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 wherein the protein kinase-related disease is cancer, diabetes, a renal disease, fibrosis, osteoarthritis, an autoimmune disease, or a blood vessel proliferative 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, 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

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 are optionally substituted with R^d, provided that R^2 and R^3 are independently selected from hydrogen or halogen only when R^9 and R^{10} are not hydrogen or C_1-C_4 alkyl; or

R^9 and R^{10}, together with the nitrogen atom to which they are attached, form a 3-to-6 membered heterocyclyl, which is optionally substituted by halogen, oxo or C_1-C_3 alkyl;

R^{11} is selected from the group consisting of hydrogen, 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 are 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 are optionally substituted with R^d;

R^{12} is selected from the group consisting of hydrogen, OR^{19}, $NR^{20}R^{21}$, 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 are 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 are optionally substituted with R^d,

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, COR^{15}, SO_2R^{15}, 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 are 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 are optionally substituted with R^d;

R^{15} is selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, and aryl;

R^{16} is selected from the group consisting of hydrogen, 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 are 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 are optionally substituted with R^d;

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 are 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 are optionally substituted with R^d,

*N*1-(3-{[3-(2,4-difluoroanilino)-6-quinoxalinyl]amino}-2,4-difluorophenyl)-1-propanesulfonamide;

N-{2,4-difluoro-3-[(3-methoxy-5-nitro-6-quinoxalinyl)amino]phenyl}methanesulfonamide;

*N*1-{3-[(5-cyano-3-hydroxy-6-quinoxalinyl)amino]-2,4-difluorophenyl}-1-propanesulfonamide;

*N*1-(3-{[5-cyano-3-(2-morpholinoethoxy)-6-quinoxalinyl]amino)-2,4-difluorophenyl)-1-propanesulfonamide;

N-(3-(5-cyano-3-ethoxyquinoxalin-6-ylamino)-2,4-difluorophenyl)propane-1-sulfonamide;

N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-2,4-difluorophenyl)propane-1-sulfonamide;

N-(3-(5-cyano-3-methoxyquinoxalin-6-ylamino)-2,6-difluorophenyl)propane-1-sulfonamide;

N-(5-(5-cyano-3-methoxyquinoxalin-6-ylamino)-2-fluorophenyl)propane-1-sulfonamid e;

N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-fluorophenyl)propane-1-sulfonamide;

N-(3-(5-cyano-3-ethoxyquinoxalin-6-ylamino)-4-fluorophenyl)benzenesulfonamide;

N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-fluorophenyl)benzenesulfonamide;

N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-4-fluorophenyl)methanesulfonamide;

N-(3-(5-cyano-3-ethoxyquinoxalin-6-ylamino)-4-fluorophenyl)methanesulfonamide;

N-(2,4-difluoro-3-(5-formyl-3-methoxyquinoxalin-6-ylamino)phenyl)propane-1-sulfonamide;

6-(2,6-difluoro-3-(propylsulfonamido)phenylamino)-3-methoxyquinoxaline-5-carboxylic acid;

methyl 6-(2,6-difluoro-3-(propylsulfonamido)phenylamino)-3-methoxyquinoxaline-5-carboxylate;

N-(2,4-difluoro-3-(3-methoxy-7-methylquinoxalin-6-ylamino)phenyl)propane-1-sulfonamide;

N-(3-(5-cyano-3-morpholinoquinoxalin-6-ylamino)-2,4-difluorophenyl)-3-fluoropropane-1-sulfonamide;

N-(3-(5-cyano-3-ethoxyquinoxalin-6-ylamino)-2,4-difluorophenyl)-3-fluoropropane-1-sulfonamide;

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-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, or a stereoisomer 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, wherein the protein kinase-related disease is cancer, diabetes, a renal disease, fibrosis, osteoarthritis, an autoimmune disease, or a blood vessel proliferative disorder.

9. The use of claim 8, wherein the protein kinase-related disease is cancer.

10. The use of claim 9, 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.