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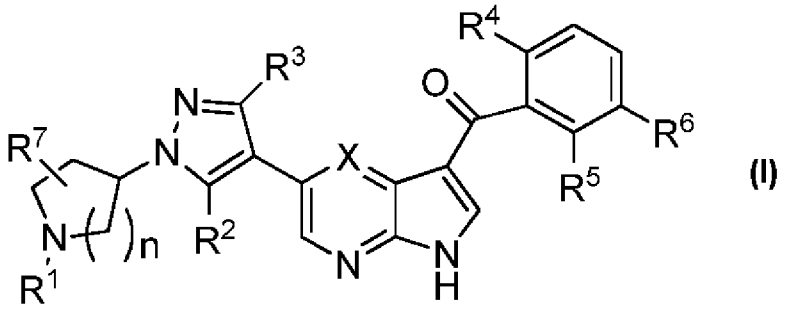


(57) Abstract: The present invention relates to novel heterocyclic compounds of Formula (I) (Formula (I)) which act as inhibitors of kinase and are useful in methods of treating, preventing or inhibiting proliferative diseases including cancer.

HETEROCYCLIC COMPOUNDS AS KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/516,505, filed on April 5, 2011, which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to novel heterocyclic compounds which act as inhibitors of kinase and are useful in methods of treating, preventing or inhibiting proliferative diseases including cancer.

BACKGROUND

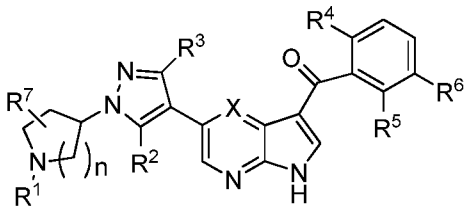
[0003] Protein kinases represent a large family of enzymes, which catalyze the phosphorylation of target protein substrates. The phosphorylation is usually a transfer reaction of a phosphate group from ATP to the protein substrate. Common points of attachment for the phosphate group to the protein substrate include, for example, a tyrosine, serine or threonine residue. Due to their activity in numerous cellular processes, protein kinases have emerged as important therapeutic targets.

[0004] Raf kinases, a family of three serine/threonine kinases, are part of the ras-MAPK signaling cascade and phosphorylate MEK. Upon growth factor stimulation, Raf-1 (or C-Raf) is activated by GTP-bound Ras and recruited to the cell membrane. Raf-1 is also thought to be able to dimerize with wild type B-Raf in a Ras-dependent process. B-raf is commonly mutated and thereby activated in many human cancers, the most frequent mutation being the V600E mutation of the kinase domain. While wild type B-Raf and Raf-1 are strongly activated by growth factor signals via Ras and Src, A-Raf is only modestly activated and has low basal activity. All three isoforms of Raf are considered to be oncogenic.

[0005] To this end, attempts have been made to identify small molecules which act as PK inhibitors. For example, diaryl ureas (WO 2004/113274) have been described as multi tyrosine kinase inhibitors. Substituted diphenylurea (WO 2000/42012) and pyrrolo [2,3-b] pyridine derivatives (WO2007/002325 and WO2007/002433) have been described as Raf kinase inhibitors. There remains a need for novel and efficacious compounds for the treatment of proliferative disorders.

SUMMARY OF THE INVENTION

[0006] In some embodiments of the present invention, there are provided compounds of Formula I:



I

or a pharmaceutically acceptable salt, solvate or a prodrug or a metabolite thereof, wherein

R^1 is hydrogen, or optionally substituted C_{1-8} alkyl;

R^2 and R^3 at each occurrence are independently selected from the group consisting of hydrogen, optionally substituted C_{1-8} alkyl, and CF_3;

R^4 and R^5 at each occurrence are independently selected from the group consisting of hydrogen, halogen, CF_3, and optionally substituted C_{1-8} alkyl;

R^6 is CF_3 or $-NR^8SO_2R^9$;

R^7 is hydrogen or optionally substituted C_{1-8} alkyl;

R^8 is hydrogen or optionally substituted C_{1-8} alkyl;

R^9 is optionally substituted C_{1-8} alkyl;

X is N or CH;

n = 1, 2, or 3.

[0007] In certain embodiments, R^1 is a hydrogen. In certain embodiments, R^1 is a methyl group. In other embodiments, R^1 is an ethyl group. In certain embodiments, R^1 is a propyl group. In other embodiments, R^2 or R^3 is hydrogen. In some embodiments, R^2 or R^3 is trifluoromethyl group. In certain embodiments, R^4 or R^5 is CI. In some embodiments, R^4 or R^5 is F. In some embodiments, R^4 is F and R^5 is CI. In some embodiments, R^6 is an n-propyl sulfonamide. In other embodiments, R^7 is hydrogen. In certain embodiments, R^8 is hydrogen. In some embodiments, R^9 is n-propyl or deutered n-propyl. In some embodiments, X is -CH or nitrogen. In still another embodiment, n is 2. In other embodiments, the compound of Formula I is in the form of pharmaceutically acceptable salt. In certain embodiments, the compound of Formula I is a hydrochloride, or methanesulfonate salt. In some embodiments, the compound of Formula I is in the form of a solvate. In other embodiments, the compound of Formula I is in the form of a metabolite. In other

embodiments, the compound of Formula I is in the form of a prodrug. In some embodiments, the compound of Formula I is an enantiomer. In other embodiments, the compound of Formula I is a diastereomer. In another embodiment, the deuterium enrichment in compounds of Formula I is at least about 1%.

[0008] In certain embodiments, there are provided compounds without limitation selected from the group consisting of:

N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH^yrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;

N-(3-(5-(l-(l-ethylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane- 1-sulfonamide;

N-(2,4-difluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide;

N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)ethanesulfonamide;

N -(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)methanesulfonamide;

N-(2,4-difluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)methanesulfonamide;

N-(4-chloro-2-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;

N-(2-chloro-4-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;

N-(2-chloro-4-fluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide;

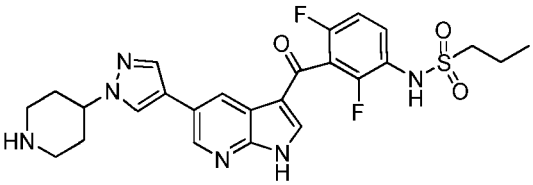
N-(2-chloro-3-(5-(l-(l-ethylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluorophenyl)propane- 1-sulfonamide;

N-(2-chloro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;

N-(2-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;

N-(4-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;

N-(4-chloro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide.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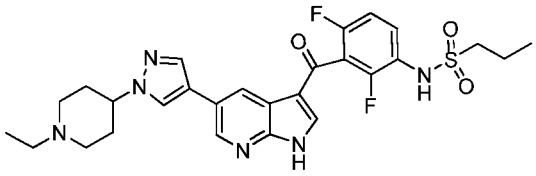
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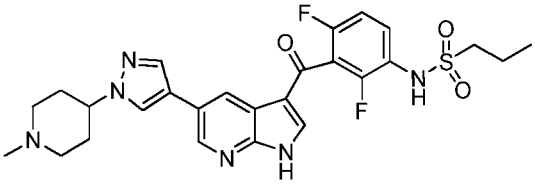
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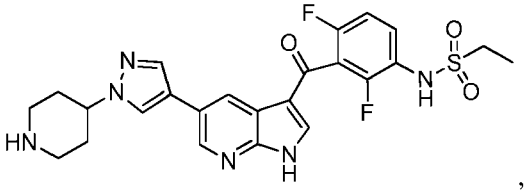
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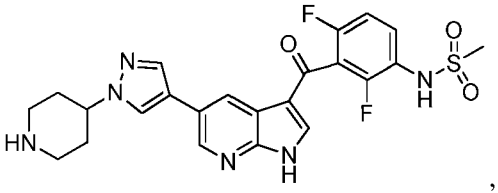
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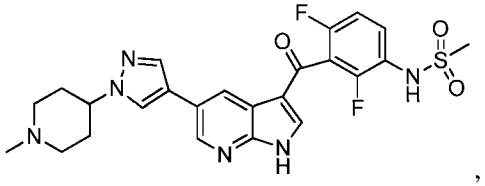
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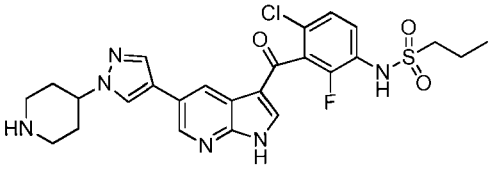
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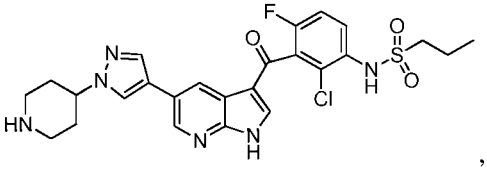
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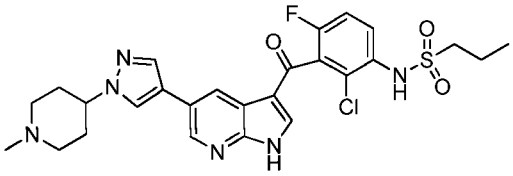
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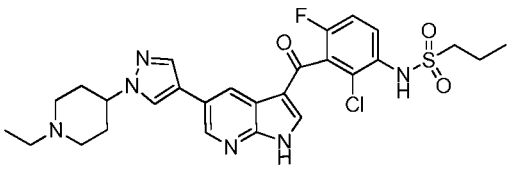
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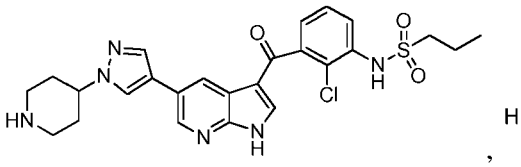
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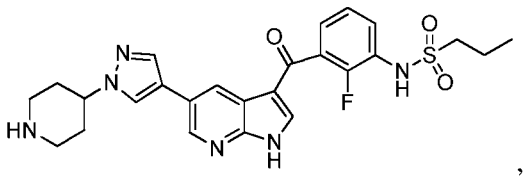
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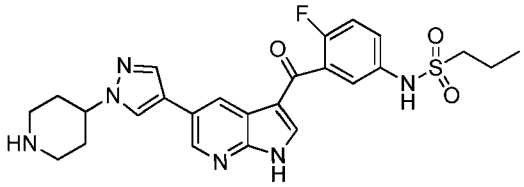
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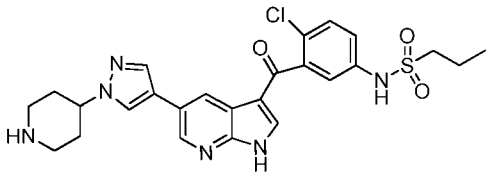

, and the like, or a pharmaceutically acceptable salt, solvate, or a prodrug, or a metabolite thereof. In some embodiments, the selected compound is in the form of a pharmaceutically acceptable salt. In certain embodiments, the selected compound is a hydrochloride, or methanesultonate salt. In some embodiments, the selected compound is in the form of a solvate. In other

embodiments, the selected compound is in the form of a metabolite. In other embodiments, the selected compound is in the form of a prodrug. In some embodiments, the selected compound has isotopic enrichment. In another embodiment, the deuterium enrichment in the selected compounds is at least about 1%.

[0009] In some embodiments, there are provided pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier. In certain embodiments, the compositions are for the treatment of a disease regulated by a protein kinase. In certain embodiments, the compositions are for or the treatment of a hyper-proliferative disorder and/or angiogenesis disorder. In some embodiments, the pharmaceutical compositions further comprise an anti-neoplastic agent, an immunosuppressant, an immunostimulant, or combination thereof. In other embodiments, the pharmaceutical compositions are suitable for oral, parenteral, or intravenous administration.

[0010] In some embodiments, the present invention provides methods for regulating the kinase signaling transduction, said method comprising administrating to a mammalian subject a therapeutically effective amount of a compound of Formula I.

[0011] In other embodiments, there are provided herein methods for treating or preventing a Raf (including all mutant kinases), c-Met, MEK kinases, Alk mediated disorder, said method comprises administrating to a mammalian subject a therapeutically effective amount of a compound of Formula I.

[0012] In yet another aspect, there are provided herein methods for inhibiting both Raf and Met kinases, said methods comprising administrating to a mammalian subject a therapeutically effective amount of a compound of Formula I.

[0013] In yet another aspect, there are provided herein methods for treating or preventing a Raf V600E mutation mediated disorder, said method comprises administrating to a mammalian subject a therapeutically effective amount of a compound of Formula I.

[0014] In other embodiments, there are provided herein methods for treating neoplasia comprising administrating to a mammalian subject in need thereof, a therapeutically effective amount of a compound of Formula I. In certain embodiments, the neoplasia is selected from skin cancer, leukemias, colon carcinoma, renal cell carcinoma, gastrointestinal stromal cancer, solid tumor cancer, myeloma, breast cancer, pancreatic carcinoma, non-small cell lung cancer, non-hodgkin' s lymphoma, hepatocellular carcinoma, thyroid cancer, bladder cancer, colorectal cancer, and prostate cancer. In certain embodiments, the neoplasia is skin cancer. In some embodiments, the methods further comprise administering one or more anti-cancer agents.

[0015] In other embodiments, there are provided methods for treating or preventing a hyper-proliferative and/or angiogenesis, said methods comprising administrating to a mammalian subject a therapeutically effective amount of a compound of Formula I.

DETAILED DESCRIPTION

Definitions

[0016] Optionally substituted alkyl means that each hydrogen in the alkyl group (usually Ci-C_8) is substituted by none, one or more halogen, hydroxyl, Ci-C_6 alkoxy, etc. Alkyl group can be either straight or branched.

[0017] Halogen means fluorine, chlorine, bromine, and iodine.

[0018] The term "isotopic enrichment" as used herein means the isotopic abundance over the natural abundance of a specified isotope. The invention also includes isotopically-labeled compounds of the invention, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as deuterium, and carbon, such as ^{13}C. Certain isotopically-labeled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in *vivo* half-life or reduced dosage requirements; and hence may be preferred in some circumstances.

[0019] The term "comprising" is meant to be open-ended, including the indicated component(s), but not excluding other elements or components.

[0020] The term "pharmaceutically acceptable" when used with reference to a compound of Formula I is intended to refer to a form of the compound that is safe for administration to a subject. For example, a free base, a salt form, a solvate, a hydrate, a prodrug or derivative form of a compound of Formula I, which has been approved for mammalian use, via oral ingestion or any other route of administration, by a governing authority or regulatory agency, such as the Food and Drug Administration (FDA) of the United States, is pharmaceutically acceptable.

[0021] Included in the compounds of Formula I are the pharmaceutically acceptable salt forms of the free-base compounds. The term "pharmaceutically-acceptable salts" embraces salts, commonly used to form alkali metal salts and to form addition salts of free acids or free bases, which have been approved by a regulatory agency. Salts are formed from ionic

associations, charge-charge interactions, covalent bonding, complexation, coordination, etc. The nature of the salt is not critical, provided that it is pharmaceutically acceptable.

[0022] The term "derivative" is broadly construed herein, and intended to encompass any salt of a compound of this invention, any ester of a compound of this invention, or any other compound, which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to modulate a kinase enzyme.

[0023] The term "prodrug", as used herein, denotes a compound which upon administration to a subject or patient is capable of providing (directly or indirectly) a compound of this invention. Examples of prodrugs would include esterified or hydroxylated compounds where the ester or hydroxyl groups would cleave *in vivo*, such as in the gut, to produce a compound according to Formula I. A "pharmaceutically-acceptable prodrug" as used herein, denotes a prodrug, which is pharmaceutically acceptable.

[0024] In some embodiments, the compound(s) of Formula I is used to treat a subject by administering the compound(s) as a pharmaceutical composition. To this end, the compound(s), in one embodiment, is combined with one or more pharmaceutically acceptable excipients, including carriers, diluents or adjuvants, to form a suitable composition, which is described in more detail herein.

[0025] The terms "treat", "treating," "treatment," and "therapy" as used herein refer to therapy, including without limitation, curative therapy, prophylactic therapy, and preventative therapy. Prophylactic treatment generally constitutes either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals.

[0026] The phrase "effective amount" is intended to quantify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies. The effective amount, in one embodiment, is administered in a single dosage form or in multiple dosage forms.

[0027] All synthetic procedures described herein can be carried out under known reaction conditions, advantageously under those described herein, either in the absence or in the presence (usually) of solvents or diluents. The solvents should be inert with respect to, and should be able to dissolve, the starting materials and other reagents used. Solvents should be able to partially or wholly solubilize the reactants in the absence or presence of catalysts, condensing agents or neutralizing agents, for example, ion exchangers, typically cation exchangers, for example, in the H^+ form. The ability of the solvent to allow and/or influence

the progress or rate of the reaction is generally dependant on the type and properties of the solvent(s), the reaction conditions including temperature, pressure, atmospheric conditions such as in an inert atmosphere under argon or nitrogen, and concentration, and of the reactants themselves.

[0028] The invention further encompasses "intermediate" compounds, including structures produced from the synthetic procedures described, whether isolated or not, prior to obtaining the finally desired compound. Structures resulting from carrying out steps from a transient starting material, structures resulting from divergence from the described method(s) at any stage, and structures forming starting materials under the reaction conditions are all "intermediates" included in the invention. Further, structures produced by using starting materials in the form of a reactive derivative or salt, or produced by a compound obtainable by means of the process according to the invention and structures resulting from processing the compounds of the invention in situ are also within the scope of the invention.

[0029] The compounds of this invention in some embodiments also are represented in multiple tautomeric forms. The invention expressly includes all tautomeric forms of the compounds described herein.

[0030] The compounds in one embodiment also occur in cis- or trans- or E- or Z- double bond isomeric forms. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

[0031] These detailed descriptions are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention

Proton NMR Spectra

[0032] Unless otherwise indicated, all ^{1}H NMR spectra were run on a Varian series Mercury 300, 400 MHz instrument or a Bruker series AV300, 400MHz instruments. Where so characterized, all observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated.

BRAF Kinase Essays

[0033] For most assays, kinase-tagged T7 phage strains were prepared in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase, infected with T7 phage and incubated with shaking at 32 °C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases were produced in HEK-293 cells and

subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20% SeaBlock, 0.17x PBS, 0.05% Tween 20, 6 mM DTT). All reactions were performed in polystyrene 96-well plates in a final volume of 0.135 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05% Tween 20, 0.5 µM non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

[0034] For an alternative assay method, the assay was performed using Kinase-Glo® Plus luminescent kinase assay kit (Promega). It measures kinase activity by quantitating the amount of ATP remaining in solution following a kinase reaction. The luminescent signal from the assay is correlated with the amount of ATP present and is inversely correlated with the amount of kinase activity. The compounds were diluted in 10% DMSO and 5 µï of the dilution was added to a 50 µï reaction so that the final concentration of DMSO is 1% in all of reactions. All of the enzymatic reactions were conducted at 30 °C for 40 minutes. The 50 µï reaction mixture contains 40 mM Tris, pH 7.4, 10 mM $MgCl_2$, 0.1 mg/ml BSA, 1 mM DTT, 0.1 mg/ml inactive MEK1 substrate, 10 µM ATP, and BRAF. After the enzymatic reaction, 50 µï of Kinase-Glo® Plus Luminescent kinase assay solution (Promega) was added to each reaction; and after incubating the plate for 5 minutes at room temperature, luminescence signal was measured using a BioTek Synergy 2 microplate reader.

[0035] For an alternative assay method, the assay was performed using the following protocol:

Reagents: Base Reaction buffer; 20 mM Hepes (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3V0_4, 2 mM DTT, 1% DMSO

Reaction Procedure:

1. Prepared indicated substrate in freshly prepared Base Reaction Buffer.
2. Delivered any required cofactors to the substrate solution above.
3. Delivered indicated kinase into the substrate solution and gently mixed.
4. Delivered compounds in DMSO into the kinase reaction mixture.

5. Delivered ^{33}P-ATP (specific activity 0.01 μCi/μï final) into the reaction mixture to initiate the reaction.
6. Incubated kinase reaction for 120 min at room temperature.
7. Reactions were spotted onto P81 ion exchange paper (Whatman # 3698-915).
8. Washed filters extensively in 0.75% phosphoric acid.
9. Compounds were tested in 10-dose IC50 mode with 3-fold serial dilution starting at 10 μM, Reactions were carried out at 10 μM ATP.

A375 Cell Essay

[0036] Cell culture: A375 was purchased from Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (Shanghai, China). The cell was cultured in DMEM(GIBCO) with 10% fetal bovine serum (GIBCO), 1% L-glutamine, 100 U/mL, penicillin G and 100 ^g/mL streptomycin. Cells were incubated at 37°C in a humidified incubator with 5% CO_2.

[0037] WST assay: Inhibition of cell growth was determined by WST assay using Cell Counting Kit-8 (CCK-8) from DOJINDO Molecular Technologies, Inc. Cells were seeded in the 96-well plates and treated with different concentrations of compounds (dilute from 100 μιηοI/L) single for 72 h. Three repeat wells per treatment were required. After adding CCK-8 10 μL to each well of the plate, the plates were incubated at 37°C for 2 h. Then the absorbance at 450 nm was measured using the Spectra Max 190 (Molecular Devices) microplate reader. The tests were repeated once. The results were presented as IC50 of the compound. IC50 was calculated with Graphpad Prism software using nonlinear regression (curve fit) type data analysis.

[0038] Examples 4, 5, 6 have been tested in the kinase BRAF (V600E) assay and all of them having Kd less than 1 nM. Example 14 had IC_{50} less than 0.5 nM in the kinase BRAF (V600E) assay. Example 14 has been tested in the BRAF wild type kinase assay and showed 5 times more potent than PLX4032. Examples 4, 5, 6 and 14 have been tested in the A375 cell assay and all of them having IC50 less than 200 nM.

[0039] Example 4, 5, 6 and 14 are much more soluble than PLX4032 when they were measured in the common media such as PBS, 0.01N HC1 and SIF.

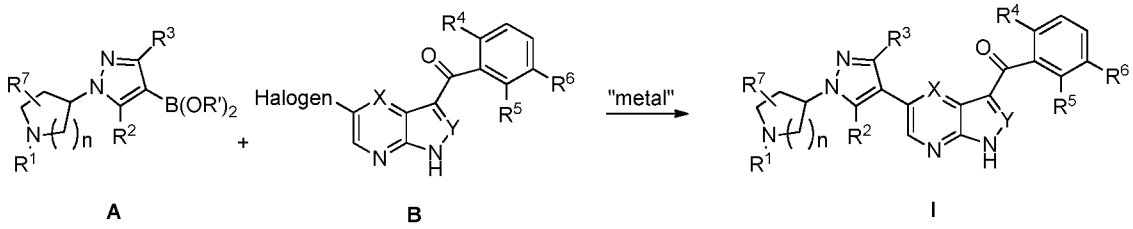
Compounds	Kd against BRAF (V600E)
PLX4032	35 nM
Example 4	0.62 nM
Example 5	0.88 nM
Example 6	0.78 nM

Synthesis of Compounds

[0040] The compounds of Formula I were synthesized according to the procedures described in the following Schemes to those skilled in the art, wherein the substituents are as defined for Formula I above, except where further noted. The synthetic methods described below are merely exemplary, and the compounds of the invention may also be synthesized by alternate routes as appreciated by persons of ordinary skill in the art.

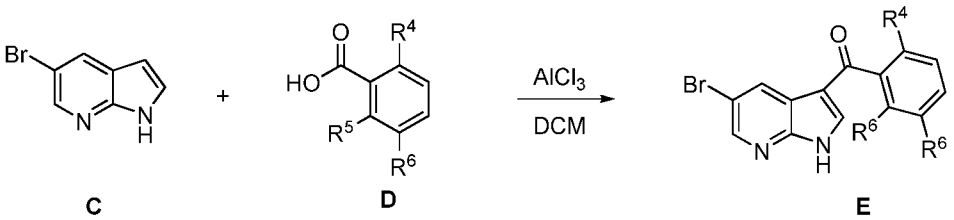
[0041] The syntheses of compounds of Formula I were conducted by transition metal catalyzed reaction as described in **Scheme 1.** The coupling reaction of boronic acid or ester **A** with halides **B** under palladium catalyzed reaction such as Suzuki reaction condition led to the synthesis of compounds of Formula I. The R' group in Scheme 1 is either hydrogen or an alkyl group.

Scheme 1



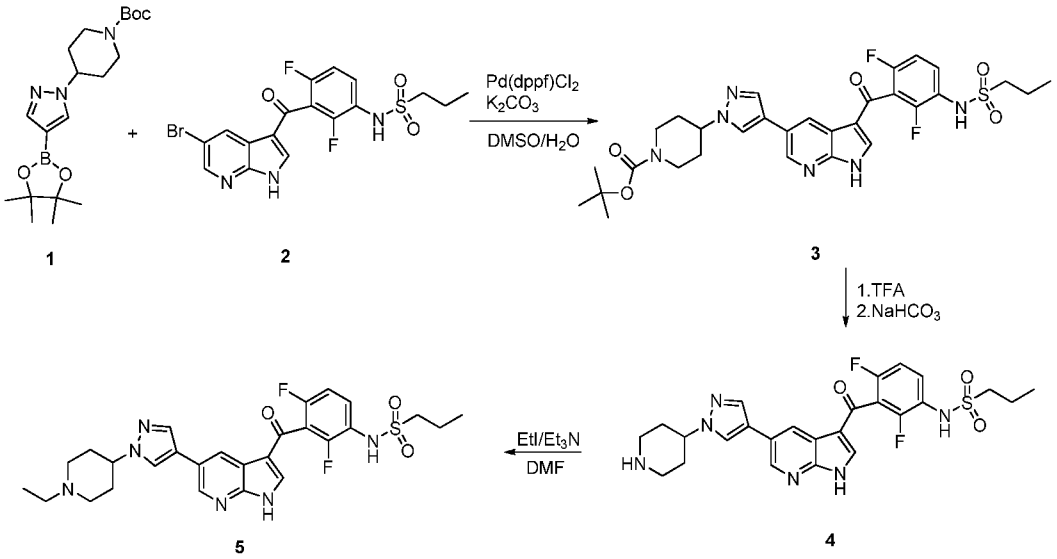
[0042] The preparation of azaindole derived compound **E** was performed according to **Scheme 2.** The Lewis acid mediated acylation reaction of **C** and **D** afforded compound **E,** which further underwent Suzuki coupling reaction to give compounds described in Formula I.

Scheme 2



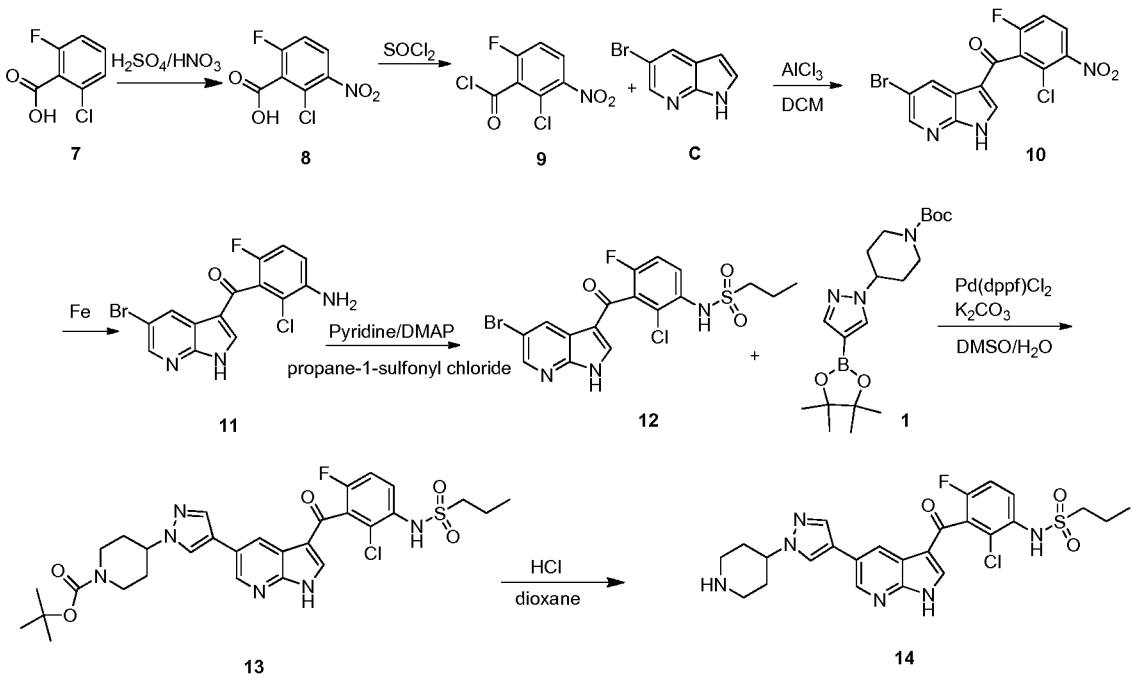
[0043] Preparations of examples 3-5 were described in **Scheme 3**. Syntheses of example 1 (*tert*-butyl 4-(4-(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)- IH-pyrazol- l-yl)piperidine-1-carboxylate, CAS 877399-74-1) and example 2 (N-(3-(5-bromo-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-l-sulfonamide , CAS 918504-27-5) have been reported in the literature and both are commercial available.

Scheme 3

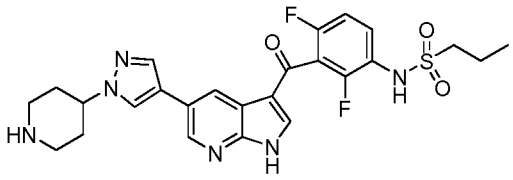


The syntheses of examples 7 to 14 were described in **Scheme 4**.

Scheme 4



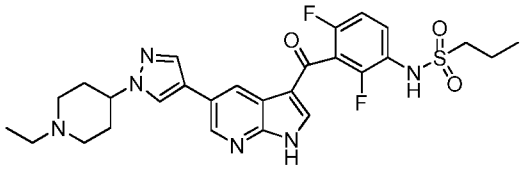
[0044] Example 4. Preparation of N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-1H-pyrrolo\2,3-b]pyridine-3-carbonyl)phenyl)propane-1-sulfonamide.



[0045] Step 1: Preparation of *tert*-butyl 4-(4-(3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-lH-pyrrolo[2,3-b]pyridin-5-yl)-lH-pyrazol-l-yl)piperidine-l-carboxylate. A mixture of *tert*-butyl 4-(4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-lH-pyrazol-l-yl)piperidine-l-carboxylate (360 mg, 0.95 mmol, 1.8 eq), and N-(3-(5-bromo-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-l-sulfonamide (236 mg, 0.52 mmol, 1.0 eq), and K_2CO_3 (351 mg, 2.5 mmol, 4.9 eq) under a nitrogen atmosphere was treated with DMSO (20 mL), water (8 mL), and $Pd(dppf)Cl_2$ (37 mg, 0.051 mmol, 0.1 eq). The mixture was purged with bubbling nitrogen for 2 minutes, and then stirred at 100 °C overnight. The reaction was cooled to room temperature, poured into water (100 mL), and extracted with ethyl acetate (6 x 50mL). The combined organic layers were washed with brine, dried over ($MgS0_4$), filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel to give the product *tert*-butyl 4-(4-(3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-l-carboxylate (220 mg).

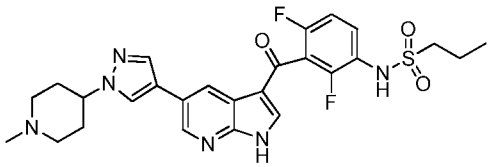
[0046] Step 2: To a solution of *tert*-butyl 4-(4-(3-(2,6-difluoro-3-(propylsulfonamido)benzoyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (420 mg, 0.67 mmol, 1.0 eq) in DCM (15 mL) was added TFA (4 mL). The reaction mixture was stirred at room temperature overnight. TLC indicated the consumption of starting material. The pH of the reaction mixture was adjusted to 8 by saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (8 x 20 mL), the combined organic layers were washed with brine, dried (MgS04), filtered, and concentrated. The crude product was purified by column chromatography on silica gel to give the desired compound N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide. ^-NMR (400MHz, DMSO-d_6, ppm): 8.68 (1H, S), 8.54 (1H, br), 8.34 (1H, S), 8.09 (1H, S), 7.98 (1H, S), 7.55-7.51, (1H, m), 7.18 (1H, t, J = 8.4 Hz), 4.30-4.27 (1H, m), 3.16-3.13 (2H, m), 3.05-3.01 (2H, m), 2.72 (2H, t, J = 12 Hz), 2.08-2.05 (2H, m), 1.96-1.90 (2H, m), 1.75-1.69 (2H, m), 0.97 (3H, t, J = 7.2 Hz). MS ***m/z*** 530 [M+l].

[0047] Example 5. Preparation of N-(3-(5-(l-(l-ethylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolor2,3-b1pyridine-3-carbonyl)-2,4-difluorophenyl)propane-l -sulfonamide.



To a solution of N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide (150 mg, 0.28 mmol, 1.0 eq) and Et_3N(86 mg, 0.85 mmol, 3.0 eq) in DMF (3 mL) was added Etl (66 mg, 0.42 mmol, 1.5 eq). The reaction mixture was stirred at room tem$_p$erature overnight. TLC indicated the consumption of starting material and the reaction was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (8 x20 mL), the combined organic layers were washed with brine, dried over ($MgS0_4$), filtered, and concentrated. The crude product was purified by column chromatography on silica gel to give the product N-(3-(5-(l-(l-ethylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-l -sulfonamide. ^{1}H-NMR (400MHz, DMSO-d_6, ppm): 8.69 (IH, S), 8.56 (IH, br), 8.42 (IH, S), 8.14 (IH, S), 7.98 (IH, S), 7.59-7.57, (IH, m), 7.30-7.28 (IH, m), 4.20 (IH, m), 3.14-3.10 (2H, m), 3.04-3.02 (2H, m), 2.50-2.43 (2H, m), 2.14-2.05 (6H, m), 1.77-1.71 (2H, m), 1.05 (3H, t, J = 7.2 Hz), 0.96 (3H, t, J = 7.2 Hz). MS ***m/z*** 558 [M+l]

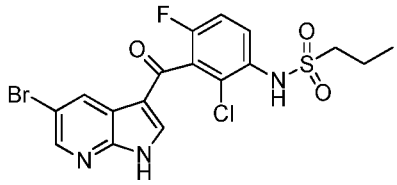
[0048] Example 6. Preparation of N-(2,4-difluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolor2,3-b1pyridine-3-carbonyl)phenyl)propane-l-sulfonamide



To a solution of N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l -sulfonamide (150 mg, 0.28 mmol, 1.0 eq) and]¾4N (86 mg, 0.85 mmol, 3.0 eq) in DMF (3 mL) was added Mel (66 mg, 0.42 mmol, 1.5 eq). The reaction mixture was stirred at room temperature overnight. TLC indicated the consumption of starting material and the reaction was quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (8 x 20 mL), the combined organic layers were washed with brine, dried (MgS04), filtered, and concentrated. The crude product was purified by column

chromatography on silica gel to give the desired product (50 mg). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm): 12.86 (brs, 1H), 9.76 (brs, 1H), 8.69 (d, *J* = 1.5 Hz, 1H), 8.56 (brs, 1H), 8.42 (s, 1H), 8.14 (s, 1H), 7.98 (s, 1H), 7.58 (t, *J* = 5.9 Hz, 1H), 7.18 (t, *J* = 6.3 Hz, 1H), 4.20 (m, 1H), 3.38 (m, 2H),3.12 (m, 2H), 2.96 (m, 2H), 2.28 (s, 3H), 2.14 (m, 2H), 2.06 (m, 2H), 1.85 (m, 2H), 0.96 (t, *J* = 5.6 Hz, 3H). MS *m/z* 544 [M+l].

[0049] Example 12. N-(3-(5-bromo-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-chloro-4 -fluorophenyl)propane- 1-sulfonamide.



[0050] Stepl. 2-Chloro-6-fluoro-3-nitrobenzoic acid. To a 50 mL single-neck round-bottom flask 2-chloro-6-fluorobenzoic acid(3.0 g, 17.1 mmol, l.Oeq) was added to H_2SO_4 (30 g) at 0 °C under an atmosphere of nitrogen and stirred for 1 hour. Then HNO_3 (1.90 g, 20.6 mmol, 1.2 eq) was added dropwise to the reaction mixture. The resulting mixture was stirred for 1 hour. The reaction mixture was poured into water (200 mL) and extracted with ethyl acetate (50 mL x 3). The organic layers were combined, dried over anhydrous sodium sulfate, filtrated and concentrated to give 2-chloro-6-fluoro-3-nitrobenzoic acid (3.1 g) as a solid. Yield: 82.2%.

[0051] Step 2. 2-Chloro-6-fluoro-3-nitrobenzoyl chloride. To 2-chloro-6-fluoro-3-nitrobenzoic acid (2.0 g) was added sulfurous dichloride (10 mL) at rt. The reaction mixture was heated to reflux and stirred for 2 hours. Then sulfurous dichloride was removed under vacuum. The product example 9 was used in the next step without further purification.

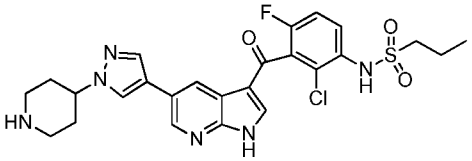
[0052] Step 3. (5-Bromo-lH-pyrrolo[2,3-b]pyridin-3-yl)-(2-chloro-6-fluoro-3-nitrophenyl)methanone. To aluminum trichloride (6.8 g, 51.4 mmol, 5.7 eq) was added methylene chloride (50 mL) under an atmosphere of nitrogen below 5 °C. Into this, 5-bromo -7-azaindole (1.27 g, 6.4 mmol, 0.71 eq) in methylene chloride (20 mL) was added. The reaction mixture was stirred for 1 hour and 2-chloro-6-fluoro-3-nitrobenzoyl chloride in methylene chloride (30 mL) was added. The reaction mixture was stirred for 6 hours and warmed to room temperature overnight. The reaction mixture was poured into water (500 mL) and extracted with ethyl acetate (150 mL x 3). Combined organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated, and the desired crude product was

purified by silica gel column chromatography to give (5-bromo-lH-pyrrolo[2,3-b]pyridin-3-yl)-(2-chloro-6-fluoro-3-nitrophenyl)methanone (2.0 g) as a yellow solid.

[0053] Step 4. (3-Amino-2-chloro-6-fluorophenyl)(5-bromo-lH-pyrrolo[2,3-b]pyridin-3-yl)methanone. (5-Bromo-lH-pyrrolo[2,3-b]pyridin-3-yl)(2-chloro-6-fluoro-3-nitrophenyl)methanone (1.6 g), Fe (896 mg), ethanol (10 ml), water (10 ml) and acetic acid (5 ml) were charged into a 50 ml single-neck round-bottom flask. The reaction mixture was heated to reflux and stirred for 2 hours. Then the reaction mixture was cooled to rt. The mixture was poured into water (50 ml) and extracted with ethyl acetate/THF (50 ml x 3, 1:1). Combined organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated. The desired crude product was purified by silica gel column chromatography to give (3-amino-2-chloro-6-fluorophenyl)(5-bromo-lH-pyrrolo[2,3-b]pyridin-3-yl)methanone (l.Og).

[0054] Step 5. Propane 1-sulfonylchloride was added dropwise (1 mL) to a solution of (3-amino-2-chloro-6-fluorophenyl)(5-bromo-lH-pyrrolo[2,3-b]pyridin-3-yl)methanone (l.Og), pyridine (3 ml), and DMAP (20 mg,) in anhydrous dichloromethane/THF (10/5 mL) at room temperature. Upon completion of the addition, the reaction mixture was refluxed overnight and evaporated *in vacuum.* The crude residue was dissolved in ethyl acetate (200 mL), washed with water (2 xlOO mL) and brine (100 mL), dried over sodium sulfate and the crude product was purified by column chromatography to give the desired compound (500 mg) as a white solid. ^{1}H-NMR (300 MHz, DMSO-d6, ppm): δ 13.10 (s, 1H), 9.63 (s, 1H), 8.51 (br, 2H), 8.20 (s, 1H), 7.66-7.61 (m, 1H), 7.43 (t, *J* = 8.7 Hz, 1H), 3.15 (t, *J* = 7.8Hz, 2H), 1.81-1.73 (m, 2H), 0.97 (t, *J* = 8.7 Hz, 3H).

[0055] Example 14. The preparation of N-(2-chloro-4-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide.



[0056] Step 1. The preparation of ieri-butyl4-(4-(3-(2-chloro-6-fluoro-3-(propylsulfonamido)benzoyl) -lH-pyrrolo[2,3-b] pyridin-5-yl)-lH-pyrazol-l-yl)piperidine-l-carboxylate. A mixture of *tert*-butyl 4-(4,5-dihydro-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan -2-yl) pyrazol-l-yl)piperidine-l-carboxylate (592 mg, 1.57 mmol, 1.5 eq), N-

(3-(5-bromo-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2-chloro-4-fluorophenyl)propane-l-sulfonamide (500 mg, 1.05 mmol, 1.0 eq), and K_2C(¾ (724 mg, 5.25 mmol, 5.0 eq) under a nitrogen atmosphere was treated with DMSO (10 mL), water (5 mL), and Pd(dppf)Cl_2 (40 mg, 8% wt). The mixture was purged with bubbling nitrogen for 2 min, and then stirred at 100 °C overnight, cooled to room temperature, poured into water (100 mL), and extracted with ethyl acetate (6 x 50mL), and the combined organic layers were washed with brine, dried (MgS04), filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel to give the desired product (500 mg).

[0057] Step 2. ieri-Butyl4-(4-(3-(2-chloro-6-fluoro-3-(propylsulfonamido)benzoyl)-lH-pyrrolo[2,3-b] pyridin-5-yl)-lH-pyrazol-l-yl)piperidine-l-carboxylate (500 mg) was dissolved with THF (5 ml). Then 15 ml saturated solution of 1,4-dioxane (HCl) was added to the reaction solution. The reaction mixture was stirred for 4 hours at rt. The solvent was removed under vacuum to give the desired product (400 mg). ^{1}H-NMR (300 MHz, DMSO-d6, ppm): 9.64 (s, IH), 9.24 (s, IH), 8.99 (s, IH), 8.71 (s, IH), 8.57 (s, IH), 8.40 (s, IH), 8.05 (d, J = 5.9 Hz, 2H), 7.64 (m, IH), 7.43 (t, J = 8.6 Hz, IH) 4.54 (m, IH), 3.39 (m, 2H),3.14 (m, 4H), 2.24 (m, 4H), 1.77 (m, 2H), 0.97 (t, J = 8.7 Hz, 3H). MS *m/z* 546 [M+l].

Indication

[0058] The present invention provides compounds which are capable of modulating one or more signal transduction pathways comprising, but not limited to Raf kinase.

[0059] By the term "modulate," it is meant that the functional activity of the pathway (or a component thereof) is changed in comparison to its normal activity in the absence of the compound. This effect includes any quality or degree of modulation, including, increasing, agonizing, augmenting, enhancing, facilitating, stimulating, decreasing, blocking, inhibiting, reducing, diminishing, and antagonizing, etc.

[0060] The compounds of the present invention can also modulate one or more of the following processes, including, but not limited to, *e.g.,* cell growth (including, *e.g.,* differentiation, cell survival, and/or proliferation), tumor cell growth (including, *e.g.,* differentiation, cell survival, and/or proliferation), tumor regression, endothelial cell growth (including, *e.g.,* differentiation, cell survival, and/or proliferation), angiogenesis (blood vessel growth), lymphangiogenesis (lymphatic vessel growth), and/or hematopoiesis {*e.g.,* T- and B-cell development, dendritic cell development, etc.).

[0061] While not wishing to be bound by any theory or mechanism of action, it has been found that compounds of the present invention possess the ability to modulate kinase activity.

The methods of the present invention, however, are not limited to any particular mechanism or how the compounds achieve their therapeutic effects. By the phrase "kinase activity," it is meant a catalytic activity in which a gamma-phosphate from adenosine triphosphate (ATP) is transferred to an amino acid residue *(e.g.,* serine, threonine, or tyrosine) in a protein substrate. A compound can modulate kinase activity, *e.g.,* inhibiting it by directly competing with ATP for the ATP-binding pocket of the kinase, by producing a conformational change in the enzyme's structure that affects its activity *(e.g.,* by disrupting the biologically-active three-dimensional structure), and by binding to and locking the kinase in an inactive conformation, etc.

Formulations and Method of Use

[0062] Treatment of diseases and disorders herein is intended to also include therapeutic administration of a compound of the invention, or a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject *(i.e.,* an animal, preferably a mammal, most preferably a human) which may be in need of preventative treatment, such as, for example, for pain, inflammation and the like. Treatment also encompasses prophylactic administration of a compound of the invention, or a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject *(i.e.,* an animal, preferably a mammal, most preferably a human). Generally, the subject is initially diagnosed by a licensed physician and/or authorized medical practitioner, and a regimen for prophylactic and/or therapeutic treatment via administration of the compound(s) or compositions of the invention is suggested, recommended or prescribed.

[0063] The amount of compound(s) which is/are administered and the dosage regimen for treating cancer with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, advantageously between about 0.01 and about 50 mg/kg, more advantageously about 0.01 and about 30 mg/kg, even more advantageously between about 0.1 and about 10 mg/kg, and even more advantageously between about 0.25 and about 1 mg/kg body weight may be appropriate, and should be useful for all methods of use disclosed herein. The daily dose can be administered in one to four doses per day.

[0064] While it may be possible to administer a compound of the invention alone, in the methods described, the compound administered normally will be present as an active ingredient in a pharmaceutical composition. Thus, in another embodiment of the invention, there is provided a pharmaceutical composition comprising a compound of this invention in combination with a pharmaceutically acceptable carrier, which includes diluents, excipients, adjuvants and the like (collectively referred to herein as "carrier" materials) as described herein, and, if desired, other active ingredients. A pharmaceutical composition of the invention may comprise an effective amount of a compound of the invention or an effective dosage amount of a compound of the invention. An effective dosage amount of a compound of the invention includes an amount less than, equal to or greater than an effective amount of the compound; for example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are required to administer an effective amount of the compound, or alternatively, a multi-dose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the compound is administered by administering a portion of the composition.

Routes of Administration

[0065] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[0066] The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nanoparticulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

[0067] Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be used as fillers in soft or hard capsules and typically include a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

[0068] The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, **11** (6), 981-986 by Liang and Chen (2001), the disclosure of which is incorporated herein by reference in its entirety.

[0069] For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

[0070] Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate. Tablets may also optionally include surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents are 30 typically in amounts of from 0.2 wt% to 5 wt% of the tablet, and glidants typically from 0.2 wt% to 1 wt% of the tablet.

[0071] Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally are present in amounts from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

[0072] Other conventional ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

[0073] Exemplary tablets contain up to about 80 wt% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

[0074] The final formulation may include one or more layers and may be coated or uncoated; or encapsulated. The formulation of tablets is discussed in detail in "Pharmaceutical Dosage Forms: Tablets, Vol. I", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X), the disclosure of which is incorporated herein by reference in its entirety.

[0075] Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

[0076] Suitable modified release formulations are described in U.S. Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles can be found in Verma et al., Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The disclosures of these references are incorporated herein by reference in their entireties.

[0077] **Parenteral Administration**

[0078] The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including micro needle) injectors, needle-free injectors and infusion techniques. Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water. The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

[0079] The solubility of compounds of the invention used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility enhancing agents.

[0080] Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

Combinations

[0081] While the compounds of the invention can be dosed or administered as the sole active pharmaceutical agent, they can also be used in combination with one or more

compounds of the invention or in conjunction with other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered simultaneously or sequentially at different times, or the therapeutic agents can be given as a single composition.

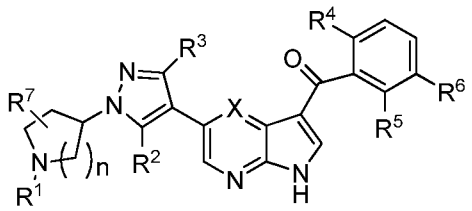
[0082] In some embodiments, methods for treatment of kinases mediated conditions or diseases, such as proliferative disorders, including cancer, comprises administration to a mammal a compound of Formula I in combination with at least one additional agent selected, by way of example only, alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

[0083] Specifically, the administration of compounds of the present invention in some embodiments are in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of cancer. The foregoing description is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, compositions and methods.

CLAIMS

What is claimed is:

1. A compound according to the Formula I:



I

or a pharmaceutically acceptable salt, solvate or a prodrug or a metabolite thereof, wherein

R^1 is hydrogen, or optionally substituted C_{1-8} alkyl;

R^2 and R^3 at each occurrence are independently selected from the group consisting of hydrogen, optionally substituted C_{1-8} alkyl, and CF_3;

R^4 and R^5 at each occurrence are independently selected from the group consisting of hydrogen, halogen, CF_3, and optionally substituted C_{1-8} alkyl;

R^6 is CF_3 or $-NR^8SO_2R^9$;

R^7 is hydrogen or optionally substituted C_{1-8} alkyl;

R^8 is hydrogen or optionally substituted C_{1-8} alkyl;

R^9 is optionally substituted C_{1-8} alkyl;

X is N or CH; and

n = 1, 2, or 3.

2. The compound of claim 1, wherein R^1 is selected from the group consisting of hydrogen, methyl, and ethyl.

3. The compound of claim 1, wherein R^2 is hydrogen.

4. The compound of claim 1, wherein R^3 is hydrogen.

5. The compound of claim 1, wherein R^4 and R^5 at each occurrence are independently selected from F and CI.

6. The compound of claim 1, wherein R^6 is n-propyl sulfonamide.

7. The compound of claim 1, wherein n is 2 and X is CH.

8. A compound or its pharmaceutically acceptable salt, or solvate thereof selected from the group consisting of:
N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;
N-(3-(5-(l-(l-ethylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane- 1-sulfonamide;
N-(2,4-difluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide;
N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)ethanesulfonamide;
N-(2,4-difluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)methanesulfonamide;
N-(2,4-difluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)methanesulfonamide;
N-(4-chloro-2-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide;
N-(2-chloro-4-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide;
N-(2-chloro-4-fluoro-3-(5-(l-(l-methylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane-l-sulfonamide;
N-(2-chloro-3-(5-(l-(l-ethylpiperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)-4-fluorophenyl)propane- 1-sulfonamide;
N-(2-chloro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;
N-(2-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide;
N-(4-fluoro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide; and
N-(4-chloro-3-(5-(l-(piperidin-4-yl)-lH-pyrazol-4-yl)-lH-pyrrolo[2,3-b]pyridine-3-carbonyl)phenyl)propane- 1-sulfonamide.

9. The compound of any of the preceding claims, wherein said compound is a hydrochloride, or methanesulfonate salt.

10. A pharmaceutical composition comprising a compound of any of the preceding claims and a pharmaceutically acceptable carrier.

11. The compound of any one of claims 1 to 9, or the pharmaceutical composition of claim 10, for use in therapy.

12. The compound of any one of claims 1 to 9, or the pharmaceutical composition of claim 10, for the treatment or prevention of a hyper-proliferative disorder.

13. The pharmaceutical composition of claim 10, further comprising an anti-neoplastic agent, an immunosuppressant, an immunostimulant, or combinations thereof.

14. A compound of claim 1 to 9 for regulating the kinase signaling transduction.

15. A compound of claim 1 to 9 for treating or preventing a Braf kinases mediated disorder.

16. A compound of claim 1 to 9 for treating neoplasia.

17. A compound of claim 1 to 9 and one or more anti-cancer agents for use in combination for treating neoplasia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32236

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/56; A61K 31/415 (2012.01)
USPC - 514/405-406
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)
USPC: 514/405-406

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/403, 408, 410 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DialogClassic: (Keywords: Pyrrolopyrazine kinase, inhibitors, neoplasia, anti-cancer, proliferative disorder, signaling, transduc?, Piperidin pyrrolo pyridine carbonyl phenyl, kinase, Pyrrolopyrazine derivative)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0286142 A1 (Ibrahim et al.) 11 November 2010 (11.11.2010) para [0005], [0007]-[0008], [0010], [0012], [0116], [0124], [0409], [0413], [0416]-[0417], [0420], [0425], [0430], [0478], [0480]-[0481], [0483]-[0484], [488], [0505], [0511]-[0513]; Table 1, compound P-2174	1-9
Y	US 2009/0118305 A1 (Bariaam et al.) 07 May 2009 (07.05.2009) especially para [0826]	1-9
A	US 2009/0215788 A1 (Elworthy et al.) 27 August 2009 (27.08.2009) para [0017], [0019], [0021]-[0022], [0037], [0040H0041], [0044]-[0045]; Table I, compound I-25	1-9
A	US 7,253,170 B2 (Dyckman et al.) 7 August 2007 (07.08.2007) col 14, ln 65; col 15, ln 11-17	1-9
Y	US 2011/0059963 A1 (Ibrahim et al.) 10 March 2011 (10.03.2011) especially pg 124, table	1-9
P/A	US 2011/0183988 A1 (Ibrahim et al.) 28 July 2011 (28.07.2011) entire document	1-9
A	US 7,902,197 B2 (Elworthy et al.) 08 March 2011 (08.03.2011) entire document	1-9
A	US 2010/0310659 A1 (Desai et al.) 09 December 2010 (09.12.2010) entire document	1-9
A	US 2009/0298820 A1 (Tsou et al.) 03 December 2009 (03.12.2009) entire document	

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
22 June 2012 (22.06.2012)	27 JUL 2012
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/32236

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.: 10-17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. Ill 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:

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.:

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.