相似的分子靶标,或者其可以作用于所公开的化合物的分子靶标的一个或多个生物化学通路的上游或下游。

[0109] 包含所公开的化合物的药物组合物包含能够改变剂量单位的物理形式的材料。在一个非限制性示例中,所述组合物包含材料,所述材料形成约束化合物的包衣。可以用于这种涂层的材料包括例如糖、虫胶、明胶或任何其他惰性包衣剂。

[0110] 包含所公开的化合物的药物组合物可以被制备为气体或气雾剂。气雾剂涵盖各种系统，包括胶体和加压包装。组合物以这种形式的递送可以包括通过使用液化气体或其他压缩气体，或通过合适的泵系统推进包含所公开的化合物的药物组合物。可以以单相、双相或三相系统递送气雾剂。

[0111] 在本发明的一些方面，包含所公开的化合物的药物组合物呈溶剂化物的形式。通过将所公开的化合物溶解于药学上可接受的溶剂中制备这些溶剂化物。药学上可接受的溶剂包括一种以上溶剂的任何混合物。这些溶剂可以包括吡啶、氯仿、丙-1-醇、油酸乙酯、乳酸乙酯、环氧乙烷、水、乙醇和任何其他溶剂，所述任何其他溶剂递送足够量的所公开的化合物以治疗疾病，而没有由于使用溶剂而引起的患者的严重并发症。

[0112] 包含所公开的化合物的药物组合物还可以包含药学上可接受的载体。载体包括可以与所公开的化合物一起施用的任何物质，其目的在于促进、协助或帮助化合物的施用或其他递送。载体包括任何液体、固体、半固体、凝胶、气雾剂，或可以与所公开的化合物组合以帮助其施用的任何其他物质。示例包括稀释剂、佐剂、赋形剂、水、油(包括石油、动物油、植物油或合成油)。这些载体包括颗粒如片剂或粉末，液体如口服糖浆或可注射液体，和可吸入气雾剂。另外的示例包括盐水、阿拉伯树胶、明胶、淀粉糊、滑石、角蛋白、胶态二氧化硅和尿素。这些载体可以进一步包括粘合剂如乙基纤维素、羧甲基纤维素、微晶纤维素或明胶；赋形剂如淀粉、乳糖或糊精；崩解剂如海藻酸、海藻酸钠、Primogel和玉米淀粉；润滑剂如硬脂酸镁或Sterotex；助流剂如胶体二氧化硅；甜味剂如蔗糖或糖精，调味剂如薄荷、水杨酸甲酯或橙味香料，或着色剂。载体的另外的示例包括聚乙二醇、环糊精、油，或可以配制在胶囊中的任何其他类似的液体载体。载体的另外的示例包括无菌稀释剂，如注射用水、盐水溶液、生理盐水、林格氏溶液、等渗氯化钠、不挥发性油如合成的单甘油酯或二甘油酯、聚乙二醇、甘油、环糊精、丙二醇或其他溶剂；抗菌剂如苯甲醇或对羟基苯甲酸甲酯；抗氧化剂如抗坏血酸或亚硫酸氢钠；螯合剂如乙二胺四乙酸；缓冲剂如乙酸盐、柠檬酸盐或磷酸盐，和用于调节紧张性(tonicity)的试剂如氯化钠或右旋糖，增稠剂，润滑剂和着色剂。

[0113] 包含所公开的化合物的药物组合物可以根据组合物的物理化学形式和施用的类型，采用多种制剂中的任何一种。这些形式包括溶液剂、混悬剂、乳剂、片剂、丸剂、小丸剂(pellet)、胶囊、包含液体的胶囊、粉末剂、缓释制剂、定向释放制剂、冻干剂(lyophylate)、栓剂、乳剂、气雾剂、喷雾剂、颗粒剂、粉末剂、糖浆剂、酏剂，或者现在已知的或尚未被公开的任何其他制剂。在E.W.Martin的“Remington’s Pharmaceutical Sciences”中描述了合适的药物载体的其他示例，其全部内容通过引用并入本文。

[0114] 施用方法包括但不限于口服施用和肠胃外施用。肠胃外施用包括但不限于皮内、肌内、腹膜内、静脉内、皮下、鼻内、硬膜外、舌下、鼻内、脑内、心室内、鞘内、阴道内、经皮、直肠、通过吸入，或局部施用至耳、鼻、眼睛或皮肤。其他施用方法包括但不限于输注技术(包括输注或快速浓注)、通过经由上皮的或粘膜皮肤的(mucocutaneous)衬里(如口腔粘膜、直肠粘膜和肠粘膜)的吸收。用于肠胃外施用的组合物可以被封装在安瓿、一次性注射器或由玻璃、塑料或其他材料制成的多剂量小瓶中。

[0115] 施用可以是全身的或局部的。局部施用是将所公开的化合物施用至需要治疗的区域。示例包括手术中的局部输注；通过局部注射的局部应用；通过导管；通过栓剂；或通过植入物。施用可以为通过在癌症、肿瘤或癌前组织的部位(或前部位)的直接注射，或者通过任

何合适的途径(包括心室内和鞘内注射)向中枢神经系统内的直接注射。可以通过心室内导管例如连接至贮器(如奥马耶贮器(Ommaya reservoir))的心室内导管,以便于心室内注射。可以通过本领域已知的许多方法中的任一种实现肺部施用。示例包括使用吸入器或喷雾器(含有雾化剂的制剂),或经由在碳氟化合物或合成的肺表面活性剂中的灌注。可以在囊泡如脂质体或任何其他天然或合成囊泡的情况下,递送所公开的化合物。

[0116] 可以通过将所公开的化合物与水溶解以形成溶液,来制备被配制成通过注射施用的药物组合物。此外,可以加入表面活性剂,以促进形成均匀的溶液或混悬液。表面活性剂包括能够与所公开的化合物非共价相互作用,以促进化合物的溶解或均匀混悬的任何络合物。

[0117] 包含所公开的化合物的药物组合物可以被制备成有助于局部或经皮施用的形式。这些制剂可以呈溶液、乳剂、软膏、凝胶基质、透皮贴剂或离子电渗装置的形式。在这些组合物中使用的基质的示例包括凡士林、羊毛脂、聚乙二醇、蜂蜡、矿物油、稀释剂例如水和醇、以及乳化剂和稳定剂、增稠剂或现在已知的或尚未公开的任何其他合适的基质。

[0118] 代表本发明的不同方面的示例如下。这些示例不应被解释为限制本公开的范围。本发明范围内的可选机械学路径和类似结构对于本领域技术人员将是显而易见的。

[0119] 实施例中的元素和行为旨在简要地阐明本发明,并且不一定根据任何特定的顺序或实施方案来呈现。

[0120] 实施例

[0121] 实施例1.激酶抑制剂的合成

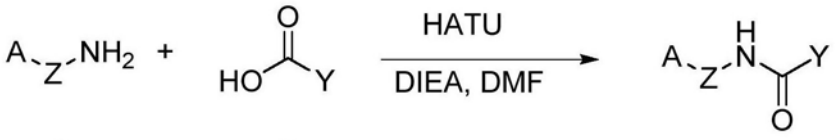
[0122] 可以经由下面概述的一般合成程序来制备本发明的不同方面。本领域技术人员将明白如何通过选择适当和相关的起始材料、合成中间体和试剂来制备本发明的其他方面。

[0123] 可以根据方案1制备式I的化合物。羧酸1与胺2在DMF(N,N-二甲基甲酰胺)中的1-[双(二甲基氨基)亚甲基]-1H-1,2,3-三唑并[4,5-b]吡啶鎓3-氧化六氟磷酸酯(HATU)介导的酰胺偶联反应生成结构3。在相同的条件下,胺4与5反应生成结构6。

[0124] 方案1

1 2 3

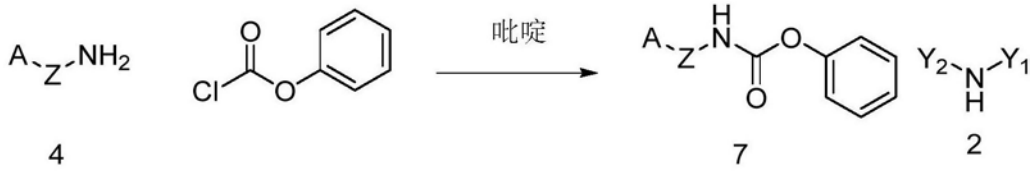
[0125]



4 5 6

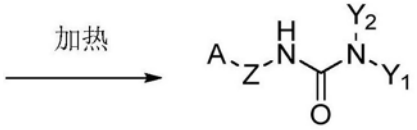
[0126] 可以根据方案2制备另一种式I的化合物。胺4与氯甲酸苯酯的偶合得到结构7,用胺2处理所述结构7,得到脲9。

[0127] 方案2



4 7 2

[0128]

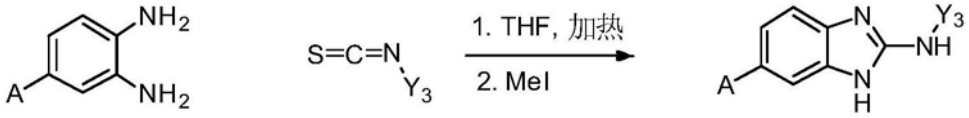


9

[0129] 可以根据方案3制备式V的化合物。将苯胺二胺10和异硫氰酸酯11在THF中加热，并用碘甲烷将所得的硫脲环化，得到氨基咪唑12。

[0130] 方案3

[0131]



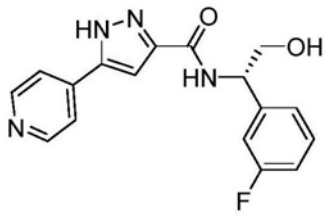
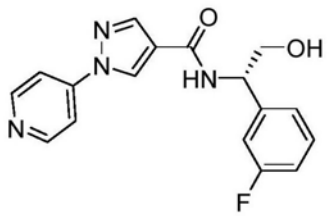
10 11 12

[0132] 实施例2.激酶抑制剂化合物

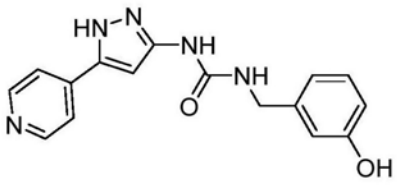
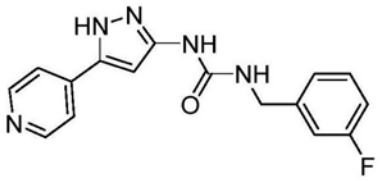
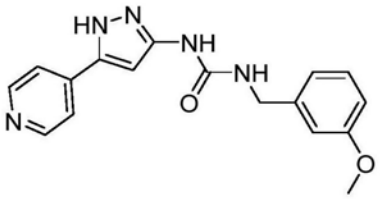
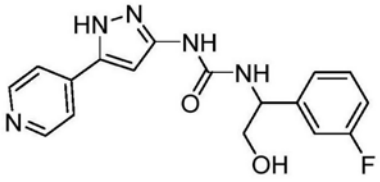
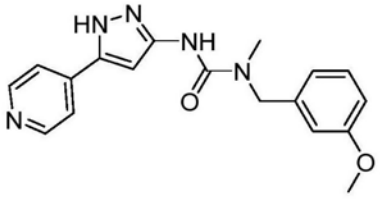
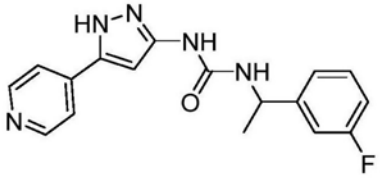
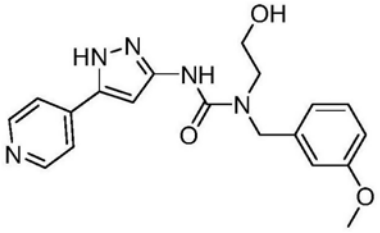
[0133] 阐明本发明的非限制性示例包括表1中所显示的那些。

[0134] 表1.激酶抑制剂化合物的非限制性示例。除非特别说明，具有手性中心的实施例化合物代表相应的R和S对映异构体的外消旋混合物，并且所有的外消旋体和分离的对映异构体均在本发明的范围内。

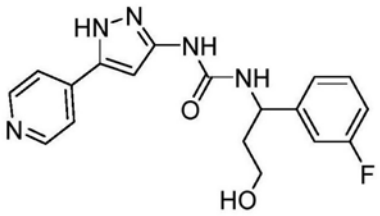
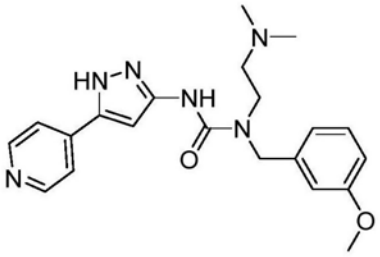
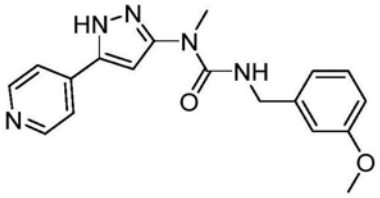
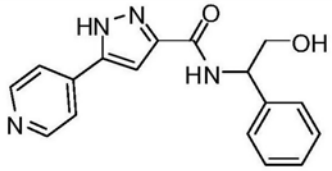
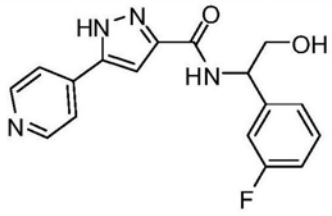
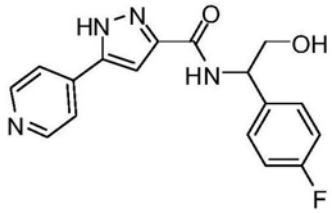
[0135]

ID	结构	M+1
1		327
2		327

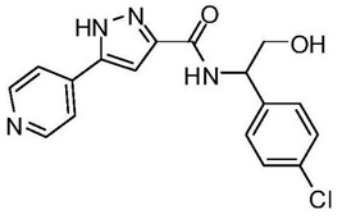
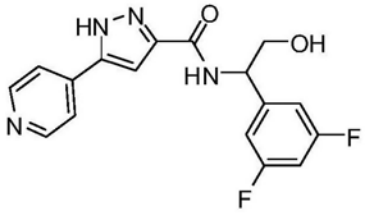
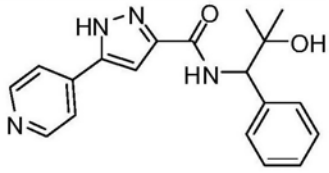
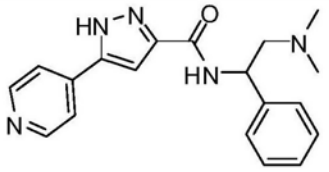
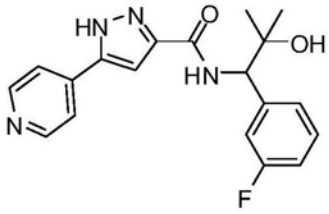
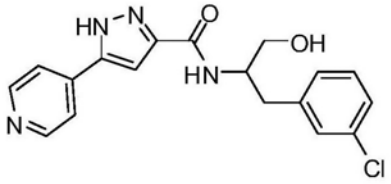
[0136]

ID	结构	M+1
3		310
4		312
5		324
6		342
7		338
8		326
9		368

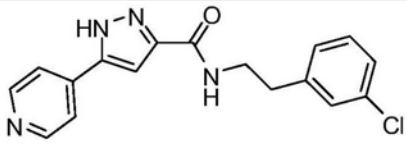
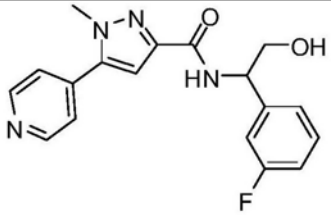
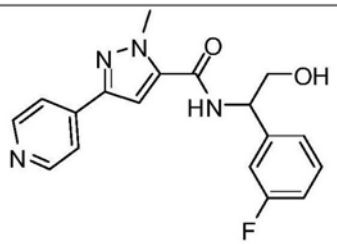
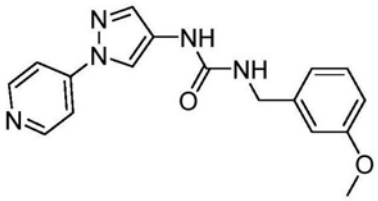
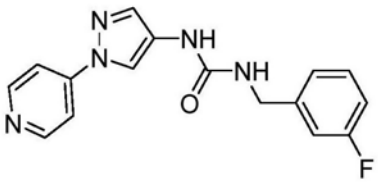
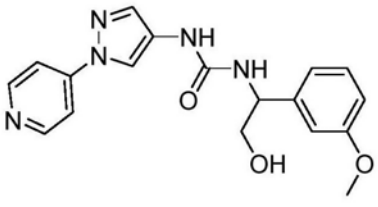
[0137]

ID	结构	M+1
10		356
11		395
12		338
13		309
14		327
15		327

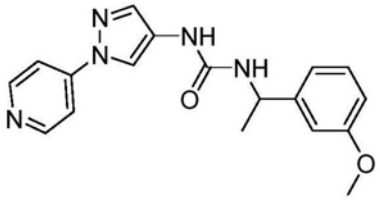
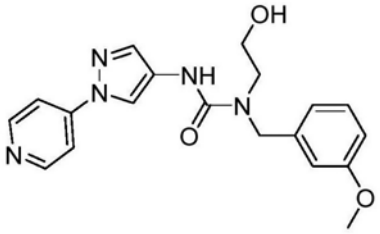
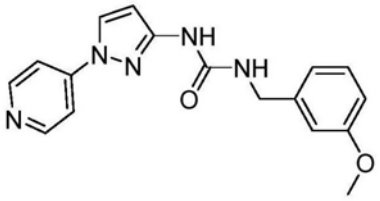
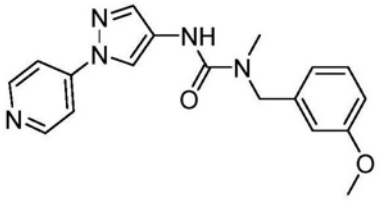
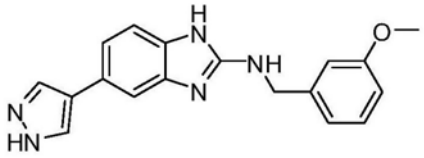
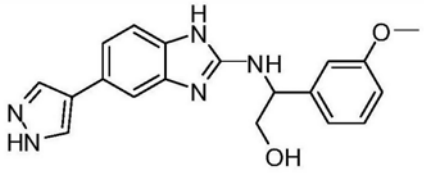
[0138]

ID	结构	M+1
16		343
17		345
18		337
19		336
20		355
21		357

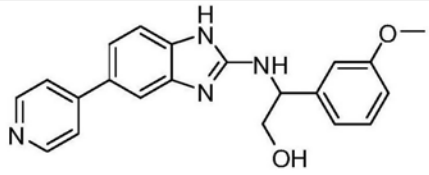
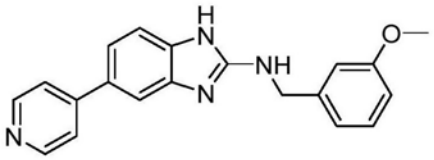
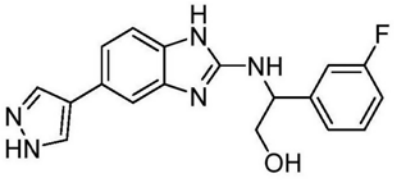
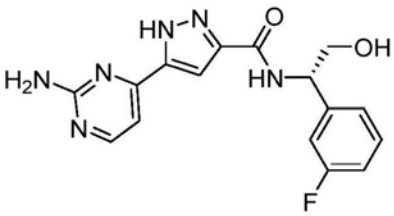
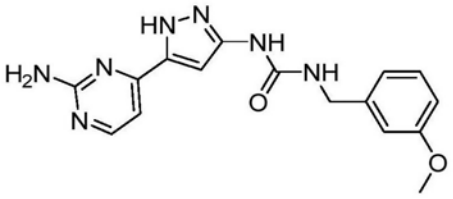
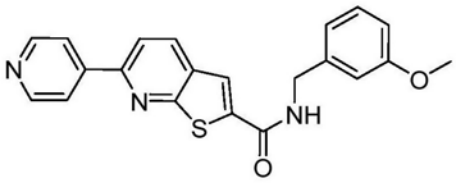
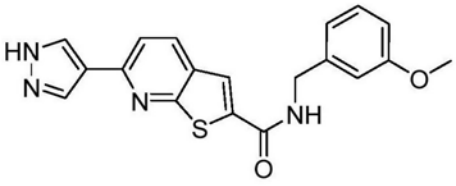
[0139]

ID	结构	M+1
22		327
23		341
24		341
25		324
26		312
27		354

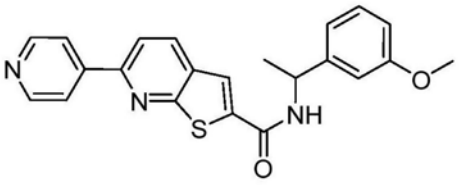
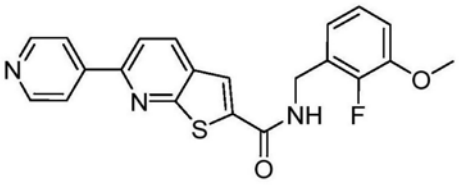
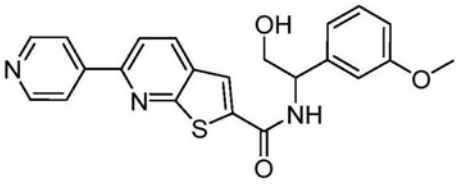
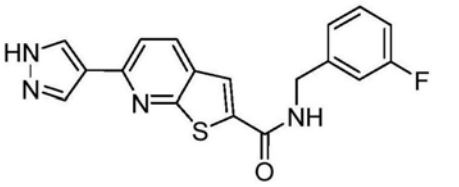
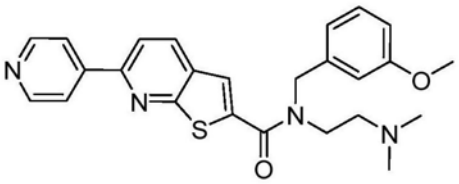
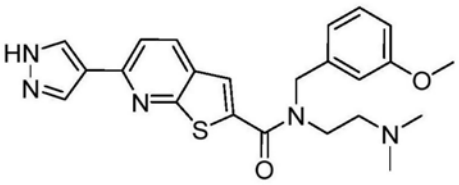
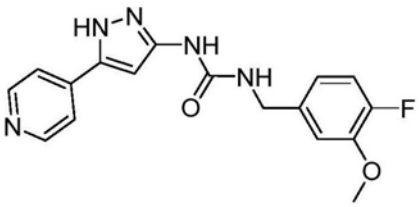
[0140]

ID	结构	M+1
28		338
29		368
30		324
31		338
32		320
33		350

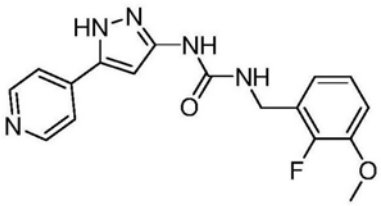
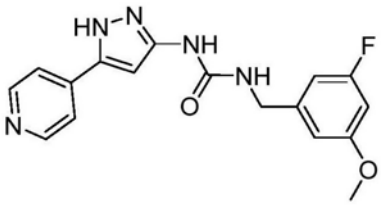
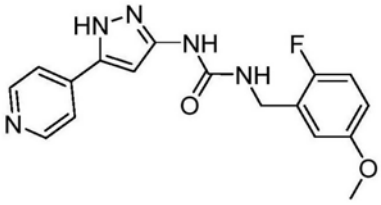
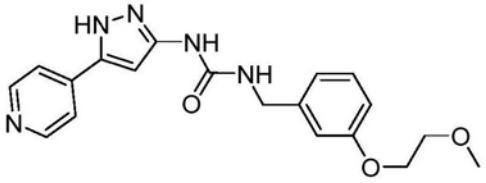
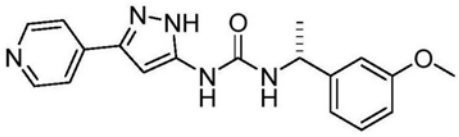
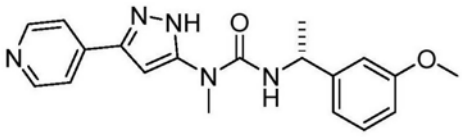
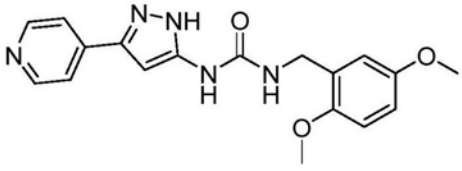
[0141]

ID	结构	M+1
34		361
35		331
36		338
37		343
38		340
39		376
40		365

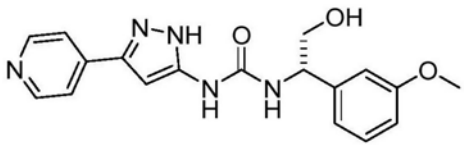
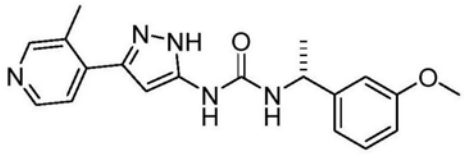
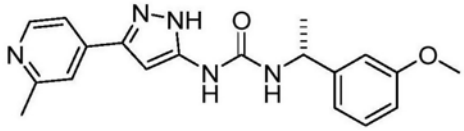
[0142]

ID	结构	M+1
41		390
42		394
43		406
44		353
45		447
46		436
47		342

[0143]

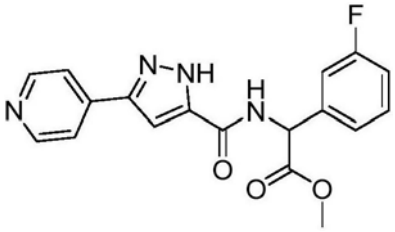
ID	结构	M+1
48		342
49		342
50		342
51		368
52		338
53		352
54		354

[0144]

ID	结构	M+1
55		354
56		352
57		352

[0145] 实施例3.化合物14的合成

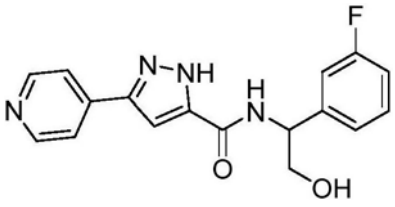
[0146] 步骤1

[0147] 

[0148] 2-(3-氟苯基)-2-(3-(吡啶-4-基)-1H-吡唑-5-甲酰胺基)乙酸甲酯

[0149] 向3-(吡啶-4-基)-1H-吡唑-5-羧酸(95mg,0.50mmol)、2-氨基-2-(3-氟苯基)乙酸甲酯盐酸盐(143mg,0.65mmol)和二异丙基乙胺(0.26mL,1.5mmol)在DMF的混合物中加入HATU(248mg,0.65mmol)。将反应物在室温搅拌3h,用水淬灭并用乙酸乙酯萃取。将有机层干燥,浓缩并通过BIOTAGE®柱色谱法纯化,以得到2-(3-氟苯基)-2-(3-(吡啶-4-基)-1H-吡唑-5-甲酰胺基)乙酸甲酯(126mg)。

[0150] 步骤2

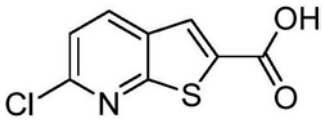
[0151] 

[0152] 化合物14

[0153] 向2-(3-氟苯基)-2-(3-(吡啶-4-基)-1H-吡唑-5-甲酰胺基)乙酸甲酯(62mg,0.17mmol)在MeOH的溶液中加入硼氢化钠(13mg,0.34mmol)。将反应物搅拌过夜,用NaOH(1N)淬灭并浓缩。通过C-18BIOTAGE®柱色谱法纯化残余物,以得到化合物14(29mg)。

[0154] 实施例4.化合物39的合成

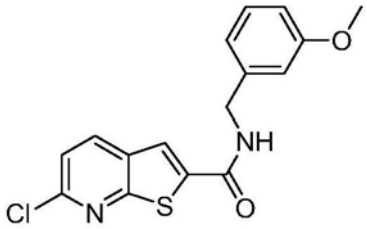
[0155] 步骤1

[0156] 

[0157] 6-氯噻吩并[2,3-b]吡啶-2-羧酸

[0158] 在-40℃,向2-溴-6-氯噻吩并[2,3-b]吡啶(100mg,0.40mmol)的乙醚混悬液中滴加正丁基锂(0.29mL,2.5M,0.72mmol)。将反应物搅拌0.5h,用过量的干冰淬灭,并在水和乙酸乙酯之间分配。将有机层干燥,浓缩并通过C-18BIOTAGE®柱色谱法纯化,以得到6-氯噻吩并[2,3-b]吡啶-2-羧酸(36mg)。

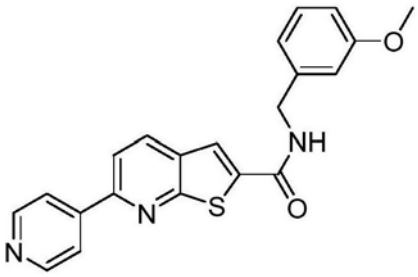
[0159] 步骤2

[0160] 

[0161] 6-氯-N-(3-甲氧基苄基)噻吩并[2,3-b]吡啶-2-甲酰胺

[0162] 按照实施例3中步骤2的合成方法,由6-氯噻吩并[2,3-b]吡啶-2-羧酸制备6-氯-N-(3-甲氧基苄基)噻吩并[2,3-b]吡啶-2-甲酰胺。

[0163] 步骤3

[0164] 

[0165] 化合物39

[0166] 将6-氯-N-(3-甲氧基苄基)噻吩并[2,3-b]吡啶-2-甲酰胺(25mg,0.075mmol)、吡啶-4-硼酸(30mg,0.22mmol)、[1,1'-双(二苯基膦基)二茂铁]二氯化钯(II)(5mg,5%)和碳酸铯(95mg,0.3mmol)在1,4-二氧六环中的混合物加热至100℃,并在氮气氛下搅拌过夜。通过硅藻土垫过滤混合物。将滤液浓缩,并通过BIOTAGE®C-18柱层析法纯化,以得到化合物39(12mg)。

[0167] 实施例5.ROCK1和ROCK2激酶抑制测试

[0168] 以下测试方案用于测量肽底物(FAM-KKLRRTLSVA-OH,其中FAM为羧基荧光素)的磷酸化。通过毛细管电泳测得肽的纯度>98%。肽被蛋白激酶ROCK1或ROCK2磷酸化。将ROCK1或ROCK2酶、底物和辅因子(ATP和Mg^{2+})组合在微量滴定板的孔中,并在25℃温育3小时。在温育结束时,通过加入含有EDTA的缓冲液来淬灭反应。使用来自Caliper Life Sciences(霍普金顿市,马萨诸塞州)的基于微流体的LABCHIP®3000药物发现系统(Drug Discovery System),通过电泳分离并定量底物和产物。

[0169] 测试混合物的组分为:

[0170] 100mM HEPES,pH 7.5

[0171] 0.1%BSA

[0172] 0.01%Triton X-100

[0173] 1mM DTT

[0174] 10mM $MgCl_2$

[0175] 10μM原钒酸钠

[0176] 10μMβ-磷酸甘油

[0177] 5μM ATP(对于ROCK1)或7μM ATP(对于ROCK2)

[0178] 1%DMSO(根据化合物)

[0179] 1.25μM FAM-KKLRRTLSVA-OH

[0180] 3nM ROCK1或2.5nM ROCK2酶

[0181] 使用LABCHIP®3000毛细管电泳仪,通过电泳分离存在于每个样品中的底物和产物肽。当底物和产物肽被分离时,观察到两个荧光峰。底物和产物峰的相对荧光强度的变化是反映酶活性的测量的参数。使用HTS Well Analyzer软件(Caliper Life Sciences,霍普金顿市,马萨诸塞州)分析毛细管电泳图(RDA采集文件)。每个样品中的激酶活性被确定为产物与总和的比例(PSR):P/(S+P),其中P为产物肽的峰高度,S为底物肽的峰高度。对于每种化合物,在不同的浓度(12个浓度的化合物,其被3X稀释区间(dilution interval)间隔)测量酶活性。制备阴性对照样品(在不存在抑制剂的情况下0%抑制)和阳性对照样品(在20mM EDTA的存在下100%抑制)一式四份,并用于计算在每个浓度的每种化合物的抑制值%。使用以下方程式确定抑制百分比(Pinh):

[0182] Pinh=(PSR0%-PSRinh)/(PSR0%-PSR100%)*100

[0183] 其中PSRinh为在抑制剂的存在下的产物总和比例,PSR0%为不存在抑制剂时的平均产物总和比例,PSR100%为100%抑制对照样品中的平均产物总和比例。使用XLfit 4软件(IBDS),通过4参数S形剂量-响应模型,通过拟合抑制曲线(Pinh相比于抑制剂浓度)来确定抑制剂的IC_{50}值。

[0184] 该测试可以用于测试表1中确定的每种示例化合物的活性。预计这些化合物中的每一种都将表现出对蛋白激酶ROCK1和/或ROCK2的抑制。

[0185] 实施例6.细胞活力测试

[0186] 在不同浓度的上面列举的化合物的存在下,在不同时间点的细胞活力被用于评价细胞毒性和化合物对细胞增殖的作用。表2总结了本发明的化合物在K562或MV411细胞系中的IC_{50}(或活性百分比)数据。

[0187] 细胞活力测试-通过来自于Promega(麦迪逊市,WI)的CELLTITER-GlO®细胞活力测试物来测量细胞活力。CELLTITER-GlO®冷光细胞活力测试是一种基于定量当前的ATP来确定培养物中活细胞的数量的均质方法(homogeneous method),所述ATP标志着代谢活性的细胞的存在。处理后,将CELLTITER-GlO®加入到处理孔中,并在37℃温育。使用Molecular Devices Spectramax酶标仪测定发冷光值。

[0188] 实验设计

[0189] 单个试剂研究-将细胞培养至70%融合,胰蛋白酶消化,计数,并以$2.5x10^3$-$5x10^3$个细胞/孔的终浓度接种于96孔平底板中(第0天)。使细胞在生长介质中温育24小时。在第1天开始用测试试剂或标准试剂处理,并持续72小时。在第72小时的时间点,含有介质的处理

物被去除。通过如上面所描述的CELLTITER-GLO®细胞活力测试物将活细胞数定量。这些研究的结果用于计算每种化合物的IC_{50}值(抑制对照的50％的细胞生长的药物浓度)。

[0190] 数据收集-对于单个药物和组合的研究,收集来自每个实验的数据,并使用以下计算将其表示为细胞生长％:

[0191] 细胞生长％＝($f_{测试}/f_{载体}$) x 100

[0192] 其中$f_{测试}$为测试的样品的发冷光值,$f_{载体}$为溶解药物的载体的发冷光值。使用Prism6软件(GraphPad)使用以下方程式生成剂量响应曲线和IC_{50}值:

[0193] $Y=\underline{(顶部-底部)}/(1+10^{((\log IC50-X)\times 坡率)})$

[0194] 其中X为浓度的对数,Y为响应。Y从底部开始,以S形到达顶部。

[0195] 实施例7.ROCK1和ROCK2激酶抑制和细胞活力测试结果

[0196] 按照实施例5和6中概述的方案,用来自表1的化合物测试ROCK1和ROCK2激酶抑制和癌细胞活力。如表2所示,化合物表现出对ROCK1和ROCK2激酶和癌细胞生长的抑制。

[0197] 实验还评价了化合物抑制在Flt3基因中携带有突变的癌细胞生长的选择性。MV411细胞系表达具有基因的内部串联重复(ITD)的Flt3的突变等位基因。参见Quentmeier等人,“FLT3Mutations in Acute Myeloid Leukemia Cell Lines,”Leukemia 17(1),2003,120-124。K562是一种不表达FLT3蛋白的慢性粒细胞白血病细胞系。参见Grafone等人,“Monitoring of FLT3Phosphorylation Status and Its Response to Drugs By Flow Cytometry in AML Blast Cells,”Hematol Oncol.26(3),2008,159-166。患有ITD-$FLT3^{+}$急性髓性白血病(AML)的患者预后极差。令人惊讶地,许多化合物对MV11细胞表现出比对K562细胞更高的功效,提示这些化合物可以用于有效治疗ITD-$FLT3^{+}$AML。

[0198] 表2.ROCK1和ROCK2激酶抑制和细胞活力

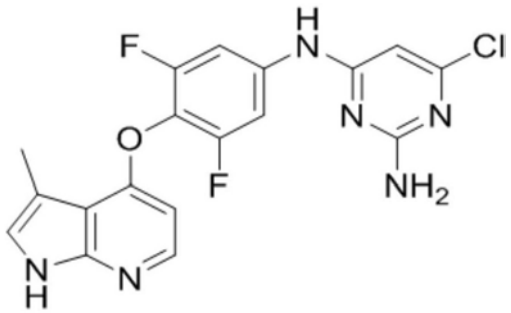
[0199]

化合物 ID	ROCK1 IC_{50} (nM)	ROCK2 IC_{50} (nM)	K562* (μM)	MV411* (μM)	FLT3-ITD$^+$选择性 (K562/MV411)
1	207	98	>100	67.6	>1
3			>100	43.7	>2
5	73	16.1	43.6	10.2	4
7	102	22.9	89.1	7.6	12
9	237	39.1	97.2	39.8	2
11	63.6	22.1	>100	14.5	>7
25	130	28.7	85	34	3
40	65.1	17.4	>100	7.1	>14
47			17.8	7.8	2
48	6400	1870			
49			17.8	7.8	2
50	1010	239	>100	7.8	>13
51			>100	17.0	>6
52	34	8.7	>100	11.2	>9
53			64.6	93.3	1
54			>100	12.6	>8
化合物 A**	3.3	2.8	0.8	0.7	1

[0200] *MV411为ITD-FLT3$^+$,K562不表达ITD-FLT3。如Onish等人,“Internal Tandem Duplication Mutations in FLT3Gene Augment Chemotaxis to Cxcl12Protein by Blocking the Down-regulation of the Rho-associated Kinase via the Cxcl12/Cxcr4Signaling Axis,”J.Biol.Chem.289(45),2014,31053-31065所报道,可以操纵Rho相关激酶用于治疗ITD-FLT3$^+$AML。

[0201] **化合物A如下所示,并且其在Schirok等人,“Design and Synthesis of Potent and Selective Azaindole-Based Rho Kinase(ROCK)Inhibitors,”ChemMedChem 3,2008,1893-1904中被描述。

[0202]



化合物 A

[0203] 除非另外定义,本文中的所有技术和科学术语具有与本发明所属领域的普通技术人员通常所理解的相同的含义。所有引用的出版物、专利和专利出版物通过引用整体并入

本文以用于所有目的。

[0204] 应该理解的是，所公开的发明不限于所描述的特定的方法、方案和材料，因为这些可以变化。还应该理解的是，本文使用的术语仅用于描述特定实施方案的目的，并不旨在限制本发明的范围，本发明的范围将仅由所附权利要求书限制。

[0205] 仅使用常规实验，本领域技术人员将认可或能够确定本文所描述的本发明的具体实施方案的许多等价物。这些等价物旨在被所附的权利要求书涵盖。