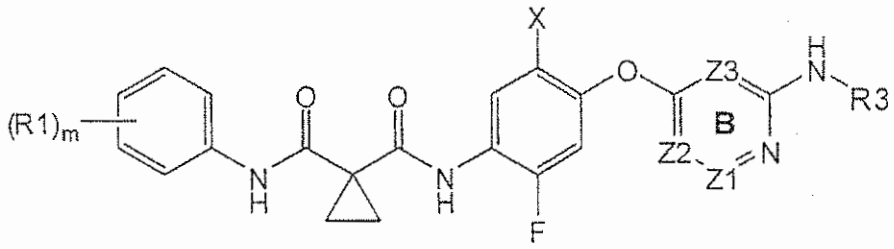
need for kinase inhibitors that are selective for a particular protein kinase. It is theorized that an unexpected increase in potency for c-MET kinase inhibition or an unexpected increase in selective c-MET inhibition relative to other kinases is observed for one or more of the embodiments disclosed herein.

Summary

[0007] Compounds described herein find utility in the treatment of mammalian cancers and especially human cancers including, but not limited to, solid tumors, gastric cancers, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, non small cell lung cancer, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary tumor sites, colonic cancers, myeloproliferative diseases, diseases wherein the etiology or progression is dependent on c-MET kinase activity, or on the activity of oncogenic forms, aberrant fusion protein forms, and mutant forms of c-MET kinase.

[0007a] In a first aspect of the present disclosure, there is provided a compound of **Formula I**,



Formula I

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

wherein

X is halogen;

Z1 and Z2 are CR2;

Z3 is CH;

each R1 is independently and individually halogen, H, C1-C6 alkyl, branched C3-C7 alkyl, C3-C7 cycloalkyl, or -CN;

each R2 is individually and independently H, halogen, C1-C6 alkyl, or cyano;

R3 is -C(O)R4, -C(O)-C6-C10-aryl, -C(O)-C4-C6-heterocyclyl, or -C(O)-C5-C6-heteroaryl, wherein

aryl is phenyl, naphthyl, tetrahydronaphthyl, indenyl or indanyl; wherein C4-C6 heterocyclyl is a 4-6 membered ring containing one or two heteroatoms selected from the group consisiting of N, O, or S with the remainder of the ring atoms comprised of carbon; wherein C5-C6 heteroaryl is a 5 or 6-membered aromatic ring where at least one of the ring atoms is an O, N, or S; and

with the proviso that when R3 is -C(O)-C4-C6-heterocyclyl, the heterocyclyl does not have a N bonding hand to -C(O);

R4 is C3-C8 cycloalkyl, C1-C7 alkyl, $-(CH_2)_p$-CN, $-(CH_2)_p$-OR6, $-(CH_2)_p$-NR6(R7),$-(CH_2)_p-SO_2$-Cl-C6-alkyl, $-(CH_2)_p$-C6-C10-aryl, $-(CH_2)_p$-C5-C6-heteroaryl, or $-(CH_2)_p$-C4-C6-heterocyclyl, wherein

each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl; and

aryl is phenyl, naphthyl, tetrahydronaphthyl, indenyl or indanyl;

each R6 and R7 is individually and independently H, C1-C6 alkyl, or C3-C8 branched alkyl;

each cycloalkyl, aryl, heteroaryl and heterocyclyl is independently substituted with $-(R25)_m$;

each R25 is individually and independently C1-C6 alkyl, branched C3-C8 alkyl, halogen, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR6, $-(CH_2)_m$-NR6(R7), $-(CH_2)_m-SO_2$-C1-C6-alkyl, $-(CH_2)_m$-C(O)NR6(R7), $-(CH_2)_m$-C(O)-C4-C6-heterocyclyl, or $-(CH_2)_m$-C4-C6-heterocyclyl, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

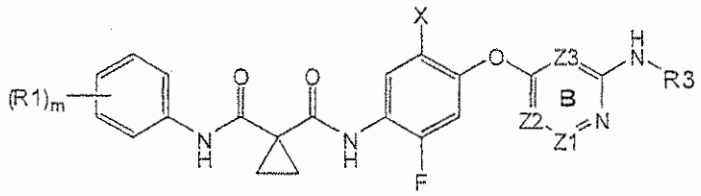
each m is individually and independently 0, 1, 2, or 3; and

p is 1, 2, or 3.

[0007b] In a second aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound as defined above and a pharmaceutically acceptable carrier.

[0007c] In a third aspect of the present disclosure, there is provided the use of a compound as defined above for the manufacture of a medicament for the treatment of cancer.

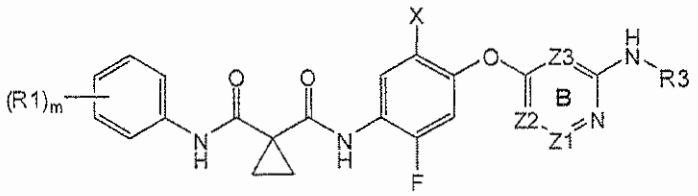
[0008] Specifically, compounds of **Formula I** are disclosed which find utility in the treatment of diseases as described above.



Formula I

[0009] In **Formula I**, X and F are regiochemically oriented with respect to each other in a mutual *para*-orientation; X is halogen or C1-C6 alkyl; and R3 is a non-hydrogen moiety regiochemically oriented *ortho*- to the **B** ring nitrogen. Compounds described herein exhibit unexpected potency for c-MET kinase inhibition and/or an unexpected increase in selective c-MET kinase inhibition relative to other kinases, particularly in comparison to other purported c-MET kinase inhibitors.

[0010] C~~In one aspect, c~~ompounds of the **Formula I** are described:



Formula I

and pharmaceutically acceptable salts, hydrates, solvates, enantiomers, stereoisomers, and tautomers thereof;

wherein

X is halogen;

Z1 and Z2 are independently and individually CR2 or N;

Z3 is CH or N;

with the proviso that ring B is not a tetrazine;

each R1 is independently and individually halogen, H, C1-C6 alkyl, branched C3-C7 alkyl, C3-C7 cycloalkyl, or –CN;

each R2 is individually and independently H, halogen, C1-C6 alkyl, or cyano;

R3 is –C(O)R4, -C(O)-C6-C10-aryl, -C(O)-C4-C6-heterocyclyl, or –C(O)-C5-C6-heteroaryl, wherein

aryl is phenyl, naphthyl, tetrahydronaphthyl, indenyl or indanyl; and

with the proviso that when R3 is –C(O)-C4-C6-heterocyclyl, the heterocyclyl does not have a N bonding hand to –C(O);

R4 is C1-C7 alkyl, C3-C8 cycloalkyl, $-(CH_2)_p$-CN, $-(CH_2)_p$-OR6, $-(CH_2)_p$-NR6(R7), $-(CH_2)_p$-SO_2-C1-C6-alkyl, $-(CH_2)_p$-C6-C10-aryl, $-(CH_2)_p$-C5-C6-heteroaryl, or $-(CH_2)_p$-C4-C6-heterocyclyl, wherein

each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl; and

aryl is phenyl, naphthyl, tetrahydronaphthyl, indenyl or indanyl;

each R6 and R7 is individually and independently H, C1-C6 alkyl, or C3-C8 branched alkyl;

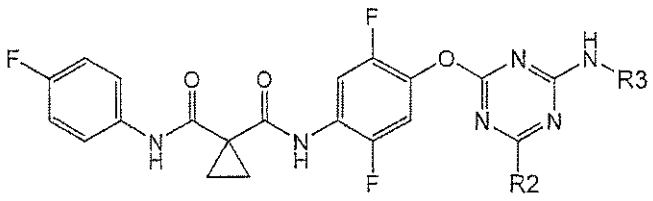
each cycloalkyl, aryl, heteroaryl and heterocyclyl is independently substituted with $-(R25)_m$;

[0023] In certain embodiments of the compound of **Formula Ij**, R3 is –C(O)R4.

[0024] In other embodiments of the compound of **Formula Ij**, R3 is -C(O)-C6-C10-aryl, -C(O)-C4-C6-heterocyclyl, or –C(O)-C5-C6-heteroaryl.

[0025] In some embodiments of the compound of **Formula I**, Z1 is CR2, and Z2 and Z3 are N.

[0026] In certain embodiments, the compound of **Formula I** is a compound of **Formula Im**,



Formula Im

or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer, or tautomer thereof.

[0027] In some embodiments of the compound of **Formula Im**, R3 is –C(O)R4.

[0028] In other embodiments of the compound of **Formula Im**, R3 is -C(O)-C6-C10-aryl, -C(O)-C4-C6-heterocyclyl, or –C(O)-C5-C6-heteroaryl.

[0029] In one embodiment, the present ~~invention~~disclosure is directed to a compound selected from the group consisting of *N*-(4-(2-acetamidopyridin-4-yloxy)-2,5-difluorophenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-acetamidopyridin-4-yloxy)-5-chloro-2-fluorophenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-acetamidopyridin-4-yloxy)-2,5-difluorophenyl)-*N*'-phenylcyclopropane-1,1-dicarboxamide, *N*-(4-(2-(2-(dimethylamino)acetamido)pyridin-4-yloxy)-2,5-difluorophenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-acetamidopyrimidin-4-yloxy)-2,5-difluorophenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-(cyclopropanecarboxamido)pyridin-4-yloxy)-2,5-difluorophenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(2,5-difluoro-4-(2-propionamidopyridin-4-yloxy)phenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(2,5-difluoro-4-((2-(2-methoxyacetamido)pyridin-4-yl)oxy)phenyl)-*N*'-(4-fluorophenyl)cyclopropane-1,1-

dicarboxamide, *N*-(2,5-difluoro-4-(2-isobutyramidopyridin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-(2-cyanoacetamido)pyridin-4-yloxy)-2,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-(azetidine-3-carboxamido)pyridin-4-yloxy)-2,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-(cyclobutanecarboxamido)pyridin-4-yloxy)-2,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (R)-*N*-(2,5-difluoro-4-((2-(2-methoxypropanamido)pyridin-4-yl)oxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, R)-*N*-(2,5-difluoro-4-((2-(2-hydroxypropanamido)pyridin-4-yl)oxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(2,5-difluoro-4-((2-pivalamidopyridin-4-yl)oxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (S)-*N*-(2,5-difluoro-4-((2-(2-methoxypropanamido)pyridin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (S)-1-((4-(2,5-difluoro-4-(1-((4-fluorophenyl)carbamoyl)cyclopropanecarboxamido)phenoxy)pyridin-2-yl)amino)-1-oxopropan-2-yl acetate, *N*-(2,5-difluoro-4-((2-(2-fluoro-2-methylpropanamido)pyridin-4-yl)oxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide and pharmaceutically acceptable salts, solvates, hydrates and tautomers thereof.

[0030] In another embodiment, the present ~~invention~~disclosure is directed to a compound selected from the group consisting of *N*-(4-(2-(cyclopropanecarboxamido)pyridin-4-yloxy)-2,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(2,5-difluoro-4-(2-propionamidopyridin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(2,5-difluoro-4-(2-isobutyramidopyridin-4-yloxy)phenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, *N*-(4-(2-acetamidopyridin-4-yloxy)-2,5-difluorophenyl)-*N'*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide.

[0031] In some embodiments, the present ~~invention~~disclosure comprises a method of treating mammalian disease wherein the disease etiology or progression is at least partially mediated by a kinase activity, wherein the kinase is a wildtype form, a mutant oncogenic form, an aberrant fusion protein form or a polymorph, the method comprising administering to a mammal in need thereof an effective amount of a compound ~~of any of claims 1-21~~as disclosed herein.

[0032] In certain embodiments, the disease etiology or progression is at least partially mediated by the kinase activity of c-MET, mutant oncogenic forms, aberrant fusion proteins, or polymorphs thereof.

[0033] In some embodiments, the ~~invention~~present disclosure is directed to a pharmaceutical composition, comprising a compound ~~of any of claims 1-21~~as disclosed herein and a pharmaceutically acceptable carrier.

[0034] In certain embodiments, the pharmaceutical composition further comprises an additive selected from adjuvants, excipients, diluents, or stabilizers.

[0035] In other embodiments the present ~~invention~~disclosure is directed to a method of treating cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, or diseases characterized by angiogenesis, such as solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases, chronic myelogenous leukemia, leukemias, papillary thyroid carcinoma, non-small cell lung cancer, mesothelioma, hypereosinophilic syndrome, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including retinopathies, diabetic retinopathy, age-related macular degeneration, hypereosinophilic syndrome, rheumatoid arthritis, asthma, chronic obstructive pulmonary, mastocytosis, or mast cell leukemia, the method comprising administering to a patient in need thereof an effective amount of a compound ~~of any of claims 1-21~~as disclosed herein.

[0036] In some embodiments, the compound is administered orally, parenterally, by inhalation, or subcutaneously.

[0037] The details of the ~~invention~~present disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present ~~invention~~disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the ~~invention~~present disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise,