[0005] FLT3 plays an important role in the proliferation and differentiation of hematopoietic stem cells. More than a dozen FLT3 inhibitors are being developed, some of which have shown promising clinical effects against AML. FLT3 receptor is also expressed in dendritic cell progenitors and inhibition of FLT3 down-regulates DC-mediated inflammatory and autoimmune responses.

[0006] c-KIT (or SCFR) is another member of the PDGFR family, and c-KIT mutations are associated with gastrointestinal stromal tumors (GIST), mast cell/myeloid leukemia, seminomas/dysgerminomas, and melanomas. Gleevec gained FDA-approval for c-KIT-mediated GIST in 2002.

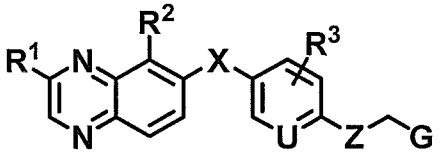
[0007] Although various tyrosine kinase inhibitors are shown to be useful therapeutics, there is still a need for type III kinase inhibitors.

SUMMARY OF INVENTION

[0008] The present disclosure relates to novel inhibitors that inhibit kinases, such as CSF-1R, c-KIT, and/or PDGFR kinases, for the treatments of diseases or disorders mediated by such kinases, e.g., cancers, autoimmune diseases, and bone resorptive diseases.

[0009] Embodiments of the disclosure are based on unexpected findings that certain quinoxaline compounds can inhibit activities of type III RTKs (e.g., PDGFRα, PDGFRβ, FLT3, c-KIT and CSF-1R). The compounds are useful in medical treatments, pharmaceutical compositions and methods for modulating the activity of CSF-1R, FLT3, c-KIT, and/or PDGFR kinases, including wildtype and/or mutated forms of CSF-1R, FLT3, c-KIT, and/or PDGFR kinases. These properties allow these quinoxaline compounds to be used in treating protein tyrosine kinase-related diseases and/or conditions.

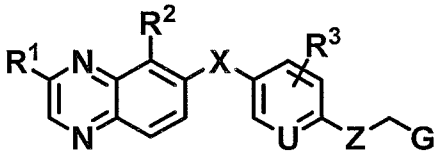
[0010] According to embodiments of this disclosure, a compound may have the general Formula I:



Formula (I)

a stereoisomer thereof, or a prodrug thereof, or a pharmaceutically acceptable salt thereof, wherein X, U, Z, G, R^1, R^2 and R^3 are as defined herein.

[0010a] A first aspect of the present disclosure relates to a compound of Formula I



Formula I

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt thereof;

wherein:

X is selected from the group consisting of CR^4R^5, NR^6, O and S;

Z is selected from the group consisting of $-NR^7-$ and $-O-$;

U is N or CR^8;

G is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycle and alkyne.

R^1 is selected from the group consisting of hydrogen, deuterium, halogen, amino, hydroxyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_5-C_6 cycloalkenyl, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, C_3-C_6 cycloalkylamino, C_1-C_6 alkoxy, C_3-C_6 cycloalkoxy, aryl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkylamino, dialkylamino, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylamino, cycloalkoxy, heterocyclyl, aryl and heteroaryl are optionally substituted with halogen, amino, hydroxyl, cyano, nitro, acyl, acyloxy, C_1-C_4 alkyl, hydroxyl C_1-C_4 alkyl, alkoxy C_1-C_4 alkyl, acyloxy C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 dialkylamino, C_3-C_6 cycloalkyl, a 3-to-6 membered heterocyclyl, aryl, and a 5-to-6 membered heteroaryl;

R^2 is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1-C_6 alkylamino, C_1-C_6 dialkylamino, C_1-C_6 alkoxy, carboxylic acid, C_1-C_6 alkyl carbonyl, C_2-C_6 alkenyl carbonyl, C_1-C_6 alkoxy carbonyl, amino carbonyl, C_1-C_6 alkylamino carbonyl and C_1-C_6 dialkylamino carbonyl;

R^3 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, cyano, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino and C_1-C_6 dialkylamino;

R^4 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy and aryl;

R^5 is selected from the group consisting of hydrogen, deuterium, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl;

R^7 is selected from the group consisting of hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl; and

R^8 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, cyano, trifluoromethyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylamino and C_1-C_6 dialkylamino.

[0011] One aspect of the disclosure relates to pharmaceutical compositions comprising compounds of Formula I and a carrier, diluent or excipient.

[0011a] Another aspect of the disclosure relates to a pharmaceutical composition as described herein for use in treating a disease or disorder mediated by CSF-1R, FLT3, c-KIT, and/or PDGFR kinase, or mediated by a mutant kinase of CSF-1R, FLT3, c-KIT, or PDGFR.

[0012] Another aspect of the disclosure relates to a method of inhibiting type III receptor tyrosine kinases, such as PDGFR, CSF-1R, FLT-3 and/or c-KIT, in a mammal. A method in accordance with embodiments of the invention comprises: administering to said mammal in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0012a] Another aspect of the disclosure relates to the use of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating a disease or disorder mediated by CSF-1R, FLT3, c-KIT, and/or PDGFR kinase, wherein a therapeutically effective amount of the pharmaceutical composition is to be administered to a subject in need thereof.

[0013] Another aspect of the disclosure relates to a method for treating a disease or disorder selected from fibrosis, bone-related diseases, cancer, autoimmune disorders, inflammatory diseases, cardiovascular diseases, pain and bums in a mammal. A method in accordance with embodiments of the invention comprises administering to said mammal in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0014] Another aspect of the disclosure relates to use of a compound of Formula I in the manufacture of a medicament for the treatment of a disease or disorder selected from fibrosis, bone-related diseases, cancer, autoimmune disorders, inflammatory diseases, cardiovascular diseases, pain and bums in a mammal.

[0015] Another aspect of the disclosure relates to a compound of Formula I, or a pharmaceutical composition thereof, for use in the treatment of a disease or disorder selected from fibrosis, bone-related diseases, cancer, autoimmune disorders, inflammatory diseases, cardiovascular diseases, pain and burns in a mammal.

[0016] Another aspect of the present disclosure relates to a pharmaceutical composition comprising a compound of this invention, a stereoisomer, tautomer, solvate, prodrug or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0017] Other aspects and advantages of the disclosure will be apparent from the following description and the appended claims.

DETAILED DESCRIPTION

[0018] 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

3-morpholino-6-((6-((4-(trifluoromethyl)benzyl)amino)pyridin-3-yl)amino)quinoxalin e- 5-carbonitrile;

6-((5-methoxy-6-((6-methylpyridin-3-yl)methoxy)pyridin-3-yl)amino)-3-morpholinoq uinoxaline-5-carbonitrile;

6-((5-methoxy-6-((6-methoxypyridin-3-yl)methoxy)pyridin-3-yl)amino)-3-morpholin oquinoxaline-5-carbonitrile;

3-((2S,6R)-2,6-dimethylmorpholino)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methox y) phenyl)amino)quinoxaline-5-carbonitrile; or

6-((3-methoxy-4-((6-methyl-1-(λ^1-oxidaneyl)-1λ^4-pyridin-3-yl)methoxy)phenyl)amin o)- 3-morpholinoquinoxaline-5-carbonitrile.

10. A pharmaceutical composition comprising the compound according to any one of claims 1-9, a stereoisomer thereof, or a prodrug thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

11. The pharmaceutical composition of claim 10 for use in treating a disease or disorder mediated by CSF-1R, FLT3, c-KIT, and/or PDGFR kinase, or mediated by a mutant kinase of CSF-1R, FLT3, c-KIT, or PDGFR.

12. Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for treating a disease or disorder mediated by CSF-1R, FLT3, c-KIT, and/or PDGFR kinase, wherein a therapeutically effective amount of the pharmaceutical composition is to be administered to a subject in need thereof.

13. The use according to claim 12, wherein the disease or disorder is a cancer.

14. The use according to claim 13, wherein the cancer is selected from the group consisting of multiple myeloma, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), prostate cancer, breast cancer, ovarian cancer, melanoma, glioblastoma multiforme, giant cell tumor of bone, non-small-cell lung cancers, giant cell tumor of the tendon sheath, metastasis of tumors to other tissues, myelofibrosis, pigmented villonodular synovitis, and gastrointestinal stromal tumor.