RAF INHIBITOR COMPOUNDS AND METHODS OF USE THEREOF

[0001] PRIORITY OF INVENTION

[0002] This application claims priority under 35 U.S.C. 119(e) from United States Provisional Patent Application Number 61/238,107, filed 28 August 2009, the content of which is incorporated herein in its entirety.

BACKGROUND OF THE INVENTION

[0003] FIELD OF THE INVENTION

[0004] The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to a process for making the compounds and to the use of the compounds in therapy. More particularly, it relates to certain substituted compounds useful for inhibiting Raf kinase and for treating disorders mediated thereby.

[0005] DESCRIPTION OF THE STATE OF THE ART

[0006] The Raf/MEK/ERK pathway is critical for cell survival, growth, proliferation and tumorigenesis. Li, Nanxin, et al. "B-Raf kinase inhibitors for cancer treatment." Current Opinion in Investigational Drugs. Vol. 8, No. 6 (2007): 452-456. Raf kinases exist as three isoforms, A-Raf, B-Raf and C-Raf. Among the three isoforms, studies have shown that B-Raf functions as the primary MEK activator. B-Raf is one of the most frequently mutated genes in human cancers. B-Raf kinase represents an excellent target for anticancer therapy based on preclinical target validation, epidemiology and drugability.

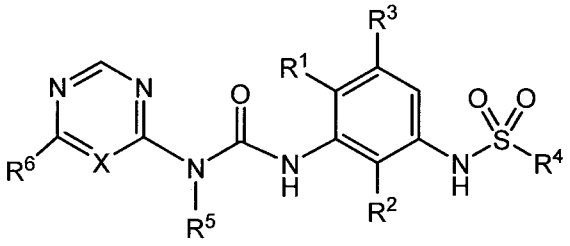
[0007] Small molecule inhibitors of B-Raf are being developed for anticancer therapy. Nexavar® (sorafenib tosylate) is a multikinase inhibitor, which includes inhibition of B-Raf, and is approved for the treatment of patients with advanced renal cell carcinoma and unresectable hepatocellular carcinoma. Other Raf inhibitors have also been disclosed or have entered clinical trials, for example RAF-265, GSK-2118436, PLX-4032, PLX-3603, and XL-281. Other B-Raf inhibitors are also known, see for example, U.S. Patent Application Publication 2006/0189627, U.S. Patent Application Publication 2006/0281751, U.S. Patent Application Publication 2007/0049603, U.S. Patent Application Publication 2009/0176809, International Patent Application Publication WO 2007/002325, International Patent Application Publication WO 2007/002433, International Patent Application Publication WO 2008/028141, International Patent Application Publication WO 2008/079903, International Patent Application Publication WO 2008/079906 and International Patent Application Publication WO 2009/012283.

[0008] International Patent Application Publication WO 2006/066913, International Patent Application Publication WO 2008/028617 and International Patent Application Publication WO 2008/079909 also disclose kinase inhibitors.

SUMMARY OF THE INVENTION

[0009] In one aspect, the invention relates to compounds that are inhibitors of Raf kinases, particularly B-Raf inhibitors. Certain hyperproliferative disorders are characterized by the overactivation of Raf kinase function, for example by mutations or overexpression of the protein. Accordingly, the compounds of the invention are useful in the treatment of hyperproliferative disorders, such as cancer.

[0010] More specifically, one aspect of the present invention provides compounds of Formula **I**:



I

and stereoisomers, tautomers and pharmaceutically acceptable salts thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6 and X are as defined herein.

[0011] Another aspect of the present invention provides methods of preventing or treating a disease or disorder modulated by B-Raf, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof. Examples of such diseases and disorders include, but are not limited to, hyperproliferative disorders (such as cancer, including melanoma and other cancers of the skin), neurodegeneration, cardiac hypertrophy, pain, migraine and neurotraumatic disease.

[0012] Another aspect of the present invention provides methods of preventing or treating a disease or disorder modulated by B-Raf, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention or a stereoisomer or pharmaceutically acceptable salt thereof. Examples of such diseases and disorders include, but are not limited to, hyperproliferative disorders (such as cancer, including melanoma and other cancers of the skin), neurodegeneration, cardiac hypertrophy, pain, migraine and neurotraumatic disease.

[0013] Another aspect of the present invention provides methods of preventing or treating cancer, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention, or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds having anti-cancer properties.

[0014] Another aspect of the present invention provides methods of preventing or treating cancer, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention, or a stereoisomer or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds having anti-cancer properties.

[0015] Another aspect of the present invention provides a method of treating a hyperproliferative disease in a mammal comprising administering a therapeutically effective amount of a compound of this invention to the mammal.

[0016] Another aspect of the present invention provides methods of preventing or treating kidney disease, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention, or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds. Another aspect of the present invention provides methods of preventing or treating polycystic kidney disease, comprising administering to a mammal in need of such treatment an effective amount of a compound of this invention, or a stereoisomer, prodrug or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds.

[0017] Another aspect of the present invention provides the compounds of the present invention for use in therapy.

[0018] Another aspect of the present invention provides the compounds of the present invention for use in the treatment of a hyperproliferative disease. In a further embodiment, the hyperproliferative disease may be cancer (or still further, a specific cancer as defined herein).

[0019] Another aspect of the present invention provides the compounds of the present invention for use in the treatment of a kidney disease. In a further embodiment, the kidney disease may be polycystic kidney disease.

[0020] Another aspect of the present invention provides the use of a compound of this invention in the manufacture of a medicament for the treatment of a hyperproliferative disease. In a further embodiment, the hyperproliferative disease may be cancer (or still further, a specific cancer as defined herein).

[0021] Another aspect of the present invention provides the use of a compound of this invention in the manufacture of a medicament for the treatment of a kidney disease. In a further embodiment, the kidney disease may be polycystic kidney disease.

[0022] Another aspect of the present invention provides the use of a compound of the present invention in the manufacture of a medicament, for use as a B-Raf inhibitor in the treatment of a patient undergoing cancer therapy.

[0023] Another aspect of the present invention provides the use of a compound of the present invention in the manufacture of a medicament, for use as a B-Raf inhibitor in the treatment of a patient undergoing polycystic kidney disease therapy.

[0024] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of the present invention for use in the treatment of a hyperproliferative disease.

[0025] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of the present invention for use in the treatment of cancer.

[0026] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of the present invention for use in the treatment of polycystic kidney disease.

[0027] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of this invention, a stereoisomer, prodrug or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0028] Another aspect of the present invention provides a pharmaceutical composition comprising a compound of this invention or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

[0029] Another aspect of the present invention provides intermediates for preparing compounds of Formulas I-IV. Certain compounds of Formulas I-IV may be used as intermediates for other compounds of Formulas I-IV.

[0030] Another aspect of the present invention includes methods of preparing, methods of separation, and methods of purification of the compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

[0031] Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims. One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[0032] DEFINITIONS

[0033] The term "alkyl" includes linear or branched-chain radicals of carbon atoms. In one example, the alkyl radical is one to six carbon atoms (C_1-C_6). In other examples, the alkyl radical is C_1-C_5, C_1-C_4 or C_1-C_3. C_0 refers to a bond. Some alkyl moieties have been abbreviated, for example, methyl ("Me"), ethyl ("Et"), propyl ("Pr") and butyl ("Bu"), and further abbreviations are used to designate specific isomers of compounds, for example, 1-propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-1-propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), 1,1-dimethylethyl or t-butyl ("t-Bu") and the like. Other examples of alkyl groups include 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$) and 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$. The abbreviations are sometimes used in conjunction with elemental abbreviations and chemical structures, for example, methanol ("MeOH") or ethanol ("EtOH").

[0034] Additional abbreviations used throughout the application include, for example, benzyl ("Bn"), phenyl ("Ph") and acetyl ("Ac").

[0035] The following terms are abbreviated: dimethylsulfoxide ("DMSO"), dimethylformamide ("DMF"), dichloromethane ("DCM") and tetrahydrofuran ("THF").

[0036] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In one example, the alkenyl radical is two to six carbon atoms (C_2-C_6). In other examples, the alkenyl radical is C_2-C_5, C_2-C_4 or C_2-C_3. Examples include, but are not limited to, ethenyl or vinyl ($-CH=CH_2$), prop-1-enyl ($-CH=CHCH_3$), prop-2-enyl ($-CH_2CH=CH_2$), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, hexa-1,3-dienyl.

[0037] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon, triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described

herein. In one example, the alkynyl radical is two to six carbon atoms (C_2-C_6). In other examples, the alkynyl radical is C_2-C_5, C_2-C_4 or C_2-C_3. Examples include, but are not limited to, ethynyl (-C≡CH), prop-1-ynyl (-C≡CCH_3), prop-2-ynyl (propargyl, CH_2C≡CH), but-1-ynyl, but-2-ynyl and but-3-ynyl.

[0038] The term "alkoxy" refers to a linear or branched monovalent radical represented by the formula -OR in which R is alkyl, alkenyl, alkynyl or cycloalkyl, which can be further optionally substituted as defined herein. Alkoxy groups include methoxy, ethoxy, 2-methoxyethoxy, propoxy, isopropoxy, mono-, di- and tri-fluoromethoxy and cyclopropoxy.

[0039] "Cycloalkyl" refers to a non-aromatic, saturated or partially unsaturated hydrocarbon ring group wherein the cycloalkyl group may be optionally substituted independently with one or more substituents described herein. In one example, the cycloalkyl group is 3 to 6 carbon atoms (C_3-C_6). In other examples, cycloalkyl is C_3-C_4 or C_3-C_5. In other examples, the cycloalkyl group, as a monocycle, is C_3-C_6 or C_5-C_6. In another example, the cycloalkyl group, as a bicycle, is C_7-C_{12}. Examples of monocyclic cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyls having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkyls include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane.

[0040] The terms "heterocyclic" or "heterocycle" or "heterocyclyl" refers to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring) cyclic group in which at least one ring atom is a heteroatom independently selected from nitrogen, oxygen, and sulfur, the remaining ring atoms being carbon. In one embodiment, heterocyclyl includes saturated or partially unsaturated 4-6 membered heterocyclyl groups, another embodiment includes 5-6 membered heterocyclyl groups. The heterocyclyl group may be optionally substituted with one or more substituents described herein. Exemplary heterocyclyl groups include, but are not limited to, oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, piperidinyl, dihydropyridinyl, tetrahydropyridinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxathiepanyl, 1,4-oxaazepanyl, 1,4-dithiepanyl, 1,4-thiazepanyl and 1,4-diazepane 1,4-dithianyl, 1,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1,4-dioxanyl, 1,3-

dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinylimidazolinyl, imidazolidinyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Heterocycles include 4 to 6 membered rings containing one or two heteroatoms selected from oxygen, nitrogen and sulfur.

[0041] The term "heteroaryl" refers to an aromatic cyclic group in which at least one ring atom is a heteroatom independently selected from nitrogen, oxygen and sulfur, the remaining ring atoms being carbon. Heteroaryl groups may be optionally substituted with one or more substituents described herein. In one example, heteroaryl includes 5-6 membered heteroaryl groups. Other examples of heteroaryl groups include, but are not limited to, pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, 1,2,3-triazolyl, 1,3,4-triazolyl, 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, 1-oxa-3,4-diazolyl, 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, 1-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Heteroaryls includes 5 to 6 membered aromatic rings containing one, two or three heteroatoms selected from oxygen, nitrogen and sulfur.

[0042] "Halogen" refers to F, Cl, Br or I.

[0043] The abbreviation "TLC" stands for thin layer chromatography.

[0044] The terms "treat" or "treatment" refer to therapeutic, prophylactic, palliative or preventative measures. In one example, treatment includes therapeutic and palliative treatment. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder, as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0045] The phrases "therapeutically effective amount" or "effective amount" mean an amount of a compound of the present invention that, when administered to a mammal in need of such treatment, sufficient to (i) treat or prevent the particular disease, condition, or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) prevent or delay the onset of one or more symptoms of the particular disease,

condition, or disorder described herein. The amount of a compound that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[0046] The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by abnormal or unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, as well as head and neck cancer. The term cancer may be used generically to include various types of cancer or specifically (as listed above).

[0047] The phrase "pharmaceutically acceptable" indicates that the substance or composition is compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[0048] The phrase "pharmaceutically acceptable salt," as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the invention.

[0049] The compounds of this invention also include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of this invention and/or for separating enantiomers of compounds of this invention.

[0050] The term "mammal" means a warm-blooded animal that has or is at risk of developing a disease described herein and includes, but is not limited to, guinea pigs, dogs, cats, rats, mice, hamsters, and primates, including humans.

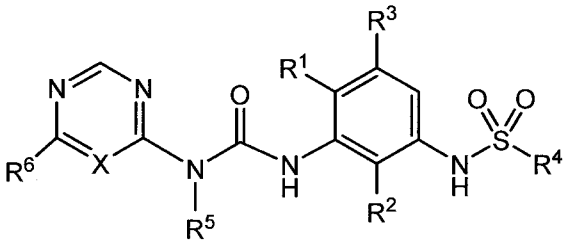
[0051] The terms “compound of this invention,” and “compounds of the present invention”, “compounds of Formulas I-IV,” unless otherwise indicated, include compounds of Formulas I, II, III, IV, stereoisomers, tautomers, solvates, metabolites, salts (e.g., pharmaceutically acceptable salts) and prodrugs thereof. Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or

more isotopically enriched atoms. For example, compounds of Formulas I, II, III and IV, 1-1, 1-2, 1-3, 1-4, 1-5, 2-1, 2-2, 3-1, 4-1, 5-1, 5-2, 5-3, 6-1, 7-1, 7-2, 8-1, 8-2, 9-1 and 9-2, wherein one or more hydrogen atoms are replaced deuterium or tritium, or one or more carbon atoms are replaced by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[0052] B-RAF INHIBITOR COMPOUNDS

[0053] The present invention provides compounds, and pharmaceutical formulations thereof, that are potentially useful in the treatment of diseases, conditions and/or disorders modulated by B-Raf.

[0054] One embodiment of this invention provides compounds of Formula **I**:



I

and stereoisomers, tautomers, prodrugs and pharmaceutically acceptable salts thereof, wherein:

[0055] X is N or CR^7;

[0056] R^1 and R^2 are independently selected from hydrogen, halogen, -CN, $-C(O)NR^6R^7$, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl and C_1-C_3 alkoxy;

[0057] R^3 is hydrogen, halogen or C_1-C_3 alkyl;

R^4 is C_3-C_5 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, 3-6 membered heterocyclyl, a 5-6 membered heteroaryl or NR^6R^7, wherein the cycloalkyl, alkyl, alkenyl, alkynyl, phenyl, heterocyclyl and heteroaryl are optionally substituted with OR^{15}, halogen, phenyl, C_3-C_4 cycloalkyl or C_1-C_4 alkyl optionally substituted with halogen;

[0058] R^5 is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl or C_3-C_5 cycloalkyl, wherein R^5 is optionally substituted with halogen;

[0059] R^6 is hydrogen or $NR^{10}R^{11}$;

[0060] R^7 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynl, C_3-C_6 cycloalkyl, 3-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are optionally substituted by halogen, oxo, OR^8, SR^8, NR^8R^9 or C_1-C_6 alkyl optionally substituted by halogen;

[0061] R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

[0062] R^8 and R^9 are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3

alkyl;

[0063] R^{10} is hydrogen;

[0064] R^{11} is hydrogen, (C_0-C_3 alkyl)$NR^{13}R^{14}$, (C_0-C_3 alkyl)OR^{13}, (C_1-C_3 alkyl)SR^{13}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are optionally substituted by halogen, oxo, OR^{15}, $NR^{15}R^{16}$ or C_1-C_3 alkyl;

[0065] R^{13} and R^{14} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

[0066] R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl; and

[0067] R^{15} and R^{16} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

[0068] R^{15} and R^{16} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl.

[0069] Another embodiment includes compounds of Formula I, and stereoisomers, tautomers, prodrugs and pharmaceutically acceptable salts thereof, wherein:

[0070] X is N or CR^7;

[0071] R^1 and R^2 are independently selected from hydrogen, halogen, CN, C_1-C_3 alkyl and C_1-C_3 alkoxy;

[0072] R^3 is hydrogen, halogen or C_1-C_3 alkyl;

[0073] R^4 is C_3-C_5 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, a 5-6 membered heteroaryl or NR^8R^9, wherein the cycloalkyl, alkyl, alkenyl, alkynyl, phenyl and heteroaryl are optionally substituted with OR^8, halogen, phenyl, C_3-C_4 cycloalkyl, or C_1-C_4 alkyl optionally substituted with halogen;

[0074] R^5 is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl or C_3-C_5 cycloalkyl, wherein R^5 is optionally substituted with halogen;

[0075] R^6 is hydrogen or $NR^{10}R^{11}$;

[0076] R^7 is hydrogen or C_1-C_3 alkyl optionally substituted with halogen, OR^8, SR^8, NR^8R^9, C_3-C_6 cycloalkyl, 4-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl;

[0077] R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

[0078] R^8 and R^9 are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl;

[0079] R^{10} is hydrogen;

[0080] R^{11} is hydrogen, (C_0-C_3 alkyl)$NR^{13}R^{14}$, (C_0-C_3 alkyl)OR^{13}, (C_1-C_3 alkyl)SR^{13}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are optionally substituted by halogen, oxo, OR^{15}, $NR^{15}R^{16}$ or C_1-C_3 alkyl;

[0081] R^{13} and R^{14} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

[0082] R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl; and

[0083] R^{15} and R^{16} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

[0084] R^{15} and R^{16} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl.

[0085] In certain embodiments, X is N.

[0086] In certain embodiments, X is CR^7. In certain embodiments, X is CH.

[0087] In certain embodiments, X is N.

[0088] In certain embodiments, R^7 is hydrogen.

[0089] In certain embodiments, R^7 is selected from hydrogen and phenyl, wherein the phenyl is optionally substituted by halogen, oxo, OR^8, SR^8, NR^8R^9 or C_1-C_6 alkyl optionally substituted by halogen. In certain embodiments, R^7 is selected from hydrogen and phenyl, wherein the phenyl is optionally substituted by halogen. In certain embodiments, R^7 is selected from hydrogen and 4-chlorophenyl.

[0090] In certain embodiments, R^1, R^2 and R^3 are independently selected from hydrogen, halogen or C_1-C_3 alkyl; R^4 is C_3-C_4 cycloalkyl or C_1-C_6 alkyl optionally substituted with OH, halogen or C_3-C_4 cycloalkyl; R^5 is hydrogen or C_1-C_3 alkyl; R^6 is hydrogen or $NR^{10}R^{11}$; R^7 is hydrogen; R^{10} is hydrogen; and R^{11} is hydrogen, C_1-C_3 alkyl, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl are optionally substituted by C_{1-3} alkyl or halogen.

[0091] In certain embodiments, R^1 and R^2 are independently selected from hydrogen, halogen, CN, C_1-C_3 alkyl or C_1-C_3 alkoxy.

[0092] In certain embodiments, R^1, R^2 and R^3 are independently selected from hydrogen, halogen or C_1-C_3 alkyl.

[0093] In certain embodiments, R^1, R^2 and R^3 are independently selected from hydrogen,

F, Cl or methyl.

[0094] In certain embodiments, R^1 and R^3 are independently selected from hydrogen, halogen or C_1-C_3 alkyl, and R^2 is Cl. In certain embodiments, R^1 and R^3 are independently selected from hydrogen, F, Cl and methyl, and R^2 is Cl.

[0095] In certain embodiments, R^1 is hydrogen, halogen, CN, C_1-C_3 alkyl or C_1-C_3 alkoxy.

[0096] In certain embodiments, R^1 is hydrogen.

[0097] In certain embodiments, R^1 is halogen. In certain embodiments, R^1 is F or Cl.

[0098] In certain embodiments, R^1 is C_1-C_3 alkyl. In certain embodiments, R^1 is methyl.

[0099] In certain embodiments, R^2 is hydrogen, halogen, CN, C_1-C_3 alkyl or C_1-C_3 alkoxy.

[00100] In certain embodiments, R^2 is hydrogen.

[00101] In certain embodiments, R^2 is halogen. In certain embodiments, R^2 is F or Cl.

[00102] In certain embodiments, R^2 is C_1-C_3 alkyl. In certain embodiments, R^2 is methyl.

[00103] In certain embodiments, R^2 is Cl.

[00104] In certain embodiments, R^2 is hydrogen.

[00105] In certain embodiments, R^3 is hydrogen, halogen or C_1-C_3 alkyl.

[00106] In certain embodiments, R^3 is hydrogen.

[00107] In certain embodiments, R^3 is halogen. In certain embodiments, R^3 is F or Cl.

[00108] In certain embodiments, R^1 and R^2 are F and R^3 is hydrogen.

[00109] In certain embodiments, R^1 is F and R^2 is Cl and R^3 is hydrogen.

[00110] In certain embodiments, R^1 is Cl and R^2 is F and R^3 is hydrogen.

[00111] In certain embodiments, R^1 is F and R^2 and R^3 are hydrogen.

[00112] In certain embodiments, R^1 and R^3 are hydrogen and R^2 is F.

[00113] In certain embodiments, R^2 and R^3 are F and R^1 is hydrogen.

[00114] In certain embodiments, R^1 is Cl and R^2 and R^3 are hydrogen.

[00115] In certain embodiments, R^1, R^2 and R^3 are F.

[00116] In certain embodiments, R^1 is F and R^2 is methyl and R^3 is hydrogen.

[00117] In certain embodiments, R^1 is methyl and R^2 is F and R^3 is hydrogen.

[00118] In certain embodiments, R^1 is F and R^2 and R^3 are hydrogen.

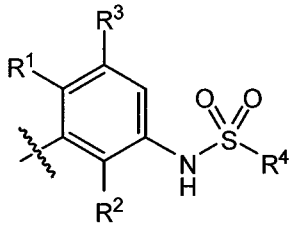
[00119] In certain embodiments, R^1 is Cl and R^2 and R^3 are hydrogen.

[00120] In certain embodiments, R^2 is F and R^1 and R^3 are hydrogen.

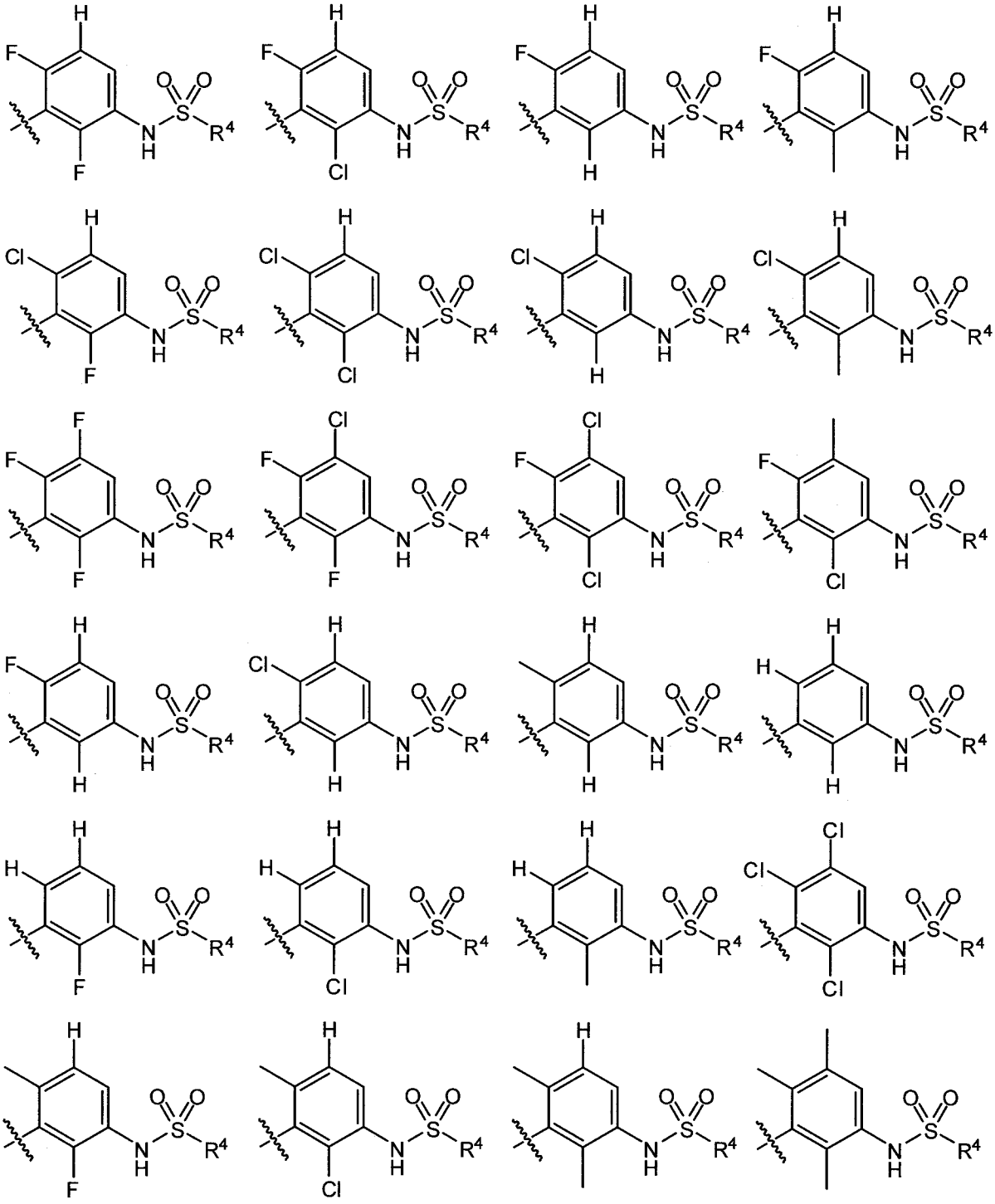
[00121] In certain embodiments, R^1 is H, R^2 is Cl and R^3 is F.

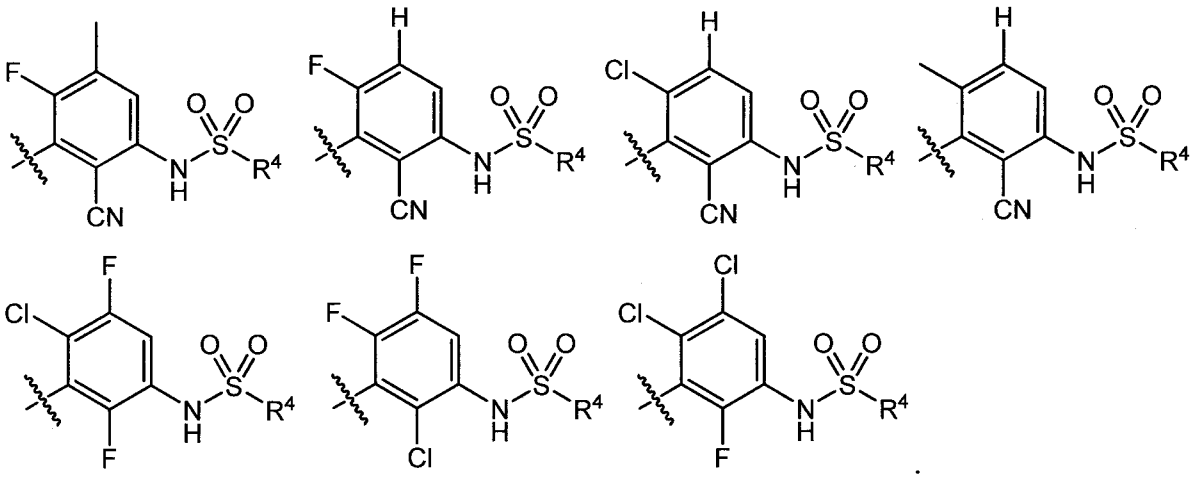
[00122] In certain embodiments, R^1 and R^3 are hydrogen and R^2 is -CN.

[00123] In certain embodiments, the residue:

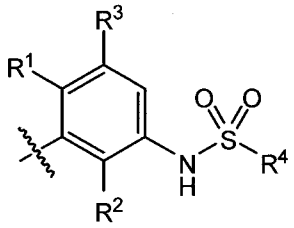


of Formula **I**, wherein the wavy line represents the point of attachment of the residue in Formula **I**, is selected from:

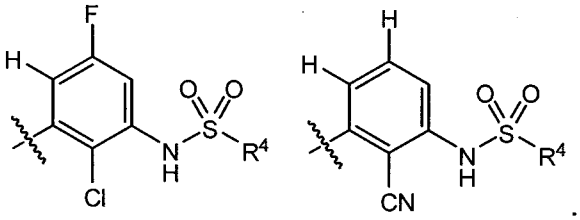




[00124] In certain embodiments, the residue:



of Formula **I**, wherein the wavy line represents the point of attachment of the residue in Formula **I**, is selected from:



[00125] In certain embodiments, R^4 is C_3-C_5 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, a 5-6 membered heteroaryl or NR^8R^9, wherein the cycloalkyl, alkyl, alkenyl, alkynyl, phenyl and heteroaryl are optionally substituted with OR^8, halogen, phenyl, C_3-C_4 cycloalkyl, or C_1-C_4 alkyl optionally substituted with halogen.

[00126] In certain embodiments, R^4 is C_3-C_4 cycloalkyl, C_1-C_6 alkyl optionally substituted with halogen or C_3-C_4 cycloalkyl, or NR^8R^9. In certain embodiments, R^8 and R^9 are independently selected from hydrogen and C_1-C_5 alkyl.

[00127] In certain embodiments, R^4 is C_3-C_5 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl, wherein the cycloalkyl, alkyl, alkenyl and alkynyl are optionally substituted with OR^8, halogen or C_3-C_4 cycloalkyl.

[00128] In certain embodiments, R^4 is cyclopropyl, ethyl, propyl, butyl, isobutyl, -CH_2Cl, –CH_2CF_3, –$CH_2CH_2CH_2F$, –$CH_2CH_2CF_3$, phenylmethyl, cyclopropylmethyl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 4-chloro-3-trifluoromethylphenyl, 1-methyl-1H-imidazol-4-yl, furan-2-yl, pyridin-2-yl, pyridin-3-yl,

thiophen-2-yl, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-N(CH_3)CH_2CH_3$, $-N(CH_3)_2$, or pyrrolidine.

[00129] In certain embodiments, R^4 is cyclopropyl, propyl, butyl, isobutyl, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CF_3$, cyclopropylmethyl, $-NHCH_2CH_2CH_3$, $-N(CH_3)CH_2CH_3$, $-N(CH_3)_2$, or pyrrolidine.

[00130] In certain embodiments, R^4 is cyclopropyl, propyl, butyl, isobutyl, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CF_3$, cyclopropylmethyl or $-NHCH_2CH_2CH_3$.

[00131] In certain embodiments, R^4 is propyl, butyl, isobutyl, $-CH_2CH_2CH_2F$, $-CH_2CH_2CF_3$ or cyclopropylmethyl.

[00132] In certain embodiments, R^4 is C_3-C_5 cycloalkyl or C_1-C_6 alkyl optionally substituted with OH, halogen or C_3-C_4 cycloalkyl.

[00133] In certain embodiments, R^4 is C_3-C_5 cycloalkyl. In certain embodiments, R^4 is C_3-C_4 cycloalkyl. In certain embodiments, R^4 is cyclopropyl or cyclobutyl.

[00134] In certain embodiments, R^4 is C_1-C_6 alkyl. In certain embodiments, R^4 is ethyl, propyl, butyl or isobutyl. In certain embodiments, R^4 is propyl.

[00135] In certain embodiments, R^4 is C_1-C_6 alkyl optionally substituted with halogen. In certain embodiments, R^4 is $-CF_3$, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CF_3$, $-CF_2CF_3$ or $-CF_2CF_2CF_3$.

[00136] In certain embodiments, R^4 is C_1-C_6 alkyl optionally substituted with OH, halogen or C_3-C_4 cycloalkyl. In certain embodiments, R^4 is cyclopropylmethyl ($-CH_2$-cyclopropyl) or cyclobutylmethyl ($-CH_2$-cyclobutyl). In certain embodiments, R^4 is cyclopropylmethyl ($-CH_2$-cyclopropyl).

[00137] In certain embodiments, R^4 is C_1-C_6 alkyl optionally substituted with phenyl. In certain embodiments, R^4 is phenylmethyl.

[00138] In certain embodiments, R^4 is phenyl optionally substituted with OR^8, halogen, C_3-C_4 cycloalkyl, or C_1-C_4 alkyl optionally substituted with halogen. In certain embodiments, R^4 is phenyl optionally substituted with halogen. In certain embodiments, R^4 is phenyl optionally substituted with C_1-C_4 alkyl optionally substituted with halogen. In certain embodiments, R^4 is phenyl optionally substituted with halogen and C_1-C_4 alkyl optionally substituted with halogen. In certain embodiments, R^4 is phenyl. In certain embodiments, R^4 is phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl or 4-chloro-3-trifluoromethylphenyl.

[00139] In certain embodiments, R^4 is a 5-6 membered heteroaryl optionally substituted with OR^8, halogen, C_3-C_4 cycloalkyl or C_1-C_4 alkyl optionally substituted with halogen. In certain embodiments, R^4 is a 5-6 membered heteroaryl optionally substituted with C_1-C_4 alkyl. In certain embodiments, R^4 is a 5-6 membered heteroaryl, wherein the heteroaryl contains one or

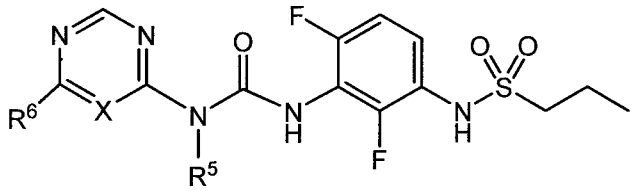
two heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. In certain embodiments, R^4 is a 5-6 membered heteroaryl, wherein the heteroaryl is imidazolyl, furanyl, pyridinyl or thiophenyl. In certain embodiments, R^4 is 1-methyl-1H-imidazol-4-yl, furan-2-yl, pyridin-2-yl, pyridin-3-yl or thiophen-2-yl.

[00140] In certain embodiments, R^4 is NR^8R^9. In certain embodiments, R^8 and R^9 are independently selected from hydrogen and C_1-C_6 alkyl. In certain embodiments, R^8 is hydrogen. In certain embodiments, R^8 is C_1-C_6 alkyl. In certain embodiments, R^8 is methyl, ethyl or propyl. In certain embodiments, R^9 is hydrogen or methyl. In certain embodiments, R^4 is selected from the group consisting of $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-N(CH_3)CH_2CH_3$ and $-N(CH_3)_2$.

[00141] In certain embodiments, R^8 and R^9 together with the nitrogen to which they are attached form a 4 to 6 membered heterocyclic ring. In certain embodiments, R^8 and R^9 together with the nitrogen to which they are attached form a 4 to 6 membered heterocyclic ring, wherein the heterocyclic ring contains one nitrogen heteroatom. In certain embodiments, R^4 is pyrrolidine.

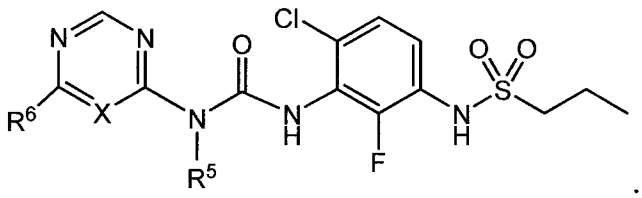
[00142] In certain embodiments, R^4 is selected from propyl, cyclopropylmethyl, $-CH_2CH_2CH_2F$ and phenyl. In a further embodiment, R^4 is selected from propyl, cyclopropylmethyl and $-CH_2CH_2CH_2F$.

[00143] In certain embodiments of Formula **I**, R^1 and R^2 are F, R^3 is hydrogen and R^4 is propyl, such that the compounds have the structure of Formula **II**:



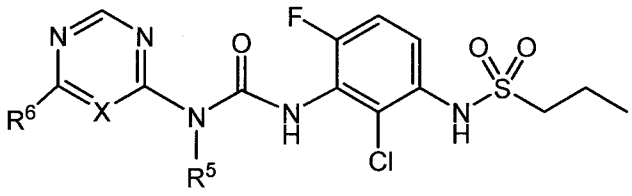
II

[00144] In certain embodiments of Formula **I**, R^1 is Cl and R^2 is F, R^3 is hydrogen and R^4 is propyl, such that the compounds have the structure of Formula **III**:



III

[00145] In certain embodiments of Formula **I**, R^1 is F and R^2 is Cl, R^3 is hydrogen and R^4 is propyl, such that the compounds have the structure of Formula **IV**:



IV

[00146] In certain embodiments, R^5 is hydrogen or C_1-C_3 alkyl. In certain embodiments, R^5 is hydrogen or methyl. In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is methyl.

[00147] In certain embodiments, R^6 is hydrogen or $NR^{10}R^{11}$. In certain embodiments, R^6 is hydrogen, NH_2, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2CH_2CH_3$, $-NHCH(CH_3)CH_2CH_3$, $-NHCH_2CH_2OH$, –NH(cyclopropyl), –NH(cyclobutyl), $-NHCH_2$(phenyl), –NH(4-fluorophenyl), –NH(4-chlorophenyl), $-NHNH_2$, –NH(1-methyl-1H-pyrazol-3-yl), –NH(tetrahyrdrofuran-3-yl) or $-NHCH_2CH_2$(6-morpholino). In certain embodiments, R^6 is hydrogen, NH_2, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2OH$, –NH(cyclopropyl), –NH(cyclobutyl), $-NHCH_2$(phenyl), –NH(4-fluorophenyl), $-NHNH_2$, –NH(1-methyl-1H-pyrazol-3-yl), –NH(tetrahyrdrofuran-3-yl) or $-NHCH_2CH_2$(6-morpholino). In certain embodiments, R^6 is , $-NHCH_2CH_2$(morpholin-1-yl).

[00148] In certain embodiments, R^6 is hydrogen.

[00149] In certain embodiments, R^6 is $NR^{10}R^{11}$, wherein R^{10} is hydrogen; and R^{11} is hydrogen, (C_0-C_3 alkyl)$NR^{13}R^{14}$, (C_0-C_3 alkyl)OR^{13}, (C_1-C_3 alkyl)SR^{13}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are optionally substituted by halogen, oxo, OR^{13}, $NR^{13}R^{14}$ or C_1-C_3 alkyl. In certain embodiments, R^6 is NH_2, $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2OH$, –NH(cyclopropyl), –NH(cyclobutyl), $-NHCH_2$(phenyl), –NH(4-fluorophenyl), $-NHNH_2$, –NH(1-methyl-1H-pyrazol-3-yl), –NH(tetrahyrdrofuran-3-yl) or $-NHCH_2CH_2$(6-morpholino).

[00150] In certain embodiments, R^6 is $NR^{10}R^{11}$ and R^{10} is hydrogen. In certain embodiments, R^6 is $NR^{10}R^{11}$, and R^{10} and R^{11} are hydrogen. In certain embodiments, R^6 is NH_2.

[00151] In certain embodiments, R^6 is $NR^{10}R^{11}$, R^{10} is hydrogen and R^{11} is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, wherein said alkyl and cycloalkyl are optionally substituted by halogen, oxo, OR^{13}, $NR^{13}R^{14}$ or C_1-C_3 alkyl. In certain embodiments, R^{11} is methyl, ethyl, propyl, isopropyl, butyl, secbutyl, cyclopropyl or cyclobutyl. In certain embodiments, R^{11} is $-CH_2CH_2OH$. In certain embodiments, R^6 is $-NHCH_2CH_2OH$. In certain embodiments, R^6 is $-NHCH_3$, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2CH_2CH_3$, $-NHCH(CH_3)CH_2CH_3$,

–NH(cyclopropyl) or –NH(cyclobutyl).

[00152] In certain embodiments, R^6 is $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is (C_0-C_3 alkyl)phenyl, wherein said alkyl and phenyl are optionally substituted by halogen, OR^{13}, $NR^{13}R^{14}$ or C_1-C_3 alkyl. In certain embodiments, R^{11} is phenyl, $–CH_2$phenyl, 4-fluorophenyl or 4-chlorophenyl. In certain embodiments, R^6 is $–NHCH_2$(phenyl), –NH(4-fluorophenyl) or –NH(4-chlorophenyl).

[00153] In certain embodiments, R^6 is $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is (C_0-C_3 alkyl)$NR^{13}R^{14}$, wherein said alkyl is optionally substituted by halogen, oxo, OR^{13}, $NR^{13}R^{14}$ or C_1-C_3 alkyl. In certain embodiments, R^{11} is NH_2. In certain embodiments, R^6 is $–NHNH_2$.

[00154] In certain embodiments, R^6 is $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, heterocyclyl and heteroaryl are optionally substituted by halogen, oxo, OR^{13}, $NR^{13}R^{14}$ or C_1-C_3 alkyl. In certain embodiments, R^{11} is N-methylpyrazolyl, tetrahydrofuranyl or $–CH_2CH_2$morpholinyl. In certain embodiments, R^6 is –NH(1-methyl-1H-pyrazol-3-yl), –NH(tetrahyrdrofuran-3-yl) or $–NHCH_2CH_2$(6-morpholino).

[00155] In certain embodiments, R^6 is $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is (C_0-C_3 alkyl)OR^{13}, wherein said alkyl, heterocyclyl and heteroaryl are optionally substituted by halogen, oxo, OR^{13}, $NR^{13}R^{14}$ or C_1-C_3 alkyl. In certain embodiments, R^{11} is $–CH_2CH_2OH$. In certain embodiments, R^6 is $–NHCH_2CH_2OH$.

[00156] In certain embodiments, R^6 is hydrogen or $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is hydrogen, C_1-C_3 alkyl, (C_0-C_3 alkyl)OR^{13}, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein the alkyl, cycloalkyl, phenyl, heterocyclyl or heteroaryl are optionally substituted by C_{1-3} alkyl or halogen.

[00157] In certain embodiments, R^6 is $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is hydrogen, C_1-C_6 alkyl, (C_0-C_3 alkyl)OR^{13}, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein the alkyl, cycloalkyl, phenyl, heterocyclyl or heteroaryl are optionally substituted by C_{1-3} alkyl or halogen.

[00158] In certain embodiments, R^7 is hydrogen or phenyl optionally substituted by halogen, oxo, OR^8, SR^8, NR^8R^9 or C_1-C_6 alkyl optionally substituted by halogen;. In certain embodiments, R^7 is 4-chlorophenyl.

[00159] In certain embodiments, R^8 and R^9 are independently hydrogen, methyl, ethyl or propyl.

[00160] It will be appreciated that certain compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended

that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention.

[00161] In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

It will also be appreciated that compounds of Formulas I-IV include tautomeric forms. Tautomers are compounds that are interconvertible by tautomerization. This commonly occurs due to the migration of a hydrogen atom or proton, accompanied by the switch of a single bond and adjacent double bond. For instance, 1,3,5-triazin-2(1H)-iminyl is a tautomeric form of 1,3,5-triazin-2-aminyl (R^6 is NH_2 and X is N in Formula I). Other tautomers of Formulas I-IV may also form at other positions, including, but not limited to, the sulfonamide or R^5/R^6 position depending on the substitution. The compounds of Formulas I-IV are intended to include all tautomeric forms.

[00162] It will also be appreciated that certain compounds of Formulas I-IV may be used as intermediates for further compounds of Formulas I-IV.

[00163] It will be further appreciated that the compounds of the present invention may exist in unsolvated, as well as solvated forms with pharmaceutically acceptable solvents, such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

[00164] The term "prodrug" as used in this application refers to a precursor or derivative form of a compound of the invention that is less active or inactive compared to the parent compound or drug and is capable of being metabolized in vivo into the more active parent form. See, e.g., Wilman, "Prodrugs in Cancer Chemotherapy" Biochemical Society Transactions, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., "Prodrugs: A Chemical Approach to Targeted Drug Delivery," Directed Drug Delivery, Borchardt et al., (ed.), pp. 247-267, Humana Press (1985). The prodrugs of this invention include, but are not limited to, N-methyl prodrugs (including N-methyl sulfonamide prodrugs), phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs, optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into the more active cytotoxic free drug.

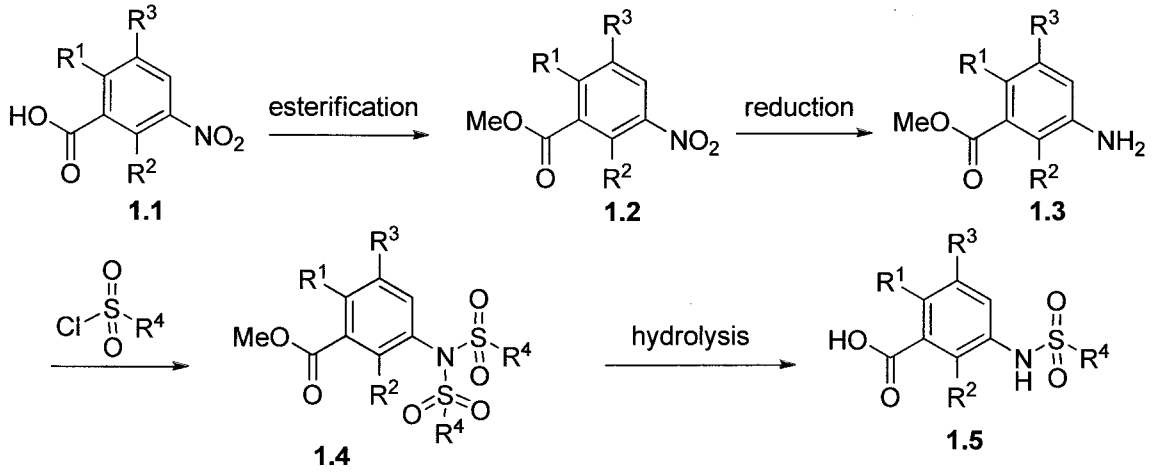
[00165] Prodrugs of compounds of Formulas I-IV may not be as active as the compounds

of Formulas I-IV in the assay as described in Example A. However, the prodrugs are capable of being converted in vivo into more active metabolites of compounds of Formulas I-IV.

[00166] SYNTHESIS OF COMPOUNDS

[00167] Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Sigma-Aldrich (St. Louis, MO), Alfa Aesar (Ward Hill, MA), or TCI (Portland, OR), or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis. v. 1-23, New York: Wiley 1967-2006 ed. (also available via the Wiley InterScience® website), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)).

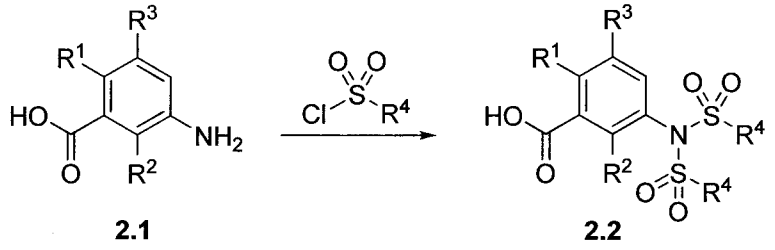
[00168] For illustrative purposes, Schemes 1-10 show general methods for preparing the compounds of the present invention, as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.



Scheme 1

[00169] Scheme 1 shows a general method for preparing a compound 1-5, wherein R^1, R^2, R^3 and R^4 are as defined herein. A benzoic acid 1.1 is esterified to a methyl benzoate 1.2 by treatment with trimethylsilyl diazomethane in MeOH or via Fischer esterification conditions, such as treatment with trimethylsilyl chloride ("TMSCl") in MeOH. Reduction of nitro

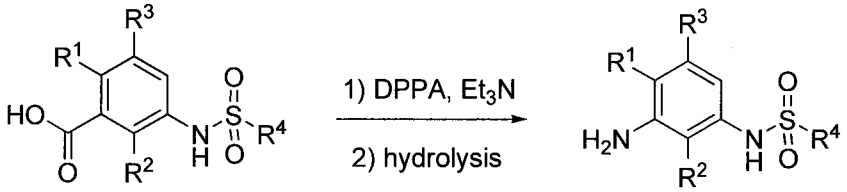
intermediate 1.2 to its amino analog 1.3 is performed using a standard condition, such as treatment with Pd/C and H_2. Bis-sulfonamide 1.4 is obtained by treatment of the aniline 1.3 with a sulfonyl chloride R^4SO_2Cl in the presence of a base, such as NEt_3, in an organic solvent, such as DCM. Hydrolysis of the compound 1.4 is accomplished under basic conditions, such as aqueous NaOH, in the appropriate solvent system, such as THF and/or MeOH, to provide a compound 1.5.



2.1 2.2

Scheme 2

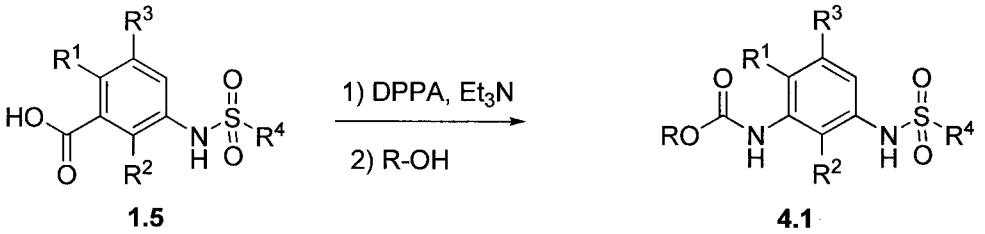
[00170] Scheme 2 shows a general method for preparing a compound 2.2, wherein R^1, R^2, R^3 and R^4 are as defined herein. An aniline 2.1 is sulfonylated in an organic solvent, such as DCM, in the presence of a base, such as NEt_3, to provide a compound 2.2.



1.5 3.1

Scheme 3

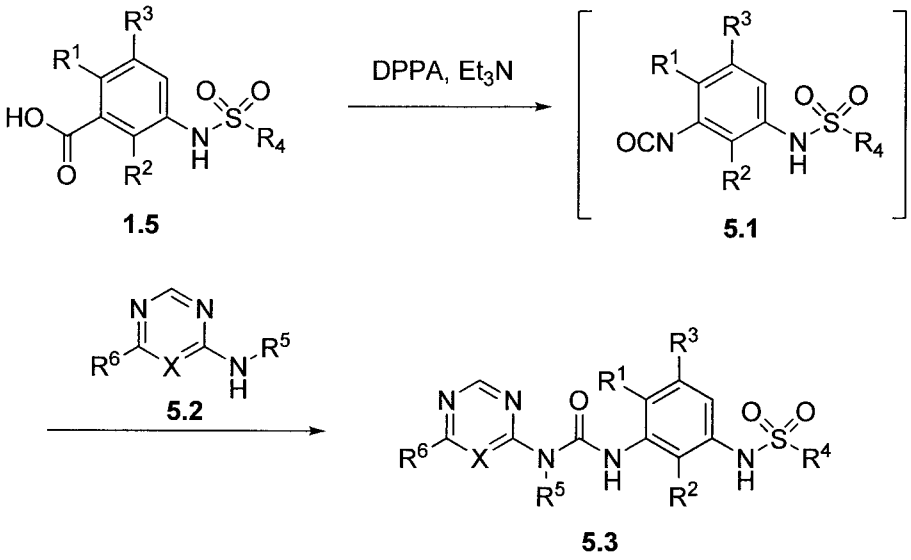
[00171] Scheme 3 shows a general method for preparing a compound 3.1, wherein R^1, R^2, R^3 and R^4 are as defined herein. A carboxylic acid 1.5 in a suitable solvent, such as THF, is treated with diphenylphosphonic azide ("DPPA") and a base such as triethylamine, and subsequently hydrolyzed to form an amine 3.1.



1.5 4.1

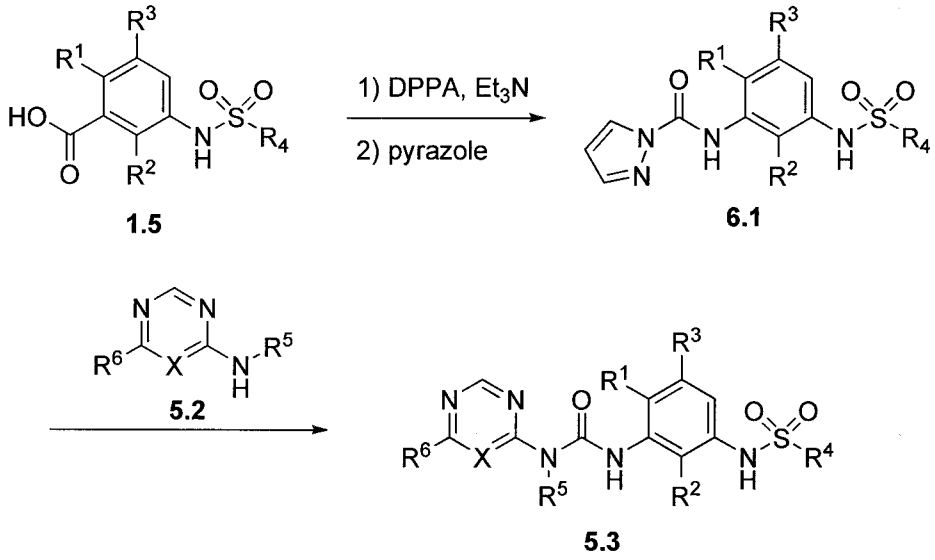
Scheme 4

[00172] Scheme 4 shows a general method for preparing a compound 4.1, wherein R^1, R^2, R^3 and R^4 are as defined herein. A carboxylic acid 1.5 in a suitable solvent, such as THF, is treated with DPPA and a base, such as triethylamine, and subsequently treated with an alcohol, such as phenol, to form a carbamate 4.1.



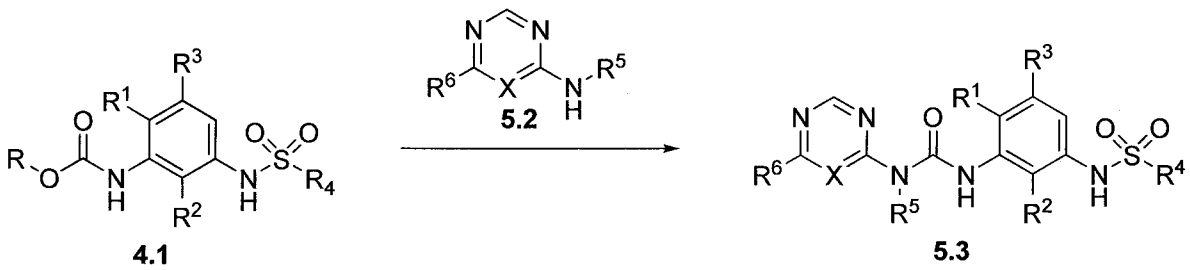
Scheme 5

[00173] Scheme 5 shows a general method for preparing a compound 5.3, wherein R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined herein. A carboxylic acid 1.5 in an appropriate solvent, such as THF, is treated with DPPA and a base, such as triethylamine, to form an isocyanato intermediate 5.1. This intermediate is not isolated but further reacted in the same pot with a six-membered heterocyclic amine 5.2 to form a compound 5.3.



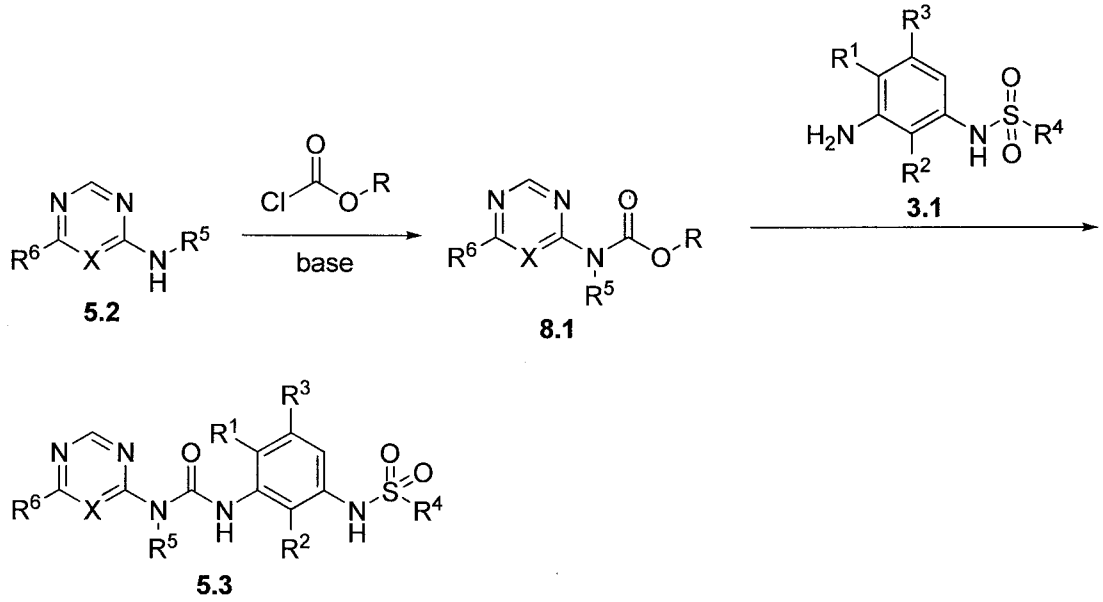
Scheme 6

[00174] Scheme 6 shows another method for preparing a compound 5.3. A carboxylic acid 1.5 in an appropriate solvent, such as THF, is treated with DPPA and a base, such as triethylamine, and subsequently reacted with pyrazole to form the 1H-pyrazole-1-carboxamide 6.1. This intermediate is further reacted with a six-membered heterocyclic amine 5.2 to form a compound 5.3.



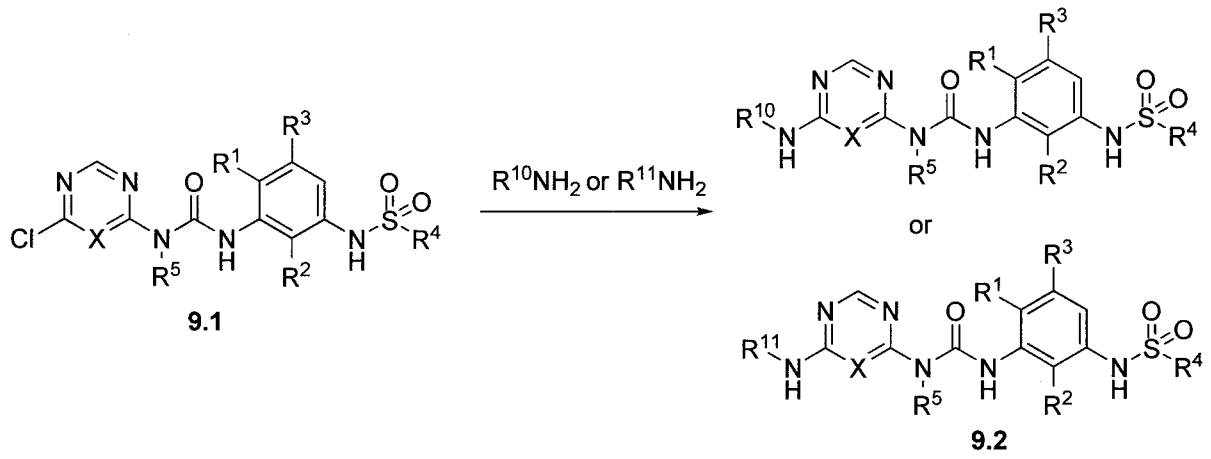
Scheme 7

[00175] Scheme 7 illustrates another general method for preparing a compound 5.3 wherein R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined herein. A carbamate 4.1 is reacted in an appropriate solvent, such as DMSO, with a six-membered heterocyclic amine 5.2 to form a compound 5.3.



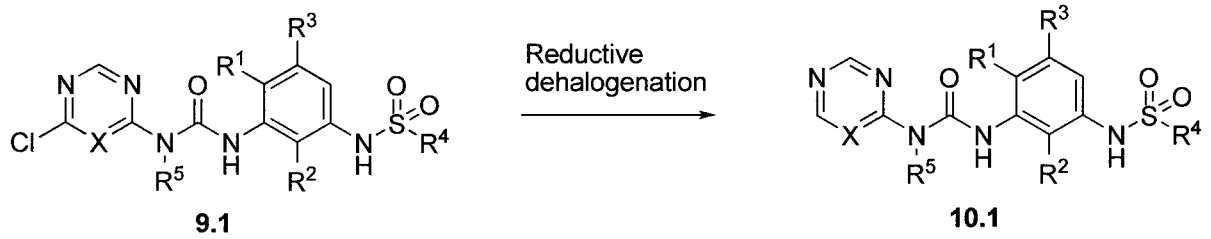
Scheme 8

[00176] Scheme 8 illustrates another general method for preparing a compound 5.3, wherein R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined herein. A six-membered heterocyclic amine 5.2 in an appropriate solvent, such as THF, is treated with a base, such as cesium carbonate, and a carbamoyl chloride, wherein R is phenyl- or benzyl, to form a carbamate 8.1. Further reaction with an aniline 3.1 furnishes a compound 5.3.



Scheme 9

Scheme 9 illustrates a method for preparing a compound 9.2, wherein R^1, R^2, R^3, R^4, R^5, R^{10}, R^{11} and X are as defined herein. A compound 9.1 in a suitable solvent, such as EtOH or iPrOH, is reacted with an amine $R^{10}NH$ or $R^{11}NH$ to form a compound 9.2.



Scheme 10

[00177] Scheme 10 illustrates a method for preparing a compound 10.1, wherein R^1, R^2, R^3, R^4, R^5 and X are as defined herein. A compound 9.1 is catalytically hydrogenated using an appropriate catalyst, such as Pd/C, in a solvent, such as EtOH, to form a compound 10.1.

[00178] In preparing compounds of Formulas I-IV, protection of remote functionalities (e.g., primary or secondary amines, etc.) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butyloxycarbonyl ("Boc"), benzyloxycarbonyl ("CBz") and 9-fluorenylmethyleneoxycarbonyl ("Fmoc"). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, et al. Greene's Protective Groups in Organic Synthesis. New York: Wiley Interscience, 2006.

[00179] METHODS OF SEPARATION

[00180] It may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common

in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed ("SMB") and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography. One skilled in the art will apply techniques most likely to achieve the desired separation.

[00181] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Enantiomers can also be separated by use of a chiral HPLC column.

[00182] A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994; Lochmuller, C. H., et al. "Chromatographic resolution of enantiomers: Selective review." J. Chromatogr., 113(3) (1975): pp. 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: Wainer, Irving W., Ed. Drug Stereochemistry: Analytical Methods and Pharmacology. New York: Marcel Dekker, Inc., 1993.

[00183] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid, can result in formation of the diastereomeric salts.

[00184] Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. Stereochemistry of Organic Compounds. New York: John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III, Peyton. "Resolution of (±)-5-Bromonornicotine. Synthesis of (R)- and (S)-Nornicotine of High Enantiomeric Purity." J. Org. Chem. Vol. 47, No. 21 (1982): pp. 4165-4167), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111).

[00185] By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Lough, W.J., Ed. Chiral Liquid Chromatography. New York: Chapman and Hall, 1989; Okamoto, Yoshio, et al. "Optical resolution of dihydropyridine enantiomers by high-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase." J. Chromatogr. Vol. 513 (1990): pp. 375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

[00186] BIOLOGICAL EVALUATION

[00187] B-Raf mutant protein 447-717 (V600E) was co-expressed with the chaperone protein Cdc37, complexed with Hsp90 (Roe, S. Mark, et al. "The Mechanism of Hsp90 Regulation by the Protein Kinase-Specific Cochaperone $p50^{cdc37}$." Cell. Vol. 116 (2004): pp. 87-98; Stancato, LF, et al. "Raf exists in a native heterocomplex with Hsp90 and p50 that can be reconstituted in a cell free system." J. Biol. Chem. 268(29) (1993): pp. 21711-21716).

[00188] Determining the activity of Raf in the sample is possible by a number of direct and indirect detection methods (US 2004/0082014). Activity of human recombinant B-Raf protein may be assessed *in vitro* by assay of the incorporation of radio labeled phosphate to recombinant MAP kinase (MEK), a known physiologic substrate of B-Raf, according to US 2004/0127496 and WO 03/022840. The activity/inhibition of V600E full-length B-Raf was

estimated by measuring the incorporation of radio labeled phosphate from [γ-^{33}P]ATP into FSBA-modified wild-type MEK (see Example A).

[00189] ADMINISTRATION AND PHARMACEUTICAL FORMULATIONS

[00190] The compounds of the invention may be administered by any convenient route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal.

[00191] The compounds may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. If parenteral administration is desired, the compositions will be sterile and in a solution or suspension form suitable for injection or infusion.

[00192] A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[00193] One embodiment of the present invention includes a pharmaceutical composition comprising a compound of Formulas I-IV, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment, the present invention provides a pharmaceutical composition comprising a compound of Formulas I-IV, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient.

[00194] Another embodiment of the present invention provides a pharmaceutical composition comprising a compound of Formulas I-IV for use in the treatment of a hyperproliferative disease.

[00195] Another embodiment of the present invention provides a pharmaceutical composition comprising a compound of Formulas I-IV for use in the treatment of cancer.

[00196] Another embodiment of the present invention provides a pharmaceutical composition comprising a compound of Formulas I-IV for use in the treatment of kidney disease. A further embodiment of the present invention provides a pharmaceutical composition comprising a compound of Formulas I-IV for use in the treatment of polycystic kidney disease.

[00197] METHODS OF TREATMENT WITH COMPOUNDS OF THE INVENTION

[00198] The invention includes methods of treating or preventing disease or condition by administering one or more compounds of this invention, or a stereoisomer or pharmaceutically acceptable salt thereof. In one embodiment, a human patient is treated with a compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle in an amount to detectably inhibit B-Raf activity.

[00199] In another embodiment, a human patient is treated with a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle in an amount to detectably inhibit B-Raf activity.

[00200] In another embodiment of the present invention, a method of treating a hyperproliferative disease in a mammal comprising administering a therapeutically effective amount of the compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, to the mammal is provided.

[00201] In another embodiment of the present invention, a method of treating a hyperproliferative disease in a mammal comprising administering a therapeutically effective amount of the compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, to the mammal is provided.

[00202] In another embodiment of the present invention, a method of treating kidney disease in a mammal comprising administering a therapeutically effective amount of the compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, to the mammal is provided. In another embodiment of the present invention, a method of treating kidney disease in a mammal comprising administering a therapeutically effective amount of the compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, to the mammal is provided. In a further embodiment, the kidney disease is polycystic kidney disease.

[00203] In another embodiment, a method of treating or preventing cancer in a mammal in need of such treatment, wherein the method comprises administering to said mammal a

therapeutically effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof. The cancer is selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, NSCLC, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia. Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

[00204] In another embodiment, a method of treating or preventing cancer in a mammal in need of such treatment, wherein the method comprises administering to said mammal a therapeutically effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof.

[00205] Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

[00206] Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of kidney disease. Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of kidney disease. In a further embodiment, the kidney disease is polycystic kidney disease.

[00207] In another embodiment, a method of preventing or treating cancer, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds having anti-cancer properties.

[00208] In another embodiment, a method of preventing or treating cancer, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formulas I-IV, or a stereoisomer or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds having anti-cancer properties.

[00209] In one further embodiment, the cancer is a sarcoma.

[00210] In another further embodiment, the cancer is a carcinoma. In one further embodiment, the carcinoma is squamous cell carcinoma. In another further embodiment, the carcinoma is an adenoma or adenocarcinoma.

[00211] In another embodiment, a method of treating or preventing a disease or disorder modulated by B-Raf, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof. Examples of such diseases and disorders include, but are not limited to, cancer. The cancer is selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, NSCLC, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia.

[00212] In another embodiment, a method of treating or preventing a disease or disorder modulated by B-Raf, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof.

[00213] In another embodiment of the present invention, a method of preventing or treating kidney disease, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds. In another embodiment of the present invention, a method of preventing or treating polycystic kidney disease, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, alone or in combination with one or more additional compounds.

[00214] Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer. The cancer is selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, NSCLC, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma,

pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's and leukemia. In a further embodiment, the use of a compound of Formulas I-IV in the manufacture of a medicament, for use as a b-Raf inhibitor in the treatment of a patient undergoing cancer therapy.

[00215] Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

[00216] Another embodiment of the present invention provides the use of a compound of Formulas I-IV, or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of polycystic kidney disease. In a further embodiment, the kidney disease is polycystic kidney disease.

[00217] Another embodiment of the present invention provides the compounds of Formulas I-IV for use in therapy.

[00218] Another embodiment of the present invention provides the compounds of Formulas I-IV for use in the treatment of a hyperproliferative disease. In a further embodiment, the hyperproliferative disease is cancer (as further defined and may be individually selected from those above).

[00219] Another embodiment of the present invention provides the compounds of Formulas I-IV for use in the treatment of kidney disease. In a further embodiment, the kidney disease is polycystic kidney disease.

[00220] COMBINATION THERAPY

[00221] The compounds of this invention and stereoisomers and pharmaceutically acceptable salts thereof may be employed alone or in combination with other therapeutic agents for treatment. The compounds of the present invention can be used in combination with one or more additional drugs, for example an anti-hyperproliferative, anti-cancer, or chemotherapeutic agent. The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound of this invention such that they do not adversely affect each other. Such agents are suitably present in combination in amounts that are effective for the purpose intended. The compounds may be administered together in a unitary pharmaceutical composition or separately and, when administered separately this may occur simultaneously or sequentially in any order. Such sequential administration may be close in time or remote in time.

[00222] A "chemotherapeutic agent" is a chemical compound useful in the treatment of cancer, regardless of mechanism of action. Chemotherapeutic agents include compounds used in "targeted therapy" and conventional chemotherapy. A number of suitable chemotherapeutic agents to be used as combination therapeutics are contemplated for use in the methods of the present invention. The present invention contemplates, but is not limited to, administration of numerous anticancer agents, such as: agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g., interferons [e.g., IFN-a, etc.] and interleukins [e.g., IL-2, etc.], etc.); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g., all-trans-retinoic acid, etc.); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like.

[00223] Examples of chemotherapeutic agents include Erlotinib (TARCEVA®, Genentech/OSI Pharm.), Bortezomib (VELCADE®, Millennium Pharm.), Fulvestrant (FASLODEX®, AstraZeneca), Sunitinib (SUTENT®, Pfizer), Letrozole (FEMARA®, Novartis), Imatinib mesylate (GLEEVEC®, Novartis), PTK787/ZK 222584 (Novartis), Oxaliplatin (Eloxatin®, Sanofi), 5-FU (5-fluorouracil), Leucovorin, Rapamycin (Sirolimus, RAPAMUNE®, Wyeth), Lapatinib (TYKERB®, GSK572016, Glaxo Smith Kline), Lonafarnib (SCH 66336), Sorafenib (NEXAVAR®, Bayer), Irinotecan (CAMPTOSAR®, Pfizer) and Gefitinib (IRESSA®, AstraZeneca), AG1478, AG1571 (SU 5271; Sugen), alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analog topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gamma1I and calicheamicin omegaI1 (Angew Chem.

Intl. Ed. Engl. (1994) 33:183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE™ (Cremophor-free), albumin-engineered nanoparticle formulations of paclitaxel (American Pharmaceutical Partners, Schaumberg, Illinois), and TAXOTERE® (doxetaxel; Rhône-Poulenc Rorer, Antony, France); chloranmbucil; GEMZAR® (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA®); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

[00224] Also included in the definition of "chemotherapeutic agent" are: (i) anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX®; tamoxifen citrate), raloxifene, droloxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON® (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE® (megestrol acetate), AROMASIN® (exemestane; Pfizer), formestanie, fadrozole, RIVISOR® (vorozole), FEMARA® (letrozole; Novartis), and ARIMIDEX® (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Raf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME®) and HER2 expression inhibitors; (viii) vaccines such as gene therapy vaccines, for example, ALLOVECTIN®, LEUVECTIN®, and VAXID®; PROLEUKIN® rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN®; ABARELIX® rmRH; (ix) anti-angiogenic agents such as bevacizumab (AVASTIN®, Genentech); (x) PI3k/AKT/mTOR pathway inhibitors, including GDC-0941 (2-(1*H*-Indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-*d*]pyrimidine), XL-147, GSK690693 and temsirolimus; (xi) Ras/Raf/MEK/ERK pathway inhibitors; and (xii) pharmaceutically acceptable salts, acids and derivatives of any of the above.

[00225] Also included in the definition of "chemotherapeutic agent" are therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG®, Wyeth).

[00226] Humanized monoclonal antibodies with therapeutic potential as chemotherapeutic agents in combination with the Raf inhibitors of the invention include: alemtuzumab, apolizumab, aselizumab, atlizumab, bapineuzumab, bevacizumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab,

nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pertuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, trastuzumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, and visilizumab.

EXAMPLES

[00227] In order to illustrate the invention, the following Examples are included. However, it is to be understood that these Examples do not limit the invention and are only meant to suggest a method of practicing the invention. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare a number of other compounds of the invention, and alternative methods for preparing the compounds of this invention are deemed to be within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

[00228] In the Examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Sigma-Aldrich, Alfa Aesar, or TCI, and were used without further purification unless otherwise indicated.

[00229] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[00230] Column chromatography purification was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SepPak cartridge (Waters) or on a Teledyne Isco Combiflash purification system using prepacked silica gel cartridges. ^{1}H NMR spectra were recorded on a Bruker AVIII 400 MHz or Bruker AVIII 500 MHz or on a Varian 400 MHz NMR spectrometer.

[00231] ^{1}H-NMR spectra were obtained as $CDCl_3$, CD_2Cl_2, CD_3OD, D_2O, DMSO-d_6, acetone-d_6 or CD_3CN solutions (reported in ppm), using tetramethylsilane (0.00 ppm) or residual solvent ($CDCl_3$: 7.25 ppm; CD_3OD: 3.31 ppm; D_2O: 4.79 ppm; DMSO-d_6: 2.50 ppm;

acetone-d_6: 2.05 ppm; CD_3CN: 1.94 ppm) as the reference standard. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintuplet), sx (sextuplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Example A

B-Raf IC_{50} Assay Protocol

[00232] Activity of human recombinant B-Raf protein may be assessed *in vitro* by assay of the incorporation of radio labeled phosphate to recombinant MAP kinase (MEK), a known physiologic substrate of B-Raf, according to US 2004/0127496 and WO 03/022840. Catalytically active human recombinant B-Raf protein is obtained by purification from sf9 insect cells infected with a human B-Raf recombinant baculovirus expression vector.

[00233] The activity/inhibition of V600E full-length B-Raf was estimated by measuring the incorporation of radio labeled phosphate from [γ-^{33}P]ATP into FSBA-modified wild-type MEK. The 30-μL assay mixtures contained 25mM Na Pipes, pH 7.2, 100mM KCl, 10mM $MgCl_2$, 5mM β-glycerophosphate, 100μM Na Vanadate, 4μM ATP, 500 nCi [γ-^{33}P]ATP, 1μM FSBA-MEK and 20nM V600E full-length B-Raf. Incubations were carried out at 22°C in a Costar 3365 plate (Corning). Prior to the assay, the B-Raf and FSBA-MEK were preincubated together in assay buffer at 1.5x (20 μL of 30nM and 1.5μM, respectively) for 15 minutes, and the assay was initiated by the addition of 10 μL of 10μM ATP. Following the 60-minute incubation, the assay mixtures were quenched by the addition of 100 μL of 25% TCA, the plate was mixed on a rotary shaker for 1 minute, and the product was captured on a Perkin-Elmer GF/B filter plate using a Tomtec Mach III Harvester. After sealing the bottom of the plate, 35 μL of Bio-Safe II (Research Products International) scintillation cocktail were added to each well and the plate was top-sealed and counted in a Topcount NXT (Packard).

[00234] The compounds of Examples 1-24 were tested in the above assay and found to have an IC_{50} of less than 1.5 μM.

Example A1

Cellular ERK 1/2 Phosphorylation Assay

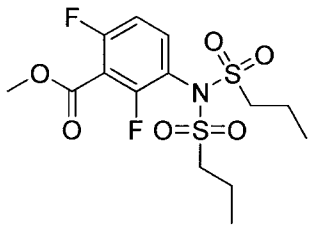
Inhibition of basal ERK1/2 phosphorylation was determined by the following in vitro cellular proliferation assay, which comprises incubating cells with a compound of Formula II for 1 hour and quantifying the fluorescent pERK signal on fixed cells and normalizing to total ERK signal.

Materials and Methods: Malme-3M cells were obtained from ATCC and grown in RPMI-1640 supplemented with 10% fetal bovine serum. Cells were plated in 96-well plates at 24,000 cells/well and allowed to attach for 16-20 hours at 37°C, 5% CO_2. The media was

removed, and DMSO-diluted compounds were added in RPMI-1640 at a final concentration of 1% DMSO. The cells were incubated with the compounds for 1 hour at 37°C, 5% CO_2. The cells were washed with PBS and fixed in 3.7% formaldehyde in PBS for 15 minutes. This was followed by washing in PBS/0.05% Tween20 and permeabilizing in -20°C 100% MeOH for 15 minutes. Cells were washed in PBS/0.05% Tween20 then blocked in Odyssey blocking buffer (LI-COR Biosciences) for 1 hour. Antibodies to phosphorylated ERK (1:400, Cell Signaling #9106, monoclonal) and total ERK (1:400, Santa Cruz Biotechnology #sc-94, polyclonal) were added to the cells and incubated 16-20 hours at 4°C . After washing with PBS/0.05% Tween20, the cells were incubated with fluorescently-labeled secondary antibodies (1:1000 goat anti-rabbit IgG-IRDye800, Rockland and 1:500 goat anti-mouse IgG-Alexa Fluor 680, Molecular Probes) for an additional hour. Cells were then washed and analyzed for fluorescence at both wavelengths using the Odyssey Infrared Imaging System (LI-COR Biosciences). Phosphorylated ERK signal was normalized to total ERK signal.

By way of example, Examples 2 and 8 had IC_{50} in the above assay of about 0.4383 and 0.1527 μM, respectively.

Example B



Methyl 2,6-difluoro-3-(*N*-(propylsulfonyl)propylsulfonamido)benzoate

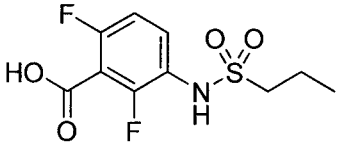
[00235] Step A: A 1 L flask was charged with 2,6-difluoro-3-nitrobenzoic acid (17.0 g, 83.7 mmol) and MeOH (170 mL, 0.5M). The flask was placed in a cold water bath, and an addition funnel charged with a 2M solution of trimethylsilyl ("TMS") diazomethane in hexanes (209 mL, 419 mmol) was attached to the flask. The TMS diazomethane solution was added slowly to the reaction flask over the course of 2 hours. A large excess of reagent was required in order for the reaction to reach completion as determined by the ceased evolution of N_2 upon further addition of reagent. The volatiles were removed *in vacuo* to afford crude methyl 2,6-difluoro-3-nitrobenzoate as a solid (18.2 g). The material was taken directly to Step B.

[00236] Step B: 10% (wt.) Pd on activated carbon (4.46 g, 4.19 mmol) was added to a 1 L flask charged with methyl 2,6-difluoro-3-nitrobenzoate (18.2 g, 83.8 mmol) under a nitrogen atmosphere. To the flask was added EtOH (350 mL, 0.25 M), and H_2 gas was passed through

the mixture for 15 minutes. The reaction mixture was stirred under two H_2 balloons overnight. The balloons were recharged with H_2 gas and the mixture was stirred an additional 4 hours. Upon consumption of the starting material and intermediate hydroxylamine as determined by TLC, N_2 gas was flushed through the reaction mixture. The mixture was then filtered through glass microfibre filter ("GF/F") paper twice. The volatiles were removed to afford crude methyl 3-amino-2,6-difluorobenzoate as an oil (15.66 g). The material was taken directly onto the next step.

[00237] Step C: Propane-1-sulfonyl chloride (23.46 mL, 209.3 mmol) was slowly added to a solution of methyl 3-amino-2,6-difluorobenzoate (15.66 g, 83.7 mmol) and triethylamine (35.00 mL, 251.1 mmol) in CH_2Cl_2 (175 mL, 0.5M) maintained in a cool water bath. The reaction mixture was stirred for 1 hour at room temperature. Water (300 mL) was added and the organic layer was separated, washed with water (2 X 300 mL) and brine (200 mL), then dried (Na_2SO_4), filtered and concentrated to an oil. The crude product was purified by column chromatography, eluting with 15% ethyl acetate ("EtOAc")/hexane. The isolated fractions were triturated with hexanes to afford methyl 2,6-difluoro-3-(*N*-(propylsulfonyl)propylsulfonamido)benzoate as a solid (24.4 g, 73% yield for 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.45 (m, 1H), 7.08-7.02 (m, 1H), 3.97 (s, 3H), 3.68-3.59 (m, 2H), 3.53-3.45 (m, 2H), 2.02-1.89 (m, 4H), 1.10 (t, J = 7.4 Hz, 6H). *m/z* (APCI-neg) M-(SO_2Pr) = 292.2.

Example C

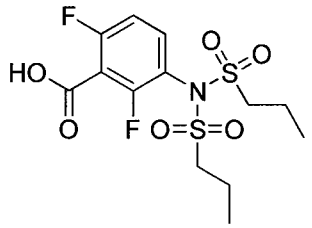


2,6-Difluoro-3-(propylsulfonamido)benzoic acid

[00238] A 1N aqueous NaOH solution (150 mL, 150 mmol) was added to a solution of methyl 2,6-difluoro-3-(*N*-(propylsulfonyl)propylsulfonamido)benzoate (20.0 g, 50.1 mmol) in 4:1 THF/MeOH (250 mL, 0.2M). The reaction mixture was stirred at room temperature overnight. The majority of the organic solvents were removed *in vacuo* (water bath temperature 35°C). 1N HCl (150 mL) was slowly added to the mixture, and the resulting solid was filtered and rinsed with water (4 X 50 mL). The material was washed with Et_2O (4 X 15 mL) to give 2,6-difluoro-3-(propylsulfonamido)benzoic acid as a solid (10.7 g, 77% yield). ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.74 (s, 1H), 7.57-7.50 (m, 1H), 7.23-7.17 (m, 1H), 3.11-3.06 (m, 2H), 1.79-1.69 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H). *m/z* (APCI-neg) M-1 = 278.0.

[00239]

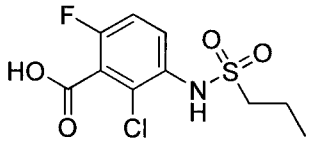
Example D



2,6-Difluoro-3-(*N*-(propylsulfonyl)propylsulfonamido)benzoic acid

[00240] Propane-1-sulfonyl chloride (1.225 mL, 10.92 mmol) was added to a mixture of 3-amino-2,6-difluorobenzoic acid (0.573 g, 3.310 mmol), triethylamine (2.030 mL, 14.56 mmol) and CH_2Cl_2 (17 mL, 0.2M) cooled to 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour. The mixture was then partitioned between saturated $NaHCO_3$ (100 mL) and ethyl acetate (75 mL). The aqueous layer was washed with ethyl acetate (50 mL) and then acidified with concentrated HCl to a pH of about 1. The acidified aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined ethyl acetate extracts were dried (over Na_2SO_4), filtered and concentrated. The resulting residue was triturated with hexanes to afford 2,6-difluoro-3-(*N*-(propylsulfonyl)propyl-sulfonamido)benzoic acid as a solid (0.948 g, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90-7.84 (m, 1H), 7.39-7.34 (m, 1H), 3.73-3.58 (m, 4H), 1.88-1.74 (m, 4H), 1.01 (t, J = 7.5 Hz, 6H). *m/z* (APCI-neg) M-(SO_2Pr) = 278.1.

Example E



2-Chloro-6-fluoro-3-(propylsulfonamido)benzoic acid

[00241] Step A: Into a 20-L 4-neck round flask was placed a solution of 2-chloro-4-fluorobenzenamine (1300 g, 8.82 mol, 1.00 equiv, 99%) in toluene (10 L), 4-methylbenzenesulfonic acid (3.1 g, 17.84 mmol, 99%), and hexane-2,5-dione (1222.5 g, 10.62 mol, 1.20 equiv, 99%). The resulting solution was heated to reflux for 1 h in an oil bath and cooled. The pH value of the solution was adjusted to 8 with sodium carbonate (1 mol/L). The resulting mixture was washed with 1x5000 mL of water and concentrated under vacuum. The crude product was purified by distillation and the fraction was collected at 140 °C to afford 1-(2-chloro-4-fluorophenyl)-2,5-dimethyl-1*H*-pyrrole (1700 g, yield: 85%).

[00242] Step B: Into a 5000-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed a solution of 1-(2-chloro-4-fluorophenyl)-2,5-

dimethyl-1*H*-pyrrole (390 g, 1.65 mol, 1.00 equiv, 95%) in tetrahydrofuran (2000 mL). The reaction vessel was cooled to -78 °C. To the above reaction vessel was added *n*-BuLi (800 mL, 1.10 equiv, 2.5%) dropwise with stirring over 80 minutes and methyl carbonochloridate (215.5 g, 2.27 mol, 1.20 equiv, 99%) dropwise with stirring over 90 minutes. The reaction solution was further stirred for 60 minutes at -78 °C and quenched by the addition of 1000 mL of NH_4Cl/water. The resulting solution was extracted with 1500 mL of ethyl acetate. The organic layers were combined, washed with 1x1500 mL of water and 1x1500 mL of sodium chloride(aq), dried over anhydrous magnesium sulfate, and concentrated under vacuum to afford methyl 2-chloro-3-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluorobenzoate (crude, 566.7 g).

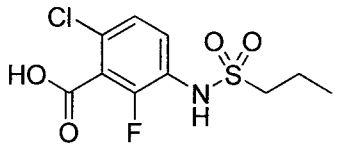
[00243] Step C: Into five 5000-mL 4-neck round-bottom flasks was placed a solution of methyl 2-chloro-3-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluorobenzoate (1500 g, 5.05 mol, 1.00 equiv, 95%) in ethanol/H_2O (7500/2500 mL), NH_2OH-HCl (5520 g, 79.20 mol, 15.00 equiv, 99%), and triethylamine (2140 g, 20.98 mol, 4.00 equiv, 99%). The resulting solution was refluxed for 18 h in an oil bath, cooled to room temperature, concentrated, and extracted with 3x3000 mL of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified using a silica gel column eluting with PE:EA (20:1-10:1) to afford methyl 3-amino-2-chloro-6-fluorobenzoate (980 g, yield: 95%).

[00244] Step D: Into four 5000-mL 4-neck round-bottom flasks was placed a solution of methyl 3-amino-2-chloro-6-fluorobenzoate (980 g, 4.76 mol, 1.00 equiv, 99%) in dichloromethane (8000 mL). Triethylamine (1454 g, 14.25 mol, 3.00 equiv, 99%) was added dropwise with stirring at 0 °C over 80 minutes followed by the addition of propane-1-sulfonyl chloride (1725 g, 11.94 mol, 2.50 equiv, 99%). The resulting solution was stirred at room temperature for 2 h, diluted with 1000 mL of water. The organic layer was washed with 1x1000 mL of hydrogen chloride and 1x1000 mL of water, dried over sodium sulfate, and concentrated to afford methyl 2-chloro-6-fluoro-3-(propylsulfonamido)benzoate as a brown solid (1500 g, 97%).

[00245] Step E: Into a 10000-mL 4-necked round-bottom flask was placed a solution of methyl 2-chloro-6-fluoro-3-(propylsulfonamido)benzoate (1500 g, 4.61 mol, 1.00 equiv, 95%) in tetrahydrofuran/H_2O (3000/3000 mL) and potassium hydroxide (1000 g, 17.68 mol, 4.50 equiv, 99%). The resulting solution was refluxed for 2 hours, cooled to room temperature and extracted with 3x2000 mL of ethyl acetate. The aqueous layers were combined and the pH was adjusted to 2 with hydrogen chloride (2 mol/L). The resulting solution was extracted with 2x3000 mL of dichloromethane. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated to afford 2-chloro-6-fluoro-3-(propylsulfonamido)benzoic acid

(517.5 g, yield: 37%). (ES, *m/z*): $[M+H]^+$ 296. ^1H NMR (400 MHz, $CDCl_3$): δ 1.058-1.096 (m, *J* = 15.2 Hz, 3H), 1.856-1.933 (m, 2H), 3.073-3.112 (m, 2H); 6.811 (1H, s), 7.156-7.199 (d, *J* = 17.2 Hz, 1H), 7.827-7.863(d, *J* = 14.4 Hz, 1H).

Example F



6-Chloro-2-fluoro-3-(propylsulfonamido)benzoic acid

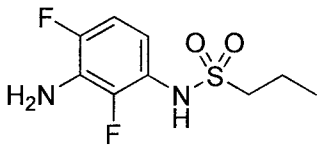
[00246] Step A: A flame dried flask equipped with a stir bar and rubber septum was charged with 4-chloro-2-fluoroaniline (5.00 g, 34.35 mmol) and anhydrous THF (170 mL). This solution was chilled to -78°C, and *n*-BuLi (14.7 mL, 1.07 eq. of 2.5M solution in hexanes) was then added over a 15 minute period. This mixture was stirred at -78°C for 20 minutes, and then a THF solution (25 mL) of 1,2-bis(chlorodimethylsilyl)ethane (7.76 g, 1.05 eq.) was added slowly (over a 10 minute period) to the reaction mixture. This was stirred for 1 hour, and then 2.5M *n*-BuLi in hexanes (15.11 mL, 1.1 eq.) was added slowly. After allowing the mixture to warm to room temperature for one hour, the mixture was chilled back to -78°C. A third allotment of *n*-BuLi (15.66 mL, 1.14 eq.) was added slowly, and the mixture was stirred at -78°C for 75 minutes. Benzyl chloroformate (7.40 g, 1.2 eq.) was then added slowly, and the mixture was stirred at -78°C for one hour. The cooling bath was then removed. The mixture was allowed to warm for 30 minutes and then quenched with water (70 mL) and concentrated HCl (25 mL). The mixture was allowed to continue to warm to room temperature. The mixture was then extracted with EtOAc. The extracts were washed twice with a saturated Na_2HCO_3 solution, once with water, dried over sodium sulfate and concentrated. The resulting residue was flashed on a 65 Biotage (30% ethyl acetate/hexane) to produce benzyl 3-amino-6-chloro-2-fluorobenzoate (4.3 g, 45%) as an oil. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.37-7.48 (m, 5H), 7.07 (dd, *J* = 8, 2 Hz, 1H), 6.87 (t, *J* = 8 Hz, 1H), 5.61 (br s, 2H), 5.40 (s, 2H).

[00247] Step B: Benzyl 3-amino-6-chloro-2-fluorobenzoate (4.3 g, 15.37 mmol) was dissolved in dry dichloromethane (270 mL). Triethylamine (5.36 mL, 2.5 eq.) was added, and the mixture was chilled to 0°C. Propane-1-sulfonyl chloride (3.63 mL, 32.3 mmol, 2.1 eq.) was then added *via* syringe, and a precipitate resulted. Once the addition was complete, the mixture was allowed to warm to room temperature, and the starting material was consumed as determined by TLC (3:1 hexane:ethyl acetate). The mixture was then diluted with dichloromethane (200 mL), washed with 2M aqueous HCl (2 X 100 mL), saturated $NaHCO_3$

solution, dried over sodium sulfate and concentrated. The resulting residue was purified on a 65 Biotage chromatography system (40% ethyl acetate/hexane) to produce benzyl 6-chloro-2-fluoro-3-(N-(propylsulfonyl)propylsulfonamido)benzoate (5.5 g, 72%) as an oil that slowly solidified upon standing. NMR ($CDCl_3$, 400 MHz) δ 7.28-7.45 (m, 7H), 5.42 (s, 2H), 3.58-3.66 (m, 2H), 3.43-3.52 (m, 2H), 1.08 (t, J = 8 Hz, 6H).

[00248] Step C: Benzyl 6-chloro-2-fluoro-3-(*N*-(propylsulfonyl)propyl-sulfonamido) benzoate (5.4 g, 10.98 mmol) was dissolved in THF (100 mL) and 1M aqueous KOH (100 mL). This mixture was refluxed for 16 hours and then allowed to cool to room temperature. The mixture was then acidified to a pH of 2 with 2M aqueous HCl and extracted with EtOAc (2 x). The extracts were washed with water, dried over sodium sulfate and concentrated to a solid that was triturated with hexanes/ether to give 6-chloro-2-fluoro-3-(propylsulfonamido)benzoic acid (2.2 g, 68%) as a solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.93 (s, 1H), 7.49 (t, J = 8 Hz, 1H), 7.38 (dd, J = 8, 2 Hz, 1H,), 3.11-3.16 (m, 2H), 1.68-1.78 (m, 2H), 0.97 (t, J = 8 Hz, 3H).

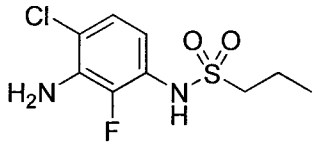
Example G



N-(3-Amino-2,4-difluorophenyl)propane-1-sulfonamide

[00249] To a solution of 2,6-difluoro-3-(propylsulfonamido)benzoic acid (4.078 g, 14.6 mmol) in THF (60 mL) was added triethylamine (4.68 mL, 33.59 mmol) and diphenyl-phosphonic azide (3.73 mL, 16.79 mmol). The reaction mixture was stirred at room temperature for 3 hours and then warmed to 80 °C for 2 hours. Water (10 mL) was added, and the mixture stirred at 80 °C for 15 hours. The reaction mixture was diluted with 300 mL of EtOAc, and the organic layer was washed with saturated aq. $NaHCO_3$ solution and brine. The solvent was removed under reduced pressure and the residual purified *via* silica gel column chromatography eluting with 30/70 EtOAc/hexane to obtain 2.03 g (55%) of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 6.90–6.80 (m, 1H), 6.51 (td, J=8.7, 5.5 Hz, 1H), 5.28 (s, 2H), 3.05–2.96 (m, 2H), 1.82–1.64 (m, 2H), 1.01–0.90 (m, 3H). LC/MS: *m/z* 251.1 [M+1].

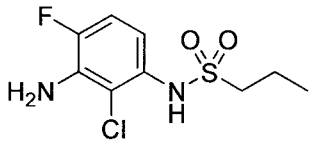
Example H



N-(3-Amino-4-chloro-2-fluorophenyl)propane-1-sulfonamide

[00250] To a solution of 6-chloro-2-fluoro-3-(propylsulfonamido)benzoic acid (1.70 g, 5.75 mmol) in THF (23 mL) was added triethylamine (1.84 mL, 13.2 mmol) and diphenylphosphonic azide (1.43 mL, 6.61 mmol). The reaction mixture was stirred at room temperature for 1 hour, warmed to 70 °C and stirred for 1 hour. Water (6 mL) was added, after which the reaction mixture was stirred again at 70 °C for 3 hours. The mixture was cooled to room temperature, ethyl acetate was added, and the layers were separated. The organic phase was dried with sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash silica gel chromatography using 0-50% EtOAc/heptane gradient to afford *N*-(3-amino-4-chloro-2-fluorophenyl)propane-1-sulfonamide (1.01 g, 66%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 7.02 (d, 1H), 6.58 (t, 1H), 5.50 (s, 2H), 3.09–2.95 (t, 2H), 1.81–1.64 (sx, 2H), 0.96 (t, 3H). LC/MS: *m/z* 267.1 [M+1].

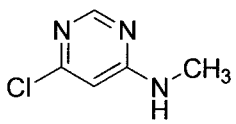
Example I



N-(3-Amino-2-chloro-4-fluorophenyl)propane-1-sulfonamide

[00251] The compound was prepared using the procedure described in Example G using 2-chloro-6-fluoro-3-(propylsulfonamido)benzoic acid instead 2,6-difluoro-3-(propyl-sulfonamido)benzoic acid as starting material. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.28-6.99 (m, 1H), 6.63 (td, J = 8.7, 5.5 Hz, 1H), 5.45 (s, 2H), 3.07–2.99 (m, 2H), 1.88–1.69 (m, 2H), 1.03–0.95 (m, 3H). LC/MS: *m/z* 267.1 [M+1].

Example J

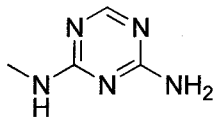


6-Chloro-*N*-methylpyrimidin-4-amine

[00252] 4,6-Dichloropyrimidine (978 mg, 6.56 mmol) was taken up in isopropanol (10 mL, 131 mmol) and cooled to 0-5 °C. A solution of 33% methylamine in ethanol

(1.768 mL, 13.2 mmol) was added, and the reaction mixture was stirred for 15 hours. The mixture was concentrated under reduced pressure and suspended in water. The title compound was obtained after filtration and drying in vacuo (772 mg, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.65 (s, 1H), 6.50 (s, 1H), 2.99 – 2.67 (m, 3H). LC/MS: *m/z* 144.1 [M+1].

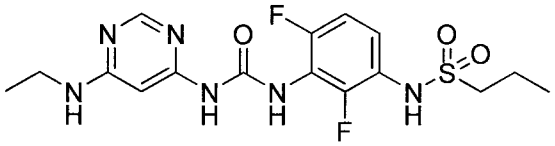
Example K



N^2-Methyl-1,3,5-triazine-2,4-diamine

[00253] 1,1-Diethoxy-N,N-dimethylmethanamine (6.86 mL, 0.0400 mol) was added to a stirred suspension of N-methyl guanidine hydrochloride (3.50 g, 0.0320 mol) in a 21% w/w solution of sodium ethoxide in ethanol (13 mL, 0.0400 mol). This reaction mixture was stirred at room temperature for 15 minutes before being heated to reflux for 4 hours. Upon cooling, the precipitated N^2-methyl-1,3,5-triazine-2,4-diamine was collected by filtration and dried over vacuum. (2.8g, 71%) Two distinct rotomers were observed by ^{1}H NMR (400 MHz, DMSO) δ 8.02 (s) + 7.88 (s) [1H], 7.09 (s) + 6.92 (s) [1H], 6.74 (s) + 6.59 (s) [2H], 2.71 (s + s, 3H).

Example 1



Propane-1-sulfonic acid {3-[3-(6-ethylamino-pyrimidin-4-yl)-ureido]-2,4-difluoro-phenyl}-amide

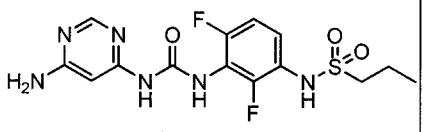
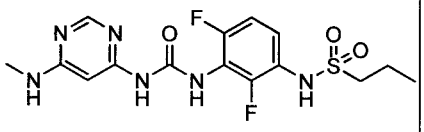
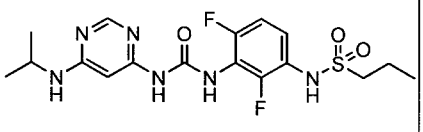
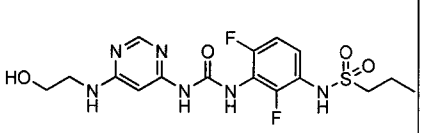
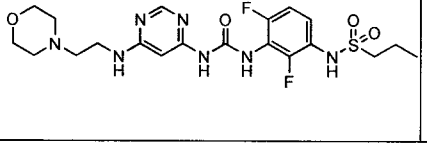
[00254] Step A: A 5 mL conical reaction vial was charged with 6-chloropyrimidin-4-amine (1043 mg, 8.05 mmol), phenylchloroformate (2.02 mL, 16.1 mmol) and cesium carbonate (5246 mg, 16.1 mmol) in THF. The reaction vessel was sealed and the mixture heated to 60 °C for 20 hours. The volatiles were removed to afford phenyl 6-chloropyrimidin-4-ylcarbamate as yellow solid (738 mg, 37%), which was used in the next step without further purification.

[00255] Step B: Phenyl 6-chloropyrimidin-4-ylcarbamate (204 mg, 0.817 mmol) and N-(3-amino-2,4-difluorophenyl)propane-1-sulfonamide (225 mg, 0.899 mmol) were taken up in 1,2-dichloroethane (3 mL, 41 mmol). The reaction mixture was heated at 90 °C for 15 hours, cooled to room temperature and concentrated under reduced pressure. Purification via silica gel column chromatography (eluent: ethylacetate/hexane 1:1) afforded N-(3-(3-(6-chloropyrimidin-4-yl)ureido)-2,4-difluorophenyl)propane-1-sulfonamide (250 mg, 75%).

[00256] Step C: N-(3-(3-(6-chloropyrimidin-4-yl)ureido)-2,4-difluorophenyl)propane-1-sulfonamide (27 mg, 0.067 mmol) was taken up in 2 mL of 2M ethylamine solution in ethanol. The mixture was heated at 60 °C for 2 hours and the solvent then removed under reduced pressure. The crude product was purified through reversed phase HPLC using 5-50% acetonitrile/water to yield the title compound (15 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 9.43 (s, 1H), 8.44 (s, 1H), 8.16 (s, 1H), 7.44 – 7.16 (m, 2H), 6.99 (t, *J* = 8.9, 1H), 6.47 (s, 1H), 2.92 (m, 2H), 2.05(m, 2H), 1.69 (m, 2H), 1.10 (t, *J* = 7.2, 3H), 0.95 (t, *J* = 7.4, 3H). LC/MS: *m/z* 415.1 [M+1]; RT = 3.34 min.

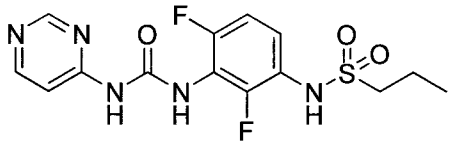
[00257] Examples 2-6 listed in Table 1 were prepared applying the procedure described in Example 1 and using appropriate amino building blocks.

Table 1

Example no.	Structure	Name	MS *m/z*	^{1}H NMR δ (400 MHz, DMSO-d6)
2		N-(3-(3-(6-aminopyrimidin-4-yl)ureido)-2,4-difluorophenyl)propane-1-sulfonamide	387.1	9.92 (s, 1H), 9.53 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.28 (dd, *J* = 14.7, 8.8, 1H), 7.08 (dd, *J* = 20.0, 9.8, 1H), 6.81 (s, 2H), 6.41 (s, 1H), 3.07 – 2.94 (m, 2H), 1.81 – 1.64 (m, 2H), 0.96 (t, *J* = 7.4, 3H)
3		N-(2,4-difluoro-3-(3-(6-(methylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide	401.1	9.83 (s, 1H), 9.48 (s, 1H), 8.18 (d, *J* = 6.8, 1H), 7.35 – 7.24 (m, 2H), 7.16 (t, *J* = 9.4, 1H), 6.45 (s, 1H), 3.14 – 2.98 (m, 2H), 2.72 (m, 3H), 1.87 – 1.63 (m, 2H), 0.99 (t, *J* = 7.4, 3H)
4		N-(2,4-difluoro-3-(3-(6-(isopropylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide	429.1	12.12 (s, 1H), 9.61 (s, 1H), 8.27 (s, 1H), 7.40 (d, *J* = 7.6, 1H), 7.30 (td, *J* = 8.9, 5.8, 1H), 7.14 (t, *J* = 8.8, 1H), 6.12 (s, 1H), 4.10 (m, 1H), 3.11 – 3.00 (m, 2H), 1.81 – 1.68 (m, 2H), 1.16 (d, *J* = 6.5, 6H), 0.97 (t, *J* = 7.4, 3H)
5		N-(2,4-difluoro-3-(3-(6-(2-hydroxyethylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide	431.1	9.83 (s, 1H), 9.49 (s, 1H), 8.19 (d, *J* = 15.6, 1H), 7.56 – 7.21 (m, 2H), 7.14 (t, *J* = 8.7, 1H), 6.52 (d, *J* = 24.6, 1H), 4.71 (m, 2H), 3.48 (m, 2H), 3.15 – 2.93 (m, 2H), 1.83 – 1.63 (m, 2H), 0.97 (t, *J* = 7.4, 3H)
6		N-(2,4-difluoro-3-(3-(6-(2-morpholinoethylamino)pyrimidin-4-yl)ureido)phenyl)propan	500.1	9.81 (s, 1H), 9.62 (s, 1H), 9.48 (s, 1H), 8.17 (s, 1H), 7.29 (dd, *J* = 14.5, 8.8, 1H), 7.13 (t, *J* = 8.9, 1H), 6.50 (d, *J* = 15.8, 1H), 3.65 – 3.50 (m,

Example no.	Structure	Name	MS *m/z*	^{1}H NMR δ (400 MHz, DMSO-d6)
		e-1-sulfonamide		4H), 3.09 – 2.98 (m, 2H), 2.48 – 2.30 (m, 8H), 1.82 – 1.66 (m, 2H), 0.97 (t, *J* = 7.4, 3H)

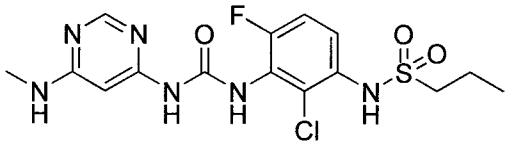
Example 7



Propane-1-sulfonic acid [2,4-difluoro-3-(3-pyrimidin-4-yl-ureido)-phenyl]-amide

[00258] N-(3-(3-(6-Chloropyrimidin-4-yl)ureido)-2,4-difluorophenyl)propane-1-sulfonamide (66 mg, 0.16 mmol) was taken up in ethanol (5 mL). Pd/C 10% (5 mg) was added, and the reaction mixture was exposed to a hydrogen atmosphere for 4 hours. The reaction mixture was filtered through a Celite® pad and further purified through silica gel flash chromatography (eluent: ethylacetacte/hexane 1:1) to obtain the title compound (41 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.20 (s, 1H), 9.05 (s, 1H), 8.68 (d, *J* = 0.8, 1H), 7.75 (d, *J* = 0.7, 1H), 7.53 – 7.26 (m, 2H), 7.14 (t, *J* = 8.8, 1H), 3.03 (dd, *J* = 8.8, 6.6, 2H), 1.74 (d, *J* = 7.6, 2H), 0.97 (dd, *J* = 9.2, 5.7, 3H). LC/MS: *m/z* 372.1 [M+1]; RT = 3.19 min.

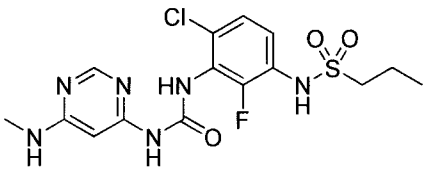
Example 8



Propane-1-sulfonic acid {2-chloro-4-fluoro-3-[3-(6-methylamino-pyrimidin-4-yl)-ureido]-phenyl}-amide

[00259] The title compound was prepared in a similar manner as Example 1, using N-(3-amino-2-chloro-4-fluorophenyl)propane-1-sulfonamide instead N-(3-amino-2,4-difluoro-phenyl)propane-1-sulfonamide in Step B and methylamine instead ethylamine in Step C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (s, 1H), 9.51 (s, 2H), 8.18 (s, 1H), 7.37 (dt, *J* = 34.9, 17.5, 1H), 7.31 (s, 1H), 6.42 (s, 1H), 3.16 – 2.97 (m, 2H), 2.76 (s, 3H), 1.76 (dd, *J* = 15.2, 7.5, 2H), 0.98 (t, *J* = 7.4, 3H). LC/MS: *m/z* 417.0 [M+1]; RT = 3.19 min.

Example 9



N-(4-Chloro-2-fluoro-3-(3-(6-(methylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide

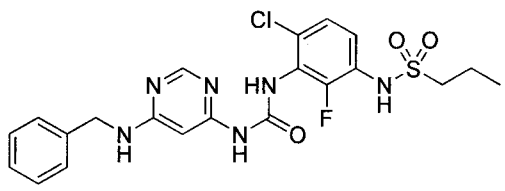
[00260] Step A: To a solution of 6-chloropyrimidin-4-amine (4.0 g, 30.9 mmol) in THF (60 mL) was added cesium carbonate (20.1 g, 61.8 mmol), followed by phenyl chloroformate (7.8 mL, 61.8 mmol). The reaction mixture was heated at 60 °C and stirred for 24 hours, after which the excess cesium carbonate was filtered off and rinsed with ethyl acetate. The organic phase was washed with water, then with a brine solution, dried with sodium sulfate, filtered and concentrated in vacuo. The crude was triturated with ethyl acetate to afford phenyl 6-chloropyrimidin-4-ylcarbamate (2.28 g, 30%), as a pale orange solid.

[00261] Step B: A solution of phenyl 6-chloropyrimidin-4-ylcarbamate (0.33 g, 1.30 mmol) and N-(3-amino-4-chloro-2-fluorophenyl)propane-1-sulfonamide (0.38 g, 1.43 mmol) in 1,2-dichloroethane (5.0 mL) was heated at 70 °C for 72 hours, after which the reaction mixture was concentrated in vacuo. The crude was purified by flash chromatography using a gradient of 0-50% EtOAc in hexane to afford N-(4-chloro-3-(3-(6-chloropyrimidin-4-yl)ureido)-2-fluorophenyl)propane-1-sulfonamide (0.41 g, 74%).

[00262] Step C: N-(4-Chloro-3-(3-(6-chloropyrimidin-4-yl)ureido)-2-fluoro-phenyl)propane-1-sulfonamide (0.08 g, 0.189 mmol) and methylamine (1.4 mL, 2.8 mmol, 2.0 M in THF) were combined with 1,2-dichloroethane (0.8 mL) in a microwave vessel and heated in a microwave to 90 °C for 25 minutes. The reaction mixture was concentrated in vacuo and the crude directly purified by reverse phase HPLC to give N-(4-chloro-2-fluoro-3-(3-(6-(methylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide (12 mg, 16%), as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (m, 2H), 9.51 (s, 1H), 8.18 (s, 1H), 7.42 – 7.17 (m, 3H), 6.43 (s, 1H), 3.17 – 2.98 (m, 2H), 2.75 (s, 3H), 1.87 – 1.62 (m, 2H), 0.97 (t, 3H). LC/MS: *m/z* 417.1 [M+1]; RT = 3.32 min.

[00263]

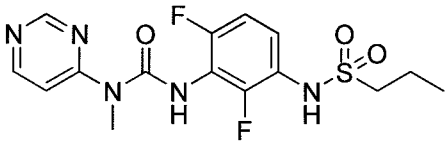
Example 10



N-(3-(3-(6-(Benzylamino)pyrimidin-4-yl)ureido)-4-chloro-2-fluorophenyl)propane-1-sulfonamide

[00264] To a solution of N-(4-chloro-3-(3-(6-chloropyrimidin-4-yl)ureido)-2-fluorophenyl)propane-1-sulfonamide (0.08 g, 0.189 mmol) in 1,2-dichloroethane (1.0 mL) was added N,N-diisopropylethylamine (0.21 mL, 1.2 mmol) and benzylamine (0.21 mL, 1.89 mmol). The reaction mixture was heated at 60 °C for 18 hours and then concentrated in vacuo. The crude was directly purified by reverse phase HPLC to give N-(3-(3-(6-(benzylamino)pyrimidin-4-yl)ureido)-4-chloro-2-fluorophenyl)propane-1-sulfonamide (30 mg, 26%), as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (br s, 1H), 9.44 (s, 1H), 8.30 (s, 1H), 8.18 (s, 1H), 7.88 (t, 1H), 7.38 – 7.11 (m, 7H), 6.56 (br s, 1H), 4.49 (br s, 2H), 2.98 – 2.86 (m, 2H), 1.69 (sx, 2H), 0.94 (t, 3H). LC/MS: *m/z* 493.1 [M+1]; RT = 4.19 min.

Example 11



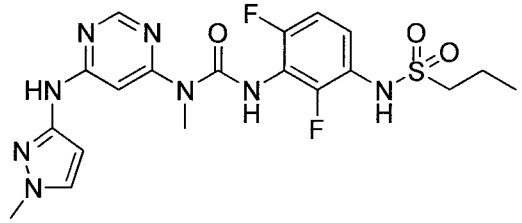
Propane-1-sulfonic acid [2,4-difluoro-3-(3-methyl-3-pyrimidin-4-yl-ureido)-phenyl]-amide

[00265] Step A: A 5 mL conical reaction vial was charged with 2,6-difluoro-3-(propylsulfonamido)benzoic acid (1049 mg, 3.76 mmol), triethylamine (1.204 mL, 8.64 mmol) and diphenylphosphonic azide (0.931 mL, 4.32 mmol) in THF (3 mL). The reaction vessel was sealed and the reaction mixture stirred at rt for 3 hours and then heated at 80 °C for 2 hours. 6-Chloro-*N*-methylpyrimidin-4-amine (674 mg, 4.69 mmol) was added followed by heating at 80 °C for 1 hour. The reaction mixture was diluted with 100 mL of EtOAc and washed with brine (2x). The organic layer was dried over sodium sulfate and filtered. Concentration under reduced pressure and subsequent purification via silica gel column chromatography (eluent: EtOAc/hexane 30:70) afforded N-(3-(3-(6-chloropyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)propane-1-sulfonamide as white solid (364 mg, 23%).

[00266] Step B: N-(3-(3-(6-Chloropyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)-propane-1-sulfonamide (26 mg, 0.06 mmol) was taken up in ethanol (5 mL). Pd/C 10% (5 mg) was added, and the reaction mixture was exposed to a hydrogen atmosphere for 4 hours. The mixture was filtered through a Celite® pad and the residue purified through silica gel flash chromatography (eluent: ethylacetacte/hexane 1:1) to obtain the title compound (11 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 9.67 (s, 1H), 9.51 (s, 1H), 8.78 (s, 1H), 7.66 (s, 1H), 7.44 – 7.28 (m, 1H), 7.19 (t, *J* = 8.7, 1H), 3.46 (s, 3H), 3.20 – 2.97 (m, 2H), 1.92 – 1.65 (m, 2H), 0.98 (t, 3H). LC/MS: *m/z* 386.1 [M+1]; RT = 3.56 min.

[00267]

Example 12

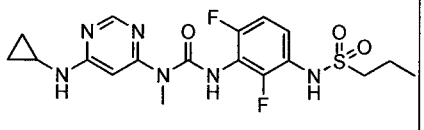
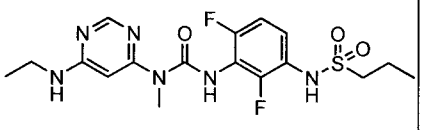


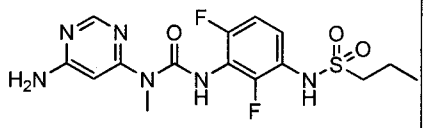
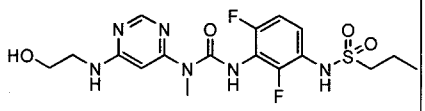
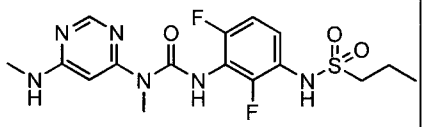
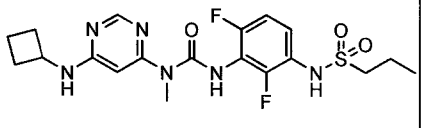
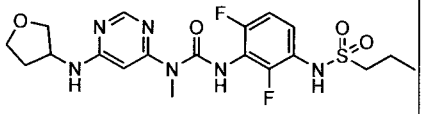
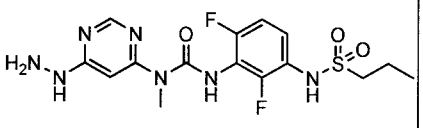
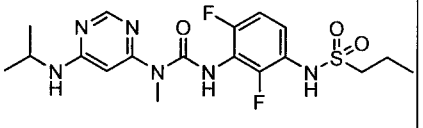
Propane-1-sulfonic acid (2,4-difluoro-3-{3-methyl-3-[6-(1-methyl-1H-pyrazol-3-ylamino)-pyrimidin-4-yl]-ureido}-phenyl)-amide

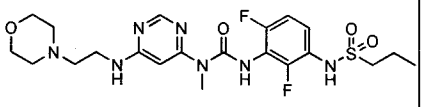
[00268] N-(3-(3-(6-Chloropyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)propane-1-sulfonamide (26 mg, 0.067 mmol) (Example 11, step A) and 1-methyl-1H-pyrazol-3-amine (60 mg, 0.67 mmol) were taken up in isopropanol (2 mL). The mixture was heated at 80 °C for 15 hours, then cooled to room temperature and concentrated under reduced pressure. The crude product was purified through reversed phase HPLC using a gradient of 5-60% acetonitrile/water to yield the title compound (3 mg, 10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 9.67 (s, 1H), 8.78 (s, 1H), 7.66 (s, 1H), 7.22 (m, 1H),7.44 – 7.28 (m, 1H), 7.19 (t, *J* = 8.7, 1H), 5.35 (m, 1H), 4.45 (s, 1H), 3.59(s, 3H), 3.46 (s, 3H), 3.20 – 2.97 (m, 2H), 1.92 – 1.65 (m, 2H), 0.97 (t, 3H). LC/MS: *m/z* 481.1 [M+1]; RT = 4.03 min.

[00269] Examples 13-22 listed in Table 2 were prepared applying the procedure described in Example 12 and using appropriate amino building blocks.

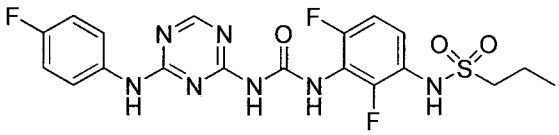
Table 2

Example no.	Structure	Name	MS *m/z*	^{1}H NMR δ (400 MHz, DMSO-d6)
13		N-(3-(3-(6-(cyclopropylamino)pyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)propane-1-sulfonamide	441.1	12.06 (s, 1H), 9.64 (s, 1H), 8.42 – 8.16 (m, 1H), 7.77 (s, 1H), 7.31 (dd, *J* = 14.4, 8.7, 1H), 7.15 (t, *J* = 9.3, 1H), 6.25 (d, *J* = 20.5, 1H), 3.34 (s, 3H), 3.11 – 2.99 (m, 2H), 2.64 (m, 1H), 1.83 – 1.66 (m, 2H), 1.03 – 0.92 (m, 3H), 0.74 (t, *J* = 13.1, 2H), 0.50 (s, 2H)
14		N-(3-(3-(6-(ethylamino)pyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)propane-1-sulfonamide	429.1	12.12 (s, 1H), 9.63 (s, 1H), 8.27 (s, 1H), 7.50 (s, 1H), 7.30 (dd, *J* = 14.5, 8.8, 1H), 7.14 (t, *J* = 8.8, 1H), 6.12 (s, 1H), 3.36 (s, 3H), 3.12 – 2.98 (m, 2H), 1.81 – 1.66 (m, 2H), 1.14 (t, *J* = 7.2, 3H), 0.97 (t, *J* = 7.4, 3H)

Example no.	Structure	Name	MS *m/z*	^{1}H NMR δ (400 MHz, DMSO-d6)
15		N-(3-(3-(6-aminopyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)propane-1-sulfonamide	401.1	12.10 (s, 1H), 9.80 (s, 1H), 8.22 (s, 1H), 7.27 (dd, *J* = 14.6, 8.8, 1H), 7.07 (t, *J* = 9.2, 1H), 6.99 (s, 2H), 6.14 (s, 1H), 3.31 (s, 3H), 3.06 – 2.88 (m, 2H), 1.83 – 1.60 (m, 2H), 0.96 (t, *J* = 7.4, 3H)
16		N-(2,4-difluoro-3-(3-(6-(2-hydroxyethylamino)pyrimidin-4-yl)-3-methylureido)phenyl)propane-1-sulfonamide	445.1	9.85 (s, 1H), 9.46 (s, 1H), 8.18 (d, *J* = 15.6, 1H), 7.58 – 7.23 (m, 2H), 7.17 (t, *J* = 8.7, 1H), 6.54 (d, *J* = 24.6, 1H), 4.73 (m, 2H), 3.46 (m, 2H), 3.33 (s, 3H), 3.17 – 2.95 (m, 2H), 1.85 – 1.65 (m, 2H), 0.99 (t, *J* = 7.4, 3H)
17		N-(2,4-difluoro-3-(3-methyl-3-(6-(methylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide	415.1	12.13 (s, 1H), 9.62 (s, 1H), 8.28 (s, 1H), 7.46 (d, *J* = 4.5, 1H), 7.38 – 7.24 (m, 1H), 7.15 (t, *J* = 9.2, 1H), 6.14 (d, *J* = 19.5, 1H), 3.35 (s, 3H), 3.12 – 3.00 (m, 2H), 2.84 (d, *J* = 3.8, 3H), 1.82 – 1.66 (m, 2H), 0.98 (t, *J* = 7.4, 3H)
18		N-(3-(3-(6-(cyclobutylamino)pyrimidin-4-yl)-3-methylureido)-2,4-difluorophenyl)propane-1-sulfonamide	455.1	12.07 (s, 1H), 9.62 (s, 1H), 8.22 (s, 1H), 7.80 (d, *J* = 7.2, 1H), 7.35 – 7.25 (m, 1H), 7.14 (t, *J* = 9.2, 1H), 6.08 (s, 1H), 4.64 – 4.20 (m, 1H), 3.37 (s, 3H), 3.12 – 2.99 (m, 2H), 2.28 (m, 2H), 1.92 (d, *J* = 9.0, 2H), 1.81 – 1.59 (m, 4H), 0.97 (t, *J* = 7.4, 3H)
19		N-(2,4-difluoro-3-(3-methyl-3-(6-(tetrahydrofuran-3-ylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide	471.1	11.97 (s, 1H), 8.30 (s, 1H), 7.75 (d, *J* = 6.6, 1H), 7.27 (dd, *J* = 14.7, 8.9, 1H), 7.07 (t, *J* = 8.9, 1H), 6.57 (s, 1H), 6.22 (d, *J* = 19.6, 1H), 4.47 (s, 1H), 3.92 – 3.80 (m, 2H), 3.73 (dt, *J* = 13.8, 6.9, 1H), 3.34 (s, 3H), 3.06 – 2.90 (m, 2H), 2.19 (td, *J* = 14.8, 7.5, 1H), 1.82 (d, *J* = 4.5, 1H), 1.78 – 1.64 (m, 2H), 0.96 (t, *J* = 7.4, 3H)
20		N-(2,4-difluoro-3-(3-(6-hydrazinylpyrimidin-4-yl)-3-methylureido)phenyl)propane-1-sulfonamide	416.1	12.26 (s, 1H), 9.62 (s, 1H), 8.54 (s, 1H), 8.21 (s, 1H), 7.38 – 7.25 (m, 1H), 7.15 (t, *J* = 9.1, 1H), 6.42 (s, 1H), 4.44 (s, 2H), 3.32 (s, 3H), 3.12 – 2.99 (m, 2H), 1.82 – 1.67 (m, 2H), 0.98 (t, *J* = 7.4, 3H)
21		N-(2,4-difluoro-3-(3-(6-(isopropylamino)pyrimidin-4-yl)-3-methylureido)phenyl)propane-1-sulfonamide	443.1	12.12 (s, 1H), 9.61 (s, 1H), 8.27 (s, 1H), 7.40 (d, *J* = 7.6, 1H), 7.30 (td, *J* = 8.9, 5.8, 1H), 7.14 (t, *J* = 8.8, 1H), 6.12 (s, 1H), 4.10 (m, 1H), 3.33 (s, 3H), 3.11 – 3.00 (m, 2H), 1.81 – 1.68 (m, 2H), 1.16 (d, *J* = 6.5, 6H), 0.97 (t,

Example no.	Structure	Name	MS *m/z*	^{1}H NMR δ (400 MHz, DMSO-d6)
				J = 7.4, 3H)
22		N-(2,4-difluoro-3-(3-methyl-3-(6-(2-morpholinoethylamino)pyrimidin-4-yl)ureido)phenyl)propane-1-sulfonamide	514.1	12.11 (s, 1H), 9.76 (s, 1H), 8.28 (s, 1H), 7.40 (s, 1H), 7.30 (dd, *J* = 14.5, 8.8, 1H), 7.14 (t, *J* = 9.1, 1H), 6.22 (s, 1H), 3.66 – 3.51 (m, 4H), 3.45 (s, 3H), 3.11 – 2.98 (m, 2H), 2.44-2.28 (m, 8H), 1.85 – 1.65 (m, 2H), 0.97 (t, *J* = 7.4, 3H)

Example 23

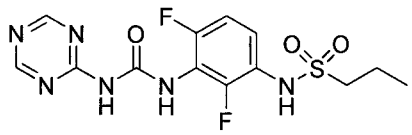


N-(2,4-Difluoro-3-(3-(4-(4-fluorophenylamino)-1,3,5-triazin-2-yl)ureido)phenyl)propane-1-sulfonamide

[00270] Step A: 2,6-Difluoro-3-(propylsulfonamido)benzoic acid (4 g, 14 mmol) was dissolved in 1,4-dioxane (100 mL) and triethylamine (2.2 mL, 16 mmol). Diphenylphosphonic azide (3.4 mL, 16 mmol) was added, and the mixture was stirred at rt for 3 hours. The mixture was added dropwise to a solution of phenol (15 g, 160 mmol) in 1,4-dioxane (100 mL) at 100 °C. The mixture was stirred at 100 °C for 3h. The mixture was cooled to rt. Silica was added, and the mixture was concentrated. The crude product was purified using flash chromatography (gradient elution, solvent: 0-30% ethyl acetate in heptanes) to yield phenyl 2,6-difluoro-3-(propylsulfonamido)phenylcarbamate (2.9 g, 55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 1H), 9.68 (s, 1H), 7.49 – 7.30 (m, 3H), 7.30 – 7.11 (m, 4H), 3.11 – 3.03 (m, 2H), 1.83 – 1.61 (m, 2H), 0.96 (t, J = 7.4, 3H).

[00271] Step B: Phenyl 2,6-difluoro-3-(propylsulfonamido)phenylcarbamate (150 mg, 0.40 mmol) and N-(4-fluorophenyl)-1,3,5-triazine-2,4-diamine (580 mg, 2.8 mmol) were suspended in DMSO (0.4 mL, 6 mmol). The mixture was stirred at 80 °C for 1 hour and 130 °C for 1 hour. The mixture was cooled to room temperature, diluted with water, and filtered. The solids were washed with water to yield N-(2,4-difluoro-3-(3-(4-(4-fluorophenylamino)-1,3,5-triazin-2-yl)ureido)phenyl)propane-1-sulfonamide as a white powder (65 mg, 32% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 – 10.41 (m, *J* = 88.3 Hz, 2H), 10.36 – 10.03 (m, *J* = 62.6 Hz, 1H), 9.69 (s, 1H), 8.51 (s, 1H), 7.82 – 7.57 (m, 2H), 7.46 – 7.30 (m, 1H), 7.29 – 6.95 (m, 3H), 3.15 – 2.99 (m, 2H), 1.83 – 1.68 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). LC/MS: *m/z* 482.1 [M+1]; RT = 4.40 min.

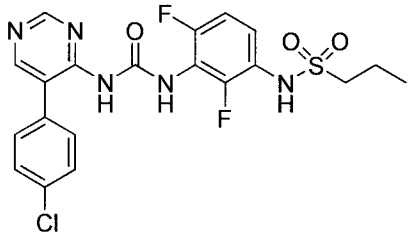
Example 24



N-(3-(3-1,3,5-Triazin-2-ylureido)-2,4-difluorophenyl)propane-1-sulfonamide

[00272] The title compound was made using the procedure described in Example 23 using appropriate starting materials. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 10.38 (s, 1H), 9.67 (s, 1H), 8.99 (s, 2H), 7.36 (td, J = 8.8, 5.8, 1H), 7.19 (t, J = 8.7, 1H), 3.12 – 3.00 (m, 2H), 1.83 – 1.66 (m, 2H), 0.98 (t, J = 7.4, 3H). LC/MS: *m/z* 273.0 [M+1].

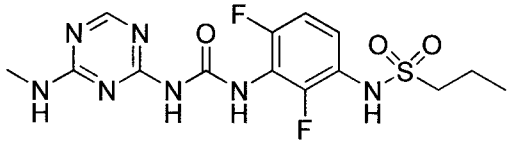
Example 25



Propane-1-sulfonic acid (3-{3-[5-(4-chloro-phenyl)-pyrimidin-4-yl]-ureido}-2,4-difluoro-phenyl)-amide

[00273] The title compound was made using the procedure described in Example 23 using appropriate starting materials. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.59 (s, 1H), 9.74 (br s, 1H), 9.03 (s, 1H), 8.87 (s, 1H), 8.50 (s, 1H), 7.57 (d, *J*=12 Hz, 2H), 7.54 (d, *J*=12 Hz, 2H), 7.32 (td, *J* = 8.9, 5.7 Hz, 1H), 7.14 (t, *J* = 9.1 Hz, 1H), 3.08 – 2.97 (m, 2H), 1.80 – 1.67 (m, 2H), 0.97 (s, 3H). LC/MS: *m/z* 482.0 [M+1]; RT = 6.00 min.

Example 26



N-(2,4-Difluoro-3-(3-(4-(methylamino)-1,3,5-triazin-2-yl)ureido)phenyl)propane-1-sulfonamide

[00274] Step A: Diphenylphosphonic azide (9.082 mL, 0.04214 mol) was added to stirred solution of 2,6-difluoro-3-(propylsulfonamido)benzoic acid (10.234 g, 0.036647 mol) and triethylamine (11.75 mL, 0.08429 mol) in tetrahydrofuran (100 mL, 1 mol) and the reaction mixture was stirred at room temperature for 3 hours and then heated to reflux for an additional hour. 1H-pyrazole (2.5 g, 0.037 mol) was added to the reaction mixture, followed by heating to

reflux for 1 additional hour. After cooling to room temperature and removal of the solvent under reduced pressure, an orange-colored oil was obtained. This crude material was purified by silica gel chromatography; eluent: 0-50% ethyl acetate: heptane. The obtained material was recrystalized from 150 mL of a solution of ethyl acetate / heptane (1:3, v/v) to give N-(2,6-difluoro-3-(propylsulfonamido)phenyl)-1H-pyrazole-1-carboxamide with 90% purity (4.4 g, 87%). ^{1}H NMR (500 MHz, DMSO-d6) δ 10.33 (s, 1H), 9.70 (s, 1H), 8.41 (d, J=2.6, 1H), 7.92 (d, J=1.1, 1H), 7.42 (td, J=8.9, 5.8, 1H), 7.22 (t, J=9.2, 1H), 6.62 (dd, J=2.7, 1.6, 1H), 3.13 – 3.03 (m, 2H), 1.80 – 1.70 (m, 2H), 1.04 – 0.93 (m, 3H). LC/MS: *m/z* 345.2 [M+1].

[00275] Step B: N-(2,6-Difluoro-3-(propylsulfonamido)phenyl)-1H-pyrazole-1-carboxamide (0.201 g, 0.584 mmol), N^2-methyl-1,3,5-triazine-2,4-diamine (73 mg, 0.58 mmol) and triethylamine (0.3 mL, 2 mmol) were suspended in dimethyl sulfoxide (0.622 mL, 8.76 mmol) and heated to 60 °C overnight and subsequently to 115 °C for an additional 24 hours. The reaction was cooled to room temperature, concentrated and purified by reverse phase HPLC to yield N-(2,4-difluoro-3-(3-(4-(methylamino)-1,3,5-triazin-2-yl)ureido)phenyl)propane-1-sulfonamide as a white solid (18.9 mg, 8%). ^{1}H NMR spectroscopy was performed at 360K to coalesce rotamers, but a small amount of decomposition was observed at elevated temperatures. ^{1}H NMR (300 MHz, DMSO-d6) δ 10.74 (s, 1H), 9.63 (s, 1H), 9.22 (s, 1H), 8.33 (s, 1H), 7.71 (s, 1H), 7.35 (dd, J = 11.6, 5.9, 1H), 7.12 (t, J = 10.2, 1H), 3.09 (dd, J = 16.3, 8.7, 2H), 2.88 (d, J = 4.7, 3H), 1.81 (dd, J = 14.9, 7.5, 2H), 1.02 (d, J = 7.4, 3H). LC/MS: *m/z* 402.0 [M+1].

[00276] Table 3 shows the activity of certain compounds of the invention tested in the above B-RAF V600E inhibition assay (Example A).

Table 3

Example	BRAF V600E IC_{50} (μM)
1	0.0280
2	0.1420
3	0.0312
4	0.1650
5	0.0635
6	0.5350
7	1.3910
8	0.0198
9	0.0089
10	0.0192
11	1.2338

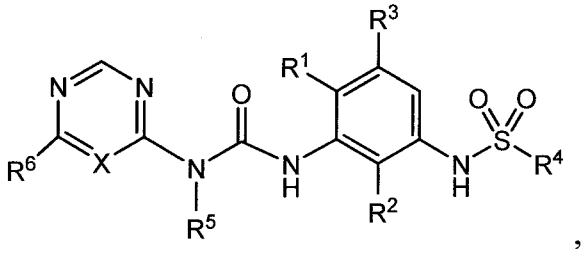
12	0.0591
13	0.0218
14	0.0256
15	0.0833
16	0.1208
17	0.0846
18	0.0836
19	0.2831
20	0.0334
21	0.1325
22	0.6163
23	0.0134
24	0.1223
25	0.2879
26	0.2352

[00277] While the invention has been described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications and equivalents, which may be included within the scope of the present invention as defined by the claims. Thus, the foregoing description is considered as illustrative only of the principles of the invention.

[00278] The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

What is claimed is:

1. A compound selected from Formula **I**:



I

stereoisomers, tautomers, prodrugs and pharmaceutically acceptable salts thereof, wherein:

X is N or CR^7;

R^1 and R^2 are independently selected from hydrogen, halogen, CN, C_1-C_3 alkyl and C_1-C_3 alkoxy;

R^3 is hydrogen, halogen or C_1-C_3 alkyl;

R^4 is C_3-C_5 cycloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, phenyl, a 5-6 membered heteroaryl or NR^8R^9, wherein the cycloalkyl, alkyl, alkenyl, alkynyl, phenyl and heteroaryl are optionally substituted with OR^8, halogen, phenyl, C_3-C_4 cycloalkyl, or C_1-C_4 alkyl optionally substituted with halogen;

R^5 is hydrogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl or C_3-C_5 cycloalkyl, wherein R^5 is optionally substituted with halogen;

R^6 is hydrogen or $NR^{10}R^{11}$;

R^7 is hydrogen or C_1-C_3 alkyl optionally substituted with halogen, OR^8, SR^8, NR^8R^9, C_3-C_6 cycloalkyl, 4-6 membered heterocyclyl, 5-6 membered heteroaryl or phenyl;

R^8 and R^9 are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

R^8 and R^9 are independently taken together with the atom to which they are attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl;

R^{10} is hydrogen;

R^{11} is hydrogen, (C_0-C_3 alkyl)$NR^{13}R^{14}$, (C_0-C_3 alkyl)OR^{13}, (C_1-C_3 alkyl)SR^{13}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl and phenyl are optionally substituted by halogen, oxo, OR^{15}, $NR^{15}R^{16}$ or C_1-C_3 alkyl;

R^{13} and R^{14} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl; and

R^{15} and R^{16} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen; or

R^{15} and R^{16} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl.

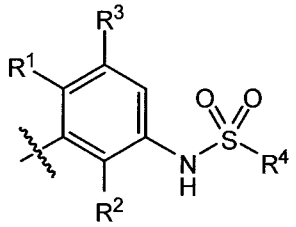
2. A compound of Claim 1, wherein X is N.

3. A compound of Claim 1, wherein X is CR^7.

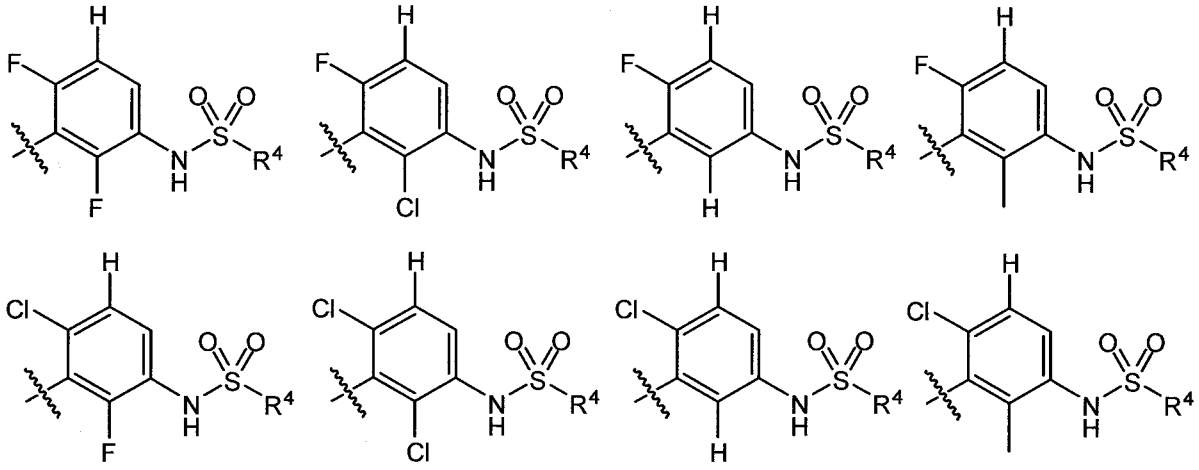
4. A compound of any one of Claims 1-3, wherein R^1, R^2 and R^3 are independently selected from hydrogen, halogen or C_1-C_3 alkyl; R^4 is C_3-C_4 cycloalkyl or C_1-C_6 alkyl optionally substituted with OH, halogen or C_3-C_4 cycloalkyl; R^5 is hydrogen or C_1-C_3 alkyl; R^6 is hydrogen or $NR^{10}R^{11}$; R^7 is hydrogen; R^{10} is hydrogen; and R^{11} is hydrogen, C_1-C_3 alkyl, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, wherein said alkyl, cycloalkyl, phenyl, heterocyclyl and heteroaryl are optionally substituted by C_{1-3} alkyl or halogen.

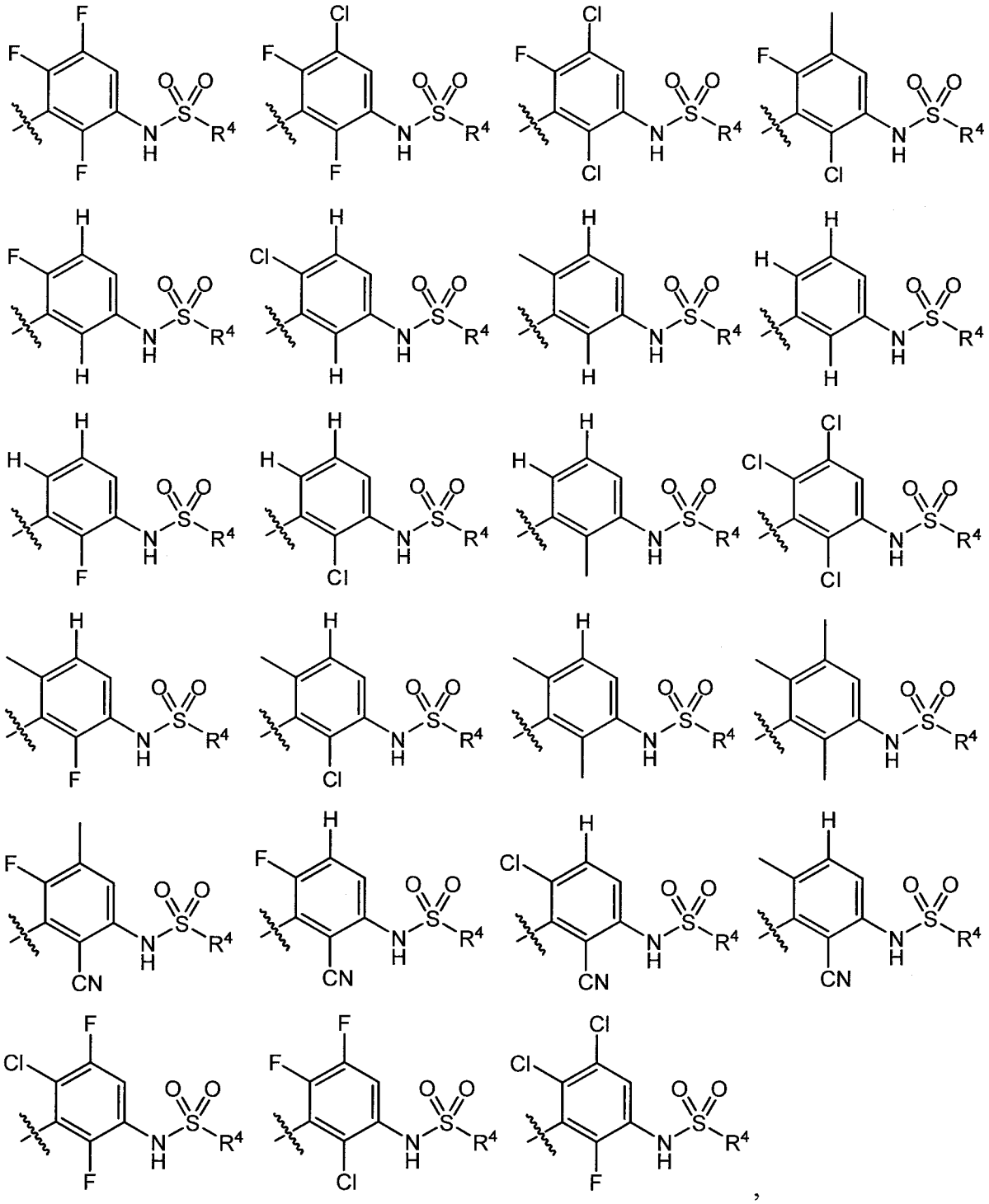
5. A compound of any one of Claims 1-4, wherein R^1, R^2 and R^3 are independently selected from hydrogen, halogen or C_1-C_3 alkyl.

6. A compound of any one of Claims 1-5, wherein the residue:



of Formula **I** is selected from:





wherein the wavy lines represent the point of attachment of the residue in Formula **I**.

7. A compound of any one of Claims 1-5, wherein R^1 and R^2 are F and R^3 is hydrogen.

8. A compound of any one of Claims 1-5, wherein R^1, R^2 and R^3 are F.

9. A compound of any one of Claims 1-5, wherein R^1 is F and R^2 is Cl and R^3 is hydrogen.

10. A compound of any one of Claims 1-5, wherein R^1 is Cl and R^2 is F and R^3 is hydrogen.

11. A compound of any one of Claims 1-5, wherein R^1 is F and R^2 is methyl and R^3 is hydrogen.

12. A compound of any one of Claims 1-5, wherein R^1 is methyl and R^2 is F and R^3 is hydrogen.

13. A compound of any one of Claims 1-5, wherein R^1 is F and R^2 and R^3 are hydrogen.

14. A compound of any one of Claims 1-5, wherein R^1 is Cl and R^2 and R^3 are hydrogen.

15. A compound of any one of Claims 1-5, wherein R^2 is F and R^1 and R^3 are hydrogen.

16. A compound of any one of Claims 1-5, wherein R^2 and R^3 are F and R^1 is hydrogen.

17. A compound of any one of Claims 1-16, wherein R^4 is cyclopropyl, ethyl, propyl, butyl, isobutyl, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CF_3$, phenylmethyl, cyclopropylmethyl, phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,5-difluorophenyl, 4-chloro-3-trifluoromethylphenyl, 1-methyl-1H-imidazol-4-yl, furan-2-yl, pyridin-2-yl, pyridin-3-yl, thiophen-2-yl, $-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$ $-N(CH_3)CH_2CH_3$, $-N(CH_3)_2$, or pyrrolidine.

18. A compound of any one of Claims 1-17, wherein R^4 is cyclopropyl, propyl, butyl, isobutyl, $-CH_2Cl$, $-CH_2CF_3$, $-CH_2CH_2CH_2F$, $-CH_2CH_2CF_3$, cyclopropylmethyl, $-NHCH_2CH_2CH_3$, $-N(CH_3)CH_2CH_3$, $-N(CH_3)_2$, or pyrrolidine.

19. A compound of any one of Claims 1-18, wherein R^4 is ethyl, propyl or $-CH_2CH_2CH_2F$.

20. A compound of any one of Claims 1-19, wherein R^4 is propyl.

21. A compound of any one of Claims 1-20, wherein R^5 is hydrogen or methyl.

22. A compound of any one of Claims 1-21, wherein R^5 is hydrogen.

23. A compound of any one of Claims 1-22, wherein R^6 is hydrogen or $NR^{10}R^{11}$; R^{10} is hydrogen; R^{11} is hydrogen, C_1-C_3 alkyl, (C_0-C_3 alkyl)OR^{13}, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, optionally substituted by C_{1-3} alkyl or halogen.

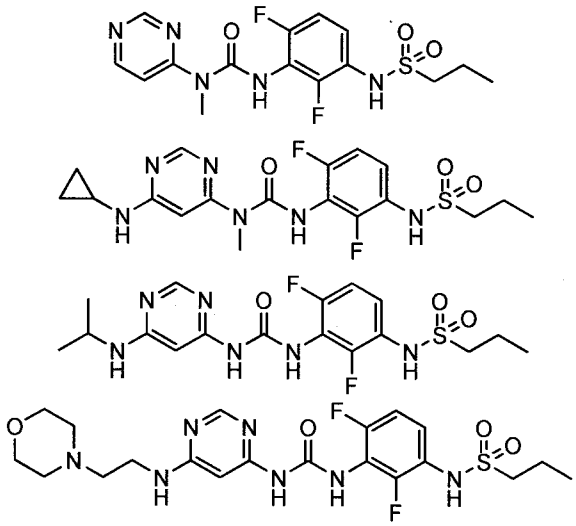
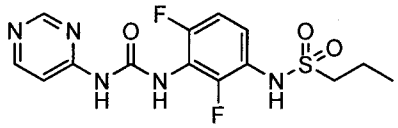
24. A compound of any one of Claims 1-23, wherein R^6 is $NR^{10}R^{11}$; R^{10} is hydrogen; and R^{11} is hydrogen, C_1-C_6 alkyl, (C_0-C_3 alkyl)OR^{13}, (C_0-C_3 alkyl)C_3-C_6 cycloalkyl, (C_0-C_3 alkyl)phenyl, (C_0-C_3 alkyl)3-6-membered heterocyclyl or (C_0-C_3 alkyl)5-6-membered heteroaryl, optionally substituted by C_{1-3} alkyl or halogen.

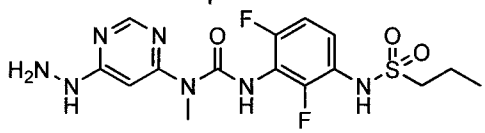
25. A compound of any one of Claims 1-23, wherein R^6 is hydrogen, NH_2, $-NHCH_3$,

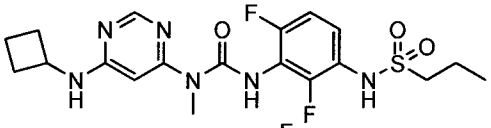
$-NHCH_2CH_3$, $-NHCH_2CH_2CH_3$, $-NHCH(CH_3)_2$, $-NHCH_2CH_2CH_2CH_3$, $-NHCH(CH_3)CH_2CH_3$, $-NHCH_2CH_2OH$, -NH(cyclopropyl), –NH(cyclobutyl), $–NHCH_2$(phenyl), -NH(4-fluorophenyl), –NH(4-chlorophenyl), $–NHNH_2$, –NH(1-methyl-1H-pyrazol-3-yl), -NH(tetrahyrdrofuran-3-yl) or $–NHCH_2CH_2$(6-morpholino).

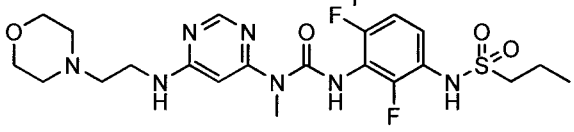
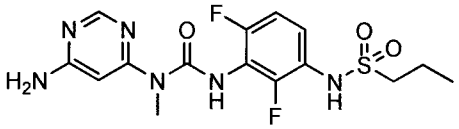
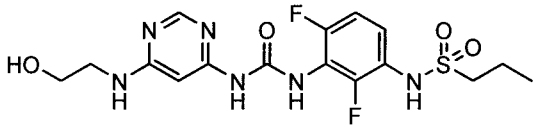
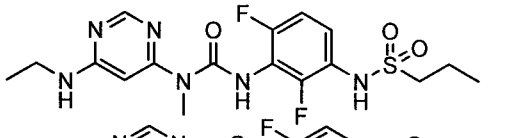
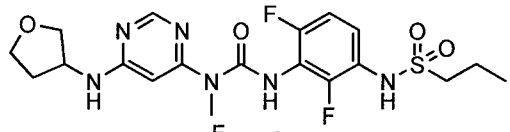
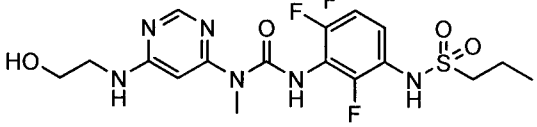
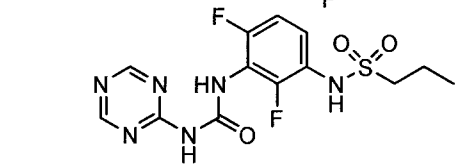
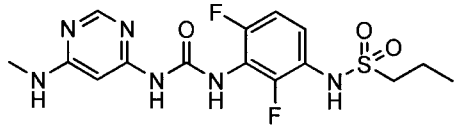
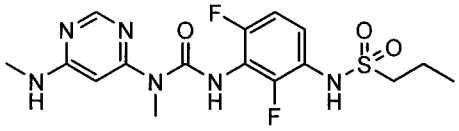
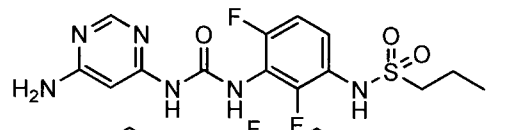
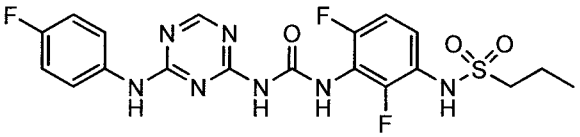
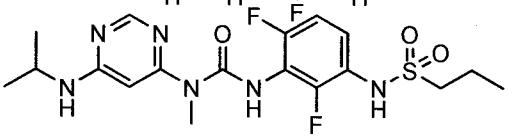
26. A compound of any one of Claims 1 or 3-25, wherein R^7 is hydrogen.

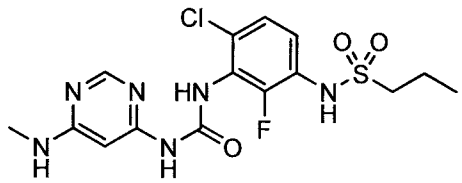
27. A compound of Formula **I** selected from:

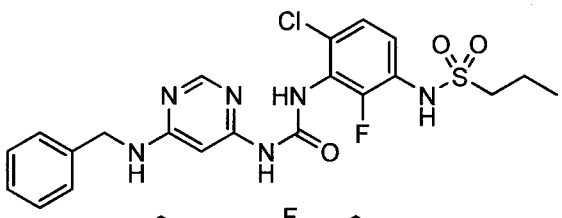



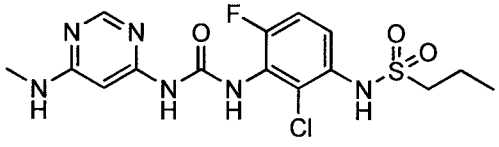


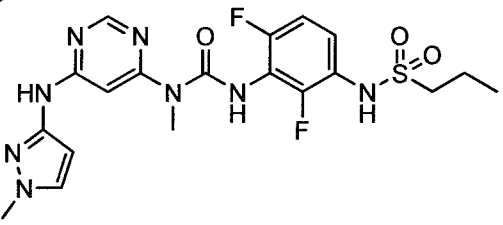


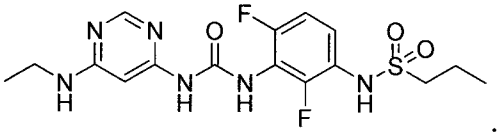























28. A pharmaceutical composition, comprising a compound of Claim 1, and a pharmaceutically acceptable carrier or excipient.

29. A method of preventing or treating a disease or disorder modulated by b-Raf, comprising administering to a mammal in need of such treatment an effective amount of a compound of Claim 1.

30. A method of preventing or treating cancer, comprising administering to a mammal in need of such treatment an effective amount of a compound of Claim 1, alone or in combination with one or more additional compounds having anti-cancer properties.

31. The method of Claim 30, wherein the cancer is a sarcoma.

32. The method of Claim 30, wherein the cancer is a carcinoma.

33. The method of Claim 32, wherein the carcinoma is squamous cell carcinoma.

34. The method of Claim 32, wherein the carcinoma is an adenoma or adenocarcinoma.

35. The method of Claim 30, wherein the cancer is breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

36. A compound as claimed in any one of Claims 1-27 for use in therapy.

37. A compound as claimed in any one of Claims 1-27 for use in the treatment of a

hyperproliferative disease.

38. Use of a compound of any one of Claims 1-27 in the manufacture of a medicament for the treatment of a hyperproliferative disease.

39. Use of a compound as claimed in any one of Claims 1-27, in the manufacture of a medicament, for use as a b-Raf inhibitor in the treatment of a patient undergoing cancer therapy.

40. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1-27 for use in the treatment of a hyperproliferative disease.

41. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1-27 for use in the treatment of cancer.