Compounds useful in the treatment of mammalian cancers and especially human cancers according to Formula I are disclosed. Pharmaceutical compositions and methods of treatment employing the compounds disclosed herein are also disclosed.
PYRIDONE AMIDES AND ANALOGS EXHIBITING ANTI-CANCER AND ANTIPROLIFERATIVE ACTIVITIES

Cross-Reference to Related Applications


Field

[0002] The present invention relates to kinase inhibitors exhibiting novel and unexpected properties useful for the treatment of various diseases including hyperproliferative diseases and cancer. More particularly, the invention is concerned with such compounds, methods of treating diseases, and methods of synthesis of the compounds. Preferably, the compounds are useful for the modulation of activity of c-MET kinase, c-MET kinase polymorphs, c-MET kinase mutants, or c-MET kinase fusion proteins in the treatment of mammalian diseases, and in particular human hyperproliferative diseases and human cancers. In some embodiments, compounds disclosed herein exhibit unexpected selectivity for modulation of c-MET kinase activity.

Background


In human therapeutics, it is desirable to provide small molecule inhibitors of a protein target within in a protein family which do not cross-inhibit closely related protein family members. These closely related protein family members are often referred to as Off-targets’, to distinguish them from the essential target of interest referred to as the ‘on target’ of the inhibitor. A small molecule which inhibits multiple protein family members, while being potent against the target of interest, can be limited in its utility as a human therapeutic due to unintended side effects and toxicities introduced due to the consequences of inhibition of these ‘off targets.’

Protein kinases constitute an important therapeutic protein family. There are approximately 518 human protein kinases. While inhibition of a desired kinase ‘on target’ is desirable for a human therapeutic, it is also desirable in many cases to provide a selective kinase inhibitor which does not substantially inhibit other kinase ‘off targets’ from within this protein family. Monoclonal antibodies are one approach to providing specific inhibitors to a specific kinase without inhibiting ‘off targets.’ Achieving this level of selectivity with small molecule inhibitors, however, is not as easily achievable nor as straightforward. Accordingly, there is a
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.

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

![Formula I](image)

wherein A is

![Pyridone Amide Structures](image)

wherein the "*" is connected to the R1-substituted phenyl ring and the "#" is connected to the amide carbonyl; and R1, R8, m, XI, X2, W, Z1, Z2, and Z3 are as defined below for Formula I.

[0009] More specifically, pyridone amide compounds of Formula II and Formula III are disclosed:
[0010] Accordingly, in one aspect, the present invention comprises a compound of Formula I, or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer or tautomer thereof, wherein:

A is

\[
\begin{align*}
* & \quad \# \\
(R_8)_m & \quad (R_8)_m \\
\end{align*}
\]

or

\[
\begin{align*}
* & \quad \# \\
(R_8)_m & \quad (R_8)_m \\
\end{align*}
\]

wherein the "*" is connected to the R1-substituted phenyl ring and the "#" is connected to the amide carbonyl;

W is \(-(\text{CH}_2)_m\)-pyrazole optionally substituted with \(-(\text{R25})_m\);

X1 is halogen or C1-C6 alkyl;

X2 is halogen or C1-C6 alkyl;
each R l is individually and independently halogen, H, C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, branched C3-C6 alkoxy, or cyano;

Z1 and Z2 are independently and individually CR2 or N;

Z3 is CR3 or N;

with the proviso that ring B is a monocyclic ring which is not a tetrazine;

each R2 is individually and independently H, halogen, C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, branched C3-C6 alkoxy, or cyano;

R3 is -NHR4, H, -NR6(R7), C1-C8 alkyl, C2-C3 alkylnyl, C3-C8 cycloalkyl, C1-C6-alkoxy-Cl-C6-alkyl-, hydroxy-C1-C6-alkyl-, cyano, cyano-C1-C6-alkyl-, C1-C6-S02-C1-C6-alkyl-, (R7)R6N-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, C6-C10 aryl, C5-C6-heteroaryl, or C5-C6-heteroaryl-Cl-C6-alkyl-, wherein

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

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

R4 is H, C1-C8 alkyl, C3-C8 cycloalkyl, -(CH2)m-C(0)R5, -(CH2)p-OR6, -(CH2)p-NR6(R7), -(CH2)p-CN, -(CH2)p-S02-C1-C6-alkyl, C6-C10 aryl, -(CH2)m-C5-C6-heteroaryl, -(CH2)m-C4-C6-heterocycl, -(CH2)m-C(0)N(R6)-C4-C6-heterocycl, or -(CH2)m-C(0)N(R6)-C5-C6-heteroaryl, wherein each alkyl or alkyne is optionally substituted with one or two C1-C6 alkyl;

R5 is C1-C7 alkyl, branched C3-C8 alkyl, C3-C8 cycloalkyl, -(CH2)m-OR6, -(CH2)m-NR6(R7), C6-C10 aryl, -(CH2)m-C5-C6-heteroaryl, or -(CH2)m-C4-C6-heterocycl, wherein

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

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

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

each R8 is individually and independently C1-C6 alkoxy, H, halogen, C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, branched C3-C6 alkoxy, or cyano;

each alkylnyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is independently and optionally substituted with -(R25)m;

each R25 is individually and independently C1-C6 alkyl, branched C3-C8 alkyl, halogen, -(CH2)m-CN, -(CH2)m-OR6, -(CH2)m-NR6(R7), -(CH2)m-S02-C1-C6-alkyl, -(CH2)m.
C(0)NR6(R7), -(CH₂)ₘ-C(0)-C₄-C₆-heterocyclyl, or-(CH₂)ₘ-C₄-C₆-heterocyclyl, wherein each alkyl or alkyylene is optionally substituted with one or two C₁-C₆ alkyl; each m is individually and independently 0, 1, 2, or 3; n is 0, 1, or 2; and each p is individually and independently 1, 2, or 3.

[0011] In some embodiments, the compound of Formula I is a compound of Formula la,

![Formula la]

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

[0012] In some embodiments of the compound of Formula la, Z₃ is CR₃.

[0013] In some embodiments, the compound of Formula Ia is a compound of Formula lb,

![Formula lb]

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

[0014] In some embodiments of the compound of Formula lb, R₃ is -NHR₄.

[0015] In some embodiments of the compound of Formula lb, R₃ is H.

[0016] In some embodiments of the compound of Formula lb, R₃ is -NR₆(R₇), (R₇)R₆N-C₁-C₆-alkyl-, C₁-C₈ alkyl, C₂-C₃ alkenyl, C₃-C₈ cycloalkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl-,
hydroxy-Cl-C6-alkyl-, cyano, cyano-Cl-C6-alkyl-, Cl-C6-S0₂-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, C6-C10 aryl, C5-C6-heteroaryl, or C5-C6-heteroaryl-Cl-C6-alkyl-, wherein each alkyl or alkyene is optionally substituted with one or two C1-C6 alkyl.

[0017] In some embodiments of the compound of Formula Ib, W is

![Formula Ib](image)

[0018] In some embodiments of the compound of Formula Ia, Z3 is CR3 and W is

![Formula Ia](image)

[0019] In some embodiments of the compound of Formula Ib, the A ring is

![A ring](image), and R8 is C1-C6 alkoxy.

[0020] In some embodiments of the compound of Formula Ib, the A ring is

![A ring](image), and R8 is ethoxy.

[0021] In some embodiments of the compound of Formula Ia, Z3 is N.

[0022] In some embodiments of the compound of Formula Ia, the compound is a compound of Formula Ic,
or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer or tautomer thereof.

[0023] In some embodiments of the compound of Formula Ic, W is

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R_{25}^N
\]

[0024] In some embodiments of the compound of Formula Ia, Z is N and W is

\[
R_{25}^N
\]

[0025] In some embodiments of the compound of Formula Ic, the A ring is

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\ast
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, and R8 is C1-C6 alkoxy.

[0026] In some embodiments of the compound of Formula Ic, the A ring is

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\]

, and R8 is ethoxy.
[0027] In some embodiments of the compound of Formula I, Z₁ is CR₂, Z₂ is N, and Z₃ is CR₃.

[0028] In some embodiments of the compound of Formula I, the compound is a compound of Formula Id,

![Formula Id](image)

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

[0029] In some embodiments of the compound of Formula Id, R₃ is -NHR₄.

[0030] In some embodiments of the compound of Formula Id, R₃ is H.

[0031] In some embodiments of the compound of Formula Id, R₃ is -NR₆(R⁷), C₁-C₈ alkyl, C₂-C₃ alkynyl, C₃-C₈ cycloalkyl, Cl-C₆-alkoxy-Cl-C₆-alkyl-, hydroxy-Cl-C₆-alkyl-, cyano, cyano-Cl-C₆-alkyl-, Cl-C₆-SO₂-Cl-C₆-alkyl-, (R⁷)R₆N-Cl-C₆-alkyl-, C₄-C₆-heterocyclyl, C₄-C₆-heterocyclyl-Cl-C₆-alkyl-, C₆-C₁₀ aryl, C₅-C₆-heteroaryl, or C₅-C₆-heteroaryl-Cl-C₆-alkyl-; and wherein each alkyl or alkenylene is optionally substituted with one or two C₁-C₆ alkyl.

[0032] In some embodiments of the compound of Formula Id, W is

![R25](image)
In some embodiments of the compound of Formula I, \(Z_1\) is \(CR_2\), \(Z_2\) is \(N\), and \(Z_3\) is \(CR_3\) and \(W\) is

![Diagram](image)

In some embodiments of the compound of Formula Id, the A ring is

![Diagram](image)

, and \(R_8\) is C1-C6 alkoxy.

In some embodiments of the compound of Formula Id, the A ring is

![Diagram](image)

, and \(R_8\) is ethoxy.

In some embodiments, the invention comprises a compound selected from the group consisting of

- \(N\)-(2,5-difluoro-4-(5-(1-methyl-1\(H\)-pyrazol-4-yl)pyrimidin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
- \(N\)-(2,5-difluoro-4-(3-(1-methyl-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
- \(N\)-(4-(3-(l-cyanomethyl)-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
- \(N\)-(2,5-difluoro-4-(3-(1-methyl-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
- \(N\)-(2-amino-3-(1-methyl-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
- \(N\)-(5-chloro-2-fluoro-4-(3-(1-methyl-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
- \(N\)-(2,5-difluoro-4-(3-(1-methyl-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide,
- \(N\)-(4-(2-amino-3-(1-methyl-1\(H\)-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-
4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, \( N \)-(4-(3-(1\text{H}-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, \( N \)-(4-(2-amino-3-(1-methyl-1\text{H}-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide and pharmaceutically acceptable salts, solvates, hydrates and tautomers thereof.

[0037] In certain embodiments, the invention 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 1-27.

[0038] 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.

[0039] In other embodiments, the present invention comprises a pharmaceutical composition, comprising a compound of any of claims 1-27 and a pharmaceutically acceptable carrier.

[0040] In certain embodiments, the composition comprises an additive selected from adjuvants, excipients, diluents, or stabilizers.

[0041] In some embodiments, the invention includes 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 1-27.

[0042] In certain embodiments of the present methods, the compound is administered orally, parenterally, by inhalation, or subcutaneously.

[0011] The details of the invention 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, illustrative methods and materials are now described. Other features, objects, and advantages of the invention 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, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

**Detailed Description**

[0012] Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications and this disclosure.

[0013] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The initial definition provided for a group or term provided in this disclosure applies to that group or term throughout the present disclosure individually or as part of another group, unless otherwise indicated.

[0014] The compounds of this disclosure include any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, and solvates thereof, as well as crystalline polymorphic forms of the disclosed compounds and any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable
salts, and solvates thereof. Thus, the terms "compound" and "compounds" as used in this disclosure refer to the compounds of this disclosure and any and all possible isomers, stereoisomers, enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, solvates, and crystalline polymorphs thereof.

Definitions
[0015] The term "alkyl" as used herein refers to a straight chain alkyl, wherein alkyl chain length is indicated by a range of numbers. In exemplary embodiments, "alkyl" refers to an alkyl chain as defined above containing 1, 2, 3, 4, 5, or 6 carbons (i.e., C1-C6 alkyl). Examples of an alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, and hexyl.

[0016] The term "branched alkyl" as used herein refers to an alkyl chain wherein a branching point in the chain exists, and the total number of carbons in the chain is indicated by a range of numbers. In exemplary embodiments, "branched alkyl" refers to an alkyl chain as defined above containing from 3, 4, 5, 6, 7, or 8 carbons (i.e., branched C3-C8 alkyl). Examples of a branched alkyl group include, but are not limited to, wopropyl, wo-butyl, secondary-butyl, and tertiary-butyl.

[0017] The term "alkoxy" as used herein refers to -O-(alkyl), wherein "alkyl" is as defined above.

[0018] The term "branched alkoxy" as used herein refers to -O-(branched alkyl), wherein "branched alkyl" is as defined above.

[0019] The term "alkylene" as used herein refers to an alkyl moiety interposed between two other atoms. In exemplary embodiments, "alkylene" refers to an alkyl moiety as defined above containing 1, 2, or 3 carbons. Examples of an alkylen group include, but are not limited to -CH=, -CH₂CH=, and -CH₂CH₂CH=. In exemplary embodiments, alkylen groups are branched.

[0020] The term "alkynyl" as used herein refers to a carbon chain containing one carbon-carbon triple bond. In exemplary embodiments, "alkynyl" refers to a carbon chain as described above containing 2 or 3 carbons (i.e., C2-C3 alkynyl). Examples of an alkynyl group include, but are not limited to, ethyne and propyne.

[0021] The term "aryl" as used herein refers to a cyclic hydrocarbon, where the ring is characterized by delocalized π electrons (aromaticity) shared among the ring members, and
wherein the number of ring atoms is indicated by a range of numbers. In exemplary embodiments, "aryl" refers to a cyclic hydrocarbon as described above containing 6, 7, 8, 9, or 10 ring atoms (i.e., C6-C10 aryl). Examples of an aryl group include, but are not limited to, benzene, naphthalene, tetralin, indene, and indane.

The term "cycloalkyl" as used herein refers to a monocyclic saturated carbon ring, wherein the number of ring atoms is indicated by a range of numbers. In exemplary embodiments, "cycloalkyl" refers to a carbon ring as defined above containing 3, 4, 5, 6, 7, or 8 ring atoms (i.e., C3-C8 cycloalkyl). Examples of a cycloalkyl group include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl.

The term "halogen" as used herein refers to fluorine, chlorine, bromine, and iodine.

The term "heterocycle" or "heterocyclyl" as used herein refers to a cyclic hydrocarbon, wherein at least one of the ring atoms is an O, N, or S, wherein the number of ring atoms is indicated by a range of numbers. Heterocyclyl moieties as defined herein have C or N bonding hands. For example, in some embodiments, a ring N atom from the heterocyclyl is the bonding atom to -C(O) to form an amide, carbamate, or urea. In exemplary embodiments, "heterocyclyl" refers to a cyclic hydrocarbon as described above containing 4, 5, or 6 ring atoms (i.e., C4-C6 heterocyclyl). Examples of a heterocycle group include, but are not limited to, aziridine, oxirane, thirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, pyran, thiopyran, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, oxazoline, tetrahydrothiophene, piperidine, tetrahydropryan, thiane, imidazolidine, oxazolidine, thiazolidine, dioxolane, dithiolane, piperrazine, oxazine, dithiane, and dioxane.

The term "heteroaryl" as used herein refers to a cyclic hydrocarbon, where at least one of the ring atoms is an O, N, or S, the ring is characterized by delocalized \( \pi \) electrons (aromaticity) shared among the ring members, and wherein the number of ring atoms is indicated by a range of numbers. Heteroaryl moieties as defined herein have C or N bonding hands. For example, in some embodiments, a ring N atom from the heteroaryl is the bonding atom to -C(O) to form an amide, carbamate, or urea. In exemplary embodiments, "heteroaryl" refers to a cyclic hydrocarbon as described above containing 5 or 6 ring atoms (i.e., C5-C6 heteroaryl). Examples of a heteroaryl group include, but are not limited to, pyrrole, furan, thiene, oxazole, thiazole, isoxazole, isothiazole, imidazole, pyrazole, oxadiazole, thiazole, triazole, tetrazole, pyridine, pyrimidine, pyrazine, pyridazine, and triazine.
The term "substituted" in connection with a moiety as used herein refers to a further substituent which is attached to the moiety at any acceptable location on the moiety. Unless otherwise indicated, moieties can bond through a carbon, nitrogen, oxygen, sulfur, or any other acceptable atom.

The term "salts" as used herein embraces pharmaceutically acceptable salts commonly used to form alkali metal salts of free acids and to form addition salts of free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Exemplary pharmaceutical salts are disclosed in Stahl, P.H., Wermuth, C.G., Eds. *Handbook of Pharmaceutical Salts: Properties, Selection and Use*; Verlag Helvetica Chimica Acta/Wiley-VCH: Zurich, 2002, the contents of which are hereby incorporated by reference in their entirety. Specific non-limiting examples of inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids include, without limitation, aliphatic, cycloaliphatic, aromatic, arylaliphatic, and heterocyclic containing carboxylic acids and sulfonic acids, for example formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, enbonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, 3-hydroxybutyric, galactaric or galacturonic acid. Suitable pharmaceutically acceptable salts of free acid-containing compounds disclosed herein include, without limitation, metallic salts and organic salts. Exemplary metallic salts include, but are not limited to, appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Exemplary organic salts can be made from primary amines, secondary amines, tertiary amines and quaternary ammonium salts, for example, tromethamine, diethylamine, tetra-N-methylammonium, N,N'-dibenzylethylediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.
The terms "administer," "administering, or "administration" as used herein refer to either directly administering a compound or pharmaceutically acceptable salt of the compound or a composition to a subject.

The term "carrier" as used herein encompasses carriers, excipients, and diluents, meaning a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ or portion of the body.

The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

The terms "effective amount" and "therapeutically effective amount" are used interchangeably in this disclosure and refer to an amount of a compound that, when administered to a subject, is capable of reducing a symptom of a disorder in a subject. The actual amount which comprises the "effective amount" or "therapeutically effective amount" will vary depending on a number of conditions including, but not limited to, the particular disorder being treated, the severity of the disorder, the size and health of the patient, and the route of administration. A skilled medical practitioner can readily determine the appropriate amount using methods known in the medical arts.

The terms "isolated" and "purified" as used herein refer to a component separated from other components of a reaction mixture or a natural source. In certain embodiments, the isolate contains at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 98%> of the compound or pharmaceutically acceptable salt of the compound by weight of the isolate.

The phrase "pharmaceutically acceptable" as used herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used in this disclosure, the term "subject" includes, without limitation, a human or an animal. Exemplary animals include, but are not limited to, mammals such as mouse, rat, guinea pig, dog, cat, horse, cow, pig, monkey, chimpanzee, baboon, or rhesus monkey.
The term “treating” as used herein with regard to a subject, refers to improving at least one symptom of the subject’s disorder. Treating can be curing, improving, or at least partially ameliorating the disorder.

The term "hydrate" as used herein refers to a compound disclosed herein which is associated with water in the molecular form, i.e., in which the H—OH bond is not split, and may be represented, for example, by the formula RT½O, where R is a compound disclosed herein. A given compound may form more than one hydrate including, for example, monohydrates (R-H₂O), dihydrates (R-2H₂O), trihydrates (R-3H₂O), and the like.

The term "solvate" as used herein refers to a compound disclosed herein which is associated with solvent in the molecular form, i.e., in which the solvent is coordinatively bound, and may be represented, for example, by the formula R‘(solvent), where R is a compound disclosed herein. A given compound may form more than one solvate including, for example, monosolvates (Resolvent)) or polysolvates (R’n(solvent)) wherein n is an integer greater than 1) including, for example, disolvates (R-2(solvent)), trisolvates (R-3(solvent)), and the like, or hemisolvates, such as, for example, R’n/2(solvent), R’n/3(solvent), Rm/4(solvent) and the like, wherein n is an integer. Solvents herein include mixed solvents, for example, methanol/water, and as such, the solvates may incorporate one or more solvents within the solvate.

The term "acid hydrate" as used herein refers to a complex that may be formed through association of a compound having one or more base moieties with at least one compound having one or more acid moieties or through association of a compound having one or more acid moieties with at least one compound having one or more base moieties, said complex being further associated with water molecules so as to form a hydrate, wherein said hydrate is as previously defined and R represents the complex herein described above.


Atropisomers are defined as a subclass of conformers which can be isolated as separate chemical species and which arise from restricted rotation about a single bond.
Regioisomers or structural isomers are defined as isomers involving the same atoms in different arrangements.

Enantiomers are defined as one of a pair of molecular entities which are mirror images of each other and non-superimposable.

Diastereomers or diastereoisomers are defined as stereoisomers other than enantiomers. Diastereomers or diastereoisomers are stereoisomers not related as mirror images. Diastereoisomers are characterized by differences in physical properties, and by some differences in chemical behavior towards achiral as well as chiral reagents.

The term "tautomer" as used herein refers to compounds produced by the phenomenon wherein a proton of one atom of a molecule shifts to another atom. See March, Advanced Organic Chemistry: Reactions, Mechanisms and Structures, 4th Ed., John Wiley & Sons, pp. 69-74 (1992). Tautomerism is defined as isomerism of the general form

\[ G-X-Y=Z \iff x=Y-Z-G \]

where the isomers (called tautomers) are readily interconvertible; the atoms connecting the groups X, Y and Z are typically any of C, H, O, or S, and G is a group which becomes an electrofuge or nucleofuge during isomerization. The most common case, when the electrofuge is H⁺, is also known as "prototropy." Tautomers are defined as isomers that arise from tautomerism, independent of whether the isomers are isolable.

ChemDraw version 8.0 or 10, (CambridgeSoft Corporation, Cambridge, MA) was used to name structures.

The following abbreviations are used in this disclosure and have the following definitions: ADP is adenosine diphosphate, ATP is adenosine triphosphate, DIEA is \( N,N \)-diisopropylethylamine, DMA is \( N,N \)-dimethylacetamide, DMF is \( N,N \)-dimethylformamide, DMSO is dimethylsulfoxide, DTT is dithiothreitol, ESI is electrospray ionization, EtOAc is ethyl acetate, GST is glutathione S-transferase, "h" is hour or hours, IC₅₀ is half maximal inhibitory concentration, min is minutes, MS is mass spectrometry, NADH is nicotinamide adenine dinucleotide, NMR is nuclear magnetic resonance, PBS is phosphate buffered saline, RT is room temperature, TBTU is 0-(Benzotriazol-1-yl \( \cdot \)-)N,\( N \),\( N \),\( N \)-tetramethyluronium tetrafluoroborate, THF is tetrahydrofuran, and Tris is tris(hydroxymethyl)aminomethane.
Compounds

In one aspect, compounds of the Formula I are described:

![Formula I](image)

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

wherein

A, W, XI, X2, Z1, Z2, Z3, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I; and

each heterocyclyl and heteroaryl individually and independently has a C or N bonding hand.

In some embodiments, a ring N atom from the heterocyclyl is the bonding atom to -C(O) to form an amide, carbamate, or urea. In other embodiments, a ring N atom from the heteroaryl is the bonding atom to -C(O) to form an amide, carbamate, or urea.

In some embodiments, compounds of the Formula I are compounds of the Formula II:

![Formula II](image)

wherein

W, X1, X2, Z1, Z2, Z3, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I.
In further embodiments, compounds of the **Formula I** are compounds of the **Formula III**:

![Formula III](image)

wherein

W, XI, X2, Z1, Z2, Z3, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.

In some embodiments, compounds of the **Formula II** are compounds of the **Formula Ila**:

![Formula Ila](image)

wherein

W, X1, X2, Z3, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.

In some embodiments, compounds of the **Formula II** are compounds of the **Formula lib**:

![Formula lib](image)

wherein...
W, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the Formula II are compounds of the Formula
lie:

![Formula lie](image)

wherein
XI, X2, Rl, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I; and
W is -(CH₂)m-pyrazole optionally substituted with -(R25)m.

[0084] In some embodiments, compounds of the Formula II are compounds of the Formula IIc.l:

![Formula IIc.l](image)

wherein
XI, X2, Rl, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;
W is -(CH₂)m-pyrazole optionally substituted with -(R25)m; and
R3 is H.
In some embodiments, compounds of the **Formula II** are compounds of the **Formula IIc.2**:

![Formula IIc.2](image)

wherein

$X_1$, $X_2$, $R_1$, $R_2$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_{25}$, $m$, $n$, and $p$ are as defined above for **Formula I**;

$W$ is -(CH$_2$)$_m$-pyrazole optionally substituted with -(R$_{25}$)$_m$; and

$R_3$ is C1-C8 alkyl, C2-C3 alkynyl, C3-C8 cycloalkyl, C1-C6-alkoxy-C1-C6-alkyl-, hydroxy-C1-C6-alkyl-, cyano, cyano-C1-C6-alkyl-, Cl-C6-S0$_2$-Cl-C6-alkyl-, -NR6(R7), (R7)R6N-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, C6-C10 aryl, C5-C6-heteroaryl, or C5-C6-heteroaryl-Cl-C6-alkyl-, wherein each alkyl or alkylenes is optionally substituted with one or two C1-C6 alkyl.

In some embodiments, compounds of the **Formula II** are compounds of the **Formula IIc.3**:

![Formula IIc.3](image)

wherein

$X_1$, $X_2$, $R_1$, $R_2$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, $R_{25}$, $m$, $n$, and $p$ are as defined above for **Formula I**;

$W$ is -(CH$_2$)$_m$-pyrazole optionally substituted with -(R$_{25}$)$_m$; and

$R_3$ is -NR6(R7) or -NHR4.
In some embodiments, compounds of the **Formula II** are compounds of the **Formula IId:**

[Diagram of formula IId]

wherein

X1, X2, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.

In some embodiments, compounds of the **Formula II** are compounds of the **Formula IId.1:**

[Diagram of formula IId.1]

wherein

R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.
In some embodiments, compounds of the Formula II are compounds of the Formula IIe:

Formula IIe

wherein

W, X1, X2, R1, R2, R8, R25, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the Formula II are compounds of the Formula IIe.1:

Formula IIe.1

wherein

W, R2, R8, R25, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the Formula II are compounds of the Formula IIe.2:

Formula IIe.2

wherein
XI, X2, R1, R2, R8, R25, m, n, and p are as defined above for **Formula I**.

[0092] In some embodiments, compounds of the **Formula II** are compounds of the **Formula IIe.3**:

![Formula IIe.3](image)

wherein

R2, R8, R25, m, and n are as defined above for **Formula I**.

[0093] In some embodiments, compounds of the **Formula II** are compounds of the **Formula IIf**:

![Formula IIf](image)

wherein

W, XI, X2, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.
In some embodiments, compounds of the Formula II are compounds of the Formula II

wherein

W, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the Formula II are compounds of the Formula

wherein

X1, X2, R1, R2, R4, R5, R6, R7, R8, R25, m, and p are as defined above for Formula I; 

W is -\text{(CH}_2\text{)}_m\text{-pyrazole optionally substituted with -(R25)}_m; and 

R3 is H.

In some embodiments, compounds of the Formula II are compounds of the Formula

wherein
XI, X2, Rl, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;

W is -(CH$_2$)$_m$-pyrazole optionally substituted with -(R25)$_m$; and

R3 is C1-C8 alkyl, C2-C3 alkynyl, C3-C8 cycloalkyl, Cl-C6-alkoxy-Cl-C6-alkyl-, hydroxy-Cl-C6-alkyl-, cyano, cyano-Cl-C6-alkyl-, Cl-C6-SO$_2$Cl-C6-alkyl-, -NR6(R7), (R7)R6N-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, C6-C10 aryl, C5-C6-heteroaryl, or C5-C6-heteroaryl-Cl-C6-alkyl-, wherein each alkyl or alkyne is optionally substituted with one or two C1-C6 alkyl.

[0097] In some embodiments, compounds of the Formula II are compounds of the Formula IIIf.4:

![Formula IIIf.4]

wherein

XI, X2, Rl, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;

W is -(CH$_2$)$_m$-pyrazole optionally substituted with -(R25)$_m$; and

R3 is -NR6(R7) or -NHR4.

[0098] In some embodiments, compounds of the Formula II are compounds of the Formula IIIf.5:

![Formula IIIf.5]
wherein
XI, X2, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for
Formula I.

In some embodiments, compounds of the Formula II are compounds of the Formula
IIIf.6:

![Formula IIIf.6](image)

wherein
R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p as defined above for Formula I.

In some embodiments, compounds of the Formula III are compounds of the
Formula Ilia:

![Formula Ilia](image)

wherein
W, XI, X2, Z3, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above
for Formula I.
In some embodiments, compounds of the **Formula III** are compounds of the **Formula IIIb**:

![Formula IIIb](image)

wherein

W, X1, X2, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.

In some embodiments, compounds of the **Formula III** are compounds of the **Formula IIIc**:

![Formula IIIc](image)

wherein

W, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for **Formula I**.

In some embodiments, compounds of the **Formula III** are compounds of the **Formula IId**:

![Formula IId](image)

wherein
XI, X2, R1, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;
W is -(CH₂)m-pyrazole optionally substituted with -(R25)ₘ; and
R₃ is H.

[00104] In some embodiments, compounds of the Formula III are compounds of the
Formula IIId.1:

![Formula IIId.1](image)

wherein
XI, X2, R1, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;
W is -(CH₂)m-pyrazole optionally substituted with -(R25)ₘ; and
R₃ is C₁-C₈ alkyl, C₂-C₃ alkynd, C₃-C₈ cycloalkyl, C₁-C₆ alkoxy-C₁-C₆ alkyl-, hydroxy-C₁-C₆ alkyl-, cyano, cyano-C₁-C₆ alkyl-, Cl-C₆-SO₂-C₁-C₆ alkyl-, -NR₆(R₇), (R₇)R₆N-C₁-C₆ alkyl-, C₄-C₆ heterocyclyl, C₄-C₆ heterocycl-C₁-C₆ alkyl-, C₆-C₁₀ aryl, C₅-C₆ heteroaryl, or C₅-C₆ heteroaryl-C₁-C₆ alkyl-, wherein each alkyl or alkyne is optionally substituted with one or two C₁-C₆ alkyl.

[00105] In some embodiments, compounds of the Formula III are compounds of the
Formula IIId.2:

![Formula IIId.2](image)

wherein
XI, X2, R1, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;

W is -(CH₂)ₘ-pyrazole optionally substituted with -(R25)ₘ; and
R3 is -NR₆(R7) or -NHR₄.

[00106] In some embodiments, compounds of the Formula III are compounds of the Formula Hie:

![Formula Hie diagram]

wherein
XI, X2, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₂₅, m, n, and p are as defined above for Formula I.

[00107] In some embodiments, compounds of the Formula III are compounds of the Formula IIIe.1:

![Formula IIIe.1 diagram]

wherein
R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₂₅, m, n, and p are as defined above for Formula I.
In some embodiments, compounds of the **Formula III** are compounds of the **Formula IIIf:**

![Formula IIIf](image)

**Formula IIIf**

wherein

W, X₁, X₂, R₁, R₂, R₈, R₂₅, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the **Formula III** are compounds of the **Formula IIIf.1:**

![Formula IIIf.1](image)

**Formula IIIf.1**

wherein

W, R₂, R₈, R₂₅, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the **Formula III** are compounds of the **Formula IIIf.2:**

![Formula IIIf.2](image)

**Formula IIIf.2**

wherein
XI, X2, R1, R2, R8, R25, m, n, and p are as defined above for Formula I.

[00111] In some embodiments, compounds of the Formula III are compounds of the Formula IIIf.3:

![Formula IIIf.3]

wherein
R2, R8, R25, m, n, and p are as defined above for Formula I.

[00112] In some embodiments, compounds of the Formula III are compounds of the Formula Illg:

![Formula Illg]

wherein
W, XI, X2, R1, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I.
In some embodiments, compounds of the Formula III are compounds of the
Formula IIIg.1:

![Formula IIIg.1](image)

wherein
W, R2, R3, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I.

In some embodiments, compounds of the Formula III are compounds of the
Formula IIIg.2:

![Formula IIIg.2](image)

wherein
X1, X2, R1, R2, R4, R5, R6, R7, R8, R25, m, n, and p are as defined above for Formula I;
W is -(CH₂)ₘ-pyrazole optionally substituted with -(R25)ₘ; and
R3 is H.

In some embodiments, compounds of the Formula III are compounds of the
Formula IIIg.3:

![Formula IIIg.3](image)
wherein

\( XI, X2, Rl, R2, R4, R5, R6, R7, R8, R25, m, \) and \( p \) are as defined above for Formula I;

\( W \) is \(-(CH_2)_m\)-pyrazole optionally substituted with \(-(R25)_m\); and

\( R3 \) is C1-C8 alkyl, C2-C3 alkynyl, C3-C8 cycloalkyl, Cl-C6-alkoxy-Cl-C6-alkyl-,
hydroxy-Cl-C6-alkyl-, cyano, cyano-Cl-C6-alkyl-, Cl-C6-S0₂Cl-C6-alkyl-, -NR6(R7),
(R7)R6N-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, C6-C10 aryl,
C5-C6-heteroaryl, or C5-C6-heteroaryl-Cl-C6-alkyl-; wherein each alkyl or alkenylene is
optionally substituted with one or two C1-C6 alkyl.

[00116] In some embodiments, compounds of the Formula III are compounds of the
Formula IIIg.4:

![Formula IIIg.4](image)

wherein

\( XI, X2, Rl, R2, R4, R5, R6, R7, R8, R25, m, n, \) and \( p \) are as defined above for Formula I;

\( W \) is \(-(CH_2)_m\)-pyrazole optionally substituted with \(-(R25)_m\); and

\( R3 \) is -NR6(R7) or -NHR4.

[00117] In some embodiments, compounds of the Formula III are compounds of the
Formula IIIg.5:

![Formula IIIg.5](image)
wherein
B, XI, X2, Rl, R2, R3, R4, R5, R6, R7, R8, R25, m, n and p are as defined above for Formula I.

[00118] In some embodiments, compounds of the Formula III are compounds of the Formula IIIg.6:

![Formula IIIg.6]

wherein
R2, R3, R4, R5, R6, R7, R8, R25, m, n and p are as defined above for Formula I.

[00119] The following embodiments are descriptive of Formula I, Formula II, Formula Ha, Formula Ile, Formula IIc.1, Formula IIc.2, Formula IIc.3, Formula lid, Formula Ild.1, Formula He, Formula IIe.2, Formula III, Formula III.2, Formula III.3, Formula III.4, Formula III.5, Formula III, Formula Ila, Formula IIIb, Formula Hid, Formula Ild.1, Formula IIId.2, Formula Ile, Formula IIIf, Formula III.2, Formula IIIg, Formula IIIg.2, Formula IIIg.3, Formula IIIg.4 and Formula IIIg.5.

[00120] In some embodiments, each XI and X2 is individually and independently halogen. In other embodiments, each XI and X2 is individually and independently F or Cl. In further embodiments, each XI and X2 is F.

[00121] In some embodiments, each R1 is individually and independently halogen. In other embodiments, each R1 is individually and independently F or Cl. In further embodiments, each R1 is F.

[00122] In some embodiments, m is 1 and R1 is halogen. In other embodiments, m is 1 and R1 is F or Cl. In further embodiments, m is 1 and R1 is F.
In some embodiments, each R₁, X₁ and X₂ is individually and independently halogen. In other embodiments, each R₁, X₁ and X₂ is individually and independently F or Cl. In further embodiments, each R₁, X₁ and X₂ is F.

Utility

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.

Administration of Compounds

In some embodiments, the compound is administered by a method selected from the group consisting of oral, parenteral, inhalation, and subcutaneous.

Treatment Methods

The disclosed methods also include treating individuals suffering from a condition selected from the group consisting of cancer, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases or diseases characterized by angiogenesis. These methods comprise administering to such individuals compounds disclosed herein, and especially those of section 1, said diseases including, but not limited to, solid tumors, malignant melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney 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, gastrointestinal stromal tumors, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including...
Various retinopathies, diabetic retinopathy and age-related macular degeneration and hypereosinophilic syndrome, rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder, mastocytosis, mast cell leukemia, a disease caused by c-c-MET kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

Pharmaceutical Preparations

[00128] The compounds disclosed herein may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

Methods of Making

[00129] The compounds of the invention are available by the general synthetic methods illustrated in the Schemes below and the accompanying examples.

[00130] Compounds 1 of the invention are assembled in a step-wise manner as illustrated in Scheme 1. Acids of formula 2 are reacted with amines of formula 3 in the presence of standard peptide coupling reagents familiar to those skilled in the art to prepare amides of formula 1. Suitable reagents for the conversion of 2 to 1 include TBTU (0-(benzotriazol-1-yl)-N,N,N',N'-tetramethyllumuronium tetrafluoroborate), PyBOP (benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate), EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) and BOP-C1 (bis(2-oxo-3-oxazolidinyl)phosphonic chloride). It is recognized that in this case and in others to follow, a carboxylic acid moiety, such as found in 2, can also be activated as an acid halide, anhydride, mixed anhydride, or as an activated ester (for example a pentafluorophenyl ester). Those skilled in the art will recognize that such activated esters can react directly with amine 3 in the absence of an added peptide coupling reagent. In the case of activated acid derivatives it will be further understood that these compounds are optionally isolated as discrete intermediates prior to their union with amines 3 to form 1. Using similar conditions, acids of formula 5 also are, in some embodiments, coupled with amine 3 to yield amides 4, additional compounds of the invention.
Non-limiting examples of Scheme 1 are illustrated in Scheme 2 for the preparation of compound 8, an example of general formula 1 (wherein R1 is 4-fluoro, m is 1, R8 is H, X1 and X2 are fluoro, Z1 and Z3 are CH, Z2 is N, and W is N-methyl-4-pyrazolyl) and compound 1.0, an example of general formula 4 (wherein R1 is 4-fluoro, m is 1, R8 is H, X1 and X2 are fluoro, Z1 and Z3 are CH, Z2 is N, and W is N-methyl-4-pyrazolyl). Thus, the combination of acid 6 (an example of general acid 2) and amine 7 (an example of general amine 3) in the presence of a peptide coupling agent, for example TBTU, provides amide 8. Using similar conditions, acid 9 (an example of general acid 5) is converted to amide 4.
Amines 3 useful for the invention are synthesized according to methods commonly known to those skilled in the art. Amines 3 contain a central ether moiety and in general terms are prepared by the reaction of amino-phenol 11 or nitro-phenol 12 with a pyridine, pyrimidine, pyridazine or triazine of general formula 13, wherein the LG-moiety of 13 represents a leaving group such as a halide or sulfonate that is displaced in a nucleophilic aromatic substitution reaction and the L-moiety of 13 is either the W-group of compound 1 or a functional group that is readily converted to the W-group of formula 1 by a series of standard synthetic methods understood by those skilled in the art. These additional steps will be understood to include the optional use of standard protecting groups as appropriate.

The nucleophilic substitution reaction involving compound 13 is typically performed in an aprotic solvent at temperatures ranging from ambient temp to 200 °C, optionally with microwave heating. Additional conditions for the conversion of JJ to 14 or 12 to 15 include the addition of a base, for example potassium feri-butoxide or sodium hydride. In some embodiments, the conversion of nitro-phenol 12 to ether 1,5 is performed in the presence of an acid, for example by treatment with HCl while heating in chlorobenzene. In some embodiments, the union of 11 or 12 with 13 is catalyzed by transition metals, for example copper (Ullmann coupling) or palladium (Buchwald-Hartwig coupling). In the instance in which nitrophenol 12 is employed, the intermediate nitro-ether 15 is converted to amine 14 by standard reducing conditions, for example, by hydrogenation, by reduction with zinc metal or by reduction with...
stannous chloride. In the instance in which the L-moiety of 14 or 15 is different than the W-moiety of 3, the L-moiety is converted to a W-moiety using conditions known to those skilled in the art. Some non-limiting examples of general Scheme 3 are shown in the following Schemes.

[00134] Alternative general syntheses of ethers of formula 15 are shown in Scheme 4. Thus, hydroxy-heteroarenes of formula 17 are reacted with 4-fluoronitrobenzenes 16 to provide ether 15, which in turn is reduced to general amines of formula 14 as described above. Conditions for the union of 16 and 17 include the use of a base, for example cesium carbonate or sodium hydride in a polar aprotic solvent such as dimethylformamide or dimethylsulfoxide with optional heating or microwave heating. Those skilled in the art will recognize that the hydroxy-heteroarene 17 also exists in a tautomeric state found as a pyridone, pyrimidinone, pyridazinone, or triazinone, the tautomeric structures of which are implicitly contained within formula 17. In certain embodiments, ethers of formula 15 can also be prepared by nitration of compounds of formula 19. Ethers of formula 19 are prepared using the conditions of Scheme 3 by the reaction of phenols of formula 18 with pyridine, pyrimidine, pyridazine or triazine of general formula 13.
A general method of preparation of general amines 3 from intermediate 1,4 is illustrated in Scheme 5. Thus, the reaction of compound 14 (prepared according to Scheme 3, L is halogen) with an organometallic reagent M-W (20) in the presence of a palladium catalyst, for example Pd(PPh₃)₄, provides compounds of formula 3. The M-group of M-W 20 represents a "metallic" functionality known to undergo palladium-catalyzed reactions with aryl halides. Examples of M-groups include boronic acids or esters, trifluoroborates, tin, copper, zinc, magnesium and lithium. These M-W reagents (20), when not commercially available, are generally prepared from analogous halides by methods familiar to those skilled in the art.

L is halogen

Scheme 5

Scheme 6 illustrates the preparation of amine 7 (an example of general amine 3 wherein X₁ and X₂ are fluoro, Z₁ and Z₃ are CH, Z₂ is N, and W is N-methyl-4-pyrazolyl) using the method of Scheme 3 and Scheme 5. Thus, the amino-phenol 21 (an example of general phenol 17 wherein X₁ and X₂ are fluoro; see Scheme 3) is reacted with potassium tert-butoxide and pyrimidine 22 (an example of general intermediate 11 wherein Z₁ and Z₃ are CH,
Z2 is N, L is iodo, and LG is chloro; see Scheme 3) to provide iodide 23, an example of general amine 14 wherein L is iodo. Further reaction of iodide 23 with pyrazole boronate 24 (an example of M-W 20 wherein M is 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) in the presence of Pd(PPh3)4 provides pyrazole 7, an example of general amine 3 wherein W is N-methyl-4-pyrazolyl.

Scheme 6

Those skilled in the art will understand that within Scheme 3, the steps leading from intermediates 14 or 15 to general amine 3 also include functional group inter-conversions at any substituted position of intermediates 14 or 15. For example, implicit within Scheme 3 would be the conversion of intermediate J4 wherein Z3 is CCl into general amine 3 wherein Z3 is CR3. A non-limiting example of this is illustrated in Scheme 7 for the preparation of NHR4-substituted amines of general formula 34 and 35. Thus, following the conditions of Scheme 3, the reaction of general nitro-phenol 12 with pyridine 25 (see Syn. Comm. (1992), 22, pg. 2829) or pyrimidine 26 (commercially available) provides 27 or 28 respectively. Reduction of the nitro moiety of 27 or 28 as described above provides 29 or 30, examples of general intermediate 14 wherein L is bromo, Z3 is CR3 and R3 is chloro. Further reaction of chloropyridine 29 or chloropyrimidine 30 with general amine NH2-R4 (31) provides 32 or 33, respectively. Further reaction of 32 or 33 with 20, as described above, provides 34 or 35, examples of general amine 3 wherein Z3 is CR3 and R3 is -NHR4.
Scheme 7

Scheme 8 illustrates an example of general Scheme 4 and Scheme 5. Thus, reaction of the chloropyridine 36 with phenol \textsubscript{1,8} and a base provides ether 37, an example of general intermediate 19 (wherein \( L \) is iodo, \( Z_1, Z_2 \) are CH, \( Z_3 \) is CR\(_3\), \( R_3 \) is \(-\text{NHR}_4\), \( R_4 \) is H). Nitration of 37 provides the nitro ether 38. Reduction of nitro 38 provides amine 39. Further reaction of 39 with M-W (20) (as described above in Scheme 5) provides amine 40, an example of general amine 3, that is used to prepare compounds of formula 1 (Scheme 1).
In some embodiments, it is desirable to incorporate temporary protecting groups to mask reactivity of certain functional groups in the course of a synthesis. Thus the reaction arrows in Scheme 1 implicitly represent either a single reaction or a reaction sequence that contains, for example, the removal of a protecting group and/or subsequent inter-conversion of substituents. By way of example, Scheme 9 illustrates a modification of Scheme 1 that provides a library of compounds of formula \( I \) with differing R5 substituents. Thus, using standard peptide coupling conditions, general acid \( 2 \) is coupled with amine \( 43 \) to provide \( 44 \). Amine \( 43 \) is an example of general amine \( 3 \) wherein Z1 and Z2 are CH, Z3 is CR3, R3 is bis(tert-butoxycarbonyl)amine. Those skilled in the art will recognize that the tert-butoxycarbonyl (BOC) groups of \( 43 \) and \( 44 \) are protecting groups that are removed upon exposure to acid. Removal of the BOC protecting groups from \( 44 \) by exposure to acid, for example trifluoroacetic acid, provides amino-pyridine \( 45 \), an example of compound \( I \) wherein Z3 is CR3 and R3 is NH2. Further treatment of \( 45 \) with a carbonylation reagent \( 46 \) provides compounds of formula \( 47 \), additional examples of compound \( I \). In carbonylation reagent \( 46 \), in some embodiments the Y-moiety is hydroxyl or halogen. When Y is hydroxyl, reagent \( 46 \) is a carboxylic acid that is coupled with amine \( 45 \) using standard peptide coupling reagents. When Y is halogen, reagent \( 46 \) is an acid halide or a haloformate that will react with amine \( 45 \) to provide an amide or carbamate. As indicated in Scheme 9, the requisite amine \( 43 \) is readily prepared from aminopyridine \( 38 \) by treatment with di-tert-butyl dicarbonate in the presence of a base, for example, triethylamine, to
obtain 41. Reduction of the nitro-moiety of 41 affords 42. Further reaction of 42 with M-W (20) (as described above in Scheme 5) provides amine 43.

Scheme 9

[00140] As an extension of Scheme 9, Scheme 10 illustrates the preparation of ureas of formulae 51, 53 and 55. Thus, amine 45 is reacted with 2,2,2-trichlorethyl chloroformate or isopropenyl chloroformate to provide the activated carbamates 48 or 49 respectively. Further reaction of 48 or 49 with amines of formula 50 provide ureas of formula 51. Additional examples of compound 1. Similarly, reaction of 48 or 49 with heterocyclic amines of formula 52 (for example, morpholine, pyrrolidine, piperidine, piperazine) provides ureas of formula 53. Additionally, reaction of 45 with isocyanates (54) directly provides ureas of formula 55.
In a manner similar to Scheme 7 and Scheme 8, Scheme 11 illustrates the preparation of amine 60, an additional example of general amine 3. Thus intermediate 56 is reacted with compounds of formula R4-X (57), wherein X is a leaving group such as halide or sulfonate, to provide R4-substituted compounds of formula 58. Reduction of the nitro group of 58 provides 59. In turn, iodide 59 is subjected to a palladium mediated coupling with 20 to provide 60, an additional example of general amine 3.
[00142] General acids 2 are prepared from pyranones of formula 61 by the sequence shown in Scheme 12. Thus, treatment of 61 (R is alkyl) with aniline 62 followed by cyclodehydration of the initial adduct (not shown) provides N-aryl pyridine esters of formula 63. Subsequent hydrolysis of 63 provides acid 2. Alternatively, ester 63 is available from the reaction of NH pyridone 64 (R is alkyl) with aryl iodide 65 in the presence of a copper catalyst. Conditions for this latter transformation include heating between 50 °C and 200 °C in the presence of copper iodide and optionally in the presence of a ligand, for example 8-hydroxyquinoline. Additionally, pyridones 63 are prepared from acyclic starting material 66 (wherein R is alkyl). The LG group of 66 is a leaving group, for example an alkoxy, dialkylamino or halo moiety. The R8 moieties in 66 are independently variable, such that they are the same or different from one another. In some embodiments, R8 is hydrogen. Reaction of 66 with aniline 62 provides 67. Further treatment of 67 with a base, for example sodium hydride, promotes cyclization to 63.

![Scheme 12](image)

[00143] Scheme 13 illustrates the preparation of acids 71 and 74, examples of general acid 5. Using methods described in *J. Med. Chem.* (2005) 51, pp 5330-5341, Meldrum's acid (68) and acid chloride 69 are combined to yield pyridone ester 70. When not commercially available,
Acid chlorides 69 are readily prepared from the corresponding acids by treatment with thionyl chloride. Saponification of ester 70 provides acid 71, an example of general amine 5. Further treatment of 70 with alkyl halide 72 in the presence of a base, for example potassium carbonate, provides the R8-substituted pyridone ester 73. Saponification of ester 73 affords acid 74, a further example of general acid 5.

**Scheme 13**

[00144] An additional synthesis of acid 74 is also illustrated in **Scheme 17** commencing with bromide 75 (see *J. Med. Chem.* (2008) 57, pp 5330-5341). Thus, alkylation of 75 with 72, as described above, provides 76. Treatment of 76 with boronic acid 77 (or analogous boronates, not shown) in the presence of a palladium catalyst and a carbonate base provides pyridine ester 73. Saponification of ester 73 provides acid 74.

[00145] A variation to the synthesis of 4-pyridones of formula 4 is shown in **Scheme 14** for the preparation of 81. Thus, treatment of pyrrole acid halide 78 (prepared by the general methods of *J. Med. Chem.* (2008) 57, pp 5330-5341) with general amine 3 provides pyrone 79. Further treatment of 79 with R8-substituted amines (80) provides pyridones 81.
In a manner related to Scheme 12, Scheme 15 illustrates a further preparation of 2-pyridone acids and amides of the invention. Using the methods of J. Med. Chem. (2009) 52, pp 1251-1254, methoxy pyridine 82 is first demethylated by treatment with iodosiltrimethylsilane. The resultant species is then reacted with boronic acid 77 in the presence of copper(II) acetate, to provide N-aryl pyridone 83. Oxidation of the aldehyde to the carboxylic acid 84 is then followed by conversion to the acid chloride (85) by treatment with thionyl chloride. Reaction of 85 with general amine 3 affords 86. Finally, replacement of the iodide with another R8 moiety by reaction of 86 with 87 provides compound 88, an example of formula 1. In the instance in which R8 is an alkoxy moiety, reagent 87 represents an alcohol (wherein M is H) or an alkoxide (wherein M is alkali) that displaces the iodide to form a carbon-oxygen bond. In the instance in which R8 is cyano, reagent 87 represents a metal cyanide (wherein M is Cu or Zn) that replaces the iodine atom of 86, in some embodiments in the presence of a transition metal, for example palladium. In the instance in which R8 is alkyl, the "M" moiety of 87 represents a "metallic" functionality known to undergo palladium-catalyzed reactions with aryl halides. Examples of M-groups include boronic acids or esters, trifluoroborates, tin, copper, zinc, magnesium and lithium. Those skilled in the art will recognize that in certain instances, an alkyl R8 is introduced as a vinylic or acetylenic moiety that is subsequently converted to an alkyl moiety by standard reducing conditions such as hydrogenation over a transition metal catalyst.
Using the synthetic procedures and methods described herein and methods known to those skilled in the art, the following compounds were made:

- \( N-(2,5\text{-difluoro-}4-(5\text{-}(1\text{-methyl}-1\text{H-pyrazol-4-yl})\text{pyrimidin-4-yloxy})\text{phenyl})-1\text{-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide} \)
- \( N-(2,5\text{-difluoro-}4-(3\text{-}(1\text{-methyl}-1\text{H-pyrazol-4-yl})\text{pyridin-4-yloxy})\text{phenyl})-1\text{-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide} \)
- \( N-(4\text{-}(3\text{-}(1\text{-cyanomethyl}-1\text{H-pyrazol-4-yl})\text{pyridin-4-yloxy})\text{phenyl})-1\text{-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide} \)
- \( N-(4\text{-}(2\text{-amino-3-(1\text{-methyl}-1\text{H-pyrazol-4-yl})pyridin-4-yloxy})\text{phenyl})-2,5\text{-difluorophenyl})-1\text{-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide} \)
- \( N-(5\text{-chloro-2-fluoro-4-(3\text{-}(1\text{-methyl}-1\text{H-pyrazol-4-yl})\text{pyridin-4-yloxy})\text{phenyl})-2-oxo-1,2-dihydropyridine-3-carboxamide} \)
- \( N-(2,5\text{-difluoro-}4-(3\text{-}(1\text{-methyl}-1\text{H-pyrazol-4-yl})\text{pyridin-4-yloxy})\text{phenyl})-5\text{-ethoxy-1-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-} \)
carboxamide, N-(4-(2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-1-methyl-4-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(3-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide.

Examples

[00148] The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

[00149] Example Al: To a solution of 4-amino-2,5-difluorophenol (0.190 g, 1.310 mmol) in DMF (10 mL) was added potassium tert-butoxide (0.168 g, 1.497 mmol). The mixture was stirred at RT for 30 min. 4-Chloro-5-iodopyrimidine (0.30 g, 1.248 mmol) was added and the reaction mixture was heated at 80 °C overnight. The reaction mixture was quenched with water and the solution was extracted with EtOAc (3x). The organic solution was washed with 5% aqueous lithium chloride solution and brine. The organics were dried over MgSO₄, filtered, and concentrated. The crude was purified by silica gel column chromatography (10% to 50% EtOAc/hexane) to obtain 2,5-difluoro-4-(5-iodopyrimidin-4-yloxy)benzenamine (160 mg, 36.7%, yield) which was used for the next reaction. MS (ESI) m/z: 349.9 (M+H⁺).

[00150] To a degassed solution of 2,5-difluoro-4-(5-iodopyrimidin-4-yloxy)benzenamine (0.23 g, 0.659 mmol) in DMF (5 mL) was added 1-methyl-pyrazole-4-boronic acid pinacol ester (0.206 g, 0.988 mmol), cesium carbonate (0.644 g, 1.977 mmol) in water (2 mL) and Pd(PPh₃)₄ (0.076 g, 0.066 mmol) and the mixture was stirred at 80 °C under an argon atmosphere for 1 hour. Water was added and the solution was extracted with EtOAc (3x). The organics were washed with 5% aqueous lithium chloride solution and brine, and then dried over MgSO₄. The
organics were filtered and concentrated under reduced pressure. The residue was treated with small amount of EtOAc and Et₂O. The solid was collected by filtration to obtain 2,5-difluoro-4-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)oxy)benzamine (0.18 g, 90% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 9.02 (s, 1 H), 8.54 (s, 1 H), 8.30 (s, 1 H), 8.09 (s, 1 H), 7.21 (m, 1 H), 6.69 (m, 1 H), 5.42 (s, 2 H), 3.89 (s, 3 H); MS (ESI) m/z: 304.1 (M+H⁺).

[00151] Example A2: 2,5-Difluoro-4-nitro-phenol (1.739 g, 9.93 mmol) and 3-bromo-4-chloro-pyridine (0.637 g, 3.31 mmol) were dissolved in chlorobenzene (6 mL) and heated at 145 °C overnight. The solvent was removed under reduced pressure and the residue partitioned between EtOAc and 10% aqueous K₂CO₃. The mixture was extracted with EtOAc (2x), and the combined organic extracts were washed with 10% aqueous K₂CO₃ and brine, dried, evaporated and purified by silica gel chromatography (hexanes/EtOAc) to yield 3-bromo-4-(2,5-difluoro-4-nitrophenoxy)pyridine (414 mg, 38% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.84 (s, 1 H), 8.51-8.45 (m, 2 H), 7.82-7.78 (m, 1 H), 7.22 (d, 1 H); MS (ESI) m/z: 331.0 (M+H⁺).

[00152] 3-Bromo-4-(2,5-difluoro-4-nitrophenoxy)pyridine (0.414 g, 1.25 mmol) was dissolved in EtOH (30 mL). Tin (II) chloride dihydrate (1.129 g, 5.00 mmol) was added and the mixture was heated at 80 °C for 4h. The solvent was removed under reduced pressure and the residue quenched with saturated aqueous NaHCO₃. The mixture was diluted with EtOAc and filtered through Celite®. The Celite® bed was washed with water (2x) and EtOAc (2x), and the filtrate was extracted with EtOAc (2x). The combined organic extracts were dried and evaporated to yield 4-(3-bromopyridin-4-yl-oxy)-2,5-difluorobenzenamine (0.42 g, 112% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.68 (s, 1 H), 8.33 (d, 1 H), 7.28-7.23 (m, 1 H), 6.76-6.71 (m, 2 H), 5.56 (br s, 2 H); MS (ESI) m/z: 301.0 (M+H⁺).

[00153] Example A3: In a sealed tube, 4-(3-bromopyridin-4-yl-oxy)-2,5-difluorobenzenamine (0.42 g, 1.395 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.363 g, 1.744 mmol), potassium carbonate (0.578 g, 4.18 mmol), and tetrakistriphenylphosphine palladium (0) (0.081 g, 0.070 mmol) were suspended in dioxane (8 mL) and water (1.333 mL). The mixture was degassed with Ar and heated at 90 °C overnight. The reaction mixture was cooled and partitioned between EtOAc and saturated aqueous NaHCO₃. The mixture was extracted with EtOAc (3x). The combined organic extracts were...
dried, evaporated and purified by silica gel chromatography (hexanes/EtOAc) to yield 2,5-
difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzenamine (272 mg, 65% yield). 

\[ ^1H \text{NMR} \ (400 \text{ MHz, DMSO}-d_6): \delta \text{ 8.80 (s, 1 H), 8.22-8.20 (m, 2 H), 8.00 (s, 1 H), 7.24-7.19 (m, 1 H), 6.76-6.71 (m, 1 H), 6.62 (d, 1 H), 5.50 (br s, 2 H), 3.78 (s, 3 H); MS (ESI) m/z: 301.0 (M+H\(^{+}\)). } \]

**Example A4:** To a solution of 4-chloropyridin-2-amine (4.00 g, 31.1 mmol) in THF (60 mL) was added lithium bis(trimethylsilyl)amide in THF (1.0 M, 65.3 mL, 65.3 mmol) at -5 \(^\circ\)C under Ar atmosphere. After 10 minutes, di-tert-butyl dicarbonate was added (7.22 mL, 31.1 mmol) and stirring was continued for 1 h. Sat. NH\(_2\)Cl solution (70 mL) was added and layers were separated. The aqueous layer was extracted with EtOAc (30 mL) and the combined organics were washed with brine, dried (Na\(_2\)SO\(_4\)) and concentrated to afford crude product, which was stirred with 30% EtOAc-hexanes (50 mL) for 5 min. The resultant suspension was filtered, washed with 30% EtOAc-hexane (2x5 mL) and dried to afford tert-butyl (4-chloropyridin-2-yl)carbamate as a white solid (5.5 g, 77% yield).

**Example A5:** A solution of tert-butyl (4-chloropyridin-2-yl)carbamate (5.5 g, 24.05 mmol) and N,N,N’,N’-tetramethylethylenediamine (7.26 mL, 48.1 mmol) in THF (100 mL) was cooled to -78 \(^\circ\)C and treated with n-BuLi (2.5 M in hexanes, 19.24 mL, 48.1 mmol) drop wise over a period of 20 minutes. The mixture was stirred at the same temperature for 1 h. A solution of iodine (12.21 g, 48.1 mmol) in THF (40 mL) was added and stirring was continued at -78 \(^\circ\)C for 30 min and at ambient temp for 1 h. Sat. aq NH\(_2\)Cl solution (80 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL) and the combined organics were washed with 10% aq. Na\(_2\)S\(_2\)O\(_3\) solution (40 mL) and brine. The extracts were dried (Na\(_2\)SO\(_4\)) and concentrated to dryness. A solution of 30% EtOAc-hexanes (30 mL) was added and the mixture was sonicated for 10 min. The resultant precipitate was collected by filtration, washed with 30% EtOAc-hexanes and dried in vacuo to afford tert-butyl (4-chloro-3-iodopyridin-2-yl)carbamate as off-white solid (5.6 g, 65% yield). 

\[ ^1H \text{NMR} \ (400 \text{ MHz, DMSO}-d_6): \delta \text{ 9.45 (s, 1 H), 8.28 (d, J = 5.6 Hz, 1 H), 7.46 (d, J = 5.6 Hz, 1 H); 1.43 (s, 9 H). } \]

**Example A6:** A solution of aqueous HBr (48%, 10 mL, 13.26 mmol) was added to tert-butyl (4-chloro-3-iodopyridin-2-yl)carbamate (4.7 g, 13.26 mmol) and the suspension was stirred at RT for 3h. The reaction mixture was diluted with water (40 mL), basified with 2N NaOH and the
resultant suspension was filtered, washed with water (4 x 1 mL) and dried to afford 4-chloro-3-iodopyridin-2-amine as white solid (3.05 g, 90% yield). MS (ESI) m/z: 254.9 (M+H+).

[00157] 4-chloro-3-iodopyridin-2-amine (3.00 g, 11.79 mmol), 2,5-difluoro phenol (4.60 g, 35.4 mmol), DBU (1.777 ml, 11.79 mmol) were combined in NMP (15 mL) and solution was stirred at 170 °C for 6h under microwave irradiation. The crude reaction mixture was poured into IN NaOH solution (70 mL), the resultant suspension was filtered, washed with water (5 x 10 mL) and dried to afford crude product which was purified by silica gel chromatography (EtOAc-hexanes) to afford 4-(2,5-difluorophenoxy)-3-iodopyridin-2-amine as white solid. (2.55 g, 62.1% yield). 1H NMR (400 MHz, OMSO-d6): δ 7.74 (d, J = 7.6 Hz, 1 H), 7.47 (m, 1 H), 7.28 (m, 1 H), 7.18 (m, 1 H), 6.25 (brs, 2 H), 5.88 (dd, J = 5.6 Hz, 1 H); MS (ESI) m/z: 349.03 (M+H+).

[00158] A chilled (-10 °C) mixture of 4-(2,5-difluorophenoxy)-3-iodopyridin-2-amine (2.31 g, 6.64 mmol) in sulfuric acid (15 ml) was treated with nitric acid (0.35 ml, 7.96 mmol) while maintaining the temperature below 0 °C. After stirring for 20 minutes, the mixture was poured into ice-cold 2 N aq. NaOH solution (100 mL of 2 N NaOH in ice) with stirring. The pH of the resultant solution was then made basic by careful addition of NaHCO3. After stirring for 30 min, the suspension was filtered, washed with water (3 x 10 mL) and dried to afford 4-(2,5-difluoro-4-nitrophenoxy)-3-iodopyridin-2-amine as light red solid (2.05 g, 79% yield). MS (ESI) m/z: 393.9 (M+H+).

[00159] To a solution of 4-(2,5-difluoro-4-nitrophenoxy)-3-iodopyridin-2-amine (0.78 g, 1.78 mmol) in EtOH (15 mL) added tin(II) chloride dihydrate (2.0 g, 8.93 mmol) and the reaction mixture was stirred at 80 °C for 3h. The mixture was cooled to RT, the solvent was removed in vacuo and crude residue was basified with NaHCO3 solution (40 mL). EtOAc (50 mL) was added to the resultant white suspension and the mixture was stirred for few minutes. It was filtered though a Celite® pad which was washed with EtOAc (4 x 5 mL), and water (3 x 4 mL). The organic layer was separated and was washed with brine, dried (Na2SO4) and concentrated to afford crude product which was purified by silica gel chromatography (EtOAc-hexanes) to afford 4-(4-amino-2,5-difluorophenoxy)-3-iodopyridin-2-amine as an off-white solid (0.33 g, 51% yield). 1H NMR (400 MHz, DMSO-d6): δ 7.69 (d, J = 5.6 Hz, 1 H), 7.12 (dd, J = 11.2 Hz, 7.6 Hz, 1 H), 6.69 (dd, J = 12.0 Hz, 8.0 Hz, 1 H), 6.13 (s, 2 H), 5.74 (d, J = 5.6 Hz, 1 H), 5.47 (s, 2 H); MS (ESI) m/z: 364.0 (M+H+).
To a degassed solution of 4-(4-amino-2,5-difluorophenoxy)-3-iodopyridin-2-amine (0.33 g, 0.91 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-IH-pyrazole (0.28 g, 1.36 mmol) in dioxane (5 mL) was added a degassed solution of K₂CO₃ (0.37 g, 2.73 mmol) in water (2 mL) and tetrakis(triphenylphosphine)palladium(0) (0.105 g, 0.09 mmol). The resultant mixture was stirred for 16 h at 90 °C. Sat. NaHCO₃ solution (35 mL) was added. The resultant mixture was extracted with EtOAc (2 x 30 mL). The combined organics were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/CH₂Cl₂) to afford 4-(4-amino-2,5-difluorophenoxy)-3-(1-methyl-1H-pyrazol-4-yl)pyridin-2-amine (188 mg, 65.2 %) as white solid (188 mg, 65.2 % yield). ^1H NMR (400 MHz, DMSO- d₆): δ 7.85 (s, 1 H), 7.70 (d, J = 6.0 Hz, 1 H), 7.57 (s, 1 H), 7.06 (dd, J = 11.2 Hz, 7.2 Hz, 1 H), 6.66 (dd, J = 12.0 Hz, 8.0 Hz, 1 H), 5.86 (d, J = 5.6 Hz, 1 H), 5.60 (s, 2 H), 5.39 (s, 2 H), 3.85 (s, 3 H); MS (ESI) m/z: 318.1 (M+H⁺).

Example A5: A mixture of 2-chloro-5-fluorophenol (1.50 g, 10.24 mmol), 3-bromo-4-chloropyridine (1.50 g, 7.79 mmol) and DBU (1.50 g, 9.85 mmol) were heated at 130 °C in NMP (10 mL) for 15 hours. The reaction mixture was cooled and partitioned between water (100 mL) and MTBE (100 mL). The organic layer was separated, washed with dilute aq NaOH and brine, dried (MgSO₄) and concentrated in vacuo to provide 3-bromo-4-(2-chloro-5-fluorophenoxy)pyridine (1.98 g, 84 % yield) as brownish oil suitable for use in the next reaction. MS (ESI) m/z: 303.9 (M+H⁺).

To a cold (-10 °C) solution of 3-bromo-4-(2-chloro-5-fluorophenoxy)pyridine (1.98 g, 6.54 mmol) in cone. sulfuric acid (5 ml) was added nitric acid (0.55 ml, 8.69 mmol). The resultant mixture was stirred at the same temp for 20 minutes and was then allowed to warm to ambient temp for 30 min. The reaction mixture was treated with crushed ice, stirred, filtered, washed and dried to provide 3-bromo-4-(2-chloro-5-fluoro-4-nitrophenoxy)pyridine, (2.08 g, 91 % yield) as orange yellow solid. ^1H NMR (400 MHz, DMSO- d₆) δ 9.00 (s, 1 H), 8.62 (m, 2H), 7.81 (d, J = 8 Hz, 1 H), 7.23(d, J =2.5 Hz, 1 H); MS (ESI) m/z: 348.9 (M+H⁺).

To a solution of 3-bromo-4-(2-chloro-5-fluoro-4-nitrophenoxy)pyridine (2.00 g, 5.75 mmol) in ethanol/water (9:1, 50 mL) was added iron powder (2.00 g, 35.8 mmol) followed by ammonium chloride (2.00 g, 37.4 mmol). The mixture was heated at 70 °C for 2 h. The reaction mixture was filtered, and the solids were washed with EtOAc. The filtrate was evaporated to
dryness. The residue was taken in ethyl acetate and washed with water and dried. The solvent was evaporated to provide 4-(3-bromopyridin-4-yloxy)-5-chloro-2-fluorobenzenamine as light brownish oil (0.98 g, 53.6 % yield). MS(ESI) m/z : 317.0/319.0 (M+H+).

[00164] To a solution of 4-(3-biOMopyridin-4-yloxy)-5-chloro-2-fluorobenzenamine, (0.300 g, 0.945 mmol) in n-butanol (5 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-lH-pyrazole (0.236 g, 1.134 mmol), S-Phos (0.078 g, 0.189 mmol), Pd2(dba)3 (0.087 g, 0.094 mmol) and potassium phosphate (0.602 g, 2.83 mmol). The resulting mixture was degassed and heated in a sealed tube at 100 °C for 20 h. The solvent from the reaction mixture was completely evaporated. The residue was stirred in a mixture of CH2Cl2-MeOH (1:1), filtered, rinsed, dried and subjected to chromatography (50-100% EtOAc-hexanes) to provide 5-chloro-2-fluoro-4-(3-(1-methyl-lH-pyrazol-4-yl)pyridin-4-yloxy)benzenamine, (0.148 g, 49.1 % yield) as white solid. 1H NMR(400 MHz, DMSO-d6): δ 8.21 (dd, J = 7.6 Hz, 5.6 Hz, 1H), 7.06 (d, J = 6.8 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.51 (d, J = 5.6 Hz, 1H), 5.51 (s, 2H), 3.88 (s, 3H); MS(ESI) m/z : 319.1 (M+H+).

[00165] Example A6: 4-(2,5-Difluoro-4-nitrophenoxo)-3-iodopyridin-2-amine (2.05 g, 5.22 mmol) (from Example A4), di-tert-butyl dicarbonate (2.66 ml, 11.47 mmol) and Et3N (0.73 ml, 5.22 mmol) were combined in THF (25 mL) and stirred for 3 h at RT. The reaction mixture was concentrated in vacuo and the residue was purified by silica gel chromatography (EtOAc-hexanes) to afford 4-(2,5-difluoro-4-nitrophenoxo)-3-iodo-2-[bis[(l,l-dimethylethoxy)carbonyl]amino]pyridine as white solid (1.63 g, 52.7% yield). 1H NMR (400 MHz, DMSO-d6): δ 8.47 (dd, J = 10 Hz, 7.2 Hz, 1H), 8.37 (d, J = 5.4 Hz, 1H), 7.67 (dd, J = 11.2 Hz, 6.8 Hz, 1H), 7.06 (d, J = 5.6 Hz, 1H), 1.34 (s, 18 H); MS (ESI) m/z: 616.1 (M+Na+).

[00166] Palladium hydroxide on carbon (0.193 g, 0.275 mmol) (contains 60% water) was added to a solution of 4-(2,5-difluoro-4-nitrophenoxy)-3-iodo-2-[bis[(l,l-dimethylethoxy)carbonyl]amino]pyridine (1.63 g, 2.75 mmol) in EtOAc (20 mL) and the mixture was hydrogenated (50) psi for 16 h. The completed reaction mixture was filtered through Celite® rinsing forward with EtOAc (2 x 10 mL). The combined filtrate was concentrated to afford 4-(2,5-difluoro-4-aminophenoxy)-3-iodo-2-[bis[(l,l-dimethylethoxy)carbonyl]amino]pyridine as colorless foam (1.5 g, 97% yield). 1H NMR (400 MHz, DMSO-d6): δ 8.21 (dd, J = 7.6 Hz, 5.6
Hz, 1 H), 7.24 (dd, J = 11.0 Hz, 7.4 Hz, 1 H), 6.71 (m, 1 H), 6.57 (d, J = 5.6 Hz, 1 H), 5.55 (s, 2
H), 1.35 (s, 1 H); MS (ESI) m/z: 564.1 (M+H+).

[00167] To a degassed solution of 4-(2,5-difluoro-4-aminophenoxy)-3-iodo-2-[bis[(l,l-
3,2-dioxaborolan-2-yl)-lH-pyrazole] (0.52 g, 2.48 mmol) in dioxane (15 mL) was added K2CO3
(0.51 g, 3.7 mmol) in water (3 mL). Tetrakis (triphenylphosphine)Palladium(O) (0.14 g, 0.12
mmol) was added and the reaction mixture was stirred at 100 °C for 3 h. The mixture was
diluted with water (40 mL) and EtOAc (50 mL). The layers were separated, and the aq. layer was
extracted with EtOAc (20 mL). The combined organics were washed with brine, dried (Na2SO4)
and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc-
hexanes) to afford 4-(4-amino-2,5-difluorophenoxy)-3-(l-methyl-lH-pyrazol-4-yl)-2-[bis[(1,1-
dimethylethoxy)carbonyl]amino]pyridine as a colorless foam (0.52 g, 81% yield). 1H NMR
(400 MHz, DMSO-d6): δ 8.17 (d, J = 5.6 Hz, 1 H), 7.84 (s, 1 H), 7.48 (d, J = 0.8 Hz, 1 H), 7.21
(dd, J = 11.2 Hz, 7.6 Hz, 1 H), 6.70 (m, 2 H), 5.50 (s, 2 H), 3.86 (s, 3 H), 1.25 (s, 18 H); MS
(ESI) m/z: 518.3 (M+H+).

[00168] Example B1: To a solution of 4-fluoroaniline (6.5 g, 58.4 mmol) in DMF (30 mL)
at ice bath temperature was added methyl 2-oxo-2H-pyran-3-carboxylate (9.0 g, 58.4 mmol).
The resulting mixture was stirred for 15 min cold and was then warmed to ambient temp for 3
hours. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI-HCl) (13.5 g,
70.0 mmol) and DMAP (1.43 g, 11.7 mmol) were added and the resulting mixture was stirred at
ambient temp overnight. The reaction mixture was poured into water (300 mL), extracted with
ethyl acetate (3 × 100 mL), washed with brine, dried over anhydrous Na2SO4 and concentrated in
vacuo to obtain methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate. This crude
product was used for the next step without further purification.

[00169] A mixture of methyl 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (14
g, 58.4 mmol) and 2N aqueous NaOH (90 mL) in methanol (150 mL) was heated at 65 °C
overnight. The cooled reaction mixture was treated with 2N HCl solution with stirring until pH
= 1. The precipitate that formed was collected by filtration, washed with water (10 mL), and
dried to give 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid (7.0 g, 53 %
yield). 1H-NMR (400 MHz, MeOH-d₄): δ 8.58 (dd, J = 7.2, 2.0 Hz, 1 H), 8.04 (dd, J = 6.8, 2.0 Hz, 1 H), 7.53 (m, 2 H), 7.31 (m, 2 H), 6.83 (t, J = 12 Hz, 1 H).

[00170] Example B2: A mixture of ethyl 2-cyanoacetate (120 g, 1.06 mol) and triethylorthooacetate (354 g, 2.12 mol) in glacial acetic acid (33 g, 0.53 mol) was stirred at 120-130 °C overnight. The mixture was concentrated under vacuum to provide crude ethyl 2-cyano-3-ethoxybut-2-enoate. The residue was stirred for 4 h in EtOAc (100 mL) to remove the impurity. The pH was adjusted with 37% HCl to pH < 2. The mixture was further purified by silica gel chromatography to afford ethyl 2-cyano-3-ethoxybut-2-enoate (90 g, 66.6% yield).

[00171] A mixture of ethyl 2-cyano-3-ethoxybut-2-enoate (194 g theory, 1.06 mol) and N,N-dimethylformamide dimethyl acetal (160 g, 1.325 mol) was stirred at 70 °C for 2 hours. The mixture was concentrated under high vacuum to provide crude ethyl 2-cyano-5-(dimethylamino)-3-ethoxypenta-2,4-dienoate. The residue was used directly without further purification.

[00172] A mixture of ethyl 2-cyano-5-(dimethylamino)-3-ethoxypenta-2,4-dienoate (150g, 0.63 mol) and HOAc (600 mL) was refluxed overnight. The mixture was concentrated to dryness under high vacuum and the residue treated with water (300 mL). The mixture was extracted with EtOAc (2 x 250 mL) to remove the impurities. The pH of the aqueous was adjusted with NaHCO₃ to pH - 9-10. The mixture was extracted with CH₂C₁₂ (3 x 300 mL). The combined organics were washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography to afford ethyl 4-ethoxy-2-oxo-1,2-dihydropyridine-3-carboxylate (90 g, 66.6% yield).

[00173] A mixture of ethyl 4-ethoxy-2-oxo-1,2-dihydropyridine-3-carboxylate (60 g, 0.284 mol), 4-fluoro phenylboronic acid (120 g, 0.853 mol), Cu(AcO)₂ (113 g, 0.568 mol) and pyridine (88 g, 1.137 mol) in CH₂C₁₂ (500 mL) was stirred at ambient temp (-25 °C) for 4 h open to air. The reaction mixture was filtered and the solids were washed with water. The filtrate was extracted with CH₂C₁₂ (2 x 250 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to afford ethyl 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate. The product was carried forward without further purification. (77 g, 95% yield).

[00174] A mixture of ethyl 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylate (60 g, 0.196 mol) and LiOH (30 g, 0.6 mol) in EtOH (200 mL) and water (100 mL) was stirred at ambient temp (-25 °C) for 16 h. The mixture was concentrated to remove EtOH. The residue was diluted with water (300 mL). The mixture was extracted with EtOAc (100 mL) to remove the impurity. The pH was adjusted with 37% HCl to pH < 2. The mixture was
extracted with EA (3 x 300 mL). The combined organics were washed with brine, dried over Na₂SO₄ and concentrated to remove EtOAc. Petroleum ether (PE) (200 mL) was added. The resultant precipitate was collected by filtration, washed with PE and dried to afford 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid. (43 g, 78.9% yield). ¹H-NMR (400 MHz, DMSO-d₆): δ 7.95 (d, J = 8.0 Hz, 1 H), 7.48 (m, 2 H), 7.35 (m, 2 H), 6.58 (d, J = 7.6 Hz, 1 H), 4.28 (q, J = 7.2 Hz, 2 H), 1.32 (t, J = 7.2 Hz, 3 H).

[00175] Example B3: A mixture of 4-fluorophenylacetyl chloride (4.91 g, 24.3 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (3.50 g, 24.3 mmol) and DIEA (5.84 g, 49.8 mmol) in CH₂Cl₂ (30 mL) was stirred for 1 h at 0 °C and at ambient temp for 2 h. The solution was diluted with CH₂Cl₂ (40 mL) and the organic phase was washed with 0.1 N HCl and brine, dried over Na₂SO₄ and evaporated to dryness. The resulting orange solid was suspended in EtOH (100 mL) and refluxed for 2 hours. The solution was evaporated and the resulting orange oil was left in the freezer overnight to give a yellow solid. The crude solid was recrystallized from EtOH to afford ethyl 4-(4-fluorophenyl)-3-oxobutanoate (5.3 g, 86.8% yield).

[00176] A mixture of ethyl 4-(4-fluorophenyl)-3-oxobutanoate (5.3 g, 21.1 mmol), and DMF-dimethylacetal (7.53 g, 63.3 mmol) in toluene (50 mL) was heated at reflux with removal of the MeOH for 2 h and was then concentrated under vacuum. The residue in MeOH (50 mL) was treated with NH₄OAc (8.1 g, 105.5 mmol) and the mixture was refluxed for 1.5 h. The precipitate was collected by filtration and successively washed with MeOH, water, and MeOH to give ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (3.3 g, 60% yield). ¹H-NMR (400 MHz, CD₃OD): δ 9.19 (d, J = 0.8 Hz, 1 H), 8.81 (d, J = 0.8 Hz, 1 H), 7.74 (dd, J = 8.8, 5.2 Hz, 2 H), 7.29 (t, J = 8.8 Hz, 2 H), 4.60 (q, J = 7.2 Hz, 2 H), 1.49 (t, J = 7.2 Hz, 3 H) [NH not visible].

[00177] A mixture of ethyl 5-(4-fluorophenyl)-4-oxo-1,4-dihydropyridine-3-carboxylate (1.5 g, 5.7 mmol) and iodomethane (0.9 g, 6.3 mmol) in saturated NaHC0₃ (25 mL) was stirred at 60 °C overnight. The mixture was filtered. The solid was concentrated under vacuum to afford ethyl 5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (1.1 g, 69.9% yield). The mixture was used directly without further purification.

[00178] A mixture of ethyl 5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (1.1 g, 4 mmol) and NaOH (1.6 g, 40 mmol) in water (25 mL) was stirred at RT overnight. The mixture was extracted with EtOAc (2 x 25 mL) to remove impurities. The
aqueous pH was adjusted to pH 1-2 with 37% HCl. The resulting precipitate was collected by filtration and dried under vacuum to afford 5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (810 mg, 81.9% yield). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 15.76 (s, 1 H), 8.49 (d, $J$ = 2.4 Hz, 1 H), 7.58 (m, 3H), 7.14 (t, $J$ = 8.8 Hz, 2 H), 3.92 (s, 3 H).

Example 1: To a solution of Example A1 (0.030 g, 0.10 mmol) in CH$_3$CN (1 mL) and DMF (1 mL) was added Example B1 (0.028 g, 0.12 mmol) and TBTU (0.035 g, 0.11 mmol). The solution was cooled to 0 °C and then DIEA (0.059 mL, 0.36 mmol) was added. The mixture was allowed to warm to RT with stirring. After 5 hours, addition Example B1 (15 mg) and TBTU (17 mg) were added and the mixture was stirred at RT overnight. The reaction mixture was treated with EtOAc and the resultant solid was filtered, washed with EtOAc and dried under vacuum to obtain N-(2,5-difluoro-4-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yloxy)phenyl)-l-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (35 mg, 68.2% yield). $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 12.4 (brs, 1 H), 9.08 (s, 1 H), 8.60 (m, 1 H), 8.58 (s, 1 H), 8.50 (m, 1 H), 8.35 (s, 1 H), 8.15 (m, 1 H), 8.12 (s, 1 H), 7.67 (m, 1 H), 7.59 (m, 2 H), 7.41 (t, $J$ = 8.8 Hz, 2 H), 6.74 (t, $J$ = 6.8 Hz, 1 H), 3.90 (s, 3 H); MS (ESI) m/z: 519.2 (M+H$^+$).

Example 2: TBTU (0.097 g, 0.301 mmol) was added to a solution of Example B1 (0.070 g, 0.301 mmol), Example A3 (0.07 g, 0.232 mmol), and DIEA (0.081 mL, 0.463 mmol) in DMF (4 mL). The mixture was stirred at room temperature for 8 h. Additional TBTU (0.097 g, 0.301 mmol) and Example B1 (0.070 g, 0.301 mmol) were added and the mixture was stirred overnight at ambient temperature. The reaction mixture was diluted with EtOAc (4 mL) and the precipitate was filtered off and washed with EtOAc. The precipitate was dried under vacuum to yield N-(2,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-l-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (97 mg, 81%). $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 12.43 (br s, 1 H), 8.85 (s, 1 H), 8.62-8.53 (m, 2 H), 8.25 (s, 1 H), 8.24 (s, 1 H), 8.15 (d, 1 H), 8.01 (s, 1 H), 7.65-7.58 (m, 3 H), 7.43-7.39 (m, 2 H), 6.77-6.72 (m, 2 H), 3.88 (s, 3 H); MS (ESI) m/z: 518.2 (M+H$^+$).

Example 3: A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.50 g, 2.58 mmol), sodium iodide (39 mg, 0.26 mmol) bromoacetonitrile (1.3 g, 10.8 mmol) and potassium carbonate (1.0 g, 7.8 mmol) in acetonitrile (10 mL) was heated at 70 °C
overnight. Water was added and the solution was extracted with EtOAc (3x). The organic was dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography (10% to 100% EtOAc/hexane) to obtain 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetonitrile (0.38g, 63% yield). MS (ESI) m/z: 234.1 (M+H⁺).

Example B 1 (0.16 g, 0.497 mmol) was combined with thionyl chloride (1.089 ml, 14.92 mmol) and the mixture heated to 60 °C for 1.5 hours then cooled to room temperature and concentrated to dryness. The resulting residue was treated with toluene and concentrated to dryness (this process repeated twice more) to afford 125 mg (100%) of 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl chloride as a pale yellow solid.

Example A2 (0.100 g, 0.332 mmol) in THF (1 mL) was treated with triethylamine (0.069 ml, 0.498 mmol) and a suspension of 1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl chloride (0.125 g, 0.498 mmol) in THF (2 mL). The mixture was blanketed with argon and stirred overnight at room temperature. The solids were removed via filtration, rinsed with THF and the filtrate was concentrated to dryness. The crude material was purified by silica gel chromatography (10-100% EtOAc/Hex) to afford N-(4-(3-bromopyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (122 mg, 71% yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO): δ 12.45 (s, 1 H); 8.74 (s, 1 H); 8.58 (m, 2 H); 8.38 (d, J = 5.6 Hz, 1 H); 8.15 (dd, J = 6.6, 2.2 Hz, 1 H); 7.67 (dd, J = 11.0, 7.3 Hz, 1 H); 7.60 (dd, J = 8.8, 4.9 Hz, 2 H); 7.41 (t, J = 8.7 Hz, 2 H); 6.89 (d, J = 5.6 Hz, 1 H); 6.74 (t, J = 7.0 Hz, 1 H); MS (ESI) m/z: 516.0, 518.0 (M+H⁺).

N-(4-(3-Bromopyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (0.119 g, 0.231 mmol) was combined with 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetonitrile (0.054 g, 0.231 mmol) and potassium carbonate (0.096 g, 0.692 mmol) in dioxane (4 mL) and water (0.667 mL), sparged with argon for several minutes, treated with tetrakis(triphenylphosphine)palladium(0) (0.013 g, 0.012 mmol) and heated to 85 °C overnight. The mixture was cooled to room temperature, treated with saturated NaHCO₃ and extracted with EtOAc (2x). The combined organics were washed with brine, dried over MgSO₄ and concentrated to dryness. The crude material was purified over silica gel (40-100% EtOAc/Hex) to afford N-(4-(3-(1-(cyanomethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-
carboxamide (30 mg, 24% yield) as an off-white solid. $^1$H NMR (400 MHz, DMSO-d$_6$): δ 12.45 (s, 1 H); 8.91 (s, 1 H); 8.61 (dd, J = 7.4, 2.1 Hz, 1 H); 8.55 (m, 1 H); 8.44 (s, 1 H); 8.29 (d, J = 5.7 Hz, 1 H); 8.24 (s, 1 H); 8.16 (dd, J = 6.6, 2.2 Hz, 1 H); 7.67 (dd, J = 11.0, 7.3 Hz, 1 H); 7.60 (dd, J = 8.7, 4.9 Hz, 2 H); 7.42 (t, J = 8.7 Hz, 2 H); 6.75 (m, 2 H); 5.54 (s, 2 H); MS (ESI) m/z: 543.1 (M+H$^+$).

Example 4: Thionyl chloride (2 mL) was added to Example B2 (0.077 g, 0.28 mmol) and the resultant solution was stirred at 60 °C for 1 h. Solvent was removed, and residue was dissolved in toluene (2 mL) and concentrated under vacuum. Co-evaporation with toluene was repeated one more time to furnish 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl chloride as white solid. This solid was dissolved in THF (2 mL) and was added to a solution of 2,5-difluoro-4-(3-(1 -methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzenamine (0.07 g, 0.23 mmol) and triethylamine (0.05 g, 0.5 mmol) in THF (2 mL). The resultant suspension was stirred at RT for 1 h. The solvent was removed in vacuo and the crude residue was purified by silica gel chromatography (MeOH/CH$_2$Cl$_2$) to afford N-(2,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide as white solid (76 mg, 58% yield). $^1$H NMR (400 MHz, DMSO-d$_6$): δ 11.23 (s, 1 H), 8.85 (s, 1 H), 8.40 (dd, J = 11.6 Hz, 7.6 Hz, 1 H), 8.25 (s, 1 H), 8.23 (s, 1 H), 8.01 (s, 1 H), 7.92 (d, J = 7.2 Hz, 1 H), 7.48 (m, 2 H), 7.36 (m, 2 H), 6.75 (d, J = 6.4 Hz, 1 H), 6.55 (d, J = 8.0 Hz, 1 H), 5.74 (s, 1 H), 4.27 (q, J = 12 Hz, 2 H), 3.88 (s, 3 H), 1.33 (q, J = 7.2 Hz, 3 H); MS (ESI) m/z: 562.2 (M+H$^+$).

Example 5: Example B1 (0.052 g, 0.22 mmol), Example A4 (0.07 g, 0.22 mmol), triethylamine (0.06 ml, 0.45 mmol), and TBTU (0.15 g, 0.45 mmol) were combined in DMF (1 mL) and the resultant mixture was stirred at RT for 4 days. The solvent was removed under vacuum and the residue was purified by silica gel chromatography (MeOH/CH$_2$Cl$_2$) to afford N-(4-(2-amino-3-(1 -methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide as white solid (67 mg, 56.2% yield). $^1$H NMR (400 MHz, DMSO-d$_6$): δ 12.35 (s, 1 H), 8.59 (dd, J = 12 Hz, 2.0 Hz, 1 H), 8.47 (dd, J = 12.4 Hz, 7.6 Hz, 1 H), 8.14 (dd, J = 6.8 Hz, 2.4 Hz, 1 H), 7.87 (s, 1 H), 7.74 (d, J = 5.6 Hz, 1 H), 7.58 (m, 3 H), 7.41 (m, 3 H), 6.72 (t, J = 12 Hz, 1 H), 5.99 (d, J = 5.6 Hz, 1 H), 5.70 (s, 2 H), 3.84 (s, 3 H); MS (ESI) m/z: 533.2 (M+H$^+$).
[00187] Example 6: A solution of Example B2 (0.400 g, 1.443 mmol) in thionyl chloride (2.00 mL) was heated at 60 °C for 1 hour. The solvent was completely removed under vacuum. The residue was co-evaporated from hexane three times to provide 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic chloride (1.529 mmol, 106 % yield) as pale pink solid (0.452 g), suitable for use in the next reaction. MS(ESI) m/z: 532.2 (M+H+).

[00188] To a solution of 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic chloride (0.275 g, 0.929 mmol) in CH2Cl2 (2 mL) was added a suspension of 5-chloro-2-fluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzenamine (0.148 g, 0.464 mmol) in pyridine (2.00 mL) at 0 °C. The resultant mixture was stirred at ambient temp for 30 min. The solvent was completely evaporated and the residue was stirred in water. The precipitate was collected by filtration and was re-crystallized from acetonitrile to provide N-(5-chloro-2-fluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (0.101 g, 37.6 % yield) as an off-white solid. The mesylate salt was prepared by treatment with one equivalent of methanesulfonic acid. 1H NMR(400 MHz, DMSO-d6) δ 11.40 (s, 1 H), 9.20 (s, 1 H), 8.62 (d, J =5.5 Hz, 1 H), 8.51 (m, 1 H), 8.47 (s, 1 H), 8.23 (s, 1 H), 8.00 (d, J =8.0 Hz, 1 H), 7.75 (d, J = 11 Hz, 1 H), 7.50 (m, 2 H), 7.41 (m, 2 H), 7.25 (d, J =2.5Hz, 1 H), 6.60 (d, J =5.5 Hz, 1 H), 4.30 (q, J = 6 Hz, 2 H), 3.92 (s, 3 H), 2.30 (s, 3 H), 1.30 (t, J = 6 Hz, 3 H); MS(ESI) m/z: 578.2 (M+H+).

[00189] Example 7: Example B3 (115 mg, 0.464 mmol), Example A3 (70 mg, 0.232 mmol), TBTU (223 mg, 0.696 mmol) and Et3N (0.194 ml, 1.392 mmol) were combined in DMF (5 mL) and stirred at RT overnight. The completed reaction was diluted with satd. NaHCO3 and extracted with EtOAc (2x). The combined organics were washed with satd. NaHCO3 (1x), brine (1x), and dried (Na2SO4), filtered and evaporated to afford crude product. This was purified by silica gel chromatography (10%-100% EtOAc; then 100% THF) to afford N-(2,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (77 mg, 62.5% yield) as a white solid. 1H NMR (400 MHz, DMSO-d6): δ 13.47 (s, 1 H); 8.81 (s, 1 H); 8.67 (d, J = 2.3 Hz, 1 H); 8.53 (dd, J = 12.6, 7.2 Hz, 1 H); 8.19-8.23 (m, 2 H); 8.12 (d, J = 2.3 Hz, 1 H); 7.98 (s, 1 H); 7.64-7.65 (m, 2 H); 7.58 (dd, J = 11.0, 7.3 Hz, 1 H); 7.23 (t, J = 8.9 Hz, 2 H); 6.74 (d, J = 5.7 Hz, 1 H); 3.87 (s, 3 H); 3.84 (s, 3 H); MS (ESI) m/z: 532.2 (M+H+).
Example 8: Using the method of Example 4, thionyl chloride (5 mL) and Example B2 (0.19 g, 0.7 mmol) were combined to prepare 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl chloride as a solid. This solid was dissolved in THF (3 mL) and added to a solution of Example A6 (0.18 g, 0.35 mmol) and Et3N (0.2 mL, 1.4 mmol) in THF (3 mL). The resultant mixture was stirred at RT for 2 h. The mixture was partitioned between EtOAc (20 mL) and sat aq NaHCO3 (30 mL). The aqueous layer was further extracted with EtOAc (15 mL) and the combined organics were washed with brine, dried (Na2SO4) and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc: hexanes) to afford N-(4-(2-[bis[(l,l-dimethylethoxy)carbonyl]amino]-3-(l-methyl-lH-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide as colorless foam (175 mg, 65% yield). 1H NMR (400 MHz, DMSO-d6): δ 11.22 (s, 1 H), 8.33 (dd, J = 12.7 Hz, 7.2 Hz, 1 H), 8.20 (d, J = 5.7 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.87 (s, 1 H), 7.48 (m, 4 H), 7.36 (t, J = 8.8 Hz, 2 H), 6.83 (d, J = 5.6 Hz, 1 H), 6.55 (d, J = 7.9 Hz, 1 H), 4.28 (q, J = 7.0 Hz, 2 H), 3.86 (s, 3 H), 1.33 (t, J = 7.1 Hz, 3 H), 1.26 (s, 18 H); MS (ESI) m/z: 777.2 (M+H+).

TFA (1 mL) was added to a solution of N-(4-(2-[bis[(l,l-dimethylethoxy)carbonyl]amino]-3-(l-methyl-lH-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (0.17 g, 0.22 mmol) in CH2Cl2 (3 mL) and the mixture was stirred at RT for 1 h. The solvent was removed and the residue was partitioned between satd NaHCO3 solution (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (25 mL) and the combined organics were washed with brine, dried (Na2SO4) and concentrated under reduced pressure to afford N-(4-(2-amino-3-(1-methyl-lH-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (120 mg, 95% yield) as an off-white solid. 1H NMR (400 MHz, DMSO-d6): δ 1.12 (s, 1 H), 8.24 (t, J = 9.8 Hz, 1 H), 7.91 (d, J = 7.8 Hz, 1 H), 7.87 (s, 1 H), 7.74 (d, J = 5.8 Hz, 1 H), 7.58 (s, 1 H), 7.47 (m, 2 H), 7.36 (t, J = 8.7 Hz, 3 H), 6.54 (d, J = 7.9 Hz, 1 H), 5.98 (d, J = 5.8 Hz, 1 H), 5.69 (s, 2 H), 4.27 (q, J = 7.0 Hz, 2 H), 3.85 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H); MS (ESI) m/z: 577.2 (M+H+).

Example 9: A suspension of 4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl chloride (freshly prepared from Example B2 (0.207 g, 0.747 mmol) using the method of Example 4) in THF (5 mL) was added to a 0 °C solution of Example A2
(0.15 g, 0.498 mmol) and N,N-diisopropylethylamine (0.870 ml, 4.98 mmol) in THF (5 ml). The mixture was allowed to warm to room temperature and stir overnight. Additional 4-ethoxy-l-(4-fluorophenyl)-2-oxo-l,2-dihydropyridine-3-carbonyl chloride [freshly prepared from Example B2 (0.207 g, 0.747 mmol)] was added and the mixture was stirred overnight at RT. Additional 4-ethoxy-l-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonyl chloride [freshly prepared from Example B2 (414 mg, 0.996 mmol)] was added to the reaction mixture. After stirring for 3 h, the mixture was partitioned between CH₂Cl₂ and sat. Na₂CO₃ (aq) and extracted with sat. Na₂CO₃ (aq) (2x). The organic extract was dried and evaporated. The crude product was purified by silica gel chromatography (hexanes/EtOAc) to yield N-(4-(3-bromopyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-l-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (0.124 g, 44.4% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 11.24 (s, 1 H), 8.74 (s, 1 H), 8.37 (m, 2 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.59 (dd, J = 10.9, 7.4 Hz, 1 H), 7.48 (dd, J = 8.8, 4.9 Hz, 2 H), 7.36 (t, J = 8.7 Hz, 2 H), 6.88 (d, J = 5.6 Hz, 1 H); 6.55 (d, J = 7.9 Hz, 1 H); 4.28 (q, J = 7.0 Hz, 2 H); 1.33 (t, J = 7.0 Hz, 3 H); MS (ESI) m/z: 560.1 (M+H⁺).

[00193] In a sealed tube, N-(4-(3-bromopyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (0.124 g, 0.221 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.064 g, 0.332 mmol), potassium carbonate (0.092 g, 0.664 mmol), and tetrakis(triphenylphosphine) palladium (0) (0.026 g, 0.022 mmol) were suspended in dioxane (6 mL) and water (1.5 mL). The mixture was degassed with Ar and heated at 85 °C overnight. Additional 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100 mg) and tetrakis(triphenylphosphine) palladium (0) (0.026 g, 0.022 mmol) were added. The reaction mixture was degassed with Ar and heated at 85 °C for 2 days. The mixture was diluted with EtOAc and extracted with sat. NaHCO₃ (aq). The organic extract was washed with brine, dried and evaporated. The crude product was purified by silica gel chromatography (25 g) eluting with DCM/MeOH to yield N-(4-(3-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (69 mg, 56.9% yield). The hydrochloride salt was formed by suspending N-(4-(3-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide (0.069 g, 0.126 mmol) in acetonitrile (2 ml) and adding 0.1 N HCl (1.51 mL, 0.151 mmol). The mixture was sonicated for 10 min. The solution was diluted with water (2 mL), frozen and lyophilized. The crude lyophilate was dried at 80 °C for 4 h under
vacuum to yield N-(4-(3-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide hydrochloride (0.069 g, 87% yield). $^1$H NMR (400 MHz, DMSO-\textit{d}_6): $\delta$ 11.32 (s, 1 H); 9.15 (s, 1 H); 8.49 (d, $J = 6.5$ Hz, 1 H); 8.43 (dd, $J = 12.5$, 7.0 Hz, 1 H); 8.33 (s, 2 H); 7.93 (d, $J = 7.8$ Hz, 1 H); 7.69 (dd, $J = 10.8$, 7.3 Hz, 1 H); 7.48 (dd, $J = 8.8$, 4.9 Hz, 2 H); 7.37 (t, $J = 8.8$ Hz, 2 H); 7.25 (d, $J = 6.5$ Hz, 1 H); 6.56 (d, $J = 7.9$ Hz, 1 H); 4.28 (q, $J = 7.0$ Hz, 2 H); 1.34 (t, $J = 7.0$ Hz, 3 H); MS (ESI) m/z: 508.2 (M+H+).

**Example 10:** Example B3 (0.05 g, 0.2 mmol), Example A6 (0.08 g, 0.15 mmol), TBTU (0.15 g, 0.46 mmol), and Et$_3$N (0.1 g, 0.1 mmol) were combined in DMF (2 mL) and the reaction mixture was stirred at RT for 48 h. The mixture was diluted with aq NaHCO$_3$ solution (30 mL) and was extracted with EtOAc (2 x 25 mL). The combined organics were washed with water (30 mL) and brine, dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc-hexanes) to provide N-(4-(2-[bis[(1,1-dimethylethoxy)carbonyl]amino]-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difuoroOphenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (85 mg, 73.6% yield) as white solid. $^1$H NMR (400 MHz, DMSO-\textit{d}_6): $\delta$ 13.51 (s, 1 H); 8.71 (d, $J = 2.4$ Hz, 1 H); 8.56 (dd, $J = 12.4$ Hz, 7.2 Hz, 1 H); 8.21 (d, $J = 5.7$ Hz, 1 H); 8.16 (d, $J = 2.3$ Hz, 1 H); 7.88 (s, 1 H); 7.69 (m, 2 H); 7.59 (dd, $J = 11.0$ Hz, 7.3 Hz, 1 H); 7.50 (d, $J = 0.7$ Hz, 1 H); 7.28 (t, $J = 8.9$ Hz, 2 H); 6.84 (m, 1 H); 3.92 (s, 3 H); 3.86 (s, 3 H); 1.26 (s, 18 H); MS (ESI) m/z: 747.2 (M+H+).

**[00195]** A solution of N-(4-(2-[bis[(1,1-dimethylethoxy)carbonyl]amino]-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide (0.15 g, 0.15 mmol) in DCM (5 mL) was treated with TFA (0.35 mL, 4.62 mmol) and the solution was stirred at RT for 3 h. The solvent was removed in vacuo and the residue was partitioned between satd NaHCO$_3$ solution (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (25 mL) and the combined organics were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford N-(4-(2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,5-difluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide as off-white solid (82 mg, 97% yield). $^1$H NMR (400 MHz, DMSO-\textit{d}_6): $\delta$ 13.43 (s, 1 H); 8.70 (d, $J = 2.4$ Hz, 1 H); 8.49 (dd, $J = 12.6$ Hz, 7.3 Hz, 1 H); 8.15 (d, $J = 2.3$ Hz, 1 H); 7.88 (s, 1 H); 7.75 (d, $J = 5.8$ Hz, 1 H); 7.69 (m, 2 H); 7.59 (d, $J = 0.8$ Hz, 1 H); 7.48 (dd, $J = 8.8$, 4.9 Hz, 2 H); 7.37 (t, $J = 8.8$ Hz, 2 H); 7.25 (d, $J = 6.5$ Hz, 1 H); 6.56 (d, $J = 7.9$ Hz, 1 H); 4.28 (q, $J = 7.0$ Hz, 2 H); 1.34 (t, $J = 7.0$ Hz, 3 H); MS (ESI) m/z: 508.2 (M+H+).
Hz, 1 H), 7.41 (dd, J = 11.2 Hz, 7.4 Hz, 1 H), 7.27 (t, J = 8.9 Hz, 2 H), 6.00 (d, J = 5.8 Hz, 1 H), 5.69 (s, 2 H), 3.91 (s, 3 H), 3.85 (s, 3 H); MS (ESI) m/z: 547.1 (M+H+).

Biological Data

c-MET Kinase Assay

Activity of c-MET kinase (Seq. ID No. 2) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system [e.g., Schindler et al. Science 2000, 289, pp. 1938-1942]. In this assay, the oxidation of NADH (thus the decrease at A340 nm) was continuously monitored spectrophotometrically. The reaction mixture (100 µL) contained c-MET (c-MET residues: 956-1390, from Invitrogen, catalogue #PV3143, 6 nM), polyE4Y (1 mg/mL), MgCl2 (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 90 mM Tris buffer containing 0.25 mM DTT, 0.2% octyl-glucoside and 1% DMSO, pH 7.5. Test compounds were incubated with c-MET (Seq. ID No. 2) and other reaction reagents at 22 °C for 0.5 h before ATP (100 µM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30 °C on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e., with no test compound). IC50 values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

c-MET Kinase (Seq ID No. 2)

[00196] MSYYHHHHDYDIPTTENLYFQGAMLVPRGSPWIPFTMKKQRQIKDLGSELV RYDARVHTPHDLRLVSARSVSPTTEMVSNESVYRATTFEDQFPNSSQNGSCRQVQYPLT DMSPILTSGSDISSPLQNTVHIDLSALNPELVQAQVHVVGSSSLVHNFENIVGRGHFCV YHGTLDDNGKKHKAVKSLNRTIDGISEVQLTEGIIMKDFSHPNVSLLGICLRSEGSPLV VLPYMHKGDLRNFIRNETHNPTVKTG9GLQVAKGMYLASKKFGVHRDLAARNCMLDEL KFTVKGDAFGLARDMYDKEYYYSVHMKTGAKLPHVMALESLSQTQKFTTKSDVWFGVL LWELMTRGAPPYPDVNTFDITYLLQGRRLLQPEYCPDPLEYVMLKCWHPKAEMRPSFSE LVSRIAIIFSTFIGEHYVHNATYVNVKCVAPYPSSLSSEDNADDEVDTFRASFWETS.
c-KIT kinase Assay

Activity of c-KIT kinase (Seq. ID No. 1) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler et al. Science 2000, 289, pp. 1938-1942). In this assay, the oxidation of NADH (thus the decrease at A340 nm) was continuously monitored spectrophotometrically. The reaction mixture (100 µl) contained c-KIT (cKIT residues T544-V976, from ProQinase, 5.4 nM), polyE4Y (1 mg/mL), MgCl₂ (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 90 mM Tris buffer containing 0.2% octyl-glucoside and 1% DMSO, pH 7.5. Test compounds were incubated with c-KIT (Seq. ID No. 1) and other reaction reagents at 22 °C for less than 2 min before ATP (200 µM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 0.5 hours at 30 °C on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 0 to 0.5 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e., with no test compound). IC50 values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

c-KIT with N-terminal GST fusion (Seq ID No. 1)

LEYWKIKGLVQPTRRLLLEYEELYEEHLYERDEGDWKRNNKFELGLEFPNLPY YIDGDVKLTQSMAIRYIADKHNNMLGGCPKERAEMGAVIDRXYGSRIAYSKDFETLKV DFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVLYMDPMCLDAFPKLV CFFKRIEAIQPDIKYLKSSKYIWPQLQGKWQATFGGDPKKSDLVPRHNTSLYKYKAGAA VLEENLYFQTYKYLKPMYEVQWKVVEEINGNNYYIDPTQLPYDHHKEWFPRNRLSFG KTLGAGAFGKVEATAVGLISDAATVAVKLKPASHELLTEREALMSLKVLSYLGNH MNIVNLLGACTIGPTVLITEEYCCYGDLLNFRRRKRDSFICSKQEDHAEAALYKLLHSKE SCSSTDSTEYDMKPGVSVPPKADKRRSVIRGYSYERDVTIPAMEDDELALLLSF SYQVAKGMAFLASKNCIHRDLAARNLTHGRITIKICDFGLARDIKNSNYVVKGNARLPV KWMAPESIFNCVYTFESDVWSWYGIFLWELFSLGSSPYGMVDSFKYKMIKEGFRMLSPEH APAEMYDIMKTCWDADPLKRPTFQIVQILIEKQISESTNHISNLANCSPNRQKPVVDHSV RINSVGSTASSQPLLVDV.
**KDR Kinase Assay**

**Assay K1**

[00200] The activity of KDR kinase was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler et al. Science 2000, 289, pp. 1938-1942). In this assay, the oxidation of NADH (thus the decrease at A340 nm) was continuously monitored spectrophotometrically. The reaction mixture (100 μμ) contained KDR (Seq ID No. 3, 1.5 nM to 7.1 nM, nominal concentration), polyE4Y (1 mg/mL), pyruvate kinase (3.5 units), lactate dehydrogenase (5.5 units), phosphoenolpyruvate (1 raM), and NADH (0.28 mM) in 60 mM Tris buffer containing 0.13% octyl-glucoside, 13 mM MgCl₂, 6.8 mM DTT, and 3.5% DMSO at pH 7.5. The reaction was initiated by adding ATP (0.2 mM, final concentration). The absorption at 340 nm was continuously monitored for 3h at 30 °C on a Polarstar Optima plate reader (BMG) or instrument of similar capacity. The reaction rate was calculated using the 1 h to 2 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e., with no test compound). IC₅₀ values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

**Assay K2**

[00201] KDR kinase assay K2 is the same as for assay K1 except that (1) a nominal concentration of 2.1 nM of enzyme was employed (2) the reaction was pre-incubated at 30 °C for 2 h prior to initiation with ATP and (3) 1.0 mM ATP (final concentration) was used to initiate the reaction.

**Assay K3**

[00202] KDR kinase assay K3 is the same as for assay K1 except that (1) a nominal concentration of 1.1 nM of enzyme was employed, (2) the buffer components per 100 μμ reaction mixture were as follows: 75 mM Tris buffer containing 0.066% octyl-glucoside, 17 mM MgCl₂, and 1%, DMSO at pH 7.5, (3) the final concentration of DTT was 0.66 mM, (4) the reaction was pre-incubated at 30 °C for 1h prior to initiation with ATP, and (5) 1.0 mM ATP (final concentration) was used to initiate the reaction.
KDR protein sequence used for screening (Seq. ID No. 3)
DPDELPLDEHCERLPYDASKWEFPRDRLKLGGPLGRAGQVIEADAFGIDKTATCRTVAVKML KEQATHSEHRLMAELKIHIGHHLNVLNLLGACTKPGGPMVIVEFCKFGNLSTYLRSKRNEF VPYKVAPEDLYKDFTLEHLICYSFQVAKGMELASRKCIRHDLAARNILSEKNVVKICDFGLAR DIYKDPDYVRKGDARLPLKWMAPETIFDRVYTIQSDVWSFGVLLWEIFSLGASPYPGVKIDEEDF CRRLEKGRTRMRAPDVTTPEMYQTMLDCWHGEPSQRPTFSELVEHLGNLLQANAQD

**FMS kinase Assay**

[00203] Activity of FMS kinase was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler et al. *Science* **2000**, 289, pp. 1938-1942). In this assay, the oxidation of NADH (thus the decrease at A340 nm) was continuously monitored spectrophotometrically. The reaction mixture (100 µl) contained FMS (purchased from Invitrogen or Millipore, 6 nM), polyE4Y (1 mg/mL), MgCl₂ (10 raM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 raM) and NADH (0.28 mM) and ATP (500 µM) in a 90 mM Tris buffer containing 0.2% octyl-glucoside and 1% DMSO, pH 7.5. The inhibition reaction was started by mixing serial diluted test compound with the above reaction mixture. The absorption at 340 nm was monitored continuously for 4 hours at 30 °C on a Polarstar Optima or Synergy 2 plate reader. The reaction rate was calculated using the 2 to 3 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (*i.e.*, with no test compound). IC₅₀ values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

**EBC-1 Cell Culture**

[00204] EBC-1 cells (catalog #JCRB0820) were obtained from the Japan Health Science Research Resources Bank, Osaka, Japan. Briefly, cells were grown in DMEM supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA) at 37 °C, 5% CO₂, 95% humidity. Cells were allowed to expand until reaching 70-95% confluency at which point they were subcultured or harvested for assay use.
EBC-1 Cell Proliferation Assay

A serial dilution of test compound was dispensed into a 96-well black clear bottom plate (Corning, Corning, NY). For each cell line, five thousand cells were added per well in 200 µL complete growth medium. Plates were incubated for 67 hours at 37 °C, 5% CO₂, 95% humidity. At the end of the incubation period 40 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS was added to each well and incubated for an additional 5 hours at 37 °C, 5% CO₂, 95% humidity. Plates were read on a Synergy2 reader (Biotek, Winooski, VT) using an excitation of 540 nM and an emission of 600 nM. Data was analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

MKN-45 Cell Culture

MKN-45 cells (catalog #JCRB0254) were obtained from the Japan Health Science Research Resources Bank, Osaka, Japan. Briefly, cells were grown in RPMI 1640 media supplemented with 10% characterized fetal bovine serum (Invitrogen, Carlsbad, CA) at 37 °C, 5% CO₂, 95% humidity. Cells were allowed to expand until reaching 70-95% confluency at which point they were subcultured or harvested for assay use.

MKN-45 Cell Proliferation Assay

A serial dilution of test compound was dispensed into a 96-well black clear bottom plate (Corning, Corning, NY). Five thousand cells were added per well in 200 µL complete growth medium. Plates were incubated for 67 hours at 37 °C, 5% CO₂, 95% humidity. At the end of the incubation period 40 µL of a 440 µM solution of resazurin (Sigma, St. Louis, MO) in PBS was added to each well and plates were incubated for an additional 5 h at 37 °C, 5% CO₂, 95% humidity. Plates were read on a Synergy2 reader (Biotek, Winooski, VT) using an excitation of 540 nM and an emission of 600 nM. Data was analyzed using Prism software (GraphPad, San Diego, CA) to calculate IC₅₀ values.

Compounds of Formula I were found to exhibit inhibitory activity in one or more of the aforementioned assays when evaluated at concentrations ≤ 10 µM. In some embodiments, compounds of Formula I exhibit greater inhibitory activity against cMET than inhibition of cKIT, KDR, FMS.
Equivalents

[00209] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically in this disclosure. Such equivalents are intended to be encompassed in the scope of the following claims.
What is claimed is:

1. A compound of **Formula I**, or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer or tautomer thereof, wherein:

   - **A** is

     ![Diagram of A](image)

     wherein the "#" is connected to the R1-substituted phenyl ring and the "*" is connected to the amide carbonyl;

   - **W** is -(CH₂)ᵐ-pyrazole optionally substituted with -(R25)ₘ⁻;
   - **X₁** is halogen or C₁-C₆ alkyl;
   - **X₂** is halogen or C₁-C₆ alkyl;
   - each **R₁** is individually and independently halogen, H, C₁-C₆ alkyl, C₃-C₈ branched alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkoxy, branched C₃-C₆ alkoxy, or cyano;
   - **Z₁** and **Z₂** are independently and individually CR₂ or N;
   - **Z₃** is CR₃ or N;
   - with the proviso that ring **B** is a monocyclic ring which is not a tetrazine;
   - each **R₂** is individually and independently H, halogen, C₁-C₆ alkyl, C₃-C₈ branched alkyl, C₃-C₈ cycloalkyl, C₁-C₆ alkoxy, branched C₃-C₆ alkoxy, or cyano;
   - **R₃** is -NHR₄, H, -NR₆(R₇), C₁-C₈ alkyl, C₂-C₃ alkynyl, C₃-C₈ cycloalkyl, C₁-C₆-alkoxy-C₁-C₆-alkyl⁻, hydroxy-C₁-C₆-alkyl⁻, cyano, cyano-C₁-C₆-alkyl⁻, C₁-C₆-SO₂-C₁-C₆-
alkyl-, (R7) R6N-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-C 1-C6-alkyl-, C6-C10 aryl, C5-C6-heteroaryl, or C5-C6-heteroaryl-C1-C6-alkyl-, wherein
  aryl is phenyl, naphthyl, tetrahydronaphthyl, indenyl or indanyl; and
  each alkyl or alkenylene is optionally substituted with one or two C1-C6 alkyl;

R4 is H, C1-C8 alkyl, C3-C8 cycloalkyl, -(CH 2) m-C(0)R5, -(CH 2) p-OR6,
-(CH 2) p-NR6(R7), -(CH 2) p-CN, -(CH 2) p-S0 2-Cl-C6-alkyl, C6-C10 aryl, -(CH 2) m-C5-C6-heteroaryl, -(CH 2) m-C4-C6-heterocyclyl, -(CH 2) m-C(0)N(R6)-C4-C6-heterocyclyl, or -(CH 2) m-C(0)N(R6)-C5-C6-heteroaryl, wherein each alkyl or alkenylene is optionally substituted with one or two C1-C6 alkyl;

R5 is C1-C7 alkyl, branched C3-C8 alkyl, C3-C8 cycloalkyl, -(CH 2) m-OR6,
-(CH 2) m-NR6(R7), C6-C10 aryl, -(CH 2) m-C5-C6-heteroaryl, or-(CH 2) m-C4-C6-heterocyclyl, wherein
  aryl is phenyl, naphthyl, tetrahydronaphthyl, indenyl or indanyl; and
  each alkyl or alkenylene is optionally substituted with one or two C1-C6 alkyl;

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

each R8 is individually and independently C1-C6 alkoxy, H, halogen, C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, branched C3-C6 alkoxy, or cyano;

  each alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl is independently and optionally 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-S0 2-Cl-C6-alkyl, -(CH 2) m-C(0)NR6(R7), -(CH 2) m-C(0)-C4-C6-heterocyclyl, or-(CH 2) m-C4-C6-heterocyclyl, wherein each alkyl or alkenylene is optionally substituted with one or two C1-C6 alkyl;

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

  n is 0, 1, or 2; and

  each p is individually and independently 1, 2, or 3.
2. The compound of claim 1, wherein the compound is a compound of Formula 1a,

![Formula 1a](image)

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

3. The compound of claim 2, wherein Z3 is CR3.

4. The compound of claim 3, wherein the compound is a compound of Formula 1b,

![Formula 1b](image)

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

5. The compound of claim 4, wherein R3 is -NHR4.

6. The compound of claim 4, wherein R3 is H.

7. The compound of claim 4, wherein R3 is -NR6(R7), (R7)R6N-Cl-C6-alkyl-, C1-C8 alkyl, C2-C3 alkynyl, C3-C8 cycloalkyl, C1-C6-alkoxy-Cl-C6-alkyl-, hydroxy-Cl-C6-alkyl-, cyano, cyano-Cl-C6-alkyl-, Cl-C6-S0, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, and wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl.
8. The compound of claim 4, wherein W is

\[ \text{Diagram} \]

9. The compound of claim 3, wherein W is

\[ \text{Diagram} \]

10. The compound of claims 8 or 9, wherein the A ring is

\[ \text{Diagram} \]

and wherein R8 is C1-C6 alkoxy.

11. The compound of claim 10, wherein the R8 is ethoxy.

12. The compound of claim 2, wherein Z3 is N.

13. The compound of claim 12, wherein the compound is a compound of Formula Ic,

\[ \text{Formula Ic} \]

or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer stereoisomer or tautomer thereof.
14. The compound of claim 13, wherein $W$ is

![Diagram](image)

15. The compound of claim 12, wherein $W$ is

![Diagram](image)

16. The compound of claims 14 or 15, wherein the A ring is

![Diagram](image)

and wherein R8 is C1-C6 alkoxy.

17. The compound of claim 16, wherein the R8 is ethoxy.

18. The compound of claim 1, wherein Z1 is CR2, Z2 is N, and Z3 is CR3.

19. The compound of claim 18, wherein the compound is a compound of Formula Id,

![Diagram](image)

**Formula Id**

or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer or tautomer thereof.
20. The compound of claim 19, wherein R3 is -NHR4.

21. The compound of claim 19, wherein R3 is H.

22. The compound of claim 19, wherein R3 is -NR6(R7), C1-C8 alkyl, C2-C3 alkenyl, C3-C8 cycloalkyl, Cl-C6-alkoxy-Cl-C6-alkyl-, hydroxy-Cl-C6-alkyl-, cyano, cyano-Cl-C6-alkyl-, Cl-C6-S02Cl-C6-alkyl-, (R7)R6N-Cl-C6-alkyl-, C4-C6-heterocyclyl, C4-C6-heterocyclyl-Cl-C6-alkyl-, C6-C10 aryl, C5-C6-heteroaryl, or C5-C6-heteroaryl-Cl-C6-alkyl-, and wherein each alkyl or alkyene is optionally substituted with one or two C1-C6 alkyl.

23. The compound of claim 19, wherein W is

![Image](https://example.com/image.png)

24. The compound of claim 18, wherein W is

![Image](https://example.com/image.png)

25. The compound of claims 23 or 24, wherein the A ring is

![Image](https://example.com/image.png)

and wherein R8 is C1-C6 alkoxy.

26. The compound of claim 25, wherein the R8 is ethoxy.

27. A compound selected from the group consisting of N-(2,5-difluoro-4-(5-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-
3-carboxamide, N-(2,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(5-chloro-2-fluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)phenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide, N-(4-(2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(3-(1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-(2-amino-3-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)-2,5-difluorophenyl)-5-(4-fluorophenyl)-1-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide and pharmaceutically acceptable salts, solvates, hydrates and tautomers thereof.

28. 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 1-27.

29. The method of claim 28, wherein 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.

30. A pharmaceutical composition, comprising a compound of any of claims 1-27 and a pharmaceutically acceptable carrier.
31. The composition of claim 30, further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.

32. 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 1-27.

33. The method of claim 32, wherein the compound is administered orally, parenterally, by inhalation, or subcutaneously.
INTERNATIONAL SEARCH REPORT

PCT/US2011/034550

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 A61K31/506 A61K31/444 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>Claims 1, 19, 23 and Examples</td>
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Date of the actual completion of the international search

11 October 2011

Date of mailing of the international search report

18/10/2011

Name and mailing address of the ISA/

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Lecai IIon, Jennifer

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