QUINOXALINE COMPOUNDS, METHOD FOR PREPARING THE SAME AND USE THEREOF

BACKGROUND OF INVENTION

Field of the Invention

[0001] The present invention relates to novel chemical compounds and methods for their use in therapy and preparation. In particular, the invention relates to certain substituted quinoxaline compounds and to the use for their inhibition, regulation and/or modulation of particular kinases and their related signal transduction pathways.

Background Art

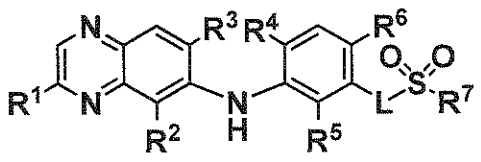
[0002] Protein kinases (PKs) play important roles in cellular signal transduction pathways that regulate various cell functions, such as differentiation, proliferation, migration, survival, and apoptosis. These enzymes catalyze the transfer of a phosphate group from ATP to a tyrosine, serine or threonine residue on a protein substrate. The phosphorylation by kinase and dephosphorylation by phosphatase are involved in countless cellular processes that respond to diverse intracellular or extracellular signals, regulation of cellular functions, and activation or deactivation of cellular operations.

[0003] Abnormal PK activity has been linked to cancer as well as metabolic, immunological, and nervous system disorders. Therefore, protein kinases are attractive therapeutic targets for human disease interventions. PK inhibitors, i.e., compounds that block the activities of PKs, have been developed and used widely for clinical applications. While more than thirty PK inhibitors have been approved for use in disease treatments, such as cancer therapy, there is still a need for new PK inhibitors to treat various disorders or to overcome drug-resistance. The identification of effective small molecule compounds that can specifically inhibit signal transduction and cellular proliferation, by modulating PK activity to regulate and modulate inappropriate cell proliferation, differentiation, or metabolism that is essential for processes leading to cancer, would be beneficial.

SUMMARY

[0004] Embodiments of the present disclosure are based on unexpected findings that certain quinoxaline compounds can inhibit activities of protein kinase (e.g., B-Raf, B-Raf^{V600E}, C-Raf). These properties allow these quinoxaline compounds to be used in treating protein kinase-related diseases including cancers.

[0005] In one aspect, embodiments of the present disclosure relate to quinoxaline compounds of formula (I)



formula (I)

or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein L is NR^8 or O, and R^1, R^2, R^3, R^4 , R^5, R^6, and R^7 are as defined below.

[0006] In accordance with any of the above-described embodiments, R^1 in formula (I) is selected from the group consisting of hydrogen, halogen, NR^9R^{10}, OR^{11}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, phenyl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloakyl, phenyl, heterocyclyl, and heteroaryl may be optionally substituted with halogen, oxo (except for phenyl or heteroaryl), OR^a, SR^a, NR^bR^c, phenyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and cyclopropyl, wherein the alkyl, alkoxy, and cyclopropyl may be optionally substituted with R^d, wherein R^9, R^{10}, R^{11}, R^a, R^b, R^c, and R^d are independently as defined below.

[0007] In accordance with any of the above-described embodiments, R^2 in formula (I) is selected from the group consisting of hydrogen, halogen, nitro, CN, OR^{11}, COR^{12}, and $NR^{13}R^{14}$, provided that R^2 is hydrogen or halogen only when R^1 is NR^9R^{10}, wherein R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} are independently as defined below.

[0008] In accordance with any of the above-described embodiments, R^3 in formula (I) is selected from the group consisting of hydrogen, halogen, hydroxy, azido, cyano, nitro, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloakyl, phenyl, heterocyclyl, and heteroaryl may be optionally substituted with halogen, oxo (except for phenyl or heteroaryl), OR^a, SR^a, NR^bR^c, phenyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and cyclopropyl, wherein the alkyl, alkoxy, and cyclopropyl may be optionally substituted with R^d, provided that R^3 is hydrogen or halogen only when R^1 is NR^9R^{10}, wherein R^a, R^b, R^c, R^9, and R^{10} are independently as defined below.

[0009] In accordance with any of the above-described embodiments, R^4, R^5 and R^6 in formula (I) are independently selected from the group consisting of hydrogen, halogen, hydroxyl, amino, CN, C_1-C_4 alkyl, alkoxy C_1-C_4 alkoxy, dialkylamino, C_1-C_4 alkoxy, and heterocyclyl.

[0010] In accordance with any of the above-described embodiments, R^7 in formula (I) is C_1-C_4 alkyl, C_1-C_4 haloalkyl, or aryl.

[0011] In accordance with any of the above-described embodiments, R^8 is selected from the group consisting of hydrogen, SO_2R^{15}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, and a 3-to-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloakyl and heterocyclyl may be optionally substituted with halogen, oxo (except for phenyl or heteroaryl), OR^a, SR^a, NR^bR^c, phenyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and cyclopropyl, wherein the alkyl, alkoxy, and cyclopropyl may be optionally substituted with R^d, wherein R^{15}, R^a, R^b, R^c, and R^d are independently as defined below.

[0012] In accordance with any of the above-described embodiments, R^9 and R^{10} are independently selected from the group consisting of hydrogen, COR^{15}, SO_2R^{15}, OR^{16}, $NR^{17}R^{18}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkyl, alkenyl,

OR^a, SR^a, NR^bR^c, phenyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and cyclopropyl, wherein the alkyl, alkoxy, and cyclopropyl may be optionally substituted with R^d, wherein R^a, R^b, R^c, and R^d are independently as defined below.

[0019] In accordance with any of the above-described embodiments, R^{17} and R^{18} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, cycloakyl, phenyl, heterocyclyl, and heteroaryl may be optionally substituted with halogen, oxo (except for phenyl or heteroaryl), OR^a, SR^a, NR^bR^c, phenyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, and cyclopropyl, wherein the alkyl, alkoxy, and cyclopropyl may be optionally substituted with R^d, wherein R^a, R^b, R^c, and R^d are independently as defined below.

[0020] In accordance with any of the above-described embodiments, R^{19} is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and aryl.

[0021] In accordance with any of the above-described embodiments, R^{20} and R^{21} are independently selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and aryl.

[0022] In accordance with any of the above-described embodiments, each R^a is independently hydrogen or C_1-C_4 alkyl.

[0023] In accordance with any of the above-described embodiments, each R^b and R^c are independently selected from the group consisting of hydrogen, SO_2R^7 and C_1-C_4 alkyl, wherein C_1-C_4 alkyl may be optionally substituted with halogen, wherein R^7 is as defined above.

[0024] In accordance with any of the above-described embodiments, each R^d is independently selected from the group consisting of halogen, oxo, C_1-C_4 alkyl, and C_1-C_4 alkoxyl, wherein the C_1-C_4 alkyl and C_1-C_4 alkoxyl may be optionally substituted with halogen.

[0025] Preferred embodiments of the present disclosure relate to a compound selected from the group consisting of *N*1-3-[(3-{2,6-difluoro-3-[(propylsulfonyl)amino]anilino}-6-quinoxalinyl)amino]-2,4-difluorophenyl-1-propanesulfonamide; *N*1-(3-{[3-(2,6-difluoroanilino)-6-quinoxalinyl]amino}-2,4-difluorophenyl)-1-propanesulfonamide; *N*1-{3-[(5-amino-3-methoxy-6-quinoxalinyl)amino]-2,4-difluorophenyl}-1-propanesulfonamide; *N*1-{2,4-difluoro-3-[(3-methoxy-5-nitro-6-quinoxalinyl)amino]phenyl}-1-propanesulfonamide; *N*1-{2,4-difluoro-3-[(3-methoxy-5-nitro-6-quinoxalinyl)amino]phenyl}-3-fluoro-1-propanesulfonamide; *N*1-(2,4-difluoro-3-{[3-(2-morpholinoethoxy)-5-nitro-6-quinoxalinyl]amino}phenyl)-1-propanesulfonamide; *N*1-(2,4-difluoro-3-[3-(2-methoxyethoxy)-5-nitro-6-quinoxalinyl]aminophenyl)-1-propanesulfonamide; *N*1-(7-{2,6-difluoro-3-[(propylsulfonyl)amino]anilino}-2-quinoxalinyl)-1-cyclopropanecarboxamide; *N*1-[3-({3-[2-(dimethylamino)ethoxy]-5-nitro-6-quinoxalinyl}amino)-2,4-difluorophenyl]-1-propanesulfonamide; *N*1-{3-[(5-cyano-3-methoxy-6-quinoxalinyl)amino]-2,4-difluorophenyl}-1-propanesulfonamide; *N*1-(2,4-difluoro-3-{[3-(2-fluoroanilino)-

3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-fluorophenyl)benzenesulfonamide; and *N*-(2-cyano-3-(5-cyano-3-methoxyquinoxalin-6-ylamino)phenyl) propane-1-sulfonamide.

[0026] Embodiments of the present disclosure relate to methods for preventing or treating a disease or disorder modulated/mediated by or related to a protein kinase. The kinase may include, but are not limited to, B-Raf, B-Raf^{V600E}, C-Raf, MEK1, etc. An exemplary method for preventing or treating a disease or disorder modulated/mediated by or related to a protein kinase comprises administering to a subject (such as, mammal) in need of such treatment an effective amount of a compound of the present disclosure or a stereoisomer, tautomer, solvate, prodrug or pharmaceutically acceptable salt thereof. Examples of such diseases and disorders include, but are not limited to, hyperproliferative disorders (such as cancer, including melanoma and other cancers of the skin), neurodegeneration, cardiac hypertrophy, pain, migraine and neurotraumatic disease, kidney diseases (such as polycystic kidney disease), etc.

[0027] The present disclosure also provides the use of a compound of the present disclosure in the manufacture of a medicament for the treatment of a hyperproliferative disease. In a further embodiment, the hyperproliferative disease may be cancer (or still further, a specific cancer as defined herein).

[0028] Another aspect of the present disclosure provides the use of an effective amount of a compound of the present disclosure in the manufacture of a medicament for the treatment of a protein kinase associated disease or disorder. In embodiments, the protein kinase associated diseases or disorders may be hyperproliferative disorders (such as cancer, including melanoma and other cancers of the skin), neurodegeneration, cardiac hypertrophy, pain, migraine and neurotraumatic disease, kidney diseases (such as polycystic kidney disease). The protein kinase may be B-Raf, and the medicament is an inhibitor of B-Raf.

[0029] Another aspect of the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, a stereoisomer, tautomer, a salt, solvate, prodrug or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0030] Other aspects and advantages of the present disclosure will be apparent from the following description and the appended claims.

DETAILED DESCRIPTION

Definition

[0031] Reference will now be made in detail to certain embodiments, examples of which are illustrated in the accompanying structures and formulas. While enumerated embodiments will be described, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many

N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-4-fluorophenyl)benzenesulfonamide;
N-(3-(5-cyano-3-ethoxyquinoxalin-6-ylamino)-4-fluorophenyl)propane-1-sulfonamide;
N-(3-(5-cyano-3-(dimethylamino)quinoxalin-6-ylamino)-4-fluorophenyl)benzenesulfonamide;
N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-2-methylphenyl)propane-1-sulfonamide;
N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-methylphenyl)propane-1-sulfonamide;
N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-4-methylphenyl)propane-1-sulfonamide;
N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-4-fluorophenyl)methanesulfonamide;
N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-2,4-difluorophenyl)-N-ethylpropane-1-sulfonamide;
N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-2,4-difluorophenyl)-N-methylpropane-1-sulfonamide;
N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-2-methylphenyl)propane-1-sulfonamide;
N-(5-(5-cyano-3-methoxyquinoxalin-6-ylamino)-2-methylphenyl)propane-1-sulfonamide;
N-(2-chloro-3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-4-fluorophenyl)propane-1-sulfonamide;
N-(2-chloro-3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-4-fluorophenyl)benzenesulfonamide;
N-(2-chloro-3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-fluorophenyl)propane-1-sulfonamide;
N-(2-chloro-3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-fluorophenyl) benzenesulfonamide; or
N-(2-cyano-3-(5-cyano-3-methoxyquinoxalin-6-ylamino)phenyl) propane-1-sulfonamide.

7. A pharmaceutical composition, comprising a compound of any one of claims **1-6**, a salt thereof, a stereoisomer thereof, or a pro-drug thereof; and a pharmaceutically acceptable carrier.

8. Use of an effective amount of the compound of any one of claims **1-6** in the manufacture of a medicament, for treating a protein kinase-related disease.

9. The use of claim **8**, wherein the protein kinase-related disease is cancer, diabetes, a renal disease, fibrosis, osteoarthritis, an autoimmune disease, or a blood vessel proliferative disorder.

10. The use of claim **9**, wherein the protein kinase-related disease is cancer.

11. The use of claim **10**, wherein the cancer is lung cancer, colon cancer, colorectal cancer, breast cancer, prostate cancer, liver cancer, pancreatic cancer, bladder cancer, gastric cancer, renal cancer, salivary gland cancer, ovarian cancer, uterine body cancer, cervical cancer, oral cancer, skin cancer, brain cancer, lymphoma, or leukemia.