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Green et al.(10) **Pub. No.: US 2006/0122185 A1**(43) **Pub. Date: Jun. 8, 2006**(54) **BICYCLIC INHIBITORS OF RHO KINASE****Publication Classification**(76) Inventors: **Jeremy Green**, Waltham, MA (US);
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544/350; 546/117(21) Appl. No.: **11/285,516**(22) Filed: **Nov. 22, 2005****Related U.S. Application Data**(60) Provisional application No. 60/630,115, filed on Nov.
22, 2004.(57) **ABSTRACT**

The present invention relates to compounds useful as inhibitors of protein kinases, particularly of ROCK. The invention also provides pharmaceutically acceptable compositions comprising said compounds and methods of using the compositions in the treatment of various disease, conditions, or disorders.

BICYCLIC INHIBITORS OF RHO KINASE**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of U.S. Provisional Application No. 60/630,115, filed Nov. 22, 2005, which is herein incorporated by reference.

TECHNICAL FIELD OF INVENTION

[0002] The present invention relates to compounds useful as inhibitors of protein kinases. The invention also provides pharmaceutically acceptable compositions comprising the compounds of the invention and methods of using the compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. Accordingly, there has been a substantial effort in medicinal chemistry to find protein kinase inhibitors that are effective as therapeutic agents.

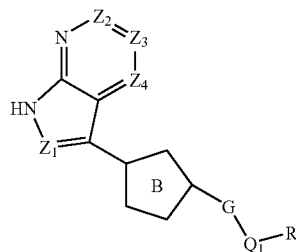
[0004] One kinase family of interest is Rho-associated coiled-coil forming protein serine/threonine kinase (ROCK), which is believed to be an effector of Ras-related small GTPase Rho. The ROCK family includes p160ROCK (ROCK-1) and ROK α /Rho-kinase/ROCK-II, protein kinase PKN, and citron and citron kinase. The ROCK family of kinases have been shown to be involved in a variety of functions including Rho-induced formation of actin stress fibers and focal adhesions and in downregulation of myosin phosphatase, platelet activation, aortic smooth muscle contraction by various stimuli, thrombin-induced responses of aortic smooth muscle cells, hypertrophy of cardiomyocytes, bronchial smooth muscle contraction, smooth muscle contraction and cytoskeletal reorganization of non-muscle cells, activation of volume-regulated anion channels, neurite retraction, neutrophil chemotaxis, wound healing, tumor invasion and cell transformation. More specifically, ROCK has been implicated in various diseases and disorders including hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia and atherosclerosis. Accordingly, the development of inhibitors of ROCK kinase would be useful as therapeutic agents for the treatment of disorders implicated in the ROCK kinase pathway.

[0005] Accordingly, there is a great need to develop inhibitors of ROCK that would be useful in treating various diseases or conditions associated with ROCK, particularly given the inadequate treatments currently available for the majority of these disorders.

SUMMARY OF THE INVENTION

[0006] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions

thereof, are effective as inhibitors of ROCK. These compounds have the general formula I:



I

[0007] or a pharmaceutically acceptable derivative thereof, wherein ring B, Z¹, Z², Z³, Z⁴, R³, G and Q¹ are as defined below.

[0008] These compounds, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of disorders, including, without limitation, hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia and atherosclerosis.

DETAILED DESCRIPTION OF THE INVENTION**[0009] Definitions**

[0010] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, and the Handbook of Chemistry and Physics, 75th Ed. 1994. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Smith, M. B. and March, J., eds. John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0011] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group. When more than one position in a given structure can be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position.

[0012] As described herein, when the term "optionally substituted" precedes a list, said term refers to all of the

subsequent substitutable groups in that list. If a substituent radical or structure is not identified or defined as “optionally substituted”, the substituent radical or structure is unsubstituted. For example, if X is halogen; optionally substituted C_{1-3} alkyl or phenyl; X may be either optionally substituted alkyl or optionally substituted phenyl. Likewise, if the term “optionally substituted” follows a list, said term also refers to all of the substitutable groups in the prior list unless otherwise indicated. For example: if X is halogen, C_{1-3} alkyl or phenyl wherein X is optionally substituted by J^X , then both C_{1-3} alkyl and phenyl may be optionally substituted by J^X . As is apparent to one having ordinary skill in the art, groups such as H, halogen, NO_2 , CN, NH_2 , OH, or OCF_3 would not be included because they are not substitutable groups.

[0013] Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable”, as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, preferably, their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40° C. or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0014] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation. Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. Further examples of aliphatic groups include methyl, ethyl, propyl, butyl, isopropyl, isobutyl, vinyl, and sec-butyl.

[0015] The term “cycloaliphatic” (or “carbocycle” or “cycloalkyl”) refers to a monocyclic C_3 - C_8 hydrocarbon or bicyclic C_8 - C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule, and wherein any individual ring in said bicyclic ring system has 3-7 members. Suitable cycloaliphatic groups include, but are not limited to, cycloalkyl, cycloalkenyl, and cycloalkynyl. Further examples of aliphatic groups include cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cycloheptenyl.

[0016] The term “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” as used herein refers to a monocyclic, bicyclic, or tricyclic ring system in which one or more ring members are an independently selected heteroatom and that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule.

In some embodiments, the “heterocycle”, “heterocyclyl”, “heterocycloaliphatic”, or “heterocyclic” group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0017] Examples of heterocyclic rings include, but are not limited to, the following monocycles: 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl; and the following bicycles: 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, benzodithiane, and 1,3-dihydro-imidazol-2-one.

[0018] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon, including any oxidized form of nitrogen, sulfur, phosphorus, or silicon, the quaternized form of any basic nitrogen, or a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl).

[0019] The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

[0020] The term “alkoxy”, or “thioalkyl”, as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[0021] The terms “haloalkyl”, “haloalkenyl” and “haloalkoxy” means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term “halogen” means F, Cl, Br, or I.

[0022] The term “aryl” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refers to monocyclic, bicyclic, and tricyclic carbocyclic ring systems having a total of six to fourteen ring members, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 3 to 7 ring members and that has a single point of attachment to the rest of the molecule. The term “aryl” may be used interchangeably with the term “aryl ring”. Examples of aryl rings would include phenyl, naphthyl, and anthracene.

[0023] The term “heteroaryl”, used alone or as part of a larger moiety as in “heteroaralkyl” or “heteroarylalkoxy”, refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, wherein each ring in the system contains 3 to 7 ring members and that has a single point of attachment to the rest of the molecule. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic”.

[0024] Further examples of heteroaryl rings include the following monocycles: 2-furanyl, 3-furanyl, N-imidazolyl,

2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, pyrazinyl, 1,3,5-triazinyl, and the following bicycles: benzimidazolyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), purinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

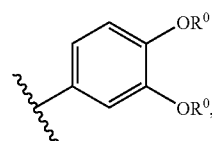
[0025] In some embodiments, an aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents. Suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group are selected from those listed in the definition of J^Q , J^R , J^V , J^U and J^X below. Other suitable substituents include: halogen; $-R^\circ$; $-OR^\circ$; $-SR^\circ$; 1,2-methylenedioxy; 1,2-ethylenedioxy; phenyl (Ph) optionally substituted with R° ; $-O(Ph)$ optionally substituted with R° ; $-(CH_2)_{1-2}(Ph)$, optionally substituted with R° ; $-CH=CH(Ph)$, optionally substituted with R° ; $-NO_2$; $-CN$; $-N(R^\circ)_2$; $-NR^\circ-C(O)R^\circ$; $-NR^\circ-C(S)R^\circ$; $-NR^\circ-C(O)N(R^\circ)_2$; $-NR^\circ-C(S)N(R^\circ)_2$; $-NR^\circ-CO_2R^\circ$; $-NR^\circ-NR^\circ-C(O)R^\circ$; $-C(O)N(R^\circ)_2$; $-NR^\circ-NR^\circ-CO_2R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-CO_2R^\circ$; $-C(O)R^\circ$; $-C(S)R^\circ$; $-C(O)N(R^\circ)_2$; $-C(S)N(R^\circ)_2$; $-OC(O)N(R^\circ)_2$; $-OC(O)R^\circ$; $-C(O)N(OR^\circ)R^\circ$; $-C(NOR^\circ)R^\circ$; $-S(O)_2R^\circ$; $-S(O)_3R^\circ$; $-SO_2N(R^\circ)_2$; $-S(O)R^\circ$; $-NR^\circ-SO_2N(R^\circ)_2$; $-NR^\circ-SO_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(=NH)-N(R^\circ)_2$; or $-(CH_2)_{0-2}NHC(O)R^\circ$; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, $-O(Ph)$, or $-CH_2(Ph)$, or, two independent occurrences of R° , on the same substituent or different substituents, taken together with the atom(s) to which each R° group is bound, form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8-membered cycloalkyl ring, wherein said heteroaryl or heterocyclyl ring has 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group of R° are selected from NH_2 , $NH(C_{1-4} \text{ aliphatic})$, $N(C_{1-4} \text{ aliphatic})_2$, halogen, $C_{1-4} \text{ aliphatic}$, OH , $O(C_{1-4} \text{ aliphatic})$, NO_2 , CN , CO_2H , $CO_2(C_{1-4} \text{ aliphatic})$, $O(\text{halo } C_{1-4} \text{ aliphatic})$, or $\text{halo}(C_{1-4} \text{ aliphatic})$, wherein each of the foregoing $C_{1-4} \text{ aliphatic}$ groups of R° is unsubstituted.

[0026] In some embodiments, an aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: $=O$, $=S$, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2(\text{alkyl})$, $=NNHSO_2(\text{alkyl})$, or $=NR^*$, where each R^* is independently selected from hydrogen or an optionally substituted C_{1-6} aliphatic. Optional substituents on the aliphatic group of R^* are selected from NH_2 , $NH(C_{1-4}$

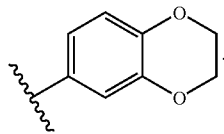
aliphatic), $N(C_{1-4} \text{ aliphatic})_2$, halogen, $C_{1-4} \text{ aliphatic}$, OH , $O(C_{1-4} \text{ aliphatic})$, NO_2 , CN , CO_2H , $CO_2(C_{1-4} \text{ aliphatic})$, $O(\text{halo } C_{1-4} \text{ aliphatic})$, or $\text{halo}(C_{1-4} \text{ aliphatic})$, wherein each of the foregoing $C_{1-4} \text{ aliphatic}$ groups of R^* is unsubstituted.

[0027] In some embodiments, optional substituents on the nitrogen of a non-aromatic heterocyclic ring include $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, an optionally substituted C_{1-6} aliphatic, optionally substituted phenyl, optionally substituted $-O(Ph)$, optionally substituted $-CH_2(Ph)$, optionally substituted $-(CH_2)_{1-2}(Ph)$; optionally substituted $-CH=CH(Ph)$; or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, two independent occurrences of R^+ , on the same substituent or different substituents, taken together with the atom(s) to which each R^+ group is bound, form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8-membered cycloalkyl ring, wherein said heteroaryl or heterocyclyl ring has 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Optional substituents on the aliphatic group or the phenyl ring of R^+ are selected from NH_2 , $NH(C_{1-4} \text{ aliphatic})$, $N(C_{1-4} \text{ aliphatic})_2$, halogen, $C_{1-4} \text{ aliphatic}$, OH , $O(C_{1-4} \text{ aliphatic})$, NO_2 , CN , CO_2H , $CO_2(C_{1-4} \text{ aliphatic})$, $O(\text{halo } C_{1-4} \text{ aliphatic})$, or $\text{halo}(C_{1-4} \text{ aliphatic})$, wherein each of the foregoing $C_{1-4} \text{ aliphatic}$ groups of R^+ is unsubstituted.

[0028] As detailed above, in some embodiments, two independent occurrences of R° (or R^+ , or any other variable similarly defined herein), may be taken together with the atom(s) to which each variable is bound to form a 5-8-membered heterocyclyl, aryl, or heteroaryl ring or a 3-8-membered cycloalkyl ring. Exemplary rings that are formed when two independent occurrences of R° (or R^+ , or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound include, but are not limited to the following: a) two independent occurrences of R° (or R^+ , or any other variable similarly defined herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^\circ)_2$, where both occurrences of R° are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R° (or R^+ , or any other variable similarly defined herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two occurrences of OR°



these two occurrences of R° are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:



It will be appreciated that a variety of other rings can be formed when two independent occurrences of R° (or R^+ , or any other variable similarly defined herein) are taken together with the atom(s) to which each variable is bound and that the examples detailed above are not intended to be limiting.

[0029] In some embodiments, an alkyl or aliphatic chain can be optionally interrupted with another atom or group. This means that a methylene unit of the alkyl or aliphatic chain is optionally replaced with said other atom or group. Examples of such atoms or groups would include, but are not limited to, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{CO}_2-$, $-\text{OC(O)}-$, $-\text{C(O)CO}-$, $-\text{C(O)}-$, $-\text{C(O)NR}-$, $-\text{C(=N-CN)}-$, $-\text{NRCO}-$, $-\text{NRC(O)O}-$, $-\text{SO}_2\text{NR}-$, $-\text{NRSO}_2-$, $-\text{NRC(O)NR}-$, $-\text{OC(O)NR}-$, $-\text{NRSO}_2\text{NR}-$, $-\text{SO}-$, or $-\text{SO}_2-$, wherein R is defined herein. Unless otherwise specified, the optional replacements form a chemically stable compound. Optional interruptions can occur both within the chain and at either end of the chain; i.e. both at the point of attachment and/or also at the terminal end. Two optional replacements can also be adjacent to each other within a chain so long as it results in a chemically stable compound. Unless otherwise specified, if the replacement or interruption occurs at the terminal end, the replacement atom is bound to an H on the terminal end. For example, if $-\text{CH}_2\text{CH}_2\text{CH}_3$ were optionally interrupted with $-\text{O}-$, the resulting compound could be $-\text{OCH}_2\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, or $-\text{CH}_2\text{CH}_2\text{OH}$.

[0030] As described herein, a bond drawn from a substituent to the center of one ring within a multiple-ring system (as shown below), represents substitution of the substituent at any substitutable position in any of the rings within the multiple ring system. For example, Figure a represents possible substitution in any of the positions shown in Figure b.

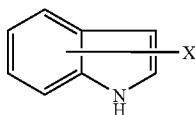


Figure a

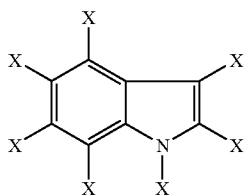


Figure b

[0031] This also applies to multiple ring systems fused to optional ring systems (which would be represented by dotted

lines). For example, in Figure c, X is an optional substituent both for ring A and ring B.

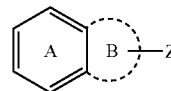


Figure c

[0032] If, however, two rings in a multiple ring system each have different substituents drawn from the center of each ring, then, unless otherwise specified, each substituent only represents substitution on the ring to which it is attached. For example, in Figure d, Y is an optionally substituent for ring A only, and X is an optional substituent for ring B only.

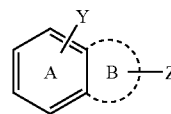


Figure d

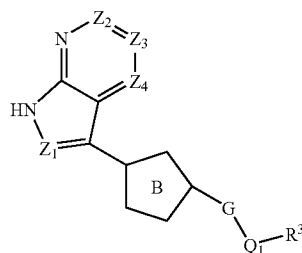
[0033] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention.

[0034] Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0035] As represented herein, the left-hand bond of Ring B is attached to the bicyclic heteroaryl ring and the right-hand bond of Ring B is attached to radical G.

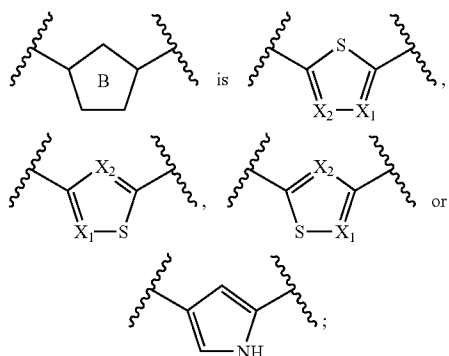
[0036] Description of Compounds of the Invention:

[0037] The present invention relates to a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:
wherein



[0038] Z_1 , Z_2 , Z_3 and Z_4 are each independently selected from N or CR^1 , wherein at least one of Z_1 , Z_2 , or Z_4 is N;

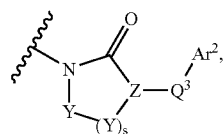
[0039] each R^1 is independently selected from H, halogen, $-CN$, $-NO_2$, or $-V_mR^1$;

[0040] G is $-NR^2$ or $-CO-$;

[0041] Q^1 is $-CO-$, $-SO_2-$, $-NR^2$, $-NR^2CO-$, $-CONR^2-$, $-SO_2NR^2-$, or is a bond;

[0042] R^2 is $-U_nR^n$;

[0043] R^3 is Q^2-Ar^1 , or when G is $-NR^2$, R^2 and Q^1-R^3 , taken together with the nitrogen atom, may form the cyclic group:



where s is 1 or 2, Z is CH or N; wherein each occurrence of Y is independently $-CO-$, $-CS-$, $-SO_2-$, $-O-$, $-S-$, $-NR^5-$, or $-C(R^5)_2-$, and R^5 is U_nR^n ;

[0044] X_1 and X_2 are each independently selected from CR or N;

[0045] each occurrence of R^4 is independently selected from halogen, CN, NO_2 , or V_mR ;

[0046] each occurrence of U or V is independently selected from an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by $-NR-$, $-S-$, $-O-$, $-CS-$, $-CO_2-$, $-OCO-$, $-CO-$, $-COCO-$, $-CONR-$, $-NRCO-$, $-NRCO_2-$, $-SO_2NR-$, $-NRSO_2-$, $-CONRNR-$, $-NRCONR-$, $-OCONR-$, $-NRNR-$, $-NRSO_2NR-$, $-SO-$, $-SO_2-$, $-PO-$, $-PO_2-$, or $-POR-$;

[0047] m and n are each independently 0 or 1;

[0048] each occurrence of R is independently selected from hydrogen or a C_{1-6} aliphatic group, wherein said aliphatic group is optionally substituted with up to five occurrences of J^R ;

[0049] each occurrence of R' is independently selected from hydrogen, a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said aliphatic group, monocyclic ring or bicyclic ring is optionally substituted with up to five occurrences of $J^{R'}$;

[0050] R'' is selected from hydrogen, a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said aliphatic group, monocyclic ring or bicyclic ring is optionally substituted with up to five occurrences of $J^{R''}$;

[0051] or two occurrences of R, R' and R'' , in any combination thereof, are taken together with the atom(s) to which they are bound to form a 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said monocyclic or bicyclic ring is optionally substituted with J^R ;

[0052] each occurrence of J^R , $J^{R'}$ and $J^{R''}$ is independently selected from halogen, L, $-(L_p)-R^j$, $-(L_p)-N(R^j)_2$, $-(L_p)-SR^j$, $-(L_p)-OR^j$, $-(L_p)-(C_{3-10} \text{ cycloaliphatic})$, $-(L_p)-(C_{6-10} \text{ aryl})$, $-(L_p)-(5-10 \text{ membered heteroaryl})$, $-(L_p)-(5-10 \text{ membered heterocyclyl})$, oxo, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, $-(L_p)-NO_2$, $-(L_p)-CN$, $-(L_p)-OH$, $-(L_p)-CF_3$, $-CO_2R^j$, $-CO_2H$, $-COR^j$, $-COH$, $-OC(O)R^j$ or $-NC(O)R^j$; or any two J^R , $J^{R'}$ or $J^{R''}$ groups, on the same substituent or different substituents, together with the atom(s) to which each J^R , $J^{R'}$ or $J^{R''}$ group is bound, form a 5-7 membered saturated, unsaturated, or partially saturated ring;

[0053] R^j is H or C_{1-6} aliphatic; or two R^j groups or an R^j group and an R, R' or R'' group, together with the atom to which they are attached, optionally form a 3-6 membered cycloaliphatic or heterocyclyl, wherein said aliphatic, cycloaliphatic or heterocyclyl is optionally substituted with R^* , $-OR^*$, $-SR^*$, $-NO_2$, $-CF_3$, $-CN$, $-CO_2R^*$, $-COR^*$, $OCOR^*$ or $NHCOR^*$, wherein R^* is H or an unsubstituted C_{1-6} aliphatic;

[0054] L is a C_{1-6} aliphatic wherein up to three methylene units are replaced by $-NH-$, $-NR^L$, $-O-$, $-S-$, $-CO_2-$, $-OC(O)-$, $-C(O)CO-$, $-C(O)-$, $-C(O)NH-$, $-C(O)NR^6-$, $-C(=N-CN)-$, $-NHCO-$, $-NR^LCO-$, $-NHC(O)O-$, $-NR^L$, $-C(O)O-$, $-SO_2NH-$, $-SO_2NR^L-$, $-NHSO_2-$, $-NR^L$, $-NR^L$, $-NHC(O)NH-$, $-NR^L$, $-NHC(O)NR^L$, $-NR^L$, $-OC(O)NH-$, $-OC(O)NR^L$, $-NHSO_2NH-$, $-NR^L$, $-NHSO_2NR^L$, $-NR^L$, $-SO-$ or $-SO_2-$;

[0055] R^L is selected from C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl or

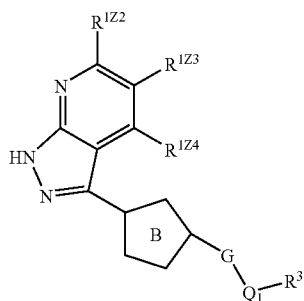
5-10 membered heterocyclyl; or two R^L groups, on the same substituent or different substituents, together with the atom(s) to which each R^L group is bound, form a 3-8 membered heterocyclyl;

[0056] each p is independently 0 or 1;

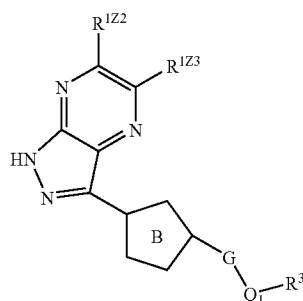
[0057] Q^2 and Q^3 are each independently selected from a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by $-NR'$ —, $-S$ —, $-O$ —, $-CS$ —, $-CO_2$ —, $-OCO$ —, $-CO$ —, $-COCO$ —, $-CONR'$ —, $-NR'CO$ —, $-NR'CO_2$ —, $-SO_2NR'$ —, $-NR'SO_2$ —, $-CONR'NR'$ —, $-NR'CONR'$ —, $-OCONR'$ —, $-NR'NR'$ —, $-NR'SO_2NR'$ —, $-SO$ —, $-SO_2$ —, $-PO$ —, $-PO_2$ —, or $-POR'$ —; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, $-CN$, $-NO_2$, or $-U_nR'$, or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

[0058] Ar^1 and Ar^2 are each independently selected from a C_{1-6} aliphatic, a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar^1 and Ar^2 are each optionally substituted with 0-5 independent occurrences of TR^7 ; wherein T is a bond or is a C_{1-6} alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by $-NR$ —, $-S$ —, $-O$ —, $-CS$ —, $-CO_2$ —, $-OCO$ —, $-CO$ —, $-COCO$ —, $-CONR$ —, $-NRCO$ —, $-NRCO_2$ —, $-SO_2NR$ —, $-NRSO_2$ —, $-CONRNR$ —, $-NRCONR$ —, $-OCONR$ —, $-NRNR$ —, $-NRSO_2NR$ —, $-SO$ —, $-SO_2$ —, $-PO$ —, $-PO_2$ —, or $-POR$ —; and each occurrence of R^7 is independently selected from $-R'$, halogen, $-NO_2$, $-CN$ or $=O$.

[0059] In another embodiment, a compound of the invention has one of formulae II-VII:



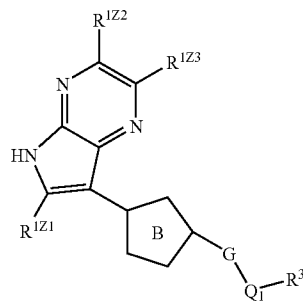
II



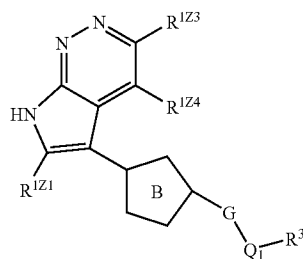
VI

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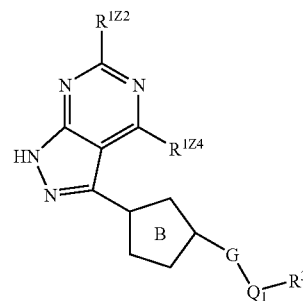
III



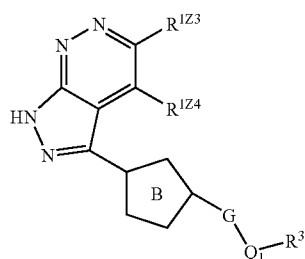
IV



V



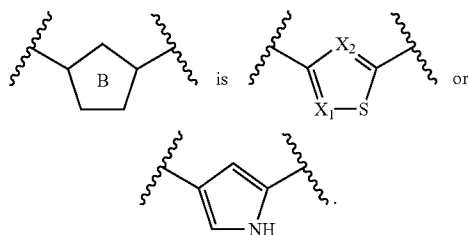
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VII

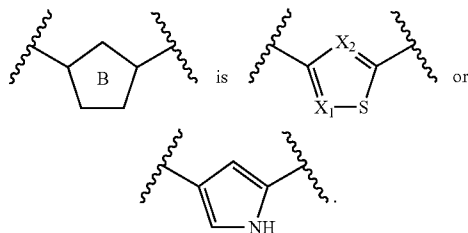
[0060] wherein R^{1Z1} , R^{1Z2} , R^{1Z3} and R^{1Z4} are each independently selected from H, halogen, $-\text{CN}$, $-\text{NO}_2$, or $-\text{V}_m\text{R}^1$. In a further embodiment, the compound has one of formulae II, III or VI.

[0061] In one embodiment, the compound is any one formulae I-VII and



In a further embodiment, the compound is either of formulae II, III or VI. In another embodiment, X_1 is CR^4 and X_2 is N or CR^4 . In a further embodiment, R^4 is H.

[0062] In one embodiment, the compound is any one of formulae I-VII and R^1 is independently selected from H, halogen or C_{1-3} aliphatic. In a further embodiment, the compound is either of formulae II, III or VI and

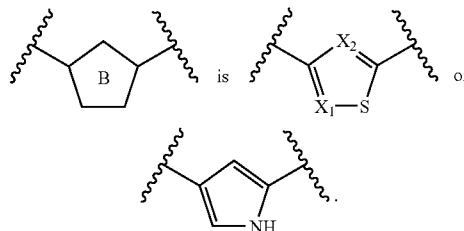


In yet a further embodiment, R^1 is independently selected from H or halogen.

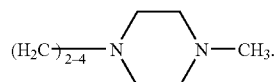
[0063] In one embodiment of formulae II-VII, R^{1Z1} , R^{1Z2} , R^{1Z3} and R^{1Z4} , if present, are each independently selected from H, halogen or C_{1-3} aliphatic. In a further embodiment, R^{1Z1} and R^{1Z2} , if present, are H. In yet another embodiment, R^{1Z3} and R^{1Z4} , if present, are H or halogen. In a further embodiment, R^{1Z3} and R^{1Z4} , if present, are H or F and at least one of R^{1Z3} and R^{1Z4} is H. In yet a further embodiment,

R^{1Z3} and R^{1Z4} , if present, are H. In another embodiment, R^{1Z1} , R^{1Z2} , R^{1Z3} and R^{1Z4} , if present, are H.

[0064] In one embodiment, the compound is any one of formulae I-VII and Q^1 is $-\text{CO}-$, $-\text{SO}_2-$, $-\text{NR}^2$, $-\text{NR}^2\text{CO}-$, $-\text{CONR}^2-$, $-\text{SO}_2\text{NR}^2-$. In a further embodiment, the compound is either of formulae II, III or VI and

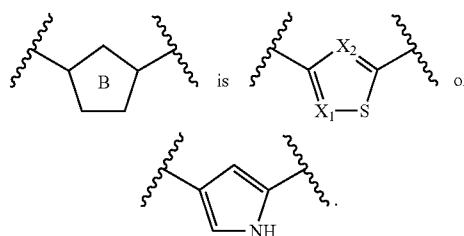


In a further embodiment, G is $-\text{NR}^2$ and Q^1 is $-\text{CO}-$, or G is $-\text{CO}-$ and Q^1 is $-\text{NR}^2-$. In yet a further embodiment, R^2 is H, $-\text{C}_{1-4}$ aliphatic, -cyclopropyl, $(\text{CH}_2)_{1-3}\text{OH}$ or



In a still further embodiment, R^2 is H.

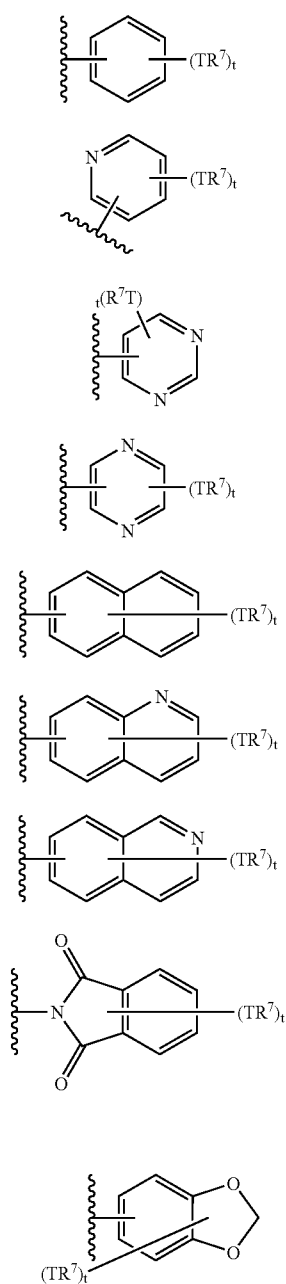
[0065] In another embodiment of the invention, the compound is any one of formulae I-VII and R^3 is $Q^2-\text{Ar}^1$. In a further embodiment, the compound is either of formulae II, III or VI and



In a further embodiment, Q^2 is $-(\text{CHR}^6)_q-$, $-(\text{CHR}^6)_q\text{O}-$, $-(\text{CHR}^6)_q\text{S}-$, $-(\text{CHR}^6)_q\text{S}(\text{O})_2-$, $-(\text{CHR}^6)_q\text{S}(\text{O})-$, $-(\text{CHR}^6)_q\text{NR}-$, or $-(\text{CHR}^6)_q\text{C}(\text{O})-$, wherein q is 0, 1, 2, or 3, and each R^6 is R^1 , $-\text{N}(\text{R})(\text{R}')$, $-(\text{CH}_2)_{1-4}\text{N}(\text{R})(\text{R}')$, $-(\text{CH}_2)_{1-4}\text{C}(\text{CH}_3)_2\text{N}(\text{R})(\text{R}')$, $-(\text{CH}_2)_{1-4}\text{CH}(\text{CH}_3)\text{N}(\text{R})(\text{R}')$, $-\text{OR}'$, $-(\text{CH}_2)_{1-4}\text{OR}'$, $-\text{NR}(\text{CH}_2)_{1-4}\text{N}(\text{R})(\text{R}')$, $-\text{NR}(\text{CH}_2)_{1-4}\text{SO}_2\text{R}'$, $-\text{NR}(\text{CH}_2)_{1-4}\text{COOR}'$, or $-\text{NR}(\text{CH}_2)_{1-4}\text{COR}'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring. In yet a further embodiment, Q^2 is $-(\text{CHR}^6)_q-$, q is 1 or 2, and R^6 is R^1 , $-\text{N}(\text{R})(\text{R}')$, $-(\text{CH}_2)_{1-4}\text{N}(\text{R})(\text{R}')$, $-\text{OR}'$, $-(\text{CH}_2)_{1-4}\text{OR}'$ or $-\text{NR}(\text{CH}_2)_{1-4}\text{SO}_2\text{R}'$. In a still further embodiment, Q^2 is $-(\text{CHR}^6)_q-$, q is 1 or 2, and each R^6 is H.

[0066] In another embodiment, Ar¹ is a C₃₋₆ aliphatic, a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ is optionally substituted with 0-5 independent occurrences of TR⁷.

[0067] In a further embodiment, Ar¹ is selected from one of



a

b

c

d

e

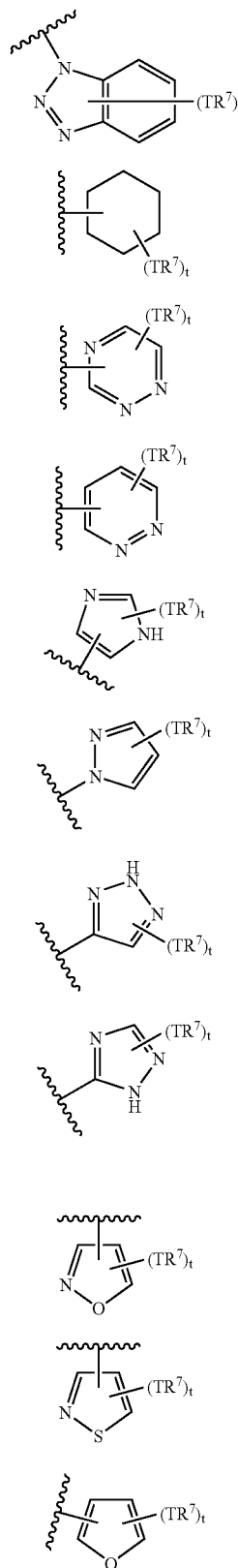
f

g

h

i

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j

k

l

m

n

o

p

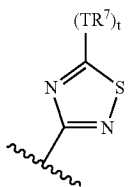
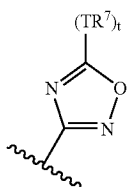
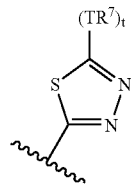
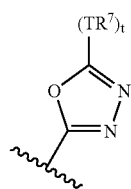
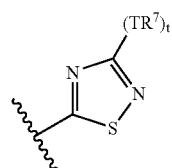
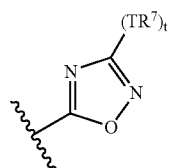
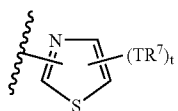
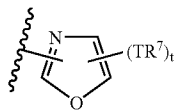
q

r

s

t

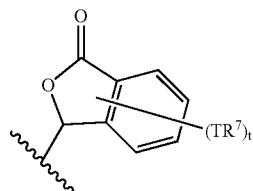
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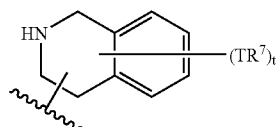
cc



v

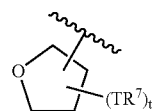
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w



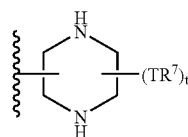
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x



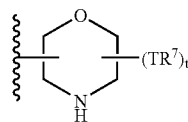
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y



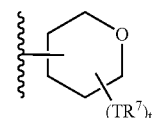
gg

z



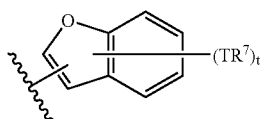
hh

ii



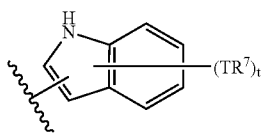
jj

aa

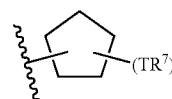


kk

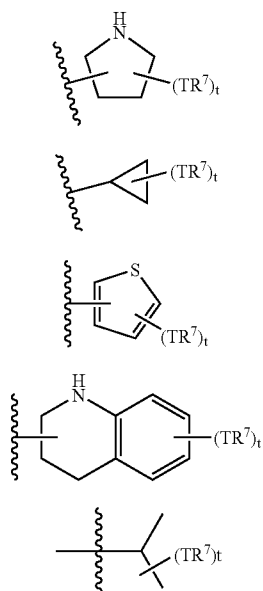
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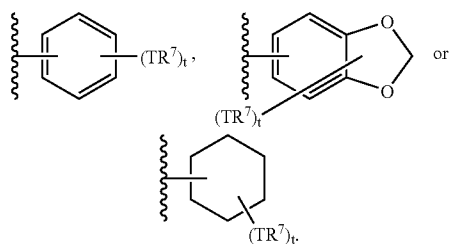
mm



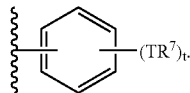
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[0068] wherein t is 0, 1, 2, 3, 4, or 5, and wherein any Ar^1 is bonded to Q through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7 . In a further embodiment, Ar^1 is



In yet a further embodiment, Ar^1 is



[0069] In some embodiments, t is 0, 1 or 2, and each TR^7 is independently selected from halogen, $-CN$, $-R'$, $-OR'$, $-NRR'$, $-OSO_2R'$, $-NRSO_2R'$, $-NRSO_2NRR'$, $-SO_2NRR'$, $-CONRR'$, $-COR'$, $-COOR'$, $-NRCOR'$ or $-SO_2R'$. In a further embodiment, TR^7 is selected from $-F$, $-Cl$, $-CN$, $-NH_2$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OR^x$, $-OCF_3$, $-NR^xSO_2R^x$, $-NR^xSO_2N(R^x)_2$, $-COOC(CH_3)_3$, $-OSO_2CH_3$, $-OH$, $-SO_2N(R^x)_2$, $-SO_2N(R^x)_2$, $-SO_2R^x$, -pyrrolidinone, tetrahydrofuran or $-D-(CH_2)_p-Y$, wherein R^x is a H or a C_{1-4}

alkyl, D is $-SO_2-$, $-SO_2NH-$, $-NHSO_2-$ or $-O-$, p is 0-3, and Y is selected from:

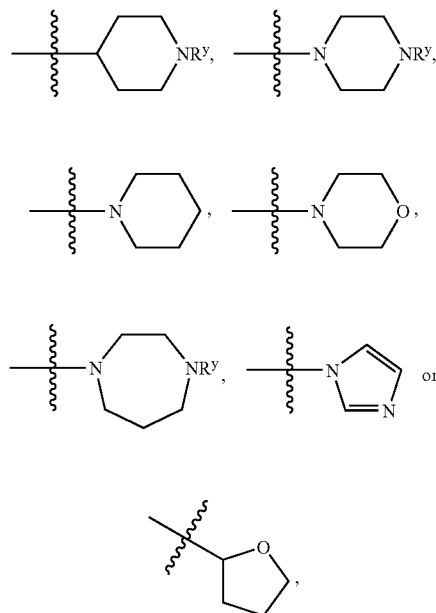
nn

oo

pp

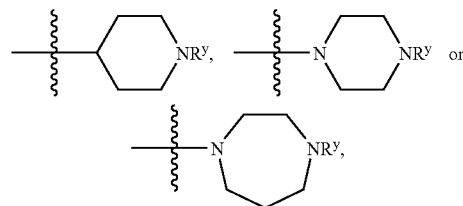
qq

rr

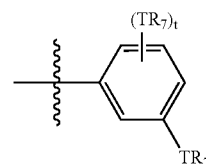


wherein R^y is H or C_{1-3} alkyl, and wherein one or more carbon atoms of Y is optionally substituted with $=O$.

[0070] In one embodiment, t is 1 or 2 and one TR^7 is $-D-(CH_2)_p-Y$, D is $-O-$, p is 2 or 3, Y is



and R^y is H or CH_3 , and wherein one or more carbon atoms of Y is optionally substituted with $=O$. In another embodiment, t is 1 or 2 and one TR^7 is $-SO_2N(R^x)_2$, $-NR^xSO_2R^x$, $-NHSO_2R^x$, $-OCF_3$, or $-OR^x$. In yet another embodiment, t is 1 or 2, and one or both TR^7 are F or Cl. In yet another embodiment, Ar^1 is



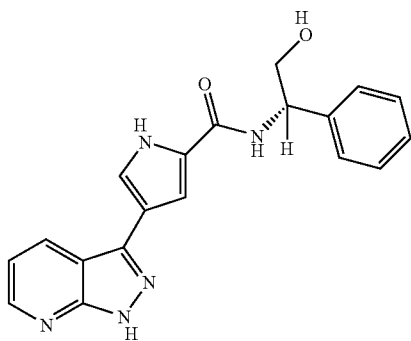
and t is 0 or 1.

[0071] Representative examples of compounds of formula I are set forth below in Table 1 below.

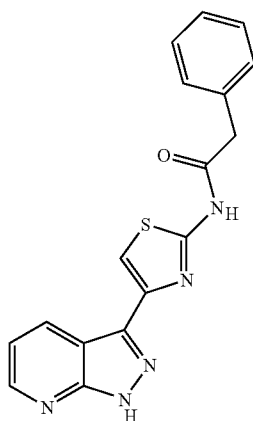
TABLE 1

Examples of Compounds of Formula I:

1



2



3

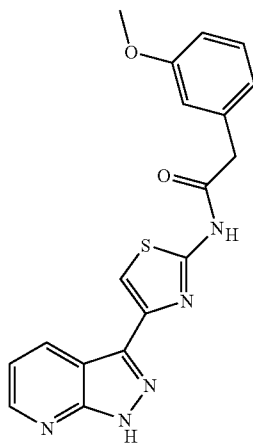
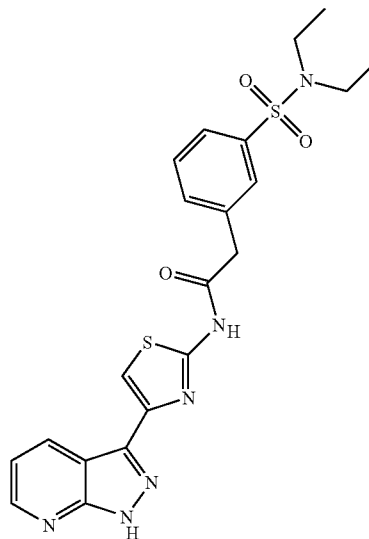


TABLE 1-continued

Examples of Compounds of Formula I:

4



5

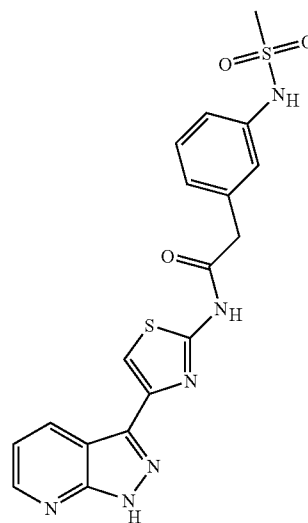


TABLE 1-continued

Examples of Compounds of Formula I:

6

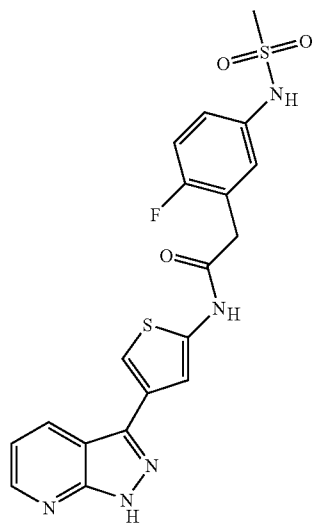
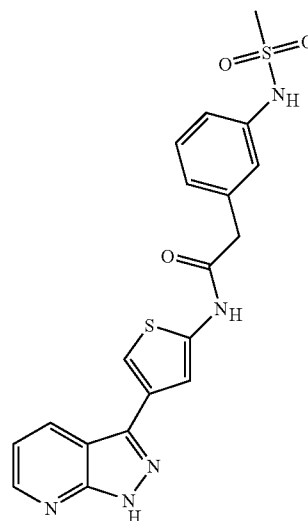


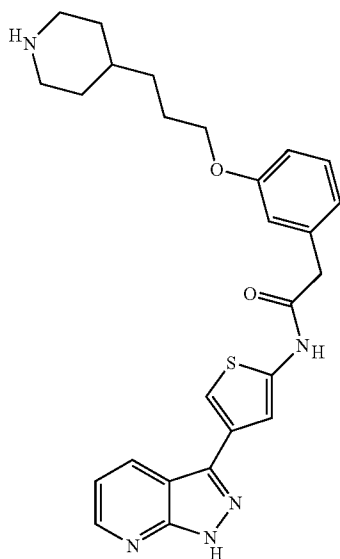
TABLE 1-continued

Examples of Compounds of Formula I:

8



7



9

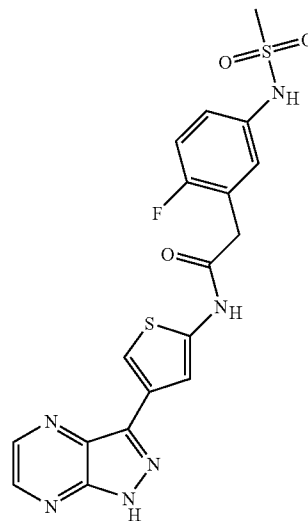
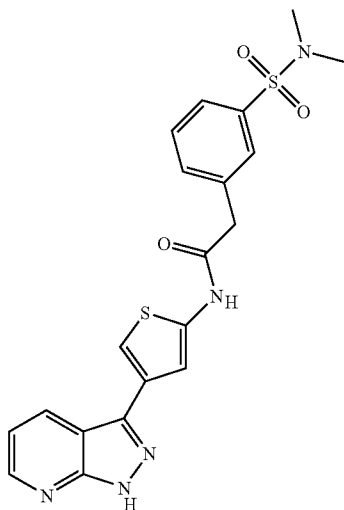


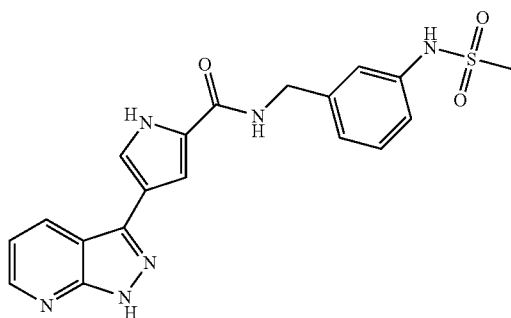
TABLE 1-continued

Examples of Compounds of Formula I:

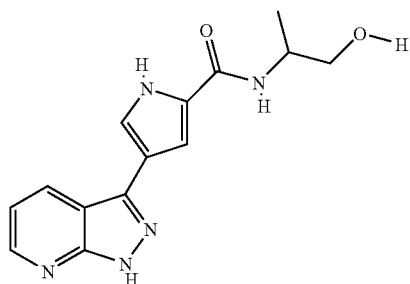
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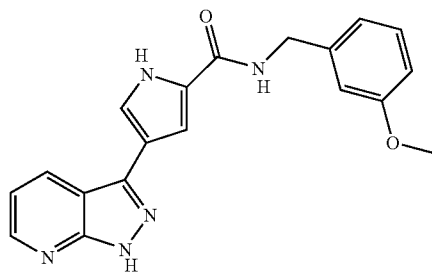
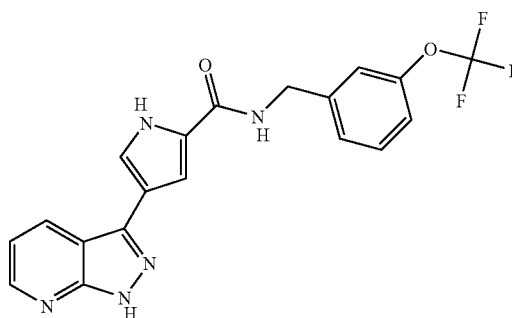


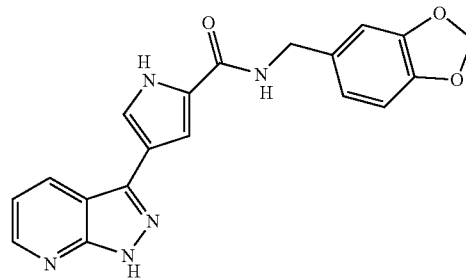
TABLE 1-continued

Examples of Compounds of Formula I:

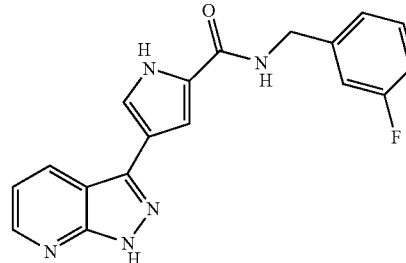
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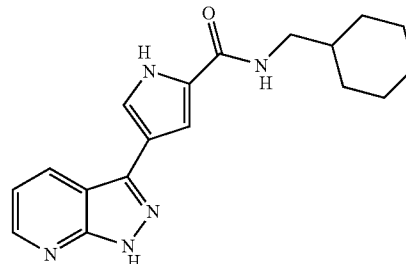
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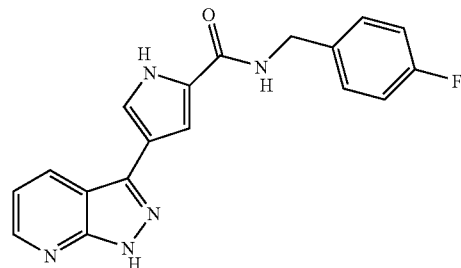
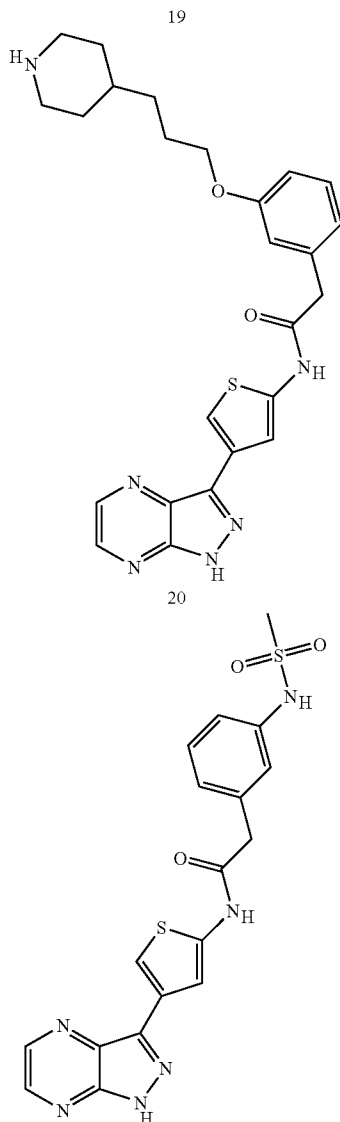


TABLE 1-continued

Examples of Compounds of Formula I:



[0072] General Synthetic Methodology

[0073] The compounds of this invention may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general schemes below, and the preparative examples that follow.

[0074] Although certain exemplary embodiments are depicted and described above and herein, it will be appreciated that compounds of the invention can be prepared according to the methods described generally above using appropriate starting materials by methods generally available to one of ordinary skill in the art.

[0075] Uses, Formulation and Administration

[0076] As discussed above, the present invention provides compounds that are inhibitors of protein kinases, and thus

the present compounds are useful for the treatment of diseases, disorders, and conditions including, but not limited to a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, psychotic disorders, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. In preferred embodiments, the compounds are useful for the treatment of hypertension, angina, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, cancer, erectile dysfunction, arteriosclerosis, spasm (cerebral vasospasm and coronary vasospasm), retinopathy (e.g., glaucoma), inflammatory disorders, autoimmune disorders, AIDS, osteoporosis, myocardial hypertrophy, ischemia/reperfusion-induced injury, endothelial dysfunction, Alzheimer's disease, or benign prostatic hyperplasia. In other embodiments, such conditions in which ROCK is known to play a role include, without limitation, hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia, or atherosclerosis.

[0077] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0078] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0079] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt or salt of an ester of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of a ROCK kinase.

[0080] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this

invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pantoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0081] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glu-

cose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0082] In yet another aspect, a method for the treatment or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder is provided comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition comprising a compound to a subject in need thereof. In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well

known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0083] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0084] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0085] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0086] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0087] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the com-

pound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or micro-emulsions that are compatible with body tissues.

[0088] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0089] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar—agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0090] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0091] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be

admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0092] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0093] As described generally above, the compounds of the invention are useful as inhibitors of protein kinases. In one embodiment, the compounds and compositions of the invention are inhibitors of ROCK, and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation of ROCK is implicated in the disease, condition, or disorder. When activation of ROCK is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as "ROCK-mediated disease" or disease symptom. Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation of ROCK is implicated in the disease state.

[0094] The activity of a compound utilized in this invention as an inhibitor of ROCK, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated ROCK. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to ROCK. Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/ROCK complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with ROCK bound to known radioligands.

[0095] The term "measurably inhibit", as used herein means a measurable change in ROCK activity between a

sample comprising said composition and ROCK and an equivalent sample comprising ROCK in the absence of said composition.

[0096] The term "ROCK-mediated condition" or "disease", as used herein, means any disease or other deleterious condition in which ROCK is known to play a role. The term "ROCK-mediated condition" or "disease" also means those diseases or conditions that are alleviated by treatment with a ROCK inhibitor. Such conditions include, without limitation, hypertension, angina, angina pectoris, cerebrovascular contraction, asthma, peripheral circulation disorder, premature birth, cancer, erectile dysfunction, arteriosclerosis, spasm (cerebral vasospasm and coronary vasospasm), retinopathy (e.g., glaucoma), inflammatory disorders, autoimmune disorders, AIDS, osteoporosis, myocardial hypertrophy, ischemia/reperfusion-induced injury, endothelial dysfunction, Alzheimer's disease, or benign prostatic hyperplasia. In other embodiments, such conditions in which ROCK is known to play a role include, without limitation, hypertension, cerebral vasospasm, coronary vasospasm, bronchial asthma, preterm labor, erectile dysfunction, glaucoma, vascular smooth muscle cell proliferation, myocardial hypertrophy, malignoma, ischemia/reperfusion-induced injury, endothelial dysfunction, Crohn's Disease and colitis, neurite outgrowth, Raynaud's Disease, angina, Alzheimer's disease, benign prostatic hyperplasia, or atherosclerosis.

[0097] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0098] For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, For example, other therapies or anticancer agents that may be used in combination with the inventive anticancer agents of the present invention include surgery, radiotherapy (in but a few examples, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleu-

kins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, Cyclophosphamide, Melphalan, Ifosfamide), antimetabolites (Methotrexate), purine antagonists and pyrimidine antagonists (6-Mercaptopurine, 5-Fluorouracil, Cytarabine, Gemcitabine), spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), antibiotics (Doxorubicin, Bleomycin, Mitomycin), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec™, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies see, <http://www.nci.nih.gov/>, a list of the FDA approved oncology drugs at <http://www.fda.gov/cder/cancer/druglistframe.htm>, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

[0099] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Exelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[0100] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0101] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating implantable medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above and a carrier suitable for coating said implantable device.

[0102] Vascular stents, for example, have been used to overcome restenosis. However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, poly-methylsiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0103] Another aspect of the invention relates to inhibiting ROCK activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of ROCK kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

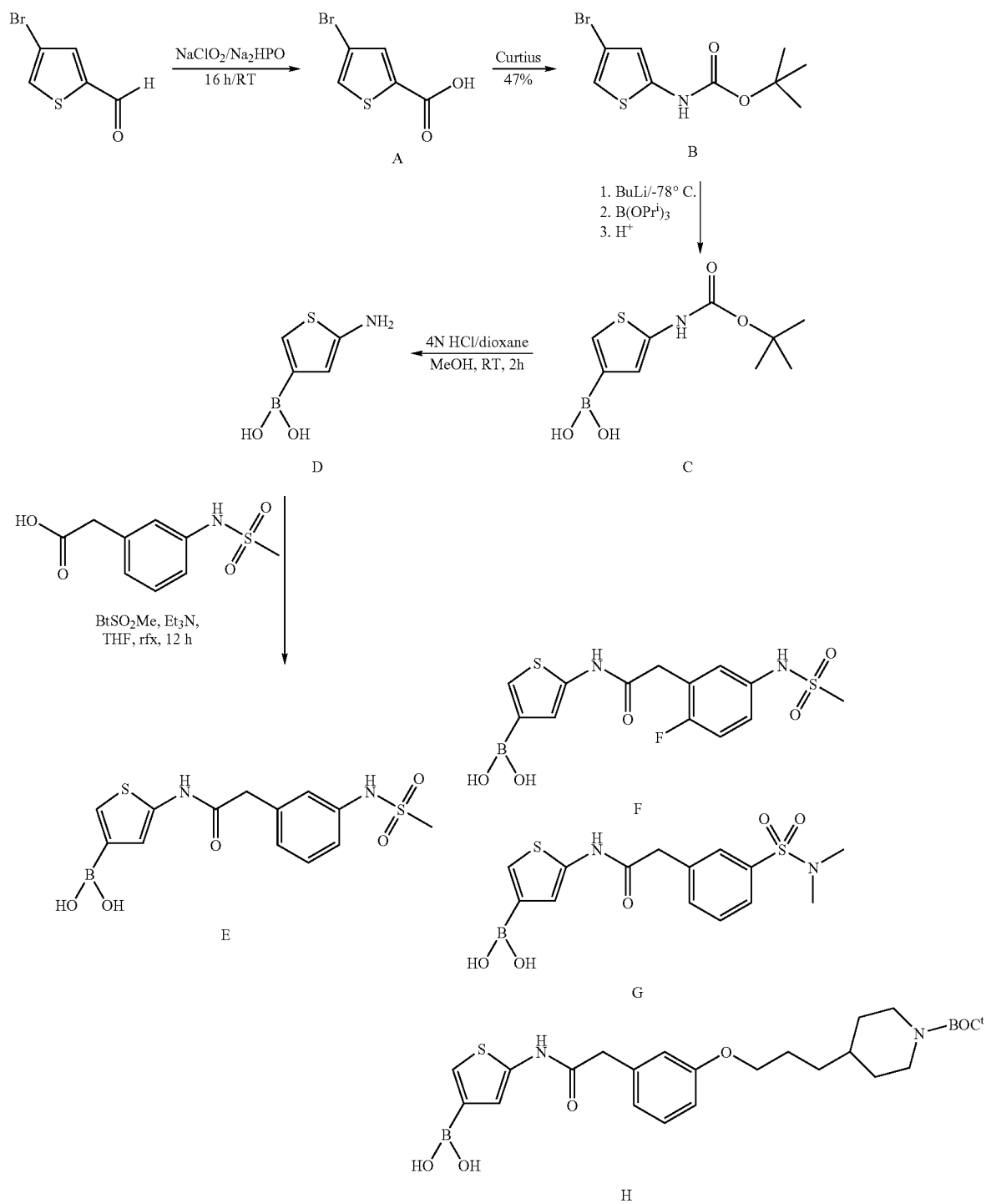
[0104] All references provided in the Examples are herein incorporated by reference. As used herein, all abbreviations, symbols and conventions are consistent with those used in the contemporary scientific literature. See, e.g., Janet S. Dodd, ed., *The ACS Style Guide: A Manual for Authors and Editors*, 2nd Ed., Washington, D.C.: American Chemical Society, 1997, herein incorporated in its entirety by reference.

EXAMPLES

Example 1

Preparation of Compound 9

[0105]



4-Bromothiophene-2-carboxylic acid (A)

[0106] A solution of sodium chlorite (47.5 g, 525 mmol) and sodium hydrogen phosphate (63.0 g, 525 mmol) in water (500 mL) was added slowly to a stirred solution of 4-bromo-2-thiophenecarboxaldehyde (50 g, 261 mmol) in tertiary butanol (600 mL) and 2-methylbutene (8 mL) in 30 min at 0° C. The cooling bath was removed and the resulting solution was stirred at room temperature for 16 h. The mixture was transferred to a separator funnel and the aqueous layer was separated. Organic layer (tertiary butanol) was concentrated under reduced pressure to give white residue, which was added to the aqueous aliquot. The total aqueous layer was acidified with 6N HCl (100 mL). The precipitated product was extracted with ethyl acetate (3×250 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to afford the title 4-bromothiophene-2-carboxylic acid (A) as a white solid (54 g, 100%). FIA MS 207 (M+1).

tert-Butyl-4-bromothiophen-2-yl-carbamate (B)

[0107] A mixture of 4-bromothiophene-2-carboxylic acid (A) (53 g, 255 mmol), diphenylphosphoryl azide (Aldrich, 70 mL, 323 mmol), triethylamine (45 mmol) in tertiary butanol (675 mL) was heated at 100° C. for 5 h and then cooled to room temperature. The solvent was evaporated to give brown gum, which was dissolved in EtOAc (500 mL). The organic solution was washed with saturated NaHCO₃ (500 mL) and water (500 mL) respectively, then dried over Na₂SO₄ and concentrated. The crude product was dissolved in CH₂Cl₂ (75 mL) and purified by flash column chromatography on silica gel (10%-15% EtOAc/hexanes) to afford title compound tert-butyl-4-bromothiophen-2-yl-carbamate (B) (47 g, 66%) as a white solid. FIA MS 278 (M+1).

5-BOC^taminothiophen-3-yl-3-boronic acid (C)

[0108] 2.5M nBuLi in hexane (7.2 mL, 18 mmol) was added dropwise to a stirred solution of tert-butyl-4-bromothiophen-2-yl-carbamate (B) (1 g, 3.6 mmol) in THF (3 mL) and toluene (11 mL) at -78° C. under nitrogen and the solution was stirred 1 h at -78° C.

[0109] Triisopropylborate (2 mL, 9 mmol) was added and the resulting thick brown solution was stirred at -78° C. for 30 min and room temperature for 30 min. 2N HCl (15 mL) and ethyl acetate (50 mL) were added and the solution was stirred 25 min. The organic layer was separated and aqueous layer was extracted with EtOAc (2×25 mL). The combined organic layers were dried (Na₂SO₄) and concentrated to give title compound 5-aminothiophen-3-yl-3-boronic acid (C) as an oil (0.8 g, 91%). The product was used for next step without purification. FIA MS 242 (M-1).

5-Aminothiophen-3-yl-3-boronic acid (D)

[0110] The crude 5-aminothiophen-3-yl-3-boronic acid (C) (0.8 g) was dissolved in 4N HCl (10 mL) and methanol (2 mL) and the solution was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure to give title compound 5-BOC^taminothiophen-3-yl-3-boronic acid (D) (0.58 g) as a brown gum. The product was used for next step without purification. FIA MS 143 (M+1).

5-(2-(3-Methylsulfonamidophenyl)acetamido)thiophen-3-yl-3-boronic acid (E)

[0111] A mixture of 5-aminothiophen-3-yl-3-boronic acid (D) (0.48 g, 3.35 mmol), 3-methylsulfonamidophenylacetic acid (0.77 g, 3.35 mmol), BtSO₂CH₃ (0.66 g, 3.35 mmol), Et₃N (3 mL) in THF (25 mL) and DMF (2 mL) was heated at 85° C. for 16 h and then cooled to room temperature. The solvent was evaporated and the crude material was dissolved in EtOAc (50 mL). The organic solution was washed with saturated NaHCO₃ (20 mL), brine (20 mL), dried (Na₂SO₄) and concentrated. The crude material was purified by chromatography. The impurities were first eluted with 40-70% EtOAc/hexanes and the product was eluted with 5-30% MeOH/CH₂Cl₂. Yield 0.54 g, 46%, FIA MS 355 (M+1).

5-(2-(5-Methylsulfonamido-2-fluorophenyl)acetamido)thiophen-3-yl-3-boronic acid (F)

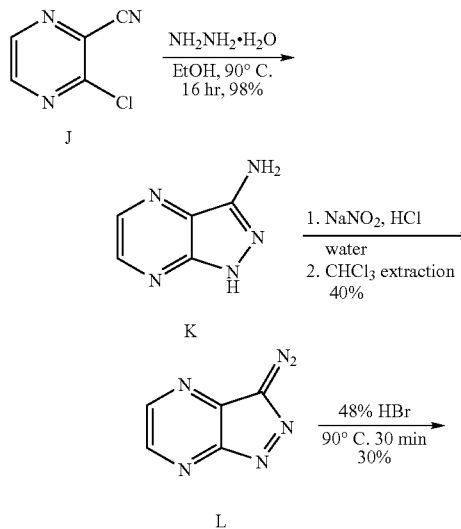
[0112] The boronic acid F was synthesized and purified in a manner similar to E using a mixture of D (0.48 g, 3.35 mmol), 3-methylsulfonamide-6-fluorophenylacetic acid (0.82 g, 3.35 mmol), BtSO₂CH₃ (0.66 g, 3.35 mmol), Et₃N (3 mL). Yield 0.43 g, 34%, FIA MS 373 (M+1).

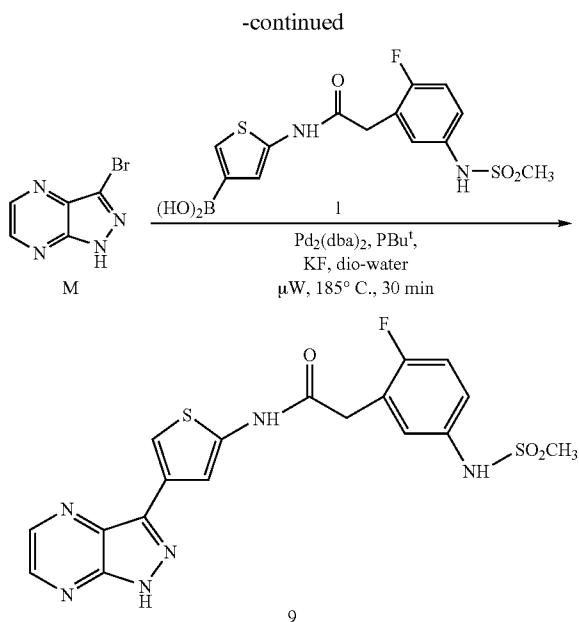
5-(2-(3-N,N-dimethylaminosulfonylbenzene)acetamido)thiophen-3-yl-3-boronic acid (G)

[0113] The boronic acid F was synthesized and purified in a manner similar to E using a mixture of D (0.48 g, 3.35 mmol), 3-N,N-dimethylsulfone phenylacetic acid (0.81 g, 3.35 mmol), BtSO₂CH₃ (0.66 g, 3.35 mmol), Et₃N (3 mL). Yield 0.64 g, 52%, FIA MS 369 (M+1).

5-(2-(3-(3-(tert-butoxycarbonyl-piperidin-4-yl)propoxy)phenyl)acetamido)thiophene-3-yl-3-boronic acid (H)

[0114] The boronic acid H was synthesized and purified in a manner similar to E using a mixture of D (0.48 g, 3.35 mmol), 2-(3-(3-(BOC^tpiperidin-4-yl)propoxy)phenyl)acetic acid (1.26 g, 3.35 mmol), BtSO₂CH₃ (0.66 g, 3.35 mmol), Et₃N (3 mL). Yield 0.57 g, 43.6%, FIA MS 503 (M+1).





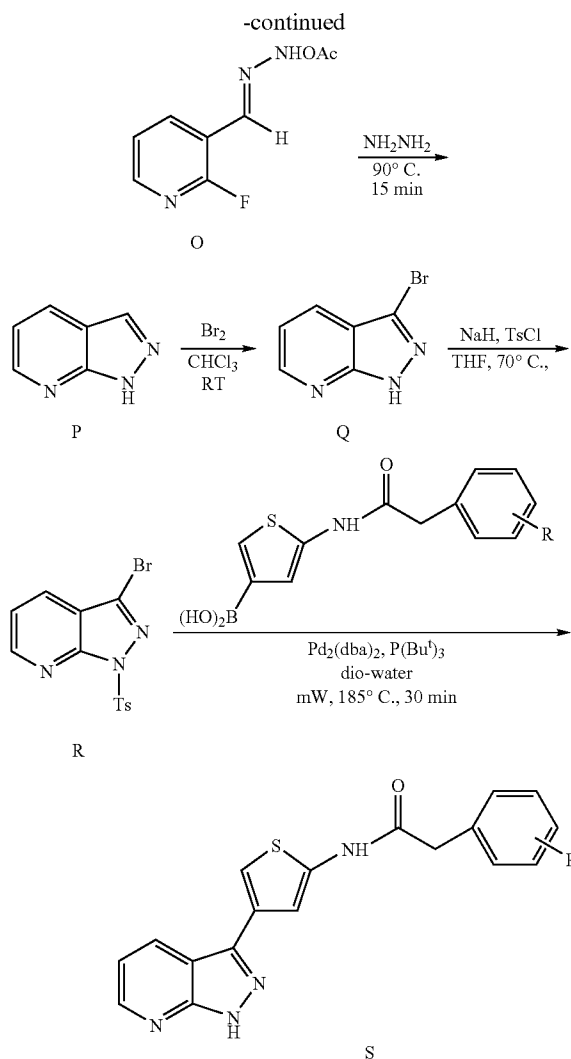
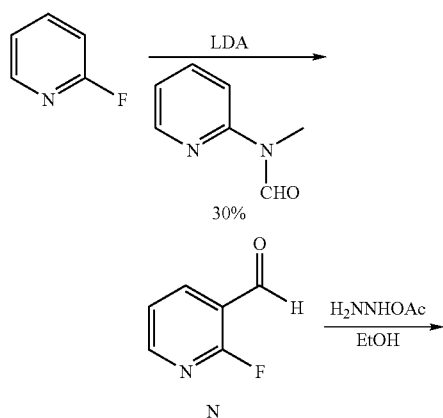
N-(4-(1H-pyrazolo[3,4-b]pyrazin-3-yl)thiophen-2-yl)-2-(5-methylsulfonamido-2-fluorophenyl)acetamide (Compound 9)

[0115] A mixture of J (0.050 g, 0.134 mmol), M (see Monatshefte für Chemie 113:731, 1992; 0.026 g, 0.134 mmol), $\text{Pd}_2(\text{dba})_3$ (0.017 g, 0.02 mmol), $\text{P}(\text{Bu}^t)_3$ (0.01 g, 0.04 mmol), $\text{KF} \cdot \text{H}_2\text{O}$ (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 185° C. in a microwave for 25 min. Solid was filtered and washed with EtOAc (1 mL). The filtrate was concentrated and the crude product was purified by preparative HPLC (5-75% CH_3CN /water, 15 min) to give title compound 9 (0.005 g) as an oil.

Example 2

Preparation of Compounds 6, 7, 8 and 10

[0116]



1 Fluoropyridine-3-carbaldehyde (N)

[0117] Under nitrogen, 2.5M nBuLi in hexane (25.6 mL, 64.37 mmol) was added dropwise to a stirred solution of isopropylamine (9 mL, 64 mmol) in THF (50 mL) and at -78° C. for 10 min. and the solution was stirred 30 min at -78° C. 2-Fluoropyridine (4.4 mL, 51.2 mmol) was added and the solution was stirred at -78° C. for 2 h. A cold solution of N-methyl-N-(pyridin-2-yl)formamide (7 g, 51.2 mmol) in THF (30 mL) were added in 15 min. The resulting solution was warmed to room temperature and stirred for 1 h. 2N HCl (15 mL) and ethyl acetate (50 mL) were added and the solution was stirred 25 min. The organic layer was separated and aqueous layer was extracted with EtOAc (2×25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude product was purified by chromatography (10-60% EtOAc/hexanes) to give title compound N (1.3 g, 20%) as a yellow oil. ^1H NMR (DMSO-d_6 , 500 MHz) δ 10.16(s, 1H), 8.53(dd, 1H), 8.38(m, 1H), 7.58(m, 1H).

(E)-N'-((2-Fluoropyridin-3-yl)methylene)acetohydrazide (O)

[0118] A solution of N (1.3 g, 10.4 mmol), acylhydrazine (1.5 g, 20.8 mmol) in ethanol (10 mL) was stirred at room temperature for 18 h. The precipitate was filtered and washed with ethanol (2×10 mL) and dried to give title compound O (0.82 g, 43%) as a white solid FIA MS 180 (M-1).

1H-Pyrazolo[3,4-b]pyridine (P)

[0119] A suspension of O (0.82 g, 4.5 mmol) in hydrazine monohydrate (5 mL) was heated at 90° C. for 15 min and poured into ice/water and extracted with ethyl acetate (3×25 mL). The organic layers were dried (Na₂SO₄) and concentrated to give title compound P (0.41 g, 77%) as a white solid. ¹H NMR (DMSO-d₆, 500 MHz) δ 13.60(brs, 1H), 8.55(d, 1H), 8.51(dd, 1H), 8.14(s, 1H), 7.18(dd, 1H); FIA MS 120 (M+1).

3-Bromo-1H-pyrazolo[3,4-b]pyridine (Q)

[0120] Bromine (0.3 mL, 5.16 mmol) was added via a micro syringe to a stirred solution of P (0.41 g, 3.45 mmol) in chloroform (10 mL). The resulting suspension was stirred at room temperature for 2 h. The solvent was evaporated and ethyl acetate (50 mL) was added. The organic layer was washed with saturated K₂CO₃ and the organic layer was concentrated without drying at 70° C. to produce title compound Q (0.63 g, 92%). ¹H NMR (DMSO-d₆, 500 MHz) δ 8.56(t, 1H), 8.05(d, 1H), 7.24(m, 1H); FIA MS 198(M-1).

3-Bromo-1-tosyl-1H-pyrazolo[3,4-b]pyridine (R)

[0121] Sodium hydride (0.05 g, 2 mmol) was added to a stirred solution of Q (0.1 g, 0.5 mmol) in THF (5 mL). The solution was stirred at room temperature for 30 min and P-TsCl (0.1 g, 0.5 mmol) was added. The resulting suspension was heated at 60° C. for 45 min. and poured into water (25 mL). The solution was extracted with ethyl acetate (2×25 mL), dried and concentrated to give title compound R (0.14, 80%). The product was unstable and therefore used for next step immediately. FIA-MS 353(M-1).

2-(2-Fluoro-5-methanesulfonylamino-phenyl)-N-[4-(1H-pyrazolo[3,4-b]pyridin-3-yl)-thiophen-2-yl]-acetamide (Compound 6).

[0122] A mixture of R (0.050 g, 0.142 mmol), F (0.053 g, 0.142 mmol), Pd₂(dba)₃ (0.017 g, 0.02 mmol), P(Bu^t)₃ (0.01

g, 0.04 mmol), KF.H₂O (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 185° C. in a microwave for 25 min. Solid was filtered and washed with EtOAc (1 mL). The filtrate was concentrated and the crude product was purified by preparative HPLC (5-75% CH₃CN/water, 15 min) to give title compound 6 (0.027 g) as an oil.

2-(3-Methanesulfonylamino-phenyl)-N-[4-(1H-pyrazolo[3,4-b]pyridin-3-yl)-thiophen-2-yl]-acetamide (Compound 8).

[0123] The title compound 8 was synthesized and purified in a manner similar to 6 using a mixture of R (0.050 g, 0.142 mmol), E (0.050 g, 0.142 mmol), Pd₂(dba)₃ (0.017 g, 0.02 mmol), P(Bu^t)₃ (0.01 g, 0.04 mmol), KF.H₂O (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL). Yield 0.03 g.

2-(3-Dimethylsulfamoyl-phenyl)-N-[4-(1H-pyrazolo[3,4-b]pyridin-3-yl)-thiophen-2-yl]-acetamide (Compound 10)

[0124] The title compound 10 was synthesized and purified in a manner similar to 6 using a mixture of R (0.050 g, 0.142 mmol), G (0.052 g, 0.142 mmol), Pd₂(dba)₃ (0.017 g, 0.02 mmol), P(Bu^t)₃ (0.01 g, 0.04 mmol), KF.H₂O (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL). Yield 0.026 g.

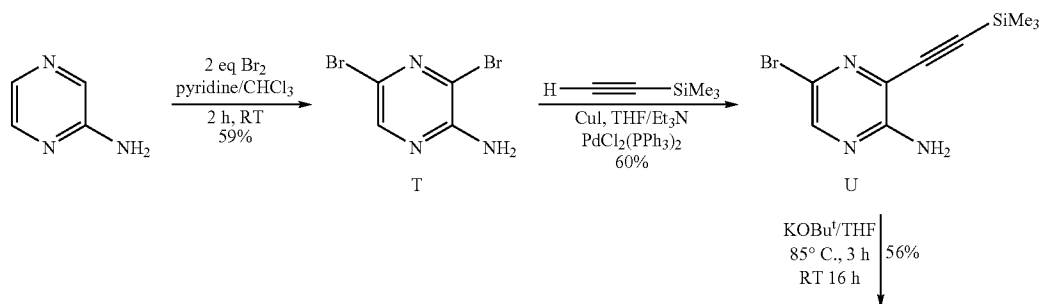
2-(3-(3-Piperidin-4-yl-propoxy)-phenyl)-N-[4-(1H-pyrazolo[3,4-b]pyridin-3-yl)-thiophen-2-yl]-acetamide (Compound 7)

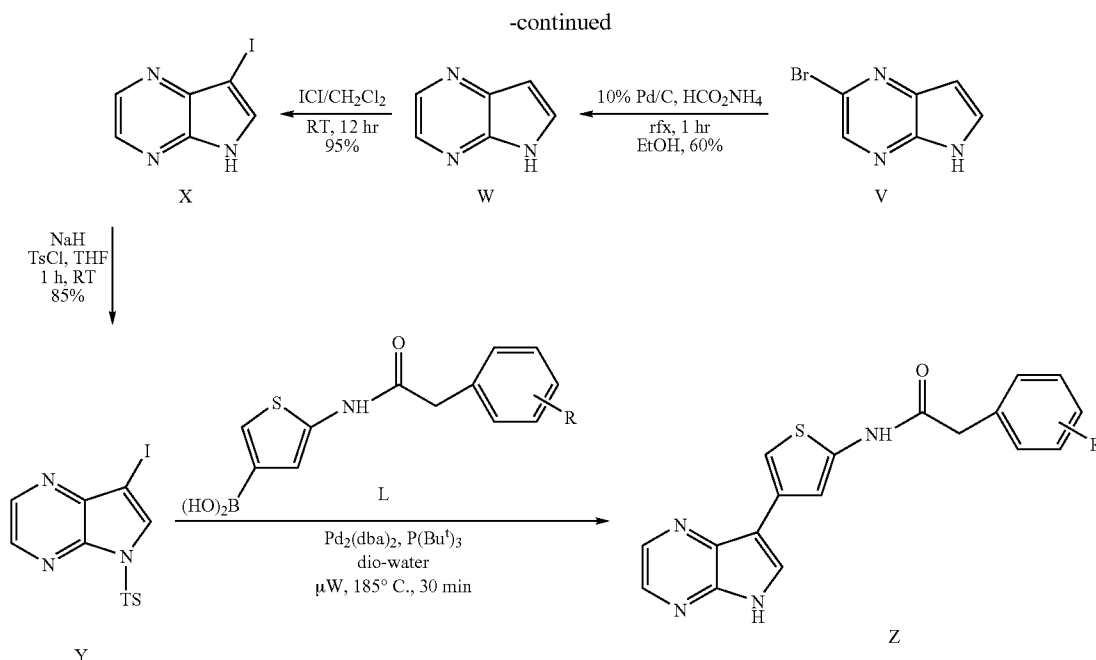
[0125] A mixture of R (0.050 g, 0.142 mmol), H (0.064 g, 0.142 mmol), Pd₂(dba)₃ (0.017 g, 0.02 mmol), P(Bu^t)₃ (0.01 g, 0.04 mmol), KF.H₂O (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 185° C. in a microwave for 25 min. Solid was filtered and washed with EtOAc (1 mL). The filtrate was concentrated. The crude product was dissolved in CH₂Cl₂ (1 mL) and TFA (1 mL). The solution was stirred at room temperature for 1 h. and concentrated. The crude product was purified by preparative HPLC (5-75% CH₃CN/water, 15 min) to give title compound 7 (0.032 g) as an oil.

Example 3

Preparation of Compounds 19 and 20

[0126]





5-Bromo-3-trimethylsilyl-ethynyl-pyrazin-2-ylamine (U)

[0127] Trimethylsilylacetylene (3.4 mL) was added to a stirred suspension of T (see J. Heterocyclic. Chem. 1982, 19,673; 6.3 g, 25.12 mmol), Pd(PPh₃)₂Cl₂ (1.7 g), CuI (0.95 g) in triethylamine (20 mL) and THF (50 mL) at room temperature and the solution was heated at 45° C. for 2 h. The solid was filtered off and the filtration was concentrated to give dark brown liquid. The crude product was purified by Biotage Horizon™ eluting with 10%-50% EtOAc/hexane to afford title compound U (4.1 g, 60%) as a yellow solid. ¹H NMR (DMSO-d₆, 500 MHz) δ 8.11(s, 1H), 6.77(bris, 2H), 7.24(m, 1H); FIA MS 270(M+1).

2-Bromo-5H-pyrrolo[2,3-b]pyrazine (V)

[0128] A solution of U (4.0 g, 14.81 mmol) in THF (25 mL) was added to a stirred suspension of potassium tert butoxide (2.5 g, 22.2 mmol) in THF (50 mL). The solution was refluxed for 3 h and then stirred at room temperature for 16 h. The solvent was evaporated and the residue was dissolved in water (100 mL) and aqueous layer was extracted with ethyl acetate (5×50 mL). Organic layer was dried and concentrated to give title compound V (1.62 g) as a yellow solid. ¹H NMR (DMSO-d₆, 500 MHz) δ 12.33(s, 1H), 8.35(s, 1H), 7.96(t, 1H), 6.63(dd, 1H); FIA MS 198(M-1).

5H-Pyrrolo[2,3-b]pyrazine (W)

[0129] 10% Palladium on carbon (1.4 g) was added to a stirred, nitrogen flushed solution of V (1.4 g, 7.14 mmol) and ammonium formate (4.2 g) in ethanol (50 mL). The solution was refluxed for 1 h and cooled to room temperature. The filtrate was concentrated to give a solid, which was washed with ethyl acetate (3×20 mL). The solvent was evaporated and the crude product was purified by Biotage Horizon eluting with 40%-80% EtOAc/hexane to afford title com-

pound W (0.313 g, 37%) as a white solid. ¹H NMR (DMSO-d₆, 500 MHz) δ 12.05(s, 1H), 8.37(d, 1H), 8.22(d, 1H), 7.85(d, 1H), 6.62(d, 1H); FIA MS 120(M+1).

7-Iodo-5H-pyrrolo[2,3-b]pyrazine (X)

[0130] 1M Solution iodine monochloride (5.26 mL, 5.26 mmol) was added to a stirred solution of W (0.313 g, 2.63 mmol) in CH₂Cl₂ (25 mL) and the solution was stirred at room temperature for 16 h. The precipitated yellow solid was filtered and suspended in ethyl acetate (50 mL) and washed with saturated NaHCO₃ (25 mL). The organic layer was dried and concentrated to give title compound 22 (0.64 g, 100%). ¹H NMR (DMSO-d₆, 500 MHz) δ 12.48(s, 1H), 8.45(d, 1H), 8.28(d, 1H), 8.10(d, 1H), 7.85(d, 1H), FIA MS 246(M+1).

7-Iodo-5-(toluene-4-sulfonyl)-5H-pyrrolo[2,3-b]pyrazine (Y)

[0131] Sodium hydride (0.04 g, 1.68 mmol) was added to a stirred solution of X (0.103 g, 0.42 mmol) in THF (10 mL). The solution was stirred at room temperature for 30 min and P-TsCl (0.81 g, 0.62 mmol) was added. The resulting suspension was heated a 60° C. for 45 min. and poured into water (10 mL). The solution was extracted with ethyl acetate (2×25 mL), dried and concentrated to give title compound Y (0.168, 85%). FIA MS 400(M+1).

2-(3-(3-Piperidin-4-yl-propoxy)-phenyl)-N-[4-(5H-pyrrolo[2,3-b]pyrazin-3-yl)-thiophen-2-yl]-acetamide (Compound 19).

[0132] A mixture of Y (0.044 g, 0.11 mmol), H (0.055 g, 0.11 mmol), Pd₂(dba)₃ (0.017 g, 0.02 mmol), P(Bu)₃ (0.01 g, 0.04 mmol), KF·H₂O (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL) was heated at 185° C. in a microwave oven for 25 min. Solid was filtered and washed

with EtOAc (1 mL). The filtrate was concentrated. The crude product was dissolved in CH_2Cl_2 (1 mL) and TFA (1 mL). The solution was stirred at room temperature for 1 h and concentrated. The crude product was purified by preparative HPLC (5-75% $\text{CH}_3\text{CN}/\text{water}$, 15 min) to give title compound 19 (0.0062 g) as an oil.

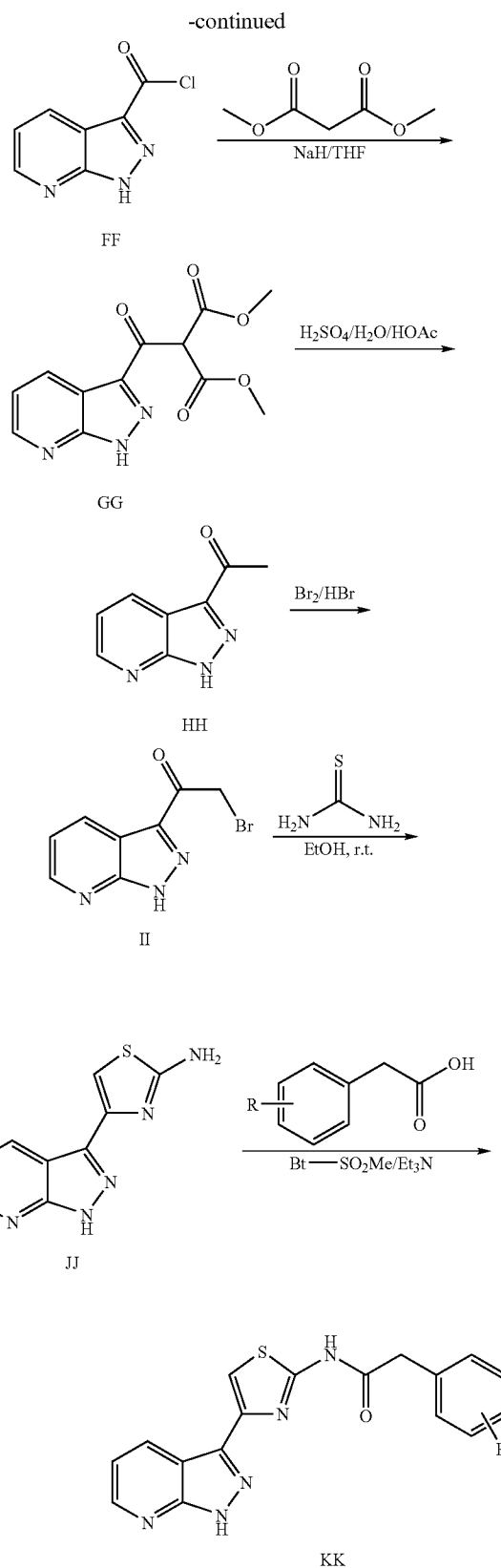
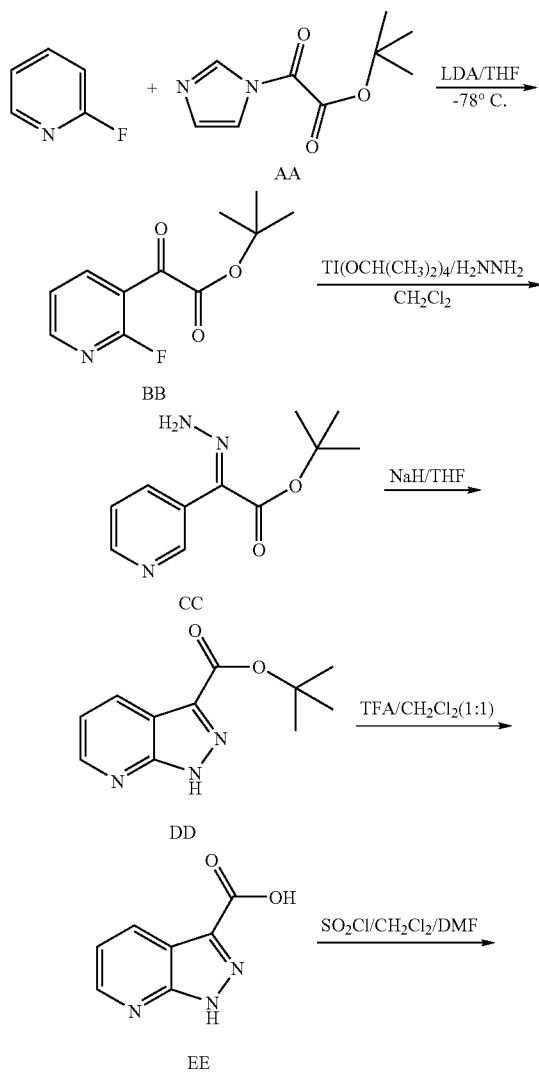
2-(3-Methanesulfonylamino-phenyl)-N-[5H-pyrralo[2,3-b]pyrazin-3-yl]-thiophen-2-yl]-acetamide (Compound 20).

[0133] The title compound 20 was synthesized and purified in a manner similar to 6 using a mixture of Y (0.050 g, 0.125 mmol), E (0.044 g, 0.125 mmol), $\text{Pd}_2(\text{dba})_3$ (0.017 g, 0.02 mmol), $\text{P}(\text{Bu}^t)_3$ (0.01 g, 0.04 mmol), $\text{KF}\cdot\text{H}_2\text{O}$ (0.1 g, 1.3 mmol) in 1,4-dioxane (2 mL) and water (0.5 mL).

Example 4

Preparation of N-(4-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazol-2-yl)-2-phenylacetamides

[0134]



t-Butyl 2-(2-fluoropyridin-3-yl)-2-oxoacetate (BB)

[0135] To a solution of 2-fluoropyridine (5.82 g, 0.0599 mol) in 150 mL THF at -78°C ., LDA (33.0 ml of 2M, 0.066 mol) was added dropwise and the reaction mixture was stirred at -78°C . for 2 h. This solution was transferred slowly into chilled to -78°C . THF (500 ml) solution of t-butyl α -oxo-1 H-imidazole-1-acetate (AA) (see J. Org. Chem. 46:211, 1981; 14.69 g, 0.0749 mol) by means of cannula under nitrogen pressure. The combined solution was continuously stirred at -78°C . for 30 min. The reaction mixture was poured into sat. NH_4Cl (500 mL). The organic phase was separated and dried (MgSO_4). After removing solvent, the product was purified by chromatography to give title compound BB (6.7 g, 49.6% yield). H NMR (CDCl_3): 1.6(s, 9H), 7.4(dd, 1H), 8.36(dd, 1H), 8.5(dd, 1H).

tert-Butyl 2-(2-fluoropyridin-3-yl)-2-hydrazonoacetate (CC)

[0136] To a solution of t-butyl 2-(2-fluoropyridin-3-yl)-2-oxoacetate (BB) in methylene dichloride at room temperature, titanium(IV) isopropoxide was added, followed by hydrazine hydrate dropwise. The reaction mixture was stirred at room temperature for 10 h, then 6 mL water was added. The reaction mixture was continuously stirred at room temperature for overnight. The reaction mixture was filtered and the filtration cake was washed with methylene chloride 3 times. After removal of solvent, the filtrate was purified by chromatography 95%/5% methylene dichloride/methanol to give the title compound CC (5.0 g, 70% yield). H NMR (CDCl_3): 1.5(s, 9H), 6.18(s, br, 2H), 7.3(dd, 1H), 7.74(dd, 1H), 8.3(dd, 1H).

tert-Butyl 1H-pyrazolo[3,4-b]pyridine-3-carboxylate (DD)

[0137] To a solution of t-butyl 2-(2-fluoropyridin-3-yl)-2-hydrazonoacetate (CC) (0.58 g, 2.42 mmol) in THF, sodium hydride (0.116 g, 60% mineral oil dispersion, 2.9 mmol) was added in portions. The reaction mixture was stirred at room temperature until no further gas was released, then warmed to 50°C . for 2 h. Ethyl acetate and brine was added to the reaction mixture and the organic layer was separated and dried over MgSO_4 . After removal of the solvent, the product was purified by chromatography with 50%/50% ethyl acetate/hexanes to give title compound DD (0.4 g, 75% yield). H NMR (CDCl_3): 1.67(s, 9H), 7.28(dd, 1H), 8.52(dd, 1H), 8.63(dd, 1H).

1H-Pyrazolo[3,4-b]pyridine-3-carboxylic acid (EE)

[0138] A THF/ CH_2Cl_2 solution of tert-butyl 1H-pyrazolo[3,4-b]pyridine-3-carboxylate (DD) (3.0 g, 13.7 mmol) was stirred at room temperature for 3 h. The solvent was removed to give title compound EE (2.2 g, 99% yield). H NMR (DMSO): 7.38(dd, 1H), 8.45(dd, 1H), 8.63(dd, 1H).

1H-Pyrazolo[3,4-b]pyridine-3-carbonyl chloride (FF)

[0139] Thionyl chloride, chloroform and a catalytic amount of DMF was added to a solution of 1H-pyrazolo[3,

4-b]pyridine-3-carboxylic acid (EE) (5.6 g, 34.3 mmol) and the mixture was refluxed overnight. The reaction mixture was cooled to room temperature and filtered. The filtration cake was washed with ether to give the title compound FF.

[0140] 2-(1H-Pyrazolo[3,4-b]pyridine-3-carbonyl)-malonic acid dimethyl ester (GG)

[0141] Sodium hydride was added in portions to a dimethylmelanate (0.33 g, 2.5 mmol)/THF solution at 0°C ., then the reaction mixture was refluxed for 1 h. A THF suspension of 1H-Pyrazolo[3,4-b]pyridine-3-carbonyl chloride (FF) was added. The reaction mixture was refluxed overnight. 1N HCl and ethyl acetate were added to the reaction mixture, the organic phase was separated and dried (MgSO_4) and the solvent was removed to give the title compound GG.

1-(1H-Pyrazolo[3,4-b]pyridin-3-yl)-ethanone (HH)

[0142] H_2SO_4 (1 mL, 98%), H_2O (5 ml) and acetic acid (7.5 ml) was added to a solution of a crude reaction product mixture of 2-(1H-pyrazolo[3,4-b]pyridine-3-carbonyl)-malonic acid dimethyl ester (GG). The mixture was heated at 120°C . for 3 h. The reaction mixture was adjusted to pH 6.5 and ethyl acetate was used to extract the product. The product was purified by chromatography with 50%/50% hexanes/ethyl acetate to give the title compound (HH). H NMR (CDCl_3): 2.80(s, 3H), 7.38(dd, 1H), 8.8.71(dd, 1H), 8.76(dd, 1H).

2-Bromo-1-(1H-pyrazolo[3,4-b]pyridin-3-yl)-ethanone (II)

[0143] To a solution of 1-(1H-pyrazolo[3,4-b]pyridin-3-yl)-ethanone (HH) (0.66 g, 4.09 mol) in HBr (8 ml, 48%), bromine (0.654 g, 4.09 mmol) was added and the reaction mixture was stirred at 65°C . for 2 h. A precipitate was formed and filtered to give the HBr salt of the title compound (II) (0.94 g, 71% yield). H NMR (DMSO): 4.93(s, 2H), 7.45(dd, 1H), 8.56(dd, 1H), 8.68(dd, 1H).

4-(1 H-Pyrazolo[3,4-b]pyridin-3-yl)-thiazol-2-ylamine (JJ)

[0144] An ethanol solution of 2-Bromo-1-(1H-pyrazolo[3,4-b]pyridin-3-yl)-ethanone HBr salt (II) (0.94 g, 2.92 mol) and thiourea (0.446 g, 5.84 mol) was stirred at room temperature overnight. A precipitate was formed and filtered to give the title compound (JJ). H NMR (DMSO): 7.03(s, bd 2H), 7.37(dd, 1H), 7.52(s, 1H), 8.6(m, 2H).

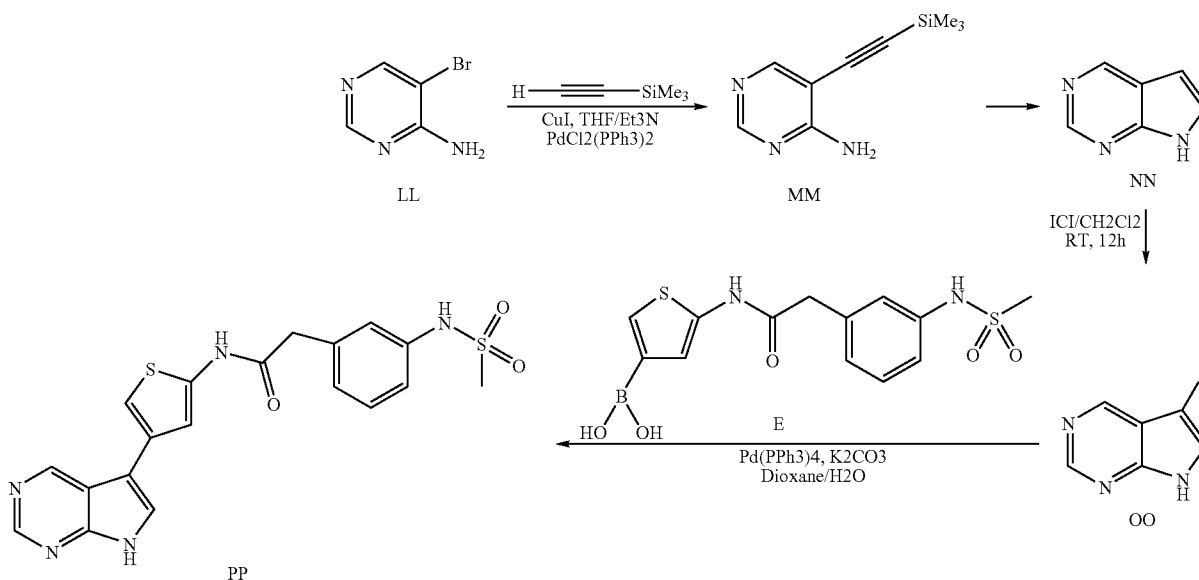
Preparation of N-(4-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazol-2-yl)-2-phenylacetamides

[0145] A suspension of 4-(1H-pyrazolo[3,4-b]pyridin-3-yl)thiazol-2-ylamine (JJ) (0.065 g, 0.3 mmol), a phenylacetic acid optionally substituted with R (0.45 mmol), and Et_3N (0.091 g, 0.9 mmol) in 2 mL THF is heated at 160°C . for 750 sec in microwave. The final product KK is purified by preparative HPLC.

Example 5

Preparation of N-(4-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)thiophen-2-yl)-2-(3-methylsulfonamidophenyl)acetamide

[0146]



5-(2-(trimethylsilyl)ethynyl)pyrimidin-4-amine (MM)

[0147] Trimethylsilylacetylene (3.4 mL) is added to a stirred suspension of LL (J. Heterocyclic Chem. 19: 1285, 1982; J. Org. Chem. 48: 1064, 1983; 25.12 mmol), Pd(PPh₃)₂Cl₂ (1.7 g), CuI (0.95 g) in triethylamine (20 mL) and THF (50 mL) at room temperature and the solution is heated at 45° C. for 2 h. The solid is filtered off and the filtrate is concentrated to give a dark brown liquid. The crude product is purified by Biotage Horizon™ to afford title compound MM.

7H-pyrrolo[2,3-d]pyrimidine (NN)

[0148] A solution of MM (14.81 mmol) in THF (25 mL) is added to a stirred suspension of potassium tert butoxide (2.5 g, 22.2 mmol) in THF (50 mL). The solution is refluxed for 3 h and then stirred at room temperature for 16 h. The solvent is evaporated and the residue is dissolved in water (100 mL) and aqueous layer is extracted with ethyl acetate (5x50 mL). Organic layer is dried and concentrated to give title compound NN.

5-iodo-7H-pyrrolo[2,3-d]pyrimidine (OO)

[0149] A 1M solution of iodine monochloride (5.26 mL, 5.26 mmol) is added to a stirred solution of NN (2.63 mmol) in CH₂Cl₂ (25 mL) and the solution is stirred at room temperature for 16 h. The precipitated yellow solid is filtered and suspended in ethyl acetate (50 mL) and washed with saturated NaHCO₃ (25 mL). The organic layer is dried and concentrated to give title compound OO.

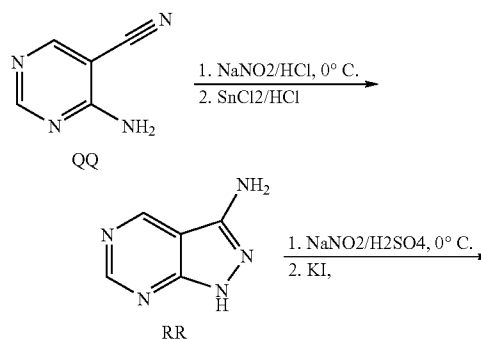
N-(4-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)thiophen-2-yl)-2-(3-methylsulfonamidophenyl)acetamide (PP)

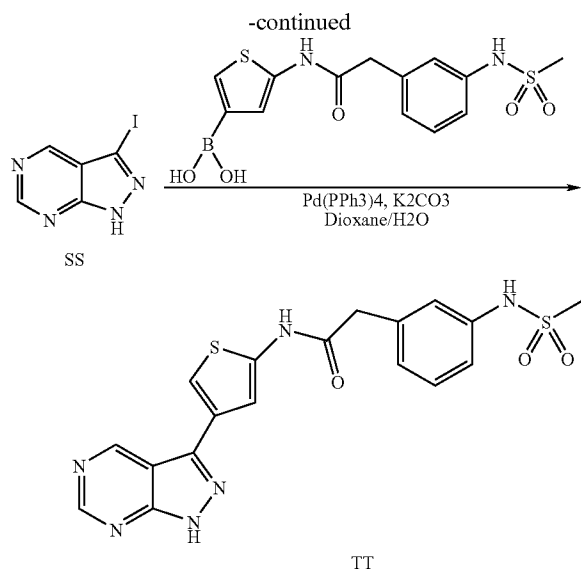
[0150] A mixture of 5-iodo-7H-pyrrolo[2,3-d]pyrimidine (OO) (1 mmol) and 5-(2-(3-methylsulfonamidophenyl)acetamido)thiophen-3-yl-3-boronic acid (E) (1.1 mmol), K₂CO₃ (3 mmol) and Pd(PPh₃)₄ (5%) in the 3 mL dioxane and 1 mL H₂O is heated in microwave to 150° C. for ten minutes. The organic layer is separated and concentrated and the title compound PP is purified by preparative HPLC.

Example 6

Preparation of N-(4-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)thiophen-2-yl)-2-(3-methylsulfonamidophenyl)acetamide

[0151]





1H-Pyrazolo[3,4-d]pyrimidin-3-amine (RR)

[0152] 4-aminopyrimidine-5-carbonitrile (QQ) (1 mmol) in 10 mL conc. HCl is cooled at 0° C., to which 1.2 equiv of NaNO₂ in 1 mL H₂O is added dropwise and reaction mixture is stirred at 0° C. for 10 min. To this reaction mixture, 5 equivalent of SnCl₂ in 5 mL conc. HCl is added and reaction mixture is stirred at room temperature overnight. 30 mL of EtOAc is added to the reaction mixture and then washed with 1N NaOH. The organic layer is separated and dried. The solvent is removed to give title compound 1H-pyrazolo[3,4-d]pyrimidin-3-amine (RR).

3-iodo-1H-pyrazolo[3,4-d]pyrimidine (SS)

[0153] 1H-pyrazolo[3,4-d]pyrimidin-3-amine (RR) (1 mmol) in 3 mL of sulfuric acid (16N) is cooled to 0° C., then 1.2 mmol of NaNO₂ in 1 mL of H₂O of water is added slowly at 0° C. The reaction mixture is stirred at 0° C. for 1 h. 4 mmol of potassium iodide in 3 mL H₂O is poured all at once. The mixture is warmed to room temperature over 1 h then brought to pH of 7.8 using solid sodium carbonate and extracted with dichloromethane. The organic phase is washed with saturated solution of sodium thiosulfate, dried on MgSO₄, and finally evaporated under reduced pressure. The crude product is purified on silica gel column chromatography to obtain the title compound (SS).

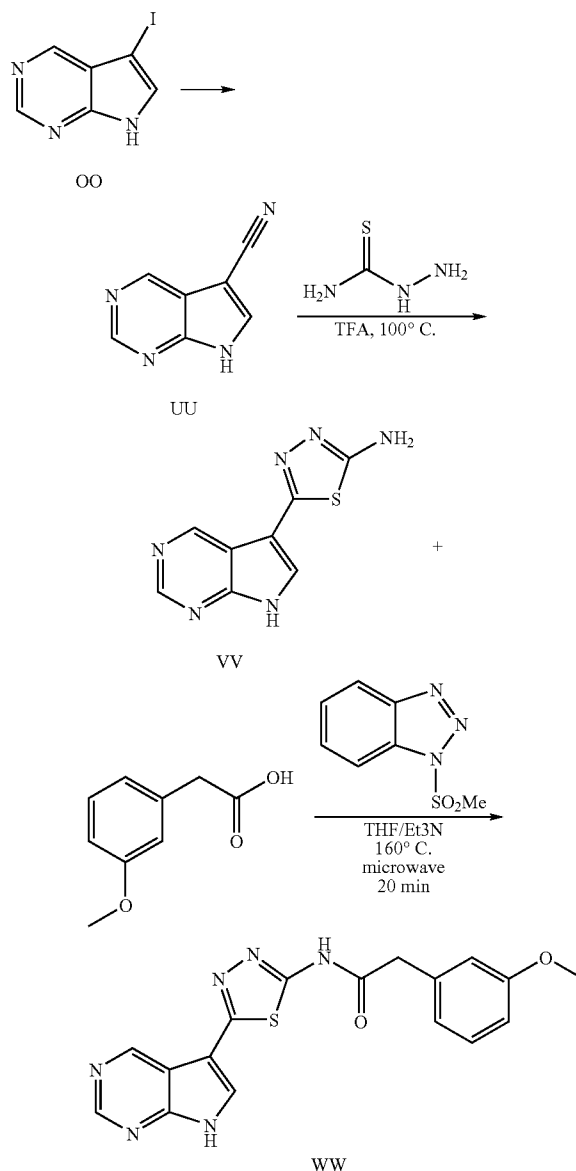
N-(4-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)thiophen-2-yl)-2-(3-methanesulfonylphenyl)acetamide (TT)

[0154] A mixture of 3-iodo-1H-pyrazolo[3,4-d]pyrimidine (SS) (1 mmol) and 5-(2-(3-methanesulfonylphenyl)acetamido)thiophen-3-yl-boronic acid (E) (1.1 mmol), K₂CO₃ (3 mmol) and Pd(PPh₃)₄ (5%) in the 3 mL dioxane and 1 mL H₂O is heated in microwave to 150° C. for ten minutes. The organic layer is separated and the title compound N-(4-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)thiophen-2-yl)-2-(3-methanesulfonylphenyl) acetamide (TT) is purified by preparative HPLC.

Example 7

Preparation of N-(5-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl)-2-(3-methoxyphenyl)acetamide

[0155]



5-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-thiadiazol-2-amine (VV)

[0156] A mixture of 7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (UU) (See Nucleosides, Nucleotides & Nucleic Acids 20: 1823, 2001; 7 mmol) and thiosemicarbazide (2.34 g, 21 mmol) in trifluoroacetic acid (25 mL) is heated in a sealed tube at 100° C. for 2 hr. The brown solution is cooled to room temperature and poured into ice. The mixture is then basified with concentrated NH₄OH and the pale brown

precipitate formed is filtered on a sintered glass filter. The solid is washed thoroughly with water (3×50 mL) and ethyl acetate (3×50 mL) and dried under vacuum to afford 5-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-thiadiazol-2-amine (VV).

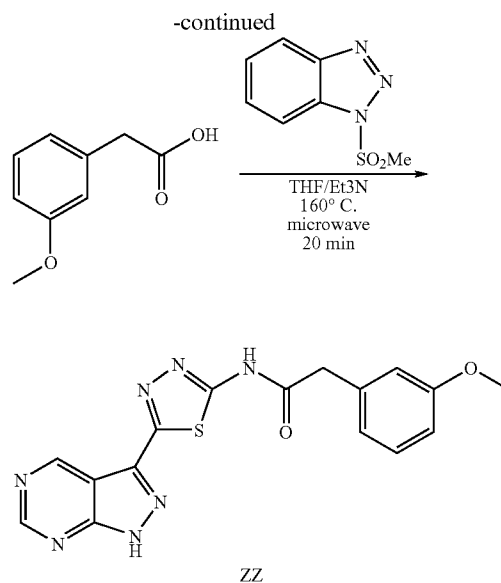
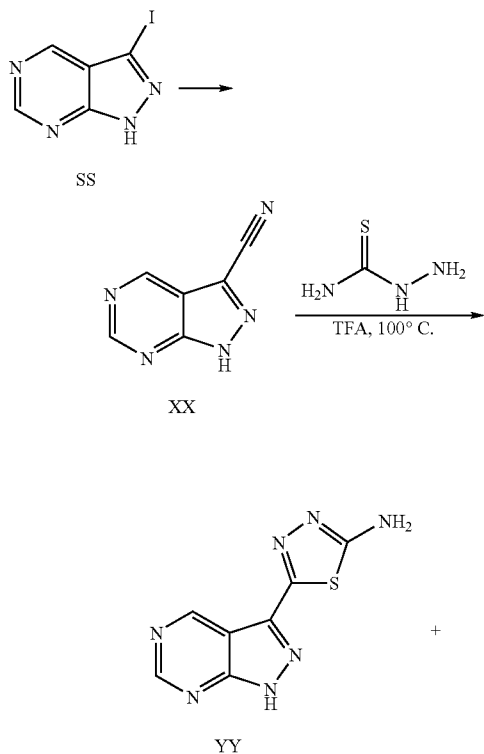
N-(5-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl)-2-(3-methoxyphenyl)acetamide (WW)

[0157] A suspension of 5-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-thiadiazol-2-amine (VV) (0.23 mmol), 3-methoxyphenylacetic acid (0.038 g, 0.23 mmol), triethylamine (0.1 mL) and BtSO_2CH_3 (0.055 g, 0.28 mmol) in THF (3 mL) and DMF (0.3 mL) is heated in a microwave oven for 20 min. The brown solution is added to water (50 mL) and ethyl acetate (50 mL). Brine (10 mL) is added to separate the layers. The organic phase is separated and washed with water (2×50 mL). The organic layer is concentrated to give a solid, which is placed in a small Buchner funnel and washed with methanol (2×5 mL) and ethyl acetate (2×5 mL). The brown solid collected is dried under vacuum to afford the desired product N-(5-(7H-pyrrolo[2,3-d]pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl)-2-(3-methoxyphenyl)acetamide (WW).

Example 8

Preparation of N-(5-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3,4-thiadiazol-2-yl)-2-(3-methoxyphenyl)acetamide

[0158]



5-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3,4-thiadiazol-2-amine (YY)

[0159] A mixture of 1H-pyrazolo[3,4-d]pyrimidine-3-carbonitrile (XX) (See Nucleosides, Nucleotides & Nucleic Acids 20: 1823, 2001; 7 mmol) and thiosemicarbazide (2.34 g, 21 mmol) in trifluoroacetic acid (25 mL) is heated in a sealed tube at 100° C. for 2 hr. The brown solution is cooled to room temperature and poured into ice. The mixture is then basified with concentrated NH_4OH and the pale brown precipitate formed is filtered on a sintered glass filter. The solid is washed thoroughly with water (3×50 mL) and ethyl acetate (3×50 mL) and dried under vacuum to afford 5-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3,4-thiadiazol-2-amine (YY).

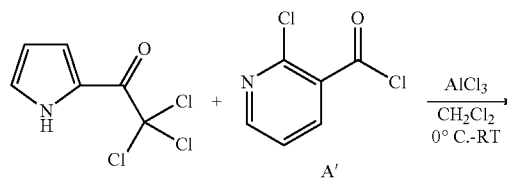
N-(5-(1H-pyrazolo[3,4-d]pyrimidin-3-yl)-1,3,4-thiadiazol-2-yl)-2-(3-methoxyphenyl)acetamide (ZZ)

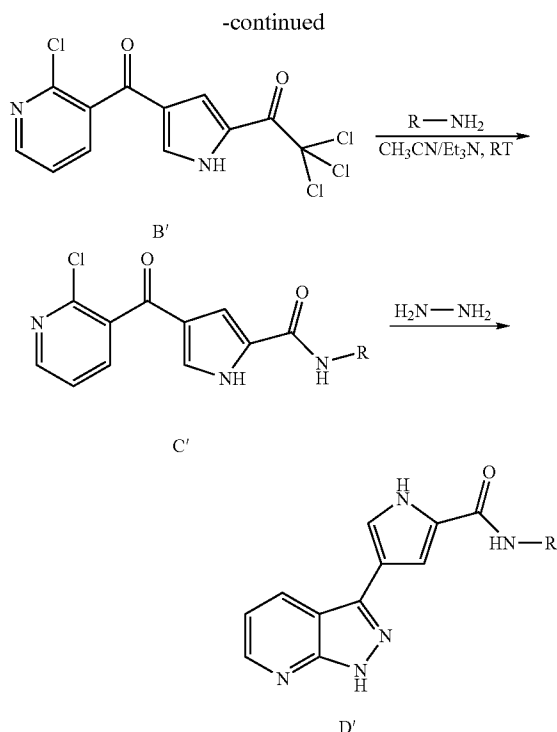
[0160] Compound ZZ is synthesized in a manner similar to compound WW using amine YY instead to give the desired compound ZZ.

Example 9

Preparation of 4-(1H-pyrazolo[3,4-b]pyridin-3-yl)-1H-pyrrole-2-carboxamides

[0161]





(2-chloropyridin-3-yl)1-(5-(2,2,2-trichloroacetyl)-1H-pyrrol-3-yl)methanone (B')

[0162] Aluminum(III) chloride (20 mmol) and compound A' (Aldrich) are dissolved in 10 mL dry CH_2Cl_2 at 0°C . 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone (10 mmol) is added dropwise and the reaction mixture is warmed to room temperature and stirred for 2 hours. The reaction mixture is poured into ice water and extracted with EtOAc. The organic layer is subsequently washed with saturated NaHCO_3 and brine. After drying and evaporation of the organic solvent, the mixture is passed through flash column chromatography to give title compound B' (540 mg, 15% yield).

[0163] Preparation of Compound C'

[0164] Compound B' (60 mg) is dissolved into CH_3CN (2 mL), to which RNH_2 (1.2 equivalent) is added, followed by triethyl amine (1.5 equivalent). The reaction mixture is stirred at room temperature overnight. After the solvent is evaporated, the reaction mixture is carried on to the next step without further purification.

[0165] Preparation of Compound D'

[0166] Compound C' (reaction mixture) is dissolved in 2 mL EtOH, to which 3 equivalent of hydrazine is added. The reaction mixture is heated in the microwave at 170°C for 10 minutes. The reaction mixture is directly applied on HPLC for purification to give title compound D'.

[0167] It will be appreciated that a variety of compounds can be prepared according to the general methods described above.

Example 10

Analytical Results

[0168] Table 2 below depicts exemplary LC mass spectral data (LC/MS), retention time (RT) and ^1H -NMR data (NMR) for certain compounds of the present invention, wherein compound numbers in Table 2 correspond to the compounds depicted in Table 1 (empty cells indicate that the test was not performed):

TABLE 2

Cmpd #	LC/MS	RT	NMR
1			
2	336.00	3.20	DMSO d-6: 3.85(s, 2H), 7.28(m, 2H), 7.39(m, 4H), 7.68(s, 1H), 8.57(d, 1H), 8.72(dd, 1H), 12.52(s, br, 1H), 13.83(s, br, 1H)
3	366.10	3.23	DMSO d-6: 3.77(s, 3H), 3.80(s, 2H), 6.82(m, 1H), 6.93(m, 2H), 7.3(m, 2H), 7.68(s, 1H), 8.56(d, 1H), 8.7(dd, 1H), 12.47(s, br, 1H), 13.75(s, br, 1H)
4	471.10	3.50	DMSO d-6: 1.03(t, 6H), 3.15(q, 4H), 3.65(s, 2H), 7.20(m, 2H), 7.5(m, 1H), 7.6(m, 2H), 7.78(s, 1H), 8.48(dd, 1H), 8.72(dd, 1H)
5	429.10	2.79	DMSO d-6: 2.93(s, 3H), 3.76(s, 2H), 6.99(d, 1H), 7.04(dd, 1H), 7.15(s, 1H), 7.25(dd, 1H), 7.29(dd, 1H), 7.64(s, 1H), 8.55(dd, 1H), 8.7(dd, 1H)
6	446.00	2.30	DMSO-d6: 11.4(brs, 1H), 8.52(m, 2H), 7.57(s, 1H), 7.27(s, 1H), 7.22(m, 1H), 6.72(m, 3H), 3.57(s, 2H), 3.17(s, 3H)
7	476.00	2.36	CD3OD: 8.54(m, 2H), 7.51(d, 1H), 7.33(d, 1H), 7.29(dd, 1H), 7.23(t, 1H), 6.91(m, 2H), 6.82(m, 1H), 4.01(t, 2H), 3.70(s, 1H), 3.34(m, 2H), 2.95(m, 2H), 1.96(m, 2H), 1.81(m, 2H), 1.65(m, 1H), 1.49(m, 2H), 1.34(m, 2H)
8	428.00	2.91	CD3OD: 8.52(m, 2H), 7.51(s, 1H), 7.14-7.33(m, 6H), 3.74(s, 2H), 2.96(s, 3H)
9	447.00	2.79	DMSO-d6: 13.98(s, 1H), 11.58(s, 1H), 9.67(s, 1H), 8.68(d, 1H), 8.62(d, 1H), 7.83(s, 1H), 7.53(d, 1H), 7.15-7.20(m, 3H), 3.77(s, 1H), 2.79(s, 3H)
10	442.00	3.02	CD3OD: 8.57(d, 1H), 8.55(d, 1H), 7.80(s, 1H), 7.68(m, 2H), 7.60(t, 1H), 7.53(d, 1H), 7.34(d, 1H), 7.30(dd, 1H), 3.88(s, 1H), 2.69(s, 6H)
11	411.00	2.32	DMSO: 11.80 s (1H), 9.72 s (1H), 8.71 t (1H), 8.50 m (2H), 7.53 m (1H), 7.49 m (1H), 7.30 t (1H), 7.20 m (2H), 7.10 m (2H), 4.45 d (2H), 2.97 s (3H)
12	286.00	1.71	MeOD: 8.72 d (1H), 8.60 d (1H), 7.60 s (1H), 7.42 s (1H), 7.34 m (1H), 4.18 m (1H), 3.59 m (2H), 1.26 d (3H)
13	348.00	2.64	MeOD: 8.58 m (2H), 7.60 s (1H), 7.40 s (1H), 7.24 m (2H), 6.94 m (2H), 6.80 d (1H), 4.55 (2H), 3.78 s (3H)
14	402.10	2.60	MeOD: 8.54 m (2H), 7.60 s (1H), 7.40 m (3H), 7.28 m (2H), 7.15 d (1H), 4.64 s (2H)
15	362.10	2.59	MeOD: 8.60 m (2H), 7.60 s (1H), 7.38 s (1H), 7.29 dd (1H), 6.87 m (2H), 6.76 m (1H), 5.91 s (2H), 4.47 s (2H)
16	335.90	2.71	MeOD: 8.56 m (2H), 7.60 s (1H), 7.39 m (3H), 7.30 m (1H), 7.05 t (2H), 4.55 s (2H)
17	324.00	2.95	MeOD: 8.55 m (2H), 7.56 s (1H), 7.36 s (1H), 7.27 m (1H), 3.20 d (2H), 1.78 m (4H), 1.67 m (2H), 1.26 m (3H), 1.0 m (2H)
18	336.00	2.70	MeOD: 8.55 m (2H), 7.60 s (1H), 7.40 s (1H), 7.34 m (1H), 7.29 m (1H), 7.18 d (1H), 7.11 d (1H), 6.97 m (1H), 4.58 s (2H)

TABLE 2-continued

Cmpd #	LC/MS	RT	NMR
19	476.00	1.70	CD3OD: 8.44(d, 1H), 8.25 (d, 1H), 7.97(s, 1H), 7.52(s, 1H), 7.33(s, 1H), 7.23(t, 1H), 6.91(m, 2H), 6.81(dd, 1H), 4.01(t, 2H), 3.68(s, 2H), 3.36(m, 2H), 2.94(m, 2H), 1.93(m, 2H), 1.80(m, 2H), 1.68(brm, 1H), 1.49(m, 2H), 1.36(m, 2H).
20	428.00	2.78	CD3OD: 8.44(d, 1H), 8.29(d, 1H), 8.01(s, 1H), 7.31(m, 2H), 7.26(s, 1H), 7.17(d, 1H), 7.14(d, 1H), 3.72(s, 2H), 2.96(s, 3H)

Example 11

ROCK Inhibition Assay

[0169] Compounds are screened for their ability to inhibit ROCK I (AA 6-553) activity using a standard coupled enzyme system (Fox et al. Protein Sci. 7: 2249, 1998). Reactions are carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl, 2 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay are 45 μM ATP (Sigma Chemicals, St Louis, Mo.) and 200 μM peptide (American Peptide, Sunnyvale, Calif.). Reactions are carried out at 30° C. and 45 nM ROCK I. Final concentrations of the components of the coupled enzyme system are 2.5 mM phosphoenolpyruvate, 350 μM NADH, 30 μg/ml pyruvate kinase and 10 μg/ml lactate dehydrogenase.

[0170] Compounds are screened for their ability to inhibit ROCK using a standard radioactive enzyme assay. Assays are carried out in a solution containing 100 mM HEPES (pH 7.5), 10 mM MgCl₂, 25 mM NaCl, 2 mM DTT and 1.5% DMSO. Final substrate concentrations in the assay are 13 μM [γ -³³P] ATP (25 mCi ³³P ATP/mmol ATP, Perkin Elmer, Cambridge, Mass./Sigma Chemicals, St Louis, Mo.) and 27 μM Myelin Basic Protein (MBP). Final enzyme concentration in the assay is 5 nM ROCK. Assays are carried out at room temperature. 1.5 μl of DMSO stock containing serial dilutions of the compound of the present invention (concentrations ranging from 10 μM to 2.6 nM) is placed in a 96 well plate. 50 μl of Solution 1 (100 mM HEPES (pH 7.5), 10 mM MgCl₂, 26 mM [γ -³³P] ATP) is added to the plate. The reaction is initiated by addition of 50 μl of Solution 2 (100 mM HEPES (pH 7.5), 10 mM MgCl₂, 4 mM DTT, 54 mM MBP and 10 nM ROCK). After 2 hours the reaction is quenched with 50 μL of 30% trichloroacetic acid (TCA, Fisher) containing 9 mM ATP. Transfer of 140 μL of the quenched reaction to a glass fiber filter plate (Corning, Cat. No. 3511) is followed by washing 3 times with 5% TCA. 50 μL of Optima Gold scintillation fluid (Perkin Elmer) is added and the plates are counted on a Top Count (Perkin Elmer). After removing mean background values for all of the data points the data is fit using Prism software to obtain a K_i(app).

[0171] Table 3 depicts enzyme inhibition data (K_i) for certain exemplary compounds. Compound numbers in Table 3 correspond to those compounds depicted in Table 1.

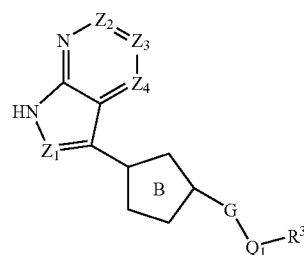
[0172] In Table 3, "A" represents a K_i of less than 0.5 μM and "B" represents a K_i of between 0.5 and 5.0 μM. the term

"Enzyme" indicates that an enzyme-linked assay was used; the term "³³P" indicates that a radioactive assay was used.

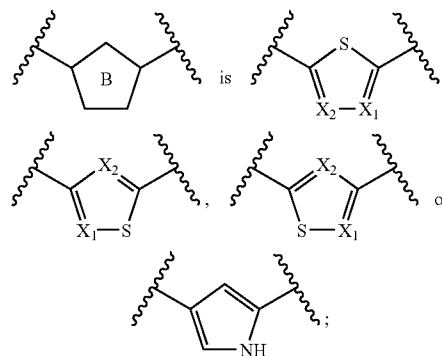
TABLE 3

Cmpd #	ROCK ³³ P	ROCK Enzyme
1		A
2	A	
3	A	
4	A	
5	A	
6	A	
7	A	
8	A	
9	A	
10	A	
11	A	
12	B	
13	A	
14	A	
15	A	
16	A	
17	A	
18	A	
19	A	
20	A	

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:
wherein



Z₁, Z₂, Z₃ and Z₄ are each independently selected from N or CR¹, wherein at least one of Z₁, Z₂, or Z₄ is N;

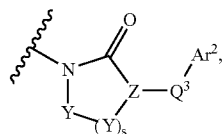
each R¹ is independently selected from H, halogen, —CN, —NO₂, or —V_mR¹;

G is —NR²— or —CO—;

Q^1 is $-\text{CO}-$, $-\text{SO}_2-$, $-\text{NR}^2$, $-\text{NR}^2\text{CO}-$, $-\text{CONR}^2-$, $-\text{SO}_2\text{NR}^2-$, or is a bond;

R^2 is $-\text{U}_n\text{R}''$;

R^3 is $Q^2-\text{Ar}^1$, or when G is $-\text{NR}^2$, R^2 and Q^1-R^3 , taken together with the nitrogen atom, may form the cyclic group:



where s is 1 or 2, Z is CH or N; wherein each occurrence of Y is independently $-\text{CO}-$, $-\text{CS}-$, $-\text{SO}_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{NR}^5-$, or $-\text{C}(\text{R}^5)_2-$, and R^5 is $\text{U}_n\text{R}''$;

X_1 and X_2 are each independently selected from CR^4 or N;

each occurrence of R^4 is independently selected from halogen, CN, NO_2 , or V_mR ;

each occurrence of U or V is independently selected from an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by $-\text{NR}-$, $-\text{S}-$, $-\text{O}-$, $-\text{CS}-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{CO}-$, $-\text{COCO}-$, $-\text{CONR}-$, $-\text{NRCO}-$, $-\text{NRCO}_2-$, $-\text{SO}_2\text{NR}-$, $-\text{NRSO}_2-$, $-\text{CONRNR}-$, $-\text{NRCONR}-$, $-\text{OCONR}-$, $-\text{NRNR}-$, $-\text{NRSO}_2\text{NR}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{PO}-$, $-\text{PO}_2-$, or $-\text{POR}-$;

m and n are each independently 0 or 1;

each occurrence of R is independently selected from hydrogen or a C_{1-6} aliphatic group, wherein said aliphatic group is optionally substituted with up to five occurrences of J^{R} ;

each occurrence of R' is independently selected from hydrogen, a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said aliphatic group, monocyclic ring or bicyclic ring is optionally substituted with up to five occurrences of J^{R} ;

R'' is selected from hydrogen, a C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said aliphatic group, monocyclic ring or bicyclic ring is optionally substituted with up to five occurrences of J^{R} ;

or two occurrences of R , R' and R'' , in any combination thereof, are taken together with the atom(s) to which

they are bound to form a 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said monocyclic or bicyclic ring is optionally substituted with J^{R} ;

each occurrence of J^{R} , $\text{J}^{\text{R}'}$ and $\text{J}^{\text{R}''}$ is independently selected from halogen, L , $-(\text{L}_p)-\text{R}^j$, $-(\text{L}_p)-\text{N}(\text{R}^j)_2$, $-(\text{L}_p)-\text{SR}^j$, $-(\text{L}_p)-\text{OR}^j$, $-(\text{L}_p)-(\text{C}_{3-10} \text{ cycloaliphatic})$, $-(\text{L}_p)-(\text{C}_{6-10} \text{ aryl})$, $-(\text{L}_p)-(\text{5-10 membered heteroaryl})$, $-(\text{L}_p)-(\text{5-10 membered heterocyclyl})$, oxo, $\text{C}_{1-4}\text{haloalkoxy}$, $\text{C}_{1-4}\text{haloalkyl}$, $-(\text{L}_p)-\text{NO}_2$, $-(\text{L}_p)-\text{CN}$, $-(\text{L}_p)-\text{OH}$, $-(\text{L}_p)-\text{CF}_3$, $-\text{CO}_2\text{R}^j$, $-\text{CO}_2\text{H}$, $-\text{COR}^j$, $-\text{COH}$, $-\text{OC}(\text{O})\text{R}^j$ or $-\text{NC}(\text{O})\text{R}^j$; or any two J^{R} , $\text{J}^{\text{R}'}$ or $\text{J}^{\text{R}''}$ groups, on the same substituent or different substituents, together with the atom(s) to which each J^{R} , $\text{J}^{\text{R}'}$ or $\text{J}^{\text{R}''}$ group is bound, form a 5-7 membered saturated, unsaturated, or partially saturated ring;

R^j is H or C_{1-6} aliphatic; or two R^j groups or an R^j group and an R , R' or R'' group, together with the atom to which they are attached, optionally form a 3-6 membered cycloaliphatic or heterocyclyl, wherein said aliphatic, cycloaliphatic or heterocyclyl is optionally substituted with R^* , $-\text{OR}^*$, $-\text{SR}^*$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{CN}$, $-\text{CO}_2\text{R}^*$, $-\text{COR}^*$, OCOR^* or NHCOR^* , wherein R^* is H or an unsubstituted C_{1-6} aliphatic;

L is a C_{1-6} aliphatic wherein up to three methylene units are replaced by $-\text{NH}-$, $-\text{NR}^{\text{L}}-$, $-\text{O}-$, $-\text{S}-$, $-\text{CO}_2-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{CO}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{NR}^6-$, $-\text{C}(=\text{N}-\text{CN})$, $-\text{NHCO}-$, $-\text{NR}^{\text{L}}\text{CO}-$, $-\text{NHC}(\text{O})\text{O}-$, $-\text{NR}^{\text{L}}\text{C}(\text{O})\text{O}-$, $-\text{SO}_2\text{NH}-$, $-\text{SO}_2\text{NR}^{\text{L}}-$, $-\text{NHSO}_2-$, $-\text{NR}^{\text{L}}\text{SO}_2-$, $-\text{NHC}(\text{O})\text{NH}-$, $-\text{NR}^{\text{L}}\text{C}(\text{O})\text{NH}-$, $-\text{NHC}(\text{O})\text{NR}^{\text{L}}-$, $-\text{NR}^{\text{L}}\text{C}(\text{O})\text{NR}^{\text{L}}-$, $-\text{OC}(\text{O})\text{NH}-$, $-\text{OC}(\text{O})\text{NR}^{\text{L}}-$, $-\text{NHSO}_2\text{NH}-$, $-\text{NR}^{\text{L}}\text{SO}_2\text{NH}-$, $-\text{NHSO}_2\text{NR}^{\text{L}}-$, $-\text{NR}^{\text{L}}\text{SO}_2\text{NR}^{\text{L}}-$, $-\text{SO}-$ or $-\text{SO}_2-$;

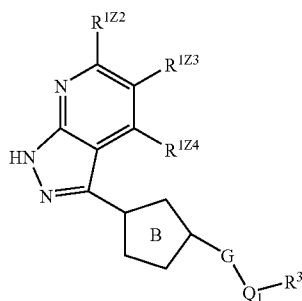
R^{L} is selected from C_{1-6} aliphatic, C_{3-10} cycloaliphatic, C_{6-10} aryl, 5-10 membered heteroaryl or 5-10 membered heterocyclyl; or two R^{L} groups, on the same substituent or different substituents, together with the atom(s) to which each R^{L} group is bound, form a 3-8 membered heterocyclyl;

each p is independently 0 or 1;

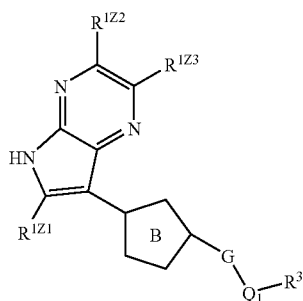
Q^2 and Q^3 are each independently selected from a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by $-\text{NR}'-$, $-\text{S}-$, $-\text{O}-$, $-\text{CS}-$, $-\text{CO}_2-$, $-\text{OCO}-$, $-\text{CO}-$, $-\text{COCO}-$, $-\text{CONR}'-$, $-\text{NR}'\text{CO}-$, $-\text{NR}'\text{CO}_2-$, $-\text{SO}_2\text{NR}'-$, $-\text{NR}'\text{SO}_2-$, $-\text{CONR}'\text{NR}'-$, $-\text{NR}'\text{CONR}'-$, $-\text{OCONR}'-$, $-\text{NR}'\text{NR}'-$, $-\text{NR}'\text{SO}_2\text{NR}'-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{PO}-$, $-\text{PO}_2-$, or $-\text{POR}'-$; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, $-\text{CN}$, $-\text{NO}_2$, or $-\text{U}_n\text{R}'$, or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

Ar¹ and Ar² are each independently selected from a C₁₋₆ aliphatic, a 3-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ and Ar² are each optionally substituted with 0-5 independent occurrences of TR⁷; wherein T is a bond or is a C₁₋₆ alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by —NR—, —S—, —O—, —CS—, —CO₂—, —OCO—, —CO—, —COCO—, —CONR—, —NRCO—, —NRCO₂—, —SO₂NR—, —NRSO₂—, —CONRNR—, —NRCONR—, —OCONR—, —NRNR—, —NRSO₂NR—, —SO—, —SO₂—, —PO—, —PO₂—, or —POR—; and each occurrence of R⁷ is independently selected from —R', halogen, —NO₂, —CN or =O.

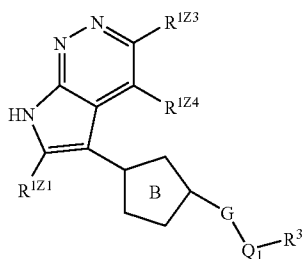
2. The compound according to claim 1, having one of formulae II-VII:



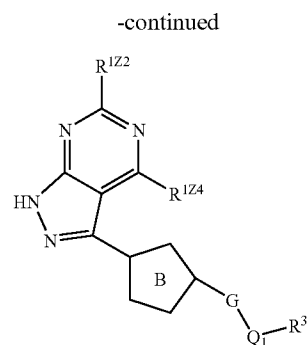
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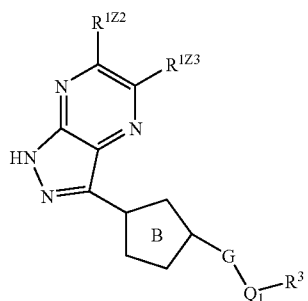
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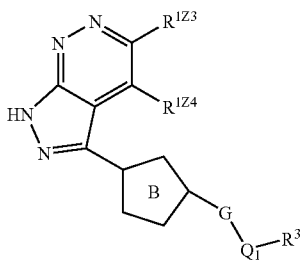
IV



V



VI



VII

wherein R^{1Z1}, R^{1Z2}, R^{1Z3} and R^{1Z4} are each independently selected from H, halogen, —CN, —NO₂, or —V_mR'.

3-4. (canceled)

5. The compound according to claim 1, wherein X₁ is CR⁴ and X₂ is N or CR⁴.

6. (canceled)

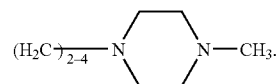
7. The compound according to claim 1, wherein each R¹ is independently selected from H, halogen or C₁₋₃ aliphatic.

8-13. (canceled)

14. The compound according to claim 1, wherein Q¹ is —CO—, —SO₂—, —NR², —NR²CO—, —CONR²—, —SO₂NR².

15. The compound according to claim 14, wherein G is —NR² and Q¹ is —CO—, or G is —CO— and Q¹ is —NR²—.

16. The compound according to claim 15, wherein R² is H, —C₁₋₄ aliphatic, -cyclopropyl, (CH₂)₁₋₃OH or



17. (canceled)

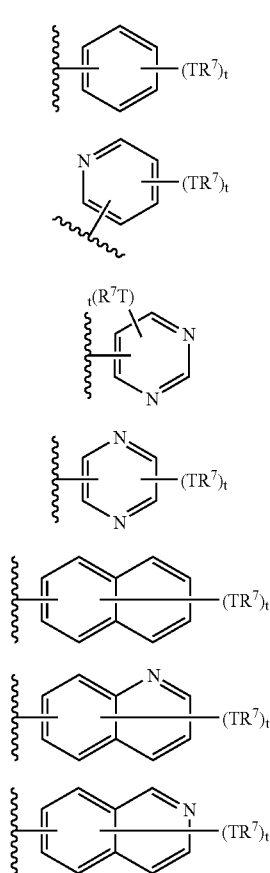
18. The compound according to claim 1, wherein R^3 is Q^2 -Ar¹.

19. The compound according to claim 18, wherein Q^2 is $-(CHR^6)_q-$, $-(CHR^6)_qO-$, $-(CHR^6)_qS-$, $-(CHR^6)_qS(O)_2-$, $-(CHR^6)_qS(O)-$, $-(CHR^6)_qNR-$, or $-(CHR^6)_qC(O)-$, wherein q is 0, 1, 2, or 3, and each R^6 is R' , $-N(R)(R')$, $-(CH_2)_{1-4}N(R)(R')$, $-(CH_2)_{1-4}C(CH_3)_2N(R)(R')$, $-(CH_2)_{1-4}CH(CH_3)N(R)(R')$, $-OR'$, $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring.

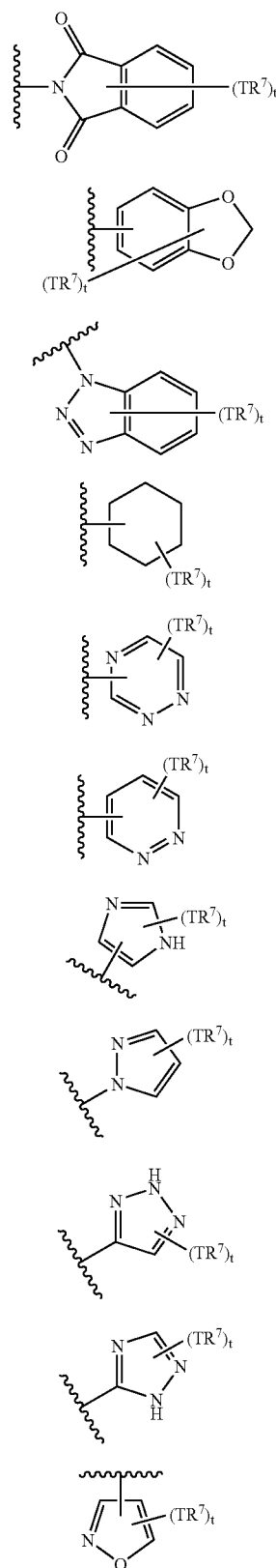
20-21. (canceled)

22. The compound according to claim 18, wherein Ar¹ is a C₃₋₆ aliphatic, a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ is optionally substituted with 0-5 independent occurrences of TR⁷.

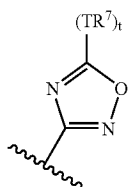
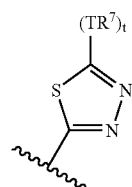
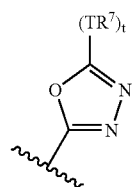
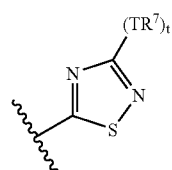
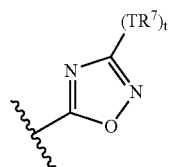
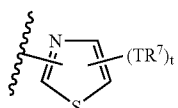
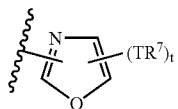
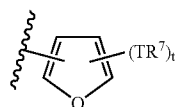
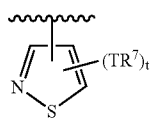
23. The compound according to claim 22, wherein Ar¹ is



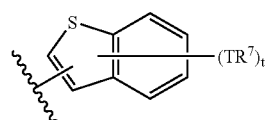
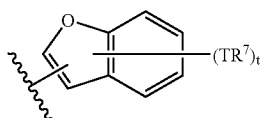
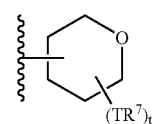
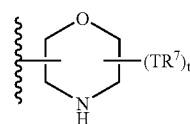
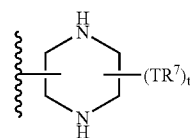
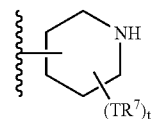
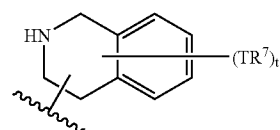
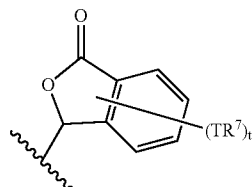
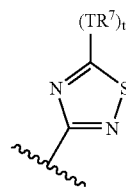
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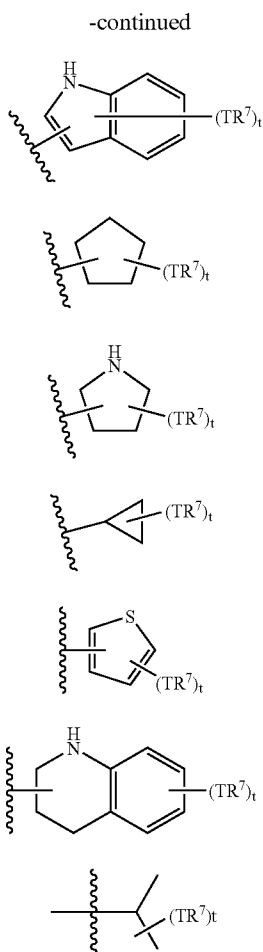


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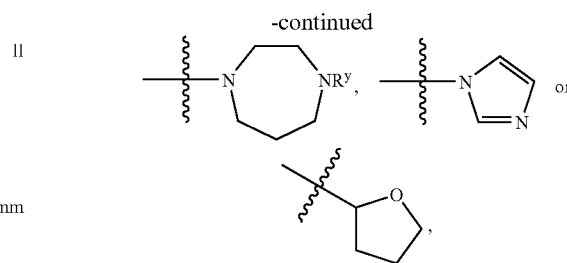
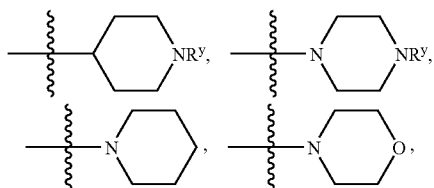




wherein t is 0, 1, 2, 3, 4, or 5, and wherein any Ar^1 is bonded to Q^2 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7 .

24-26. (canceled)

27. The compound according to claim 22, wherein TR^7 is selected from $-F$, $-Cl$, $-CN$, $-NH_2$, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-OR^x$, $-OCF_3$, $-NR^xSO_2R^x$, $-NR^xSO_2N(R^x)_2$, $-COOC(CH_3)_3$, $-OSO_2CH_3$, $-OH$, $-SO_2N(R^x)_2$, $-SO_2N(R^x)_2$, $-SO_2R^x$, -pyrrolidinone, tetrahydrofuran or $-D-(CH_2)_p-Y$, wherein R^x is a H or a C_{1-4} alkyl, D is $-SO_2-$, $-SO_2NH-$, $-NHSO_2-$ or $-O-$, p is 0-3, and Y is selected from:



wherein R^y is H or C_{1-3} alkyl, and wherein one or more carbon atoms of Y is optionally substituted with $=O$.

28-31. (canceled)

32. The compound according to claim 1, wherein said compound has a structure depicted in Table 1.

33. A composition comprising an effective amount of compound according to claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

34. The composition of claim 33, additionally comprising a therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

35. A method of inhibiting ROCK kinase activity in a biological sample; which method contacting said biological sample with a compound of claim 1 or a composition comprising said compound.

36. A method of treating or lessening the severity of a disease condition or disorder selected from a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder, comprising the step of administering to said patient a compound according to claim 1 or a composition comprising said compound.

37. The method of claim 36, comprising the additional step of administering to said patient an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an anti-psychotic agent, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein: said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

38-40. (canceled)