PYRROLO[2,3-B]PYRIDINE DERIVATIVES AS KINASE MODULATORS

RELATED PATENT APPLICATIONS

[0001] This application claims priority to U.S. Provisional App. No. 60/876,953, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor", filed December 21, 2006, and is related to U.S. Patent App. No. 11/473,347, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor", filed June 21, 2006, which claims the benefit of U.S. Provisional App. No. 60/731,528, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor", filed October 28, 2005, and U.S. Provisional App. No. 60/692,960, entitled "Compounds and Methods for Kinase Modulation, and Indications Therefor", filed June 22, 2005, all of which are incorporated herein by reference in their entireties and for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates to kinases and compounds which modulate kinases, and uses therefor. Particular embodiments contemplate disease indications which are amenable to treatment by modulation of kinase activity by the compounds of the present invention.

BACKGROUND OF THE INVENTION

[0003] The information provided herein is intended solely to assist the understanding of the reader. None of the information provided nor references cited is admitted to be prior art to the present invention. Each of the references cited herein is incorporated herein by reference in its entirety.

[0004] Receptor protein kinases regulate key signal transduction cascades that control or are involved in the control of a plethora of physiological functions including cellular growth and proliferation, cell differentiation, cellular development, cell division, cell adhesion, stress response, short-range contact-mediated axonal guidance, transcription regulation, aberrant mitogenesis, angiogenesis, abnormal endothelial cell-cell or cell-matrix interactions during vascular development, inflammation, lymphohematopoictic stem cell activity, protective immunity against specific bacteria, allergic asthma, aberrant tissue-specific responses to the activation of the JNK signal transduction pathway, cell transformation, memory, apoptosis, competitive activity-dependent synapse modification at the neuromuscular synapse, immunological mediation of disease, and calcium regulation.

[0005] Specific disease states associated with aberrant regulation of protein kinases include, for example without limitation, acrocephalo-syndactyly type I, acute myeloid leukemia, AIDS-induced

non-Hodgkin's lymphoma, Alzheimer's disease, amyotrophic lateral sclerosis, arthritis, asthma, atherosclerosis, atopic dermatitis, autoimmune diseases, bacterial infection, bladder cancer, cancer of the breast, cancer of the central nervous system, cancer of the colon, cancer of the endometrium, cancer of the fallopian tube, cancer of the gastrointestinal tract, cancer of the ovary, heart failure, chronic myeloid leukemia, colon carcinoma, colorectal cancer, chronic obstructive pulmonary disease (COPD), Crouzon Syndrome, diabetes, diabetic nephropathy, emphysema, endometriosis, epidermoid cancer, fibrotic disorders, gastrointestinal stromal tumor (GIST), glomerulonephritis, Graves' disease, head injury, hepatocellular carcinoma, Hirschsprung's disease, human gliomas, immunodeficiency diseases, inflammatory disorders, ischemic stroke, Jackson-Weiss syndrome, leiomyosarcoma, leukemias, lupus nephritis, malignant melanoma, malignant nephrosclerosis, mastocytosis, mast cell tumors, melanoma of the colon, MEN2 syndromes, metabolic disorders, migraine, multiple sclerosis, myeloproliferative disorders, nephritis, neurodegenerative diseases, neurotraumatic diseases, non small cell lung cancer, organ transplant rejection, osteoporosis, pain, Parkinson's disease, Pfeiffer Syndrome, polycystic kidney disease, primary lymphoedema, prostate cancer, psoriasis, vascular restenosis, rheumatoid arthritis, dermal and tissue scarring, selective T-cell defect (STD), severe combined immunodeficiency (SCID), small cell lung cancer, spinal cord injury, squamous cell carcinoma, systemic lupus erythematosis, testicular cancer, thrombotic microangiopathy syndromes, Wegener's granulomatosis, X-linked agammaglobulinemia, viral infection, diabetic retinopathy, alopecia, erectile dysfunction, macular degeneration, chronic lymphocytic leukemia (CLL), myelodysplastic syndrome (MDS), neurofibromatosis, and tuberous sclerosis.

[0006] This application is related to the following published patent applications: WO 2004024895, US 20040142864, WO 2004078923, US 20050170431, WO 2005028624, US 20050164300, and WO 2005062795, each of which are hereby incorporated by reference herein in their entireties including all specifications, figures, and tables, and for all purposes.

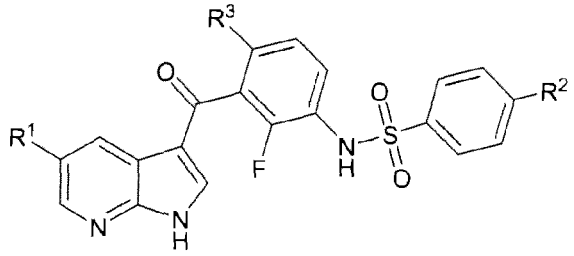
SUMMARY OF THE INVENTION

[0007] Compounds are contemplated that are active on protein kinases in general, including, but not limited to, Abl, Akt1, Akt2, Akt3, ALK, Alk5, A-Raf, B-Raf, Brk, Btk, Cdk2, CDK4, CDK5, CDK6, CHK1, c-Raf-1, Csk, EGFR, EphA1, EphA2, EphB2, EphB4, Erk2, Fak, FGFR1, FGFR2, FGFR3, FGFR4, Flt1, Flt3, Flt4, Fms, Frk, Fyn, Gsk3α, Gsk3β, HCK, Her2/Erbb2, Her4/Erbb4, IGF1R, IKK beta, Irak4, Itk, Jak1, Jak2, Jak3, Jnk1, Jnk2, Jnk3, Kdr, Kit, Lck, Lyn, MAP2K1, MAP2K2, MAP4K4, MAPKAPK2, Met, Mnk1, MLK1, p38, PDGFRA, PDGFRB, PDPK1, Pim1, Pim2, Pim3, PKC alpha, PKC beta, PKC theta, Plk1, Pyk2, Ret, ROCK1, ROCK2, Ron, Src, Stk6, Syk, TEC, Tie2, TrkA, TrkB, Yes, and/or Zap70, including any mutations of these kinases. In some aspects, the compounds are active on protein kinases including A-Raf, B-Raf and/or c-Raf-1, including any mutations thereof. In some aspects, compounds are of Formula I, Formula II, or Formula III, as

described below.

[0008] Also contemplated in accordance with the present invention are methods for the use of the above-described compounds in treating diseases and conditions associated with regulation of the activity of the above-described kinases. Thus, the use of compounds for therapeutic methods involving modulation of protein kinases are provided, as well as compounds that can be used for therapeutic methods involving modulation of protein kinases.

[0009] In some embodiments, compounds have the structure according to the following Formula I:



Formula I

all salts, prodrugs, tautomers and isomers thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from fluoro, -OH, $-NH_2$, $-C(O)OH$, $-C(O)NH_2$, $-OR^7$, $-NR^8R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^2 is selected from the group consisting of halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$,

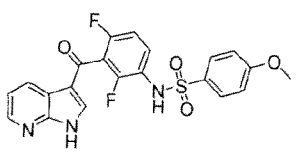
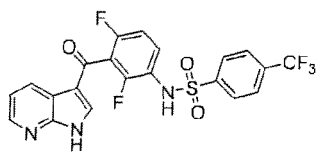
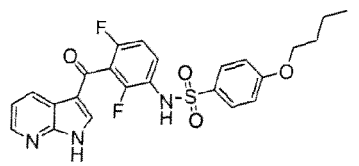
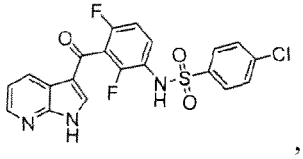
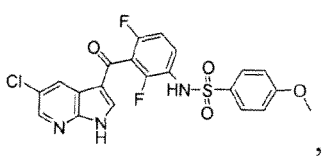
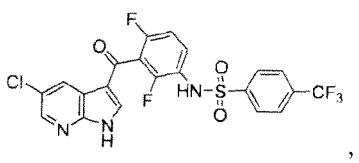
$-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl is optionally substituted with one or more substituents selected from fluoro, $-OR^7$, $-NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^2 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^3 is selected from the group consisting of hydrogen, fluoro and chloro;

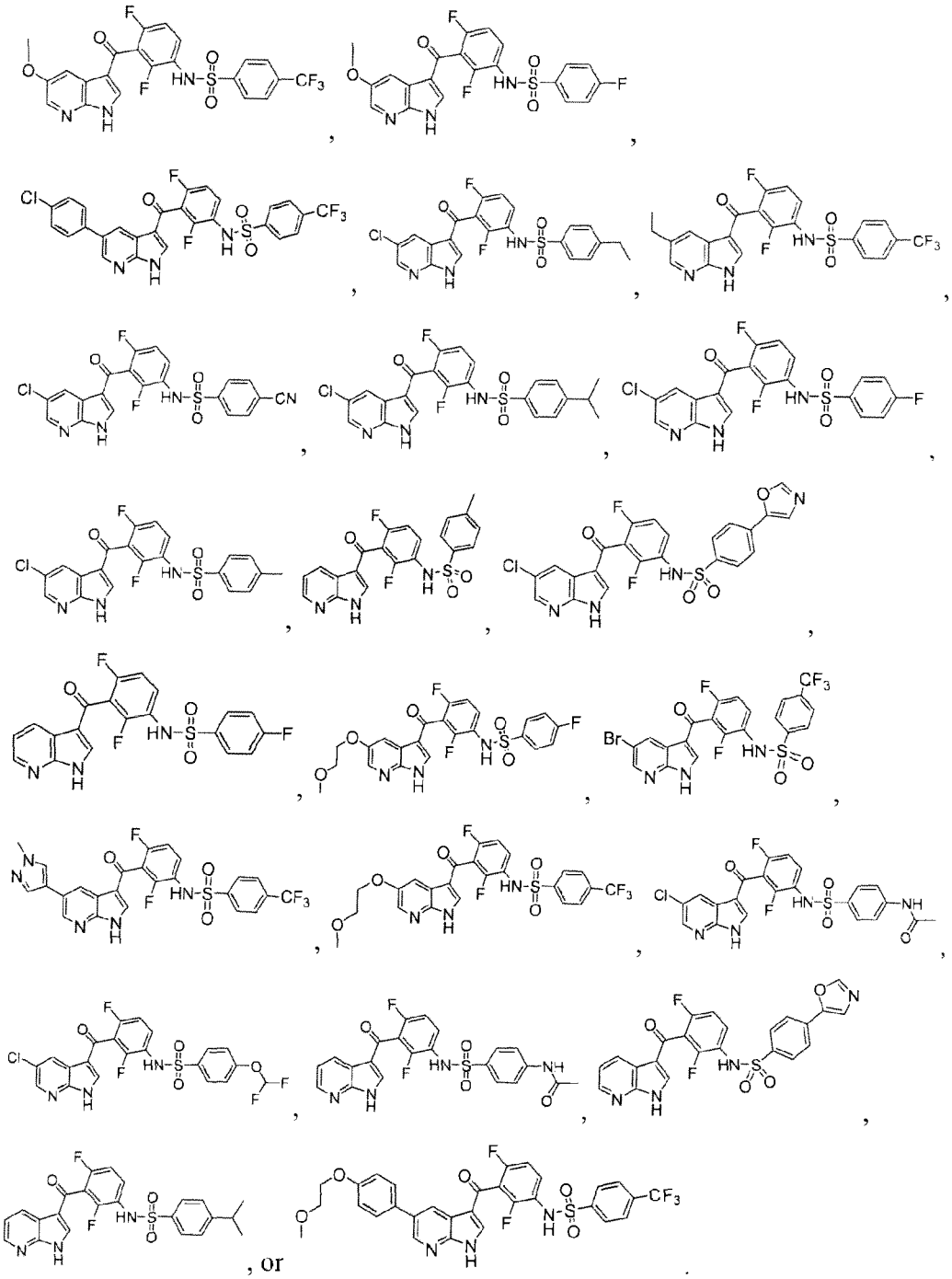
R^7 is selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^7 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^8 at each occurrence is independently hydrogen or lower alkyl; and

R^9 at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy, provided, however, the compound is not


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[0010] In some embodiments of compounds of Formula I, R^1 is selected from the group consisting of hydrogen, -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and

heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and R^2 is selected from the group consisting of -CN, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-C(O)NR^8R^7$, $-C(O)R^7$, $-S(O)_2NR^8R^7$, $-S(O)R^7$, $-S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^2 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

[0011] In some embodiments of compounds of Formula I, R^1 is hydrogen, -CN, $-NR^8R^7$, $-OR^7$, $-S(O)_2R^7$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ and $-S(O)_2R^7$, and R^2 is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ or $-S(O)_2R^7$.

[0012] In some embodiments of compounds of Formula I, R^1 is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkoxy substituted C_{2-6}alkoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, and cycloalkylamino, and R^2 is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, or cycloalkylamino.

[0013] In one embodiment of compounds of Formula I, the compound is selected from the group consisting of:

4-Butoxy-N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0007**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-pyrazol-1-yl-benzenesulfonamide (**P-0008**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-isopropoxy-

benzenesulfonamide (**P-0011**),

4-tert-Butyl-N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0014**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-0015**),

N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide (**P-0018**),

N-{2,4-Difluoro-3-[5-(4-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide (**P-0019**),

4-Difluoromethoxy-N-{2,4-difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-benzenesulfonamide (**P-0020**),

N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-0021**),

N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide (**P-0022**),

N-{2,4-Difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-0023**),

N-{2,4-Difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide (**P-0025**),

N-{2,4-Difluoro-3-[5-(1-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-0026**),

N-{3-[5-(1,5-Dimethyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-4-propyl-benzenesulfonamide (**P-0027**),

N-[2,4-Difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-0030**),

N-[3-(5-Cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide (**P-0031**),

(E)-3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-acrylic acid methyl ester (**P-0032**),

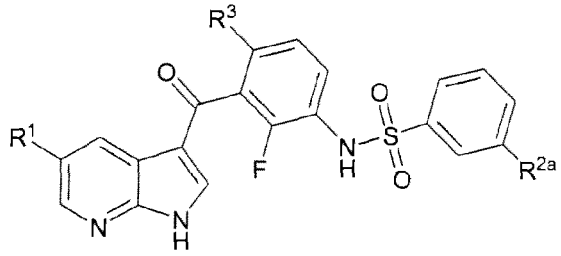
3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid methyl ester (**P-0033**),

3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid (**P-0034**),

3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N-ethyl-propionamide (**P-0035**) and

all salts, prodrugs, tautomers, and isomers thereof.

[0014] In some embodiments, compounds have the structure according to the following Formula II:



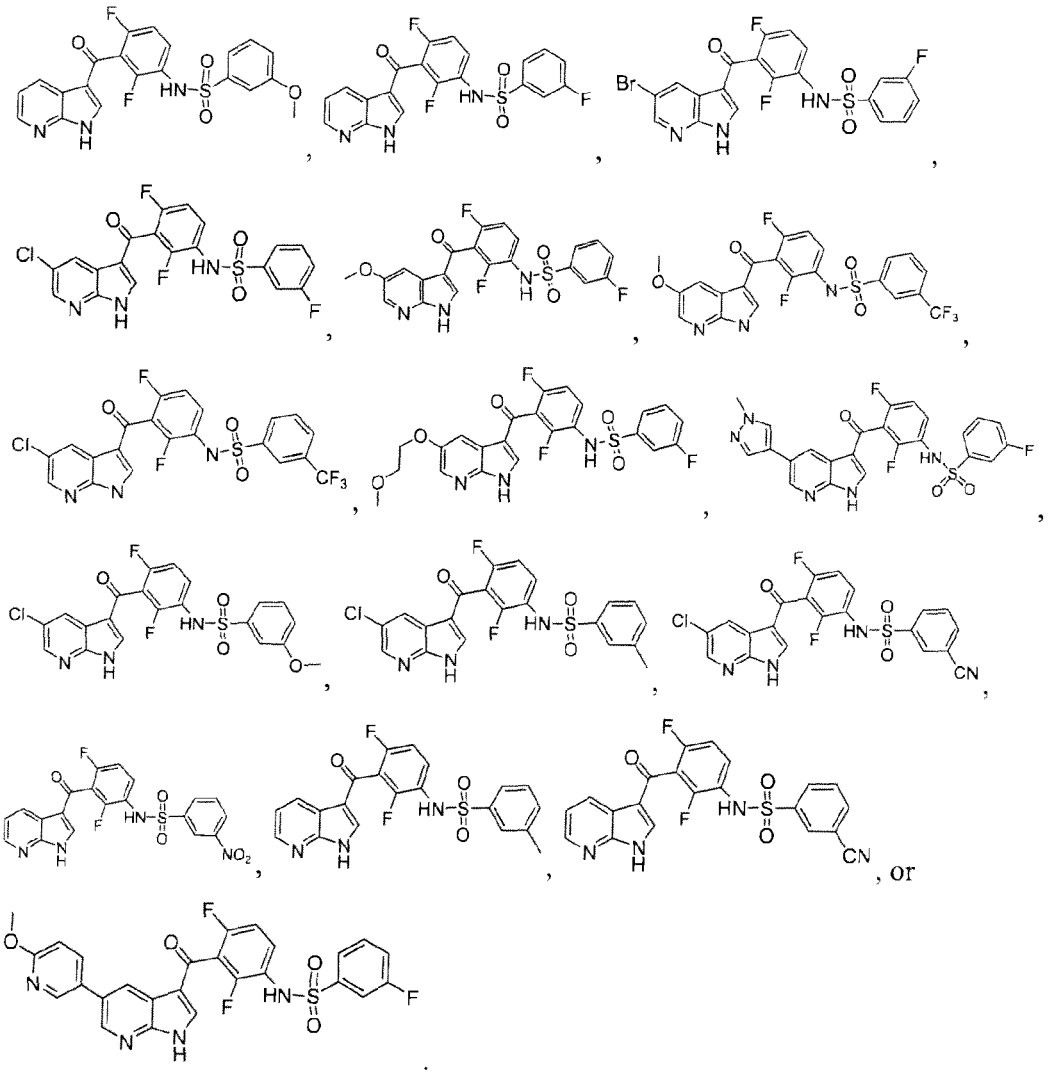
Formula II

all salts, prodrugs, tautomers and isomers thercof,

wherein:

R^{2a} is as defined for R^2 for Formula I; and

R^1 and R^3 are as defined for Formula I, provided, however, the compound is not



[0015] In some embodiments of compounds of Formula II, R^1 is selected from the group consisting of hydrogen, -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -$C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and R^{2a} is selected from the group consisting of -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{2a} or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -$C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

[0016] In some embodiments of compounds of Formula II, R^1 is hydrogen, -CN, -NR^8R^7, -OR^7, -$S(O)_2R^7$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NR^8R^7, -OR^7 and -$S(O)_2R^7$, and R^{2a} is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, -NR^8R^7, -OR^7 or -$S(O)_2R^7$.

[0017] In some embodiments of compounds of Formula II, R^1 is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkoxy substituted C_{2-6}alkoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, and cycloalkylamino, and R^{2a} is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, or cycloalkylamino.

[0018] In one embodiment of compounds of Formula II, the compound is selected from the group consisting of:

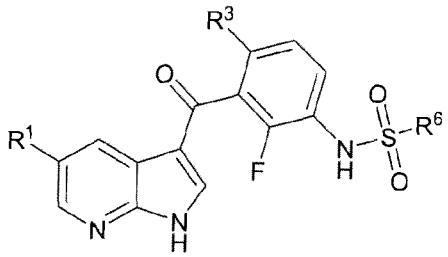
3-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenylsulfamoyl]-benzoic acid (**P-0004**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-difluoromethoxy-benzenesulfonamide (**P-0016**),

3-Difluoromethoxy-N-{2,4-difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-benzenesulfonamide (**P-0024**) and

all salts, prodrugs, tautomers, and isomers thereof.

[0019] In some embodiments, compounds have the structure according to the following Formula III:



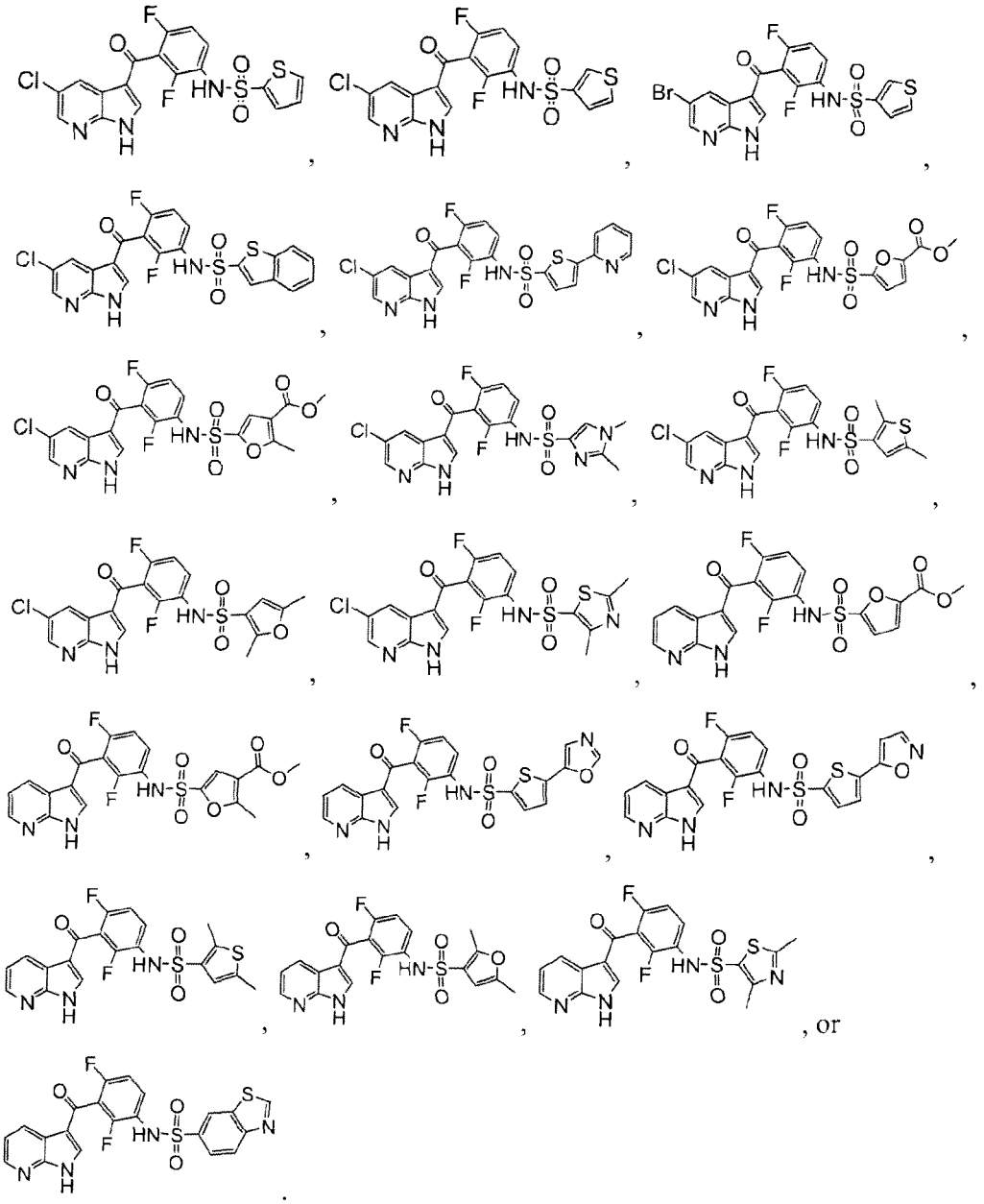
Formula III

all salts, prodrugs, tautomers and isomers thereof,

wherein:

R^6 is heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, cycloalkyl, hetcrocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, $-C(O)OH$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OR^7$, $-NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of R^6 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

R^1, R^3, R^7, R^8, and R^9 are as defined for Formula I, provided, however, the compound is not



[0020] In some embodiments of compounds of Formula III, R^1 is selected from the group consisting of hydrogen, -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of

-OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and R^6 is heteroaryl optionally substituted with one or more substituents selected from the group consisting of -CN, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-C(O)NR^8R^7$, $-C(O)R^7$, $-S(O)_2NR^8R^7$, $-S(O)R^7$, $-S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of R^6 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

[0021] In some embodiments of compounds of Formula III, R^1 is hydrogen, -CN, $-NR^8R^7$, $-OR^7$, $-S(O)_2R^7$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ and $-S(O)_2R^7$, and R^6 is heteroaryl optionally substituted with one or more of -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ or $-S(O)_2R^7$.

[0022] In some embodiments of compounds of Formula III, R^1 is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkoxy substituted C_{2-6}alkoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, and cycloalkylamino, and R^6 is heteroaryl optionally substituted with one or more of -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, or cycloalkylamino.

[0023] In one embodiment of compounds of Formula III, the compound is selected from the group consisting of:

Benzo[b]thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0001**),

5-Methyl-2-trifluoromethyl-furan-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0002**),

5-Oxazol-5-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0003**),

2-Oxo-2H-chromene-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0005**),

5-Isoxazol-5-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0006**),

Benzothiazole-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0009**),

1-Methyl-3-trifluoromethyl-1H-pyrazole-4-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0010**),

Benzo[1,2,5]thiadiazoe-5-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0013**),

5-Methyl-benzo[b]thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0017**),

5-Methyl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0028**),

1-Methyl-1H-pyrazole-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0029**),

Pyridine-2-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0036**) and

all salts, prodrugs, tautomers, and isomers thereof.

[0024] In some embodiments of the above compounds, compounds are excluded where N (except where N is a heteroaryl ring atom), O, or S is bound to a carbon that is also bound to N (except where N is a heteroaryl ring atom), O, or S, except where the carbon forms a double bond with one of the heteroatoms, such as in an amide, carboxylic acid, and the like; or where N (except where N is a heteroaryl ring atom), O, C(S), C(O), or $S(O)_n$ (n is 0-2) is bound to an alkene carbon of an alkenyl group or bound to an alkyne carbon of an alkynyl group; accordingly, in some embodiments compounds which include linkages such as the following are excluded from the compounds provided: $-NR-CH_2-NR-$, $-O-CH_2-NR-$, $-S-CH_2-NR-$, $-NR-CH_2-O-$, $-O-CH_2-O-$, $-S-CH_2-O-$, $-NR-CH_2-S-$, $-O-CH_2-S-$, $-S-CH_2-S-$, -NR-CH=CH-, -CH=CH-NR-, -NR-C≡C-, -C≡C-NR-, -O-CH=CH-, -CH=CH-O-, -O-C≡C-, -C≡C-O-, $-S(O)_{0-2}-CH=CH-$, $-CH=CH-S(O)_{0-2}-$, $-S(O)_{0-2}-C≡C-$, $-C≡C-S(O)_{0-2}-$, -C(O)-CH=CH-, -CH=CH-C(O)-, -C≡C-C(O)-, or -C(O)-C≡C-, -C(S)-CH=CH-, -CH=CH-C(S)-, -C≡C-C(S)-, or -C(S)-C≡C-.

[0025] In reference to compounds herein, unless clearly indicated to the contrary, specification of a compound or group of compounds includes pharmaceutically acceptable salts of such compound(s), prodrug(s), and all stereoisomers thereof. In reference to compositions, kits, methods of use, etc. of compounds of Formula I, Formula II, or Formula III described herein, it is understood that a

compound of Formula I includes all sub-embodiments thereof, a compound of Formula II includes all sub-embodiments thereof, and a compound of Formula III includes all sub-embodiments thereof, unless indicated otherwise.

[0026] In one aspect, methods are provided for treating a protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of one or more compounds of Formula I, Formula II, or Formula III. The terms "treat," "therapy," and like terms refer to the administration of material, e.g., one or more compounds of Formula I, Formula II, or Formula III, in an amount effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or condition, i.e., indication, and/or to prolong the survival of the subject being treated. The term "protein kinase mediated disease or condition" refers to a disease or condition in which the biological function of a protein kinase affects the development, course and/or symptoms of the disease or condition, and/or in which modulation of the protein kinase alters the development, course, and/or symptoms of the disease or condition. A protein kinase mediated disease or condition includes a disease or condition for which modulation provides a therapeutic benefit, e.g. wherein treatment with protein kinase inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of one or more compounds of Formula I, Formula II, or Formula III in combination with one or more other therapies for the disease or condition.

[0027] In one aspect, methods are provided for treating a protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a compound of any one or more of Formula I, Formula II, or Formula III.

[0028] In one aspect, the invention provides methods for treating a Raf protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of one or more compounds of Formula I, Formula II, or Formula III. The terms "Raf protein kinase mediated disease or condition," "Raf mediated disease or condition," and the like refer to a disease or condition in which the biological function of a Raf kinase, including any mutations thereof, affects the development, course and/or symptoms of the disease or condition, and/or in which modulation of the Raf protein kinase alters the development, course, and/or symptoms of the disease or condition. The Raf protein kinase includes, but is not limited to, A-Raf, mutations of A-Raf, B-Raf, mutations of B-Raf, c-Raf-1 and mutations of c-Raf-1. In some embodiments, the Raf protein kinase is B-Raf mutation V600E. In some embodiments, the Raf protein kinase is B-Raf mutation V600E/T529I. In some embodiments, the disease or condition is a cancer that is amenable to treatment by an inhibitor of the V600E mutant B-Raf. In some embodiments, the disease or condition is a cancer that is amenable to treatment by an inhibitor of the V600E/T529I mutant B-Raf. The Raf

protein kinase mediated disease or condition includes a disease or condition for which Raf inhibition provides a therapeutic benefit, e.g. wherein treatment with Raf inhibitors, including compounds described herein, provides a therapeutic benefit to the subject suffering from or at risk of the disease or condition. In one aspect, the method involves administering to the subject an effective amount of one or more compounds of Formula I, Formula II, or Formula III in combination with one or more other therapies for the disease or condition. Similarly, the terms "A-Raf, B-Raf or c-Raf-1 protein kinase mediated disease or condition," "A-Raf, B-Raf or c-Raf-1 mediated disease or condition," and the like refer to a disease or condition in which the biological function of an A-Raf, B-Raf or c-Raf-1 kinase, respectively, including any mutations thereof, affects the development, course and/or symptoms of the disease or condition, and/or in which modulation of the A-Raf, B-Raf or c-Raf-1 protein kinase, respectively, alters the development, course, and/or symptoms of the disease or condition.

[0029] In some embodiments, a compound of Formula I, Formula II, or Formula III is an inhibitor of a Raf kinase and has an IC_{50} of less than 500 nm, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM as determined in a generally accepted Raf kinase activity assay. In some embodiments, a compound of Formula I, Formula II, or Formula III will have an IC_{50} of less than 500 nm, less than 100 nM, less than 50 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 1 nM with respect to A-Raf, B-Raf, c-Raf-1, B-Raf V600E mutant, or B-Raf V600E/T529I mutant. In some embodiments, a compound of Formula I, Formula II, or Formula III will selectively inhibit one Raf kinase relative to one or more other Raf kinases. In some embodiments, the compound of Formula I, Formula II, or Formula III will selectively inhibit the effects of a mutation of the Raf kinase relative to the wild type kinase, for example B-Raf V600E mutant relative to wild type B-Raf.

[0030] Further to any of the above mentioned embodiments, a compound will also inhibit the effects of a mutation of the kinase, including, but not limited to, a mutation that is related to a disease state, such as a cancer. For example, B-Raf V600E mutant is present in a high percentage of some cancers, such as melanoma, and compounds of Formula I, Formula II, or Formula III will inhibit the kinase activity of this mutant.

[0031] Further to any of the above embodiments, a compound may selectively inhibit one kinase relative to one or more other kinases, where preferably inhibition is selective with respect to any other kinases, whether a kinase discussed herein, or other kinases. In some embodiments, the compound may selectively inhibit the effects of a mutation of the kinase relative to the wild type kinase, for example B-Raf V600E mutant relative to wild type B-Raf. In some embodiments, the compound may selectively inhibit Fms relative to Kit. Selective inhibition of one kinase relative to another is such that the IC_{50} for the one kinase may be at least about 2-fold, also 5-fold, also 10-fold, also 20-fold,

also 50-fold, or at least about 100-fold less than the IC_{50} for any of the other kinases as determined in a generally accepted kinase activity assay.

[0032] In another aspect, compositions are provided that include a therapeutically effective amount of one or more compounds of Formula I, Formula II, or Formula III and at least one pharmaceutically acceptable carrier, excipient, and/or diluent, including combinations of any two or more compounds of Formula I, Formula II or Formula III. The composition can further include a plurality of different pharmacologically active compounds, which can include a plurality of compounds of Formula I, Formula II, and/or Formula III. In another aspect, the composition can include one or more compounds of Formula I, Formula II, or Formula III along with one or more compounds that are therapeutically effective for the same disease indication. In one aspect, the composition includes one or more compounds of Formula I, Formula II, or Formula III along with one or more compounds that are therapeutically effective for the same disease indication, wherein the compounds have a synergistic effect on the disease indication. In one aspect, the composition includes one or more compounds of Formula I, Formula II, or Formula III effective in treating a cancer and one or more other compounds that are effective in treating the cancer, further wherein the compounds are synergistically effective in treating the cancer.

[0033] In another aspect, methods are provided for treating a protein kinase mediated disease or condition in an animal subject, wherein the method involves administering to the subject an effective amount of a composition including one or more compounds of Formula I, Formula II, or Formula III.

[0034] In one aspect, the invention provides methods for treating a disease or condition mediated by A-Raf, B-Raf, c-Raf-1, B-Raf V600E mutant, or B-Raf V600E/T529I mutant by administering to the subject an effective amount of a composition including one or more compounds of Formula I, Formula II or Formula III. In one aspect, the invention provides methods for treating a disease or condition mediated by A-Raf, B-Raf, c-Raf-1, B-Raf V600E mutant, or B-Raf V600E/T529I mutant by administering to the subject an effective amount of a composition including one or more compounds of Formula I, Formula II, or Formula III in combination with one or more other suitable therapies for treating the disease. In one aspect, the invention provides methods for treating a cancer mediated by B-Raf V600E mutant or B-Raf V600E/T529I mutant by administering to the subject an effective amount of a composition including one or more of Formula I, Formula II, or Formula III in combination with one or more suitable anticancer therapies, such as one or more chemotherapeutic drugs.

[0035] In one aspect, the invention provides a method of treating a cancer by administering to the subject an effective amount of a composition including one or more compounds of Formula I, Formula II, or Formula III, in combination with one or more other therapies or medical procedures

effective in treating the cancer. Other therapies or medical procedures include suitable anticancer therapy (e.g. drug therapy, vaccine therapy, gene therapy, photodynamic therapy) or medical procedure (e.g. surgery, radiation treatment, hyperthermia heating, bone marrow or stem cell transplant). In one aspect, the one or more suitable anticancer therapies or medical procedures is selected from treatment with a chemotherapeutic agent (e.g. chemotherapeutic drug), radiation treatment (e.g. x-ray, γ-ray, or electron, proton, neutron, or α particle beam), hyperthermia heating (e.g. microwave, ultrasound, radiofrequency ablation), Vaccine therapy (e.g. AFP gene hepatocellular carcinoma vaccine, AFP adenoviral vector vaccine, AG-858, allogeneic GM-CSF-secretion breast cancer vaccine, dendritic cell peptide vaccines), gene therapy (e.g. Ad5CMV-p53 vector, adenovector encoding MDA7, adenovirus 5-tumor necrosis factor alpha), photodynamic therapy (e.g. aminolevulinic acid, motexafin lutetium), surgery, and bone marrow and stem cell transplantation.

[0036] In a preferred embodiment, the invention provides a method of treating a cancer by administering to the subject an effective amount of a composition including one or more compounds of Formula I, Formula II, or Formula III, in combination with one or more suitable chemotherapeutic agents. In one aspect, the one or more suitable chemotherapeutic agents is selected from an alkylating agent, including, but not limited to, adozelesin, altretamine, bizelesin, busulfan, carboplatin, carboquone, carmustine, chlorambucil, cisplatin, cyclophosphamide, dacarbazine, estramustine, fotemustine, hepsulfam, ifosfamide, improsulfan, irofulven, lomustine, mechlorethamine, melphalan, oxaliplatin, piposulfan, semustine, streptozocin, temozolomide, thiotepa, and treosulfan; an antibiotic, including, but not limited to, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, menogaril, mitomycin, mitoxantrone, neocarzinostatin, pentostatin, and plicamycin; an antimetabolite, including, but not limited to, azacitidine, capecitabine, cladribine, clofarabine, cytarabine, decitabine, floxuridine, fludarabine, 5-fluorouracil, ftorafur, gemcitabine, hydroxyurea, mercaptopurine, methotrexate, nelarabine, pemetrexed, raltitrexed, thioguanine, and trimetrexate; an immunotherapy, including, but not limited to, alemtuzumab, bevacizumab, cetuximab, galiximab, gemtuzumab, panitumumab, pertuzumab, rituximab, tositumomab, trastuzumab, and 90 Y ibritumomab tiuxetan; a hormone or hormone antagonist, including, but not limited to, anastrozole, androgens, buserelin, diethylstilbestrol, exemestane, flutamide, fulvestrant, goserelin, idoxifene, letrozole, leuprolide, magestrol, raloxifene, tamoxifen, and toremifene; a taxane, including, but not limited to, DJ-927, docetaxel, TPI 287, paclitaxel and DHA-paclitaxel; a retinoid, including, but not limited to, alitretinoin, bexarotene, fenretinide, isotretinoin, and tretinoin; an alkaloid, including, but not limited to, etoposide, homoharringtonine, teniposide, vinblastine, vincristine, vindesine, and vinorelbine; an antiangiogenic agent, including, but not limited to, AE-941 (GW786034, Neovastat), ABT-510, 2-methoxyestradiol, lenalidomide, and thalidomide; a topoisomerase inhibitor, including, but not limited to, amsacrine, edotecarin, exatecan, irinotecan (also active metabolite SN-38 (7-ethyl-10-hydroxy-camptothecin)), rubitecan, topotecan, and 9-aminocamptothecin; a kinase inhibitor,

including, but not limited to, erlotinib, gefitinib, flavopiridol, imatinib mesylate, lapatinib, sorafenib, sunitinib malate, AEE-788, AG-013736, AMG 706, AMN107, BMS-354825, BMS-599626, UCN-01 (7-hydroxystaurosporine), and vatalanib; a targeted signal transduction inhibitor including, but not limited to bortezomib, geldanamycin, and rapamycin; a biological response modifier, including, but not limited to, imiquimod, interferon-α, and interleukin-2; and other chemotherapeutics, including, but not limited to 3-AP (3-amino-2-carboxyaldehyde thiosemicarbazone), aminoglutethimide, asparaginase, bryostatin-1, cilengitide, E7389, ixabepilone, procarbazine, sulindac, temsirolimus, tipifarnib. Preferably, the method of treating a cancer involves administering to the subject an effective amount of a composition including one or more of Formula I, Formula II, or Formula III in combination with a chemotherapeutic agent selected from 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, vinblastine, bevacizumab, cetuximab, or erlotinib.

[0037] In another aspect, the invention provides a method of treating or prophylaxis of a disease or condition in a mammal, by administering to the mammal a therapeutically effective amount of one or more compounds of Formula I, Formula II, or Formula III, a prodrug of such compound, or a pharmaceutically acceptable salt of such compound or prodrug. The compound can be alone or can be part of a composition. In another aspect, the invention provides a method of treating or prophylaxis of a disease or condition in a mammal, by administering to the mammal a therapeutically effective amount of one or more compounds of Formula I, Formula II, or Formula III, a prodrug of such compound, or a pharmaceutically acceptable salt of such compound or prodrug in combination with one or more other suitable therapies for the disease or condition.

[0038] In a related aspect, the invention provides kits that include a composition as described herein. In some embodiments, the composition is packaged, e.g., in a vial, bottle, flask, which may be further packaged, e.g., within a box, envelope, or bag; the composition is approved by the U.S. Food and Drug Administration or similar regulatory agency for administration to a mammal, e.g., a human; the composition is approved for administration to a mammal, e.g., a human, for a protein kinase mediated disease or condition; the invention kit includes written instructions for use and/or other indication that the composition is suitable or approved for administration to a mammal, e.g., a human, for a protein kinase-mediated disease or condition; and the composition is packaged in unit dose or single dose form, e.g., single dose pills, capsules, or the like.

[0039] In aspects involving treatment or prophylaxis of a disease or condition with one or more compounds of Formula I, Formula II, or Formula III, the disease or condition is, for example without limitation, neurologic diseases, including, but not limited to, cerebrovascular ischemia, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis, dementia, senile chorea, and Huntington's disease; neoplastic diseases and associated

complications, including, but not limited to, chemotherapy-induced hypoxia, gastrointestinal stromal tumors (GISTs), prostate tumors, mast cell tumors (including canine mast cell tumors), acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, melanoma, mastocytosis, gliomas, glioblastoma, astrocytoma, neuroblastoma, sarcomas (e.g. sarcomas of neuroectodermal origin, leiomyosarcoma), carcinomas (e.g. lung, breast, pancreatic, colon, hepatocellular, renal, female genital tract, squamous cell, carcinoma in situ), lymphoma (e.g. histiocytic lymphoma, non-Hodgkin's lymphoma), MEN2 syndromes, neurofibromatosis (including Schwann cell neoplasia), myelodysplastic syndrome, leukemia, tumor angiogenesis, cancers of the thyroid, liver, bone, skin, brain, central nervous system, pancreas, lung (e.g. small cell lung cancer, non small cell lung cancer), breast, colon, bladder, prostate, gastrointestinal tract, endometrium, fallopian tube, testes and ovary, and metastasis of tumors to other tissues; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, bone pain, cancer-related pain and migraine; cardiovascular diseases, including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, reperfusion injury and ischemia (e.g. cerebrovascular ischemia, liver ischemia); inflammation including, but not limited to, age-related macular degeneration, rheumatoid arthritis, allergic rhinitis, inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, systemic lupus erythematosis, Sjogren's Syndrome, Wegener's granulomatosis, psoriasis, scleroderma, chronic thyroiditis, Grave's disease, myasthenia gravis, multiple sclerosis, osteoarthritis, endometriosis, scarring (e.g. dermal, tissue), vascular restenosis, fibrotic disorders, hypereosinophilia, CNS inflammation, pancreatitis, nephritis, atopic dermatitis, and hepatitis; immunodeficiency diseases ,including, but not limited to, severe combined immunodeficiency (SCID), organ transplant rejection, and graft versus host disease; renal or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, interstitial nephritis, Lupus nephritis, prostate hyperplasia, chronic renal failure, tubular necrosis, diabetes-associated renal complications, and hypertrophy; metabolic diseases, including, but not limited to, type 1 diabetes, type 2 diabetes, metabolic syndrome, obesity, hepatic steatosis, insulin resistance, hyperglycemia, lipolysis and obesity; infection, including, but not limited to, *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, and sepsis; pulmonary diseases, including, but not limited to, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), asthma, allergy, bronchitis, emphysema, and pulmonary fibrosis; genetic developmental diseases, including, but not limited to, Noonan's syndrome, Crouzon syndrome, acrocephalo-syndactyly type I, Pfeiffer's syndrome, Jackson-Weiss syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC) and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; disorders of bone structure, mineralization and bone reformation and resorption, including, but not limited to, osteoporosis, increased risk of fracture, Paget's disease, hypercalcemia, and metastatis of cancer to

bone; Grave's disease; Hirschsprung's disease; lymphoedema; selective T-cell defect (STD); X-linked agammaglobulinemia; diabetic retinopathy; alopecia; erectile dysfunction; and tuberous sclerosis.

[0040] In aspects involving treatment or prophylaxis of a disease or condition with one or more compounds of Formula I, Formula II, or Formula III, the invention provides methods for treating an A-Raf-mediated, B-Raf-mediated or c-Raf-1-mediated disease or condition in an animal subject (e.g. a mammal such as a human, other primates, sports animals, animals of commercial interest such as cattle, farm animals such as horses, or pets such as dogs and cats), e.g., a disease or condition characterized by abnormal A-Raf, B-Raf, and/or c-Raf-1 activity (e.g. kinase activity). Invention methods involve administering to the subject suffering from or at risk of an A-Raf-mediated, B-Raf-mediated, and/or c-Raf-1-mediated disease or condition an effective amount of one or more compounds of Formula I, Formula II or Formula III. In one embodiment, the A-Raf-meditated, B-Raf-mediated, and/or C-Raf mediated disease is selected from the group consisting of neurologic diseases, including, but not limited to, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma) neurofibromatosis, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases, including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, and reperfusion injury; inflammation including, but not limited to, psoriasis, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, including, but not limited to, organ transplant rejection, graft versus host disease; renal or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia; metabolic disorders, including, but not limited to, obesity; infection, including, but not limited to, *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, and sepsis; pulmonary diseases, including, but not limited to, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases, including, but not limited to, Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; and diseases associated with muscle regeneration or degeneration, including, but not limited to, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular

Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency).

[0041] In a related aspect, one or more compounds of Formula I, Formula II, or Formula III, can be used in the preparation of a medicament for the treatment of an A-Raf-mediated, B-Raf-mediated or c-Raf-1-mediated disease or condition selected from the group consisting of neurologic diseases, including, but not limited to, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma) neurofibromatosis, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases, including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, and reperfusion injury; inflammation including, but not limited to, psoriasis, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, including, but not limited to, organ transplant rejection, graft versus host disease; renal or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia; metabolic disorders, including, but not limited to, obesity; infection, including, but not limited to, *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, and sepsis; pulmonary diseases, including, but not limited to, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases, including,

but not limited to, Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases; and diseases associated with muscle regeneration or degeneration, including, but not limited to, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency).

[0042] The compounds of Formula I, Formula II, or Formula III with kinase activity IC_{50} less than 10 μM as determined in a standard assay described herein can be used to treat the following exemplary protein kinase mediated diseases and conditions related to protein kinases A-Raf, B-Raf and/or c-Raf-1, including any mutations thereof; for example without limitation:

modulation of A-Raf, which is related to neurologic diseases such as multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma), neurofibromatosis, myelodysplastic syndrome, leukemia, tumor angiogenesis; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, cancer-related pain and migraine; and diseases associated with muscle regeneration or degeneration, including, but not limited to, vascular restenosis, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive

spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency);

modulation of B-Raf and/or c-Raf-1, which is related to neurologic diseases, including, but not limited to, multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma) neurofibromatosis, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma; pain of neuropathic or inflammatory origin, including, but not limited to, acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases, including, but not limited to, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, and reperfusion injury; inflammation including, but not limited to, psoriasis, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, including, but not limited to, organ transplant rejection, graft versus host disease; renal or prostatic diseases, including, but not limited to, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia; metabolic disorders, including, but not limited to, obesity; infection, including, but not limited to, *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, and sepsis; pulmonary diseases, including, but not limited to, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases, including, but not limited to, Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest

syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases.

[0043] Additional aspects and embodiments will be apparent from the following Detailed Description and from the claims.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0044] As used herein the following definitions apply unless clearly indicated otherwise:

[0045] "Halogen" refer to all halogens, that is, chloro (Cl), fluoro (F), bromo (Br), or iodo (I).

[0046] "Hydroxyl" or "hydroxy" refer to the group -OH.

[0047] "Thiol" refers to the group -SH.

[0048] "Lower alkyl" alone or in combination means an alkane-derived radical containing from 1 to 6 carbon atoms (unless specifically defined) that includes a straight chain alkyl or branched alkyl. The straight chain or branched alkyl group is attached at any available point to produce a stable compound. In many embodiments, a lower alkyl is a straight or branched alkyl group containing from 1-6, 1-4, or 1-2, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like. A "substituted lower alkyl" denotes lower alkyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkyl" denotes a lower alkyl group substituted with one or more fluoro atoms, such as perfluoroalkyl, where preferably the lower alkyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, when optionally substituted alkyl is an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkyl R group is such that substitution of the alkyl carbon bound to any -O-, -S-, or -N- of the moiety (except where -N- is a heteroaryl ring atom) excludes substituents that would result in any -O-, -S-, or -N- of the substituent (except where -N- is a heteroaryl ring atom) being bound to the alkyl carbon bound to any -O-, -S-, or -N- of the moiety .

[0049] "Lower alkenyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) and at least one, preferably 1-3, more preferably 1-2, most preferably one, carbon to carbon double bond. Carbon to carbon double bonds may be either contained within a straight chain or branched portion. Examples of lower alkenyl groups include ethenyl, propenyl, isopropenyl, butenyl, and the like. A "substituted lower alkenyl" denotes lower alkenyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5,

also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkenyl" denotes a lower alkenyl group substituted with one or more fluoro atoms, where preferably the lower alkenyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, substitution of alkenyl groups are such that -F, -C(O)-, -C(S)-, -C(NH)-, -S(O)-, $-S(O)_2-$, -O-, -S-, or N (except where N is a heteroaryl ring atom), are not bound to an alkene carbon thereof. Further, where alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, -O-, -S-, or N thereof (except where N is a heteroaryl ring atom) are not bound to an alkene carbon of the alkenyl substituent or R group. Further, where alkenyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkenyl R group is such that substitution of the alkenyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the alkenyl carbon bound to any O, S, or N of the moiety. An "alkenyl carbon" refers to any carbon within an alkenyl group, whether saturated or part of the carbon to carbon double bond. An "alkene carbon" refers to a carbon within an alkenyl group that is part of a carbon to carbon double bond.

[0050] "Lower alkynyl" alone or in combination means a straight or branched hydrocarbon containing 2-6 carbon atoms (unless specifically defined) containing at least one, preferably one, carbon to carbon triple bond. Examples of alkynyl groups include ethynyl, propynyl, butynyl, and the like. A "substituted lower alkynyl" denotes lower alkynyl that is independently substituted, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound. For example "fluoro substituted lower alkynyl" denotes a lower alkynyl group substituted with one or more fluoro atoms, where preferably the lower alkynyl is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions are attached at any available atom to produce a stable compound, substitution of alkynyl groups are such that -F, -C(O)-, -C(S)-, -C(NH)-, -S(O)-, $-S(O)_2-$, -O-, -S-, or N (except where N is a heteroaryl ring atom) are not bound to an alkyne carbon thereof. Further, where alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)R, and the like, substitution of the moiety is such that any -C(O)-, -C(S)-,-S(O)-, $-S(O)_2-$, -O-, -S-, or N thereof (except where N is a heteroaryl ring atom) are not bound to an alkyne carbon of the alkynyl substituent or R group. Further, where alkynyl is a substituent of another moiety or an R group of a moiety such as -OR, -NHR, -C(O)NHR, and the like, substitution of the alkynyl R group is such that substitution of the alkynyl carbon bound to any O, S, or N of the moiety (except where N is a heteroaryl ring atom) excludes substituents that would result in any O, S, or N of the substituent (except where N is a heteroaryl ring atom) being bound to the alkynyl carbon bound to any O, S, or N of the moiety. An

"alkynyl carbon" refers to any carbon within an alkynyl group, whether saturated or part of the carbon to carbon triple bond. An "alkyne carbon" refers to a carbon within an alkynyl group that is part of a carbon to carbon triple bond.

[0051] "Cycloalkyl" refers to saturated or unsaturated, non-aromatic monocyclic, bicyclic or tricyclic carbon ring systems of 3-10, also 3-8, more preferably 3-6, ring members per ring, such as cyclopropyl, cyclopentyl, cyclohexyl, adamantyl, and the like. A "substituted cycloalkyl" is a cycloalkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0052] "Heterocycloalkyl" refers to a saturated or unsaturated non-aromatic cycloalkyl group having from 5 to 10 atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N, and are optionally fused with benzo or heteroaryl of 5-6 ring members. Heterocycloalkyl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. Heterocycloalkyl is also intended to include compounds in which a ring carbon may be oxo substituted, i.e. the ring carbon is a carbonyl group, such as lactones and lactams. The point of attachment of the heterocycloalkyl ring is at a carbon or nitrogen atom such that a stable ring is retained. Examples of heterocycloalkyl groups include, but are not limited to, morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, pyrrolidonyl, piperazinyl, dihydrobenzofuryl, and dihydroindolyl. A "substituted heterocycloalkyl" is a heterocycloalkyl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0053] "Aryl" alone or in combination refers to a monocyclic or bicyclic ring system containing aromatic hydrocarbons such as phenyl or naphthyl, which may be optionally fused with a cycloalkyl of preferably 5-7, more preferably 5-6, ring members. A "substituted aryl" is an aryl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0054] "Heteroaryl" alone or in combination refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, preferably 1-4, more preferably 1-3, even more preferably 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or nitrogen atom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl,

pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. "Nitrogen containing heteroaryl" refers to heteroaryl wherein any heteroatoms are N. A "substituted heteroaryl" is a heteroaryl that is independently substituted, unless indicated otherwise, with one or more, preferably 1, 2, 3, 4 or 5, also 1, 2, or 3 substituents, attached at any available atom to produce a stable compound.

[0055] "Lower alkoxy" denotes the group $-OR^z$, where R^z is lower alkyl. A "substituted lower alkoxy" denotes lower alkoxy in which R^z is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I, Formula II, or Formula III, including descriptions of substituted cycloalkyl, heterocycloalkyl, aryl and heteroaryl, attached at any available atom to produce a stable compound. Preferably, substitution of lower alkoxy is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkoxy" denotes lower alkoxy in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkoxy is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkoxy are attached at any available atom to produce a stable compound, substitution of alkoxy is such that O, S, or N (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkoxy O. Further, where alkoxy is described as a substituent of another moiety, the alkoxy oxygen is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0056] "Lower alkylthio" denotes the group $-SR^{aa}$, where R^{aa} is lower alkyl. A "substituted lower alkylthio" denotes lower alkylthio in which R^{aa} is lower alkyl substituted with one or more substituents as indicated herein, for example, in the description of compounds of Formula I, Formula II, or Formula III, including descriptions of substituted cycloalkyl, heterocycloalkyl, aryl and heteroaryl, attached at any available atom to produce a stable compound. Preferably, substitution of lower alkylthio is with 1, 2, 3, 4, or 5 substituents, also 1, 2, or 3 substituents. For example "fluoro substituted lower alkylthio" denotes lower alkylthio in which the lower alkyl is substituted with one or more fluoro atoms, where preferably the lower alkylthio is substituted with 1, 2, 3, 4 or 5 fluoro atoms, also 1, 2, or 3 fluoro atoms. While it is understood that substitutions on alkylthio are attached at any available atom to produce a stable compound, substitution of alkylthio is such that O, S, or N (except where N is a heteroaryl ring atom), are not bound to the alkyl carbon bound to the alkylthio S. Further, where alkylthio is described as a substituent of another moiety, the alkylthio sulfur is not bound to a carbon atom that is bound to an O, S, or N of the other moiety (except where N is a heteroaryl ring atom), or to an alkene or alkyne carbon of the other moiety.

[0057] "Amino" or "amine" denotes the group $-NH_2$. "Mono-alkylamino" denotes the group $-NHR^{bb}$ where R^{bb} is lower alkyl. "Di-alkylamino" denotes the group $-NR^{bb}R^{cc}$, where R^{bb} and R^{cc} are

independently lower alkyl. "Cycloalkylamino" denotes the group $-NR^{dd}R^{ee}$, where R^{dd} and R^{ee} combine with the nitrogen to form a 5-7 membered heterocycloalkyl, where the heterocycloalkyl may contain an additional heteroatom within the ring, such as O, N, or S, and may also be further substituted with lower alkyl. Examples of 5-7 membered heterocycloalkyl include, but are not limited to, piperidine, piperazine, 4-methylpiperazine, morpholine, and thiomorpholine. While it is understood that when mono-alkylamino, di-alkylamino, or cycloalkylamino are substituents on other moieties that are attached at any available atom to produce a stable compound, the nitrogen of mono-alkylamino, di-alkylamino, or cycloalkylamino as substituents is not bound to a carbon atom that is bound to an O, S, or N of the other moiety.

[0058] As used herein, the term "composition" refers to a formulation suitable for administration to an intended animal subject for therapeutic purposes that contains at least one pharmaceutically active compound and at least one pharmaceutically acceptable carrier or excipient.

[0059] The term "pharmaceutically acceptable" indicates that the indicated material does not have properties that would cause a reasonably prudent medical practitioner to avoid administration of the material to a patient, taking into consideration the disease or conditions to be treated and the respective route of administration. For example, it is commonly required that such a material be essentially sterile, e.g., for injectibles.

[0060] In the present context, the term "therapeutically effective" or "effective amount" indicates that the materials or amount of material is effective to prevent, alleviate, or ameliorate one or more symptoms of a disease or medical condition, and/or to prolong the survival of the subject being treated.

[0061] In the present context, the terms "synergistically effective" or "synergistic effect" indicate that two or more compounds that are therapeutically effective, when used in combination, provide improved therapeutic effects greater than the additive effect that would be expected based on the effect of each compound used by itself.

[0062] As used herein, the terms "ligand" and "modulator" are used equivalently to refer to a compound that changes (i.e., increases or decreases) the activity of a target biomolecule, *e.g.*, an enzyme such as a kinase. Generally a ligand or modulator will be a small molecule, where "small molecule refers to a compound with a molecular weight of 1500 daltons or less, or preferably 1000 daltons or less, 800 daltons or less, or 600 daltons or less. Thus, an "improved ligand" is one that possesses better pharmacological and/or pharmacokinetic properties than a reference compound, where "better" can be defined by one skilled in the relevant art for a particular biological system or therapeutic use.

[0063] In the context of compounds binding to a target, the terms "greater affinity" and "selective" indicates that the compound binds more tightly than a reference compound, or than the same compound in a reference condition, *i.e.*, with a lower dissociation constant. In some embodiments, the greater affinity is at least 2, 3, 4, 5, 8, 10, 50, 100, 200, 400, 500, 1000, or 10,000-fold greater affinity.

[0064] As used herein in connection with compounds of the invention, the term "synthesizing" and like terms means chemical synthesis from one or more precursor materials.

[0065] By "assaying" is meant the creation of experimental conditions and the gathering of data regarding a particular result of the experimental conditions. For example, enzymes can be assayed based on their ability to act upon a detectable substrate. A compound or ligand can be assayed based on its ability to bind to a particular target molecule or molecules.

[0066] As used herein, the term "modulating" or "modulate" refers to an effect of altering a biological activity, especially a biological activity associated with a particular biomolecule such as a protein kinase. For example, an agonist or antagonist of a particular biomolecule modulates the activity of that biomolecule, *e.g.*, an enzyme, by either increasing (e.g. agonist, activator), or decreasing (e.g. antagonist, inhibitor) the activity of the biomolecule, such as an enzyme. Such activity is typically indicated in terms of an inhibitory concentration (IC_{50}) or excitation concentration (EC_{50}) of the compound for an inhibitor or activator, respectively, with respect to, for example, an enzyme.

[0067] The present invention concerns compounds of Formula I, and all sub-generic formulae, compounds of Formula II and all sub-generic formulae, and compounds of Formula III and all sub-generic formulae that are modulators of protein kinases, for example without limitation, the compounds are modulators of at least one of the kinases selected from the group consisting of A-Raf, B-Raf, c-Raf-1, and and any mutants thereof, and the use of such compounds in the treatment of diseases or conditions.

Kinase targets and indications of the invention

[0068] Protein kinases play key roles in propagating biochemical signals in diverse biological pathways. More than 500 kinases have been described, and specific kinases have been implicated in a wide range of diseases or conditions (i.e., indications), including for example without limitation, cancer, cardiovascular disease, inflammatory disease, neurological disease, and other diseases. As such, kinases represent important control points for small molecule therapeutic intervention. Description of specific target protein kinases contemplated by the present invention follow:

[0069] **A-Raf:** Target kinase B-Raf (i.e., v-raf murine sarcoma 3611 viral oncogene homolog 1) is a 67.6 kDa serine/threonine kinase encoded by chromosome Xp11.4-p11.2 (symbol: ARAF). The mature protein comprises RBD (i.e., Ras binding domain) and phorbol-ester/DAG-type zinc finger domain and is involved in the transduction of mitogenic signals from the cell membrane to the nucleus. A-Raf inhibitors may be useful in treating neurologic diseases such as multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma), neurofibromatosis, myelodysplastic syndrome, leukemia, tumor angiogenesis; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, cancer-related pain and migraine; and diseases associated with muscle regeneration or degeneration, including, but not limited to, vascular restenosis, sarcopenia, muscular dystrophies (including, but not limited to, Duchenne, Becker, Emery-Dreifuss, Limb-Girdle, Facioscapulohumeral, Myotonic, Oculopharyngeal, Distal and Congenital Muscular Dystrophies), motor neuron diseases (including, but not limited to, amyotrophic lateral sclerosis, infantile progressive spinal muscular atrophy, intermediate spinal muscular atrophy, juvenile spinal muscular atrophy, spinal bulbar muscular atrophy, and adult spinal muscular atrophy), inflammatory myopathies (including, but not limited to, dermatomyositis, polymyositis, and inclusion body myositis), diseases of the neuromuscular junction (including, but not limited to, myasthenia gravis, Lambert-Eaton syndrome, and congenital myasthenic syndrome), myopathies due to endocrine abnormalities (including, but not limited to, hyperthyroid myopathy and hypothyroid myopathy) diseases of peripheral nerve (including, but not limited to, Charcot-Marie-Tooth disease, Dejerine-Sottas disease, and Friedreich's ataxia), other myopathies (including, but not limited to, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, and periodic paralysis), and metabolic diseases of muscle (including, but not limited to, phosphorylase deficiency, acid maltase deficiency, phosphofructokinase deficiency, debrancher enzyme deficiency, mitochondrial myopathy, carnitine deficiency, carnitine palmatyl transferase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, and myoadenylate deaminase deficiency).

[0070] **B-Raf:** Target kinase B-Raf (i.e., v-raf murine sarcoma viral oncogene homolog B1) is a 84.4 kDa serine/threonine kinase encoded by chromosome 7q34 (symbol: BRAF). The mature protein comprises RBD (i.e., Ras binding domain), C1 (i.e., protein kinase C conserved region 1) and STK (i.e., serine/threonine kinase) domains.

[0071] Target kinase B-Raf is involved in the transduction of mitogenic signals from the cell membrane to the nucleus and may play a role in the postsynaptic responses of hippocampal neurons. As such, genes of the RAF family encode kinases that are regulated by Ras and mediate cellular

responses to growth signals. Indeed, B-Raf kinase is a key component of the RAS->Raf->MEK->ERK/MAP kinase signaling pathway, which plays a fundamental role in the regulation of cell growth, division and proliferation, and, when constitutively activated, causes tumorigenesis. Among several isoforms of Raf kinase, the B-type, or B-Raf, is the strongest activator of the downstream MAP kinase signaling.

[0072] The BRAF gene is frequently mutated in a variety of human tumors, especially in malignant melanoma and colon carcinoma. The most common reported mutation was a missense thymine (T) to adenine (A) transversion at nucleotide 1796 (T1796A; amino acid change in the B-Raf protein is Val<600> to Glu<600>) observed in 80% of malignant melanoma tumors. Functional analysis reveals that this transversion is the only detected mutation that causes constitutive activation of B-Raf kinase activity, independent of RAS activation, by converting B-Raf into a dominant transforming protein. Based on precedents, human tumors develop resistance to kinase inhibitors by mutating a specific amino acid in the catalytic domain as the "gatekeeper". (Balak, et. al., Clin Cancer Res. 2006, 12:6494-501). Mutation of Thr-529 in BRAF to Ile is thus anticipated as a mechanism of resistance to BRAF inhibitors, and this can be envisioned as a transition in codon 529 from ACC to ATC.

[0073] Niihori et al., report that in 43 individuals with cardio-facio-cutaneous (CFC) syndrome, they identified two heterozygous KRAS mutations in three individuals and eight BRAF mutations in 16 individuals, suggesting that dysregulation of the RAS-RAF-ERK pathway is a common molecular basis for the three related disorders (Niihori et al., Nat Genet. 2006, 38(3):294-6).

[0074] **c-Raf-1:** Target kinase c-Raf-1 (i.e., v-raf murine sarcoma viral oncogene homolog 1) is a 73.0 kDa STK encoded by chromosome 3p25 (symbol: RAF1). c-Raf-1 can be targeted to to the mitochondria by BCL2 (i.e., oncogene B-cell leukemia 2) which is a regulator of apoptotic cell death. Active c-Raf-1 improves BCL2-mediated resistance to apoptosis, and c-Raf-1 phosphorylates BAD (i.e., BCL2-binding protein). c-Raf-1 is implicated in carcinomas, including colorectal, ovarian, lung and renal cell carcinoma. C-Raf-1 is also implicated as an important mediator of tumor angiogenesis (Hood, J.D. et al., 2002, Science **296**, 2404). C-Raf-1 inhibitors may also be useful for the treatment of acute myeloid leukemia and myelodysplastic syndromes (Crump, Curr Pharm Des 2002, 8(25):2243-8). Raf-1 activators may be useful as treatment for neuroendocrine tumors, such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma (Kunnimalaiyaan et al., Anticancer Drugs 2006, 17(2):139-42).

[0075] B-Raf and/or C-Raf-1 inhibitors may be useful in treating neurologic diseases such as multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease (AD), Parkinson's disease; neoplastic diseases including, but not limited to, melanoma, glioma, sarcoma, carcinoma (e.g. colorectal, lung, breast, pancreatic, thyroid, renal, ovarian), lymphoma (e.g. histiocytic lymphoma)

neurofibromatosis, acute myeloid leukemia, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuroendocrine tumors such as medullary thyroid cancer, carcinoid, small cell lung cancer and pheochromocytoma; pain of neuropathic or inflammatory origin, including acute pain, chronic pain, cancer-related pain, and migraine; cardiovascular diseases including heart failure, ischemic stroke, cardiac hypertrophy, thrombosis (e.g. thrombotic microangiopathy syndromes), atherosclerosis, reperfusion injury; inflammation including, but not limited to, psoriasis, arthritis and autoimmune diseases and conditions, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease (IBD); immunodeficiency diseases, organ transplant rejection, graft versus host disease; renal or prostatic diseases including diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia; metabolic disorders, obesity; infection, including, but not limited to *Helicobacter pylori, Hepatitis* and *Influenza* viruses, fever, sepsis; pulmonary diseases including chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome (ARDS); genetic developmental diseases such as Noonan's syndrome, Costello syndrome, (faciocutaneoskeletal syndrome), LEOPARD syndrome, cardio-faciocutaneous syndrome (CFC), and neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases.

Kinase Activity Assays

[0076] A number of different assays for kinase activity can be utilized for assaying for active modulators and/or determining specificity of a modulator for a particular kinase or group or kinases. In addition to the assay mentioned in the Examples below, one of ordinary skill in the art will know of other assays that can be utilized and can modify an assay for a particular application. For example, numerous papers concerning kinases describe assays that can be used.

[0077] Additional alternative assays can employ binding determinations. For example, this sort of assay can be formatted either in a fluorescence resonance energy transfer (FRET) format, or using an AlphaScreen (*a*mplified *l*uminescent *p*roximity *h*omogeneous *a*ssay) format by varying the donor and acceptor reagents that are attached to streptavidin or the phosphor-specific antibody.

Organic Synthetic Techniques

[0078] A wide array of organic synthetic techniques exist in the art to facilitate constructing potential modulators. Many of these organic synthetic methods are described in detail in standard reference sources utilized by those skilled in the art. One example of such a reference is March, 1994, Advanced Organic Chemistry; Reactions, Mechanisms and Structure, New York, McGraw Hill. Thus, the techniques useful to synthesize a potential modulator of kinase function are readily available to those skilled in the art of organic chemical synthesis.

Alternative Compound Forms or Derivatives

[0079] Compounds contemplated herein are described with reference to both generic formulae and specific compounds. In addition, invention compounds may exist in a number of different forms or derivatives, all within the scope of the present invention. Alternative forms or derivatives, such as (a) Isomers, Prodrugs, and Active Metabolites (b) Tautomers, Stereoisomers, Regioisomers, and Solvated Forms (c) Prodrugs and Metabolites (d) Pharmaceutically acceptable salts and (e) Polymorphic forms, are described, for example, in US Patent Application Serial number 11/473,347 (see also, PCT publication WO2007002433), the disclosure of which is hereby incorporated by reference in its entirety.

Administration

[0080] The methods and compounds will typically be used in therapy for human subjects. However, they may also be used to treat similar or identical indications in other animal subjects. In this context, the terms "subject," "animal subject," and the like refer to human and non-human vertebrates, e.g. mammals, such as non-human primates, sports and commercial animals, e.g., equines, bovines, porcines, ovines, rodents, and pets, e.g., canines and felines. A description of possible methods and routes of administration may be found, for example, in US Patent Application Serial number 11/473,347 (see also, PCT publication WO2007002433), the disclosure of which is hereby incorporated by reference in its entirety.

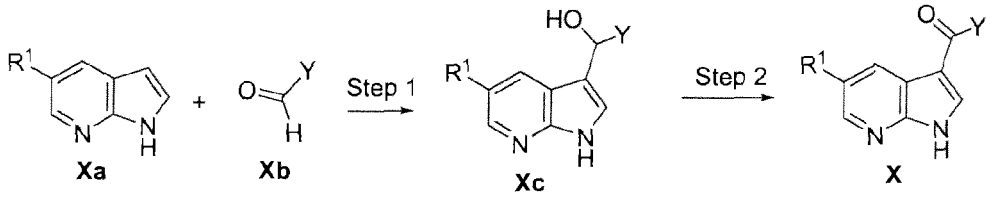
EXAMPLES

[0081] A number of examples illustrative of the present invention are described below. In most cases, alternative techniques could also be used. The examples are intended to be illustrative and are not limiting or restrictive to the scope of the invention. Unless specifically noted to the contrary, in cases where a compound number is not preceeded by a "P-" (e.g., "P-0001") in the Examples section, compound naming and/or enumeration is not related to naming and/or enumeration employed in other sections of this application. Similarly, structure and substituent naming and enumeration within the Examples are independent of structure and substituent naming and enumeration in above sections of this application unless clearly indicated otherwise.

[0082] In the following Examples, it is understood that the solvents and reagents used or suggested are not limiting, and can be substituted appropriately with solvents and reagents known to those of skill in the art. Reaction products may be isolated by means known in the art, such as extraction with a suitable solvent, precipitation from a suitable solvent, chromatography using a suitable solvent system, including silica gel column chromatography, HPLC, preparative TLC, and the like. Exemplary methods for synthesis of compounds of the present invention may be found in US Patent

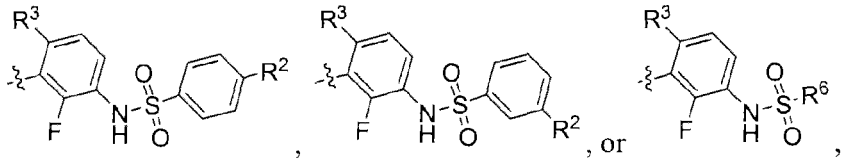
Application Serial number 11/473,347 (see also, PCT publication WO2007002433), the disclosure of which is hereby incorporated by reference. The 1H-pyrrolo[2,3-b]pyridine core of compounds described in the examples may also be referred to as 7-azaindole in the examples.

Example 1. Synthesis of compounds of Formula X



Step 1 - Preparation of compounds of Formula Xc and Xd

[0083] To a compound of Formula Xa (R^1 is as defined in paragraph [**0009**]) and a compound of Formula Xb (Y is consistent with compounds of Formula I, Formula II, or Formula III, e.g. Y is:

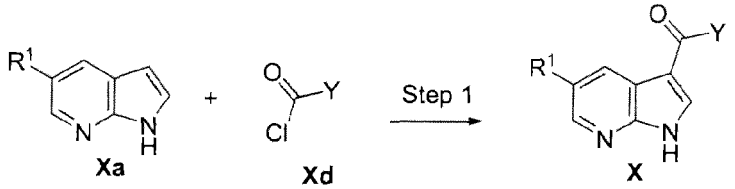


, where R^2 and R^3 are as defined in paragraph [**0009**], and R^6 is as defined in paragraph [**0017**], where ~ indicates the attachment point to the carbonyl carbon) is added an appropriate solvent (e.g. methanol) followed by an appropriate base (e.g. potassium hydroxide, sodium methoxide). The reaction is typically allowed to stir at room temperature overnight. Isolation by conventional means (e.g. extraction, washing and filtering) affords a mixture containing compound of Formula Xc, which may be isolated by silica gel chromatography if desired.

Step 2 - Preparation of compounds of Formula X

[0084] To a compound of Formula Xc in an appropriate solvent (e.g. tetrahydrofuran) is added an oxidizing agent (e.g.Dess-Martin periodane, TEMPO, DDQ). Typically, the reaction is allowed to stir at room temperature for 20 minutes. Isolation by conventional means (e.g. extraction and silica gel column chromatography) affords compounds of Formula X.

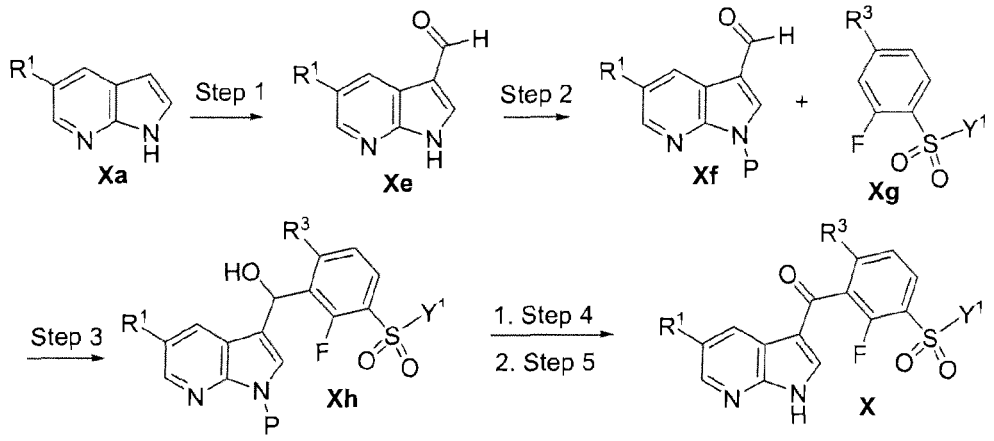
Example 2. Synthesis of Compounds of Formula X



Step -1- Synthesis of compound of Formula X

[0085] Compound of Formula X is synthesized by reacting a compound of Formula Xa (see Example 1) with a compound of Formula Xd (Y is as defined in Example 1), e.g. benzoyl chloride, in the presence of a Lewis acid (e.g. aluminum trichloride) in an inert solvent (e.g. dichloromethane) under an inert atmosphere (e.g. argon) at room temperature or with heating up to reflux for 1-18 hours. The desired compound X is isolated by extraction and silica gel column chromatography.

Example 3. Synthesis of Compounds of Formula X



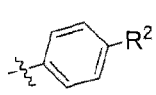
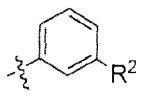
Step - 1 – Synthesis of compound Xe

[0086] Compound of Formula Xe can be synthesized by reacting a compound of Formula Xa (see Example 1) with hexamethyltetramine and acetic acid in water with heating to reflux for two hours. After cooling, the desired compound precipitates and may be collected by filtration.

Step - 2 – Synthesis of compound of Formula Xf

[0087] Compound of Formula Xf, where P is a nitrogen protecting group, is synthesized by reacting a compound Xe with an appropriate reagent to introduce a protecting group (e.g. triisopropylsilylchloride) and a base (e.g. sodium hydride) in a solvent (e.g. tetrahydrofuran) typically at room temperature for 8-12 hours. The desired compound is isolated by conventional means (e.g. extraction).

Step - 3 – Synthesis of compound of Formula Xh

[0088] Compound of Formula Xh is synthesized by reacting a compound of Formula Xf in a solvent (e.g. tetrahydrofuran) with an organolithium reagent (e.g. phenyl lithium) in a solvent (e.g. tetrahydrofuran) under an inert atmosphere, cooled to -78 °C. An appropriate organolithium reagent can also be prepared by reacting compounds of Formula Xg, where Y^1 is , ,

or -R^6 (indicates attachment point to the sulfone), where R^2, R^3 and R^6 are as defined in Example 1, with an organolithium reagent (e.g. butyllithium) in a solvent (e.g. tetrahydrofuran) under an inert atmosphere, cooled to -78 °C. The reaction is typically allowed to warm to room temperature and stirred for 30 minutes. The desired compound is isolated by conventional means (e.g. extraction).

Step - 4 – Synthesis of an intermediate of compound of Formula X

[0089] An intermediate of compound of Formula X is synthesized by reacting a compound of Formula Xh with an appropriate reagent to remove the protecting group, P, (e.g. *tetra*–n-butyl ammonium fluoride) in an appropriate solvent (e.g. tetrahydrofuran). The final product is isolated by standard procedures (e.g. extraction).

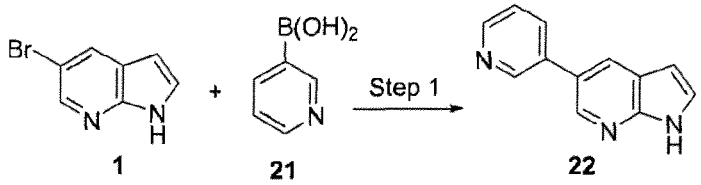
Step - 5 – Synthesis of compound of Formula X

[0090] Compound of Formula X is synthesized by reacting the intermediate from Step 4 with an oxidizing agent (e.g. Dess-Martin periodane, TEMPO) in an aprotic solvent (e.g. tetrahydrofuran) typically at room temperature for 20 minutes. The desired compound is isolated by conventional means (e.g. extraction and silica gel chromatography).

Example 4: Synthesis of 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine 22.

[0091] 5-Pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** was synthesized in one step from 5-bromo-1H-pyrrolo[2,3-b]pyridine **1** as described in Scheme 7.

Scheme 7



Step 1 – Preparation of 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (22):

[0092] To 5-bromo-7-azaindole (**1**, 1.00 g, 5.08 mmol) in water (13.0 mL) and acetonitrile (36 mL) were added pyridine-3-boronic acid (**21**, 1.0 g, 8.1 mmol), potassium carbonate (1.79 g, 0.0130 mol) and Tetrakis(triphenylphosphine)palladium(0) (50.0 mg, 0.043 mmol) under an atmosphere of nitrogen. The reaction mixture was heated to 170 °C overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified with silica gel column chromatography eluting with 25% ethyl acetate in hexane to provide a light yellow solid (**22**, 820 mg, 82%). MS(ESI)$[M+H^+]^+$ = 196.1.

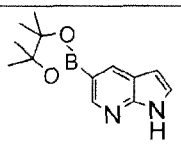
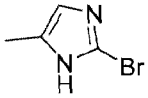
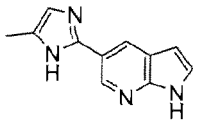
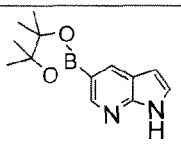
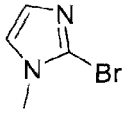
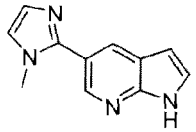
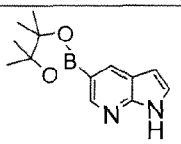
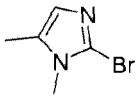
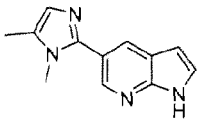
[0093] Additional compounds were prepared following the protocol of Scheme 7, either by substituting pyridine-3-boronic acid with an appropriate boronic acid or by substituting the 5-bromo-7-azaindole with 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and reacting with a suitable aryl or heteroaryl halide (i.e. coupling with the boronic acid ester on the azaindole, and the halide on the group to be coupled to the 5-position of the azaindole). The following compounds were prepared by this procedure:

5-(5-Methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine (**34**),

5-(1-Methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine (**35**), and

5-(1,5-Dimethyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine (**59**).

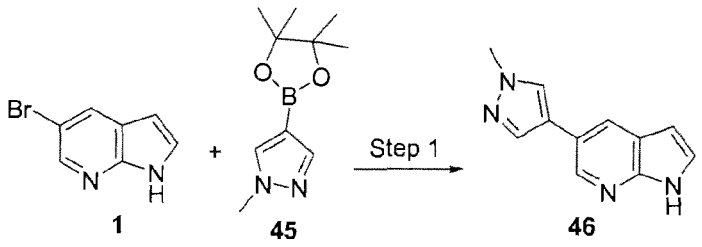
The following table indicates either 5-bromo-7-azaindole or 5-(4,4,5,5-Tetramethyl-[1,3,2] dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine starting material (column 1) and the appropriate reagent to be coupled to the 5 position of the azaindole (column 2) to afford the resulting compound (column 3), with the observed mass given in column 4.

Starting azaindole	Reagent coupled to 5 position	Compound	MS(ESI) $[M+H^+]^+$ observed
			199.2
			199.2
			213.2

Example 5: Synthesis of 5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine 46.

[0094] 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **46** was synthesized in one step from 5-bromo-1H-pyrrolo[2,3-b]pyridine **1** as shown in Scheme 12.

Scheme 12



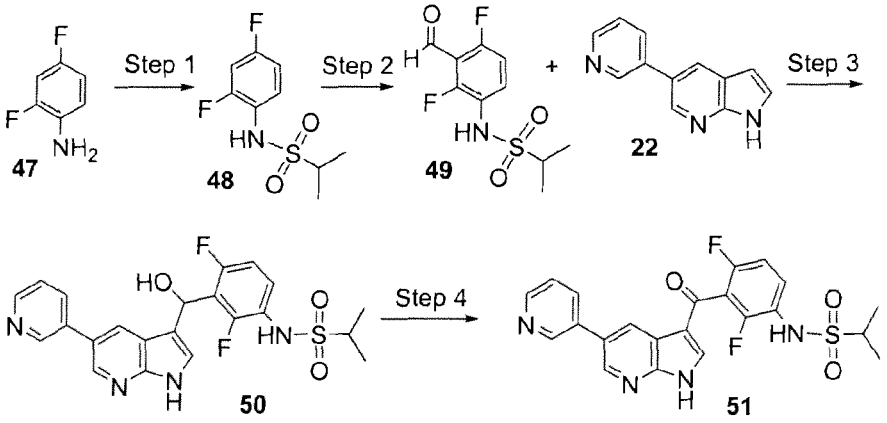
Step 1 – Preparation of 5-(1-Methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine (46):

[0095] To 5-bromo-7-azaindole (**1**, 1.04 g, 5.28 mmol) in 1.00 M potassium carbonate in water (15.8 mL) and tetrahydrofuran (50.0 mL) were added 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (**45**, 1.65 g, 7.92 mmol), Tetrakis(triphenylphosphine)-palladium(0) (0.305 mg, 0.26 mmol) and tetra-n-butylammonium iodide (0.20 g, 0.53 mmol). The reaction mixture was stirred at 70 °C overnight. The reaction mixture was poured into water and the organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified with silica gel column chromatography eluting with 25% ethyl acetate in hexane to provide a light yellow solid (**46**, 670 mg, 64.0%). MS(ESI)$[M+H^+]^+$ = 199.4.

Example 6: Preparation of propane-2-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide 51.

[0096] Propane-2-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide **51** was synthesized in four steps from 2,4-difluorophenylamine **47** as shown in Scheme 13.

Scheme 13



Step 1 – Preparation of propane-2-sulfonic acid (2,4-difluoro-phenyl)-amide (48):

[0097] To 2,4-difluoro-phenylamine (**47**, 4.0 mL, 40.0 mmol) in dichloromethane (50 mL) were added pyridine (3.37 mL, 42.3 mmol), propane-2-sulfonyl chloride (6.00 g, 42.3 mmol) and

dimethylaminopyridine (0.20 g, 1.64 mmol) under an atmosphere of nitrogen. The reaction was stirred at 45 °C overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated and purified by silica gel column chromatography 3% methanol in methylene chloride to give a white solid (**48**, 8.0 g, 85%). MS(ESI) $[M-H^+]^-$ = 234.0.

*Step 2 – Preparation of propane-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**49**):*

[0098] To propane-2-sulfonic acid (2,4-difluoro-phenyl)-amide (**48**, 2.35 g, 9.95 mmol) in tetrahydrofuran (70 mL) under an atmosphere of nitrogen cooled with a dry ice/acetone bath was added 1.60 M of n-butyllithium (1.60 M in hexane, 6.53 mL, 10.45 mmol). The reaction was stirred for 40 minutes, and then another portion of n-butyllithium (1.60 M in hexane, 6.84 mL, 10.94 mmol). The reaction was stirred for 1 hour and N,N-dimethylformamide (0.92 mL, 11.9 mmol) was added. The reaction was allowed to warm to room temperature overnight. The reaction was poured into water extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography (dichloromethane/methanol 5%) to give the compound (**49**, 1.4 g, 53.4%). MS(ESI) $[M - H^+]^-$ = 263.4.

*Step 3 – Preparation of propane-2-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**50**):*

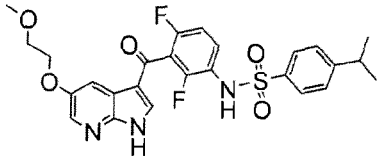
[0099] To propane-2-sulfonic acid (2,4-difluoro-3-formyl-phenyl)-amide (**49**, 220.0 mg, 0.83 mmol) in methanol (15 mL) was added 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine (**22**, 150.0 mg, 0.77 mmol, prepared as described in Example 4) and potassium hydroxide (537.0 mg, 9.6 mmol) under an atmosphere of nitrogen. The reaction was stirred at room temperature overnight. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% methanol in dichloromethane to give the compound (**50**, 160 mg, 45.3%). In this step, minor compound propane-2-sulfonic acid {2,4-difluoro-3-[methoxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide was also formed and isolated. MS(ESI) $[M + H^+]^+$ = 460.1.

*Step 4 – Preparation of propane-2-sulfonic acid [2,4-difluoro-3-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**51**):*

[0100] To propane-2-sulfonic acid {2,4-difluoro-3-[hydroxy-(5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-amide (**50**, 40.0 mg, 0.087 mmol) in tetrahydrofuran (10 mL) was added Dess-Martin periodane (48.0 mg, 0.11 mmol). The reaction was stirred at room temperature for 5 minutes. The reaction was poured into sodium thiosulfate and potassium carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium

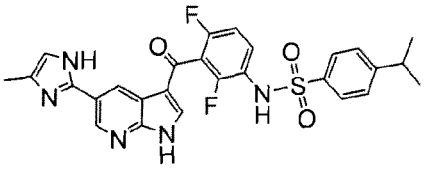
sulfate and filtrated. The filtrate was concentrated and purified by silica gel column chromatography eluting with 5% methanol in methylene chloride to give the compound (**51**, 13.4 mg, 33.5%). MS(ESI) $[M + H^+]^+ = 458.1$.

[0101] N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide **P-0018**



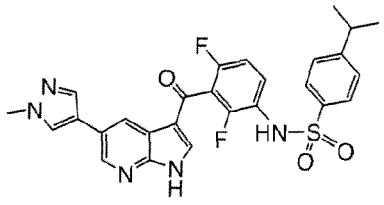
was prepared following the protocol of Scheme 13, substituting propane-2-sulfonyl chloride with 4-isopropyl-phenyl sulfonyl chloride in step 1 and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** with 5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine **19** in step 3. MS(ESI) $[M - H^+]^- = 530$.

[0102] N-{2,4-Difluoro-3-[5-(4-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide **P-0019**



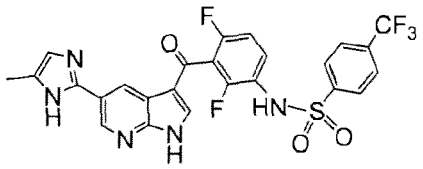
was prepared following the protocol of Scheme 13, substituting propane-2-sulfonyl chloride with 4-isopropyl-phenyl sulfonyl chloride in Step 1 and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** with 5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine **34** (see Example 4) in step 3. MS(ESI) $[M - H^+]^- = 536$.

[0103] N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide **P-0022**



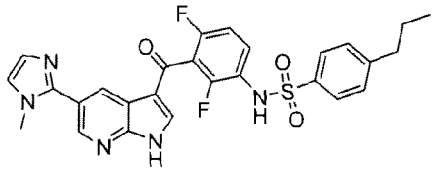
was prepared following the protocol of Scheme 13, substituting propane-2-sulfonyl chloride with 4-isopropyl-phenyl sulfonyl chloride in Step 1 and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** with 5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine **46** (see Example 5) in step 3. MS(ESI) $[M - H^+]^- = 536$.

[0104] N-{2,4-Difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide **P-0025**



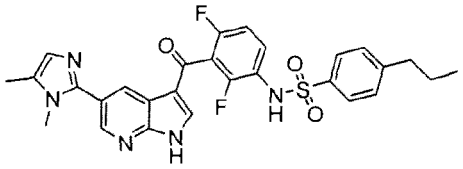
was prepared following the protocol of Scheme 13, substituting propane-2-sulfonyl chloride with 4-trifluoromethyl-phenyl sulfonyl chloride in Step 1 and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** with 5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine **34** (see Example 4).
MS(ESI) $[M - H^+]^-$ = 562.

[0105] N-{2,4-Difluoro-3-[5-(1-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide **P-0026**



was prepared following the protocol of Scheme 13, substituting propane-2-sulfonyl chloride with propane sulfonyl chloride in Step 1 and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** with 5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine **35** (see Example 4).
MS(ESI) $[M - H^+]^-$ = 536.2.

[0106] N-{3-[5-(1,5-Dimethyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-4-propyl-benzenesulfonamide **P-0027**

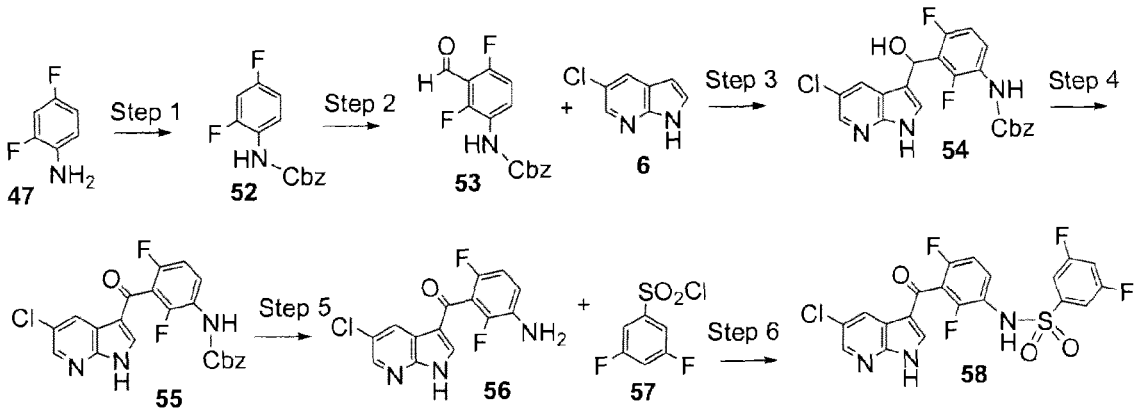


was prepared following the protocol of Scheme 13, substituting propane-2-sulfonyl chloride with propane sulfonyl chloride in Step 1 and 5-pyridin-3-yl-1H-pyrrolo[2,3-b]pyridine **22** with 5-(1,5-dimethyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine (**59**) (see Example 4). MS(ESI) $[M - H^+]^-$ = 550.1.

Example 7: Synthesis of N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3,5-difluorobenzenesulfonamide 58

[0107] Compound **P-1841** was synthesized in six steps from 2,4-difluoroaniline **47** as shown in Scheme 14.

Scheme 14



Step 1 - Preparation of (2,4-difluoro-phenyl)-carbamic acid benzyl ester (52):

[0108] To 2,4-difluoroaniline (**47**, 7.0 mL, 0.070 mol) in 100 mL of dichloromethane was added pyridine (11 mL, 0.14 mol) and benzyl chloroformate (11.9 mL, 0.0834 mol). The reaction mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and $KHSO_4$ solution. The organic layer was dried ($MgSO_4$), concentrated and crystallized from hexanes to give compound **52** (15.6 g, 85%).

Step 2 - Preparation of (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (53):

[0109] Into a round bottom flask was added (2,4-difluoro-phenyl)-carbamic acid benzyl ester (**52**, 3.83 g, 14.5 mmol) in tetrahydrofuran (148 mL, 1.82 mol). The solution was chilled to – 78 °C and n-butyllithium (1.60 M in hexane, 19.1 mL, 30.0 mmol) was added over 30 minutes followed by the addition of, N,N-dimethylformamide (1.12 mL, 14.5 mol). The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and crystallized from ether to give compound **53** (3.0 g, 71%).

Step 3 - Preparation of {2,4-difluoro-3-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid benzyl ester (54):

[0110] Into a round bottom flask was added 5-chloro-1H-pyrrolo[2,3-b]pyridine (**6**, 0.524 g, 3.43 mmol) in methanol (5.00 mL, 0.123 mol). Potassium hydroxide (0.800 g, 14.2 mmol) and (2,4-difluoro-3-formyl-phenyl)-carbamic acid benzyl ester (**53**, 1.02 g, 3.5 mmol) were added and the reaction mixture was stirred overnight. The reaction mixture was poured into 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and crystallized from ethyl acetate to give compound **54** (710 mg, 46%). MS(ESI)$[M+H^+]^+$ = 444.

*Step 4 - Preparation of [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-carbamic acid benzyl ester (**55**):*

[0111] Into a round bottom flask was added {2,4-difluoro-3-[hydroxy-(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]-phenyl}-carbamic acid benzyl ester (**54**, 1.01 g, 2.28 mmol) in tetrahydrofuran (5.00 mL, 0.0616 mol). Dess-Martin periodinane (1.20 g, 2.89 mmol) was added in portions. The reaction mixture was stirred at ambient temperature for 10 minutes, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel chromatography to give compound **55** (914 mg, 91%). MS(ESI)$[M+H^+]^+$ = 442.

*Step 5 - Preparation of (3-Amino-2,6-difluoro-phenyl)-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl) -methanone (**56**):*

[0112] [2,4-difluoro-3-(1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-carbamic acid benzyl ester (**55**, 800 mg, 1.81 mmol) was added to 10 M NaOH (15.00 mL) and warmed to reflux overnight. The reaction mixture was diluted with 30 mL of water and was extracted with ethyl acetate to give compound **56** (450 mg, 81%).

*Step 6 -Preparation of N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3,5-difluorobenzenesulfonamide (**58**):*

[0113] Into a microwave reaction vessel were combined (3-amino-2,6-difluoro-phenyl)-(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl) -methanone (**56**, 50 mg, 0.16 mmol), 3,5-difluorobenzenesulfonyl chloride (**57**, 103 mg, 0.49 mmol), pyridine (0.5 mL, 6.1820 mol) and tetrahydrofuran (3.0 mL,). The reaction was warmed in the CEM microwave at 300 watts, 130 °C for 10 minutes. The reaction mixture was partitioned between ethyl acetate and brine. The organic layer was collected, dried over Na_2SO_4, filtered and concentrated. The compound (**58**) was isolated using column chromatography (silica, hexane:ethyl acetate 70:30) to obtain 36 mg (46%) compound. MS = 482.0.

[0114] Additional compounds were prepared following the protocol of Scheme 14, optionally substituting 5-chloro-1H-pyrrolo[2,3-b]pyridine **6** with an appropriate azaindole in Step 3 and/or 3,5-difluorobenzenesulfonyl chloride **57** with an appropriate sulfonyl chloride in Step 6. The following compounds were prepared by this procedure:

Benzo[b]thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0001**),

5-Methyl-2-trifluoromethyl-furan-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0002**),

5-Oxazol-5-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0003**),

3-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenylsulfamoyl]-benzoic acid (**P-0004**),

2-Oxo-2H-chromene-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0005**),

5-Isoxazol-5-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0006**),

4-Butoxy-N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0007**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-pyrazol-1-yl-benzenesulfonamide (**P-0008**),

Benzothiazole-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0009**),

1-Methyl-3-trifluoromethyl-1H-pyrazole-4-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0010**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-isopropoxy-benzenesulfonamide (**P-0011**),

Benzo[1,2,5]thiadiazoe-5-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0013**),

4-tert-Butyl-N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide (**P-0014**),

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide (**P-0015**),N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-difluoromethoxy-benzenesulfonamide (**P-0016**),

5-Methyl-benzo[b]thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide (**P-0017**),

3-Difluoromethoxy-N-{2,4-difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-benzenesulfonamide (**P-0020**),

N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-0021**),

N-{2,4-Difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide (**P-0023**),

3-Difluoromethoxy-N-{2,4-difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-benzenesulfonamide (**P-0024**),

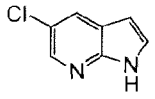
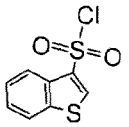
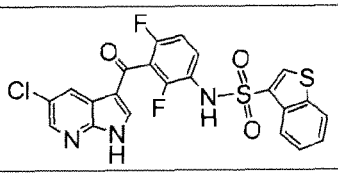
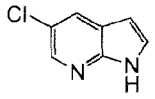
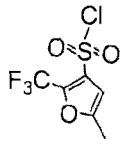
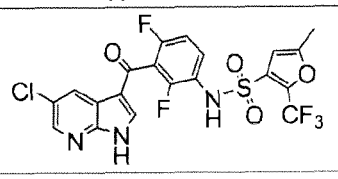
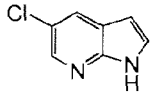
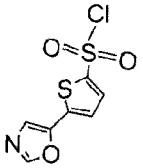
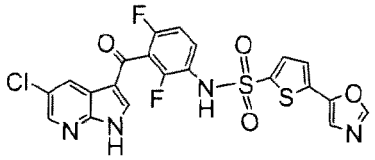
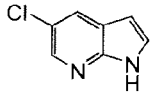
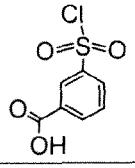
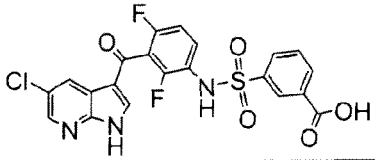
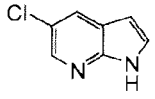
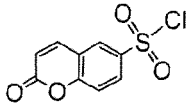
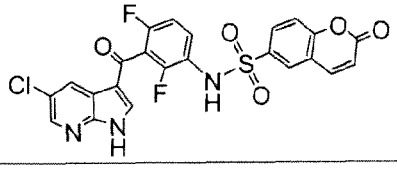
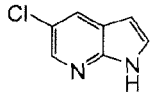
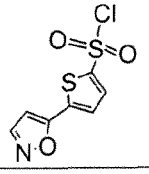
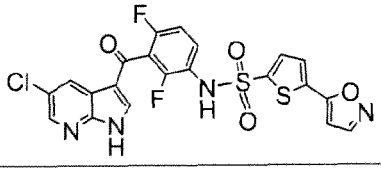
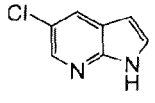
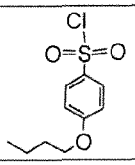
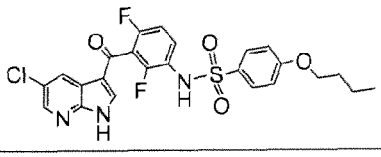
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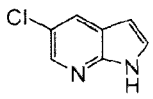
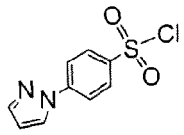
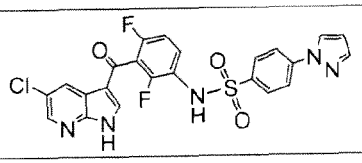
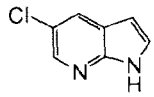
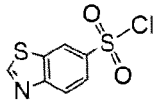
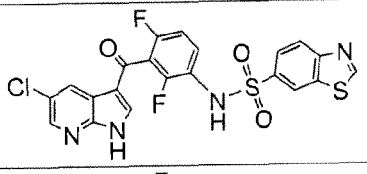
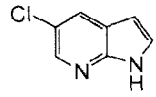
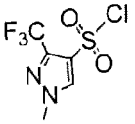
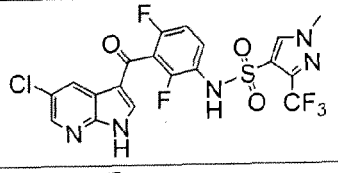
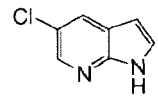
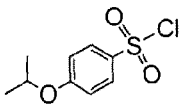
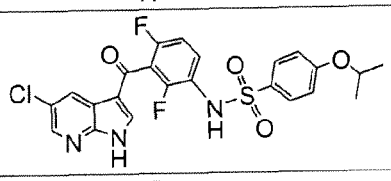
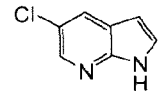
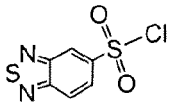
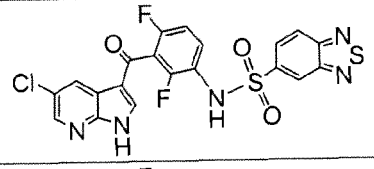
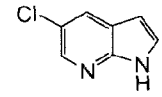
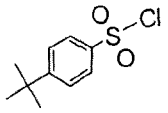
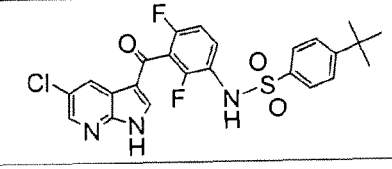
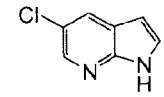
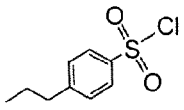
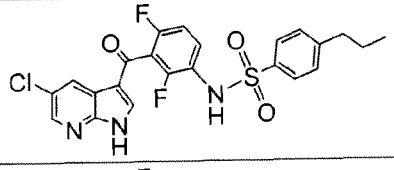
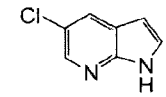
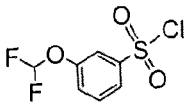
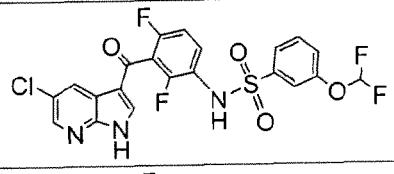
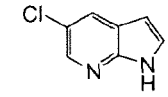
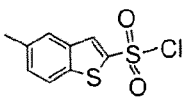
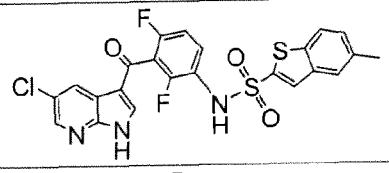
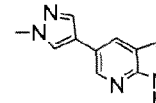
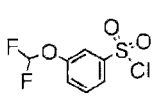
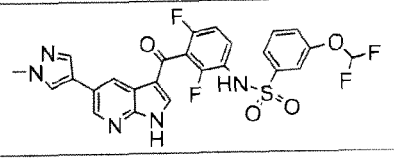
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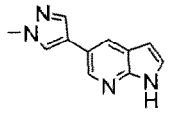
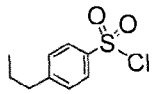
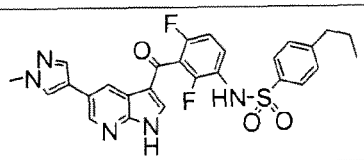
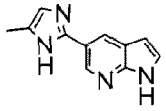
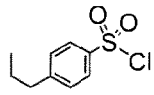
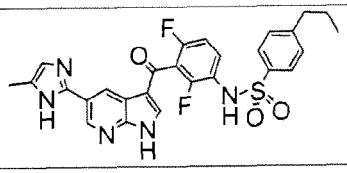
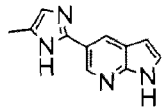
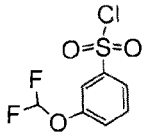
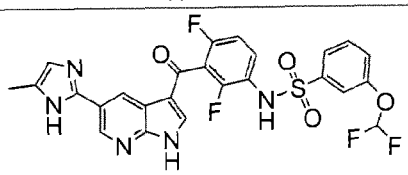
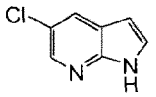
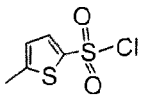
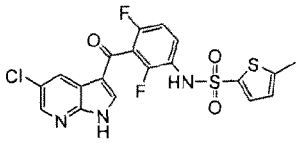
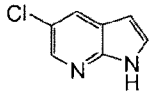
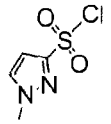
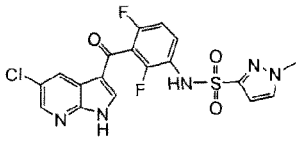
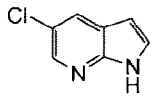
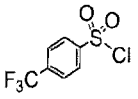
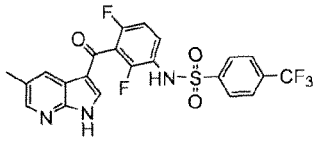
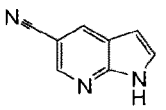
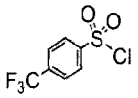
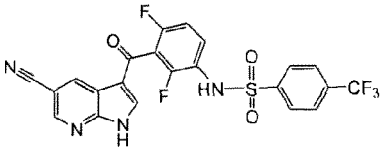
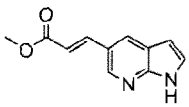
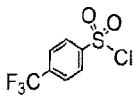
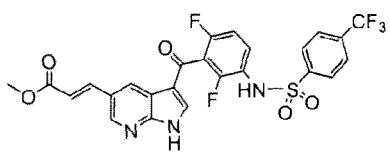
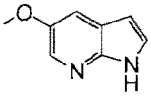
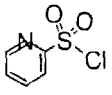
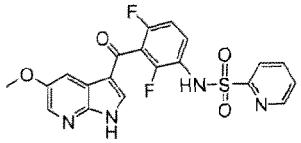
(E)-3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-acrylic acid methyl ester (**P-0032**), and

Pyridine-2-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-amide (**P-0036**).

The following table indicates the azaindole used in step 3 (column 2) and the sulfonyl chloride used in step 6 (column 3) to afford the target compound (column 4). The compound number is provided in column 1, with the observed mass given in column 5.

	Azaindole	Sulfonyl chloride	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0001				503.96
P-0002				
P-0003				520.3
P-0004				491.9
P-0005				515.9
P-0006				521.1
P-0007				519.9

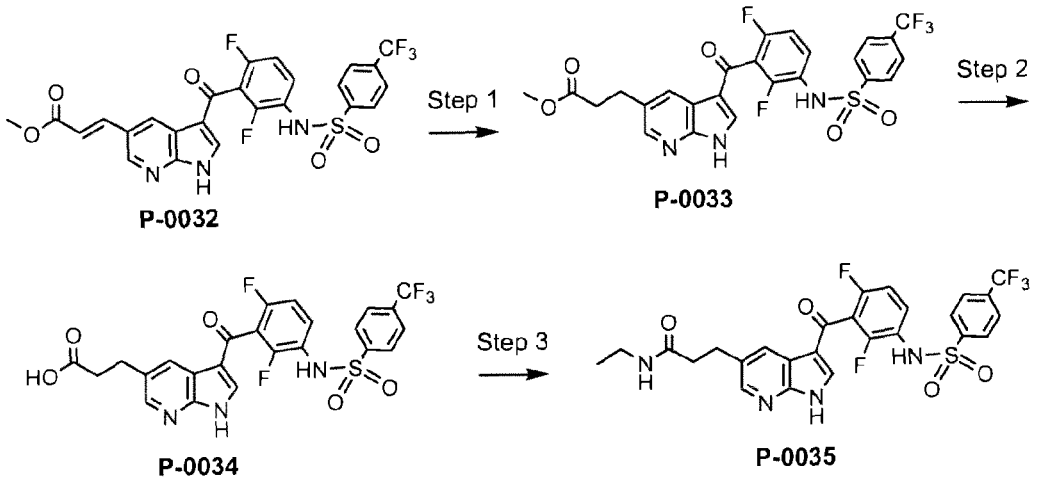
	Azaindole	Sulfonyl chloride	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0008				514.3
P-0009				505.1
P-0010				520.3
P-0011				505.9
P-0013				505.9
P-0014				503.9
P-0015				490.3
P-0016				514.3
P-0017				517.9
P-0020				560

	Azaindole	Sulfonyl chloride	Compound	MS(ESI) $[M+H^+]^+$ observed
P-0021				536
P-0023				536
P-0024				560
P-0028				469
P-0029				453
P-0030				496
P-0031				507
P-0032				566
P-0036				445

Example 8: Synthesis of 3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N-ethyl-propionamide P-0035.

[0115] 3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N-ethyl-propionamide **P-0035** was synthesized in three steps from (E)-3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-acrylic acid methyl ester **P-0032** as shown in Scheme 15.

Scheme 15



*Step 1 –Preparation of 3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid methyl ester **(P-0033)**:*

[0116] To (E)-3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-acrylic acid methyl ester (**P-0032**, 229 mg , 0.41 mmol, prepared as described in Example 7) was added methanol (15 mL) and tetrahydrofuran (5 mL). The solution was degassed with nitrogen for 5 minutes, followed by the addition of Pd/C (10% weight, 30 mg). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 18 hrs. After removing Pd/C and volatiles, the residue was purified through a quick silica plug eluted with ethyl acetate. Solvent was removed to provide an off-white solid (**P-0033**, 222 mg, 96%). MS (ESI) $[M+H^+]^+$=568.3.

*Step 2 – Preparation of 3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid **(P-0034)**:*

[0117] To 3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid methyl ester (**P-0033**, 215 mg, 0.38 mmol) dissolved in tetrahydrofuran (30 mL) was added 1 N lithium hydroxide solution (15 mL). The mixture was heated at 50 °C for 2 hrs, then acidified to pH~1-2 with 6 N HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered and

concentrated to provide an off-white solid (**P-0034**, 202 mg, 96%). MS (ESI) $[M+H^+]^+$=554.0.

*Step 3 – Preparation of 3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N-ethyl-propionamide (**P-0035**):*

[0118] To 3-{3-[2,6-difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid (**P-0034**, 42 mg, 0.076 mmol) dissolved in tetrahydrofuran (3 mL) was added a 2.0 M solution of ethylamine in tetrahydrofuran (110 µL, 0.23 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (29 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 16 hrs, then extracted with ethyl acetate and water. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The desired compound was isolated by silica gel column chromatography (methanol/dichloromethane), with the eluting solvents removed via lyophilizing to provide a white fluffy solid (**P-0035**, 13 mg, 30%). MS (ESI) $[M+H^+]^+$= 581.0.

Example 9: Kinase Activity Assays

[0119] Assays for the activity of B-Raf, B-Raf V600E, B-Raf V600E/T529I or c-Raf-1 are known in the art, for example as described in US Patent Application Serial number 11/473,347 (see also, PCT publication WO2007002433), the disclosure of which is hereby incorporated by reference in its entirety.

[0120] Representative compounds screened by at least one of the methods described in US Patent Application Serial number 11/473,347, or by similar methods, having IC_{50} of less than 10 µM under the test conditions employed are shown in tables 1a (B-Raf), 1b (B-Raf V600E), 1c (B-Raf V600E/T529I), and 1d (c-Raf-1).

Table 1a. Representative compounds with activity toward kinase B-Raf with $IC_{50} \leq 10$ µM under the test conditions employed.

B-Raf	P-0001, P-0002, P-0003, P-0005, P-0006, P-0007, P-0009, P-0011, P-0013, P-0014, P-0015, P-0016, P-0017, P-0018, P-0019, P-0020, P-0021, P-0022, P-0023, P-0024, P-0025, P-0026, P-0027, P-0028, P-0030, P-0031, P-0032, P-0033, P-0034, P-0035, P-0036

Table 1b. Representative compounds with activity toward kinase B-Raf V600E with $IC_{50} \leq 10$ µM under the test conditions employed.

B-Raf V600E	P-0001, P-0002, P-0003, P-0005, P-0006, P-0007, P-0009, P-0013, P-0014, P-0015, P-0016, P-0017, P-0019, P-0020, P-0021, P-0022, P-0023, P-0024, P-0025, P-0028, P-0029, P-0030, P-0031, P-0032, P-0033, P-0034, P-0035

Table 1c. Representative compounds with activity toward kinase B-Raf V600E/T529I with $IC_{50} \leq 10$ μM under the test conditions employed.

B-Raf V600E T529I	P-0003, P-0005, P-0006

Table 1d. Representative compounds with activity toward kinase c-Raf-1 with $IC_{50} \leq 10$ μM under the test conditions employed.

c-Raf-1:	P-0001, P-0002, P-0003, P-0005, P-0006, P-0007, P-0008, P-0009, P-0011, P-0013, P-0014, P-0015, P-0016, P-0017, P-0018, P-0019, P-0020, P-0021, P-0022, P-0023, P-0025, P-0030, P-0031

Example 10: Efficacy of Compounds in Combination with Standard-of-Care Chemotherapeutic agents in four human cancer cell lines.

[0121] Compounds of the invention, such as compounds of Formula I, Formula II, or Formula III, in combination with a standard chemotherapeutic agent, such as 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, or vinblastine, can be assessed for their effectiveness in killing human tumor cells. Human tumor cell lines, such as A-375 (malignant melanoma), SK-MEL-2 (malignant melanoma, skin metastasis), COLO 205 (colorectal adenocarcinoma, ascites metastasis) or SW-620 (colorectal adenocarcinoma, lymph node metastasis) can be treated with a compound of Formula I, Formula II, or Formula III alone, or in combination with one of the above-mentioned chemotherapeutic agents.

[0122] Tumor cells are grown as a monolayer at 37 °C in a humidified atmosphere (5% CO_2, 95% air). Cells are grown in a suitable culture medium, e.g. RPMI 1640 (Ref BE12-702F, Cambrex, Verviers, Belgium) containing 2 mM L-glutamine and supplemented with 10% fetal bovine serum (Ref DE14-801E, Cambrex). For experimental use, the tumor cells are detached from the culture flask by a 5-minute treatment with trypsin-versene (Ref 02-007E, Cambrex), diluted in Hanks' medium without calcium or magnesium (Ref BE10-543F, Cambrex). Trypsin treatment is neutralized by culture medium addition. The cells are counted in a hemocytometer and their viability assessed by 0.25% trypan blue exclusion.

[0123] The cell lines are checked for mycoplasma contamination with the Mycotect assay kit (Ref 15672-017, Invitrogen, Cergy-Pontoise, France) in accordance with the manufacturer's instructions. The mycoplasma test is assayed from the culture supernatants of the cell lines and compared to negative and positive controls.

[0124] The tumor cells (10,000 *per* well) are plated in 96-well flat-bottom microtitration plates (Ref 055260, Nunc, Dutscher, Brumath, France) and incubated at 37 °C for 24 hours before treatment in 100 µl of drug-free culture medium supplemented with 10% FBS. In order to assess the IC_{50} of each compound to be used for each cell line, the tumor cells are incubated in a 200 µl final volume of RPMI 1640 supplemented with 10% FBS and containing either a compound of Formula I, Formula II, or Formula III, or one of 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, or vinblastine. The compounds are tested in a suitable concentration range, such as 10^{-8} to 10^{-3} M for a compound of Formula I, Formula II, or Formula III, 5-fluorouracil, dacarbazine or gefitinib, 10^{-9} to 10^{-4} M for carboplatin, oxaliplatin, or temozolomide, 10^{-11} to 10^{-6} M for paclitaxel or SN-38, and 10^{-15} to 10^{-10} M for vinblastine. Compounds of Formula I, Formula II, or Formula III are dissolved in DMSO and diluted with culture medium to the desired concentrations. 5-fluorouracil (50 mg/ml, Dakota Pharm, LePlessis Robinson, France), carboplatin (10 mg/ml, Aguettant, Lyon, France), and paclitaxel (6 mg/ml, Bristol-Myers Squibb SpA, Rueil Malmaison, France), are diluted with culture medium to the desired concentrations. Dacarbazine (Sigma, Saint Quentin Fallavier, France) and vinblastine (Lilly France S.A., Saint Cloud, France) are dissolved in NaCl 0.9% and diluted with culture medium to the desired concentrations. Gefitinib is dissolved in a mixed solution of RPMI 1640 and DMSO and diluted with culture medium to the desired concentrations (maximum final DMSO of 0.1% v/v). SN-38 (LKT Laboratories, Inc., St. Paul, Minnesota) is dissolved in DMSO and diluted with culture medium to the desired concentrations (maximum final DMSO of 0.1% v/v). Temozolomide (LKT Laboratories, Inc., St. Paul, Minnesota) is dissolved in water for injection and diluted with culture medium to the desired concentrations. Cells are incubated for 96 hours in the presence of test substances at 37 °C under 5% CO_2. At the end of treatments, the cytotoxic activity is evaluated by an MTT assay.

[0125] For the MTT assay, at the end of the cells treatment, 20 µl of a 5 mg/ml solution 0.22 µm filtered tetrazolium reagent (MTT, Ref M2128, Sigma) in Phosphate Buffered Saline (PBS, Ref BE17-517Q, Cambrex), is added in each well. Culture plates are incubated for 2 h at 37 °C. The resulting supernatant is removed and formazan crystals dissolved with 200 µl of DMSO *per* well. Absorbency (OD) is measured at 570 nm in each well using VICTOR$^{3™}$ 1420 multilabeled counter (Wallac, PerkinElmer, Courtaboeuf, France).

[0126] The IC_{50} for each compound on each cell line is determined from the OD measurements of each sample. The dose response inhibition of cell proliferation is expressed as:

$$IC = (OD \text{ of drug exposed cells} / OD \text{ of drug free wells}) \times 100.$$

The mean of multiple measurements for each concentration is plotted vs. the drug concentration. The dose-response curves are plotted using XLFit 3 (IDBS, United Kingdom). The IC_{50} (drug concentration to obtain 50% inhibition of cell proliferation) determination values are calculated using

the XLFit 3 from semi-log curves. The IC_{50} value determined for each compound in each cell line is used to determine the concentration of a compound of Formula I, Formula II, or Formula III, and of the standard chemotherapeutic to be used in combination.

[0127] The cells are treated with a combination of five concentrations of a compound of Formula I, Formula II, or Formula III and five concentrations of one of 5-fluorouracil, carboplatin, dacarbazine, gefitinib, oxaliplatin, paclitaxel, SN-38, temozolomide, or vinblastine, based on the IC_{50} results. The compounds and cells are treated per the IC50 determination described above and assayed by the MTT assay.

[0128] The results are assessed to determine whether the combination is synergistic or antagonistic. The compound interactions are calculated by multiple drug effect analysis and are performed by the median equation principle according to the methodology described by Chou and Talalay (Adv. Enzyme Regul. 1984, **22**: 27-55).

[0129] The combination index (CI) will be calculated by the Chou *et al.* equation (Adv. Enzyme Regul. 1984, **22**: 27-55 ; Encyclopaedia of human biology, Academic Press, 1991, **2**: 371-9; Synergism and Antagonism in Chemotherapy, Academic Press, 1991, 61-102) which takes into account both the potency (D_m or IC_{50}) and the shape of the dose-effect curve (the m value). The general equation for the CI of the two compounds is given by:

$$CI = \frac{(D)_1}{(D_x)_1} + \frac{(D)_2}{(D_x)_2} + \frac{(D)_1(D)_2}{(D_x)_1(D_x)_2}$$

where:

$(D_x)_1$ and $(D_x)_2$ in the denominators are the doses (or concentrations) for compound 1 and compound 2 alone which demonstrate x% of inhibition, whereas $(D)_1$ and $(D)_2$ in the numerators are doses of both compounds (1 and 2) in combination that also inhibit x% (iso-effective). CI<1, =1, and >1 indicate synergism, additive effect and antagonism, respectively.

[0130] The $(D_x)_1$ and $(D_x)_2$ can be calculated from the median-effect equation of Chou *et al.* (J. Natl. Cancer Inst. 1994, **86**: 1517-24):

$$D_x = D_m\left(\frac{f_a}{(1-f_a)}\right)^{1/m}$$

where:

D_m is the median-effect dose that is obtained from the anti-log of x-intercept of the median-effect plot, $x = \log(D)$ *versus* $y = \log\{f_a/(1-f_a)\}$, or $D_m = 10^{-(y\text{-intercept})/m}$; and m is the slope of the median-effect plot and f_a is the fraction of cells affected by the treatment.

Each CI will be calculated with CalcuSyn software (Biosoft, UK) from the mean affected fraction at each drug *ratio* concentration.

[0131] Additional examples of certain methods contemplated by the present invention may be found in the following applications: U.S. Patent Publ. No. 2006/058339, App. Ser. No. 11/154,287; U.S. Patent Publ. No. 2006/058340, App. Ser. No. 11/154,988; U.S. Prov. App. No. 60/682,076, filed May 17, 2005; U.S. Prov. App. No. 60/682,058, filed May 17, 2005; U.S. Prov. App. No. 60/682,063, filed May 17, 2005; U.S. Prov. App. No. 60/682,051, filed May 17, 2005; U.S. Prov. App. No. 60/682,042, filed May 17, 2005; U.S. Prov. App. No. 60/692,750, filed June 22, 2005; and U.S. Prov. App. No. 60/692,960, filed June 22, 2005; U.S. Prov. App. No. 60/731,528, filed October 28, 2005, U.S. Patent App. No. 11/435,381, filed May 16, 2006, and U.S. Patent App. No. 11/473,347, filed June 21, 2006, each of which are hereby incorporated by reference herein in their entireties including all specifications, figures, and tables, and for all purposes.

[0132] All patents and other references cited in the specification are indicative of the level of skill of those skilled in the art to which the invention pertains, and are incorporated by reference in their entireties, including any tables and figures, to the same extent as if each reference had been incorporated by reference in its entirety individually.

[0133] One skilled in the art would readily appreciate that the present invention is well adapted to obtain the ends and advantages mentioned, as well as those inherent therein. The methods, variances, and compositions described herein as presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art, which are encompassed within the spirit of the invention, are defined by the scope of the claims.

[0134] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, variations can be made to crystallization or co-crystallization conditions for Ret and Ret surrogate proteins and/or various kinase domain sequences can be used.

Thus, such additional embodiments are within the scope of the present invention and the following claims.

[0135] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. Thus, for an embodiment of the invention using one of the terms, the invention also includes another embodiment wherein one of these terms is replaced with another of these terms. In each embodiment, the terms have their established meaning. Thus, for example, one embodiment may encompass a method "comprising" a series of steps, another embodiment would encompass a method "consisting essentially of" the same steps, and a third embodiment would encompass a method "consisting of" the same steps. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

[0136] In addition, where features or aspects of the invention are described in terms of Markush groups or other grouping of alternatives, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group or other group.

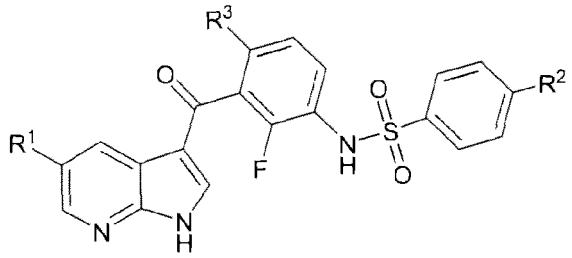
[0137] Also, unless indicated to the contrary, where various numerical values are provided for embodiments, additional embodiments are described by taking any 2 different values as the endpoints of a range. Such ranges are also within the scope of the described invention.

[0138] Thus, additional embodiments are within the scope of the invention and within the following claims.

CLAIMS

What is claimed is:

1. A compound having the chemical structure of Formula I,



all salts, prodrugs, tautomers and isomers thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, -C(O)OH, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from fluoro, -OH, $-NH_2$, C(O)OH, $-C(O)NH_2$, $-OR^7$, $-NR^8R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^2 is selected from the group consisting of halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, -C(O)OH, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl is optionally substituted with one or more substituents selected from fluoro, $-OR^7$, $-NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^2 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$,

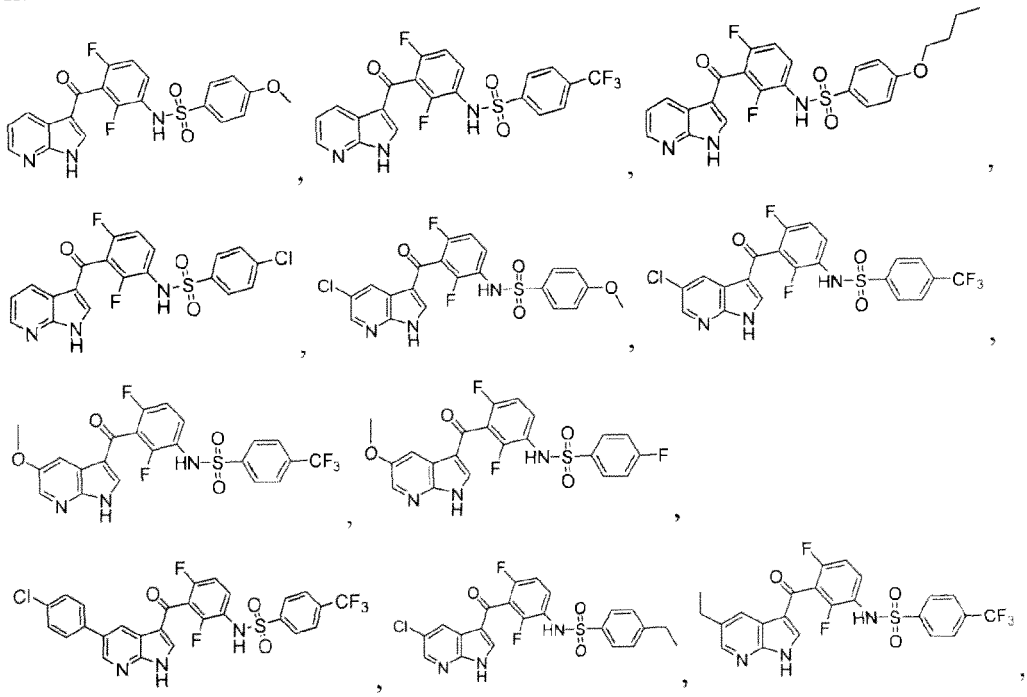
-C(O)R^9, -C(O)NR^8R^9, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

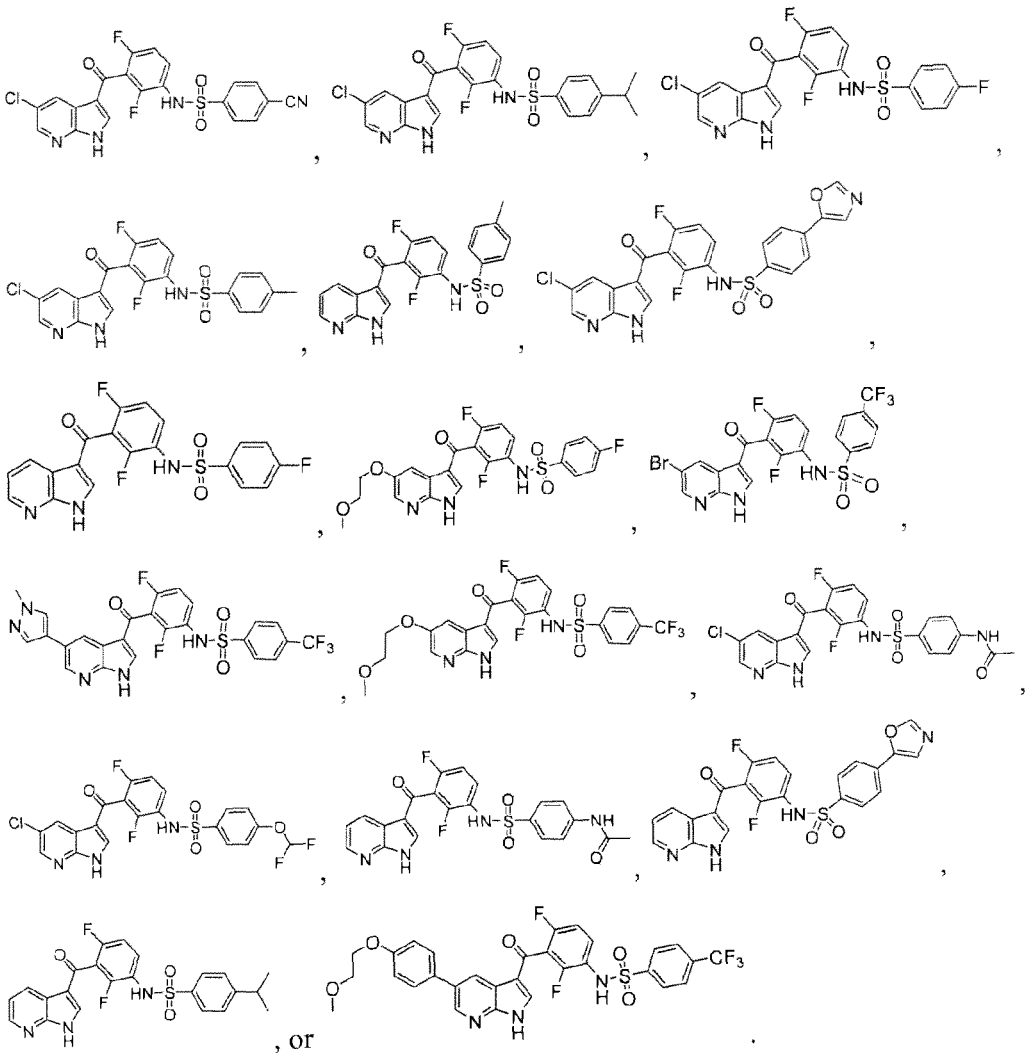
R^3 is selected from the group consisting of hydrogen, fluoro and chloro;

R^7 is selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^7 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -C(O)NR^8R^9, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

R^8 at each occurrence is independently hydrogen or lower alkyl; and

R^9 at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy, provided, however, the compound is not





2. The compound of Claim 1, wherein:

R^1 is selected from the group consisting of hydrogen, -CN, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-C(O)NR^8R^7$, $-C(O)R^7$, $-S(O)_2NR^8R^7$, $-S(O)R^7$, $-S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

R^2 is selected from the group consisting of -CN, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8S(O)_2R^7$, $-C(O)NR^8R^7$, $-C(O)R^7$, $-S(O)_2NR^8R^7$, $-S(O)R^7$, $-S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^2 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

3. The compound of Claim 2, wherein:

R^1 is hydrogen, -CN, $-NR^8R^7$, $-OR^7$, $-S(O)_2R^7$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ and $-S(O)_2R^7$, and

R^2 is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ or $-S(O)_2R^7$.

4. The compound of Claim 3, wherein:

R^1 is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkoxy substituted C_{2-6}alkoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, and cycloalkylamino, and

R^2 is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, or cycloalkylamino.

5. The compound of Claim 1, wherein the compound is selected from the group consisting of:

4-Butoxy-N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide,

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-pyrazol-1-yl-benzenesulfonamide,

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-isopropoxy-benzenesulfonamide,

4-tert-Butyl-N-[3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-benzenesulfonamide,

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-propyl-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(2-methoxy-ethoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(4-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide,

4-Difluoromethoxy-N-{2,4-difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(1-methyl-1H-pyrazol-4-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-isopropyl-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-trifluoromethyl-benzenesulfonamide,

N-{2,4-Difluoro-3-[5-(1-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-4-propyl-benzenesulfonamide,

N-{3-[5-(1,5-Dimethyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-4-propyl-benzenesulfonamide,

N-[2,4-Difluoro-3-(5-methyl-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-4-trifluoromethyl-benzenesulfonamide,

N-[3-(5-Cyano-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-4-trifluoromethyl-benzenesulfonamide,

(E)-3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-acrylic acid methyl ester,

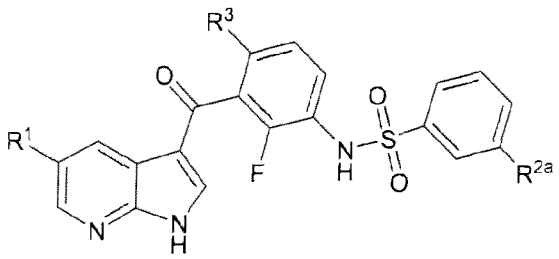
3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid methyl ester,

3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-propionic acid,

3-{3-[2,6-Difluoro-3-(4-trifluoromethyl-benzenesulfonylamino)-benzoyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-N-ethyl-propionamide; and

all salts, prodrugs, tautomers, and isomers thereof.

6. A compound having the chemical structure of Formula II,



all salts, prodrugs, tautomers and isomers thereof,

wherein:

R^1 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, -C(O)OH, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from fluoro, -OH, $-NH_2$, C(O)OH, $-C(O)NH_2$, $-OR^7$, $-NR^8R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

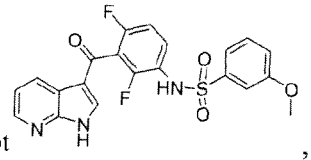
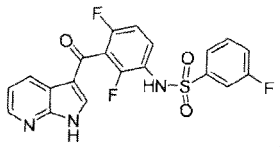
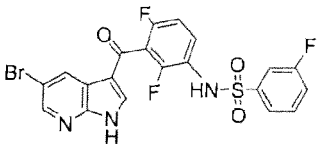
R^{2a} is selected from the group consisting of halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, -C(O)OH, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl is optionally substituted with one or more substituents selected from fluoro, $-OR^7$, $-NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{2a} or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

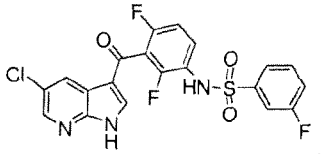
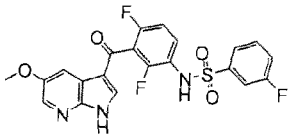
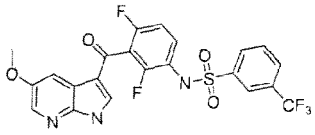
R^3 is selected from the group consisting of hydrogen, fluoro and chloro;

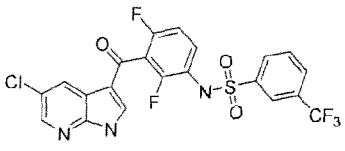
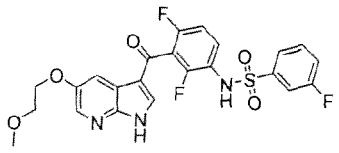
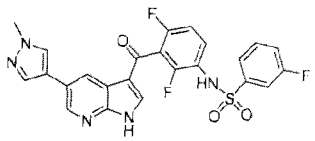
R^7 is selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^7 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

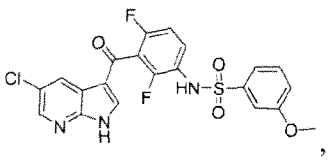
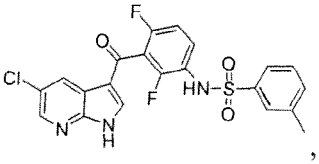
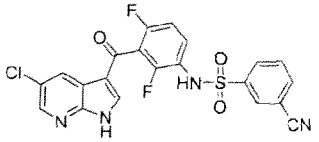
R^8 at each occurrence is independently hydrogen or lower alkyl; and

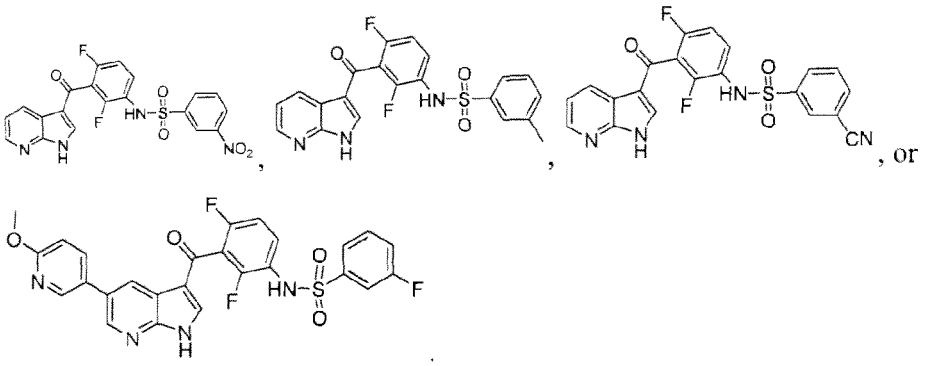
R^9 at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and wherein heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy, provided, however, the compound is

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7. The compound of Claim 6, wherein:

R^1 is selected from the group consisting of hydrogen, -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -$C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

R^{2a} is selected from the group consisting of -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^{2a} or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -$C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

8. The compound of Claim 7, wherein:

R^1 is hydrogen, -CN, $-NR^8R^7$, $-OR^7$, $-S(O)_2R^7$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ and $-S(O)_2R^7$, and

R^{2a} is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, $-NR^8R^7$, $-OR^7$ or $-S(O)_2R^7$.

9. The compound of Claim 8, wherein:

R^1 is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkoxy substituted C_{2-6}alkoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, and cycloalkylamino, and

R^{2a} is -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, or cycloalkylamino.

10. The compound of Claim 6, wherein the compound is selected from the group consisting of:

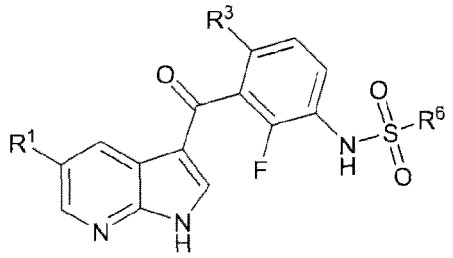
3-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenylsulfamoyl]-benzoic acid,

N-[3-(5-Chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-3-difluoromethoxy-benzenesulfonamide,

3-Difluoromethoxy-N-{2,4-difluoro-3-[5-(5-methyl-1H-imidazol-2-yl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-phenyl}-benzenesulfonamide; and

all salts, prodrugs, tautomers, and isomers thereof.

11. A compound having the chemical structure of Formula III,



all salts, prodrugs, tautomers and isomers thereof,

R^1 is selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, -C(O)OH,

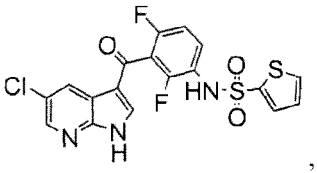
$-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from fluoro, -OH, $-NH_2$, C(O)OH, $-C(O)NH_2$, $-OR^7$, $-NR^8R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl, lower alkenyl or lower alkynyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

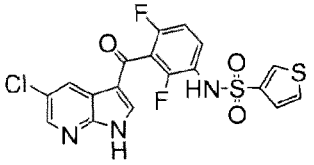
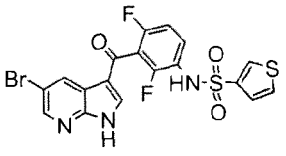
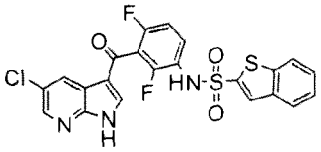
R^3 is selected from the group consisting of hydrogen, fluoro and chloro;

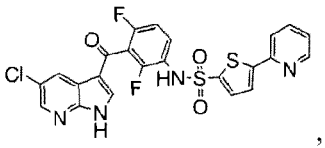
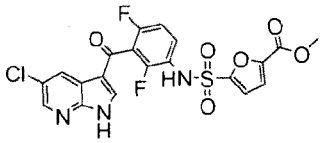
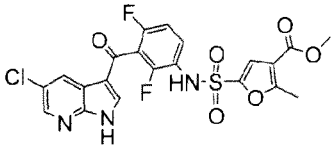
R^6 is heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, -OH, $-NH_2$, -CN, $-NO_2$, -C(O)OH, $-S(O)_2NH_2$, $-C(O)NH_2$, $-C(S)NH_2$, $-NHC(O)NH_2$, $-NHC(S)NH_2$, $-NHS(O)_2NH_2$, $-OR^7$, $-SR^7$, $-NR^8R^7$, $-C(O)R^7$, $-C(S)R^7$, $-C(O)OR^7$, $-C(O)NR^8R^7$, $-C(S)NR^8R^7$, $-S(O)_2NR^8R^7$, $-NR^8C(O)R^7$, $-NR^8C(S)R^7$, $-NR^8S(O)_2R^7$, $-NR^8C(O)NH_2$, $-NR^8C(O)NR^8R^7$, $-NR^8C(S)NH_2$, $-NR^8C(S)NR^8R^7$, $-NR^8S(O)_2NH_2$, $-NR^8S(O)_2NR^8R^7$, $-S(O)R^7$, and $-S(O)_2R^7$, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, $-OR^7$, $-NR^8R^7$, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of R^6 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

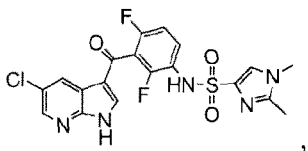
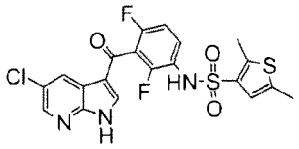
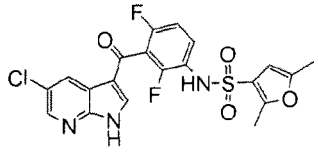
R^7 is selected from the group consisting of lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^7 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, $-NH_2$, -CN, $-NO_2$, $-S(O)_2NH_2$, $-C(O)NH_2$, $-OR^9$, $-SR^9$, $-NR^8R^9$, $-NR^8C(O)R^9$, $-NR^8S(O)_2R^9$, $-S(O)_2R^9$, $-S(O)_2NR^8R^9$, $-C(O)R^9$, $-C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino;

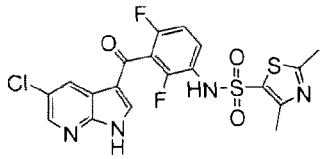
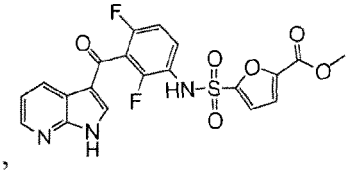
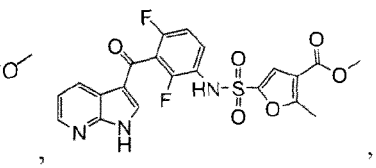
R^8 at each occurrence is independently hydrogen or lower alkyl; and

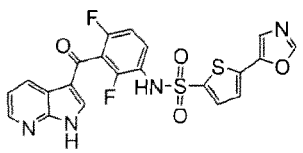
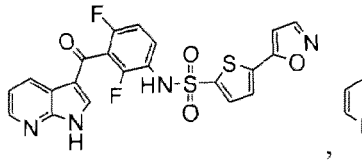
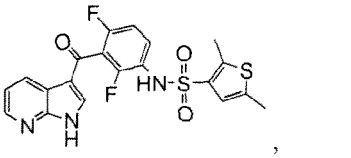
R^9 at each occurrence is independently selected from the group consisting of lower alkyl, heterocycloalkyl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, and cycloalkylamino, and heterocycloalkyl and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, -CN, lower alkyl, fluoro substituted lower alkyl, lower alkoxy and fluoro substituted lower alkoxy, provided, however, the compound is not ,

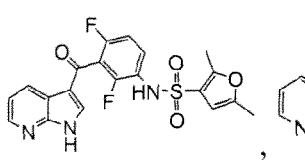
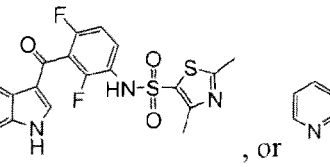
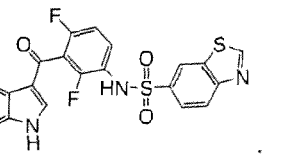
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12. The compound of Claim 11, wherein:

R^1 is selected from the group consisting of hydrogen, -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as R^1 or as substituents of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -$C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino; and

R^6 is heteroaryl optionally substituted with one or more substituents selected from the group consisting of -CN, -OR^7, -SR^7, -NR^8R^7, -$NR^8C(O)R^7$, -$NR^8S(O)_2R^7$, -$C(O)NR^8R^7$, -$C(O)R^7$, -$S(O)_2NR^8R^7$, -$S(O)R^7$, -$S(O)_2R^7$, halogen, lower alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of fluoro, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio, fluoro substituted lower alkylthio, mono-alkylamino, di-alkylamino, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, and wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl as a substituent of R^6 or as a substituent of lower alkyl are optionally substituted with one or more substituents selected from the group consisting of -OH, -NH_2, -CN, -NO_2, -$S(O)_2NH_2$, -$C(O)NH_2$, -OR^9, -SR^9, -NR^8R^9, -$NR^8C(O)R^9$, -$NR^8S(O)_2R^9$, -$S(O)_2R^9$, -$S(O)_2NR^8R^9$, -$C(O)R^9$, -$C(O)NR^8R^9$, halogen, lower alkyl, fluoro substituted lower alkyl, and cycloalkylamino.

13. The compound of Claim 12, wherein:

R^1 is hydrogen, -CN, -NR^8R^7, -OR^7, -$S(O)_2R^7$, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, -NR^8R^7, -OR^7 and -$S(O)_2R^7$, and

R^6 is heteroaryl optionally substituted with one or more of -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, -NR^8R^7, -OR^7 or -$S(O)_2R^7$.

14. The compound of Claim 13, wherein:

R^1 is hydrogen, -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkoxy substituted C_{2-6}alkoxy, aryl or heteroaryl, wherein aryl or heteroaryl are optionally substituted with one or more substituents selected from the group consisting of fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, and cycloalkylamino, and

R^6 is heteroaryl optionally substituted with one or more of -CN, fluoro, chloro, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, mono-alkylamino, di-alkylamino, or cycloalkylamino.

15. The compound of Claim 11, wherein the compound is selected from the group consisting of:

Benzo[b]thiophene-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

5-Methyl-2-trifluoromethyl-furan-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

5-Oxazol-5-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

2-Oxo-2H-chromene-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

5-Isoxazol-5-yl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

Benzothiazole-6-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

1-Methyl-3-trifluoromethyl-1H-pyrazole-4-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

Benzo[1,2,5]thiadiazoe-5-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

5-Methyl-benzo[b]thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

5-Methyl-thiophene-2-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

1-Methyl-1H-pyrazole-3-sulfonic acid [3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluoro-phenyl]-amide,

Pyridine-2-sulfonic acid [2,4-difluoro-3-(5-methoxy-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-phenyl]-

amide; and

all salts, prodrugs, tautomers, and isomers thereof.

16. A composition comprising: a pharmaceutically acceptable carrier; and a compound according to any of Claims **1-15**.

17. A method for treating a subject suffering from or at risk of an A-Raf-mediated, B-Raf-mediated and/or c-Raf-1-mediated disease or condition, comprising administering to the subject an effective amount of a compound of any of Claims **1-15** or a composition of Claim **16**.

18. The method of Claim **17**, wherein the compound or composition is approved for administration to a human.

19. The method of Claim **18**, wherein the disease or condition is selected from the group consisting of multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease, Parkinson's disease, melanoma, glioma, sarcoma, cancer of the colon, lung, breast, pancreas, thyroid, ovary, liver, or kidney, medullary thyroid cancer, carcinoid, small cell lung cancer, pheochromocytoma, lymphoma, neurofibromatosis, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuropathic pain, inflammatory pain, acute pain, chronic pain, cancer-related pain, migraine, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis, atherosclerosis, reperfusion injury, psoriasis, arthritis, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease, immunodeficiency diseases, organ transplant rejection, graft versus host disease, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia, obesity, *Helicobacter pylori* infection, *Hepatitis* infection, *Influenza virus* infection, fever, sepsis, chronic obstructive pulmonary disease, acute respiratory distress syndrome, Noonan's syndrome, Costello syndrome, LEOPARD syndrome, cardio-faciocutaneous syndrome, neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases, sarcopenia, muscular dystrophy, motor neuron diseases, inflammatory myopathies, diseases of the neuromuscular junction, myopathies due to endocrine abnormalities, diseases of peripheral nerve, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, periodic paralysis and metabolic diseases of muscle.

20. A kit comprising a compound according to any of Claims **1-15** or a composition according to Claim **16**.

21. The kit of Claim 20, wherein the compound or composition is approved for a medical indication selected from the group consisting of multi-infarct dementia, head injury, spinal cord injury, Alzheimer's disease, Parkinson's disease, melanoma, glioma, sarcoma, cancer of the colon,

lung, breast, pancreas, thyroid, ovary, liver, or kidney, medullary thyroid cancer, carcinoid, small cell lung cancer, pheochromocytoma, lymphoma, neurofibromatosis, myelodysplastic syndrome, leukemia, tumor angiogenesis, neuropathic pain, inflammatory pain, acute pain, chronic pain, cancer-related pain, migraine, heart failure, ischemic stroke, cardiac hypertrophy, thrombosis, atherosclerosis, reperfusion injury, psoriasis, arthritis, osteoarthritis, endometriosis, scarring, vascular restenosis, fibrotic disorders, rheumatoid arthritis, inflammatory bowel disease, immunodeficiency diseases, organ transplant rejection, graft versus host disease, diabetic nephropathy, polycystic kidney disease, nephrosclerosis, glomerulonephritis, prostate hyperplasia, obesity, *Helicobacter pylori* infection, *Hepatitis* infection, *Influenza virus* infection, fever, sepsis, chronic obstructive pulmonary disease, acute respiratory distress syndrome, Noonan's syndrome, Costello syndrome, LEOPARD syndrome, cardio-faciocutaneous syndrome, neural crest syndrome abnormalities causing cardiovascular, skeletal, intestinal, skin, hair and endocrine diseases, sarcopenia, muscular dystrophy, motor neuron diseases, inflammatory myopathies, diseases of the neuromuscular junction, myopathies due to endocrine abnormalities, diseases of peripheral nerve, myotonia congenita, paramyotonia congenita, central core disease, nemaline myopathy, myotubular myopathy, periodic paralysis and metabolic diseases of muscle.