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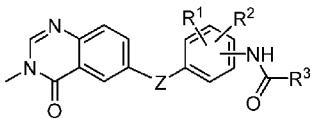

(I).

(57) Abstract: Provided herein are small molecule protein kinase modulators having the formula I. Pharmaceutical compositions comprising such, and their uses in treating one or more conditions are also disclosed.

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MODULATORS OF PROTEIN KINASES

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application No. 63/323,095, filed March 24, 2022, the entire contents of which are incorporated herein by reference.

BACKGROUND

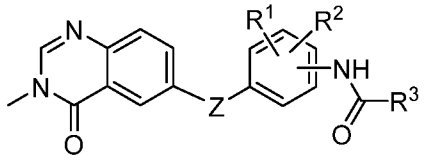
[0002] The more than 523 typical and atypical kinases in the human kinome represent a constellation of enzymes that catalyze the transfer of a phosphate group from ATP to a variety of amino acid residues, such as tyrosine, serine, and threonine. By so doing, these enzymes and their interrelated networks are effectors of cellular signal transduction. In particular, receptor tyrosine kinases (RTKs) coupled with their downstream intracellular kinases and phosphatases mediated cascades and feedback loops establish critical conduits for the transfer and regulation of signals from the cell exterior into the nucleus where transcriptional regulation takes place. Phosphate transfer to specific sites on proteins results in enzyme activation or inactivation, changes in conformation, increased or decreased affinity for other proteins, appropriate localization, and in some cases targeting of proteins for degradation by the proteosome. Kinase inhibitors, design strategies, and various mechanisms of inhibition have been extensively reviewed [Zhang J., et.al. *Nature Reviews Cancer* (2009) 9: 28-39; Blanc J. et.al., Anti-Cancer Agents in Med. Chem. (2013) 13, 17 pages; Gross S. et.al., *J. Clin. Invest.* (2015) 125(5); 1780-9; Cosgarea I. et.al., *J. der Deutsch. Dermatol. Gesellschaft,* (2017) 887-93, DOI: 10.1111/ddg.13321]. In addition, mechanistically similar lipid kinases, such as PI3Ks and SPK1, also contribute to the regulatory process (Brown J.R., et.al., *BMC Evolutionary Biology* (2011) 11(4): 1471-2148; Alvarez S.E., et.al., *Nature* (2010) 465: 1084–1088).

[0003] Because these processes regulate essential functions in cell growth, proliferation, differentiation and development, division, adhesion, angiogenesis, stress responses, cell-cell or cell-matrix interactions, short range contact-mediated axional guidance and mitogenesis, the activities of RTKs and their downstream kinase partners in signal transduction are tightly regulated and balanced through control of external receptor ligands as well as expression of receptors, receptor antagonists, decoy receptors, and through redundancies or crosstalk between signaling pathways. Therefore, the aberrant expression of kinases or activating mutations in kinases, inactivating mutations in negative regulators, and alterations in

phosphatase expression or activity, are known to participate in a variety of diseases, including many cancers.

SUMMARY

[0004] Provided herein are compounds having the Formula **I**.



(**I**);

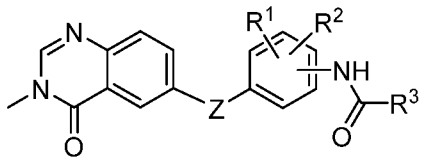
and pharmaceutically acceptable salts thereof, wherein Z, R^1, R^2, and R^3 are as defined herein. These compounds act as modulators of protein kinase (e.g., kinase inhibitors) and are useful in treating conditions responsive to the inhibition of protein kinase (e.g., cancer). See e.g., **Table 1**.

[0005] Also provided are pharmaceutically acceptable compositions comprising the disclosed protein kinase inhibitors.

DETAILED DESCRIPTION

1. General Description of Compounds

[0006] In a first embodiment, provided is a compound having the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

Z can be NH or O;

R^1 and R^2 are each independently selected from hydrogen, halo and (C_1-C_4)alkyl;

R^3 is phenyl or heteroaryl, each of which is optionally substituted with 1 to 2 groups selected from R^a;

R^a is selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, halo, -S(O)[(C_1-C_4)alkyl], -$S(O)_2$[(C_1-C_4)alkyl], -S(C_1-C_4)alkyl, -NH(C_1-C_4)alkyl, -N[(C_1-C_4)alkyl]$_2$, phenyl, and 4- to 6-membered heteroaryl, wherein said phenyl and 4- to 6-membered heteroaryl are each optionally substituted with 1 to 2 groups selected from R^b; and wherein said (C_1-C_4)alkyl, (C_1-C_4)alkoxy, and -S(C_1-C_4)alkyl are each optionally substituted with –NR^cR^d;

R^b is selected from halo and (C_1-C_4)alkyl; and

R^c and R^d are each independently selected from hydrogen and (C_1-C_4)alkyl.

2. Definitions

[0007] When used in connection to describe a chemical group that may have multiple points of attachment, a hyphen (-) designates the point of attachment of that group to the variable to which it is defined. For example, -NH(C_1-C_4)alkyl means that the point of attachment for this group occurs on the nitrogen atom.

[0008] The terms "halo" and "halogen" refer to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

[0009] The term "alkyl" when used alone or as part of a larger moiety, such as "haloalkyl", and the like, means saturated straight-chain or branched monovalent hydrocarbon radical. Unless otherwise specified, an alkyl group typically has 1-4 carbon atoms, *i.e.,* (C_1-C_4)alkyl.

[0010] "Alkoxy" means an alkyl radical attached through an oxygen linking atom, represented by –O-alkyl. For example, "(C_1-C_4)alkoxy" includes methoxy, ethoxy, proproxy, and butoxy.

[0011] The term "haloalkyl" includes mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, bromine, and iodine (e.g., -CF_3, -CHF_2, etc.

[0012] "Haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen atom such as, e.g., but are not limited to –$OCHF_2$ or –OCF_3.

[0013] The term "heteroaryl" used alone or as part of a larger moiety refers to a 5- to 12-membered (e.g., a 5- to 7-membered or 5- to 6-membered) aromatic radical containing 1-4 heteroatoms selected from N, O, and S. A heteroaryl group may be mono- or bi-cyclic. Monocyclic heteroaryl includes, for example, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, triazinyl, tetrazinyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, etc. Bi-cyclic heteroaryls include groups in which a monocyclic heteroaryl ring is fused to one or more aryl or heteroaryl rings. Nonlimiting examples include indolyl, imidazopyridinyl, benzooxazolyl, benzooxodiazolyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, quinazolinyl, quinoxalinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrazolopyridinyl, thienopyridinyl, thienopyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. It will be understood that when specified, optional substituents on a heteroaryl group may be present on any substitutable position and, include, *e.g.*, the position at which the heteroaryl is attached.

[0014] The terms "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, pigs, horses, sheep, goats and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

[0015] The term "inhibit," "inhibition" or "inhibiting" includes a decrease in the baseline activity of a biological activity or process e.g., to inhibit the activity of one or more kinases.

[0016] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some aspects, treatment may be administered after one or more symptoms have developed, *i.e.*, therapeutic treatment. In other aspects, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of exposure to a particular organism, or other susceptibility factors), *i.e.*, prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to delay their recurrence.

[0017] The term "pharmaceutically acceptable carrier" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

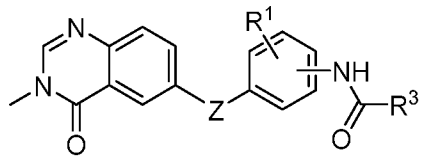
[0018] For use in medicines, the salts of the compounds described herein refer to non-toxic "pharmaceutically acceptable salts." Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include e.g. salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, methanesulfonic, and p-toluenesulfonic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable

base(s). Suitable pharmaceutically acceptable basic salts include e.g., ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, benzoates and salts with amino acids such as glutamic acid.

[0019] The term "effective amount" or "therapeutically effective amount" refers to an amount of a compound described herein that will elicit a desired or beneficial biological or medical response of a subject e.g., a dosage of between 0.01 - 100 mg/kg body weight/day.

3. Description of Exemplary Compounds:

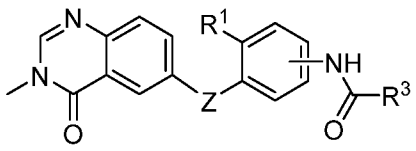
[0020] In a second embodiment, the compound of Formula **I** is of the Formula **II**:



(**II**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

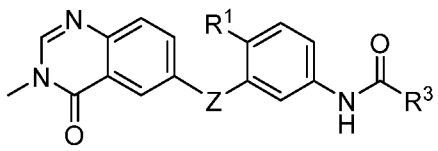
[0021] In a third embodiment, the compound of Formula **I** is of the Formula **III**:



(**III**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

[0022] In a fourth embodiment, the compound of Formula **I** is of the Formula **IV**:



(**IV**);

or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **I**.

[0023] In a fifth embodiment, R^1 in the compound of any one of Formulae **I** to **IV**, or a pharmaceutically acceptable salt thereof, is (C_1-C_4)alkyl, wherein the remaining variables are as described above for Formula **I**. Alternatively, as part of a fifth embodiment, R^1 in the compound of any one of Formulae **I** to **IV**, or a pharmaceutically acceptable salt thereof, is methyl, wherein the remaining variables are as described above for Formula **I**.

[0024] In a sixth embodiment, R^3 in the compound of any one of Formulae **I** to **IV**, or a pharmaceutically acceptable salt thereof, is selected from phenyl, oxazolyl, thiazolyl, pyrazolyl, furanyl, imidazolyl, indolyl, and pyrrolyl, each of which are optionally substituted with 1 to 2 groups selected from R^a, wherein the remaining variables are as described above for Formula **I** or the fifth embodiment.

[0025] In a seventh embodiment, R^a in the compound of any one of Formulae **I** to **IV**, or a pharmaceutically acceptable salt thereof, is selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, -S(O)[$(C_1\text{-}C_4)$alkyl], -S$(O)_2$[$(C_1\text{-}C_4)$alkyl], -S$(C_1\text{-}C_4)$alkyl, phenyl, and 4- to 6-membered heteroaryl, wherein said phenyl and 4- to 6-membered heteroaryl are each optionally substituted with 1 to 2 groups selected from R^b and wherein said $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, and -S$(C_1\text{-}C_4)$alkyl are each optionally substituted with $-NR^cR^d$, wherein the remaining variables are as described above for Formula **I** or the fifth or sixth embodiment. Alternatively, as part of a seventh embodiment, R^a in the compound of any one of Formulae **I** to **IV**, or a pharmaceutically acceptable salt thereof, is selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, -S(O)[$(C_1\text{-}C_4)$alkyl], -S$(O)_2$[$(C_1\text{-}C_4)$alkyl], -S[$(C_1\text{-}C_4)$alkyl]N[$(C_1\text{-}C_4)$alkyl]$_2$, -O[$(C_1\text{-}C_4)$alkyl]N[$(C_1\text{-}C_4)$alkyl]$_2$, phenyl, pyrazolyl, and imidazolyl wherein said phenyl, pyrazolyl, and imidazolyl are each optionally substituted with 1 to 2 groups selected from R^b, wherein the remaining variables are as described above for Formula **I** or the fifth or sixth embodiment.

[0026] In an eighth embodiment, R^b in the compound of any one of Formulae **I** to **IV**, or a pharmaceutically acceptable salt thereof, is selected from halo and $(C_1\text{-}C_4)$alkyl, wherein the remaining variables are as described above for Formula **I** or the fifth, sixth, or seventh embodiment.

[0027] Compounds having the disclosed formulae are further disclosed in the Exemplification and are included in the present disclosure. Pharmaceutically acceptable salts thereof as well as the neutral forms are included.

4. Uses, Formulation and Administration

[0028] The compounds and compositions described herein are generally useful for modulating the activity of protein kinase. In some aspects, the compounds and pharmaceutical compositions described herein inhibit the activity of protein kinase.

[0029] In some aspects, the compounds and pharmaceutical compositions described herein are useful in treating a disorder associated with protein kinase function. Thus, provided herein are methods of treating a condition associated with protein kinase function,

comprising administering to a subject in need thereof, a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof. Also provided is the use of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a condition associated with protein kinase function. Also provided is a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof, for use in treating a condition associated with protein kinase function.

[0030] In some aspects, the compounds and pharmaceutical compositions described herein are useful in treating a condition selected from an inflammatory disease, a neurodegenerative disease, cardiovascular disease, metabolic disease, pain, and cancer.

[0031] Examples of inflammatory disease include, but are not limited to, rheumatoid arthritis, psoriatic arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, osteo-arthritis, progression of atherosclerotic plaques, bone metastasis, asthma, interstitial cystitis, atopic dermatitis, psoriasis and systemic lupus erythematosus (SLE).

[0032] Examples of neurodegenerative disease include, but are not limited to, Alzheimer's, Parkinson's disease, and multiple sclerosis.

[0033] Examples of cardiovascular disease include, but are not limited to, hypertension, coronary and cerebral vasospasm, restenosis, atherosclerosis, stroke, and heart failure

[0034] Examples of metabolic disease include, but are not limited to, type 1 diabetes, type 2 diabetes.

[0035] Examples of cancer include, but are not limited to, colon, lung, ovarian, kidney, pancreatic, thyroid, hepatocellular, renal, gastric, breast, and brain cancers.

[0036] In certain aspects, a pharmaceutical composition described herein is formulated for administration to a patient in need of such composition. Pharmaceutical compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the pharmaceutical compositions described herein may be aqueous or oleaginous suspension. These suspensions

may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents.

[0037] In some aspects, the pharmaceutical compositions are administered orally.

[0038] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the pharmaceutical composition.

EXEMPLIFICATION

[0039] Kinase compounds disclosed herein are synthesized according to the following examples. As used below, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN: acetonitrile

°C: degrees Celsius

d: chemical shift in parts per million downfield from tetramethylsilane

dichloromethane (CH_2Cl_2)

DCM: dimethylformamide

DMF: dimethylsulfoxide

Et_2O: diethyl ether

EtOAc: ethyl acetate

ES^+: electrospray ionization

Et: ethyl

g: gram(s)

Hex: hexanes

h: hour(s)

HPLC: high performance liquid chromatography

Hz: hertz

J: coupling constant (in NMR spectrometry)

LCMS: liquid chromatography mass spectrometry

m: micro

m: multiplet (spectral); meter(s); milli

M: molar

M^+: parent molecular ion

Me: methyl

MeOH: methanol

MHz: megahertz

min: minute(s)

mol: mole(s); molecular (as in mol wt)

mL: milliliter

NIS: *N*-iodosuccinimide

MS: mass spectrometry

nm: nanometer(s)

NMR: nuclear magnetic resonance

pH: potential of hydrogen; a measure of the acidity or basicity of an aqueous solution

PE: petroleum ether

rt: room temperature

s: singlet (spectral)

t: triplet (spectral)

T: temperature

TFA: trifluoroacetic acid

THF: tetrahydrofuran

General Analytical Techniques

[0040] LCMS

[0041] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of Nexera XR HPLC stack (20 Series) with Nexera X2 SPD-M30A DAD and LCMS-2020 mass spectrometer using LabSolutions, v.5.89 software under the following parameters: Column temp: 45ºC, Sample temp: 18ºC. Gradient elution methods, mobile phase eluents, and columns are shown below.

[0042] Alternatively, Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu SCL-10AVP HPLC/PE SCIEX API 100/365 mass spectrometer under the following parameters: Column: Agilent, Eclipse XDB-C18; Length:50 mm; Diameter: 3 mm; pore size: 2.7 micron. Column temp: 50 ºC, Sample temp: room temperature. Gradient elution methods and mobile phase eluents are shown below.

[0043] Solvent A (0.1% Trifluoroacetic acid in water, pH =2.3)

[0044] Solvent B (0.1% Trifluoroacetic acid in acetonitrile)

[0045] 05991008_AA0 (0.8 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	0
0.2	95	0
10.2	0	100
12.2	0	100
12.4	95	5
14.0	95	5

[0046] 00951008_BB1 (0.8 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
0.2	100	0
10.2	5	95
12.5	5	95
13.0	100	0
14.5	100	0

[0047] 05991008_BB1 (0.8 mL/min flow) – mixed mode column 1

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
0.2	95	5
10.2	0	100
12.2	0	100
12.4	95	5
14.5	95	5

[0048] 05990510_AA0 (1.0 mL/min flow) – RP column 2

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
0.2	95	5
5.2	0	100
6.2	0	100
6.25	95	5
8.0	95	5

[0049] 05991008_BB1HT (0.8 mL/min flow, column temp 50ºC) – mixed mode column 2

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
0.2	95	5
10.2	0	100
12.2	0	100

12.4	95	5
14.2	95	5

[0050] Method A-6; polar_6min_100_1500 (1.5 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	95	5
0.1	95	5
3.6	0	100
4.6	0	100
4.7	95	5

[0051] Method B; polar_6min_100_1500 (1.0 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	95	5
0.01	95	5
0.50	0	100
1.49	95	5
4	0	100

[0052] Method A-12; polar_12min_100_1500 (1.5 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	95	5
0.01	95	5
9.6	0	100
10.6	0	100
10.7	95	5

[0053] **Neutral mobile phase**

[0054] Solvent A (20 mM ammonium acetate in 10% MeOH/water, pH 7.4)

[0055] Solvent B (100% acetonitrile)

[0056] **Acidic mobile phase**

[0057] Solvent A (0.1% formic acid in water, pH 2.3)

[0058] Solvent B (0.1% formic acid in acetonitrile)

[0059] **Columns**

[0060] RP column 1: ACE EXCEL 3 C18; 3.0 um, 100 x 3 mm (Mac-Mod Part # EXL-111-1003U)

[0061] RP column 2: Zorbax Eclipse XDB C8; 1.8 um, 50 x 4.6 mm (Agilent Part # 922975-906)

[0062] Mixed Mode column 1: Scherzo SM-C18; 3.0 um, 100 x 3 mm (Imtakt Part # SM034)

[0063] Mixed Mode column 2: Scherzo SM-C18; 3.0 um, 75 x 2 mm (Imtakt Part # SM023)

[0064] **HPLC**

[0065] Preparative High-performance liquid chromatography (HPLC) was performed on a Shimadzu HPLC equipped with 2 x LC-10ADvp pumps, Rheodyne 7725i manual injection valve, SPD-10AVvp UV/vis detector, SCL-10Avp system controller, and FRC-10A fraction follector using LabSolutions Lite, v.6.43 SP1 software and under the following conditions: Column temp: ambient; sample temp: ambient. Elution methods and mobile phase eluents are shown below.

[0066] Preparative isocratic HPLC 1 [Method RP-2525-2080]

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0.0	8	75	25
20.0	8	75	25
20.4	8	5	95
24.0	8	5	95
24.5	8	75	25
30.0	8	75	25

[0067] Preparative HPLC gradient [Method RP-2040-2099]

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0.0	9.99	80	20
20.0	9.99	60	40
20.4	9.99	5	95
24.0	9.99	5	95
24.5	9.99	80	20
30.0	9.99	80	20

[0068] **Neutral mobile phase**

[0069] Solvent A (20 mM ammonium acetate in 10% MeOH/water, pH = 7.4)

[0070] Solvent B (100% acetonitrile)

[0071] **Acidic mobile phase**

[0072] Solvent A (0.1% formic acid in water, pH =2.3)

[0073] Solvent B (100% acetonitrile)

[0074] **Columns**

[0075] RP: MACCEL PREP2005; 10.0 um; 50 x 20 mm (Bischoff Part # B052 0F180PS100)

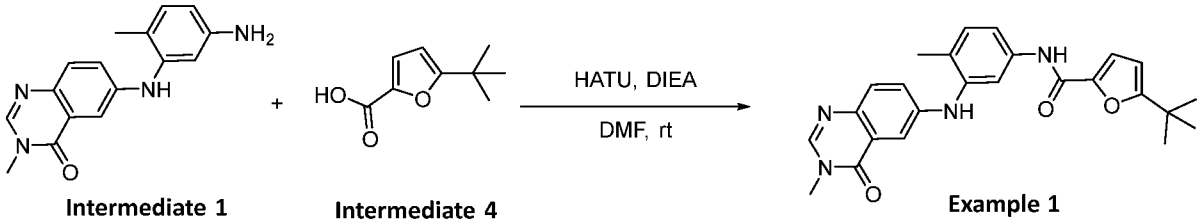
[0076] YMC-Pack ODS-A; 5.0 um; 150 x 10 mm (YMC Part # AA12S05-1510WT)

[0077] ACE 5 C18-PFP; 5.0 um; 150 x 10 mm (Avantor-ACE Part # ACE-1210-1510)

[0078] GPC: TSKgel a-2500; 7.0 um, 300 x 7.8 mm; (TOSOH Part # 0018339)

[0079] ^{1}H NMR Proton NMR was performed on the Varian Inova 500 spectrometer operating at 500 MHz in $CDCl_3$, DMSO-d_6, or MeOD.

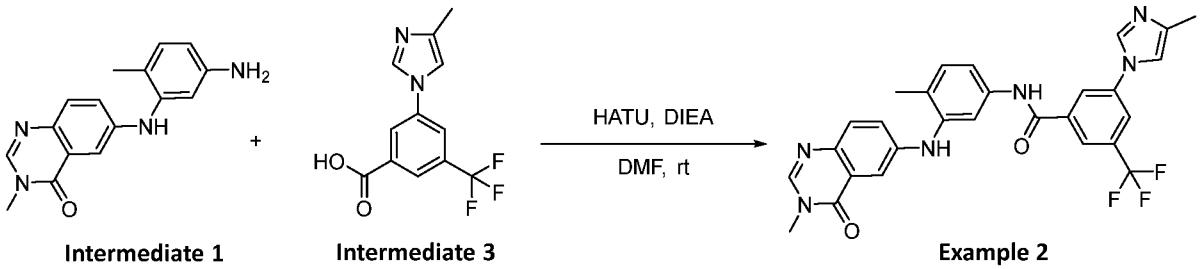
[0080] **Synthesis of 5-tert-butyl-N-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]furan-2-carboxamide [Example 1]:**



Intermediate 1 Intermediate 4 Example 1

[0081] A solution of 6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3H)-one Intermediate 1 (37 mg, 0.131 mmol, 1.00 eq) in DMF (1 mL, 0.1306 M) was added Diisopropylethylamine (0.045 mL, 0.261 mmol, 2.00 eq), 5-tert-Butyl-2-furoic acid Intermediate 4 (28 mg, 0.164 mmol, 1.26 eq) and HATU (0.074 g, 0.196 mmol, 1.50 eq). The mixture was stirred at rt for 3h and directly purified by HPLC to provide 5-tert-butyl-N-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]furan-2-carboxamide Example 1 (38 mg, 0.0863 mmol, 66.09 % yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.35 (dd, J = 8.2, 2.2 Hz, 1H), 7.23 – 7.15 (m, 2H), 6.26 (d, J = 3.4 Hz, 1H), 3.44 (s, 3H), 2.16 (s, 3H), 1.28 (s, 9H). MS(ESI$^+$) *m/z* calc'd for $[M+H]^+[C_{25}H_{26}N_4O_3+H]^+$: 431.2 found: 431.8 , t_R = 2.29 mins. [Method: B].

[0082] **Synthesis of 3-(4-Methylimidazol-1-yl)-*N*-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]-5-(tri-fluoromethyl)benzamide [Example 2]**



Intermediate 1 Intermediate 3 Example 2

[0083] To a solution of 3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)benzoic acid Intermediate 3 (40 mg, 0.150 mmol, 1.40 eq) in DMF (1 mL, 0.0535 M) was added Diisopropylethylamine (0.056 mL, 0.321 mmol, 3.00 eq), *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluor-ophosphate N-oxide (61 mg, 0.161 mmol, 1.50 eq) and stirred at rt for 10 min. Then a solution of 6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3H)-one Intermediate 1 (30 mg, 0.107

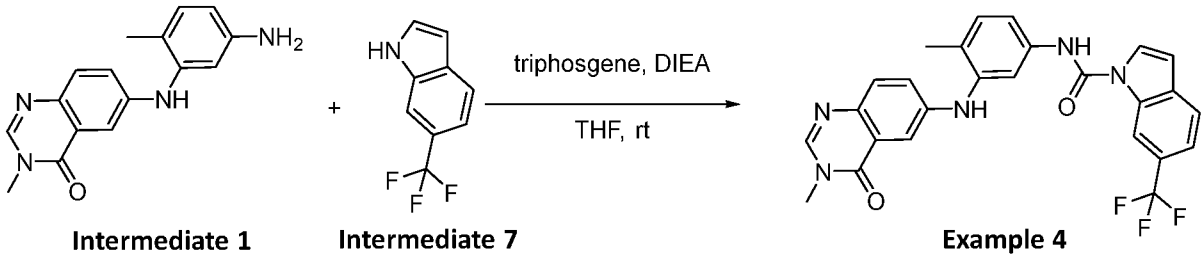
mmol, 1.00 eq) in DMF (1 mL, 0.0535 M) was added and stirred for 24h. The reaction mixture was quenched with aq sat $NaHCO_3$ (10 mL) and stirred for 1 h. The solid was filtered through a fritted funnel and the filter cake was washed with aq sat $NaHCO_3$ (2 x 5 mL), 1M LiCl (10 mL), H_2O (2 x 5 mL). The solid was dried and washed with MeOH (3 x 5 mL), dried overnight under high vacuum to afford 3-(4-methylimidazol-1-yl)-N-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]-5-(trifluoromethyl)benzamide Example 2 (15 mg, 0.0279 mmol, 26.11 % yield) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.39 (s, 1H), 8.38 (d, J = 13.4 Hz, 2H), 8.20 (s, 1H), 8.15 – 8.09 (m, 2H), 7.98 (s, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.70 – 7.66 (m, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.25 (d, J = 8.2 Hz, 1H), 3.44 (d, J = 1.3 Hz, 3H), 2.18 (s, 3H), 2.16 (s, 3H). MS(ESI$^+$) m/z calc'd for $[M+H]^+[C_{28}H_{23}F_3N_6O_2+H]^+$: 533.19 found: 532.6, LCMS t_R = 1.82 mins. [Method B].

[0084] Synthesis of *N*-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]furan-2-carboxamide [Example 3]:

Intermediate 1 Intermediate 6 Example 3

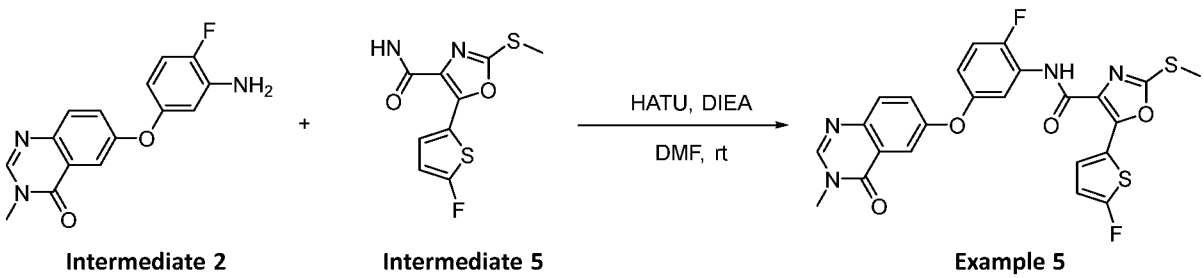
[0085] 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (0.078 g, 0.206 mmol, 1.05 eq) was added to a solution of 6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3*H*)-one Intermediate 1 (0.055 g, 0.196 mmol, 1.00 eq), diisopropylethylamine (0.060 mL, 0.343 mmol, 1.75 eq), and 2-furancarboxylic acid Intermediate 6 (0.033 g, 0.294 mmol, 1.50 eq) in DMF (1.962 mL, 0.1000 M) at rt . After 16 hours of stirring, the reaction was quenched with half saturated $NaHCO_3$ (aq.). The resulting precipitate was collected via vacuum filtration, rinsed with water (2x), and dried on high vac to afford *N*-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]furan-2-carboxamide Example 3 (0.050 g, 0.134 mmol, 68.07 % yield) as an off-white solid. ^{1}H NMR (600 MHz, DMSO) δ 10.08 (s, 1H), 8.14 (s, 1H), 7.96 (s, 1H), 7.90 (dd, J = 1.6, 0.7 Hz, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.42 (dd, J = 4.6, 2.4 Hz, 1H), 7.41 (dd, J = 4.1, 2.5 Hz, 1H), 7.28 (dd, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.68 (dd, J = 3.5, 1.7 Hz, 1H), 3.46 (s, 3H), 2.17 (s, 3H); MS(ES$^+$) m/z calc'd for $[M+H]^+$ $[C_{21}H_{18}N_4O_3]^+$: 374.39, found 375.0, t_R= 3.11 min [Analytical method: 05990510_AA1.lcm; Column: Zorbax Eclipse XDB-C8 (4.6 mm X 50 mm)].

[0086] Synthesis of N-(4-methyl-3-((3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino)phenyl)-6-(trifluoromethyl)-1H-indole-1-carboxamide [Example 4]



[0087] To a solution of 6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3H)-one Intermediate 1 (30 mg, 0.107 mmol, 1.00 eq) in THF (2 mL, 0.0535 M) was added DIEA (0.075 mL, 0.428 mmol, 4.00 eq) followed by triphosgene (13 mg, 0.0428 mmol, 0.400 eq) at rt and stirred for 30 min. Then 6-trifluoromethylindole Intermediate 7 (22 mg, 0.118 mmol, 1.10 eq) was added to the reaction mixture and was stirred at rt for 1 h, 40°C o/n and 80°C for 2 days until consumption of aniline. The reaction mixture was concentrated and the residue was purified by column chromatography over silica gel, SilicaSep, CombiFlash, 12g cartridge (dry load, eluting with 2% MeOH in DCM) to afford N-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]-6-(trifluoromethyl)indole-1-carboxamide Example 4 (0.015 g, 0.0297 mmol, 27.76 % yield) as a white solid. ^{1}H NMR (500 MHz, Chloroform-d) δ 10.13 (s, 1H), 8.53 (s, 1H), 8.24 (d, J = 3.7 Hz, 1H), 8.13 (s, 1H), 8.01 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.53 (dd, J = 13.4, 8.5 Hz, 2H), 7.48 – 7.40 (m, 2H), 7.34 (dd, J = 8.2, 2.1 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.87 (d, J = 3.7 Hz, 1H), 3.40 (s, 3H), 2.19 (s, 3H).MS(ESI$^+$) *m/z* calc'd for [M+H]$^+$: 492.2 found: 492.4 , t_R = 2.69 mins [Method B].

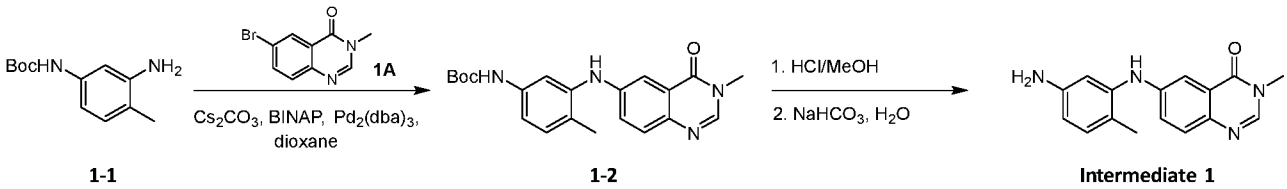
[0088] Synthesis of N-[2-fluoro-5-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-5-(5-fluoro-2-thienyl)-2-methylsulfanyl-oxazole-4-carboxamide [Example 5]:



[0089] To a stirred mixture of6-(3-amino-4-fluorophenoxy)-3-methylquinazolin-4(3H)-one Intermediate 2 (32 mg, 0.111 mmol, 1.00 eq) and 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylic acid Intermediate 5 (34 mg, 0.133 mmol, 1.20 eq) in DMF at 25C was added HATU (63 mg, 0.166 mmol, 1.50 eq) and N,N-Diisopropylethylamine

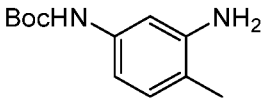
(0.058 mL, 0.332 mmol, 3.00 eq). The reaction mixture was stirred at room temperature with LCMS monitoring. the reaction was complete after overnight. quenched with aq. Na2CO3, stirred for 30 minutes, filtered, washed with 1M LiCl and water, afforded a crude 39 mg which was triturated with ethyl acetate-ether twice. The crude material was purified by flash chromatography over silica gel, ISCO, CombiFlash, 4g cartridge (dry load, 0-10% MeOH in DCM)to provide solid which then recrystallized from DCM-hexane, dried on high vacuum pump over the weekend to afford N-[2-fluoro-5-(3-methyl-4-oxo-quinazolin-6-yl)oxy-phenyl]-5-(5-fluoro-2-thienyl)-2-methylsulfanyl-oxazole-4-carboxamide Example 5 (23 mg, 0.0426 mmol, 38.55 % yield) as a beige solid. ^{1}H NMR (500 MHz, DMSO- d_6) δ 9.76 (s, 1H), 8.32 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.66 (dd, J = 6.4, 3.0 Hz, 1H), 7.62 (t, J = 4.3, 4.3 Hz, 1H), 7.58 (dd, J = 8.8, 2.9 Hz, 1H), 7.50 (d, J = 2.9 Hz, 1H), 7.42 (dd, J = 10.3, 9.0 Hz, 1H), 7.03 (dt, J = 8.9, 3.5, 3.5 Hz, 1H), 6.88 (dd, J = 4.3, 2.0 Hz, 1H), 3.47 (s, 3H), 2.77 (s, 3H). MS(ES$^+$) m/z cala'd for [M+H] 527.06: found 527.2 , LCMS t_R = 3.13 min [Method:B].

[0090] Synthesis of 6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3H)-one [Intermediate 1]:



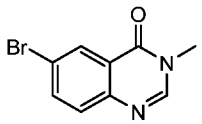
1-1 1-2 Intermediate 1

[0091] Tert-butyl (3-amino-4-methylphenyl)carbamate [1-1]:



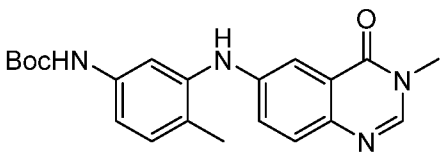
[0092] Available from commercial sources

[0093] 6-bromo-3-methylquinazolin-4(3H)-one [1A]:



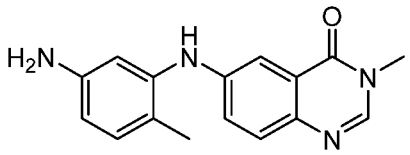
[0094] Available from commercial sources

[0095] Tert-butyl (4-methyl-3-((3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino)phenyl)carbamate [2-1]:



[0096] A stirred mixture of tert-butyl N-(3-amino-4-methyl-phenyl)carbamate 1-1 (8.9 g, 40.04 mmol), 6-bromo-3-methylquinazolin-4(3H)-one 1A (9.3 g, 39.2 mmol), Cs_2CO_3 (39.1 g, 120.1 mmol), BINAP (2.49 g, 4.04 mmol) in dioxane (180 ml) was treated with $Pd_2(dba)_3$ (1.83 mg, 4.04 mmol). The reaction mixture was heated to 80 ^{0}C for 23h. The reaction was then quenched with 10% NaOH(aq) and extracted with EtOAc. The organics were washed with NaCl(sat) and then Na_2SO_4(S). The organics were removed under reduced pressure and the resulting solid was treated with DCM (300 ml). The resulting precipitate was collected by vacuum filtration to provide tert-butyl N-[4-methyl-3-[(3-methyl-4-oxo-quinazolin-6-yl)amino]phenyl]carbamate 1-**2** (10.60 g, 27.6 mmol, 70.36 % yield) an off white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ9.22 (s, 1H), 8.11 (s, 1H), 7.91 (s, 1H), 7.49 (s, 1H), 7.38 (s, 1H), 7.32 (s, 1H), 7.11 (q, J = 8.7, 8.7, 8.3 Hz, 2H), 3.44 (s, 3H), 2.09 (s, 3H), 1.43 (s, 9H). MS(ES$^+$) m/z cala'd for $[M+H]^+$ $[C8H7BrN2O+H]^+$: 381.2 found 381.1 , LCMS t_R= 4.40 min [Method:B].

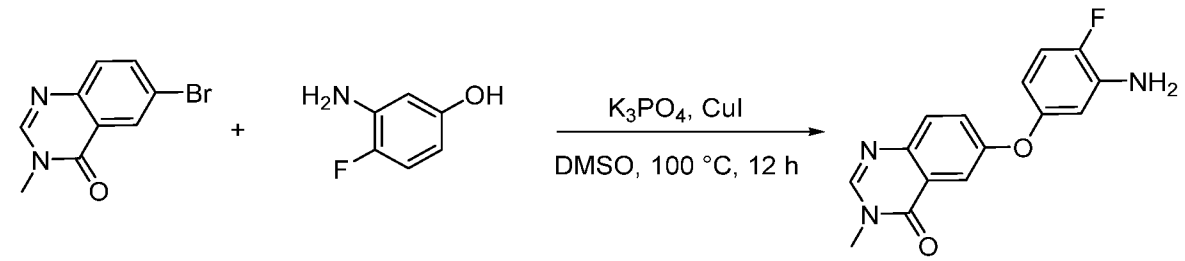
[0097] **6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3H)-one [Intermediate 1]:**



[0098] A solution of tert-butyl (4-methyl-3-((3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)amino)phenyl)carbamate 2 (60.0 g, 158 mmol, 1.00 *eq*) in HCl/MeOH (4 M, 960 mL, 24.4 *eq*) was stirred at 20 °C for 12 h. LC-MS showed that 2 was consumed completely and one main peak with the desired mass was detected. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with EtOAc (30 mL * 2), then it was filtered and the filter cake was dried in vacuo. The residue was dissolved by water (1000 mL), then saturated aqueous $NaHCO_3$ solution was added to the mixture to adjust pH ~ 8. The aqueous phase was extracted with EtOAc (500 mL * 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was triturated with MTBE (30 mL * 2), then it was filtered, and the filter cake was dried in vacuo. 6-((5-amino-2-methylphenyl)amino)-3-methylquinazolin-4(3H)-one Intermediate 1 (25.7 g, 90.1 mmol, 57.1% yield, 98.4% purity) was obtained as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.09 (s, 1H), 7.71 (s, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.35 – 7.28 (m, 2H), 6.88 (d, J = 8.1 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 6.28 (dd, J = 8.0, 2.3 Hz, 1H), 4.84 (s, 2H), 3.44 (s,

3H), 2.00 (s, 3H). MS(ES$^+$) m/z cala'd for $[M+H]^+$ $[C_{16}H_{17}N_4O+H]^+$: 281.1 found 281.2 , LCMS t_R= 1.08 min [Method:B].

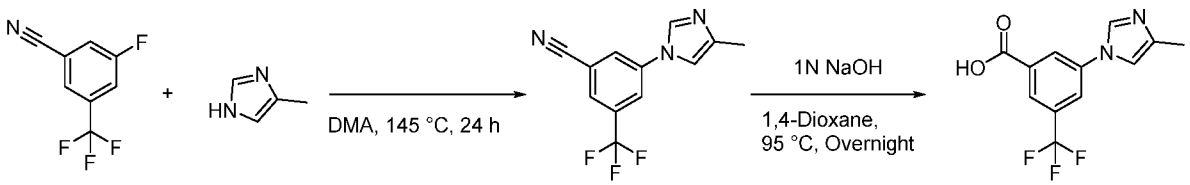
[0099] Synthesis of 6-(3-amino-4-fluoro-phenoxy)-3-methyl-quinazolin-4-one [Intermediate 2]:



2-1 **2-2** **Intermediate 2**

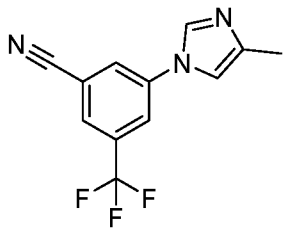
[00100] An oven dried round-bottom flask was charged with 6-bromo-3-methylquinazolin-4(3H)-one 2-1 (35.00 g, 146 mmol), 3-amino-4-fluorophenol 2-2 (37.20 g, 293 mmol), K_3PO_4 (62.10 g, 293 mmol), CuI (2.79 g, 14.6 mmol) and picolinic acid (3.60 g, 29.2 mmol). To this mixture was added DMSO (500 ml), and the flask was purged with nitrogen gas for 20 min. The reaction was then heated at 100 °C for 12 h. The reaction was cooled to room temperature, and crushed ice (500 ml) was added. The precipitate obtained was filtered and washed with EtOAc (500 ml), then suspended in a mixture of 20% methanol in DCM solution (1500 ml), and filtered to remove the residual copper iodide. The filtrate was evaporated to get 6-(3-amino-4-fluoro-phenoxy)-3-methyl-quinazolin-4-one Intermediate 2 (31.00 g, 72.22 %) as a greyish brown solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.29 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.50 (dd, J = 8.8, 2.9 Hz, 1H), 7.44 (d, J = 2.9 Hz, 1H), 7.02 (dd, J = 11.2, 8.7 Hz, 1H), 6.46 (dd, J = 7.7, 2.9 Hz, 1H), 6.22 (dt, J = 8.6, 3.2, 3.2 Hz, 1H), 5.35 (s, 2H), 3.46 (s, 3H). MS (ES$^+$) m/z calcd for $[M+H]^+$ $[C_{15}H_{12}FN_3O_2+H]^+$: 285.1 found 286.0, LCMS t_R= 1.60 min [Method: B]

[00101] Synthesis of 3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)benzoic acid [Intermediate 3]:



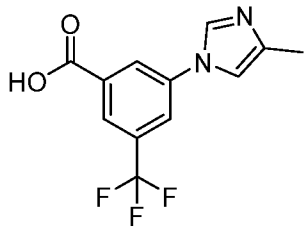
3-1 **3-2** **3-3** **Intermediate 3**

[00102] 3-(4-Methylimidazol-1-yl)-5-(trifluoromethyl)benzonitrile [3-3]:



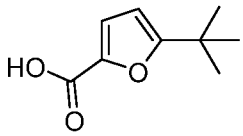
[00103] A stirred solution of 4-Methyl-1H-imidazole 3-2 (1.45 g, 17.7 mmol, 3.10 eq) and 3-Fluoro-5-(trifluoromethyl)benzonitrile 3-1 (1.08 g, 5.70 mmol, 1.00 eq) in DMA (5 mL, 1.1401 M) was heated to 145 °C for 24h. Reaction mixture was cooled to rt, water (10 mL) was added to it before it was extracted with ethyl acetate (3 x 10 mL). Organic part was washed with water followed by brine and concentrated. Crude was purified by column chromatography over silica gel, ISCO, 40g cartridge, eluting with 0-40% EtOAc in Hexane to give 3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)benzonitrile 3-3 (730 mg, 2.87 mmol, 50.42 % yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.40 (s, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 7.71 (s, 1H), 2.15 (s, 3H). MS(ESI$^+$) *m/z* calc'd for $[M+H]^+[C_{12}H_8F_3N_3+H]^+$: 252.2, found: 252.2 , t_R = 2.75 mins. [Method: A-12].

[00104] Synthesis of 3-(4-Methylimidazol-1-yl)-5-(trifluoromethyl)benzoic acid [Intermediate 3]:



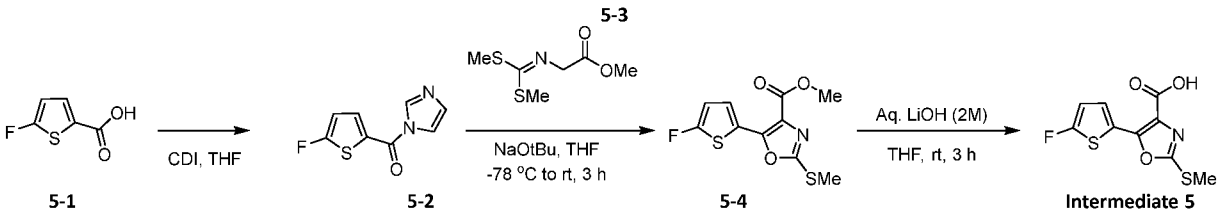
[00105] To a solution of 3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)benzonitrile 3-3 (696 mg, 2.77 mmol, 1.00 eq) in 1,4-Dioxane (15 mL, 0.1847 M) was added 1N NaOH (14 mL, 13.8 mmol, 5.00 eq). The mixture was stirred at 95°C o/n. The reaction mixture was evaporated and diluted with H_2O. The mixture was acidified with 3N HCl and extracted with EtOAc (3 x 50 ml). The combined organic layers were washed with brine, dried, filtered and evaporated to afford 3-(4-methylimidazol-1-yl)-5-(trifluoromethyl)benzoic acid Intermediate 3 (0.70 g, 2.59 mmol, 93.53 % yield) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.71 (s, 1H), 8.54 (s, 1H), 8.48 (s, 1H), 8.27 (s, 1H), 8.21 – 8.17 (m, 1H), 2.34 (s, 3H). MS(ESI$^+$) *m/z* calc'd for $[M+H]^+[C_{12}H_9F_3N_2O_2+H]^+$: 271.1, found:271.1, t_R = 1.12 mins. [Method: B].

[00106] **Synthesis of 5-(tert-butyl)furan-2-carboxylic acid [Intermediate 4]:**

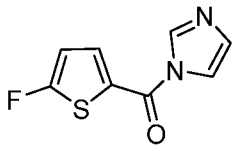


[00107] Available from commercial sources

[00108] Synthetic Scheme of 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylic acid [Intermediate 5]:

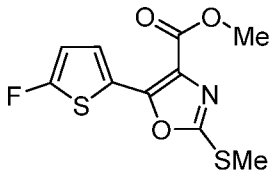


[00109] **(5-fluorothiophen-2-yl)(1H-imidazol-1-yl)methanone [5-2]:**



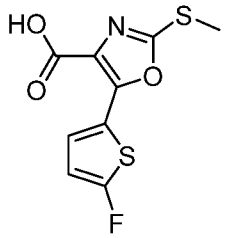
[00110] To a solution of 5-fluorothiophene-2-carboxylic acid 5-1 (20.0 g, 137 mmol) in THF (0.3 M) was added CDI (27 g, 166.6 mol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The solution was diluted with EtOAc (3.0 L), washed with water, brine, dried with $MgSO_4$, and concentrated. The crude material was recrystallized from EtOAc : hexane (1 : 10) to afford (5-fluorothiophen-2-yl)(1H-imidazol-1-yl)methanone **5-2** as pale yellow solid (24 g).

[00111] **methyl 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylate [5-4]:**



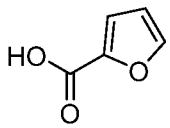
[00112] To a mixture of methyl 2-((bis(methylthio)methylene)amino)acetate 5-2 (28.0 g, 144 mmol) in THF (400 mL) at -78 °C was added NaOtBu (18 g, 184.8 mmol) and the mixture was stirred for 30 min. A solution of (5-fluorothiophen-2-yl)(1H-imidazol-1-yl)methanone 5-3 (crude) in THF (125 mL) was then added dropwise, and the mixture was allowed to warm slowly to room temperature and stirred for 2 h. The solution was then diluted with EtOAc, washed with water, brine, and dried with $MgSO_4$. The solvent was removed by rotary evaporation, and the crude was triturated with 10 : 1 hexane : ethyl acetate twice to afford methyl 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylate 5-4 as beige solid (27.3 g, 73% yield). MS (ES^+) m/z calcd. for $[M+H]^+$ $[C10H8FNO3S2+H]^+$: 274.3 found 274.3, LCMS t_R= 2.85 min [Method B].

[00113] Synthesis of 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylic acid [Intermediate 5]:



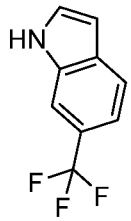
[00114] Methyl 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylate 5-4 (37 g, 135.4 mmol) was dissolved in THF (900 mL) and 2N LiOH (400 mL, 808 mmol, 2N aqueous solution) was added to the reaction mixture dropwise and degassed with nitrogen for 5 min. The reaction mixture was stirred for 3 h at room temperature and volatiles were removed under reduced pressure. Water (100 mL) was added to the residue and reaction mixture was gradually acidified with 2N HCl (pH ~ 2), stirred for 15 min and filtered. The filter cake was dried under high vacuum and then azeotroped with toluene (3 X 100 mL) to afford pure 5-(5-fluorothiophen-2-yl)-2-(methylthio)oxazole-4-carboxylic acid Intermediate 5 (32.6 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.82 (d, J = 3.8 Hz, 1H), 6.96 (d, J = 3.8 Hz, 1H), 2.69 (s, 3H). MS (ES^+) m/z calcd. for $[M+H]^+$ $[C9H6FNO3S2+H]^+$: 260.0 found 260.2, LCMS t_R= 2.39 min [Method B].

[00115] Synthesis of Furan-2-carboxylic acid [Intermediate 6]:



[00116] Available from commercial sources

[00117] Synthesis of 6-(trifluoromethyl)-1H-indole [Intermediate 7]:



[00118] Available from commercial sources

Biochemical Assays

1. Kinase Panel

[00119] The disclosed compounds were tested for activity against a panel of at least 300 kinases. Kinase panel screening was conducted by Nanosyn (Santa Clara, CA 95051) using an enzymatic inhibition assay accepted as valid by those skilled in the art (e.g., the Caliper

LabChip® mobility shift assay, an ADP detection assay, or time-resolved fluorescence detection technology. Compounds were screened at a concentration of 5 μM using an ATP concentration at the Km for each of the respective kinases and a 30-minute pre-incubation time-point.

[00120] A selection of kinases from that panel in which one or more of the disclosed compounds showed inhibition of kinase activity is shown below in **Table 1**. In the table, kinase inhibition is classified by: A = 95% or greater, B = 90%-94%, C = 80%-89%, and D = 79% and less with a compound concentration of 5 μM.

Table 1

Kinase	Ex1	Ex2	Ex3	Ex4	Ex5
Abl1	A	A		E	E
Abl2	A	A		D	E
BMX	D	D		E	E
BRAF	A	A		A	D
BRAF (V600E)	A	A		A	D
BRK	D	B		E	E
CRAF	A	A		A	C
CSF1R	A	A		D	E
CSK	A	A		D	E
DDR1	A	A		A	E
DDR2	A	A		A	E
EPHA1	C	B		D	E
EPHA2	A	A		A	E
EPHA4	A	A		A	E
EPHA5	A	A		A	E
EPHA6	B	A		A	E
EPHA7	D	A		E	E
EPHA8	A	A		A	E
EPHB1	A	A		B	E
EPHB2	A	A		A	E
EPHB3	A	B		C	E
EPHB4	A	A		A	E
FGFR2	D	D		E	E
FGR	C	C		E	E
FLT1	B	B		E	E
FLT4	B	B		E	E
KIT	A	A		D	E
LCK	A	A		D	E
LYNA	A	A		B	E
LYNB	A	A		B	E

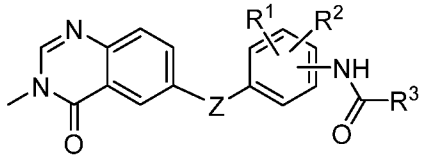
P38a	A	A		A	E
P38b	B	A		C	E
PDGFRa	A	A		A	E
PDGFRb	A	A		D	E
RET	A	A		C	E
RIPK1	D	D		E	E
RIPK2	A	A		C	E
SRC	C	A		D	E
TAOK2	E	D		E	E
TAOK3	E	D		E	E
TIE2	E	C		E	E
TNK1	E	E		E	E

[00121] While we have described a number of embodiments, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

[00122] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

1. A compound having the Formula **I**:



(**I**);

or a pharmaceutically acceptable salt thereof, wherein

Z can be NH or O;

R^1 and R^2 are each independently selected from hydrogen, halo, and (C_1-C_4)alkyl;

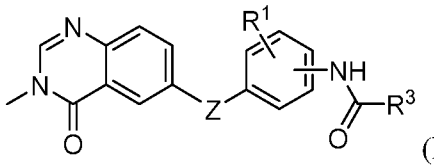
R^3 is phenyl or heteroaryl, each of which is optionally substituted with 1 to 2 groups selected from R^a;

R^a is selected from (C_1-C_4)alkyl, halo(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo(C_1-C_4)alkoxy, halo, -S(O)[(C_1-C_4)alkyl], -$S(O)_2$[(C_1-C_4)alkyl], -S(C_1-C_4)alkyl, -NH(C_1-C_4)alkyl, -N[(C_1-C_4)alkyl]$_2$, phenyl, and 4- to 6-membered heteroaryl, wherein said phenyl and 4- to 6-membered heteroaryl are each optionally substituted with 1 to 2 groups selected from R^b; and wherein said (C_1-C_4)alkyl, (C_1-C_4)alkoxy, and -S(C_1-C_4)alkyl are each optionally substituted with –NR^cR^d;

R^b is selected from halo and (C_1-C_4)alkyl; and

R^c and R^d are each independently selected from hydrogen and (C_1-C_4)alkyl.

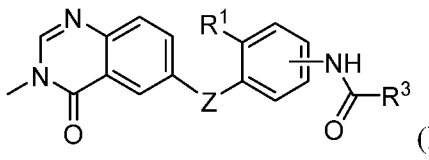
2. The compound of Claim 1, wherein the compound is of the Formula **II**:



(**II**);

or a pharmaceutically acceptable salt thereof.

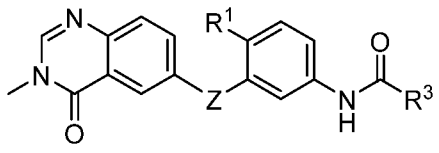
3. The compound of Claim 1 or 2, wherein the compound is of the Formula **III**:



(**III**);

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of Claims 1 to 3, wherein the compound is of the Formula **IV**:



(**IV**);

or a pharmaceutically acceptable salt thereof.

5. The compound of any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is $(C_1\text{-}C_4)$alkyl.

6. The compound of any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^1 is methyl.

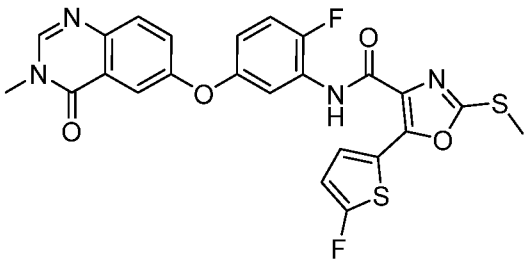
7. The compound of any one of Claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from phenyl, oxazolyl, thiazolyl, pyrazolyl, furanyl, imidazolyl, indolyl, and pyrrolyl, each of which are optionally substituted with 1 to 2 groups selected from R^a.

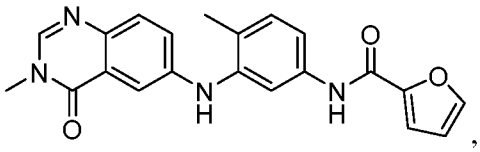
8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^a is selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, -S(O)[$(C_1\text{-}C_4)$alkyl], -$S(O)_2$[$(C_1\text{-}C_4)$alkyl], -S$(C_1\text{-}C_4)$alkyl, phenyl, and 4- to 6-membered heteroaryl, wherein said phenyl and 4- to 6-membered heteroaryl are each optionally substituted with 1 to 2 groups selected from R^b and wherein said $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, and -S$(C_1\text{-}C_4)$alkyl are each optionally substituted with $–NR^cR^d$;

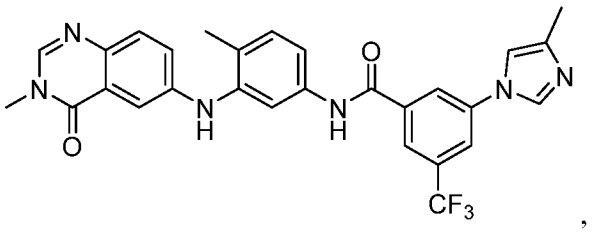
9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^a is selected from $(C_1\text{-}C_4)$alkyl, halo$(C_1\text{-}C_4)$alkyl, -S(O)[$(C_1\text{-}C_4)$alkyl], -$S(O)_2$[$(C_1\text{-}C_4)$alkyl], -S[$(C_1\text{-}C_4)$alkyl]N[$(C_1\text{-}C_4)$alkyl]$_2$, -O[$(C_1\text{-}C_4)$alkyl]N[$(C_1\text{-}C_4)$alkyl]$_2$, phenyl, pyrazolyl, and imidazolyl wherein said phenyl, pyrazolyl, and imidazolyl are each optionally substituted with 1 to 2 groups selected from R^b.

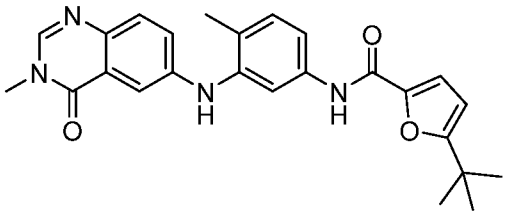
10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^b is selected from halo and $(C_1\text{-}C_4)$alkyl.

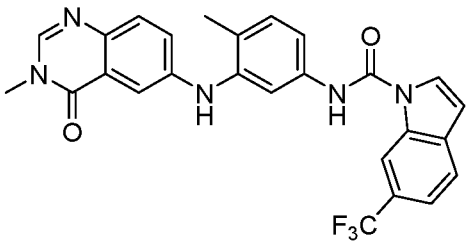
11. The compound of Claim 1, wherein the compound is selected from:


,


,


,


, and


, or a pharmaceutically acceptable salt of any of the foregoing.

12. A pharmaceutical composition comprising a compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

13. A method of treating a condition responsive to the inhibition of the serine/threonine protein kinase Raf family comprising administering to the subject a therapeutically effective amount of the compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/16049

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/167, A61K 31/505, A61K 31/16 (2023.01)
ADD. A61K 31/33 (2023.01)

CPC - INV. A61K 31/167, A61K 31/505, A61K 31/16

ADD. A61K 31/33

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"Pubchem CID 145485237", Create date: 12 December 2019 (12.12.2019), entire document, especially page 2, compound listed	1-3
A	US 2009/0118261 A1 (Aquila et al.), 07 May 2009 (07.05.2009), entire document, especially para[0005]-[0032]	1-3
A	WO 2021/250521 A1 (Array Biopharma Inc.), 16 December 2021 (16.12.2021), entire document, especially page 4, ln 5-33; Figure 1	1-3
A	WO 2022/261250 A1 (C4 Therapeutics, Inc.), 15 December 2022 (15.12.2022), entire document, especially page 3, compound 157; page 5, ln 1-29	1-3
A	US 8,937,078 B2 (Bembernek et al.), 20 January 2015 (20.01.2015), entire document, especially col 8, ln 40-67; col 9, ln 1-32	1-3
A	WO 2015/001491 A1 (Rhizen Pharmaceuticals SA), 08 January 2015 (08.01.2015), entire document, especially para[13]-[15]	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 2023 (11.05.2023)	AUG 14 2023
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 23/16049

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-10, 12-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
----see supplemental box----

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/16049

Box III: lack of unity

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-3 and 11 are directed to a compound having a structure of Formula I as seen in instant claim 1. Claim 1 will be searched to the extent that it encompasses the first species of claim 1, represented by a compound of Formula I wherein Z is NH; R1 is hydrogen, halo, or (C1-C4)alkyl; R2 is H; R3 is phenyl wherein the phenyl is optionally substituted with 1 to 2 groups selected from Ra; Ra is selected from (C1-C4)alkyl, halo(C1-C4)alkyl, hydroxy(C1-C4)alkyl, (C1-C4)alkoxy, halo(C1-C4)alkoxy, halo, -S(O)[(C1-C4)alkyl], -S(O)2[(C1-C4)alkyl], -S(C1-C4)alkyl, -NH(C1-C4)alkyl, -N[(C1-C4)alkyl]2, phenyl, and 4- to 6-membered heteroaryl, wherein said phenyl and 4- to 6-membered heteroaryl are each optionally substituted with 1 to 2 groups selected from Rb; and wherein said (C1-C4)alkyl, (C1-C4)alkoxy, and -S(C1-C4)alkyl are each optionally substituted with -NRcRd; Rb is selected from halo and (C1-C4)alkyl; and RC and Rd are each independently selected from hydrogen and (C1-C4)alkyl. It is believed that claims 1-3 read on this first named invention, and thus these claims will be searched without fee. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of Formula I wherein Z is O; R1 is hydrogen, halo, or (C1-C4)alkyl; R2 is H; R3 is phenyl wherein the phenyl is optionally substituted with 1 to 2 groups selected from Ra; Ra is selected from (C1-C4)alkyl, halo(C1-C4)alkyl, hydroxy(C1-C4)alkyl, (C1-C4)alkoxy, halo(C1-C4)alkoxy, halo, -S(O)[(C1-C4)alkyl], -S(O)2[(C1-C4)alkyl], -S(C1-C4)alkyl, -NH(C1-C4)alkyl, -N[(C1-C4)alkyl]2, phenyl, and 4- to 6-membered heteroaryl, wherein said phenyl and 4- to 6-membered heteroaryl are each optionally substituted with 1 to 2 groups selected from Rb; and wherein said (C1-C4)alkyl, (C1-C4)alkoxy, and -S(C1-C4)alkyl are each optionally substituted with -NRcRd; Rb is selected from halo and (C1-C4)alkyl; and RC and Rd are each independently selected from hydrogen and (C1-C4)alkyl. (i.e., claims 1-3).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Each invention in Group I+ includes the technical feature of a unique compound of Formula I, which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound of Formula I.

These shared technical features, however, do not provide a contribution over the prior art as being obvious over US 2009/0118261 A1 to Aquila et al. (hereinafter 'Aquila'). Aquila teaches a compound having the Formula I as seen in instant claim 1 or a pharmaceutically acceptable salt thereof, wherein: Z is NH; R1 is C1alkyl; R2 is hydrogen; R3 is phenyl (para[0005], 'Accordingly, the present invention provides a compound of formula (I)...wherein'; see formula (I); para[0006], 'Ring A is carbocyclyl...'; para[0046], 'Ring A is phenyl...'; para[0008], 'n is 0...'; para[0009], 'R2 is hydrogen...'; para[0010], 'X is NR15...'; para[0011], 'G is C which is attached to X of formula (I); A, E, and J are independently CR16...'; para[0012], 'R3 is hydrogen...R16 is hydrogen...'; para[0013], 'R4 is C1 alkyl...R15 is hydrogen...'; para[0014], 'the bond between the -NR5- and -CR3- of formula (I) is a double bond wherein R5 is absent...') but does not teach a specific example or embodiment comprising a compound of formula I listed in instant claim 1. However, based on Aquila's teaching, it would have been obvious to a person of ordinary skill in the art to isolate the specific compound by routine experimentation because Aquila teaches a broad compound of the formula including a compound of formula I listed instant claim 1 (see para[0005]; see formula (I)).

As said compound was known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+. The inventions of Group I+ thus lack unity under PCT Rule 13.

Note:
Claims 4-10 and 12-13 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).