



US 20110189167A1

(19) **United States**

(12) **Patent Application Publication**  
**FLYNN et al.**

(10) **Pub. No.: US 2011/0189167 A1**  
(43) **Pub. Date:** **Aug. 4, 2011**

(54) **METHODS AND COMPOSITIONS FOR THE TREATMENT OF MYELOPROLIFERATIVE DISEASES AND OTHER PROLIFERATIVE DISEASES**

(76) Inventors: **Daniel L. FLYNN**, Lawrence, KS (US); **Peter A. PETILLO**, Lawrence, KS (US); **Michael D. KAUFMAN**, Lawrence, KS (US)

(21) Appl. No.: **12/850,256**

(22) Filed: **Aug. 4, 2010**

**Related U.S. Application Data**

(63) Continuation-in-part of application No. 12/105,408, filed on Apr. 18, 2008.

(60) Provisional application No. 60/913,216, filed on Apr. 20, 2007.

**Publication Classification**

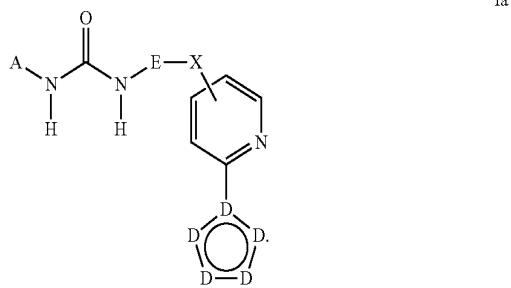
(51) **Int. Cl.**

*A61K 39/395* (2006.01)  
*A61K 31/454* (2006.01)  
*A61K 31/506* (2006.01)  
*A61K 31/519* (2006.01)  
*A61P 35/00* (2006.01)  
*A61P 19/00* (2006.01)  
*A61P 11/00* (2006.01)

(52) **U.S. Cl.** ..... **424/133.1**; 514/341; 514/252.18; 514/275; 514/252.19; 514/253.06; 514/249; 424/142.1

(57) **ABSTRACT**

Methods of modulating a kinase activity of a wild-type kinase species, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing, are provided which employ compounds of the formula Ia:



**METHODS AND COMPOSITIONS FOR THE TREATMENT OF MYELOPROLIFERATIVE DISEASES AND OTHER PROLIFERATIVE DISEASES**

**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of application Ser. No. 12/105,408 filed Apr. 18, 2008, which claims the benefit of Provisional Application 60/913,216 filed Apr. 20, 2007, the contents of both of which are incorporated by reference herein in their entirety.

**FIELD OF THE INVENTION**

[0002] The present invention relates to novel kinase inhibitors and modulator compounds useful for the treatment of various diseases. More particularly, the invention is concerned with such compounds, methods of treating diseases, and methods of synthesis of the compounds. Preferably, the compounds are useful for the modulation of kinase activity of c-ABL, c-KIT, VEGFR, PDGFR, FLT-3, c-MET, FGFR, the HER family, cFMS, RET, oncogenic forms thereof, disease causing polymorphs thereof, and aberrant fusion proteins thereof.

**BACKGROUND OF THE INVENTION**

[0003] Several members of the protein kinase family have been clearly implicated in the pathogenesis of various proliferative and myeloproliferative diseases and thus represent important targets for treatment of these diseases. Some of the proliferative diseases relevant to this invention include cancer, rheumatoid arthritis, atherosclerosis, and retinopathies. Important examples of kinases which have been shown to cause or contribute to the pathogenesis of these diseases include c-ABL kinase and the oncogenic fusion protein BCR-ABL kinase; c-KIT kinase, c-MET, the HER family of kinases, PDGF receptor kinases; VEGF receptor kinases; FLT-3 kinase, RET kinase, and c-FMS kinase.

[0004] c-ABL kinase is an important non-receptor tyrosine kinase involved in cell signal transduction. This ubiquitously expressed kinase—upon activation by upstream signaling factors including growth factors, oxidative stress, integrin stimulation, and ionizing radiation—localizes to the cell plasma membrane, the cell nucleus, and other cellular compartments including the actin cytoskeleton (Van Etten, *Trends Cell Biol.* (1999) 9: 179). There are two normal isoforms of ABL kinase: ABL-1A and ABL-1B. The N-terminal half of c-ABL kinase is important for autoinhibition of the kinase domain catalytic activity (Pluk et al, *Cell* (2002) 108: 247). Details of the mechanistic aspects of this autoinhibition have recently been disclosed (Nagar et al, *Cell* (2003) 112: 859). The N-terminal myristoyl amino acid residue of ABL-1B has been shown to intramolecularly occupy a hydrophobic pocket formed from alpha-helices in the C-lobe of the kinase domain. Such intramolecular binding induces a novel binding area for intramolecular docking of the SH2 domain and the SH3 domain onto the kinase domain, thereby distorting and inhibiting the catalytic activity of the kinase. Thus, an intricate intramolecular negative regulation of the kinase activity is brought about by these N-terminal regions of c-ABL kinase. An aberrant dysregulated form of c-ABL is formed from a chromosomal translocation event, referred to as the Philadelphia chromosome (P. C. Nowell et al, *Science* (1960)

132: 1497; J. D. Rowley, *Nature* (1973) 243: 290). This abnormal chromosomal translocation leads aberrant gene fusion between the ABL kinase gene and the breakpoint cluster region (BCR) gene, thus encoding an aberrant protein called BCR-ABL (G. Q. Daley et al, *Science* (1990) 247: 824; M. L. Gishizky et al, *Proc. Natl. Acad. Sci. USA* (1993) 90: 3755; S. Li et al, *J. Exp. Med.* (1999) 189: 1399). The BCR-ABL fusion protein does not include the regulatory myristylation site (B. Nagar et al, *Cell* (2003) 112: 859) and as a result functions as an oncoprotein which causes chronic myeloid leukemia (CML). CML is a malignancy of pluripotent hematopoietic stem cells. The p210 form of BCR-ABL is seen in 95% of patients with CML, and in 20% of patients with acute lymphocytic leukemia and is exemplified by sequences such as e14a2 and e13a2. The corresponding p190 form, exemplified by the sequence e1 a2 has also been identified. A p185 form has also been disclosed and has been linked to being causative of up to 10% of patients with acute lymphocytic leukemia. It will be appreciated by one skilled in the art that “p210 form”, “p190 form” and “p185 form” each describe a closely related group of fusion proteins, and that Sequence ID's used herein are merely representative of each form and are not meant to restrict the scope solely to those sequences.

[0005] c-KIT (KIT, CD117, stem cell factor receptor) is a 145 kDa transmembrane tyrosine kinase protein that acts as a type-III receptor (Pereira et al. *J Carcin.* (2005), 4: 19). The c-KIT proto-oncogene, located on chromosome 4q11-21, encodes the c-KIT receptor, whose ligand is the stem cell factor (SCF, steel factor, c-KIT ligand, mast cell growth factor, Morstyn G, et al. *Oncology* (1994) 51(2):205. Yarden Y, et al. *Embo J* (1987) 6(11):3341). The receptor has tyrosine-protein kinase activity and binding of the ligands leads to the autophosphorylation of c-KIT and its association with substrates such as phosphatidylinositol 3-kinase (Pi3K). Tyrosine phosphorylation by protein tyrosine kinases is of particular importance in cellular signaling and can mediate signals for major cellular processes, such as proliferation, differentiation, apoptosis, attachment, and migration. Defects in c-KIT are a cause of piebaldism, an autosomal dominant genetic developmental abnormality of pigmentation characterized by congenital patches of white skin and hair that lack melanocytes. Gain-of-function mutations of the c-KIT gene and the expression of phosphorylated c-KIT are found in most gastrointestinal stromal tumors and mastocytosis. Further, almost all gonadal seminomas/dysgerminomas exhibit c-KIT membranous staining, and several reports have clarified that some (10-25%) have a c-KIT gene mutation (Sakuma, Y. et al. *Cancer Sci* (2004) 95:9, 716). C-KIT defects have also been associated with testicular tumors including germ cell tumors (GCT) and testicular germ cell tumors (TGCT).

[0006] The role of c-KIT expression has been studied in hematologic and solid tumors, such as acute leukemias (Cortes J. et al. *Cancer* (2003) 97(11):2760) and gastrointestinal stromal tumors (GIST, Fletcher C. D. et al. *Hum Pathol* (2002) 33(5):459). The clinical importance of c-KIT expression in malignant tumors relies on studies with Gleevec® (imatinib mesylate, ST1571, Novartis Pharma AG Basel, Switzerland) that specifically inhibits tyrosine kinase receptors (Lefevre G. et al. *J Biol Chem* (2004) 279(30):31769). Moreover, a clinically relevant breakthrough has been the finding of anti-tumor effects of this compound in GIST, a group of tumors regarded as being generally resistant to conventional chemotherapy (de Silva C M, Reid R: *Pathol Oncol*

*Res* (2003) 9(1):13-19). GIST most often become Gleevec resistant and molecularly targeted small therapies that target c-KIT mutations remain elusive.

[0007] c-MET is a unique receptor tyrosine kinase (RTK) located on chromosome 7p and activated via its natural ligand hepatocyte growth factor. c-MET is found mutated in a variety of solid tumors (Ma P. C. et al. *Cancer Metastasis* (2003) 22:309). Mutations in the tyrosine kinase domain are associated with hereditary papillary renal cell carcinomas (Schmidt L et al. *Nat. Genet.* (1997) 16:68; Schmidt L, et al. *Oncogene* (1999) 18:2343), whereas mutations in the sema and juxtamembrane domains are often found in small cell lung cancers (SCLC; Ma P. C. et al. *Cancer Res* (2003) 63:6272). Many activating mutations are also found in breast cancers (Nakopoulou et al. *Histopath* (2000) 36(4): 313). The panoply of tumor types for which c-MET mediated growth has been implicated suggests this is a target ideally suited for modulation by specific c-MET small molecule inhibitors.

[0008] The TPR-MET oncogene is a transforming variant of the c-MET RTK and was initially identified after treatment of a human osteogenic sarcoma cell line transformed by the chemical carcinogen N-methyl-N-nitro-N-nitrosoguanidine (Park M. et al. *Cell* (1986) 45:895). The TPR-MET fusion oncoprotein is the result of a chromosomal translocation, placing the TPR3 locus on chromosome 1 upstream of a portion of the c-MET gene on chromosome 7 encoding only for the cytoplasmic region. Studies suggest that TPR-MET is detectable in experimental cancers (e.g. Yu J. et al. *Cancer* (2000) 88:1801). Dimerization of the M, 65,000 TPR-MET oncoprotein through a leucine zipper motif encoded by TPR leads to constitutive activation of the c-MET kinase (Zhen Z. et al. *Oncogene* (1994) 9:1691). TPR-MET activates wild-type c-MET RTK and can activate crucial cellular growth pathways, including the Ras pathway (Aklilu F. et al. *Am J Physiol* (1996) 271:E277) and the phosphatidylinositol 3-kinase (PI3K)/AKT pathway (Ponsetto C. et al. *Mol Cell Biol* (1993) 13:4600). Conversely, in contrast to c-MET RTK, TPR-MET is ligand independent, lacks the CBL binding site in the juxtamembrane region in c-MET, and is mainly cytoplasmic. c-MET immunohistochemical expression seems to be associated with abnormal  $\beta$ -catenin expression, and provides good prognostic and predictive factors in breast cancer patients.

[0009] The majority of small molecule kinase inhibitors that have been reported have been shown to bind in one of three ways. Most of the reported inhibitors interact with the ATP binding domain of the active site and exert their effects by competing with ATP for occupancy. Such inhibitors are referred to as Type I kinase inhibitors. Other inhibitors have been shown to bind to a separate hydrophobic region of the protein known as the "DFG-in-conformation" pocket, and still others have been shown to bind to both the ATP domain and the "DFG-in-conformation" pocket. The latter two types of kinase inhibitors are referred to as Type II kinase inhibitors. Some of the kinase inhibitors of the present invention are Type II inhibitors. Examples specific to inhibitors of Raf kinases can be found in Lowinger et al., *Current Pharmaceutical Design* (2002) 8: 2269-2278; Dumas, J. et al., *Current Opinion in Drug Discovery & Development* (2004) 7: 600-616; Dumas, J. et al., WO 2003068223 A1 (2003); Dumas, J., et al., WO 9932455 A1 (1999), and Wan, P. T. C., et al. *Cell* (2004) 116: 855-867.

[0010] Physiologically, kinases are regulated by a common activation/deactivation mechanism wherein a specific activa-

tion loop sequence of the kinase protein binds into a specific pocket on the same protein which is referred to as the switch control pocket (see WO 2004061084 and WO 2007008917 for further details). Such binding occurs when specific amino acid residues of the activation loop are modified for example by phosphorylation, oxidation, or nitrosylation. The binding of the activation loop into the switch pocket results in a conformational change of the protein into its active form (Huse, M. and Kuriyan, J. *Cell* (109) 275-282). Some of the inhibitors of the present invention induce kinases to adopt inactive conformations through inhibitor binding at least in part into the switch control pocket.

#### BRIEF SUMMARY OF THE INVENTION

[0011] Compounds of the present invention find utility in the treatment of hyperproliferative diseases, including autoimmune diseases and other diseases characterized by hypervasculization or proliferation of myeloid, mast cells, fibroblasts, synoviocytes, or monocytes; mammalian cancers and especially human cancers including but not limited to melanomas; a disease caused by c-ABL kinase, oncogenic forms thereof, aberrant fusion proteins thereof including BCR-ABL kinase and polymorphs thereof; a disease caused by FLT-3 kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof; a disease caused by cMET kinase, oncogenic forms thereof, aberrant fusion proteins thereof including TPR-MET; a disease caused by KDR kinase or PDGFR kinases; a disease caused by HER kinases, oncogenic forms thereof and polymorphs thereof; a disease caused by RET kinase, oncogenic forms thereof, aberrant fusion proteins thereof; a disease caused by c-FMS kinase, oncogenic forms thereof and polymorphs thereof; a disease caused by a c-KIT kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof; and diseases caused by any of the foregoing kinases, oncogenic forms thereof, and aberrant fusion proteins thereof, including but not limited to, chronic myelogenous leukemia, acute lymphocytic leukemia, acute myeloid leukemia, other myeloproliferative disorders, a disease caused by metastasis of primary solid tumors to secondary sites, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, mesothelioma, hypereosinophilic syndrome, a disease caused or maintained by pathological vascularization, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies, i.e. diabetic retinopathy and age-related macular degeneration, non small cell lung cancer, breast cancers, kidney cancers, colon cancers, cervical carcinomas, papillary thyroid carcinoma, melanomas, autoimmune diseases including rheumatoid arthritis, multiple sclerosis, lupus, asthma, human inflammation, rheumatoid spondylitis, ostero-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic obstructive pulmonary disease, bone resorptive diseases, bone cancer, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, gastrointestinal stromal tumors, mastocytosis, mast cell leukemia, and combinations thereof.

#### DETAILED DESCRIPTION OF THE INVENTION

[0012] The following descriptions refer to various compounds, stereo-, regiosomers and tautomers of such compounds and individual moieties of the compounds thereof.

**[0013]** Cycloalkyl refers to monocyclic saturated carbon rings taken from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, and cyclooctanyl;

Aryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring; preferred aryl rings are taken from phenyl, naphthyl, tetrahydronaphthyl, indenyl, and indanyl;

Heteroaryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms including nitrogen, oxygen, or sulfur of at least one carbocyclic or heterocyclic ring; heteroaryl rings are taken from, but not limited to, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, indolyl, indolinyl, isoindolyl, isoindolinyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolonyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazolonopyridinyl, thiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolonopyrimidinyl, thiazolopyrimidinyl, thiazolonopyrimidinyl, oxazolopyrimidinyl, oxazolonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, benzisothiazo line-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzodiazepinyl, benzoxapinyl, and benzoxazepinyl;

Heterocycl refers to monocyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms; heterocycl rings include, but are not limited to, oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalanyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl;

Poly-aryl refers to two or more monocyclic or fused aryl bicyclic ring systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring wherein the rings contained therein are optionally linked together;

Poly-heteroaryl refers to two or more monocyclic or fused bicyclic systems characterized by delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms including nitrogen, oxygen, or sulfur of at least one carbocyclic or heterocyclic ring wherein the rings contained therein are optionally linked together, wherein at least one of the monocyclic or fused bicyclic rings of the poly-heteroaryl system is taken from heteroaryl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocycl as defined broadly above;

Poly-heterocycl refers to two or more monocyclic or fused bicyclic ring systems containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized  $\pi$  electrons (aromaticity) shared among the ring carbon or heteroatoms wherein the rings contained

therein are optionally linked, wherein at least one of the monocyclic or fused bicyclic rings of the poly-heteroaryl system is taken from heterocycl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocycl as defined broadly above;

Alkyl refers to straight or branched chain C1-C6alkyls;

Halogen refers to fluorine, chlorine, bromine, and iodine;

Alkoxy refers to —O-(alkyl) wherein alkyl is defined as above;

Alkoxyalkyl refers to -(alkyl)-O-(alkyl) wherein alkyl is defined as above;

Alkoxycarbonyl refers to —C(O)O-(alkyl) wherein alkyl is defined as above;

Carboxyl C1-C6alkyl refers to —(C1-C6)alkyl wherein alkyl is defined as above;

Substituted in connection with a moiety refers to the fact that a further substituent may be attached to the moiety to any acceptable location on the moiety.

**[0014]** The term salts embraces pharmaceutically acceptable salts commonly used to form alkali metal salts of free acids and to form addition salts of free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, arylaliphatic, and heterocycl containing carboxylic acids and sulfonic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, 3-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable salts of free acid-containing compounds of the invention include metallic salts and organic salts. More preferred metallic salts include, but are not limited to appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIA) salts and other physiological acceptable metals. Such salts can be made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from primary amines, secondary amines, tertiary amines and quaternary ammonium salts, including in part, tromethamine, diethylamine, tetra-N-methylammonium, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine.

**[0015]** The term prodrug refers to derivatives of active compounds which revert in vivo into the active form. For example, a carboxylic acid form of an active drug may be esterified to create a prodrug, and the ester is subsequently converted in vivo to revert to the carboxylic acid form. See Ettmayer et. al, *J. Med. Chem.*, 2004, 47 (10): 2393-2404 and Lorenzi et. al, *J. Pharm. Exp. Therapeutics*, 2005, 883-900 for reviews.

**[0016]** Structural, chemical and stereochemical definitions are broadly taken from IUPAC recommendations, and more specifically from Glossary of Terms used in Physical Organic Chemistry (IUPAC Recommendations 1994) as summarized by P. Müller, *Pure Appl. Chem.*, 66, 1077-1184 (1994) and Basic Terminology of Stereochemistry (IUPAC Recommendations 1996) as summarized by G. P. Moss *Pure and Applied Chemistry*, 68, 2193-2222 (1996). Specific definitions are as

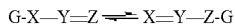
follows: Atropisomers are defined as a subclass of conformers which can be isolated as separate chemical species and which arise from restricted rotation about a single bond.

[0017] Regiosomers or structural isomers are defined as isomers involving the same atoms in different arrangements.

[0018] Enantiomers are defined as one of a pair of molecular entities which are mirror images of each other and non-superimposable.

[0019] Diastereomers or diastereoisomers are defined as stereoisomers other than enantiomers. Diastereomers or diastereoisomers are stereoisomers not related as mirror images. Diastereoisomers are characterized by differences in physical properties, and by some differences in chemical behavior towards achiral as well as chiral reagents.

[0020] Tautomerism is defined as isomerism of the general form

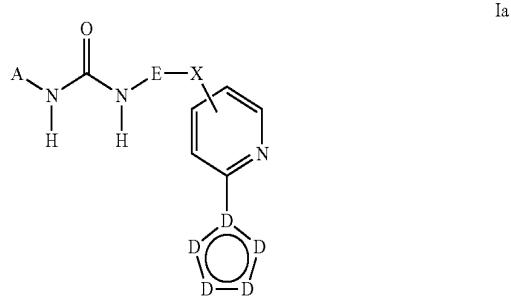


where the isomers (called tautomers) are readily interconvertible; the atoms connecting the groups X, Y, Z are typically any of C, H, O, or S, and G is a group which becomes an electrofuge or nucleofuge during isomerization. The commonest case, when the electrofuge is  $\text{H}^+$ , is also known as “protropy”.

[0021] Tautomers are defined as isomers that arise from tautomerism, independent of whether the isomers are isolable.

#### First Aspect of the Invention—Compounds, Methods, Preparations and Adducts

[0022] The invention includes compounds of the formula Ia:



and wherein the pyridine ring may be optionally substituted with one or more R20 moieties;

each D is individually taken from the group consisting of C, CH, C—R20, N—Z3, and N, such that the resultant ring is a pyrazole;

wherein E is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl;

E may be optionally substituted with one or two R16 moieties;

wherein A is a ring system selected from the group consisting of phenyl, naphthyl, cyclopentyl, cyclohexyl, G1, G2, and G3;

G1 is a heteroaryl taken from the group consisting of pyrrolyl, furyl, thiényl, oxazolyl, thiazolyl, isoxazol-4-yl, isoxazol-5-yl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl, pyridinyl, and pyrimidinyl;

G2 is a fused bicyclic heteroaryl taken from the group consisting of indolyl, indolinyl, isoindolyl, isoindolinyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl,

benzisoxazolyl, benzothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazolonopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazolonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolonopyrimidinyl, thiazolopyrimidinyl, thiazolonopyrimidinyl, oxazolopyrimidinyl, oxazolonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, benzothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxazepinyl, and benzoxazepinyl;

G3 is a heterocyclyl taken from the group consisting of oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, imidazolonyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalanyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl;

the A ring may be optionally substituted with one or two R2 moieties;

X is selected from the group consisting of  $—\text{O}—$ ,  $—\text{S}(\text{CH}_2)_n—$ ,  $—\text{N}(\text{R}3)(\text{CH}_2)_n—$ ,  $—(\text{CH}_2)_p—$ , and wherein the carbon atoms of  $—(\text{CH}_2)_n—$ ,  $—(\text{CH}_2)_p—$ , of X may be further substituted by oxo or one or more C1-C6alkyl moieties;

when A, G1, G2 or G3 has one or more substitutable sp2-hybridized carbon atoms, each respective sp2 hybridized carbon atom may be optionally substituted with a Z1 substituent;

when A, G1, G2 or G3 has one or more substitutable sp3-hybridized carbon atoms, each respective sp3 hybridized carbon atom may be optionally substituted with a Z2 substituent;

when A, G1, G2 or G3 has one or more substitutable nitrogen atoms, each respective nitrogen atom may be optionally substituted with a Z4 substituent;

each Z1 is independently and individually selected from the group consisting of C1-6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, halogen, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, cyano, C1-C6alkoxy, fluoroC1-C6alkoxy wherein the alkyl moiety can be partially or fully fluorinated,  $—(\text{CH}_2)_n\text{OH}$ , oxo, C1-C6alkoxyC1-C6alkyl,  $(\text{R}4)_2\text{N}(\text{CH}_2)_n—$ ,  $(\text{R}3)_2\text{N}(\text{CH}_2)_n—$ ,  $(\text{R}4)_2\text{N}(\text{CH}_2)_q\text{N}(\text{R}4)(\text{CH}_2)_n—$ ,  $(\text{R}4)_2\text{N}(\text{CH}_2)_q\text{O}(\text{CH}_2)_n—$ ,  $(\text{R}3)_2\text{NC(O)}—$ ,  $(\text{R}4)_2\text{NC(O)}—$ ,  $(\text{R}4)_2\text{NC(O)C}1\text{—C}6\text{alkyl}—$ ,  $—(\text{R}4)\text{NC(O)R}8$ , C1-C6alkoxycarbonyl-, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl,  $(\text{R}3)_2\text{NSO}_2—$ ,  $—\text{SOR}3$ ,  $(\text{R}4)_2\text{NSO}_2—$ ,  $—\text{N}(\text{R}4)\text{SO}_2\text{R}8$ ,  $—\text{O}(\text{CH}_2)_q\text{OC}1\text{—C}6\text{alkyl}$ ,  $—\text{SO}_2\text{R}3$ ,  $—\text{SOR}4$ ,  $—\text{C(O)R}8$ ,  $—\text{C(O)R}6$ ,  $—\text{C(=NOH)R}6$ ,  $—\text{C(=NOR}3\text{)R}6$ ,  $—(\text{CH}_2)_n\text{N}(\text{R}4)\text{C(O)R}8$ ,  $—\text{N}(\text{R}3)(\text{CH}_2)_q\text{O-alkyl}$ ,  $—\text{N}(\text{R}3)(\text{CH}_2)_q\text{N}(\text{R}4)_2$ , nitro,  $—\text{CH}(\text{OH})\text{CH}(\text{OH})\text{R}4$ ,  $—\text{C(=NH)N}(\text{R}4)_2$ ,  $—\text{C(=NOR}3\text{)N}(\text{R}4)_2$ , and  $—\text{NHC(=NH)R}8$ , R17 substituted G3, R17 substituted pyrazolyl and R17 substituted imidazolyl;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0023] each Z2 is independently and individually selected from the group consisting of aryl, C1-C6alkyl, C3-C8cycloalkyl, branched C3-C7alkyl, hydroxyl, hydroxyC1-C6alkyl-, cyano,  $(\text{R}3)_2\text{N}—$ ,  $(\text{R}4)_2\text{N}—$ ,  $(\text{R}4)_2\text{NC1—C}6\text{alkyl}—$ ,  $(\text{R}4)_2\text{NC2—C}_6\text{alkylN}(\text{R}4)(\text{CH}_2)_n—$ ,  $(\text{R}4)_2\text{NC2—C}6\text{alkylO}(\text{CH}_2)_n—$ ,  $(\text{R}3)_2\text{NC(O)}—$ ,  $(\text{R}4)_2\text{NC(O)}—$ ,

(R4)<sub>2</sub>NC(O)—C1-C6alkyl-, carboxyl, -carboxyC1-C6alkyl, C1-C6alkoxycarbonyl-, C1-C6alkoxycarbonylC1-C6alkyl-, (R3)<sub>2</sub>NSO<sub>2</sub>—, (R4)<sub>2</sub>NSO<sub>2</sub>—, —SO<sub>2</sub>R8, —(CH<sub>2</sub>)<sub>n</sub>N(R4)C(O)R8, —C(O)R8, ==O, ==NOH, and ==N(OR6);

in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, hydroxyC2-C6alkyl-, C1-C6alkoxycarbonyl-, —C(O)R8, R8C(O)(CH<sub>2</sub>)<sub>n</sub>—, (R4)<sub>2</sub>NC(O)—, (R4)<sub>2</sub>NC(O)C1-C6alkyl-, R8C(O)N(R4)(CH<sub>2</sub>)<sub>q</sub>—, (R3)<sub>2</sub>NSO<sub>2</sub>—, (R4)<sub>2</sub>NSO<sub>2</sub>—, —(CH<sub>2</sub>)<sub>q</sub>N(R3)<sub>2</sub>, and —(CH<sub>2</sub>)<sub>q</sub>N(R4)<sub>2</sub>;

each Z4 is independently and individually selected from the group consisting of C1-C6alkyl, branched C<sub>3-7</sub>alkyl, hydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, (R4)<sub>2</sub>N—C2-C6alkyl-, (R4)<sub>2</sub>N—C2-C6alkylIN(R4)—C2-C6alkyl-, (R4)<sub>2</sub>N—C2-C6alkyl—O—C2-C6alkyl-(R4)<sub>2</sub>NC(O)C1-C6alkyl-, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, —C2-C6alkylIN(R4)C(O)R8, R8-C(=NR3)-, —SO<sub>2</sub>R8, and —COR8;

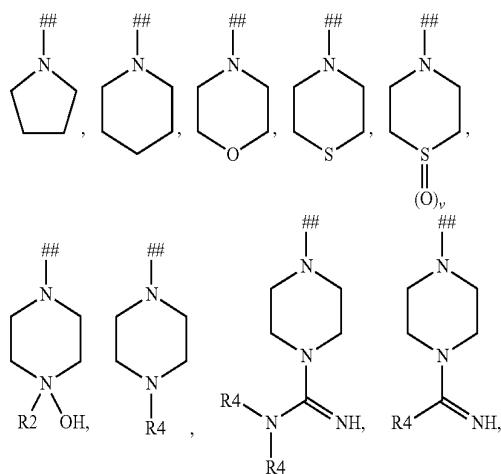
in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each R2 is selected from the group consisting of H, C1-C6alkyl, branched C3-C8alkyl, R19 substituted C3-C8cycloalkyl-, fluoroC1-C6alkyl- wherein the alkyl is fully or partially fluorinated, halogen, cyano, C1-C6alkoxy-, and fluoroC1-C6alkoxy- wherein the alkyl group is fully or partially fluorinated, hydroxyl substituted C1-C6alkyl-, hydroxyl substituted branched C3-C8alkyl-, cyano substituted C1-C6alkyl-, cyano substituted branched C3-C8 alkyl-, (R3)<sub>2</sub>NC(O)C1-C6 alkyl-, (R3)<sub>2</sub>NC(O)C3-C8 branched alkyl-;

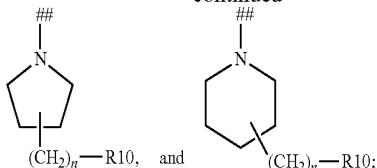
wherein each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, and C3-C8cycloalkyl;

each R4 is independently and individually selected from the group consisting of H, C1-C6 alkyl, hydroxyC1-C6alkyl-, dihydroxyC1-C6alkyl-, C1-C6 alkoxyC1-C6 alkyl, branched C3-C7 alkyl, branched hydroxyC1-C6 alkyl, branched C1-C6 alkoxyC1-C6alkyl-, branched dihydroxyC1-C6alkyl-, —(CH<sub>2</sub>)<sub>n</sub>N(R7)<sub>2</sub>, —(CH<sub>2</sub>)<sub>p</sub>C(O)N(R7)<sub>2</sub>, —(CH<sub>2</sub>)<sub>n</sub>C(O)OR3, R19 substituted C3-C8 cyclo alkyl-;

each R5 is independently and individually selected from the group consisting of



-continued



and wherein the symbol (##) is the point of attachment to Z3; each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8cycloalkyl-;

each R7 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl-, dihydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, branched C3-C7alkyl, branched hydroxyC2-C6alkyl-, branched C1-C6alkoxyC2-C6alkyl-, branched dihydroxyC2-C6alkyl-, —(CH<sub>2</sub>)<sub>n</sub>C(O)OR3, R19 substituted C3-C8 cyclo alkyl- and —(CH<sub>2</sub>)<sub>n</sub>R17;

each R8 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, fluoroC1-C6alkyl- wherein the alkyl moiety is partially or fully fluorinated, R19 substituted C3-C8cycloalkyl-, —OH, C1-C6alkoxy, —N(R3)<sub>2</sub>, and —N(R4)<sub>2</sub>;

each R10 is independently and individually selected from the group consisting of —CO<sub>2</sub>H, —CO<sub>2</sub>C1-C6alkyl, —C(O)N(R4)<sub>2</sub>, OH, C1-C6alkoxy, and —N(R4)<sub>2</sub>;

each R16 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or fully fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)<sub>2</sub>, —N(R4)<sub>2</sub>, R3 substituted C2-C3alkynyl- and nitro;

each R17 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or fully fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)<sub>2</sub>, —N(R4)<sub>2</sub>, and nitro;

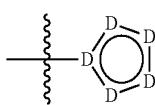
each R19 is independently and individually selected from the group consisting of H, OH and C1-C6alkyl;

each R20 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or fully fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)<sub>2</sub>, —N(R4)<sub>2</sub>, —N(R3)C(O)R3, —C(O)N(R3)<sub>2</sub> and nitro and

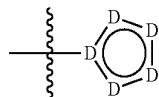
wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxylalkyl-, and alkoxyalkyl and attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocycl ring;

and k is 0 or 1; n is 0-6; p is 1-4; q is 2-6; r is 0 or 1; t is 1-3; v is 1 or 2; m is 0-2; and stereo-, regiosomers and tautomers of such compounds.

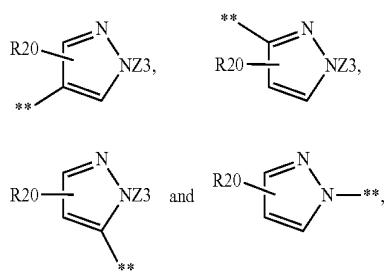
1.1 Compounds of Formula Ia which Exemplify Preferred D Moieties



[0024] In a preferred embodiment of compounds of formula Ia, said compounds have preferred



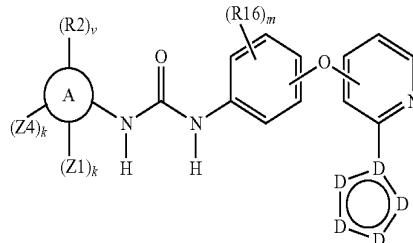
moieties of the formula:



wherein the symbol (\*\*) indicates the point of attachment to the pyridine ring.

#### 1.1.1 Compounds of Formula Ia which Exemplify Preferred A Moieties

[0025] In a preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ib

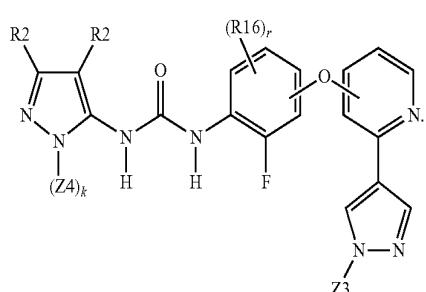


Ib

wherein A is any possible isomer of pyrazole.

#### 1.1.2 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

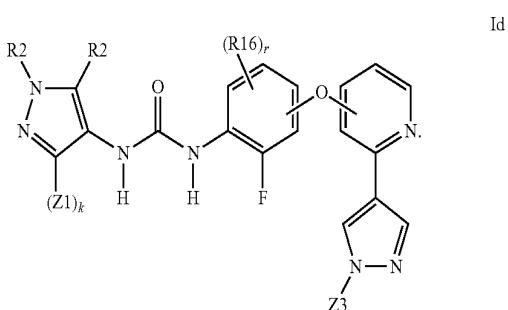
[0026] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Ic



Ic

#### 1.1.3 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

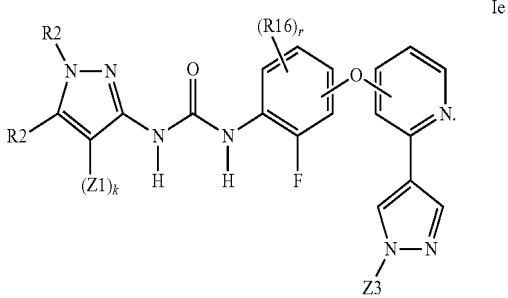
[0027] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Id



Id

#### 1.1.4 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

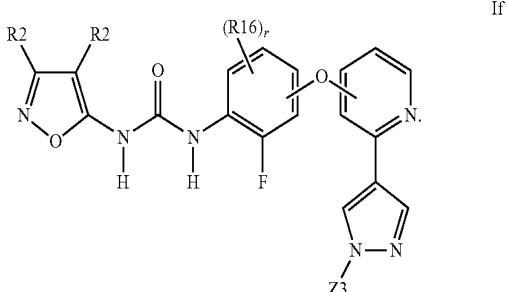
[0028] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Ie



Ie

#### 1.1.5 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

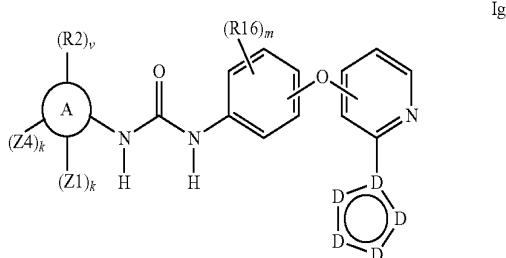
[0029] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula If



If

**1.1.6 Compounds of Formula Ia which Exemplify Preferred A Moieties**

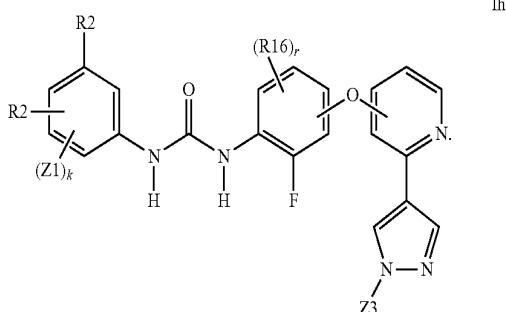
[0030] In a preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ig



wherein A is selected from the group consisting of any isomer of phenyl and pyridine.

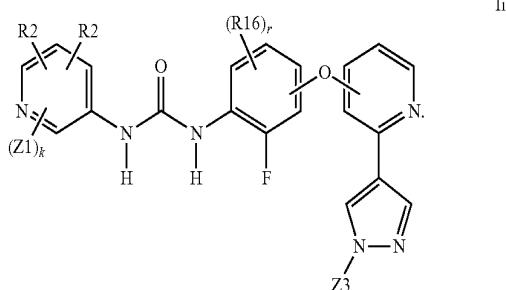
**1.1.7 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties**

[0031] In a more preferred embodiment of compounds of formula Ig, said compounds have structures of formula Ih



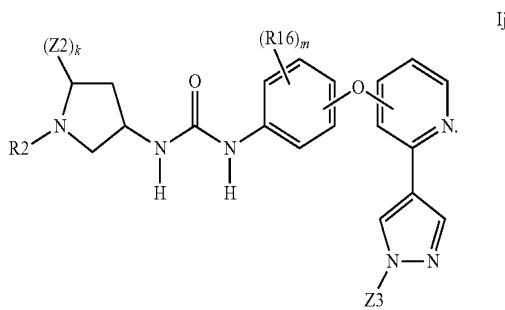
**1.1.8 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties**

[0032] In a more preferred embodiment of compounds of formula Ig, said compounds have structures of formula Ii



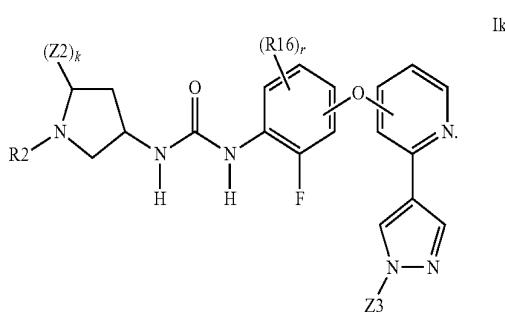
**1.1.9 Compounds of Formula Ia which Exemplify Preferred A Moieties**

[0033] In a preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ij



**1.1.10 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties**

[0034] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ik



**1.1.11 Most Preferred Compounds of Formula Ia**

[0035] 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea, 1-(4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea, 1-(5-tert-butylisoxazol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)pyridin-4-yloxy)phenyl)urea, 1-(5-tert-butylisoxazol-3-yl)-3-(4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-(trifluoromethyl)pyridin-3-yl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylisoxazol-3-yl)urea, 1-(2,3-difluorophenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)



4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-methyl-5-(trifluoromethyl)pyridin-3-yl)urea, 1-(2-tert-butyl-4-(piperazin-1-yl)pyrimidin-5-yl)-3-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-tert-butyl-4-morpholinopyrimidin-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(1-methyl-1H-pyrazol-4-yl)-5-(trifluoromethyl)pyridin-3-yl)urea, and 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea.

## 1.2 Methods

### 1.2a Methods of Protein Modulation

[0036] The invention includes methods of modulating kinase activity of a variety of kinases, e.g. c-ABL kinase, BCR-ABL kinase, FLT-3, VEGFR-2 kinase mutants, c-MET, c-KIT, PDGFR kinases, the HER family of kinases, RET kinase, and c-FMS kinase. The kinases may be wildtype kinases, oncogenic forms thereof, aberrant fusion proteins thereof or polymorphs of any of the foregoing. The method comprises the step of contacting the kinase species with compounds of the invention and especially those set forth in sections section 1. The kinase species may be activated or unactivated, and the species may be modulated by phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, inhibition of phosphorylation, oxidation or nitrosylation of said kinase by another enzyme, enhancement of dephosphorylation, reduction or denitrosylation of said kinase by another enzyme, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

### 1.2b Treatment Methods

[0037] The methods of the invention also include treating individuals suffering from a condition selected from the group consisting of cancer and hyperproliferative diseases. These methods comprise administering to such individuals compounds of the invention, and especially those of section 1, said diseases including, but not limited to, a disease caused by c-ABL kinase, oncogenic forms thereof, aberrant fusion proteins thereof including BCR-ABL kinase and polymorphs thereof; a disease caused by FLT-3 kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof; a disease caused by cMET kinase, oncogenic forms thereof, aberrant fusion proteins thereof including TPR-MET; a disease caused by KDR kinase or PDGFR kinases; a disease caused by HER kinases, oncogenic forms thereof and polymorphs thereof; a disease caused by RET kinase, oncogenic forms thereof, aberrant fusion proteins thereof; a disease caused by c-FMS kinase, oncogenic forms thereof and polymorphs thereof; a disease caused by a c-KIT kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof; and diseases caused by any of the foregoing kinases, oncogenic forms thereof, and aberrant fusion proteins thereof, including but not limited to, chronic myelogenous leukemia, acute lymphocytic leukemia, acute myeloid leukemia, other myeloproliferative disorders, a disease caused by metastasis of primary solid tumors to second-

ary sites, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, mesothelioma, hypereosinophilic syndrome, a disease caused or maintained by pathological vascularization, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies, i.e. diabetic retinopathy and age-related macular degeneration, non small cell lung cancer, breast cancers, kidney cancers, colon cancers, cervical carcinomas, papillary thyroid carcinoma, melanomas, autoimmune diseases including rheumatoid arthritis, multiple sclerosis, lupus, asthma, human inflammation, rheumatoid spondylitis, osteoarthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic obstructive pulmonary disease, bone resorptive diseases, bone cancer, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, gastrointestinal stromal tumors, mastocytosis, mast cell leukemia, and combinations thereof. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

### [0038] Dosage

[0039] The methods of the present invention may be used to prevent, treat, or reduce the severity of cancer or hyperproliferative diseases. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, body surface area, general health, sex, ethnicity and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0040] Administration of a compound of the invention or pharmaceutically active agent described herein can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes. In some instances, administration will result in the release of the inhibitor or pharmaceutically active agent described herein into the bloodstream.

[0041] In one embodiment, the inhibitor or pharmaceutically active agent described herein is administered orally.

[0042] Depending on the intended mode of administration, the compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syr-

ups, powders, liquids, suspensions, or the like, preferably in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those skilled in the pharmaceutical arts.

[0043] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0044] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using dissolution or suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, aqueous dextrose, glycerol, ethanol, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0045] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0046] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous injection or intramuscular injection, or to slow the rate of systemic absorption upon oral administration. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Modified or sustained release formulations, well known in the art, may also be utilized in formulations to control the rate of absorption of an orally administered compound. Alternatively, modified or sustained absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also pre-

pared by entrapping the compound in liposomes or micro-emulsions that are compatible with body tissues.

[0047] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders or diluents such as starches, lactose, sucrose, glucose, mannitol, cellulose, saccharin, glycine, and silicic acid, b) binders such as, for example, magnesium aluminum silicate, starch paste, tragacanth, carboxymethylcellulose, methyl cellulose, alginates, gelatin, polyvinylpyrrolidinone, magnesium carbonate, natural sugars, corn sweeteners, sucrose, waxes and natural or synthetic gums such as acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators or disintegrants such as quaternary ammonium compounds, starches, agar, methyl cellulose, bentonite, xanthan gum, algic acid, and effervescent mixtures, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, silica, stearic acid, calcium stearate, magnesium stearate, sodium oleate, sodium acetate, sodium chloride, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0048] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a modified or sustained manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0049] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tabletting lubricants and other tabletting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a modified or

sustained manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0050] The compound of the invention or pharmaceutically active agent described herein can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in U.S. Pat. No. 5,262,564.

[0051] The compound of the invention or pharmaceutically active agent described herein can also be delivered by the use of monoclonal antibodies as individual carriers to which the compound or pharmaceutically active agent described herein are coupled or conjugated. The compound or pharmaceutically active agent described herein can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compound or pharmaceutically active agent described herein can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

[0052] Furthermore, a compound or pharmaceutically active agent described herein may be coupled, absorbed, adsorbed, or conjugated to a medical device including but not limited to stents.

[0053] Parenteral injectable administration can be used for subcutaneous, intramuscular, intra-articular, or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

[0054] One embodiment, for parenteral administration employs the implantation of a slow-release or sustained-released system, according to U.S. Pat. No. 3,710,795, incorporated herein by reference.

[0055] The compositions can be sterilized or contain non-toxic amounts of adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, pH buffering agents, and other substances, including, but not limited to, sodium acetate or triethanolamine oleate. In addition, they can also contain other therapeutically valuable substances.

[0056] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The compound or pharmaceutically active agent described herein is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Furthermore, the compound or pharmaceutically active agent described herein can be administered in intranasal form via topical use of suitable intranasal vehicles. Additionally, the present invention contemplates the use of transdermal patches or via other transdermal routes, using those forms of transdermal skin patches and formulations well known to those of ordinary skill in that art. Transdermal patches have the added advantage of providing controlled delivery of a

compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0057] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, preferably from about 1% to about 70% of the compound or pharmaceutically active agent described herein by weight or volume.

[0058] The dosage regimen utilizing the compound of the invention or pharmaceutically active agent described herein can be selected in accordance with a variety of factors including type, species, age, weight, body surface area, sex, ethnicity, and medical condition of the subject; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the subject; and the particular compound or pharmaceutically active agent described herein employed. A person skilled in the art can readily determine and prescribe the effective amount of the drug useful for treating or preventing a proliferative disorder.

[0059] Effective dosage amounts of the compound of the invention or pharmaceutically active agent described herein, when administered to a subject, range from about 0.05 to about 3,500 mg of compound or pharmaceutically active agent described herein per day. Unit dosage compositions for in vivo or in vitro use can contain about 0.01, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100.0, 250.0, 500.0 or 1000.0 mg of the compound described herein. In one embodiment, the unit dosage compositions are in the form of a tablet that can be scored. Effective plasma levels of the compound or pharmaceutically active agent described herein can be achieved from dosages from about 0.002 mg to about 50 mg per kg of body weight per day. The amount of a compound of the invention or pharmaceutically active agent described herein that is effective in the treatment or prevention of cancer or hyperproliferative disease can be determined by clinical techniques that are known to those of skill in the art. In addition, in vitro and in vivo assays can optionally be employed to help identify optimal dosage ranges. The precise dose to be employed can also depend on the route of administration, and the seriousness of the proliferative disorder being treated and can be decided according to the judgment of the practitioner and each subject's circumstances in view of, e.g., published clinical studies. Suitable effective dosage amounts, however, can range from about 10 micrograms to about 5 grams about every 4 h, although they are typically about 500 mg or less per every 4 hours. In one embodiment the effective dosage is about 0.01 mg, 0.5 mg, about 1 mg, about 50 mg, about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1 g, about 1.2 g, about 1.4 g, about 1.6 g, about 1.8 g, about 2.0 g, about 2.2 g, about 2.4 g, about 2.6 g, about 2.8 g, about 3.0 g, about 3.2 g, about 3.4 g, about 3.6 g, about 3.8 g, about 4.0 g, about 4.2 g, about 4.4 g, about 4.6 g, about 4.8 g, or about 5.0 g, every 4 hours. Equivalent dosages can be administered over various time periods including, but not limited to, about every 2 hours, about every 6 hours, about every 8 hours, about every 12 hours, about every 24 hours, about every 36 hours, about every 48 hours, about every 72 hours, about every week, about every two weeks, about every three weeks, about every month, and about every two months. The effective dosage amounts described herein refer to total amounts administered; that is, if more than one compound of the invention or pharmaceutically active agent described

herein is administered, the effective dosage amounts correspond to the total amount administered.

[0060] The dosage regimen utilizing the compound of the invention or pharmaceutically active agent described herein can be selected in accordance with a variety of factors including type, species, age, weight, body surface area, sex, ethnicity, and medical condition of the subject; the severity of the cancer or hyperproliferative disorder to be treated; the route of administration; the renal or hepatic function of the subject; and the particular inhibitor or pharmaceutically active agent described herein employed. A person skilled in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the proliferative disorder.

[0061] The compound of the invention or pharmaceutically active agent described herein can be administered in a single daily dose, or the total daily dosage can be administered in divided doses of two, three or four times daily. When administered in the form of a transdermal delivery system, the dosage administration can be continuous rather than intermittent throughout the dosage regimen. Dosage strengths of topical preparations including creams, ointments, lotions, aerosol sprays and gels, contain the compound or pharmaceutically active agent described herein ranging from about 0.1% to about 15%, w/w or w/v.

#### [0062] Combination

[0063] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[0064] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be administered simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0065] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0066] In certain embodiments, a combination of one additional agent and a compound of the invention are described. In some embodiments, two or more additional agents may be administered with a compound of the invention. In other embodiments, a combination of three or more additional agents may be administered with a compound of the invention. In some embodiments, the additional agent is selected from taxanes such as taxol, taxotere or their analogues; alkylating agents such as cyclophosphamide, ifosfamide, melphalan, hexamethylmelamine, thiopeta or dacarbazine; antimetabolites such as pyrimidine analogues, for instance 5-fluorouracil, cytarabine, capecitabine, azacitidine, and gemcitabine or its analogues such as 2-fluorodeoxycytidine;

folic acid analogues such as methotrexate, idarubicin or trimetrexate; spindle poisons including vinca alkaloids such as vinblastine, vincristine, vinorelbine and vindesine, or their synthetic analogues such as navelbine, or estramustine and a taxoid; platinum compounds such as cisplatin; epipodophyllotoxins such as etoposide or teniposide; steroids such as prednisone; antibiotics such as daunorubicin, doxorubicin, bleomycin or mitomycin, enzymes such as L-asparaginase, topoisomerase inhibitors such as topotecan or pyridobenzimidazole derivatives; and various agents such as procarbazine, mitoxantrone; biological response modifiers or growth factor inhibitors such as interferons or interleukins; inhibitors of growth factors, for example Bevacizumab and Ranibizumab; kinase inhibitors including Cetuximab, Imatinib, Trastuzumab, Gefitinib, Pegaptanib, Sorafenib, Dasatinib, Bosutinib, AP-24534 also defined as 3-(2-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide, Sunitinib, Erlotinib, Nilotinib, Lapatinib, Panitumumab, Pazopanib, Crizotinib, the JAK inhibitor CP-690,550, and the SYK inhibitor Fostamatinib. In other embodiments, the other agent in addition to a compound of the invention is Imatinib.

[0067] Other examples of agents the compounds of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for HIV such as ritonavir; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinirole, pramipexole, bromocriptine, pergolide, trihexyphenidyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, methotrexate, azathioprine, cyclophosphamide, and sulfasalazine; TNF blockers including Humira®, Enbrel®, and Remicade®; IL-1 RA including Kineret® and Rilonacept; anti-CD20 agents including Rituxin®; immunomodulatory and immunosuppressive agents such as abatacept, cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; bone resorptive inhibitory agents including denosumab and bisphosphonates including zoledronic acid; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents that prolong or improve pharmacokinetics such as cytochrome P450 inhibitors (i.e., inhibitors of metabolic breakdown) and CYP3A4 inhibitors (e.g., ketokonazole and ritonavir), and agents for treating immunodeficiency disorders such as gamma globulin.

[0068] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[0069] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two

active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0070] The amount of both, an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of an inventive can be administered.

[0071] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01-100 mg/kg body weight/day of the additional therapeutic agent can be administered.

[0072] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0073] In some embodiments, the compositions comprise an amount of an anticancer inhibitor described herein, e.g., a kinase inhibitor, and another anticancer agent which together are effective to treat or prevent cancer. In another embodiment, the amount of the anticancer inhibitor described herein and another anticancer agent is at least about 0.01% of the combined combination chemotherapy agents by weight of the composition. When intended for oral administration, this amount can be varied from about 0.1% to about 80% by weight of the composition. Some oral compositions can comprise from about 4% to about 50% of the anticancer inhibitor described herein and another anticancer agent. Other compositions of the present invention are prepared so that a parenteral dosage unit contains from about 0.01% to about 2% by weight of the composition.

[0074] The present methods for treating or preventing cancer or a hyperproliferative disease in a subject in need thereof can further comprise administering another prophylactic or therapeutic agent to the subject being administered an anticancer inhibitor or an anti-proliferative inhibitor described herein. In one embodiment the other prophylactic or therapeutic agent is administered in an effective amount. The other prophylactic or therapeutic agent includes, but is not limited to, an anti-inflammatory agent, an anti-renal failure agent, an anti-diabetic agent, an anti-cardiovascular disease agent, an antiemetic agent, a hematopoietic colony stimulating factor, an anxiolytic agent, and an opioid or non-opioid analgesic agent.

[0075] In a further embodiment, the anticancer inhibitor described herein can be administered prior to, concurrently with, or after an antiemetic agent, or on the same day, or within 1 hour, 2 hours, 12 hours, 24 hours, 48 hours or 72 hours of each other.

[0076] In another embodiment, the anticancer inhibitor described herein can be administered prior to, concurrently with, or after a hematopoietic colony stimulating factor, or on

the same day, or within 1 hour, 2 hours, 12 hours, 24 hours, 48 hours, 72 hours, 1 week, 2 weeks, 3 weeks or 4 weeks of each other.

[0077] In still another embodiment, the anticancer inhibitor described herein can be administered prior to, concurrently with, or after an opioid or non-opioid analgesic agent, or on the same day, or within 1 hour, 2 hours, 12 hours, 24 hours, 48 hours or 72 hours of each other.

[0078] In yet another embodiment, the anticancer inhibitor described herein can be administered prior to, concurrently with, or after an anxiolytic agent, or on the same day, or within 1 hour, 2 hours, 12 hours, 24 hours, 48 hours or 72 hours of each other.

[0079] Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective amount range. In one embodiment of the invention, where, another therapeutic agent is administered to a subject, the effective amount of the anticancer compound or anti-proliferative compound described herein is less than its effective amount would be where the other therapeutic agent is not administered. In this case, without being bound by theory, it is believed that the anticancer compound or anti-proliferative compound described herein and the other therapeutic agent act synergistically to treat or prevent cancer or hyperproliferative disease.

[0080] Antiemetic agents useful in the methods of the present invention include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylleucine monoethanolamine, alizapride, azasetron, benzquiamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxypendyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinol, thiethylperazine, thioproperazine, and tropisetron.

[0081] Hematopoietic colony stimulating factors useful in the methods of the present invention include, but are not limited to, filgrastim, sargramostim, molgramostim and epoietin alfa.

[0082] Opioid analgesic agents useful in the methods of the present invention include, but are not limited to, morphine, heroin, hydromorphone, hydrocodone, oxymorphone, oxycodone, metopon, apomorphine, normorphine, etorphine, buprenorphine, meperidine, loperamide, anileridine, ethoheptazine, piminidine, betaprodine, diphenoxylate, fentanyl, sufentanil, alfentanil, remifentanil, levorphanol, dextromethorphan, phenazocine, pentazocine, cyclazocine, methadone, isomethadone and propoxyphene.

[0083] Non-opioid analgesic agents useful in the methods of the present invention include, but are not limited to, acetaminophen, acetaminophen plus codeine, aspirin, celecoxib, rofecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, indomethacin, ketorolac, meclofenamate, mefanamic acid, nabumetone, naproxen, piroxicam and sulindac.

[0084] Anxiolytic agents useful in the methods of the present invention include, but are not limited to, buspirone, and benzodiazepines such as diazepam, lorazepam, oxazepam, chlorazepate, clonazepam, chlordiazepoxide and alprazolam.

### 1.3 Pharmaceutical Preparations

[0085] The compounds of the invention, especially those of section 1 may form a part of a pharmaceutical composition by combining one or more such compounds with a pharmaceu-

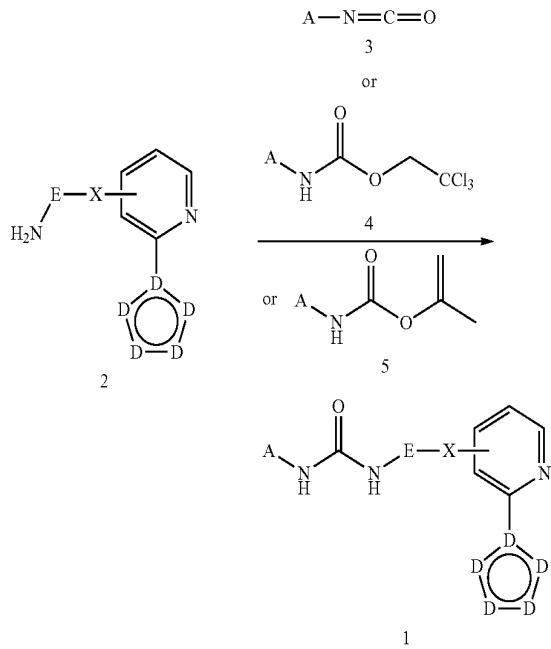
tically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

#### Section 2. Synthesis of Compounds of the Present Invention

**[0086]** The compounds of the invention are available by the procedures and teachings of WO 2006/071940, incorporated by reference, and by the general synthetic methods illustrated in the Schemes below and the accompanying examples.

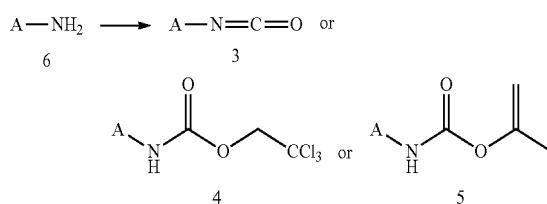
**[0087]** As indicated in Scheme 1, ureas of general formula 1 can be readily prepared by the union of amines of general formula 2 with isocyanates 3 or isocyanate surrogates, for example trichloroethyl carbamates (4) or isopropenyl carbamates (5). Preferred conditions for the preparation of compounds of general formula 1 involve heating a solution of 4 or 5 with 2 in the presence of a tertiary base such as diisopropylethylamine, triethylamine or N-methylpyrrolidine in a solvent such as dimethylformamide, dimethylsulfoxide, tetrahydrofuran or 1,4-dioxane at a temperature between 50 and 100° C. for a period of time ranging from 1 hour to 2 days.

Scheme 1



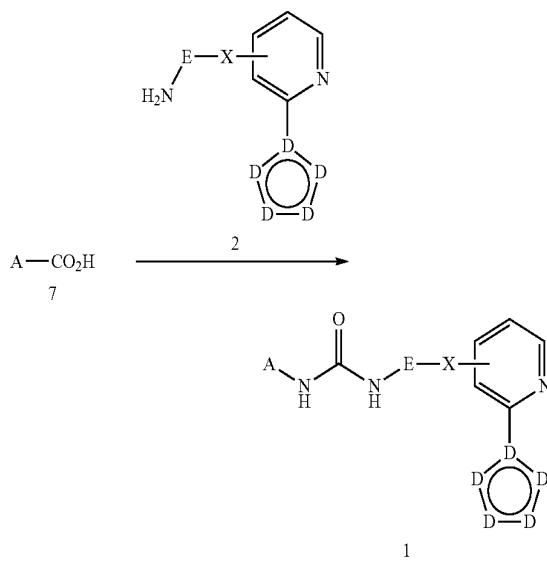
**[0088]** As shown in Scheme 2, isocyanates 3 can be prepared from amines A-NH<sub>2</sub> 6 with phosgene, or a phosgene equivalent such as diphosgene, triphosgene, or N,N-dicarbonylimidazole. Trichloroethyl carbamates 4 and isopropenyl carbamates 5 are readily prepared from amines A-NH<sub>2</sub> (6) by acylation with trichloroethyl chloroformate or isopropenyl chloroformate by standard conditions familiar to those skilled in the art. Preferred conditions for the preparation of 4 and 5 include treatment of compound 6 with the appropriate chloroformate in the presence of pyridine in an aprotic solvent such as dichloromethane or in the presence of aqueous hydroxide or carbonate in a biphasic aqueous/ethyl acetate solvent system.

Scheme 2

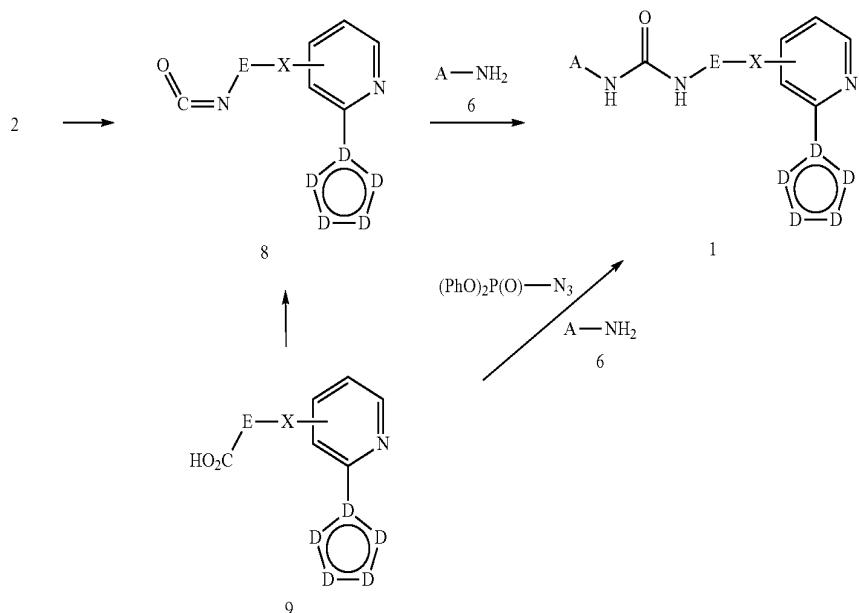


**[0089]** Additionally, compounds of formula 1 can also be prepared from carboxylic acids 7 by the intermediacy of in-situ generated acyl azides (Curtius rearrangement) as indicated in Scheme 3. Preferred conditions for Scheme 3 include the mixing of acid 7 with amine 2 and diphenylphosphoryl azide in a solvent such as 1,4-dioxane or dimethylformamide in the presence of base, such as triethylamine, and raising the temperature of the reaction to about 80-120° C. to affect the Curtius rearrangement.

Scheme 3

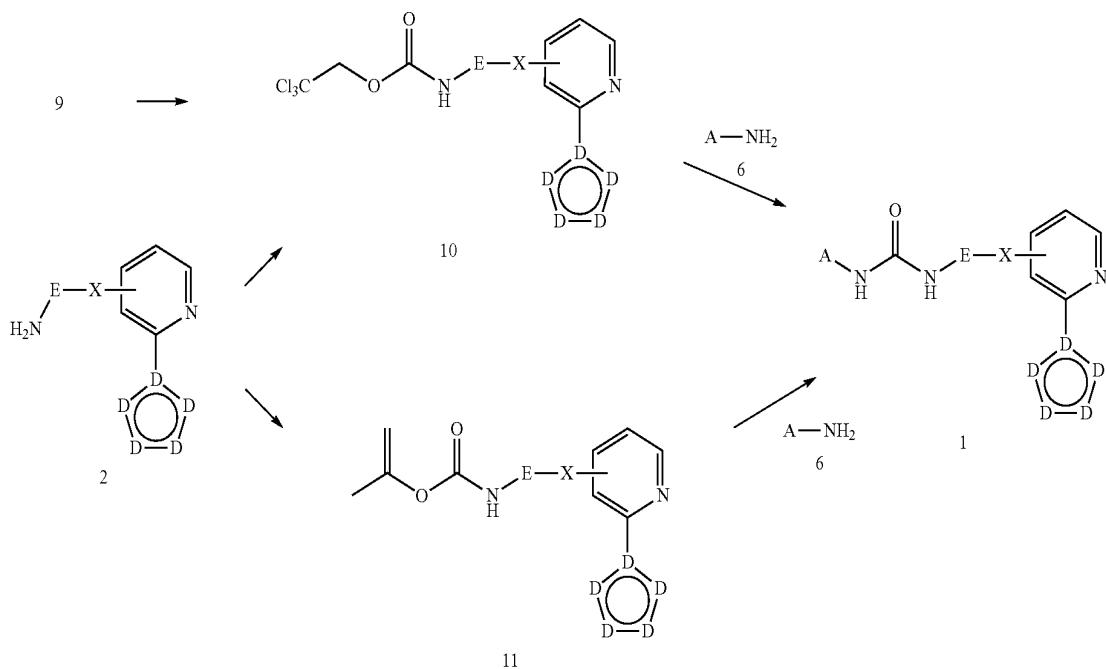


**[0090]** By analogy to Schemes 1 and 3 above, it will be recognized by those skilled in the art that the compounds of formula 1 can also be prepared by the union of amines A-NH<sub>2</sub> 6 with isocyanates 8 (Scheme 4). Isocyanates 8 can be prepared from general amines 2 by standard synthetic methods. Suitable methods for example, include reaction of 2 with phosgene, or a phosgene equivalent such as diphosgene, triphosgene, or N,N-dicarbonylimidazole. In addition to the methods above for converting amines 2 into isocyanates 8, the isocyanates 8 can also be prepared in situ by the Curtius rearrangement and variants thereof. Those skilled in the art will further recognize that isocyanates 8 need not be isolated, but may be simply generated in situ. Accordingly, acid 9 can be converted to compounds of formula 1 either with or without isolation of 8. Preferred conditions for the direct conversion of acid 9 to compounds of formula 1 involve the mixing of acid 9, amine A-NH<sub>2</sub> 6, diphenylphosphoryl azide and a suitable base, for example triethylamine, in an aprotic solvent, for example dioxane. Heating said mixture to a temperature of between 80 and 120° C. provides the compounds of formula 1.

Scheme 4

**[0091]** Additionally, compounds of formula 1 can also be prepared from amines 2 by first preparing stable isocyanate equivalents, such as carbamates (Scheme 5). Especially preferred carbamates include trichloroethyl carbamates (10) and isopropenyl carbamates (11) which are readily prepared from amine 2 by reaction with trichloroethyl chloroformate or isopropenyl chloroformate respectively using standard conditions familiar to those skilled in the art. Further reaction of

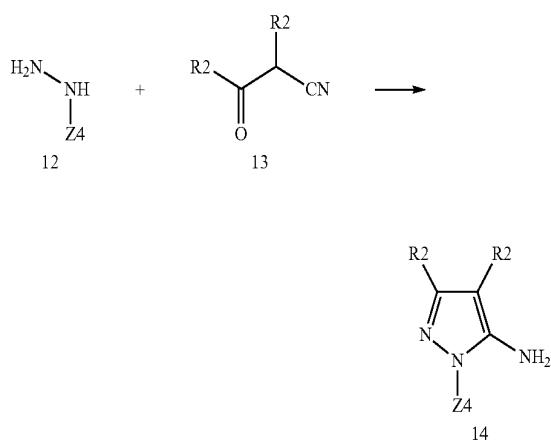
carbamates 10 or 11 with amine A-NH<sub>2</sub> 6 provides compounds of formula 1. Those skilled in the art will further recognize that certain carbamates can also be prepared from acid 9 by Curtius rearrangement and trapping with an alcoholic co-solvent. For example, treatment of acid 9 (Scheme 5) with diphenylphosphoryl azide and trichloroethanol at elevated temperature provides trichloroethyl carbamate 10.

Scheme 5

**[0092]** Many methods exist for the preparation of amines A-NH<sub>2</sub> 6 and acids A-CO<sub>2</sub>H 7, depending on the nature of the A-moiety. Indeed, many such amines (6) and acids (7) useful for the preparation of compounds of formula 1 are available from commercial vendors. Some non-limiting preferred synthetic methods for the preparation of amines 6 and acids 7 are outlined in the following schemes and accompanying examples.

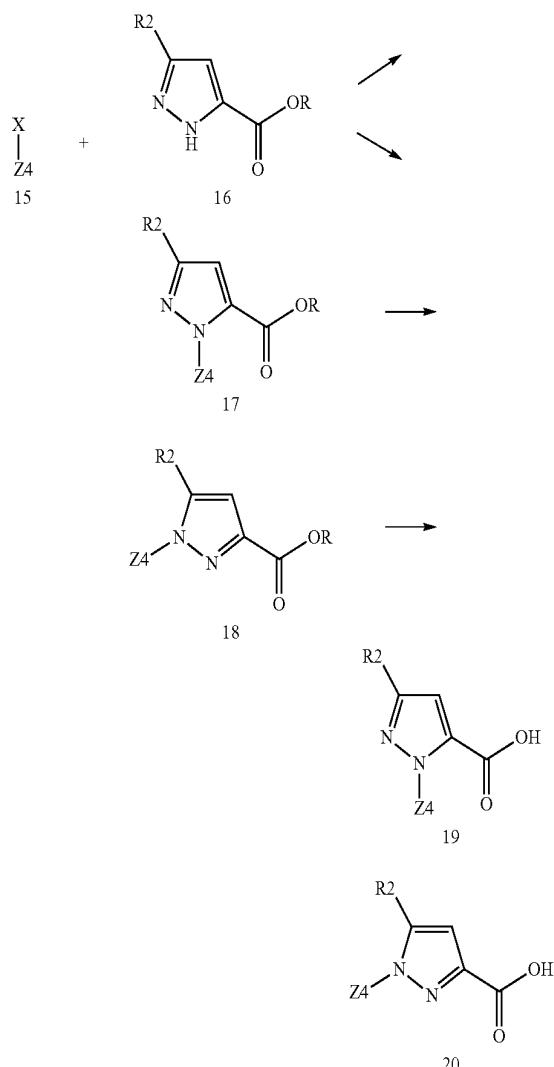
**[0093]** As illustrated in Scheme 6, Z4-substituted pyrazol-5-yl amines 14 (a preferred aspect of A-NH<sub>2</sub> 6, Scheme 2) are available by the condensation of hydrazines 12 and beta-keto nitriles 13 in the presence of a strong acid. Preferred conditions for this transformation are by heating in ethanolic HCl. Many such hydrazines 12 are commercially available. Others can be prepared by conditions familiar to those skilled in the art, for example by the diazotization of amines followed by reduction or, alternately from the reduction of hydrazones prepared from carbonyl precursors.

Scheme 6



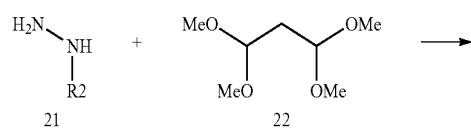
**[0094]** Another preferred method for constructing Z4-substituted pyrazoles is illustrated by the general preparation of pyrazole acids 19 and 20. (Scheme 7), aspects of general acid A-CO<sub>2</sub>H 7 (Scheme 3). As indicated in Scheme 7, pyrazole 5-carboxylic esters 17 and 18 can be prepared by the alkylation of pyrazole ester 16 with Z4-X 15, wherein X represents a leaving group on a Z4 moiety such as a halide, triflate, or other sulfonate. Preferred conditions for the alkylation of pyrazole 16 include the use of strong bases such as sodium hydride, potassium tert-butoxide and the like in polar aprotic solvents such as dimethylsulfoxide, dimethylformamide or tetrahydrofuran. Z4-substituted pyrazoles 17 and 18 are isomers of one another and can both be prepared in the same reactions vessel and separated by purification methods familiar to those skilled in the art. The esters 17 and 18 in turn can be converted to acids 19 and 20 using conditions familiar to those skilled in the art, for example saponification in the case of ethyl esters, hydrogenation in the case of benzyl esters or acidic hydrolysis in the case of tert-butyl esters.

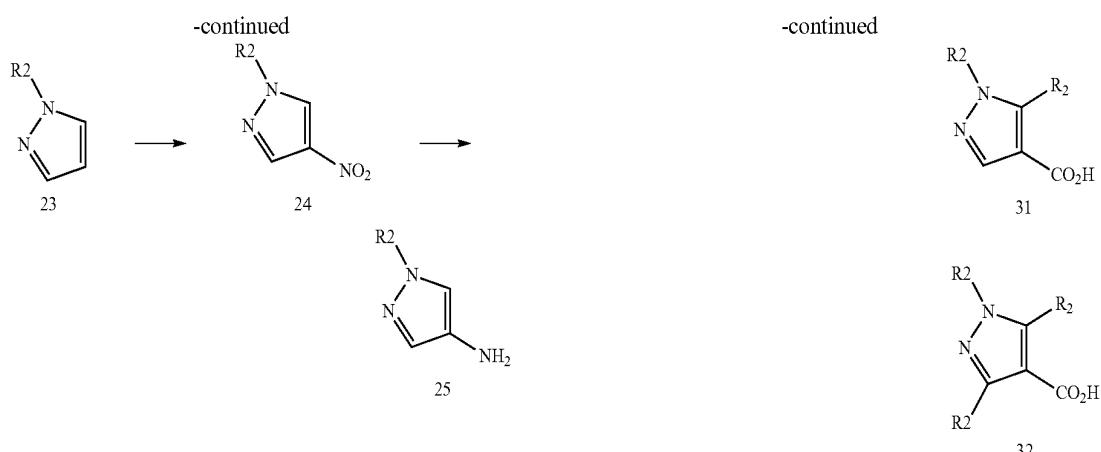
Scheme 7



**[0095]** Scheme 8 illustrates the preparation of pyrazole amine 25, a further example of general amine A-NH<sub>2</sub> 6. Acid-catalyzed condensation of R2-substituted hydrazine 21 with 1,1,3,3-tetramethoxypropane 22 provides R2-substituted pyrazole 23. Those skilled in the art will further recognize that R2-substituted pyrazole 23 can also be prepared by direct alkylation of pyrazole. Pyrazole 23 can be regioselectively nitrated to provide nitro-pyrazole 24 by standard conditions familiar to those skilled in the art. Finally, hydrogenation of nitro-pyrazole 24 employing a hydrogenation catalyst, such as palladium or nickel provides pyrazole amine 25, an example of general amine A-NH<sub>2</sub> 6.

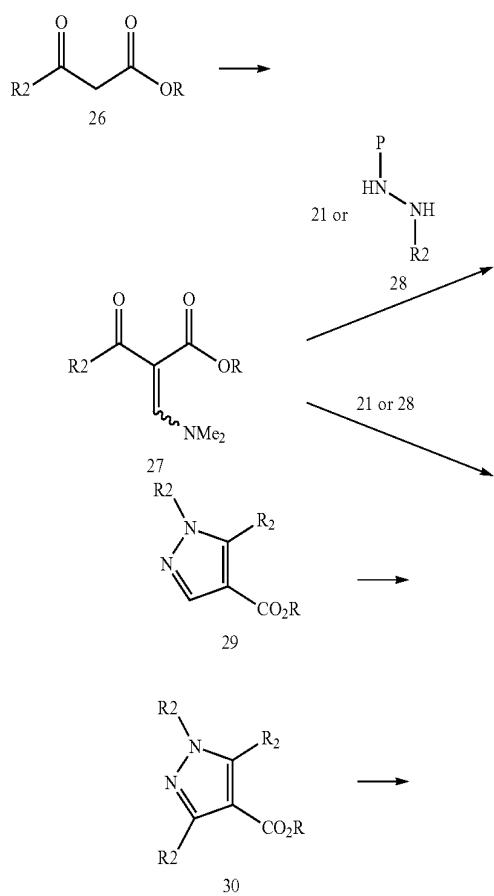
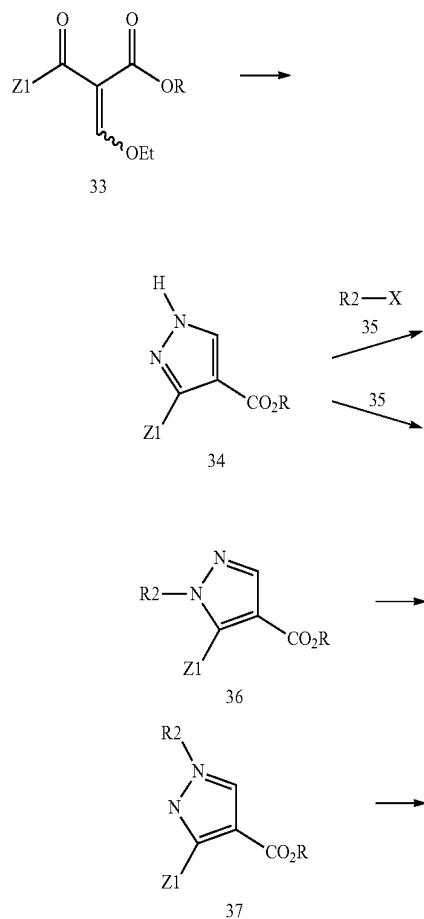
Scheme 8



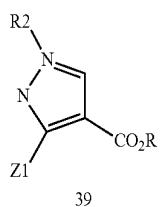
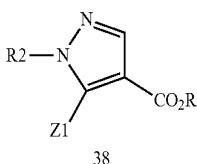


**[0096]** Additional pyrazoles useful for the synthesis of compounds of formula 1 can be prepared as described in Scheme 9. Thus, keto-ester 26 can be reacted with N,N-dimethylformamide dimethyl acetal to provide 27. Reaction of 27 with either 21 or 28 (wherein P is an acid-labile protecting group) in the presence of acid provides 29 or 30. In practice, both 29 and 30 can be obtained from the same reaction and can be separated by standard chromatographic conditions. In turn, esters 29 and 30 can be converted to acids 31 and 32 respectively as described in Scheme 7.

**[0097]** In a manner similar to Scheme 9, NH-pyrazole 34 can be prepared by reaction of acrylate 33 with hydrazine (Scheme 10). Alkylation of 34 with R<sub>2</sub>-X 35 as described above for Scheme 7 provides mixtures of pyrazole esters 36 and 37 which are separable by standard chromatographic techniques. Further conversion of esters 36 and 37 to acids 38 and 39 can be accomplished as described in Scheme 7.

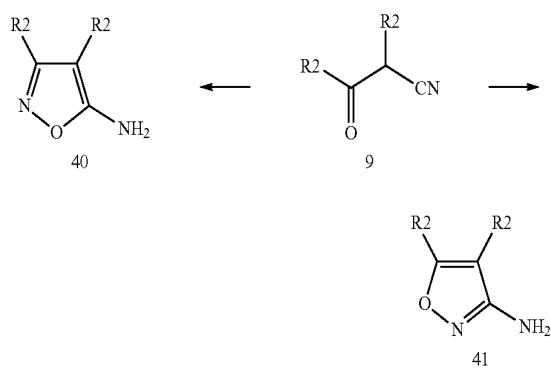
Scheme 9Scheme 10

-continued



**[0098]** General amines 6 containing an isoxazole ring can be prepared as described in Scheme 11. Thus, by analogy to Scheme 6, reaction of keto-nitrile 9 with hydroxylamine can provide both the 5-aminoisoxazole 40 and 3-aminoisoxazole 41. Preferred conditions for the formation of 5-aminoisoxazole 40 include the treatment of 9 with hydroxylamine in the presence of aqueous sodium hydroxide, optionally in the presence of an alcoholic co-solvent at a temperature between 0 and 100° C. Preferred conditions for the formation of 3-aminoisoxazole 41 include the treatment of 9 with hydroxylamine hydrochloride in a polar solvent such as water, an alcohol, dioxane or a mixture thereof at a temperature between 0 and 100° C.

Scheme 11



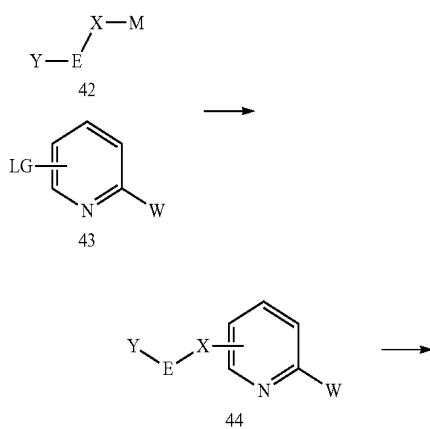
**[0099]** Amines 2 useful for the invention can be synthesized according to methods commonly known to those skilled in the art. Amines of general formula 2 contain three rings and can be prepared by the stepwise union of three monocyclic subunits as illustrated in the following non-limiting Schemes. Scheme 12 illustrates one mode of assembly in which an E-containing subunit 42 is combined with the central pyridine ring 43 to provide the bicyclic intermediate 44. In one aspect this general Scheme, the “M” moiety of 42 represents a hydrogen atom of a heteroatom on the X linker that participates in a nucleophilic aromatic substitution reaction with monocycle 43. Such reactions may be facilitated by the presence of bases (for example, potassium tert-butoxide), thus M may also represent a suitable counterion (for example potassium, sodium, lithium, or cesium) within an alkoxide, sulfide

or amide moiety. Alternately, the “M” group can represent a metallic species (for example, copper, boron, tin, zirconium, aluminum, magnesium, lithium, silicon, etc.) on a carbon atom of the X moiety that can undergo a transition-metal-mediated coupling with monocycle 43.

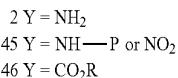
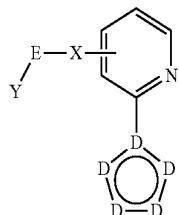
**[0100]** The “Y” group of monocyclic species 42 is an amine or an amine surrogate, such as an amine masked by a protecting group (“P” in formula 45), a nitro group, or a carboxy acid or ester that can be used to prepare an amine via known rearrangement. Examples of suitable protecting groups “P” include but are not limited to tert-butoxycarbonyl (Boc), benzoyloxycarbonyl (Cbz), and acetamide. In the instances wherein the “Y”-group of intermediate 42 is not an amine, the products of Scheme 11 will be amine surrogates such as 45 or 46 that can be converted to amine 2 by a deprotection, reduction or rearrangement (for example, Curtius rearrangement) familiar to those skilled in the art.

**[0101]** In these instances, the “LG” of monocycle 43 represents a moiety that can either be directly displaced in a nucleophilic substitution reaction (with or without additional activation) or can participate in a transition-mediated union with fragment 42. The W group of monocycle 43 or bicycle 44 represents a moiety that allows the attachment of the pyrazole. In one aspect, the “W” group represents a halogen atom that will participate in a transition-metal-mediated coupling with a pre-formed heterocyclic reagent (for example a boronic acid or ester, or heteroaryl stannane) to give rise to amine 2. In another aspect, the “W” group of 43 and 44 represents a functional group that can be converted to a five-membered heterocycle by an annulation reaction. Non-limiting examples of such processes would include the conversion of a cyano, formyl, carboxy, acetyl, or alkynyl moiety into a pyrazole moiety. It will be understood by those skilled in the art that such annulations may in fact be reaction sequences and that the reaction arrows in Scheme 11 may represent either a single reaction or a reaction sequence. Additionally, the “W” group of 44 may represent a leaving group (halogen or triflate) that can be displaced by a nucleophilic nitrogen atom of a pyrazole ring.

Scheme 12

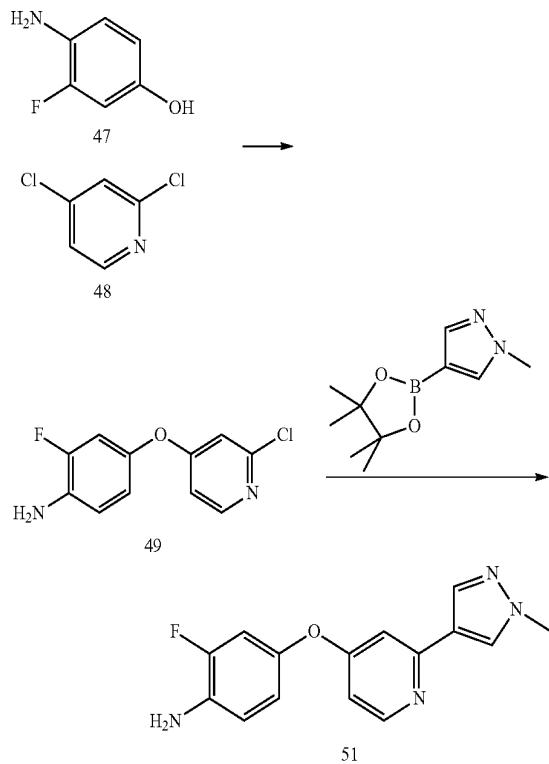


-continued



**[0102]** Some non-limiting examples of general Scheme 12 are illustrated in the Schemes below. Scheme 13 illustrates the preparation of pyrazole 51, an example of general amine 2. In Scheme 13, commercially available 3-fluoro-4-aminophenol (47) is reacted with potassium tert-butoxide and 2,4-dichloropyridine 48 to provide chloropyridine 49. The preferred solvent for this transformation is dimethylacetamide at a temperature between 80 and 100° C. Subsequent union of chloropyridine 49 with the commercially available pyrazole-4-boronic acid pinacol ester 50 in the presence of a palladium catalyst, preferably palladium tetrakis(triphenylphosphine), provides amine 51.

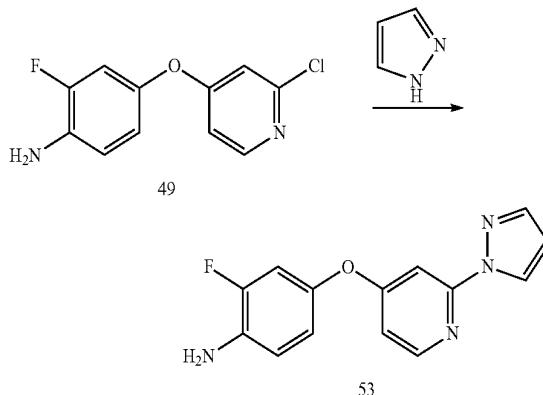
Scheme 13



**[0103]** Scheme 14 illustrates a non-limiting examples of Scheme 12 wherein the “W” group is a leaving group for nucleophilic aromatic substitution. Thus, amine 53, an example of general amine 2, can be prepared from general intermediate 49 by reaction with pyrazole (52). Preferred

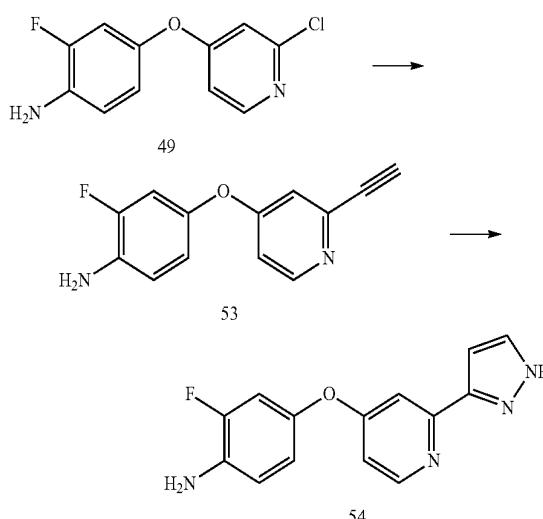
conditions include the use of polar aprotic solvents such as 1-methyl-2-pyrrolidinone, dimethylacetamide, or dimethylsulfoxide in the presence of non-nucleophilic bases such as potassium carbonate, sodium hydride, 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), and the like. Preferred temperatures are from ambient temperature up to about 250° C. and may optionally include the use of microwave irradiation or sonication.

Scheme 14



**[0104]** Scheme 15 illustrates the preparation of amine 54, a non-limiting example of a general amine of formula 2 by way of an annulation sequence according to general Scheme 12. Conversion of chloropyridine 49 into alkyne 53 can be accomplished by Sonogashira cross-coupling with trimethylsilylacetylene, followed by aqueous hydrolysis of the trimethylsilyl group, conditions familiar to those skilled in the art. Further reaction of alkyne 53 with trimethylsilyl diazomethane at elevated temperature affords the pyrazole amine 54 (see for example, Tsuzuki, et. al, *J. Med. Chem.*, 2004, (47), 2097).

Scheme 15



**[0105]** Additional preferred synthetic methods for the preparation of compounds of formula 1 are found in the following examples.

#### Section 4. Examples

**[0106]** General Method A: To a solution of the starting pyrazole amine (1 eq) in EtOAc were added 2,2,2-trichloroethylchloroformate (1.1 eq) and saturated NaHCO<sub>3</sub> (2-3 eq) at 0° C. After stirring for 3 h at RT, the layers were separated and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under vacuum to yield the crude TROC carbamate of the pyrazole amine.

**[0107]** To the TROC carbamate (1 eq) in DMSO were added diisopropylethylamine (2 eq), the appropriate amine (2 eq) and the mixture was stirred at 60° C. for 16 h or until all the starting carbamate was consumed. Water was added to the mixture and the product was extracted with EtOAc (2×25 mL). The combined organic extracts were washed with brine solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield crude product, which was purified by column chromatography to yield the target compound.

**[0108]** General Method B: To a suspension of the amine (usually 0.67 mmol) in EtOAc (2 mL) was added aqueous 1N NaOH. The reaction mixture was cooled to 0° C. and treated with isopropenyl chloroformate (0.1 mL, 0.94 mmol) over 30 sec. The reaction mixture was stirred for 15 min at 0° C. and 1 h at RT. The reaction was poured into THF-EtOAc (1:1; 40 mL) and washed with H<sub>2</sub>O (2×10 mL) and brine (2×10 mL). The organics were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated and the residue purified via column chromatography or recrystallization to provide the target (prop-1-en-2-yl)carbamate. To the carbamate (usually 0.26 mmol) was added the appropriate amine (usually 0.26 mmol) in THF (2 mL) and 1-methylpyrrolidine (catalytic amount) and the reaction mixture was stirred at 60° C. for 18 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and hexane (0.5 mL) solution, and stirred for 10 min. The resultant solid was filtered and dried.

**[0109]** General Method C: To a stirring solution of the carboxylic acid (0.24 mmol) and TEA (1.2 mmol) in 1,4-dioxane (4.5 mL) at RT was added DPPA (0.29 mmol). After stirring for 0.5 h at RT, the appropriate amine (0.71 mmol) was added and the reaction was stirred with heating at 100° C. for 2 h. The reaction was cooled to RT, diluted with brine (15 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by chromatography to afford the target compound.

**[0110]** General Method D: To a stirring suspension of amine (3.2 mmol, 1.0 eq) in THF (6 mL) at -78° C. was added 1.0M LiHMDS/THF (6.4 mmol, 2.00 eq). After 30 min at -78° C., the resulting solution was treated with isopropenyl chloroformate (3.2 mmol, 1.0 eq). After another 30 min at -78° C., the completed reaction was diluted with 3M HCl, warmed to RT and extracted with EtOAc (2×). The combined organics were washed with H<sub>2</sub>O (1×), satd. NaHCO<sub>3</sub> (1×), and brine (1×), dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to afford the target prop-1-en-2-yl carbamate which was used as is, purified by silica gel chromatography or recrystallized.

**[0111]** To the carbamate (usually 0.26 mmol) was added the appropriate amine (usually 0.26 mmol) in THF (2 mL) and 1-methylpyrrolidine (catalytic amount) and the reaction was stirred at 60° C. for 18 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and hexane (0.5 mL) solution, and stirred for 10 min. The resultant solid was filtered and dried and the resulting solid converted to the amine hydrochloride salt by

treatment with 0.1 N HCl solution and lyophilization or purified via column chromatography.

**[0112]** General Method E: To a stirring solution of amine (2 mmol, 1.00 eq) and pyridine (4 mmol, 2.00 eq) in CH<sub>2</sub>Cl<sub>2</sub> (18 mL) at RT was added isopropenyl chloroformate (1.87 mmol, 1.05 eq). After 4 hours the reaction was washed with 3M HCl (1×), satd. NaHCO<sub>3</sub> (1×), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and evaporated to afford the target prop-1-en-2-yl carbamate. The material was used as is in the next reaction.

**[0113]** To the carbamate (usually 0.26 mmol) was added the appropriate amine (usually 0.26 mmol) in THF (2 mL) and 1-methylpyrrolidine (catalytic amount) and the reaction was stirred at 60° C. for 18 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and hexane (0.5 mL) solution, and stirred for 10 min. The resultant solid was filtered and dried.

**[0114]** General Method F: To a solution of amine (6.53 mmol) in ethyl acetate (20 mL) at RT was added a solution of sodium bicarbonate (11.90 mmol) in water (20 mL) and isopropenyl chloroformate (9.79 mmol). The resultant mixture was stirred for 3 h at RT. The organic layer was separated. The aqueous layer was extracted once with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was used without further purification or purified via recrystallization or chromatography to provide the corresponding prop-1-en-2-yl carbamate.

#### Example A1

**[0115]** A suspension of 3-fluoro-4-aminophenol (8.0 g, 63.0 mmol) in dimethylacetamide (80 mL) was de-gassed in vacuo and treated with potassium tert-butoxide (7.3 g, 65 mmol). The resultant mixture was stirred at RT for 30 min. 2,4-Dichloropyridine (8 g, 54 mmol) was added and the mixture was heated to 80° C. for 12 h. The solvent was removed under reduced pressure to give a residue which was partitioned between water and EtOAc (3×100 mL). The organic layers were washed with saturated brine, dried (MgSO<sub>4</sub>), concentrated in vacuo and purified by silica gel column chromatography to give 4-(2-chloro-pyridin-4-yloxy)-2-fluorophenylamine (11 g, 86% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 8.24 (d, J=5.7 Hz, 1H), 7.00 (dd, J=9.0, 2.7 Hz, 1H), 6.89-6.73 (m, 4H), 5.21 (br s, 2H); MS (ESI) m/z: 239.2 (M+H<sup>+</sup>).

**[0116]** A solution of 4-(2-chloropyridin-4-yloxy)-2-fluorobenzenamine (3 g, 12.6 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (5.2 g, 25.2 mmol), and Na<sub>2</sub>CO<sub>3</sub> (2.7 g, 25.2 mmol) in DME (18 mL) and water (6 mL) was sparged with nitrogen for 20 min. Pd(PPh<sub>3</sub>)<sub>4</sub> (729 mg, 0.63 mmol) was added and the resulting mixture was heated to 100° C. for 16 h. The solvent was removed under reduced pressure and the crude product was suspended in water and extracted with EtOAc. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, concentrated in vacuo and purified via silica gel chromatography to give 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzenamine (2 g, 56% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 8.31 (d, J=5.7 Hz, 1H), 8.21 (s, 1H), 7.92 (s, 1H), 7.12 (d, J=2.4 Hz, 1H), 6.96 (m, 1H), 6.85-6.72 (m, 2H), 6.56 (m, 1H), 5.15 (s, 2H), 3.84 (s, 3H); MS (ESI) m/z: 285.0 (M+H<sup>+</sup>).

#### Example A2

**[0117]** 4-amino-phenol (8.9 g, 81.6 mmol) and potassium tert-butoxide (10.7 g, 95.2 mmol) were suspended in DMF

(100 mL) and stirred at RT for 30 min. 2,4-Dichloro-pyridine (10 g, 68 mmol) was added and the resulting mixture was heated to 90° C. for 3 h. The solvent was removed under vacuum and the residue was extracted with DCM (2×100 mL). The combined organics were dried ( $\text{MgSO}_4$ ), concentrated in vacuo and purified by silica gel chromatography to afford 4-(2-chloro-pyridin-4-yloxy)-phenylamine (9.0 g, 60% yield).  $^1\text{H}$  NMR (DMSO-d<sub>6</sub>):  $\delta$  8.21 (d, J=5.6 Hz, 1H), 6.85-6.82 (m, 4H), 6.61 (d, J=6.6 Hz, 2H), 5.17 (s, 2H); MS (ESI) m/z: 221 (M+H<sup>+</sup>).

[0118] 4-(2-Chloro-pyridin-4-yloxy)-phenylamine (0.7 g, 3.2 mmol), 1-methyl-4-(4,4,5,5-tetramethyl)-[1,3,2]dioxaborolan-2-yl)-4H-pyrazole (1.0 g, 4.8 mmol),  $\text{Cs}_2\text{CO}_3$  (4.0 g, 12.3 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.45 g, 0.4 mmol) were combined in a mixture of DMF and water (3; 1.20 mL). The reaction mixture was degassed, blanketed with argon and heated to 90° C. overnight. The reaction mixture was diluted with water and extracted with EtOAc (3×50 mL). The combined organics were washed with saturated brine, dried ( $\text{MgSO}_4$ ), concentrated in vacuo and purified by silica gel chromatography to provide 4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)benzenamine (0.7 g, 74% yield).  $^1\text{H}$  NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.29 (d, J=5.7 Hz, 1H), 8.19 (s, 1H), 7.90 (s, 1H), 7.10 (d, J=2.4 Hz, 1H), 6.83 (d, J=8.7 Hz, 2H), 6.62 (d, J=8.7 Hz, 2H), 6.52 (dd, J=2.4, 5.7 Hz, 1H), 5.10 (s, 2H), 3.84 (s, 3H); MS (ESI) m/z: 267.3 (M+H<sup>+</sup>).

### Example A3

[0119] 1,2,3-Trifluoro-4-nitro-benzene (30 g, 0.17 mol), benzyl alcohol (18.4 g, 0.17 mol) and  $\text{K}_2\text{CO}_3$  (35 g, 0.25 mol) were combined in DMF (300 mL) and were stirred at RT for 8 h. Water (300 mL) was added, and the mixture was extracted with EtOAc (3×500 mL). The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ), concentrated in vacuo and purified by column chromatography on silica gel to give 1-benzyloxy-2,3-difluoro-4-nitro-benzene (16 g, 36% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.06 (m, 1H), 7.49-7.30 (m, 6H), 5.37 (s, 2H).

[0120] A solution of 1-benzyloxy-2,3-difluoro-4-nitro-benzene (14 g, 52.8 mmol) in MeOH (200 mL) was stirred with Pd/C (10%, 1.4 g, 1.3 mmol) under a hydrogen atmosphere (30 psi) for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to afford 4-amino-2,3-difluorophenol (7 g, 92.1% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.05 (s, 1H), 6.45 (t, J=8.8 Hz, 1H), 6.34 (t, J=9.2 Hz, 1H), 4.67 (s, 2H); MS (ESI) m/z: 146.1 [M+H]<sup>+</sup>.

[0121] 4-amino-2,3-difluorophenol (6 g, 41.4 mmol) and potassium tert-butoxide (4.9 g, 43.5 mmol) were suspended in DMAc (200 mL) and stirred at RT for 30 min under Ar atmosphere. 2,4-Dichloropyridine (6.1 g, 41.4 mmol) was added, and the resulting mixture was heated at 70° C. for 8 h. The reaction mixture was filtered, concentrated in vacuo and purified by silica gel chromatography to afford 4-(2-chloro-pyridin-4-yloxy)-2,3-difluoro-phenylamine (7 g, 66% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.27 (d, J=6.0 Hz, 1H), 7.05 (s, 1H), 6.95 (m, 1H), 6.92 (m, 1H), 6.62 (m, 1H), 5.60 (s, 2H); MS (ESI) m/z: 257.1 [M+H]<sup>+</sup>.

[0122] Nitrogen was bubbled though a solution of 4-(2-chloro-pyridin-4-yloxy)-2,3-difluoro-phenylamine (2 g, 7.8 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.6 g, 7.8 mmol) and  $\text{Na}_2\text{CO}_3$  (1.65 g, 15.6 mmol) in DME (12 mL) and  $\text{H}_2\text{O}$  (4 mL) for 20 min.  $\text{Pd}(\text{PPh}_3)_4$  (450 mg, 0.4 mmol), was added and then resulting mixture was degassed in vacuo, blanketed with nitrogen and

heated to 70° C. for 16 h. The reaction was concentrated to dryness under reduced pressure. The crude product was suspended in water and extracted with EtOAc (3×10 mL). The organic layer was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and purified by silica gel chromatography to give 2,3-difluoro-4-[2-(1-methyl-1H-pyrazol-4-yl)-pyridin-4-yloxy]-phenylamine (1.3 g, 55% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.40 (d, J=6.0 Hz, 1H), 8.32 (s, 1H), 8.02 (s, 1H), 7.26 (s, 1H), 6.96 (t, J=8.8 Hz, 1H), 6.71-6.68 (m, 2H), 5.62 (s, 2H), 3.92 (s, 3H); MS (ESI) m/z: 303.2 [M+H]<sup>+</sup>.

### Example A4

[0123] A solution of 1,3-difluoro-2-methyl-benzene (15 g, 0.12 mol) in conc.  $\text{H}_2\text{SO}_4$  (100 mL) was treated drop wise with 65%  $\text{HNO}_3$  (11.4 g, 0.12 mol) at -10° C. and the resultant mixture was stirred for about 30 min. The mixture was poured into ice-water and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give 1,3-difluoro-2-methyl-4-nitro-benzene (16 g, 78% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (m, 1H), 6.95 (m, 1H), 2.30 (s, 3H).

[0124] 1,3-Difluoro-2-methyl-4-nitro-benzene (16 g, 0.092 mol), benzyl alcohol (10 g, 0.092 mol) and  $\text{K}_2\text{CO}_3$  (25.3 g, 0.18 mol), were combined in DMF (300 mL) and heated to 100° C. overnight. The mixture was poured into water and extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and purified by silica gel chromatography to give 1-benzyloxy-3-fluoro-2-methyl-4-nitro-benzene (8 g, 33% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.04 (t, J=8.8 Hz, 1H), 7.30-7.46 (m, 5H), 7.08 (d, J=9.2 Hz, 1H), 5.28 (s, 2H), 2.13 (s, 3H).

[0125] Using a procedure analogous to Example A3, 1-benzyloxy-3-fluoro-2-methyl-4-nitro-benzene (8 g, 0.031 mol) was hydrogenated to give 4-amino-3-fluoro-2-methyl-phenol (4.2 g, 96% yield).  $^1\text{H}$  NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.61 (s, 1H), 6.36 (m, 2H), 4.28 (s, 2H), 1.96 (s, 3H); MS (ESI) m/z: 142.1 [M+H]<sup>+</sup>.

[0126] Potassium tert-butoxide (3.5 g, 31 mmol) was added to a solution of 4-amino-3-fluoro-2-methyl-phenol (4.2 g, 30 mmol) in dimethylacetamide. The mixture was stirred at RT for 30 min. A solution of 2,4-dichloropyridine (4.38 g, 30 mmol) in dimethylacetamide was added and the mixture was heated at 100° C. overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in ethyl acetate (200 mL) and filtered through silica gel. The filter cake was washed with ethyl acetate and the combined filtrates were concentrated in vacuo and purified by silica gel chromatography to give 4-(2-chloro-pyridin-4-yloxy)-2-fluoro-3-methyl-phenylamine (3.2 g, 42% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.21 (d, J=6.4 Hz, 1H), 6.84 (d, J=2.0 Hz, 1H), 6.81 (dd, J=5.6, 2.4 Hz, 1H), 6.67-6.65 (m, 2H), 5.13 (s, 2H), 1.91 (s, 3H); MS (ESI) m/z: 253.2 [M+H]<sup>+</sup>.

[0127] Using a procedure analogous to Example A3, 4-(2-chloro-pyridin-4-yloxy)-2-fluoro-3-methyl-phenylamine (1.0 g, 3.3 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1 g, 4.8 mmol),  $\text{Na}_2\text{CO}_3$  (0.84 g, 6.6 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.25 g, 0.2 mmol) were combined to give 2-fluoro-3-methyl-4-[2-(1-methyl-1H-pyrazol-4-yl)-pyridin-4-yloxy]-phenylamine (0.74 g, 75% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.27 (d, J=6.4 Hz, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 7.07 (s, 1H), 6.68-6.61 (m,

2H), 6.45 (dd, J=5.6, 2.4 Hz, 1H), 5.06 (s, 2H), 3.82 (s, 3H), 1.95 (s, 3H); MS (ESI) m/z: 299.2 [M+H]<sup>+</sup>.

#### Example B1

**[0128]** To an aqueous solution of sodium hydroxide solution (40.00 g, 1 mol, in 200 ml of water) was added hydroxylamine hydrochloride (24.00 g, 346 mmol) and pivaloylacetoneitrile (40.00 g, 320 mmol). The resulting solution was stirred at 50° C. for 3 hrs. The reaction mixture cooled and the resultant white crystalline solid filtered, washed with water and dried to provide 3-t-butylisoxazol-5-amine as a white crystalline solid (34 g, yield 76% yield). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 6.41 (brs, 2H), 4.85 (s, 1H), 1.18 (s, 9H); LC-MS (ES, m/z, M+H)<sup>+</sup> 141.3.

#### Example B2

**[0129]** Methyl hydrazine and 4,4-dimethyl-3-oxopenanenitrile were combined according to literature procedures to yield 3-t-butyl-1-methyl-1H-pyrazol-5-amine. See WO 2006/071940.

#### Example B3

**[0130]** t-Butylhydrazine and 1,1,3,3-tetramethoxypropane were combined according to literature procedures to yield 1-t-butyl-1H-pyrazol-4-amine. See Ger. Offen., DE3332270, 21 Mar. 1985.

#### Example B4

**[0131]** To a suspension of KCN (1.90 g, 29.1 mmol) in MeOH (35 mL) was added dropwise 3-bromo-1,1,1-trifluoropropan-2-one oxime (5.00 g, 24.3 mmol) in MeOH (72 mL) at RT. The reaction mixture was stirred at RT for 3 hours. The solution was concentrated in vacuo, the residue was dissolved in EtOAc and stirred at RT. The solid was filtered and the filtrate was evaporated to obtain the crude product. The crude product was purified by silica gel column chromatography (EtOAc/hexanes) to obtain 3-(trifluoromethyl)isoxazol-5-amine (1.38 g, 37% yield). MS (ESI) m/z: 153.0 (M+H<sup>+</sup>).

#### Example B5

**[0132]** Using a procedure analogous to Example B6, ethyl 1-tert-butyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (750 mg, 2.84 mmol) was converted to 1-tert-butyl-5-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (646 mg, 94% yield) using lithium hydroxide hydrate (357 mg, 8.51 mmol). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>), δ 1.63 (s, 9H), 7.92 (s, 1H); MS (ESI) m/z: 259.0 (M+Na<sup>+</sup>).

#### Example B6

**[0133]** In ethanol (10 mL) was placed the tert-butylhydrazine hydrochloride (1.35 g, 10.8 mmol) and ethyl 2-((dimethylamino)methylene)-3-oxobutanoate (2.00 g, 10.8 mmol). The mixture warmed to reflux and stirred for 2 hrs, then cooled to RT and stirred overnight. The mixture was evaporated at reduced pressure to give an oil which was dissolved in ether (25 mL) and washed successively with water (25 mL), saturated sodium bicarbonate (25 mL) and brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), evaporated at reduced pressure and purified by chromatography (S1-25 column, ethyl acetate/hexanes) to give ethyl 1-tert-butyl-5-methyl-1H-pyrazole-4-carboxylate (1.48 g, 65% yield) as an oil. MS (ESI) m/z: 211.0 (M+H<sup>+</sup>).

**[0134]** In a mixture of ethanol:water:dioxane (1:1:1, 21 mL) was placed ethyl 1-tert-butyl-5-methyl-1H-pyrazole-4-carboxylate (1.48 g, 7.04 mmol) and lithium hydroxide hydrate (886 mg, 21.12 mmol). The reaction was stirred at 40° C. for 3 hrs and then at RT overnight. The reaction was diluted with water (25 mL) and ether (25 mL). The ether layer was discarded and the aqueous phase made acidic (pH~4) with 1N HCl. The acidic phase was then extracted with ethyl acetate (2×25 mL) and the combined ethyl acetate layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated at reduced pressure to give 1-tert-butyl-5-methyl-1H-pyrazole-4-carboxylic acid as a white solid (1.12 g, 87% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 1.56 (s, 9H), 2.67 (s, 3H), 7.65 (s, 1H), 12.13 (s, 1H); MS (ESI) m/z: 183.0 (M+H<sup>+</sup>).

#### Example B7

**[0135]** A solution of nBuLi in hexanes (242 mL, 387 mmol) was added to a -78° C. solution of diisopropylamine (39.1 g, 387 mmol) in anhydrous THF (300 mL) and the resultant mixture was stirred for 30 min at -78° C. A solution of ethyl cyclopentanecarboxylate (50 g, 352 mmol) in anhydrous THF (150 mL) was added dropwise into the mixture and the reaction mixture was stirred at -78° C. for 1 h. Iodomethane (79.2 g, 558 mmol) was added dropwise and the resulting mixture was warmed to RT and stirred overnight. The mixture was poured into water and extracted with ethyl ether. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to give ethyl 1-methylcyclopentanecarboxylate (47 g, 85%). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 4.03 (q, J=7.2 Hz, 2H), 1.37-2.03 (m, 8H), 1.15-1.12 (m, 6H).

**[0136]** Ethyl 1-methylcyclopentanecarboxylate (47 g, 301 mmol), acetonitrile (14.5 g, 363 mmol), NaH (18 g, 450 mmol), NaOH (6.8 g, 170 mmol) and hydroxylamine hydrochloride (4 g, 57 mmol) were sequentially combined by a procedure analogous to Example B10 to provide 3-(1-methylcyclopentyl)isoxazol-5-amine (7 g, 70% yield over 2 steps). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 6.41 (s, 2H), 4.81 (s, 1H), 1.91-1.86 (m, 2H), 1.67-1.48 (m, 6H), 1.19 (s, 3H); MS (ESI) m/z: 167.1 (M+H<sup>+</sup>).

#### Example B8

**[0137]** Sodium metal (13.8 g, 0.5 mol) was added portion-wise to ice-cold anhydrous EtOH (700 mL). After complete dissolution of the Na, a mixture of 3,3-dimethylbutan-2-one (50 g, 0.5 mol) and oxalic acid diethyl ester (77 ml, 0.5 mol) was added drop-wise. The reaction mixture was stirred in ice-salt bath until TLC indicated completion of the reaction. Acetic acid (38.1 ml, 0.5 mol) was added and the mixture was stirred at RT for 30 min. The reaction mixture was cooled in an ice-salt bath and treated with hydrazine hydrate (29.4 g, 0.5 mol). After complete addition, the mixture was warmed to RT and stirred until judged complete by TLC. The reaction mixture was concentrated under reduced pressure and re-dissolved in EtOAc. The EtOAc solution was washed with NaHCO<sub>3</sub>, brine and water, dried (MgSO<sub>4</sub>) and concentrated in vacuo. The resultant solid was washed with cold petroleum ether to give ethyl 3-tert-butyl-1H-pyrazole-5-carboxylate (49 g, 50% yield over two steps) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.65 (s, 1H), 4.38 (q, J=6.8 Hz, 2H), 1.39 (t, J=6.8 Hz, 3H), 1.35 (s, 1H); MS (ESI) m/z: 197.2 (M+H<sup>+</sup>).

**[0138]** Potassium t-butoxide (2.6 g, 23 mmol) was dissolved in DMSO (10 mL) and to this solution was added ethyl 3-tert-butyl-1H-pyrazole-5-carboxylate (4.5 g, 23 mmol) in small portions and stirred under Ar for 15 min. To this solution was added t-butyl-bromoacetate (5.4 g, 28 mmol) slowly at 0° C. with stirring for 45 min at RT. Sat. NH<sub>4</sub>Cl solution was added and product was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford (7.0 g) coupled product as a pasty mass. The above pasty mass was dissolved in TFA (10 mL) and stirred for 3 h at RT. Solvents were removed, water (100 mL) was added and product was extracted with DCM (3×50 mL). The combined organic extracts were washed with brine solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield 2-(3-tert-butyl-5-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetic acid (5.8 gm, 100%) as a pasty mass. <sup>1</sup>H NMR (400 MHz, Acetone-d<sub>6</sub>): δ 6.78 (s, 1H), 5.25 (s, 2H), 4.30 (q, J=7.2 Hz, 2H), 1.35-1.30 (m, 12H); MS (ESI) m/z: 255.2 [M+H]<sup>+</sup>.

**[0139]** To a solution of acid (0.41 g, 1.6 mmol) in DMF (5 mL) was added PyBop (0.84 g, 1.6 mmol), DIPEA (0.42 g, 3.2 mmol) and dimethylamine hydrochloride (0.26 g, 3.2 mmol). After stirring the mixture for 1 h at RT, water (50 mL) was added, and the product was extracted with ethyl acetate (2×30 mL). The combined organic layers were washed with 3M HCl solution (1×30 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford crude product which was purified by chromatography (EtOAc/DCM) to afford ethyl 3-tert-butyl-1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazole-5-carboxylate (0.25 g, 55%) as a thick paste. <sup>1</sup>H NMR (400 MHz, Acetone-d<sub>6</sub>): δ 6.73 (s, 1H), 5.35 (s, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.15 (s, 3H), 2.90 (s, 3H), 1.33-1.28 (m, 12H); MS (ESI) m/z: 282.3 [M+H]<sup>+</sup>.

**[0140]** To a solution of ethyl 3-tert-butyl-1-(2-(dimethylamino)-2-oxoethyl)-1H-pyrazole-5-carboxylate (1.16 g, 4 mmol) in THF (10 mL) was added 1M borane/THF (12 mL, 12 mmol) at 0° C. under Ar and stirring continued for 12 h at 60° C. The mixture was cooled to 0° C., quenched with 3M HCl solution and heated to 60° C. for 30 min. The mixture was basified with solid NaHCO<sub>3</sub> to pH around 8 and the product was extracted with CHCl<sub>3</sub> (2×30 mL). The combined organics were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo and purified by silica gel chromatography to provide ethyl 3-tert-butyl-1-(2-(dimethylamino)ethyl)-1H-pyrazole-5-carboxylate as a pasty mass (0.47 g, 43% yield). <sup>1</sup>H NMR (400 MHz, MeOH-d<sub>4</sub>): δ 6.73 (s, 1H), 4.66 (t, J=6.8 Hz, 2H), 4.35 (q, J=7.2 Hz, 2H), 2.80 (t, J=7.2 Hz, 2H), 2.34 (s, 6H), 1.38 (t, J=7.2 Hz, 3H), 1.31 (s, 9H); MS (ESI) m/z: 268.2 [M+H]<sup>+</sup>.

**[0141]** To a solution of ethyl 3-tert-butyl-1-(2-(dimethylamino)ethyl)-1H-pyrazole-5-carboxylate (0.47 g, 1.8 mmol) in THF (10 mL) was added aqueous LiOH (0.22 g, 5.3 mmol, 5 mL) and the mixture was stirred for 16 h at RT. Solvents were removed, the thick liquid was diluted with water (5 mL) and acidified with 50% aq. acetic acid solution to pH 5-6. The product was extracted with EtOAc (2×50 mL) and the combined organics were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to afford 3-tert-butyl-1-(2-(dimethylamino)ethyl)-1H-pyrazole-5-carboxylic acid as a pasty mass (0.12 g, 29% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 6.56 (s, 1H), 4.66 (t, J=6.0 Hz, 2H), 3.17 (t, J=6.0 Hz, 2H), 2.53 (s, 6H), 1.17 (s, 9H); MS (ESI) m/z: 240.3 [M+H]<sup>+</sup>.

#### Example B9

**[0142]** NaH (6.8 g, 0.17 mol) was added portionwise to a 0° C. solution of 1H-pyrazole (10 g, 0.15 mol) in DMF (150 mL)

and the resulting mixture was stirred at RT for 30 min. 2-Iodo-propane (30 mL, 0.3 mol) was added dropwise to the above mixture at 0° C., then the reaction mixture was stirred at RT for 10 h. H<sub>2</sub>O was added and the mixture was extracted with ethyl ether (3×100 mL). The combined organic layers were washed with brine, (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo and the residue distilled under reduced pressure to afford 1-isopropyl-1H-pyrazole (6.6 g, 40% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.68 (d, J=1.6 Hz, 1H), 7.38 (d, J=1.2 Hz, 1H), 6.17 (t, J=2.0 Hz, 1H), 4.46 (m, 1H), 1.37 (d, J=6.8 Hz, 6H).

**[0143]** To a solution of 1-isopropyl-1H-pyrazole (5 g, 45.5 mmol) in conc. H<sub>2</sub>SO<sub>4</sub> (50 mL) was added KNO<sub>3</sub> (5.0 g, 50 mmol) portionwise at 0° C. After the addition, the resulting mixture was heated to 50° C. for 8 h. The reaction mixture was cooled to RT, poured into ice water, and the mixture was extracted with EtOAc. The combined organics were washed with saturated Na<sub>2</sub>CO<sub>3</sub> solution, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo and purified via column chromatography to provide 1-isopropyl-4-nitro-1H-pyrazole (3.2 g, 46% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.99 (s, 1H), 8.32 (s, 1H), 4.65 (m, 1H), 1.51 (d, J=6.8 Hz, 6H).

**[0144]** A solution of 1-isopropyl-4-nitro-1H-pyrazole (3 g, 19 mmol) in EtOH (30 mL) was stirred under a hydrogen atmosphere for 2 h in the presence of 10% Pd/C (300 mg). The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford 1-isopropyl-1H-pyrazol-4-ylamine (1.8 g, 75% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 6.99 (s, 1H), 6.84 (s, 1H), 4.23 (m, 1H), 3.70 (s, 2H), 1.28 (d, J=6.8 Hz, 6H); MS (ESI) m/z: 126.2 [M+H]<sup>+</sup>.

#### Example B10

**[0145]** A solution of ethyl cyclopentanecarboxylate (prepared by esterification of commercially available cyclopentanecarboxylic acid, 30 g, 0.21 mol) and acetonitrile (10.1 g, 0.25 mol) in dry THF (80 mL) was added dropwise to a suspension of NaH (12.5 g, 0.31 mol) in dry THF (80 mL) and the resulting mixture was refluxed overnight. The reaction mixture was concentrated under reduced pressure and partitioned between water and EtOAc. The aqueous layer was separated, adjusted to pH 8 and extracted with EtOAc. The combined extracts were washed with brine, dried (MgSO<sub>4</sub>), and concentrated to give 3-cyclopentyl-3-oxopropanenitrile (26 g, 90% yield), which was used in the next step without further purification. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 4.06 (s, 2H), 2.92 (m, 1H), 1.41-1.77 (m, 8H).

**[0146]** Hydroxylamine hydrochloride (6 g, 86 mmol) and 3-cyclopentyl-3-oxopropanenitrile (10 g, 73 mmol) were added to a solution of NaOH (9 g, 225 mmol) in water (100 mL) and the resulting mixture was heated at 50° C. overnight. The precipitate was collected by filtration, washed with water, and dried to give 3-cyclopentylisoxazol-5-amine (6.7 g, 61% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 6.43 (s, 2H), 4.77 (s, 1H), 2.84 (m, 1H), 1.87-1.51 (m, 8H); MS (ESI) m/z: 153.1 [M+H]<sup>+</sup>.

#### Example B11

**[0147]** A mixture of 1,1,3,3-tetramethoxy-propane (13.6 g, 83 mmol) and 1-cyclopentylhydrazine-2-carboxylic acid tert-butyl ester from Ex B18 (16.6 g, 83 mmol) in water (150 mL) was treated with conc HCl (21 mL, 252 mmol) and the resulting mixture was heated at reflux overnight. The reaction mixture was allowed to cool to RT and was extracted with ether. The extracts were washed with brine, dried over anhy-

drous  $\text{MgSO}_4$  and filtered. The filtrate was concentrated in vacuo to give 1-cyclopentyl-1H-pyrazole (8.0 g, 71% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.52 (s, 1H), 7.43 (s, 1H), 6.24 (s, 1H), 4.68 (m, 1H), 2.20-1.71 (m, 8H); MS (ESI) m/z: 137.1 [M+H]<sup>+</sup>

[0148] To a suspension of  $\text{Na}_2\text{CO}_3$  (13 g, 124 mmol) in DCM (100 mL) was added 1-cyclopentyl-1H-pyrazole (8.35 g, 62 mmol) and  $\text{Br}_2$  (3.2 mL, 62.3 mmol). The resulting mixture was stirred at RT overnight. The solids were removed by filtration and the filter cake was washed with DCM. The filtrate was washed with water and brine, was dried over anhydrous  $\text{MgSO}_4$ , and was concentrated in vacuo to give 4-bromo-1-cyclopentyl-1H-pyrazole (14 g, 93% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.46 (s, 1H), 7.44 (s, 1H), 4.64 (m, 1H), 2.18-1.67 (m, 8H); MS (ESI) m/z: 215.0 [M+H]<sup>+</sup>.

[0149] To a solution of 4-bromo-1-cyclopentyl-1H-pyrazole (9.0 g, 42 mmol) in THF (100 mL) at -78° C. under nitrogen was added a solution of n-BuLi in hexanes (2.5 M, 18.5 mL, 46.2 mmol). The resulting mixture was stirred at -78° C. for 30 min. Dry-ice (solid  $\text{CO}_2$ ) was added at -78° C. and the reaction mixture was allowed to slowly warm to RT overnight. The solvent was removed under reduced pressure. Water was added, and the mixture was acidified (pH 3) by the addition of aq. HCl. The aqueous layer was extracted with EtOAc, and the extracts were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. The residue was recrystallized (EtOAc-petroleum ether) to provide 1-cyclopentyl-1H-pyrazole-4-carboxylic acid (3.5 g, 47% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  12.50 (br s, 1H), 8.31 (s, 1H), 7.85 (s, 1H), 4.78 (m, 1H), 2.16-1.68 (m, 8H); MS (ESI) m/z: 181.0 [M+H]<sup>+</sup>.

#### Example B12

[0150] A solution of ethyl trifluoroacetate (14.2 g, 0.1 mol) and anhydrous acetonitrile (5.0 g, 0.12 mol) in THF (100 mL) was added dropwise to a suspension of NaH (60%, 6.0 g, 0.15 mol) in THF (100 mL) at 80° C. The resulting mixture was heated to reflux overnight, and then cooled to RT. The reaction mixture was concentrated in vacuo and the residue was diluted with EtOAc and 10% aq HCl. The organic layer was washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to yield crude 4,4,4-trifluoro-3-oxo-butynonitrile (15 g), which was used without further purification.

[0151] A solution of methylhydrazine (5.0 g, 60 mmol) and 4,4,4-trifluoro-3-oxo-butynonitrile (9.8 g, 71 mmol) in EtOH (50 mL) was treated with conc. HCl (5 mL) and the resultant mixture was heated to reflux overnight. The solvent was removed in vacuo and the crude product was dissolved in EtOAc washed with saturated aq.  $\text{Na}_2\text{CO}_3$  solution until the washings were pH 8. The organics were concentrated and purified by prep-HPLC to provide 2-methyl-5-trifluoromethyl-2H-pyrazol-3-ylamine (2.07 g, 21% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta$  5.57 (s, 1H), 5.54 (br s, 2H), 3.55 (s, 3H); MS (ESI) m/z: 166.1 (M+H)<sup>+</sup>.

#### Example B13

[0152] A solution of hydrazine hydrate (459 mg, 9.16 mmol) in ethanol (5 mL) was added to a solution of ethyl 3-ethoxy-2-(trifluoroacetyl)acrylate (2.00 g, 8.33 mmol) in ethanol (15 mL) at 0° C. The reaction was allowed to warm to RT and stirred for 24 hrs. The reaction was concentrated in vacuo, dissolved in ethyl acetate (30 mL), washed with 5% citric acid (25 mL), saturated sodium bicarbonate (25 mL)

and brine (25 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to afford ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (1.365 g, 79% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  1.24 (t, 3H), 4.22 (q, 2H), 8.56 (s, 1H); MS (ESI) m/z: 209.0 (M+H)<sup>+</sup>.

[0153] Isopropyl iodide (1.225 g, 7.21 mmol) was added to a solution of ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (500 mg, 2.402 mmol) and DIEA (652 mg, 5.04 mmol) in DMF (5 mL) and the reaction stirred at RT for 3 h and 60° C. for 3 h. The reaction was diluted with ethyl acetate (30 mL), washed with 5% citric acid (30 mL), saturated sodium bicarbonate (30 mL) and brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give an oil. LC and LCMS showed starting material still present (~40%). The oil was dissolved in DMF (4 mL), treated with DIEA (652 mg, 5.04 mmol), isopropyl iodide (1.22 g, 7.21 mmol) and catalytic 4-dimethylaminopyridine (~5 mg) and stirred at RT overnight. The reaction was diluted with ethyl acetate (30 mL), washed with 5% citric acid (30 mL), saturated sodium bicarbonate (30 mL) and brine (30 mL), dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and purified by column chromatography (ethyl acetate/hexane) to afford ethyl 1-isopropyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (266 mg, 44% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  1.26 (s, 9H), 1.43 (d, 6H), 4.23 (q, 2H), 4.64 (hp, 1H), 8.62 (s, 1H); MS (ESI) m/z: 251.0 (M+H)<sup>+</sup>.

[0154] A solution of ethyl 1-isopropyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (266 mg, 1.06 mmol) and lithium hydroxide (102 mg, 4.25 mmol) in ethanol:water:dioxane (1:1:1, 6 mL) was warmed to 40° C. and stirred overnight. The mix cooled to RT, diluted with water (25 mL) and washed with ether (20 mL). The aqueous phase made acidic with 3N HCl (pH~2) and extracted with ethyl acetate (2×15 mL). The combined ethyl acetate layers were washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give 1-isopropyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (199 mg, 84% yield) as a white solid. MS (ESI) m/z: 223.0.

#### Example B14

[0155] In a procedure analogous to Example B6, isopropylhydrazine hydrochloride (896 mg, 8.10 mmol) and ethyl 2-acetyl-3-(dimethylaminomethylene)acrylate (1.50 g, 8.10 mmol) were combined and purified by chromatography (ethyl acetate/hexane) to afford ethyl 1-isopropyl-5-methyl-1H-pyrazole-4-carboxylate (faster elution, 537 mg),  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  1.30 (t, 3H), 1.39 (d, 6H), 4.23 (q, 2H), 4.61 (hp, 1H), 7.82 (s, 1H); MS (ESI) m/z: 197.0 (M+H)<sup>+</sup> and ethyl 1-isopropyl-3-methyl-1H-pyrazole-4-carboxylate (slower elution, 91 mg),  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ),  $\delta$  1.29 (t, 3H), 1.42 (d, 6H), 2.36 (s, 3H), 4.21 (q, 2H), 4.49 (hp, 1H), 8.24 (s, 1H); MS (ESI) m/z: 197.0 (M+H)<sup>+</sup>.

[0156] In a procedure analogous to Example B6, ethyl 1-isopropyl-5-methyl-1H-pyrazole-4-carboxylate (537 mg, 2.74 mmol) and lithium hydroxide (459 mg, 10.95 mmol) were combined to give 1-isopropyl-5-methyl-1H-pyrazole-4-carboxylic acid (323 mg, 70% yield) as an off white solid. MS (ESI) m/z: 169.0 (M+H)<sup>+</sup>.

#### Example B15

[0157] In a procedure analogous to Example B6, ethyl 1-isopropyl-3-methyl-1H-pyrazole-4-carboxylate from Example B14 (91 mg, 0.464 mmol) and lithium hydroxide

(78 mg, 1.855 mmol) were combined to afford 1-isopropyl-3-methyl-1H-pyrazole-4-carboxylic acid (62 mg, 79% yield). MS (ESI) m/z: 169.0 ( $M+H^+$ ).

#### Example B16

[0158] 3-nitro-5-(trifluoromethyl)pyridin-2-ol (6.80 g, 32.7 mmol) and quinoline (2.72 g, 21.06 mmol) were combined in a 200 mL round-bottom flask with an oversized magnetic stir bar. The assembly was cooled with an RT water bath. Phosphorus oxychloride (4.07 ml, 43.7 mmol) was cautiously added with vigorous stirring. After 5 min, the resulting gel would no longer stir. The apparatus was equipped with a reflux condenser and was transferred to a 120° C. oil bath. The gel quickly melted and stirring resumed with gentle refluxing. After 3 h, the mixture was cooled to RT and added portion wise to ice water with vigorous stirring. Sodium hydroxide was added to adjust the alkalinity to pH 8-9 and the mixture was extracted with EtOAc (2×100 mL) and  $\text{CH}_2\text{Cl}_2$  (2×100 mL). The combined organics were dried ( $\text{MgSO}_4$ ), concentrated in vacuo and chromatographed (EtOAc/ $\text{CH}_2\text{Cl}_2$ ) provided 2-chloro-3-nitro-5-(trifluoromethyl)pyridine (6.65 g, 90% yield) as a yellow liquid.  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.21 (m, 1H), 9.09 (m, 1H).

[0159] A Parr hydrogenation flask was charged with 10% Palladium on carbon, 50% wet (0.050 g, 0.023 mmol) and ethanol (10 mL). Triethylamine (1.0 ml, 3.09 mmol), 2-chloro-3-nitro-5-(trifluoromethyl)pyridine (0.70 g, 3.09 mmol) and an additional 10 mL of ethanol were added. The flask was purged of air, charged with 48 psi of hydrogen, and shaken for 6 h. The reaction mixture was purged of hydrogen in vacuo and filtered through Celite®, washing with EtOAc (20 mL) and EtOH (20 mL). The filtrate was concentrated in vacuo and the product npartitioned between EtOAc (40 mL) and water (20 mL). The organics were washed with sat aq  $\text{NaHCO}_3$  (20 mL) and brine (20 mL), dried ( $\text{MgSO}_4$ ) and concentrated in vacuo to provide 5-(trifluoromethyl)pyridin-3-amine (498 mg, 99% yield).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  8.14 (m, 1H), 8.00 (s, 1H), 7.13 (m, 1H), 5.84 (s, 2H); MS (ESI) m/z 163.0 ( $M+H^+$ ).

#### Example B17

[0160] 5-Bromopyridin-3-amine (0.433 g, 2.5 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.630 g, 3.75 mmol),  $\text{Cs}_2\text{CO}_3$  (3.10 g, 9.5 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.289 g, 0.25 mmol) were suspended in DMF/ $\text{H}_2\text{O}$  (3:1, 20 mL). The reaction mixture was degassed with  $\text{N}_2$  and heated at 90° C. for 16 h. Solvent was removed under reduced pressure. The residue was diluted with  $\text{H}_2\text{O}$  (20 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (20 mL), dried, concentrated in vacuo and purified by chromatography to afford 5-(prop-1-en-2-yl)pyridin-3-amine (0.773 g, 230%) as a dark yellow oil. MS (ESI) m/z: 135.0 ( $M+H^+$ ).

[0161] To a solution of 5-(prop-1-en-2-yl)pyridin-3-amine (0.773 g, 2.48 mmol) in ethanol (8 mL) was added 10% Pd/C (0.132 g, 0.124 mmol) and the resulting suspension was stirred under a hydrogen atmosphere (1 atm) for 18 h. The reaction was filtered through Celite® and washed forward with EtOH. The filtrate was concentrated, diluted with EtOAc (30 mL) and washed with  $\text{H}_2\text{O}$  (1×15 mL) and brine (1×15 mL). The aqueous phase was back-extracted with EtOAc (1×20 mL). The combined organic layers were dried ( $\text{MgSO}_4$ )

and concentrated to afford 5-isopropylpyridin-3-amine (0.453 g, 134%) as a light yellow oil. MS (ESI) m/z: 137.1 ( $M+H^+$ ).

#### Example B18

[0162] A mixture of cyclopentanone (20 g, 238 mmol) and hydrazinecarboxylic acid tert-butyl ester (31.4 g, 0.238 mol) in MeOH (300 mL) was stirred at RT for 2 h. The reaction mixture was concentrated in vacuo and the resulting solid was dried under vacuum to give 1-cyclopentylidenehydrazine-2-carboxylic acid tert-butyl ester (47.1 g, 100% yield).

[0163] Sodium cyanoborohydride (6.4 g, 0.101 mol) was added portion-wise to a suspension of 1-cyclopentylidenehydrazine-2-carboxylic acid tert-butyl ester (20 g, 0.101 mol) in a mixture of acetic acid and methanol (288 mL, 1:1). The resulting solution was stirred at RT for 2 h. The reaction mixture was neutralized with 1 N aq NaOH and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with saturated  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give 1-cyclopentylhydrazine-2-carboxylic acid tert-butyl ester (18.4 g) as an oil.

[0164] To a solution of 1-cyclopentylhydrazine-2-carboxylic acid tert-butyl ester (18.4 g, 92 mmol) in a mixture of ethanol (300 mL) and conc. HCl (7.7 mL, 92 mmol) was added ethyl 2-acetyl-3-(dimethylamino)acrylate (25.5 g, 0.138 mol). The resulting mixture was refluxed for 2 h. The reaction was concentrated in vacuo, dissolved in  $\text{CH}_2\text{Cl}_2$  (300 mL), washed with satd  $\text{NaHCO}_3$ , and brine, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and purified by chromatography on silica gel to give ethyl 1-cyclopentyl-5-methyl-1H-pyrazole-4-carboxylate (15.6 g, 76% yield).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  8.15 (s, 1H), 4.61 (m, 1H), 4.15 (q,  $J=8$  Hz, 2H), 2.29 (s, 3H), 2.04-1.97 (m, 2H), 1.89-1.85 (m, 2H), 1.78-1.71 (m, 2H), 1.62-1.59 (m, 2H), 1.23 (t,  $J=8$  Hz, 3H).

[0165] A solution of ethyl 1-cyclopentyl-5-methyl-1H-pyrazole-4-carboxylate (15.5 g, 70 mmol) in EtOH (200 mL) was treated with a solution of LiOH (6 g, 250 mmol) in water (100 mL) and the resultant mixture was stirred at 60° C. overnight. The reaction was concentrated in vacuo and the residue was partitioned between EtOAc and water. The aqueous layer was acidified with aq HCl (2 M) to pH 3 and was extracted with EtOAc. The extract was concentrated under reduced pressure to give 1-cyclopentyl-5-methyl-1H-pyrazole-4-carboxylic acid (8.7 g, 64% yield).  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  12.05 (br s, 1H), 8.10 (s, 1H), 4.60 (m, 1H), 2.28 (s, 3H), 2.04-1.97 (m, 2H), 1.89-1.85 (m, 2H), 1.78-1.71 (m, 2H), 1.62-1.59 (m, 2H); MS (ESI) m/z: 194.99 [ $M+H^+$ ].

#### Example B19

[0166] A solution of 2,4-dinitrobenzenesulfonic acid (16.5 g, 62.0 mmol) in minimum quantity of  $\text{CH}_3\text{CN}$  was added at once to a translucent solution of iodo benzene diacetate (10 g, 31.0 mmol) in  $\text{CH}_3\text{CN}$  (100 mL). The reaction mixture was stirred for 1 hour at RT. The solution was chilled in ice and then the solution was kept in freezer. The solid was filtered and washed with  $\text{Et}_2\text{O}$  to obtain [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benzene (HDNIB) (13.9 g, 96% yield).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ):  $\delta$  9.91 (brs, 1H), 8.71 (d,  $J=2.4$  Hz, 1H), 8.56 (dd,  $J=2.0$ , and 8.4 Hz, 1H), 8.38 (m, 2H), 8.24 (d,  $J=8.4$  Hz, 1H), 7.88 (m, 1H), 7.77 (m, 2H).

[0167] A solution of ethyl pyruvate (2.0 g, 17.2 mmol) and HDNIB (9.7 g, 20.7 mmol) in trimethylacetonitrile (15 mL)

was heated to reflux for 3 hours. After the reaction mixture was cooled to RT, 2,6-lutidine (0.2 mL, 1.7 mmol) was added. The reaction mixture was refluxed for an additional 8 hours. The reaction was checked by LC-MS and the solvent was removed. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$ , washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and purified via silica gel column chromatography (EtOAc/hexane) to obtain ethyl 2-tert-butylloxazole-5-carboxylate (1.0 g, 29% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.89 (s, 1H), 4.42 (d, J=7.2 Hz, 2H), 1.49 (s, 9H), 1.43 (d, J=7.2 Hz, 3H); MS (ESI) m/z: 198.1 (M+H<sup>+</sup>).

[0168] To a stirring suspension of ethyl 2-tert-butylloxazole-5-carboxylate (1.0 g, 5.07 mmol) in 1:1:1 THF/EtOH/H<sub>2</sub>O (15 mL) at RT was added LiOH·H<sub>2</sub>O (486 mg) and the mixture was stirred at RT for 3 hours. The reaction mixture was checked by LC-MS and the completed reaction was concentrated to an aqueous residue, acidified (pH 3-4) with 3M HCl and extracted with EtOAc (3x). The combined organics were washed with brine (1x), dried ( $\text{MgSO}_4$ ) and evaporated to afford desired product, 2-tert-butylloxazole-5-carboxylic acid (0.67 g, 78% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  12.9 (brs, 1H), 8.62 (s, 1H), 1.30 (s, 9H); (ESI) m/z: 170.0 (M+H<sup>+</sup>).

#### Example B20

[0169] To a solution of 1-tert-butyl-1H-pyrrole-3-carbaldehyde (0.339 g, 2.24 mmol) in acetone (40 mL) was added, over a 2 h period, a solution of KMnO<sub>4</sub> (0.708 g, 4.48 mmol) in Acetone/H<sub>2</sub>O (1:1, 60 mL). After 3 h, the reaction was poured into a solution of 10% NaHSO<sub>3</sub>/1N HCl (120 mL) and the solution was extracted with DCM (3x60 mL). The combined extracts were washed with H<sub>2</sub>O (2x60 mL) and 5% NaHCO<sub>3</sub> (3x60 mL). The bicarbonate washes were carefully acidified to pH 3 and extracted with DCM (3x60 mL). The combined organic layers were washed with brine (1x), dried ( $\text{MgSO}_4$ ) and concentrated afford 1-tert-butyl-1H-pyrrole-3-carboxylic acid (0.270 g, 72% yield) as a white solid. MS (ESI) m/z: 168.1 (M+H<sup>+</sup>).

#### Example B21

[0170] A 60% Sodium hydride (5.16 g, 129 mmol) slurry in benzene (20 mL) was warmed to 80° C. for 15 min and then treated sequentially and dropwise (over 15 min.), first with a solution of propionitrile (7.11 g, 129 mmol) and second with a solution of methyl trimethylacetate (7.50 g, 64.6 mmol). The mixture was stirred at 80° C. overnight. The reaction was cooled to RT, quenched with i-propanol (25 mL) and water (25 mL) and diluted with ethyl acetate (50 mL). The mixture was acidified (6N HCl, pH~1) and the organic phase separated. The organic phase was washed with brine (25 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give 2-methyl pivaloylacetone nitrile as an oil.

[0171] Hydroxylamine hydrochloride (5.61 g, 81 mmol) was added portionwise to a solution of sodium hydroxide (11.62 g, 291 mmol) at 0° C. in water (40 mL). The mixture was stirred until a complete salvation occurred. To this was then added crude 2-methyl pivaloylacetone nitrile, the solution was warmed to 50° C. for 4 hrs, cooled to RT and allowed to stand overnight. The white solid was collected by filtration, washed with water (4x10 mL) and air dried for 1 hr to afford 3-tert-butyl-4-methylisoxazol-5-amine (4.25 g, 42% yield).

$^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  1.19 (s, 9H), 1.79 (s, 3H), 6.09 (br. s, 2H); MS (ESI) m/z: 155.1 (M+H<sup>+</sup>).

#### Example B22

[0172] 5-Bromopyridin-3-amine (0.94 g, 5.43 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.076 g, 0.109 mmol) and ethynyltrimethylsilane (0.64 g, 6.52 mmol) were combined in TEA (12.0 mL). After stirring for 5 min, CuI (0.010 g, 0.054 mmol) was added. The reaction mixture was flushed with N<sub>2</sub> and stirred at RT overnight, followed by at 55° C. overnight. The reaction was filtered and the solid was washed with EtOAc (30 mL). The combined organics were concentrated in vacuo and purified by chromatography to afford 5-(2-(trimethylsilyl)ethynyl)pyridin-3-amine (0.279 g, 27% yield) as a white solid. MS (ESI) m/z: 191.1 (M+H<sup>+</sup>).

[0173] To a solution of 5-(2-(trimethylsilyl)ethynyl)pyridin-3-amine (0.279 g, 1.466 mmol) in MeOH (2.0 mL) was added K<sub>2</sub>CO<sub>3</sub> (0.304 g, 2.20 mmol). The reaction was stirred at RT overnight. Solvent was removed under reduced pressure and the residue was extracted with EtOAc (2x). The combined organic layers were washed with H<sub>2</sub>O (1x) and brine (1x), dried ( $\text{MgSO}_4$ ) and concentrated to afford 5-ethynylpyridin-3-amine (0.168 g, 97%) as a light yellow solid.

[0174] 5-Ethynylpyridin-3-amine (0.122 g, 1.03 mmol) and 10% Pd/C (0.11 g, 0.102 mmol) were suspended in MeOH (15 mL). This was hydrogenated (42 psi) in a Parr hydrogenation apparatus overnight. The reaction was filtered through Celite® and washed forward with MeOH. The filtrate was concentrated to afford 5-ethylpyridin-3-amine (0.070 g, 56% yield) as a light yellow oil.  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  7.72 (d, J=2.4 Hz, 1H), 7.58 (d, J=1.6 Hz, 1H), 6.71 (t, J=2.0 Hz, 1H), 5.16 (s, 2H), 2.43 (q, J=7.2 Hz, 2H), 1.11 (t, J=7.6 Hz, 3H).

#### Example B23

[0175] In ethanol (5 mL) was placed the t-butylhydrazine hydrochloride (0.79 g, 6.3 mmol) and ethyl 2-acetyl-3-(dimethylaminomethylene)acrylate (1.0 g, 6.3 mmol). The mixture was refluxed for 8 hours. The mix was evaporated at reduced pressure to give an oil. The oil was dissolved in ether (25 mL) and washed successively with water (25 mL), saturated sodium bicarbonate (25 mL) and brine (25 mL) was dried ( $\text{Na}_2\text{SO}_4$ ), concentrated in vacuo and purified by silica gel column chromatography (EtOAc/hexanes) to obtain ethyl 1-tert-butyl-5-methyl-1H-pyrazole-3-carboxylate (0.60 g, 45% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  6.54 (s, 1H), 4.22 (q, J=7.2 Hz, 2H), 2.44 (s, 3H), 2.42 (s, 3H), 1.57 (s, 9H), 1.25 (t, J=7.2 Hz, 3H); MS (ESI) m/z: 211.1 (M+H<sup>+</sup>).

[0176] To a solution of ethyl 1-tert-butyl-5-methyl-1H-pyrazole-3-carboxylate (0.60 g, 2.85 mmol) in a mix of ethanol:water:dioxane (1:1:1, 9 mL) was added lithium hydroxide (0.48 mg, 11.4 mmol). The mixture was stirred at 40° C. for 5 hours. The solution was checked by LC-MS and diluted with water (10 mL) and the pH adjusted to ~2 with 1N HCl. The solution was extracted with EtOAc (2x10 mL) and the combined organic phases washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo to obtain 1-tert-butyl-5-methyl-1H-pyrazole-3-carboxylic acid (0.50 g, 96% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  12.4 (s, 1H), 5.47 (s, 1H), 2.42 (s, 3H), 1.56 (s, 9H); MS (ESI) m/z: 183.1 (M+H<sup>+</sup>).

#### Example B24

[0177] 4-nitroimidazole (0.500 g, 4.42 mmol), 2-iodopropane (0.553 mL, 5.53 mmol) and powdered K<sub>2</sub>CO<sub>3</sub> (0.917 g,

6.63 mmol) were combined and stirred in DMF (25 ml) at 50° C. After 5 h, the reaction was cooled to RT. The reaction was diluted with EtOAc and filtered to remove inorganic salts, rinsing forward with EtOAc. The filtrate was evaporated to near dryness. The residue was diluted in EtOAc, washed with H<sub>2</sub>O (2x) and brine (1x), dried (MgSO<sub>4</sub>) and evaporated to afford 1-isopropyl-4-nitro-1H-imidazole (0.66 g 96% yield) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.51 (s, 1H), 7.98 (s, 1H), 4.52-4.49 (m, 1H), 1.44 (d, 6H); MS (ESI) m/z: 156.0 (M+H<sup>+</sup>), 178.0 (M+Na<sup>+</sup>).

[0178] 1-isopropyl-4-nitro-1H-imidazole (0.66 g, 4.25 mmol) was hydrogenated (1 atm) over 10% Pd/C (50% w/w H<sub>2</sub>O) (0.905 g, 0.425 mmol) in EtOAc (43 ml) overnight. The completed reaction was filtered through Celite®, rinsing forward with EtOAc (30-35 ml). The combined filtrates containing 1-isopropyl-1H-imidazol-4-amine were used directly in the next reaction. MS (ESI) m/z: 126.1 (M+H<sup>+</sup>).

[0179] To a stirring solution of 1-isopropyl-1H-imidazol-4-amine (0.532 g, 4.25 mmol) in EtOAc (70 ml) was added Troc-Cl (0.614 ml, 4.46 mmol) followed by satd. NaHCO<sub>3</sub> (17.23 ml, 12.75 mmol). The biphasic mixture was stirred briskly at RT. After 6 h, the layers were separated and the aqueous was extracted with EtOAc (1x). The combined organics were washed with satd. NaHCO<sub>3</sub> (1x) and brine (1x), dried, evaporated and triturated (EtOAc/hexanes). The solids were collected by filtration, rinsed with hexanes and dried on the filter to afford 2,2,2-trichloroethyl 1-isopropyl-1H-imidazol-4-ylcarbamate (0.392 g, 31% yield) as a pink-orange solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.2 (s, 1H), 7.49 (s, 1H), 7.02 (s, 1H), 4.80 (s, 2H), 4.3-4.25 (m, 1H), 1.35 (d, 6H); MS (ESI) m/z: 300.0 (M+Fl<sup>+</sup>), 302.0 (M+2+H<sup>+</sup>).

#### Example B25

[0180] A solution of 2-chloro-3-nitro-5-(trifluoromethyl)pyridine from Example B16 (400 mg, 1.766 mmol) in THF (5 mL) was treated sequentially with dimethyl malonate (250 µl, 2.187 mmol) and sodium hydride (60%, 85 mg, 2.119 mmol). The resultant mixture was stirred at RT overnight. The mixture was diluted with EtOAc and washed with 0.1 M aq HCl, water, and brine, dried (MgSO<sub>4</sub>), concentrated in vacuo and purified by silica gel chromatography to provide dimethyl 2-(3-nitro-5-(trifluoromethyl)pyridin-2-yl)malonate (320 mg, 56% yield) of sufficient purity for the next step. MS (ESI) m/z: 323.0 (M+H<sup>+</sup>).

[0181] Dimethyl 2-(3-nitro-5-(trifluoromethyl)pyridin-2-yl)malonate (320 mg, 0.993 mmol) was combined with aq HCl (3 M, 5 mL, 15.00 mmol) and the mixture was heated to reflux overnight. The reaction mixture was cooled to RT and poured into EtOAc. Aqueous NaOH (2 M, 10 mL, 20 mmol) was added and the organic layer was separated and washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated in vacuo to provide 2-methyl-3-nitro-5-(trifluoromethyl)pyridine (53 mg, 9% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.19 (s, 1H), 8.80 (s, 1H), 2.82 (s, 3H).

[0182] 2-Methyl-3-nitro-5-(trifluoromethyl)pyridine (51 mg, 0.247 mmol) and 10% Pd/C, (50% wet, 10 mg, 4.70 µmol) in EtOH (10 mL) were combined in a Parr hydrogenation flask. The reaction mixture was purged of air under vacuum and pressurized with hydrogen (33 psi). The flask was shaken for 18 h. An additional portion of 10% Pd/C, (50% wet, 20 mg, 9.40 µmol) was added and the mixture was hydrogenated (40 psi) overnight. The reaction mixture was filtered through Celite® and the filter cake was washed with EtOH. The combined filtrate and washings were concentrated

in vacuo and purified by silica gel chromatography to provide 2-methyl-5-(trifluoromethyl)pyridin-3-amine (17 mg, 39% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 7.93 (s, 1H), 7.13 (s, 1H), 5.56 (s, 2H), 2.31 (s, 3H); MS (ESI) m/z: 177.0 (M+H<sup>+</sup>).

#### Example B26

[0183] Using a procedure analogous to Example B27, 2-tert-butyl-4-chloropyrimidine-5-carboxylate from Example B27 (0.30 g, 1.24 mmol) and tert-butyl piperazine-1-carboxylate (1.15 g, 6.18 mmol) in presence of NMP (catalytic amount) were combined to afford 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-tert-butylpyrimidine-5-carboxylic acid (0.36 g, 80% yield). MS (ESI) m/z: 365.0 (M+H<sup>+</sup>).

#### Example B27

[0184] In ethanol (40 mL) was placed t-butylcarbamidine hydrochloride (3.71 g, 27.2 mmol). This was treated with 21% sodium ethoxide in ethanol (8.80 g, 27.2 mmol) and stirred at RT for 15 min. To this was added the diethyl ethoxymethylenemalonate (5.87 g, 27.2 mmol) and the reaction mixture was stirred overnight at RT. The reaction mixture was refluxed for 1 hour and then cooled to RT. The solution was evaporated, the residue dissolved in water (100 mL) and the pH adjusted to 3-4 (wet litmus) with acetic acid. The mixture formed a precipitate. The solid collected by filtration, washed with water (50 mL) and dried in vacuo to obtain ethyl 2-tert-butyl-4-hydroxypyrimidine-5-carboxylate (2.18 g, 36% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.6 (brs, 1H), 8.44 (s, 1H), 4.20 (q, J=7.2 Hz, 2H), 1.25 (s, 9H), 1.23 (t, J=7.2 Hz, 3H); MS (ESI) m/z: 225.0 (M+H<sup>+</sup>).

[0185] In cold (~0° C.) POCl<sub>3</sub> (20 mL) was dropped triethylamine (0.55 mL) with stirring. To this was added in parts ethyl 2-tert-butyl-4-hydroxypyrimidine-5-carboxylate (2.18 g, 9.72 mmol). The mixture then warmed to 40° C. and stirred under Argon for 1 hour. The mixture was evaporated until free of POCl<sub>3</sub>, diluted with CHCl<sub>3</sub> (100 mL) and poured carefully into ice (300 mL). The solution was stirred until it reached RT. The organic phase was separated, washed with sodium bicarbonate (100 mL), water (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to give ethyl 2-tert-butyl-4-chloropyrimidine-5-carboxylate (2.0 g, 85% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.12 (s, 1H), 4.34 (q, J=6.8 Hz, 2H), 1.33 (s, 9H), 1.27 (t, J=6.8 Hz, 3H); MS (ESI) m/z: 243.0 (M+H<sup>+</sup>).

[0186] To a solution of ethyl 2-tert-butyl-4-chloropyrimidine-5-carboxylate (0.30 g, 1.24 mmol) in NMP (3 mL) was added morpholine (0.54 g, 6.16 mmol) and it was heated at 80° C. for 1.5 hour. The reaction was checked by LC-MS, water was added and the solution was extracted with ethyl acetate (3x). The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent was removed to obtain tert-butyl 4-(5-(3-tert-butyl-5-(ethoxycarbonyl)-1H-pyrazol-1-yl)pyridin-2-yl)piperazine-1-carboxylate. MS (ESI) m/z: 294.0 (M+H<sup>+</sup>).

[0187] To a stirring suspension of ethyl 2-tert-butyl-4-morpholinopyrimidine-5-carboxylate (0.36 g, 1.24 mmol) in 1:1 THF/EtOH/H<sub>2</sub>O (9 ml) at RT was added LiOH·H<sub>2</sub>O (130 mg, 4.95 mmol) and the mixture was stirred overnight at RT. The reaction mixture was checked by LC-MS and the completed reaction was concentrated to an aqueous residue, acidified (pH 3-4) with 3M HCl and the solution was extracted with EtOAc (3x). The combined organics were washed with brine (1x), dried (MgSO<sub>4</sub>), filtered and concen-

trated in vacuo. The crude was dissolved in isopropanol and the solids (LiCl and NaCl) were filtered and washed with isopropanol. The filtrate was concentrated to obtain the desired product, 2-tert-butyl-4-morpholinopyrimidine-5-carboxylic acid (0.15 g, 46% yield). MS (ESI) m/z: 266.0 (M+H<sup>+</sup>).

#### Example B28

[0188] 3-Nitro-5-(trifluoromethyl)pyridin-2-ol (6.80 g, 32.7 mmol) and quinoline (2.72 g, 21.06 mmol) were combined in a 200 mL round-bottom flask with an oversized magnetic stir bar. The assembly was cooled with an RT water bath. Phosphorus oxychloride (4.07 mL, 43.7 mmol) was cautiously added with vigorous stirring. After 5 min, the resulting gel would no longer stir. The apparatus was equipped with a reflux condenser and was transferred to a 120° C. oil bath. The gel quickly melted and stirring resumed with gentle refluxing. After 3 h, the mixture was cooled to RT and added portion-wise to ice water with vigorous stirring. Sodium hydroxide was added to adjust the alkalinity to pH 8-9 and the mixture was extracted with EtOAc (2×100 mL) and CH<sub>2</sub>Cl<sub>2</sub> (2×100 mL). The combined organics were dried (MgSO<sub>4</sub>), concentrated in vacuo and purified via chromatography on silica gel (EtOAc—CH<sub>2</sub>Cl<sub>2</sub>) to provide 2-chloro-3-nitro-5-(trifluoromethyl)pyridine (6.65 g, 90% yield) as a yellow liquid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.21 (m, 1H), 9.09 (m, 1H). [0189] 2-Chloro-3-nitro-5-(trifluoromethyl)pyridine (406 mg, 1.79 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (559 mg, 2.69 mmol), cesium carbonate (1752 mg, 5.38 mmol) and palladium tetrakis (207 mg, 0.179 mmol) were combined in DMF (3 mL) and water (1 mL). The headspace was evacuated and back-filled with nitrogen (4x). The mixture was heated to 90° C. overnight. The mixture was poured into EtOAc (40 mL) and washed with water (3×20 mL) and satd brine (3×20 mL). The organics were concentrated in vacuo and purified by silica gel chromatography to provide 2-(1-methyl-1H-pyrazol-4-yl)-5-(trifluoromethyl)pyridin-3-amine (21 mg, 5% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.29 (s, 1H), 8.13 (br s, 1H), 7.98 (s, 1H), 7.40 (d, J=2.0 Hz, 1H), 5.55 (s, 2H), 3.91 (s, 3H); MS (ESI): m/z 473.0 (M+H<sup>+</sup>).

#### Example 1

[0190] Using General Method A, Example B1 (0.072 g, 0.23 mmol) and Example A1 (0.062 g, 0.22 mmol) were combined and the resultant product purified via column chromatography to yield 1-(3-t-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, which was converted to corresponding mesylate salt (0.0685 g, 57% yield) by reacting with methanesulfonic acid (1.0 eq). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 10.4 (s, 1H), 8.89 (s, 1H), 8.59-8.57 (m, 2H), 8.24-8.20 (m, 2H), 7.65 (s, 1H), 7.45 (dd, J=11.6, 2.4 Hz, 1H), 7.17 (dd, J=8.8, 1.2 Hz, 1H), 7.12 (d, J=4.8 Hz, 1H), 6.09 (s, 1H), 3.93 (s, 3H), 2.33 (s, 3H), 1.26 (s, 9H); MS (ESI) m/z: 451.2 (M+H<sup>+</sup>).

#### Example 2

[0191] Using general method C, Example B2 (0.0712 g, 0.30 mmol) and Example A1 (0.0853 g, 0.30 mmol) were combined and the resultant product purified via column chromatography to yield 1-(3-t-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.139 g, 100% yield) as a white foam. <sup>1</sup>H

NMR (DMSO-d<sub>6</sub>): δ 8.99-8.95 (m, 2H), 8.58-8.56 (m, 2H), 8.28-8.23 (m, 2H), 7.65 (s, 1H), 7.42 (dd, J=11.6, 2.4 Hz, 1H), 7.14-7.11 (m, 2H), 3.91 (s, 3H), 3.61 (s, 3H), 2.32 (s, 3H), 1.20 (s, 9H); MS (ESI) m/z: 464.2 (M+H<sup>+</sup>).

#### Example 3

[0192] In THF (10 mL) was placed Example A1 (87 mg, 0.31 mmol) and 3-trifluoromethylphenylisocyanate (60 mg, 0.32 mmol). The mixture was stirred overnight at RT. Hexane was added and then the solution was stirred for 1 h. The solid was filtered and dried under vacuum to obtain 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (126 mg, 88% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.39 (s, 1H), 8.68 (d, J=2.0 Hz, 1H), 8.36 (d, J=5.6 Hz, 1H), 8.25 (s, 1H), 8.15 (t, J=8.8 Hz, 1H), 8.08 (s, 1H), 7.96 (s, 1H), 7.51 (m, 2H), 7.32 (m, 1H), 7.26 (dd, J=2.8, and 12.0 Hz, 1H), 7.23 (d, J=2.4 Hz, 1H), 7.01 (dt, J=1.2, and 8.8 Hz, 1H), 6.67 (dd, J=2.4, and 5.6 Hz, 1H), 3.84 (s, 3H); LC-MS (EI) m/z: 472.0 (M+H<sup>+</sup>).

#### Example 4

[0193] Using general method B, 5-t-butylisoxazol-3-amine (60 mg, 0.27 mmol) and Example A1 (76 mg, 0.27 mmol) were combined and the resultant product purified via column chromatography to yield 1-(5-t-butylisoxazol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (40 mg, 38% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.83 (s, 1H), 8.83 (br s, 1H), 8.36 (d, J=5.6 Hz, 1H), 8.25 (s, 1H), 8.15 (t, J=9.2 Hz, 1H), 7.96 (s, 1H), 7.27 (dd, J=2.8, and 11.6 Hz, 1H), 7.22 (d, J=2.4 Hz, 1H), 7.01 (m, 1H), 6.67 (dd, J=2.8, and 6.0 Hz, 1H), 6.47 (s, 1H), 3.84 (s, 3H), 1.28 (s, 9H); LC-MS (EI) m/z: 451.2 (M+H<sup>+</sup>).

#### Example 5

[0194] Using General Method B, Example B3 (0.061 g, 0.27 mmol), and Example A1 (0.078, 0.27 mmol) were combined and the resultant product purified via column chromatography to yield 1-(1-t-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (42 mg, 34% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.71 (s, 1H), 8.62 (s, 1H), 8.54-8.52 (m, 2H), 8.26 (t, J=9.2 Hz, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.58 (brs, 1H), 7.42 (s, 1H), 7.37-7.34 (m, 1H), 7.09-7.06 (m, 2H), 3.90 (s, 3H), 2.28 (s, 3H), 1.47 (s, 9H); MS (ESI) m/z: 450.2 (M+H<sup>+</sup>).

#### Example 6

[0195] Using General Method A and purification via chromatography (ethyl acetate/hexane), 3-trifluoromethyl-5-aminopyridine (250 mg, 1.54 mmol) was converted to 2,2,2-trichloroethyl 5-(trifluoromethyl)pyridin-3-ylcarbamate (215 mg, 41% yield) and isolated as a thick oil. MS (ESI) m/z: 339.0 (M+H<sup>+</sup>).

[0196] Using General Method A, 2,2,2-trichloroethyl 5-(trifluoromethyl)pyridin-3-ylcarbamate (215 mg, 0.637 mmol) and Example A2 (170 mg, 0.637 mmol) were combined and purified by reverse phase chromatography (C18-25 column, acetonitrile/water/0.1% TFA) to give a foam. The residue was treated with 10% potassium carbonate (2 mL) and the mix extracted with ethyl acetate (2×25 mL). The combined organic phases were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo to afford 1-(4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-(trifluoromethyl)pyridin-3-yl)urea (140 mg, 41% yield).

luoromethyl)pyridin-3-yl)urea (121 mg, 41% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 3.84 (s, 3H), 6.58-6.60 (m, 1H), 7.13 (d, 2H), 7.20 (s, 1H), 7.57 (d, 2H), 7.94 (s, 1H), 8.23 (s, 1H), 8.33 (d, 1H), 8.42 (s, 1H), 8.54 (s, 1H), 8.78 (s, 1H), 9.13 (s, 1H), 9.29 (s, 1H); MS (ESI) m/z: 455.3 (M+H<sup>+</sup>).

#### Example 7

[0197] Using General Method B, the prop-1-en-2-yl carbamate of Example B4 (60 mg, 0.25 mmol) and Example A1 (72 mg, 0.25 mmol) in presence of N-methylpyrrolidine (catalytic amount) were combined and the resultant product purified via tituration with methylene chloride and filtration to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(trifluoromethyl)isoxazol-5-yl)urea (80 mg, 68% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 11.0 (s, 1H), 8.90 (brs, 1H), 8.36 (d, J=6.0 Hz, 1H), 8.24 (s, 1H), 8.04 (t, J=9.2 Hz, 1H), 7.94 (s, 1H), 7.28 (dd, J=2.8, and 11.6 Hz, 1H), 7.23 (d, J=2.4 Hz, 1H), 7.03 (m, 1H), 6.67 (dd, J=2.4, and 5.6 Hz, 1H), 6.49 (s, 1H), 3.83 (s, 3H); MS (ESI) m/z: 463.0 (M+H<sup>+</sup>).

#### Example 8

[0198] Prop-1-en-2-yl 1-tert-butyl-1H-pyrazol-4-ylcarbamate (0.074 g, 0.331 mmol), synthesized from Example B3 using General Method E, was reacted with Example A9 (0.100 g, 0.331 mmol) in presence of N-methylpyrrolidine (0.005 g, 0.06 mmol) in dioxane (2 ml) at 80° C. for 15 hours. The completed reaction was concentrated in vacuo and purified via recrystallization (hexanes/ethyl acetate) to provide 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.102 g, 66% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.71 (brs, 1H), 8.69 (s, 1H), 8.34 (d, J=6 Hz, 1H), 8.24 (s, 1H), 7.97 (m, 1H), 7.95 (s, 1H), 7.79 (s, 1H), 7.40 (s, 1H), 7.23 (d, J=2.2 Hz, 1H), 7.12 (m, 1H), 6.69 (dd, J=5.5, 2.5 Hz, 1H), 3.82 (s, 3H), 1.45 (s, 9H); MS (ESI) m/z: 468.0 (MAl).

#### Example 9

[0199] Using general method C, Example B5 (60 mg, 0.25 mmol) and Example A1 (72 mg, 0.25 mmol) in presence of DPPA (60 μL, 0.25 mmol) and (39 μL, 0.25 mmol) were combined and the resultant product purified via column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 1-(1-tert-butyl-5-(trifluoromethyl)-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (75 mg, 57% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.10 (brs, 1H), 8.53 (s, 1H), 8.35 (d, J=6.0 Hz, 1H), 8.24 (s, 1H), 8.18 (t, J=8.8 Hz, 1H), 7.94 (m, 2H), 7.24 (dd, J=2.4, and 11.6 Hz, 1H), 7.20 (d, J=2.4 Hz, 1H), 6.98 (m, 1H), 6.66 (dd, J=2.4, and 5.6 Hz, 1H), 3.83 (s, 3H), 1.57 (s, 9H); MS (ESI) m/z: 518.0 (M+H<sup>+</sup>).

#### Example 10

[0200] Using General Method C, Example B6 (50 mg, 0.27 mmol) and Example A1 (78 mg, 0.27 mmol) in presence of DPPA (65 μL, 0.27 mmol) and (42 μL, 0.27 mmol) were combined and the resultant product purified via column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 1-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (55 mg, 43% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.57 (brs, 1H), 8.35 (d, J=5.6 Hz, 1H), 8.25 (s, 1H), 8.20 (t, J=9.2 Hz, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.44 (s, 1H), 7.22 (m, 2H), 6.97 (m, 1H),

6.66 (dd, J=2.4, and 5.6 Hz, 1H), 3.84 (s, 3H), 2.31 (s, 3H), 1.54 (s, 9H); MS (ESI) m/z: 464.2 (M+H<sup>+</sup>).

#### Example 11

[0201] Using general method D, 2-amino-5-t-butyl-1,3,4-thiadiazole (0.5000 g, 3.2 mmol) was converted to prop-1-en-2-yl 5-tert-butyl-1,3,4-thiadiazol-2-ylcarbamate (0.73 g, 95% yield) as a beige solid which was used as is in the next reaction. <sup>1</sup>H NMR (400 MHz, acetone-d<sub>6</sub>): δ 4.77-4.66 (m, 2H), 1.95 (s, 3H), 1.38 (s, 9H); MS (ESI) m/z: 242.3 (M+H<sup>+</sup>).

[0202] Prop-1-en-2-yl 5-tert-butyl-1,3,4-thiadiazol-2-ylcarbamate (60 mg, 0.249 mmol), Example A1 (70.7 mg, 0.249 mmol), and 1-methylpyrrolidine (1.293 μL, 0.012 mmol) were combined in THF (2.5 ml) and stirred with heating at 70° C. overnight in a sealed screw-cap vial. The completed reaction was cooled to RT and purified directly by reverse phase chromatography to afford 1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (84 mg, 72% yield) as an off-white solid following lyophilization. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.04 (brs, 1H), 8.54-8.52 (m, 1H), 8.48 (brs, 1H), 8.2-8.16 (m, 2H), 7.54 (brs, 1H), 7.44-7.40 (m, 1H), 7.15-7.13 (m, 1H), 7.01-7.00 (m, 1H), 3.91 (s, 3H), 1.39 (s, 9H); MS (ESI) m/z: 438.0 (M+H<sup>+</sup>).

#### Example 12

[0203] Using General Method C, Example B8 (0.15 g, 0.63 mmol), Example A1 (0.15 g, 0.53 mmol) in presence of triethylamine (0.16 g, 1.58 mmol) and DPPA (0.29 g, 1.05 mmol) were combined to afford 1-(3-tert-butyl-1-(2-(dimethylamino)ethyl)-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.085 g, 31% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.23 (s, 1H), 9.07 (s, 1H), 8.41 (d, J=5.6 Hz, 1H), 8.29 (s, 1H), 8.15 (t, J=9.2 Hz, 1H), 8.00 (s, 1H), 7.31-7.27 (m, 2H), 7.04 (dt, J=9.2 Hz, 1.2 Hz, 1H), 6.71 (dd, J=5.6 Hz, 2.0 Hz, 1H), 6.11 (s, 1H), 4.03 (t, J=6.8 Hz, 2H), 3.89 (s, 3H), 2.61 (t, J=6.8 Hz, 2H), 2.60 (s, 6H), 1.24 (s, 9H); MS (ESI) m/z: 521.3 (M+H<sup>+</sup>).

#### Example 13

[0204] Using General Method B, the prop-1-en-2-yl carbamate of Example B7 (60 mg, 0.24 mmol) and Example A1 (68 mg, 0.24 mmol) in presence of N-methylpyrrolidine (catalytic amount) were combined and the resultant product purified via tituration with CH<sub>2</sub>Cl<sub>2</sub> and filtration to afford 1-(3-cyclopentylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (71 mg, 62% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.3 (s, 1H), 8.77 (brs, 1H), 8.37 (d, J=6.0 Hz, 1H), 8.26 (s, 1H), 8.11 (t, J=8.8 Hz, 1H), 7.96 (s, 1H), 7.28 (dd, J=2.4, and 11.6 Hz, 1H), 7.24 (d, J=2.4 Hz, 1H), 7.03 (m, 1H), 6.68 (dd, J=2.4, and 5.6 Hz, 1H), 6.02 (s, 1H), 3.85 (s, 3H), 1.95 (m, 2H), 1.62 (m, 6H), 1.26 (s, 3H); MS (ESI) m/z: 477.0 (M+H<sup>+</sup>).

#### Example 14

[0205] Using general method B, the prop-1-en-2-yl carbamate of Example B10 (60 mg, 0.25 mmol) and Example A1 (72 mg, 0.25 mmol) in presence of N-methylpyrrolidine (catalytic amount) were combined and the resultant product purified via tituration with CH<sub>2</sub>Cl<sub>2</sub> and filtration to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-methylcyclopentyl)isoxazol-5-yl)

urea (68 mg, 58% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  10.3 (s, 1H), 8.78 (brs, 1H), 8.37 (d, J=5.6 Hz, 1H), 8.26 (s, 1H), 8.11 (t, J=9.2 Hz, 1H), 7.96 (s, 1H), 7.28 (dd, J=2.8, and 12.0 Hz, 1H), 7.24 (d, J=2.4 Hz, 1H), 7.03 (m, 1H), 6.68 (dd, J=2.8, and 6.0 Hz, 1H), 5.98 (s, 1H), 3.85 (s, 3H), 3.02 (m, 1H), 1.95 (m, 2H), 1.62 (m, 6H); MS (ESI) m/z: 463.0 (M+H<sup>+</sup>).

#### Example 15

[0206] Using General Method C, Example B11 (60 mg, 0.33 mmol) and Example A1 (95 mg, 0.33 mmol) in presence of DPPA (79  $\mu\text{L}$ , 0.33 mmol) and (51  $\mu\text{L}$ , 0.33 mmol) were combined and the resultant product purified via column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 1-(1-cyclopentyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (53 mg, 34% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.70 (s, 1H), 8.51 (d, J=2.0 Hz, 1H), 8.37 (d, J=5.6 Hz, 1H), 8.26 (s, 1H), 8.18 (t, J=8.8 Hz, 1H), 7.96 (s, 1H), 7.78 (s, 1H), 7.22 (m, 2H), 6.99 (m, 1H), 6.67 (dd, J=2.4, and 5.6 Hz, 1H), 4.62 (m, 1H), 3.86 (s, 3H), 2.03 (m, 2H), 1.87 (m, 2H), 1.76 (m, 2H), 1.61 (m, 2H); MS (ESI) m/z: 462.3 (M+H<sup>+</sup>).

#### Example 16

[0207] Using General Method D, Example B12 (0.20 g, 1.2 mmol) and isopropenyl chloroformate (0.15 mL) in presence of LiHMDS (1.0M, 2.5 mL) were combined to afford prop-1-en-2-yl 1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-ylcarbamate (0.2 g, 67% yield). MS (ESI) m/z: 250.0 (M+H<sup>+</sup>).

[0208] Using General Method D, prop-1-en-2-yl 1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-ylcarbamate (60 mg, 0.24 mmol) and Example A1 (68 mg, 0.24 mmol) in presence of N-methylpyrrolidine (catalytic amount) were combined and the resultant product purified via titration with CH<sub>2</sub>Cl<sub>2</sub> and filtration to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)urea (51 mg, 45% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.30 (s, 1H), 8.99 (d, J=2.4 Hz, 1H), 8.38 (d, J=5.6 Hz, 1H), 8.27 (s, 1H), 8.16 (t, J=9.2 Hz, 1H), 7.97 (s, 1H), 7.29 (dd, J=2.4, and 11.6 Hz, 1H), 7.24 (d, J=2.4 Hz, 1H), 7.04 (m, 1H), 6.69 (dd, J=2.4, and 5.6 Hz, 1H), 6.63 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H); MS (ESI) m/z: 476.0 (M+H<sup>+</sup>).

#### Example 17

[0209] The prop-1-en-2-yl carbamate of Example B3 (0.075 g, 0.335 mmol), prepared using General Method E, was reacted with Example A4 (0.1 g, 0.335 mmol) in presence of N-methylpyrrolidine (0.006 g, 0.06 mmol) in dioxane (2 ml) at 80° C. for 15 hours. The completed reaction was concentrated in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate) to provide 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.115 g, 74% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.74 (s, 1H), 8.52 (brs, 1H), 8.39 (d, J=6 Hz, 1H), 8.29 (s, 1H), 8.07 (t, J=9 Hz, 1H), 7.98 (s, 1H), 7.84 (s, 1H), 7.45 (s, 1H), 7.20 (d, J=2.3 Hz, 1H), 6.96 (m, 1H), 6.58 (dd, J=5.5, 2.5 Hz, 1H), 3.88 (s, 3H), 2.08 (brs, 3H), 1.52 (s, 9H); MS (ESI) m/z: 464.2 (M+H<sup>+</sup>).

#### Example 18

[0210] Using General Method C, Example B13 (100 mg, 0.450 mmol), triethylamine (52 mg, 0.518 mmol), Example

A1 (128 mg, 0.450 mmol) and DPPA (142 mg, 0.518 mmol) were combined, purified by reverse phase chromatography (C18-25 column, acetonitrile/water), treated with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (2x20 mL). The combined organic phases washed with brine (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo, dissolved in acetonitrile/water and lyophilized to give 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-isopropyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)urea (112 mg, 49% yield).  $^1\text{H}$  NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  1.48 (d, 6H), 3.92 (s, 3H), 4.63 (hp, 1H), 6.73-6.75 (m, 1H), 7.06-7.08 (m, 1H), 7.29 (s, 1H), 7.29-7.34 (m, 1H), 8.03 (s, 1H), 8.27-8.32 (m, 3H), 8.40-8.44 (m, 1H), 8.73 (s, 1H), 9.15 (s, 1H); MS (ESI) m/z: 504.0 (MAI).

#### Example 19

[0211] Using General Method C, Example B14 (150 mg, 0.892 mmol), triethylamine (104 mg, 1.026 mmol), Example A1 (254 mg, 0.892 mmol) and DPPA (282 mg, 1.026 mmol) were combined and purified by chromatography (methanol/dichloromethane) to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-isopropyl-5-methyl-1H-pyrazol-4-yl)urea (98 mg, 24% yield) as a foam.  $^1\text{H}$  NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  1.44 (d, 6H), 2.29 (s, 3H), 4.00 (s, 3H), 4.56 (hp, 1H), 7.10 (br s, 1H), 7.15-7.18 (m, 1H), 7.43-7.46 (m, 1H), 7.62 (s, 2H), 8.30 (br s, 1H), 8.38 (t, 1H), 8.44 (s, 1H), 8.58-8.62 (m, 2H), 8.78 (br s, 1H); MS (ESI) m/z: 450.2 (M+H<sup>+</sup>).

#### Example 20

[0212] Using General Method C, Example B15 (62 mg, 0.369 mmol), triethylamine (43 mg, 0.424 mmol), Example A1 (105 mg, 0.369 mmol) and DPPA (117 mg, 0.424 mmol) were combined and purified by column chromatography (methanol/dichloromethane) to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-isopropyl-3-methyl-1H-pyrazol-4-yl)urea (88 mg, 53% yield) as a foam.  $^1\text{H}$  NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  1.46 (d, 6H), 2.22 (s, 3H), 3.98 (s, 3H), 4.45 (hp, 1H), 6.89 (br s, 1H), 7.11-7.14 (m, 1H), 7.37-7.41 (m, 1H), 7.44 (br s, 1H), 7.88 (s, 1H), 8.15 (br s, 1H), 8.37 (t, 1H), 8.44-8.53 (m, 3H), 8.77 (s, 1H); MS (ESI) m/z: 450.2 (M+H<sup>+</sup>).

#### Example 21

[0213] A mixture of Example A1 (2.0 g, 7.04 mmol) and saturated aq NaHCO<sub>3</sub> (100 mL) in EtOAc (100 mL) was cooled in an ice bath and treated with isopropenyl chloroformate (1.6 mL, 14.64 mmol). The reaction mixture was allowed to slowly warm to RT overnight. The organic layer was separated and washed with sat aq NaHCO<sub>3</sub> (25 mL) and brine (25 mL), dried (MgSO<sub>4</sub>), concentrated in vacuo and was re-crystallized (diethyl ether) to provide prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate (2.32 g, 90% yield).  $^1\text{H}$  NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.69 (br s, 1H), 8.38 (d, J=5.6 Hz, 1H), 8.26 (s, 1H), 7.96 (d, J=0.8 Hz, 1H), 7.67 (br t, J=8.4 Hz, 1H), 7.27 (d, J=2.4 Hz, 1H), 7.22 (dd, J=11.2, 2.4 Hz, 1H), 7.00 (m, 1H), 6.69 (dd, J=5.6, 2.4 Hz, 1H), 4.74 (m, 1H), 4.72 (s, 1H), 3.84 (s, 3H), 1.92 (s, 3H); MS (ESI) m/z: 369.1 (M+H<sup>+</sup>).

#### Example B16

[0214] (81 mg, 0.500 mmol), prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbam-

ate (180 mg, 0.489 mmol) and N-methylpyrrolidine (4.25 mg, 0.050 mmol) were combined in THF (1 mL) and heated to 55° C. for 48 h. The reaction mixture was concentrated in vacuo and purified by silica gel chromatography to provide 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-(trifluoromethyl)pyridin-3-yl)urea (168 mg, 72% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 9.60 (s, 1H), 8.89 (d, J=1.7 Hz, 1H), 8.77 (d, J=2.4 Hz, 1H), 8.59 (d, J=1.0 Hz, 1H), 8.46 (t, J=2.0 Hz, 1H), 8.39 (d, J=5.8 Hz, 1H), 8.27 (s, 1H), 8.13 (t, J=9.0 Hz, 1H), 7.98 (s, 1H), 7.29 (dd, J=11.8, 2.6 Hz, 1H), 7.26 (d, J=2.5 Hz, 1H), 7.05 (m, 1H), 6.70 (dd, J=5.6, 2.2 Hz, 1H), 3.86 (s, 3H); MS (ESI): m/z 473.0 (M+H<sup>+</sup>).

#### Example 22

[0215] Using General Method F, Example B17 (0.453 g, 2.48 mmol) was converted to prop-1-en-2-yl5-isopropylpyridin-3-ylcarbamate (0.185 g, 34%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.10 (s, 1H), 8.44 (d, J=2.4 Hz, 1H), 8.16 (d, J=2.0 Hz, 1H), 7.84 (s, 1H), 4.77 (t, J=1.2 Hz, 1H), 4.74 (s, 1H), 2.91 (m, 1H), 1.94 (d, J=0.8 Hz, 3H), 1.21 (d, J=6.8 Hz, 6H); MS (ESI) m/z: 221.1 (M+H<sup>+</sup>).

[0216] Prop-1-en-2-yl 5-isopropylpyridin-3-ylcarbamate (0.053 g, 0.24 mmol), Example A1 (0.068 g, 0.238 mmol) and N-methylpyrrolidine (0.0020 g, 0.024 mmol) were combined in THF (1.0 mL). The mixture was heated at 55° C. for 12 h. Solvent was removed and the residue was purified by chromatography to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea (0.0648 g, 61% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.23 (s, 1H), 8.75 (d, J=2.0 Hz, 1H), 8.45 (d, J=2.0 Hz, 1H), 8.42 (d, J=4.8 Hz, 1H), 8.31 (s, 1H), 8.22 (t, J=8.8 Hz, 1H), 8.18 (d, J=1.6 Hz, 1H), 8.02 (s, 1H), 7.90 (t, J=1.8 Hz, 1H), 7.32 (dd, J=12.0, 2.8 Hz, 1H), 7.29 (d, J=2.0 Hz, 1H), 7.06 (m, 1H), 6.73 (dd, J=5.6, 2.4 Hz, 1H), 3.90 (s, 3H), 2.97 (m, 1H), 1.27 (d, J=6.8 Hz, 6H); MS (ESI) m/z: 447.3 (M+H<sup>+</sup>).

#### Example 23

[0217] Using General Method C, Example B18 0.133 g, 0.686 mmol), triethylamine (0.139 g, 1.372 mmol), DPPA (0.189 g, 0.686 mmol) and Example A1 (0.130 g, 0.457 mmol) were combined and the residue purified via recrystallization (acetonitrile) to afford 1-(1-cyclopentyl-5-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.11 g, 50.6% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 8.72 (s, 1H), 8.45 (m, 2H), 8.33 (m, 2H), 8.05 (s, 1H), 7.86 (s, 1H), 7.32 (m, 2H), 7.07 (m, 1H), 6.75 (dd, J=6, 2.5 Hz, 1H), 4.56 (m, 1H), 3.94 (s, 3H), 2.19 (s, 3H), 2.09-1.59 (m, 8H); MS (ESI) m/z: 476.2 (M+H<sup>+</sup>).

#### Example 24

[0218] Using General Method A, benzo[d]isoxazol-3-amine (500 mg, 3.37 mmol) and Troc-Cl (1.185 g, 5.59 mmol) were combined, purified by column chromatography (ethyl acetate/hexanes), triturated with hexanes (30 mL), filtered and dried to afford 2,2,2-trichloroethyl benzo[d]isoxazol-3-ylcarbamate. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 5.15 (s, 2H), 7.50 (t, 1H), 7.77-7.83 (m, 2H), 8.16 (d, 1H), 11.51 (s, 1H); MS (ESI) m/z: 310.9 (M+H<sup>+</sup>).

[0219] Using General Method A, 2,2,2-trichloroethyl benzo[d]isoxazol-3-ylcarbamate (109 mg, 0.352 mmol) and

Example A1 (100 mg, 0.352 mmol) were combined and purified by normal phase chromatography (methanol/dichloromethane) and reverse phase chromatography (acetonitrile/water) to give a white solid. The solid was slurried in saturated sodium bicarbonate (4 mL)/ethyl acetate (15 mL), filtered, washed with water (5 mL) and ethyl acetate (5 mL) and dried to afford 1-(benzo[d]isoxazol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (17 mg, 10% yield). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 3.96 (s, 3H), 6.85 (br s, 1H), 7.21-7.25 (m, 1H), 7.37-7.54 (m, 3H), 7.80 (br s, 2H), 8.11 (br s, 1H), 8.29-8.41 (m, 3H), 8.52 (br s, 1H), 9.56 (br s, 1H), 10.64 (br s, 1H); MS (ESI) m/z: 445.1 (M+H<sup>+</sup>).

#### Example 25

[0220] 2,2,2-trichloroethyl 3-tert-butylisoxazol-5-ylcarbamate (0.125 g, 0.397 mmol), synthesized according to General Method A from Example B1, was reacted with Example A3 (0.100 g, 0.331 mmol) in dioxane (2 ml) in presence of N-methylpyrrolidine (0.028 g, 0.331 mmol) at 80° C. for 13 hours. The reaction mixture was concentrated in vacuo and the residue purified via recrystallization (methanol) to provide 1-(3-tert-butylisoxazol-5-yl)-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.043 g, 28% yield) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 10.54 (s, 1H), 9.10 (s, 1H), 8.52 (d, J=6 Hz, 1H), 8.42 (s, 1H), 8.12 (s, 1H), 8.06 (m, 1H), 7.41 (brs, 1H), 7.35 (m, 1H), 6.87 (dd, J=6, 2.5 Hz, 1H), 6.20 (s, 1H), 3.98 (s, 3H), 1.38 (s, 9H); MS (ESI) m/z: 469.1 (M+H<sup>+</sup>).

#### Example 26

[0221] Using General Method C, Example B19 (50 mg, 0.30 mmol) and Example A1 (84 mg, 0.30 mmol) in presence of DPPA (70  $\mu$ L, 0.30 mmol) and (45  $\mu$ L, 0.30 mmol) were combined and the resultant product purified via column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to afford 1-(2-tert-butyloxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (22 mg, 17% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 9.33 (s, 1H), 8.65 (brs, 1H), 8.36 (brd, J=5.6 Hz, 1H), 8.25 (s, 1H), 8.18 (brt, J=9.2 Hz, 1H), 7.95 (s, 1H), 7.75 (s, 2H), 7.24 (m, 1H), 7.21 (s, 1H), 6.99 (m, 1H), 6.67 (m, 1H), 3.84 (s, 3H), 1.30 (s, 9H); MS (ESI) m/z: 451.2 (M+H<sup>+</sup>).

#### Example 27

[0222] 3-Amino-5-(trifluoromethyl)pyridin-2(1H)-one (44 mg, 0.247 mmol), prop-1-en-2-yl2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate from Example 21 (85 mg, 0.231 mmol) and N-methylpyrrolidine (7.5 mg, 0.088 mmol) were combined in 1,4-dioxane (0.8 mL). The resultant mixture was heated to 80° C. After 13 h, the mixture was cooled to RT and diluted with ethyl acetate (3 mL). The resultant precipitate was collected by filtration, washed with ethyl acetate and dried in vacuo to provide 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-oxo-5-(trifluoromethyl)-1,2-dihydropyridin-3-yl)urea as an off-white solid (65 mg, 58% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.47 (s, 1H), 9.56 (s, 1H), 9.35 (s, 1H), 8.36 (d, J=5.3 Hz, 1H), 8.25 (br s, 2H), 8.17 (t,

$J=9.4$  Hz, 1H), 7.96 (s, 1H), 7.59 (s, 1H), 7.25-7.22 (m, 2H), 7.00 (d,  $J=8.5$  Hz, 1H), 6.68 (m, 1H), 3.84 (s, 3H); MS (ESI) m/z: 489.1 ( $M+H^+$ ).

#### Example 28

[0223] To a solution of 5-tert-butyl-2-methylfuran-3-carbonyl chloride (0.341 g, 1.699 mmol) in THF (2 mL) added lithium hydroxide (0.107 g, 2.55 mmol) in water (1 mL) and the mixture was stirred for 2 h at RT. Solvent was removed in vacuo and the residue was acidified with 2N HCl to afford solid which was filtered and air dried to afford 5-tert-butyl-2-methylfuran-3-carboxylic acid (0.29 g, 94% yield) as a white solid. MS (ESI) m/z: 183.1 ( $M+H^+$ ).

[0224] Using General Method C 5-tert-butyl-2-methylfuran-3-carboxylic acid (0.07 g, 0.37 mmol), Example A1 (0.07 g, 0.25 mmol), triethylamine (0.07 g, 0.75 mmol) and DPPA (0.13 g, 0.5 mmol) were combined to afford 1-(5-tert-butyl-2-methylfuran-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.065 g, 56% yield) as a white solid.  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.60 (s, 1H), 8.36-8.34 (m, 2H), 8.24 (s, 1H), 8.17 (t,  $J=9.2$  Hz, 1H), 7.95 (s, 1H), 7.23-7.20 (m, 2H), 6.96 (dd,  $J=8.8$  Hz, 2.4 Hz, 1H), 6.65 (dd,  $J=5.6$  Hz, 2.4 Hz, 1H), 6.26 (s, 1H), 3.84 (s, 3H), 2.16 (s, 3H), 1.19 (s, 9H); MS (ESI) m/z: 464.2 ( $M+H^+$ ).

#### Example 29

[0225] Using General Method B, 6-fluorobenzo[d]thiazol-2-amine (2.00 g, 11.89 mmol) was converted to prop-1-en-2-yl 6-fluorobenzo[d]thiazol-2-ylcarbamate (2.00 g, 67% yield) as a white solid.  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  12.33 (s, 1H), 7.86 (dd,  $J=9$ , 3 Hz, 1H), 7.69 (dd,  $J=9$ , 5 Hz, 1H), 7.24 (dt,  $J=9$ , 2.5 Hz, 1H), 4.84 (s, 1H), 4.80 (s, 3H), 1.94 (s, 3H); MS (ESI) m/z: 253.1 ( $M+H^+$ ).

[0226] Prop-1-en-2-yl 6-fluorobenzo[d]thiazol-2-ylcarbamate (0.060 g, 0.238 mmol) was reacted with Example A1 (0.068 g, 0.238 mmol) in the presence of a catalytic amount of N-methylpyrrolidine in dioxane (5 mL) at 70° C. for 3 hours. The reaction mixture was cooled and the product filtered, washed and dried to provide 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-fluorobenzo[d]thiazol-2-yl)urea (0.08 g, 70% yield) as a white solid.  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  11.03 (s, 1H), 9.15 (s, 1H), 8.38 (d,  $J=6$  Hz, 1H), 8.26 (s, 1H), 8.15 (t,  $J=9$  Hz, 1H), 7.96 (s, 1H), 7.85 (dd,  $J=9$ , 2.5 Hz, 1H), 7.68 (m, 1H), 7.31 (dd,  $J=12$ , 2.5 Hz, 1H), 7.24 (m, 2H), 7.04 (m, 1H), 6.69 (dd,  $J=6$ , 2.5 Hz, 1H), 3.84 (s, 3H); MS (ESI) m/z: 479.1 ( $M+H^+$ ).

#### Example 30

[0227] Using General Method C, Example B20 (0.070 g, 0.419 mmol), TEA (0.088 mL, 0.628 mmol), DPPA (0.135 mL, 0.628 mmol) and Example A1 (0.119 g, 0.419 mmol) were combined to afford 1-(1-tert-butyl-1H-pyrrol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.011 g, 6% yield) as a white solid.  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.51 (s, 1H), 8.36-8.34 (m, 2H), 8.25-8.19 (m, 2H), 7.95 (s, 1H), 7.22-7.18 (m, 2H), 6.99 (t,  $J=2.0$  Hz, 1H), 6.95 (m, 1H), 6.72 (t,  $J=2.8$  Hz, 1H), 6.65 (dd,  $J=5.6$ , 2.4 Hz, 1H), 5.86 (t,  $J=2.0$  Hz, 1H), 3.84 (s, 3H), 1.43 (s, 9H); MS (ESI) m/z: 449.2 ( $M+H^+$ ).

#### Example 31

[0228] Using General Method A, 2,2,2-trichloroethyl 3-tert-butyl-4-methylisoxazol-5-ylcarbamate (100 mg, 0.30 mmol), prepared via General Method A from Example B21 and Example A1 (86 mg, 0.30 mmol) in presence of DIEA

(0.12 mL) were combined and the resultant product purified via column chromatography (EtOAc/hexanes) to afford 1-(3-tert-butyl-4-methylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (65 mg, 46% yield).  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.15 (s, 1H), 8.83 (brs, 1H), 8.36 (d,  $J=5.6$  Hz, 1H), 8.25 (s, 1H), 8.05 (t,  $J=9.2$  Hz, 1H), 7.96 (s, 1H), 7.26 (dd,  $J=2.8$ , and 12.0 Hz, 1H), 7.23 (d,  $J=2.0$  Hz, 1H), 7.00 (m, 1H), 6.67 (dd,  $J=2.4$ , and 5.6 Hz, 1H), 3.84 (s, 3H), 1.96 (s, 3H), 1.29 (s, 9H); MS (ESI) m/z: 465.2 ( $M+H^+$ ).

#### Example 32

[0229] A mixture of prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate from Example 21 (0.096 g, 0.262 mmol), Example B22 (0.032 g, 0.262 mmol) and N-methylpyrrolidine (2.23 mg, 0.026 mmol) in dioxane (1.0 mL) was heat at 70° C. overnight. Solvent was removed under reduced pressure. The residue was purified by chromatography to afford 1-(5-ethylpyridin-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.054 g, 47% yield) as a white solid.  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.39 (s, 1H), 8.82 (d,  $J=2.0$  Hz, 1H), 8.50 (d,  $J=2.4$  Hz, 1H), 8.41 (d,  $J=5.6$  Hz, 1H), 8.31 (s, 1H), 8.20-8.14 (m, 2H), 8.01 (s, 1H), 7.88 (d,  $J=2.0$  Hz, 1H), 7.31-7.27 (m, 2H), 7.04 (d,  $J=9.2$  Hz, 1H), 6.74 (dd,  $J=5.6$ , 2.6 Hz, 1H), 3.87 (s, 3H), 2.64 (q,  $J=7.6$  Hz, 2H), 1.21 (t,  $J=7.6$  Hz, 3H); MS (ESI) m/z: 433.1 ( $M+H^+$ ).

#### Example 33

[0230] To a solution of 3-cyclopropyl-1-methyl-1H-pyrazol-5-amine (60 mg, 0.434 mmol) in dioxane (1 mL) was added prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate from Example 21 (0.16 g, 0.434 mmol), and DBU (6.61 mg, 0.043 mmol) and the mixture was stirred overnight at 70° C. The reaction was checked by LC-MS, solvent was removed and the residue was purified by silica gel column chromatography (EtOAc/hexane → CH<sub>2</sub>Cl<sub>2</sub>/MeOH). Pure fractions were combined and concentrated. The residue was dissolved in CH<sub>3</sub>CN:H<sub>2</sub>O (1:1, 2 mL) and lyophilized to obtain 1-(3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (26 mg, 13% yield).  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.92 (s, 1H), 8.82 (d,  $J=2.0$  Hz, 1H), 8.39 (d,  $J=6.0$  Hz, 1H), 8.28 (s, 1H), 8.18 (t,  $J=9.6$  Hz, 1H), 7.99 (s, 1H), 7.26 (m, 2H), 7.02 (m, 1H), 6.70 (dd,  $J=2.4$ , and 6.0 Hz, 1H), 3.87 (s, 3H), 3.59 (s, 3H), 1.76 (m, 1H), 0.80 (m, 2H), 0.59 (m, 2H); MS (ESI) m/z: 448.1 ( $M+H^+$ ).

#### Example 34

[0231] Example B24 (100 mg, 0.333 mmol), Example A1 (95 mg, 0.333 mmol) and iPr<sub>2</sub>NEt (0.127 mL, 0.732 mmol) were combined in DMSO (4 mL) and stirred with heating at 80° C. After 72 h, the crude reaction mixture was purified directly without aqueous workup by reverse phase chromatography to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-isopropyl-1H-imidazol-4-yl)urea (110 mg, 60% yield) as the TFA salt.  $^1$ H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.49 (s, 1H), 9.11 (brs, 1H), 8.50 (brs, 1H), 8.49 (d, 1H), 8.41 (s, 1H), 8.16-8.13 (m, 1H), 8.05 (s, 1H), 7.47-7.38 (brm, 2H), 7.37-7.31 (m, 1H), 7.09-7.05 (m,

1H), 6.92-6.87 (m, 1H), 4.55-4.46 (m, 1H), 3.88 (s, 3H), 1.44 (d, 6H); MS (ESI) m/z: 436.1 (M+H<sup>+</sup>).

#### Example 35

[0232] Using General Method C, 1-tert-butyl-5-oxopyrrolidine-3-carboxylic acid (0.1 g, 0.54 mmol), Example A1 0.15 g, 0.54 mmol), Et3N (0.23 mL, 1.62 mmol) and DPPA (0.18 mL, 0.81 mmol) were combined and purified by silica gel column chromatography (EtOAc $\rightarrow$ CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to obtain 1-(1-tert-butyl-5-oxopyrrolidin-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (0.13 g, 50% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.35 (d, J=5.6 Hz, 1H), 8.29 (brs, 1H), 8.24 (s, 1H), 8.15 (t, J=9.2 Hz, 1H), 7.94 (s, 1H), 7.19 (m, 2H), 7.01 (d, J=6.8 Hz, 1H), 6.95 (m, 1H), 6.64 (m, 1H), 4.14 (m, 1H), 3.84 (s, 3H), 3.71 (m, 1H), 3.22 (dd, J=3.6, and 10.4 Hz, 1H), 2.60 (m, 1H), 2.07 (m, 1H), 1.32 (s, 9H); MS (ESI) m/z: 467.2 (M+H<sup>+</sup>).

#### Example 36

[0233] To a stirring solution of 1-(1-tert-butyl-5-oxopyrrolidine-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea from Example 35 (95 mg, 0.20 mmol) in dry THF (3 mL) at RT was added 1.0 M LAH/THF (0.81 mL, 0.82 mmol). The resulting mixture was stirred overnight at RT. It was carefully quenched by the sequential addition of H<sub>2</sub>O (0.1 mL), 3M NaOH (0.1 mL) and H<sub>2</sub>O (0.3 mL) and then EtOAc was added. The mixture was stirred at RT for 4 hours. The solution was filtered through a pad of Celite<sup>o</sup> and washing forward with EtOAc. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo and purified via silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH), dissolved in CH<sub>3</sub>CN:H<sub>2</sub>O (1:1 2 mL) and lyophilized to obtain 1-(1-tert-butylpyrrolidin-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (45 mg, 49% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.42 (brs, 1H), 8.34 (d, J=6.0 Hz, 1H), 8.24 (s, 1H), 8.16 (t, J=8.8 Hz, 1H), 7.94 (s, 1H), 7.16 (m, 2H), 6.93 (m, 2H), 6.63 (dd, J=2.4, and 5.6 Hz, 1H), 4.05 (m, 1H), 3.84 (s, 3H), 2.3-2.8 (m, 4H), 2.03 (m, 1H), 1.48 (m, 1H), 1.01 (s, 9H); MS (ESI) m/z: 453.1 (M+H<sup>+</sup>).

#### Example 37

[0234] Using a procedure analogous to Example 21, Example B25 (16 mg, 0.091 mmol), prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate from Example 21 (35 mg, 0.095 mmol) and N-methylpyrrolidine (1 mg, 0.012 mmol) were combined in 1,4-dioxane (0.8 mL) at 60° C. to afford 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-methyl-5-(trifluoromethyl)pyridin-3-yl)urea (28 mg, 63% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.30 (s, 1H), 8.79 (s, 1H), 8.68 (s, 1H), 8.47 (s, 1H), 8.37 (d, J=5.6 Hz, 1H), 8.25 (s, 1H), 8.22 (t, J=9.4 Hz, 1H), 7.96 (s, 1H), 7.28 (dd, J=12.3, 1.9 Hz, 1H), 7.23 (s, 1H), 7.02 (m, 1H), 6.67 (m, 1H), 3.84 (s, 3H), 2.57 (s, 3H); MS (ESI) m/z: 487.2 (M+H<sup>+</sup>).

#### Example 38

[0235] Using General Method C, Example B23 (64 mg, 0.35 mmol), Example A1 (0.1 g, 0.35 mmol), Et<sub>3</sub>N (54  $\mu$ L, 0.38 mmol) DPPA (83  $\mu$ L, 0.38 mmol) were combined and purified by reverse-phase column chromatography (CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA)) provide the TFA salt of 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea. The salt was treated with EtOAc and NaHCO<sub>3</sub> and then the solution was stirred at RT for 1 hour. The organic was separated, dried

(Na<sub>2</sub>SO<sub>4</sub>), and titrated (Et<sub>2</sub>O) to obtain 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (55 mg, 35% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.38 (brs, 1H), 8.35 (m, 1H), 8.30 (m, 1H), 8.25 (s, 1H), 7.95 (m, 1H), 7.25 (dd, J=2.4, and 12.0 Hz, 1H), 7.20 (d, J=2.0 Hz, 1H), 7.00 (m, 1H), 6.67 (dd, J=2.4, and 5.6 Hz, 1H), 5.82 (brs, 1H), 3.84 (s, 3H), 2.36 (s, 3H), 1.54 (s, 9H); MS (ESI) m/z: 464.2 (M+H<sup>+</sup>).

#### Example 40

[0236] Using General Method C, Example B26 (70 mg, 0.19 mmol) and Example A1 (55 mg, 0.19 mmol) in presence of DPPA (55  $\mu$ L, 0.21 mmol) and (30  $\mu$ L, 0.21 mmol) were combined and the resultant product purified via column chromatography (methanol/methylene chloride) to afford tert-butyl 4-(2-tert-butyl-5-(3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)ureido)pyrimidin-4-yl)piperazine-1-carboxylate. MS (ESI) m/z: 646.3 (M+H<sup>+</sup>). This was then treated with HCl (4.0 M, in dioxane) to afford tert-butyl 4-(2-tert-butyl-5-(3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)ureido)pyrimidin-4-yl)piperazine-1-carboxylate HCl salt (67 mg, 56% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.51 (brs, 1H), 9.31 (brs, 2H), 8.68 (brs, 1H), 8.51 (m, 2H), 8.36 (brs, 1H), 8.20 (t, J=9.2 Hz, 1H), 7.65 (brs, 1H), 7.41 (brd, J=11.6 Hz, 1H), 7.12 (brd, J=9.6 Hz, 1H), 7.06 (brs, 1H), 3.95 (m, 4H), 3.90 (s, 3H), 3.26 (m, 4H), 1.35 (s, 9H); MS (ESI) m/z: 646.3 (M+H<sup>+</sup>).

#### Example 41

[0237] Using General Method C, Example B27 (60 mg, 0.23 mmol) and Example A1 (64 mg, 0.23 mmol) in presence of DPPA (57  $\mu$ L, 0.23 mmol) and (36  $\mu$ L, 0.23 mmol) were combined and the resultant product purified via column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 1-(2-tert-butyl-4-morpholinopyrimidin-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea (94 mg, 76% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.95 (brs, 1H), 8.39 (s, 1H), 8.36 (d, J=5.6 Hz, 1H), 8.24 (m, 2H), 8.16 (t, J=9.6 Hz, 1H), 7.95 (s, 1H), 7.24 (dd, J=2.8, and 11.6 Hz, 1H), 7.21 (d, J=2.4 Hz, 1H), 7.00 (m, 1H), 6.66 (dd, J=2.4, and 6.0 Hz, 1H), 3.84 (s, 3H), 3.71 (m, 4H), 3.49 (m, 4H)m 1.29 (s, 9H); MS (ESI) m/z: 547.3 (M+H<sup>+</sup>).

#### Example 42

[0238] A mixture of Example A1 (2.0 g, 7.04 mmol) and saturated aq NaHCO<sub>3</sub> (100 mL) in EtOAc (100 mL) was cooled in an ice bath and treated with isopropenyl chloroforamate (1.6 mL, 14.64 mmol). The reaction mixture was allowed to slowly warm to RT overnight. The organic layer was separated and washed with sat aq NaHCO<sub>3</sub> (25 mL) and brine (25 mL), dried (MgSO<sub>4</sub>), concentrated in vacuo and re-crystallized (diethylether) to provide prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate (2.32 g, 90% yield). <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  9.69 (br s, 1H), 8.38 (d, J=5.6 Hz, 1H), 8.26 (s, 1H), 7.96 (d, J=0.8 Hz, 1H), 7.67 (br t, J=8.4 Hz, 1H), 7.27 (d, J=2.4 Hz, 1H), 7.22 (dd, J=11.2, 2.4 Hz, 1 H), 7.00 (m, 1H), 6.69 (dd, J=5.6, 2.4 Hz, 1H), 4.74 (m, 1H), 4.72 (s, 1H), 3.84 (s, 3 H), 1.92 (s, 3H); MS (ESI) m/z: 369.1 (M+H<sup>+</sup>).

#### Example B28

[0239] (20 mg, 0.083 mmol), prop-1-en-2-yl 2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenylcarbamate (30 mg, 0.083 mmol) and N-methylpyrrolidine (1 mg, 0.012 mmol) were combined in THF (1.5 mL) and heated to

55° C. in capped vial for 6 days. 1,8-Diazabicyclo[5.4.0]undecene-7-ene (1 drop) was added and the mixture was heated for an additional 3 h at 55° C. The solvent was removed in vacuo and the residue was purified by silica gel chromatography. A second reverse-phase chromatography provided 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(1-methyl-1H-pyrazol-4-yl)-5-(trifluoromethyl)pyridin-3-yl)urea (16 mg, 35% yield). <sup>1</sup>H NMR (400 MHz, Acetone-d<sub>6</sub>): δ 9.15 (s, 1H), 8.81 (s, 1H), 8.61 (s, 1H), 8.59 (s, 1H), 8.40-8.31 (m, 3H), 8.13 (s, 1H), 8.04 (s, 1H), 7.94 (s, 1H), 7.19 (d, J=2.4 Hz, 1H), 7.09 (dd, J=11.6, 2.6 Hz, 1H), 7.02 (m, 1H), 6.71 (dd, J=5.6, 2.6 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H); MS (ESI): m/z 553.2 (M+H<sup>+</sup>).

[0240] Using the synthetic procedures and methods described herein and methods known to those skilled in the art, the following compounds were made:

[0241] 1-(3-tert-butylisoxazol-5-yl)-3-(3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea, 1-(5-tert-butylisoxazol-3-yl)-3-(4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-chloro-3-(trifluoromethyl)phenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylisoxazol-3-yl)urea, 1-(2,3-difluorophenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(isopropylisoxazol-5-yl)urea, 1-(3,5-dichlorophenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-cyclohexyl-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-cyclopentyl-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-chlorophenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-isopropyl-1H-pyrazol-4-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-fluoro-5-(trifluoromethyl)phenyl)urea, 1-(3-tert-butylphenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-methyl-3-(1-methylcyclopentyl)-1H-pyrazol-5-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-fluoro-5-(methylphenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-fluoro-5-methylphenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-isopropylphenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(5-fluoro-2-methylphenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-cyclopentyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-fluorophenyl)urea, 1-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(1-isopropyl-1H-pyrazol-4-yl)urea, 1-cyclohexyl-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-cyclohexyl-3-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(1-cyclopentyl-5-methyl-1H-pyrazol-4-yl)-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea,

yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-fluoropyridin-3-yl)urea, 1-(3-cyanophenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(1-cyclopentyl-1H-pyrazol-4-yl)-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-isopropylisoxazol-5-yl)urea, 1-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-methylpyridin-3-yl)urea, 1-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-trifluoromethyl)pyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-(trifluoromethyl)pyridin-3-yl)urea, 1-(5-chloropyridin-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, and 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-isopropyl-1-methyl-1H-pyrazol-5-yl)urea.

[0242] Using the synthetic procedures and methods described herein and methods known to those skilled in the art, the following compounds are made:

[0243] 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methyl-1H-pyrazol-1-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1H-pyrazol-5-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)pyridin-3-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(cyanomethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)urea, 1-(4-(2-(1-(2-amino-2-oxo ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(cyanomethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(2-

morpholino ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea 1-(2,3-difluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(3-(dimethylamino)propyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyridin-2-yl)urea, 1-(3-fluoro-4-(2-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-fluoro-4-(2-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(3-(dimethylamino)propyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(5-tert-butylpyridin-3-yl)-3-(2-fluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methyl-1H-pyrazol-1-yl)pyridin-4-yloxy)phenyl)urea, 1-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1H-pyrazol-5-yl)urea, 1-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1H-pyrazol-5-yl)urea, 1-(2-fluoro-3-methyl-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea, 1-(2,3-difluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea.



(pyrrolidin-1-yl)phenyl)-3-(2-fluoro-5-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yloxy)phenyl)urea, 1-(2-fluoro-5-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yloxy)phenyl)-3-(3-methyl-5-(pyrrolidin-1-yl)phenyl)urea, 1-(2-fluoro-5-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yloxy)phenyl)-3-(3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(2-fluoro-5-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(3-chloro-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-(2-fluoro-5-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yloxy)phenyl)urea, 1-(2-fluoro-5-(6-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-chloro-5-(pyrrolidin-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-methyl-5-(pyrrolidin-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-chloro-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(pyrrolidin-1-yl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-methyl-5-(pyrrolidin-1-yl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(3-chloro-5-(pyrrolidin-1-yl)phenyl)-3-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(pyrrolidin-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-chloro-5-(pyrrolidin-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-methyl-5-(pyrrolidin-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(pyrrolidin-1-yl)phenyl)urea,

urea, 1-(3-chloro-5-(pyrrolidin-1-yl)phenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-methyl-5-(pyrrolidin-1-yl)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(pyrrolidin-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(3-chloro-5-(4-methyl-1H-imidazol-1-yl)phenyl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-(pyrrolidin-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-chloro-5-(pyrrolidin-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-methyl-5-(pyrrolidin-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-chloro-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-3-fluorophenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(pyrrolidin-1-yl)phenyl)urea, 1-(3-chloro-5-(pyrrolidin-1-yl)phenyl)-3-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-methyl-5-(4-methyl-1H-imidazol-1-yl)phenyl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(piperidin-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)urea, 145-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(4-methylpiperazin-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-methyl-5-(4-methylpiperazin-1-yl)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-chloro-5-(4-methylpiperazin-1-yl)phenyl)urea, 145-(2-(1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)phenyl)urea, 1-(2-fluoro-5-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-



1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-oxo-6-(pyrrolidin-1-yl)indolin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-(4-methyl-1H-imidazol-1-yl)-2-oxoindolin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-oxo-6-(piperidin-1-yl)indolin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-morpholino-2-oxoindolin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-(4-methylpiperazin-1-yl)-2-oxoindolin-3-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-oxo-6-(pyrrolidin-1-yl)indolin-3-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-(4-methyl-1H-imidazol-1-yl)-2-oxoindolin-3-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-oxo-6-(piperidin-1-yl)indolin-3-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-morpholino-2-oxoindolin-3-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(6-(4-methylpiperazin-1-yl)-2-oxoindolin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(piperidin-1-yl)quinolin-6-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-methyl-1H-imidazol-1-yl)quinolin-6-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(piperidin-1-yl)quinolin-6-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-methylpiperazin-1-yl)quinolin-6-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(piperidin-1-yl)quinolin-6-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-methyl-1H-imidazol-1-yl)quinolin-6-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(morpholinoquinolin-6-yl)urea, 1-(3-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(2-(4-methylpiperazin-1-yl)quinolin-6-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)-1-methyl-1H-pyrazol-5-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(3-(1-hydroxy-2-methylpropan-2-yl)isoxazol-5-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-(2-hydroxypropan-2-yl)pyridin-3-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(cyanomethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)urea, 1-(4-(2-(1-(2-amino-2-oxo ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(cyanomethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(2-morpholino ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-propyl-1H-pyrazol-4-yl)pyridin-4-yloxy)

phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(3-(dimethylamino)propyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2,3-difluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyridin-2-yl)urea, 1-(3-fluoro-4-(2-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(5-isopropylpyridin-3-yl)urea, 1-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)-3-(4-(trifluoromethyl)pyridin-2-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(3-fluoro-4-(2-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-(2-(1-(dimethylamino)propyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)-2,3-difluorophenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,3-difluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(5-tert-butylpyridin-3-yl)-3-(2-fluoro-4-(2-(1-(3-hydroxypropyl)-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea, and 1-(5-tert-butylpyridin-3-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yloxy)phenyl)urea.

#### Section 4. Biological Data

**[0244] c-ABL Kinase (Seq. ID no. 1) Assay**

[0245] Activity of c-ABL kinase (Seq. ID no. 1) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at A<sub>340 nm</sub>) was continuously monitored spectrophotometrically. The reaction mixture (100 µl) contained c-ABL kinase (1 nM, c-ABL from deCode Genetics), peptide substrate (EAIIYAAPFAKKK, 0.2 mM), MgCl<sub>2</sub> (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 90 mM Tris buffer containing 0.2% octyl-glucoside and 3.5% DMSO, pH 7.5. Test compounds were incubated with c-ABL (Seq. ID no. 1) and other reaction reagents at 30° C. for 2 h before ATP (500 µM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC<sub>50</sub> values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

## c-ABL kinase

(Seq. ID no. 1)

GTSMDPSSPNYDKWEMERTDITMKHKLGGQYGEVYEGVWKYSLTVAVTLKEDTMEVE  
 EFLKEAAVMKEIKHPNLVQLLGVC TREPPFYIITEFMTYGNLLDYLR ECNRQEVNAVLL  
 YMATQISSAMEYLEKKNF IHRDLAARNCLVGENHLVKADFGLSRLMTGDTYTAHAGAKF  
 PIKWTAPESLAYNKF SI KSDVWAFGVLLWEIATYGMSPYPGIDL SQVYELLEKD YR MERP  
 EGCPEKVYELMRACWQWNPSDRPSFAEIHQAFETMFQE

## c-ABL Kinase (Seq. ID no. 2) Assay

**[0246]** Activity of T315I c-ABL kinase (Seq. ID no. 2) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at  $A_{340\text{ nm}}$ ) was continuously monitored spectrophotometrically. The reaction mixture (100  $\mu\text{l}$ ) contained c-ABL kinase (4.4 nM, M315I c-ABL from deCode Genetics), peptide substrate (EAIYAAPFAKKK, 0.2 mM), MgCl<sub>2</sub> (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH

(0.28 mM) in 90 mM Tris buffer containing 0.2% octyl-glucoside and 1% DMSO, pH 7.5. Test compounds were incubated with T315I c-ABL (Seq. ID no. 2) and other reaction reagents at 30° C. for 1 h before ATP (500  $\mu\text{M}$ ) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC<sub>50</sub> values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

## c-ABL T315I kinase

(Seq. ID no. 2)

GTSMDPSSPNYDKWEMERTDITMKHKLGGQYGEVYEGVWKYSLTVAVTLKEDTMEVE  
 EFLKEAAVMKEIKHPNLVQLLGVC TREPPFYIITEFMTYGNLLDYLR ECNRQEVNAVLL  
 YMATQISSAMEYLEKKNF IHRDLAARNCLVGENHLVKADFGLSRLMTGDTYTAHAGAKF  
 PIKWTAPESLAYNKF SI KSDVWAFGVLLWEIATYGMSPYPGIDL SQVYELLEKD YR MERP  
 EGCPEKVYELMRACWQWNPSDRPSFAEIHQAFETMFQE

## BCR-ABL p210-e14a2

(Seq. ID no. 3)

MVDPGVFAEAQKQFPDSEPPRMELRSVGDIQEELERCKASIRRLQEVNQERFRMIYLO  
 TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASARPQPA PADGADPPPAAEPEARPDGE  
 GSPGKARPGTARRPGAAASGERDDRGPPASA LRSNFERIRKGHGQPGADA EKP FYVN  
 EFHHERGLVKVNDKDEVSDRISLGSQAMQMERKKSQHAGSSVGADASRPYGRSSSESSC  
 GVDGDYEDAELNPRFLKDNLIDANGGSRPWPWPLEYQPYQSIIYVG  
 GIMEGEKGKPLRLSQ  
 STSEQEKRLTWPRRS YSPRSFEDCGGGYT PDCSSNEMLT SSEEDFSSGOSSRVSPSP  
 RMFRDKRSRSPSQNSQSFDS SPPTPQCHKRHRCPVVSEATIVGVRKTGQIWPNDDEG  
 AFHGDADGSFGTPPGYGCADRAEQQRRHQDGLPYI DSDPSSSPHLSKGRGSRDALVSG  
 ALKSTKASELDLK GLEM R KWLSGILASEETYL SHLEALLLP MKPLKA AATT SQPVLTS  
 QQETIFLPKVELEYIHKESYDGLP RVQWSHQ QVGDLPQKLASQLGVYFQ  
 VDNYGV  
 AMMAEKCQCQANAQFAEISENL RARSNKDAKPTTKNSLETLLYKPVDRVTRSTLVHDL  
 LKHTPASHPDHPLQDALRISQNFQFLSSIN EETP RRSQMTVKKG EHRQLLKDSFM  
 VELVE  
 GARKLRHVFLFTD LCTKLKKQSGGKTQYDCKWYIPLTDL SFQMVD ELEAVPNIP  
 LPV  
 DEE DAL KIKIS QKSDI QRE KRANGSKATERLKKL SEQES LLLLMSPSMAFR  
 VHSRN  
 GKS YTF LISSD YERA E WREN I RE QQK CFS L TS VEL QML TN  
 CVK LQTVHSIPLTIN  
 KEDDES PG LY GFLN VI VH SAT GF QOSS KAL QRPV ASDF E P  
 OGL SE A RWS KEN LLAGPS  
 END PNL FV ALY DF VAS GDNTL SIT KGE KLR VLG YHN GE  
 CE A QT KNG QGW VP S NY IT P  
 NS LEKHSWYHGPV S RNA A EYPL S GING S FLV RE S ESS PS QR S I S LRY  
 EGRV YHYRINTA  
 SDG KLYV S S ESR FNT L AEL VHH HST VAD GLL HYP  
 PAKR NK PTV G VSP NY DKW EMER  
 TD IT MKH KLGG QYGEV YEGV WKYS LTVA VTL KEDT MVE E EFL  
 KE A AV MKE IKH PNL V  
 QLL GV CTRE PPF YI I TE FMT YGN LL DYL REC NRQ EVNA VLL  
 YM AT QISSA ME YLE KK NF  
 I HR DL A ARN CLV GEN H LV KAD FG LS RL MTG DT YTA HAG AKF PI KWT  
 APE SLAY NKF SI  
 SDV WA FG VLL WE IAT YGM SP YPG ID RS QV YEL LE KD YR MRK PEG CPE KV YEL MRAC WQ  
 W  
 PSDR P SFA E I HQ AF ET MF Q PESS I DHE VPK R GAV T L L Q  
 APE L PT K RT SR RAA  
 EH RDT DV P E M P HSK Q G Q E S D P L D H E P A V S P L L P R K E R G P P E G G L N  
 A E D E R L L P K D K T N L  
 F S A L I K K K K T A P T P K R S S F R E M D Q P E R R G A G E E G R D I S N G A L A F T P L D  
 T A D P A K S  
 P K P S N G A G V P N G A L R E S G G S G F R S P H L W K S S T L T S S R L A T  
 G E E E G G G S S K R F L R S C S V  
 S C V P H G A K D T E W R S V T L P R D L Q S T G R Q D S S T F G G H K S E K P A L P R K  
 R A G E N R S D Q V T R G P  
 V T P P P R L V K K N E E A A D E V F K D I M E S S P G S S P P N L T P K P L R R Q V T  
 V A P A S G L P H K E E A W K G  
 S A L G T P A A E P V T P T S K A G S G A P R G T S K G P A E E S R V R H K H S S E S P  
 G R D K G K L S K L K P  
 P P P P A A S A G K A G G K P S Q R P G Q E A A G E A V L G A K T K A T S L V D A V  
 N S D A A K P S Q P A E G L K K P V  
 L P A T P K P H P A K P S G T P I S P A P V P L S T L P S A S S A L A G D Q P S S T A F I P  
 L I S T R V S L R K T R Q P  
 PER AS G A I T K G V V L D S T E A L C L A I S G N S E Q M A S H S A V  
 LEAG K N L Y T F C V S Y V D S I Q Q M R N  
 K F A F R E A I N K L E N N L R E L Q I C P A S A G S G P A A T Q D F S K  
 L L S S V K E I S D I V Q R

-continued

BCR-ABL p210-e13a2

(Seq. ID no. 4)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQEALERCKASIRRLQEVENQERFRMIYLQ  
 TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQAPADGADPPPABEPEEARPDGE  
 GSPGKARPGTARRPGAAASGERDDRGPSPASVALRSNFERIRKGHGQPGADAEPFVNV  
 EFHHERGLVKVNDKEVSDRISLGSQAMQMERKKSQHAGSSVGDASRPPYGRSSSESSC  
 GVDGTYEDAELNPRFLKDNLIDANGSRPPWPLEYQPYQSIVVGGIMEEGGKGPLLRSQ  
 STSEQEKRLTWPRRSYSPRSFDSSSPPTPQCHKRHRHCPVVVEATIVGVRKTQIWPNDDEG  
 RMFRDKSRSPSNSQSFDSSEPPQCHKRHRHCPVVVEATIVGVRKTQIWPNDDEG  
 AFHGDADGSFGTPGYGAADRAEEQRHQDGLPYIDDSPSSSPHLSKGRGSRDALVSG  
 ALKSTKASELDLEKGLEMRKWVLSGILASEETYLSHLEALLPMKPLKAATTSQLVPLTS  
 QQIETIFFKVEIHKESYGLFPRVQOWSHQQRVQDFQQLASQLGVYRAFVDNYGV  
 AMEMAEKKCQANAAEISENLRARSNKDAKDPITKNSLETLLYKPVDRVTRSTLVHDL  
 LKHTPAHDPHLLQDALRISQNFLLSENEITPRRQSMTVKGEHRQLLKDSFMVELVE  
 GARKLRHVFLFTDLLCTKLKQSGGKTCQYDKWYIPLTDLSFQMVDELEAVPNIPVLP  
 DEELDALKIKISQIKSDIQREKRANKGSKATERLKKLSEQESLLLMSPSMAFRVHSRN  
 GKSYTFLISSDYERAEWRENIREQQQKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTIN  
 KEEALQRWNSDENPQLSSEARWNRSKENLLAGPSSENDPNLFVALYDFVASGDNTLSITK  
 GEKLRLVLYNHNGEWCEAQTKNGQGWVPSNYITPVNSLEKHSWYHGPVSRNAAEYPLSSG  
 INGSFLVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSERSFNLAELVHHST  
 VADGLITTLHYPAKCRNKPTVYGVSPNYDKWEMERTDTIMKHKGQQYGEVYEGVWKKY  
 SLTVAVKTLKEDTMVEEFLKEAAMKEIKHPNLVQQLLGVC TREPPFYIITEFMTYGNLL  
 DYLRCNRQEVNAVVLLYMATQISSAMEYLEKKNFIIHDLAARNCLVGENHLVKVADPGL  
 SRLMTGDTYTAHAGAKPIKWTAPESLAYNKFSIKSDVWAFVLLWEIATYGMSPYPGID  
 RSQVYELLEDYRMKRPEGCPEKVYELMRACWQNPNSDRPSFAEIHQAFETMFQESSISD  
 EVEKELGKQGVRAVTLLQAPELPTKRTSRRAEHRDTDVPEMPHSKGQGESDPLDH  
 EPAVSPLLPRKERGPPEGGLNEDERLLPKDCKTNTLFSALIKKKKTAPTPPKRSSFREM  
 DGQPERRGAGEEEGRDI SNGALAFTPPLDADPAKSPKPSNGAGVNGALRESGGSGFRSP  
 HLWKKSTSLLSLATGEEEGGSSSKRFRLRSCSVSCVPHGAKDTEWSVTLPRLQSTG  
 RQFDSTSFTGGHKSEKPALPRKRAGENRSDQVTRGTVTPPPRLVKKNEEADEVFKD  
 SPGSSPPNLTPKPLRQVTVAPASGLPHKEEAWKGSALGTPAAAEPVPTPSKAGSGAPRG  
 TSKGPAEESRVRRHKHSESPPRDKGKLSKLKPAAPPPPAASAGKAGGKPSQRPQEAAG  
 EAFLGAKTKATSLSDAVNSDAAKPSQPAEGLKPKVLPATPKPHPAKPSGTPISPAPVPLS  
 TLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPERASGAIKGVLDSLTEALCLAI  
 GNSEQMASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQICPASA  
 GSGPAATQDFSKLSSVKEISDIVQR

BCR-ABL p190-e1a2

(Seq. ID no. 5)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQEALERCKASIRRLQEVENQERFRMIYLQ  
 TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQAPADGADPPPABEPEEARPDGE  
 GSPGKARPGTARRPGAAASGERDDRGPSPASVALRSNFERIRKGHGQPGADAEPFVNV  
 EFHHERGLVKVNDKEVSDRISLGSQAMQMERKKSQHAGSSVGDASRPPYGRSSSESSC  
 GVDGTYEDAELNPRFLKDNLIDANGSRPPWPLEYQPYQSIVVGGIMEEGGKGPLLRSQ  
 STSEQEKRLTWPRRSYSPRSFDCCGGYTPDCSSNENLTSSEEDFSSGQSSRVSPPTY  
 RMFRDKSRSPSNSQSFDSSEPPQCHKRHRHCPVVVEATIVGVRKTQIWPNDDEG  
 AFHGDAAEALQRPVASDFEPQGLSEARWNSENLLAGPSSENDPNLFVALYDFVASGDNTL  
 SITKGEKLRLVLYNHNGEWCEAQTKNGQGWVPSNYITPVNSLEKHSWYHGPVSRNAAEY  
 LSSGINGSFLVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSERSFNLAELV  
 HHSTVADGLITTLHYPAKCRNKPTVYGVSPNYDKWEMERTDTIMKHKGQQYGEVYEGV  
 WKYSLTVAVKTLKEDTMVEEFLKEAAMKEIKHPNLVQQLLGVC TREPPFYIITEFMTY  
 GNLLDYLRECNRQEVNAVVLLYMATQISSAMEYLEKKNFIIHDLAARNCLVGENHLVK  
 DFGLSRLMTGDTYTAHAGAKPIKWTAPESLAYNKFSIKSDVWAFVLLWEIATYGMSPY  
 PGIDRSQVYELLEDYRMKRPEGCPEKVYELMRACWQNPNSDRPSFAEIHQAFETMFQES  
 SISDEVEKELGKQGVRAVTLLQAPELPTKRTSRRAEHRDTDVPEMPHSKGQGESD  
 PLDHEPAVSPLLPRKERGPPEGGLNEDERLLPKDCKTNTLFSALIKKKKTAPTPPKRSS  
 FREMDGQPERRGAGEEEGRDI SNGALAFTPPLDADPAKSPKPSNGAGVNGALRESGGSG  
 FRSPHLWKKSTSLLSLATGEEEGGSSSKRFRLRSCSVSCVPHGAKDTEWSVTLPRL  
 QSTGRQFDSTSFTGGHKSEKPALPRKRAGENRSDQVTRGTVTPPPRLVKKNEEADEVFKD  
 IMESSPGSSPPNLTPKPLRQVTVAPASGLPHKEEAWKGSALGTPAAAEPVPTPSKAGSG  
 APRGTSKGPAAEESRVRRHKHSESPPRDKGKLSKLKPAAPPPPAASAGKAGGKPSQRPQ  
 EAAGEAVLGAKTAKTSLSDAVNSDAAKPSQPAEGLKPKVLPATPKPHPAKPSGTPISPAP  
 VPLSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPERASGAIKGVLDSLTEALC  
 LAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQIC  
 PASAGSGPAATQDFSKLSSVKEISDIVQR

BCR-ABL p210-e14a2 T315I

(Seq. ID no. 6)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQEALERCKASIRRLQEVENQERFRMIYLQ  
 TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQAPADGADPPPABEPEEARPDGE  
 GSPGKARPGTARRPGAAASGERDDRGPSPASVALRSNFERIRKGHGQPGADAEPFVNV  
 EFHHERGLVKVNDKEVSDRISLGSQAMQMERKKSQHAGSSVGDASRPPYGRSSSESSC  
 GVDGTYEDAELNPRFLKDNLIDANGSRPPWPLEYQPYQSIVVGGIMEEGGKGPLLRSQ  
 STSEQEKRLTWPRRSYSPRSFDCCGGYTPDCSSNENLTSSEEDFSSGQSSRVSPPTY  
 RMFRDKSRSPSNSQSFDSSEPPQCHKRHRHCPVVVEATIVGVRKTQIWPNDDEG  
 AFHGDADGSFGTPGYGAADRAEEQRHQDGLPYIDDSPSSPHLSKGRGSRDALVSG  
 ALKSTKASELDLEKGLEMRKWVLSGILASEETYLSHLEALLPMKPLKAATTSQLVPLTS

-continued

QQIETIFFKVEPELYEIHKESYDGLFPRVQQWSHQQRVGDLFQKLASQLGVYRAFDNYGV  
 AMEMAEKCCQANAQFAEISENLRARSNKDAKPTTKNSLETLLYKPVDRVRSTLVLHDL  
 LKHTPASHDPHPLLQDALRISQNFLSSINEEITPQQSMVTVKGEHRQLLKDSFMVELVE  
 GARKLRHVFLFTDLLCTKLKQSGGKTQQYDCKWYIPLTDLSFQMVDLEAVPNIPLPV  
 DEELDALKIKISQIKSDIQREKRANKGSKATERLKKKLSEQESLLLLMSPSMAFRVHSRN  
 GKSYTFLISSDYERAEWRENIREQQKCFRSFSLTSVLEQMLTNSCVQLQTVHSIPLTIN  
 KEDDESPGLYGFNLNVIVHSATGKQSSKALQRPVASDFEPQGLSEAARWNSENLLAGPS  
 ENDPNFLVALYDFVAVGDNTLSITKGEKLRVLYGNHNGEWECAQTKNGQGVPSNYITPV  
 NSLEKHSWYHGPVSRNAEYPLSSGINGSFLVRESESSPSQRSISLRYEGRVYHYRINTA  
 SDGKLYVSSERSRFNTLAELVHHHSTVADGLITLHYPAPKRNPVTVGVSPNYDKWEMER  
 TDITMKHKLGGQYGEVYEGVWKYSLTAVAKTLKEDTMEEVEFLKEAAVMKEIKHPNLV  
 QLLGVCCTREPPFYIIEFMTYGNLLDYLRRECNRQEVNAVLLYMATQISSAMEYLEKKNF  
 IHRDLAARNCLVGENHLKVADFGSLRMLMTGDTYTAHAGAKPKIWTAPESLAYNKFISK  
 SDVWAFGVLLWEIATYGMSPYGDLSRQVYELLEKDYRMKRPVYELMRACWQWN  
 PSDRPSFAEIHQAFETMFQESSISDEVEKELGKOGVRAVTLLQPAEPLPTKTRTSRRRAA  
 EHRDTTDVPEMPHSKGQGESDPLDHEPAVSPLLPRKERGPPEGGLNEDERLLPKDKKTNL  
 PSALIKKKKTAFTPPKRSSSFRMDGQPERRGAGEEEGRDIISNGALAFTPLDADPAKS  
 PKPSNGAGVPGNALRESGGSGFRSPHLWKKSTSRLATGEEEGGSSSKRFLRCSV  
 SCVPHGAKDTEWRSVTPRDLQSTGRFDSTFGHKS EKPALPRKRAGENRSRDQVTRGT  
 VTPPRLVKNNEADEVFKDIMESPQGSPNPLTPKPLRRQTVAPASGLPHKEAWKG  
 SALGTPAAAEPVPTSKAGSGAPRGTSGPAAESRVRRHKSSESPGRDGKLSKLKPAP  
 PPPAASAGKAGGKPSQRPQEAAGEAVLGAKTATSLVDAVNSDAAKPSQPAEGLKKPV  
 LPATPKPHPAKPSGTPISPAPVPLSTPLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQP  
 PERASGAIKGVVLSTEALCLAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSTQQMRN  
 KFAFREAINKLENNLRELQICPASAGSGPAATQDFSKLLSSVKEISDIVQR

BCR-ABL p210-e13a2 T315I

(Seq. ID no. 7)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERKASIRRLQEVNQERFRMIYLO  
 TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQAPADGADPPAEEPEARPDGE  
 GSPGKARPGTARRPGAAASGERDRGPPASVAALRSNFERIRKGHGPQGADAEPKPFYVN  
 EFHHERGLVKVNDKEVSDRISLGSQAMQMERKKSQHGAGSSVGDASRPPYGRRSSESSC  
 GVDGYEDAELNPRFLKDNLIANGGSRPPWPLEYQPYQSIYVGGIMEGEKGKPLRSQ  
 STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY  
 RMFRDKSRSPSQNSQSFDSSSPPTPQCHKRHRCPVVVSEATIVGVRKTQIWPNDDEG  
 AFHGDAEALQRPVASDFEPQGLSEAARWNSENLLAGPSENDPNLFVALYDFVAVGDNTL  
 SITKGEKLRVLYGNHNGEWECAQTKNGQGVPSNYITPVNSLEKHSWYHGPVSRNAEYPLSSG  
 INGSFLVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSERSRFNTLAELVHHHST  
 VADGLITLHYPAPKRNPVTVGVSPNYDKWEMERTDITMKHKLGGQYGEVYEGVWKY  
 SLTAVAKTLKEDTMEEVEFLKEAAVMKEIKHPNLUVQLLGVCTREPPFYIIIEFMTYGNLL  
 DYLRECNRQEVNAVLLYMATQISSAMEYLEKKNFIRDLAARNCLVGENHLVKA  
 SRLMTGDTYTAHAGAKPKIWTAPESLAYNFSIKSDWAFGVLLWEIATYGMSPYGD  
 RSQVYELLEKDYRMKRPVYELMRACWQWNPSDRPSFAEIHQAFETMFQESSISD  
 EVEKELGKQGVRAVTLLQPAEPLPTKTRTSRRAEHDRTTDVPEMPHSKGQGESDPLD  
 HEPAVSPLLPRKERGPPEGGLNEDERLLPKDKKTNLFSALIKKKKTAFTPPKRSSSFR  
 DGQPERRGAGEEEGRDIISNGALAFTPLDADPAKSPKPSNGAGVPGNALRESGGSGFRSP  
 HLWKKSTSRLATGEEEGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTPRDLQSTG  
 RQFDSTSFGHHKSEKPKLPRKRAGENRSRDQVTRGTVTPPRLVKKNEEADEVFKDIMES  
 SPGSPSPNLTQPKLRRQVTVAPASGLPKHEEAWKGSALGTPAAAEPVPTPSKAGSGAPRG  
 TSKGPAEESRVRRHKSSESPGRDKGKLSKLKPAPPPPAAASAGKAGGKPSQRPQEAAG  
 EAVALGAKTATSLVDAVNSDAAKPSQPAEGLKPKVLPATPKPKPAKPSGTPISPAPVPLS  
 TLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQP  
 ERASGAIKGVVLSTEALCLAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSTQQMRN  
 KFAFREAINKLENNLRELQICPASAGSGPAATQDFSKLLSSVKEISDIVQR

BCR-ABL p190-e1a2

(Seq. ID no. 8)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERKASIRRLQEVNQERFRMIYLO  
 TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQAPADGADPPAEEPEARPDGE  
 GSPGKARPGTARRPGAAASGERDRGPPASVAALRSNFERIRKGHGPQGADAEPKPFYVN  
 EFHHERGLVKVNDKEVSDRISLGSQAMQMERKKSQHGAGSSVGDASRPPYGRRSSESSC  
 GVDGYEDAELNPRFLKDNLIANGGSRPPWPLEYQPYQSIYVGGIMEGEKGKPLRSQ  
 STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY  
 RMFRDKSRSPSQNSQSFDSSSPPTPQCHKRHRCPVVVSEATIVGVRKTQIWPNDDEG  
 AFHGDAEALQRPVASDFEPQGLSEAARWNSENLLAGPSENDPNLFVALYDFVAVGDNTL  
 SITKGEKLRVLYGNHNGEWECAQTKNGQGVPSNYITPVNSLEKHSWYHGPVSRNAEYPLSSG  
 LSSGINGSFLVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSERSRFNTLAELVH  
 HHSTVADGLITLHYPAPKRNPVTVGVSPNYDKWEMERTDITMKHKLGGQYGEVYEGV  
 WKKYSLTAVAKTLKEDTMEEVEFLKEAAVMKEIKHPNLUVQLLGVCTREPPFYIIIEFMTY

-continued

GNLLDYLRECNRQE VNAAV VLLYMATQI SSMAYLE KKNFI HRLAARNCLVGENHLVKVA  
 DFGLSRLMTGDTYTAHAGAKFP IKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPY  
 PGIDRSQVYELLEKD YRMKRP ECGPEK VYELMRA C WQWNPSDRPSFAEIHQA FETMFQES  
 SISDEVEKELGKQGV RGAVTTL LQAPELPTKTRTSRRAAEHRTTDVPEMHSKGQGESD  
 PLDHEPAVSPPLPRKERGPPEGGLNEDERLLPKDKKTNLFSALIKKKKTAPTPKRSSS  
 FREMDGQPERRGAGEEEGRDI SNGALAFPTLDTADPAKSPKPSNGAGVPGNALRESGGSG  
 FRSPHLWKKSTLTSSRLATGEEEGGGSSSKRFLRSCSVSCVPHGAKDTEWSVTLPRLD  
 QSTGRQFDSSTFGGHKSEKP ALPRKRAGENRS DQVTRGTVTTPRVLVKKNEEADEVFKD  
 IMESSPGSSPPNLTPKPLRQVTVAPASGLP HKEEAWKGSALGTPAAAEPVPTSKAGSG  
 APRGTSKGPAEESRVRHHKHSSESPGRDKGKL SKLKPA PPPPAASAGKAGGKPSQRPGQ  
 EAAGEAVLGAKTKATSLVD AVNSDAAKPSQPAEGLKKPVLPATPKPHPAKPSGT PISPAP  
 VPLSTLPSASSALAGDQPSSTAIFIPLISTRVSLRKTRQPERASGAITKGVL DSTEALC  
 LAISGNSEQMA SHASVLEAGK NLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQIC  
 PASAGSGPAA TQDFSKL LSSVKEIS DIVQR

#### c-KIT Kinase (Seq. ID no. 9) Assay

**[0247]** Activity of c-KIT kinase (Seq. ID no. 9) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at A340 nm) was continuously monitored spectrophotometrically. The reaction mixture (100 µl) contained c-KIT (cKIT residues T544-V976, from ProQinase, 5.4 nM), polyE4Y (1 mg/ml), MgCl<sub>2</sub> (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 90 mM Tris buffer containing 0.2% octyl-glucoside and 1% DMSO, pH 7.5. Test compounds were incubated with C-MET (Seq. ID no. 9) and other reaction reagents at 22° C. for <2 min before ATP (200 µM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 0.5 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 0 to 0.5 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC<sub>50</sub> values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

#### c-MET Kinase (Seq. ID no. 10) Assay

**[0248]** Activity of c-MET kinase (Seq. ID no. 10) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at A340 nm) was continuously monitored spectrophotometrically. The reaction mixture (100 µl) contained c-MET (c-MET residues: 956-1390, from Invitrogen, catalogue #PV3143, 6 nM), polyE4Y (1 mg/ml), MgCl<sub>2</sub> (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 90 mM Tris buffer containing 0.25 mM DTT, 0.2% octyl-glucoside and 1% DMSO, pH 7.5. Test compounds were incubated with C-Met (Seq. ID no. 10) and other reaction reagents at 22° C. for 0.5 h before ATP (100 µM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC<sub>50</sub> values were calculated from a series of percent inhibition values determined at a range of inhibitor concentrations using software routines as implemented in the GraphPad Prism software package.

#### c-KIT with N-terminal GST fusion

(Seq. ID no. 9)

LGYW KIKGLVQPTRLLLEY LEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVKL P  
 TQSMAI IRYIADKHNLGGCPKERA EISMLEGAVDIRYGV SRIAYS KDFETLKVDPLSKLP  
 EMLKMFEDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRIEAIPQ  
 IDKYLKSSKYIWPLQGWQATFGGGDHPPKS DLVPRHNQTSLYKKAGSAAVLEENLYFQGT  
 YKYLQKPMYEVQWKVVEEINGNNYVYIDPTQLPYDHKWEFPRNRLSGKTLGAGAFGKVVE  
 ATAYGLIKSDAAMTVAVKMLKPSAHLTEREALMSELKVL SYLGNHMNIVNLLGACTIGGPT  
 LVITEYCCYGDLLNFLRKRDSFICSKQEDHAEALYKNLLHSKESSCS DNSTNEYMDMKPG  
 VS YVVP TKADKRRSRV RIGSYIERDVT PAIMEDDELAL DLEDLLSF SYQAKGMAFLASKNC  
 IHRDLAARNIL LTHGRITKICDFGLARDIKND S NYVVKG NARLPVKW MAPESI FNCV YT F  
 SDVWSY GIGFLWELFSLGSSPYPGMPVDSKPYKMI KEGFRMLSPEHAPAEMYDIMKTCWDAD  
 PLKRPTFKQIVQ LIEKQI SESTNH IY S NLANCSPNRQKP VVDHSVRIN SVGSTASSSQPL

## c-MET Kinase

(Seq ID no. 10)

MSYYHHHHHDYDIPPTENLYPQGAMLVPRGSPWIPFTMKRKQIKDLGSELVRYDARVHT  
 PHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSSQNGSCRQVQYPLTDMSPILTSG  
 DSDISSLQNTVHIDL SALNPELVQAVQHVGSSSLIVHFNEVIGRGHFGCVYHGTLLD  
 NDGKKIHCAVKSLNRITDIEVSQFLTEGIIMKDFSHPNVLSSLLGICLRSEGSPLVLPYM  
 KHGDLRNFIRNEETHNPTVKDLIGFGLQVAKGMKYLASKKFVHRDLAARNCMLDEKFTVKVA  
 DFGLARDMYDKEYYSVHNKTGAKLPVKWMALESLQTQKFTTKSDVWSFGVLLWELMTRGAP  
 PYPDVNTFDITVYLLQGRRLQPEYCPDPLYEVMLKCWHPKAEMRPSFSELVSRSIAIFST  
 FIGEHYVHVNVATYVNVCVAPYPSLSSEDNADDEVDTLPASFWETS

TABLE 1

Example	Biological Data Summary. Biochemical IC <sub>50</sub> values of compounds of Formula I.			
	ABL Enzyme Assay	ABL T315I Enzyme Assay	c-KIT Enzyme Assay	c-MET Enzyme Assay
1	+++	+++	+++	++
2	+++	+++	+++	++
3	+++	+++	+++	++
4	+++	+++	n/a	++
5	+++	+++	+++	+
6	+++	+++	+++	+
7	+++	+++	n/a	+
8	+++	+++	+++	++
9	+++	‡	+++	+
10	+++	+	+++	+
11	+++	+++	+++	+
12	+++	+++	+++	+
13	+++	+	n/a	++
14	+++	+++	+++	++
15	+++	+++	+++	+
16	+++	++	n/a	+
17	+++	+++	n/a	++
18	+++	n/a	n/a	+
19	++	++	n/a	+
20	+++	+++	n/a	+
21	+++	+++	+++	++
22	+++	+++	+++	++
23	+++	n/a	n/a	n/a
24	+++	n/a	+++	+
25	+++	+++	+++	+++
26	+++	n/a	n/a	n/a
27	+++	+++	+++	++
28	+++	+++	+++	+
29	+++	n/a	n/a	n/a
30	+++	+++	n/a	+
31	+++	+++	n/a	n/a
32	+++	+++	n/a	n/a
33	++	++	n/a	n/a
34	+++	+++	n/a	n/a
35	++	+	n/a	n/a
36	++	+	n/a	n/a
37	+++	+++	n/a	n/a
38	+++	++	n/a	n/a
39	+++	+++	n/a	n/a
40	+++	++	n/a	‡
41	++	‡	‡	‡
42	+++	+++	+++	++

+++ = &lt;0.1 μM;

++ = &lt;1.0 μM;

+ = &lt;10 μM;

‡ &lt;100 μM;

n/a = not available

The biochemical IC<sub>50</sub> values of other compounds disclosed herein are at least 10 μM against c-ABL enzyme.

## Cell Culture

[0249] BaF3 cells (parental or transfected with the following: wild type p210 BCR-ABL and T315I p210 BCR-ABL) was obtained from Professor Richard Van Etten (New England Medical Center, Boston, Mass.). Briefly, cells were grown in RPMI 1640 supplemented with 10% characterized fetal bovine serum (HyClone, Logan, Utah) at 37 degrees Celsius, 5% CO<sub>2</sub>, 95% humidity. Cells were allowed to expand until reaching 80% saturation at which point they were subcultured or harvested for assay use.

## Cell Proliferation Assay

[0250] A serial dilution of test compound was dispensed into a 96 well black clear bottom plate (Corning, Corning, N.Y.). For each cell line, three thousand cells were added per well in complete growth medium. Plates were incubated for 72 hours at 37 degrees Celsius, 5% CO<sub>2</sub>, 95% humidity. At the end of the incubation period Cell Titer Blue (Promega, Madison, Wis.) was added to each well and an additional 4.5 hour incubation at 37 degrees Celsius, 5% CO<sub>2</sub>, 95% humidity was performed. Plates were then read on a BMG Fluostar Optima (BMG, Durham, N.C.) using an excitation of 544 nM and an emission of 612 nM. Data was analyzed using Prism software (Graphpad, San Diego, Calif.) to calculate IC50's.

TABLE 2

Example	Biological Data Summary. Whole Cell Antiproliferation IC <sub>50</sub> values of compounds of Formula I.	
	Ba/F3 p210 whole cell proliferation assay	Ba/F3 p210 T315I whole cell proliferation assay
1	+++	+++
2	+++	+++
3	+++	+++
4	+++	+++
5	+++	+++
6	+++	+++
7	+++	++
8	+++	+++
9	+++	++
10	+++	++
11	+++	+++
12	+++	+++

TABLE 2-continued

Biological Data Summary. Whole Cell Antiproliferation IC <sub>50</sub> values of compounds of Formula I.		
Example	Ba/F3 p210 whole cell proliferation assay	Ba/F3 p210 T315I whole cell proliferation assay
13	+++	+++
14	+++	+++
15	+++	+++
16	+++	++
17	+++	+++
18	+++	+++
19	+++	+
20	+++	++
21	+++	+++
22	+++	+++
23	+++	++
24	+++	‡
25	+++	+++
26	n/a	n/a
27	+++	+++
28	+++	++
29	++	‡
30	+++	++

TABLE 2-continued

Biological Data Summary. Whole Cell Antiproliferation IC <sub>50</sub> values of compounds of Formula I.		
Example	Ba/F3 p210 whole cell proliferation assay	Ba/F3 p210 T315I whole cell proliferation assay
31	+++	+++
32	+++	+++
33	++	++
34	+++	++
35	++	‡
36	+	‡
37	+++	+++
38	++	‡
39	++	+
40	++	++
41	++	++
42	+++	+++

+++ = &lt;0.1 µM;

++ = &lt;1.0 µM;

+ = &lt;10 µM;

‡ &lt;100 µM;

n/a = not available

## SEQUENCE LISTING

&lt;160&gt; NUMBER OF SEQ ID NOS: 11

<210> SEQ ID NO 1  
<211> LENGTH: 278  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 1

Gly Thr Ser Met Asp Pro Ser Ser Pro Asn Tyr Asp Lys Trp Glu Met  
1               5               10               15

Glu Arg Thr Asp Ile Thr Met Lys His Lys Leu Gly Gly Gln Tyr  
20              25              30

Gly Glu Val Tyr Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr Val Ala  
35              40              45

Val Lys Thr Leu Lys Glu Asp Thr Met Glu Val Glu Glu Phe Leu Lys  
50              55              60

Glu Ala Ala Val Met Lys Glu Ile Lys His Pro Asn Leu Val Gln Leu  
65              70              75              80

Leu Gly Val Cys Thr Arg Glu Pro Pro Phe Tyr Ile Ile Thr Glu Phe  
85              90              95

Met Thr Tyr Gly Asn Leu Leu Asp Tyr Leu Arg Glu Cys Asn Arg Gln  
100            105            110

Glu Val Asn Ala Val Val Leu Leu Tyr Met Ala Thr Gln Ile Ser Ser  
115            120            125

Ala Met Glu Tyr Leu Glu Lys Lys Asn Phe Ile His Arg Asp Leu Ala  
130            135            140

Ala Arg Asn Cys Leu Val Gly Glu Asn His Leu Val Lys Val Ala Asp  
145            150            155            160

Phe Gly Leu Ser Arg Leu Met Thr Gly Asp Thr Tyr Thr Ala His Ala  
165            170            175

---

-continued

---

Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ser Leu Ala Tyr  
180 185 190

Asn Lys Phe Ser Ile Lys Ser Asp Val Trp Ala Phe Gly Val Leu Leu  
195 200 205

Trp Glu Ile Ala Thr Tyr Gly Met Ser Pro Tyr Pro Gly Ile Asp Leu  
210 215 220

Ser Gln Val Tyr Glu Leu Leu Glu Lys Asp Tyr Arg Met Glu Arg Pro  
225 230 235 240

Glu Gly Cys Pro Glu Lys Val Tyr Glu Leu Met Arg Ala Cys Trp Gln  
245 250 255

Trp Asn Pro Ser Asp Arg Pro Ser Phe Ala Glu Ile His Gln Ala Phe  
260 265 270

Glu Thr Met Phe Gln Glu  
275

<210> SEQ ID NO 2  
<211> LENGTH: 278  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

Gly Thr Ser Met Asp Pro Ser Ser Pro Asn Tyr Asp Lys Trp Glu Met  
1 5 10 15

Glu Arg Thr Asp Ile Thr Met Lys His Lys Leu Gly Gly Gln Tyr  
20 25 30

Gly Glu Val Tyr Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr Val Ala  
35 40 45

Val Lys Thr Leu Lys Glu Asp Thr Met Glu Val Glu Glu Phe Leu Lys  
50 55 60

Glu Ala Ala Val Met Lys Glu Ile Lys His Pro Asn Leu Val Gln Leu  
65 70 75 80

Leu Gly Val Cys Thr Arg Glu Pro Pro Phe Tyr Ile Ile Ile Glu Phe  
85 90 95

Met Thr Tyr Gly Asn Leu Leu Asp Tyr Leu Arg Glu Cys Asn Arg Gln  
100 105 110

Glu Val Asn Ala Val Val Leu Leu Tyr Met Ala Thr Gln Ile Ser Ser  
115 120 125

Ala Met Glu Tyr Leu Glu Lys Lys Asn Phe Ile His Arg Asp Leu Ala  
130 135 140

Ala Arg Asn Cys Leu Val Gly Glu Asn His Leu Val Lys Val Ala Asp  
145 150 155 160

Phe Gly Leu Ser Arg Leu Met Thr Gly Asp Thr Tyr Thr Ala His Ala  
165 170 175

Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala Pro Glu Ser Leu Ala Tyr  
180 185 190

Asn Lys Phe Ser Ile Lys Ser Asp Val Trp Ala Phe Gly Val Leu Leu  
195 200 205

Trp Glu Ile Ala Thr Tyr Gly Met Ser Pro Tyr Pro Gly Ile Asp Leu  
210 215 220

Ser Gln Val Tyr Glu Leu Leu Glu Lys Asp Tyr Arg Met Glu Arg Pro  
225 230 235 240

Glu Gly Cys Pro Glu Lys Val Tyr Glu Leu Met Arg Ala Cys Trp Gln  
245 250 255

---

-continued

---

Trp Asn Pro Ser Asp Arg Pro Ser Phe Ala Glu Ile His Gln Ala Phe  
260 265 270

Glu Thr Met Phe Gln Glu  
275

<210> SEQ ID NO 3  
<211> LENGTH: 2031  
<212> TYPE: PRT  
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

Met Val Asp Pro Val Gly Phe Ala Glu Ala Trp Lys Ala Gln Phe Pro  
1 5 10 15

Asp Ser Glu Pro Pro Arg Met Glu Leu Arg Ser Val Gly Asp Ile Glu  
20 25 30

Gln Glu Leu Glu Arg Cys Lys Ala Ser Ile Arg Arg Leu Glu Gln Glu  
35 40 45

Val Asn Gln Glu Arg Phe Arg Met Ile Tyr Leu Gln Thr Leu Leu Ala  
50 55 60

Lys Glu Lys Lys Ser Tyr Asp Arg Gln Arg Trp Gly Phe Arg Arg Ala  
65 70 75 80

Ala Gln Ala Pro Asp Gly Ala Ser Glu Pro Arg Ala Ser Ala Ser Arg  
85 90 95

Pro Gln Pro Ala Pro Ala Asp Gly Ala Asp Pro Pro Pro Ala Glu Glu  
100 105 110

Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro  
115 120 125

Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp  
130 135 140

Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg  
145 150 155 160

Ile Arg Lys Gly His Gly Gln Pro Gly Ala Asp Ala Glu Lys Pro Phe  
165 170 175

Tyr Val Asn Val Glu Phe His His Glu Arg Gly Leu Val Lys Val Asn  
180 185 190

Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met  
195 200 205

Gln Met Glu Arg Lys Lys Ser Gln His Gly Ala Gly Ser Ser Val Gly  
210 215 220

Asp Ala Ser Arg Pro Pro Tyr Arg Gly Arg Ser Ser Glu Ser Ser Cys  
225 230 235 240

Gly Val Asp Gly Asp Tyr Glu Asp Ala Glu Leu Asn Pro Arg Phe Leu  
245 250 255

Lys Asp Asn Leu Ile Asp Ala Asn Gly Gly Ser Arg Pro Pro Trp Pro  
260 265 270

Pro Leu Glu Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Ile Met  
275 280 285

Glu Gly Glu Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu  
290 295 300

Gln Glu Lys Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser  
305 310 315 320

Phe Glu Asp Cys Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu

---

-continued

---

325	330	335
Asn Leu Thr Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg		
340	345	350
Val Ser Pro Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg		
355	360	365
Ser Pro Ser Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro		
370	375	380
Thr Pro Gln Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser		
385	390	395
Glu Ala Thr Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn		
405	410	415
Asp Asp Glu Gly Ala Phe His Gly Asp Ala Asp Gly Ser Phe Gly Thr		
420	425	430
Pro Pro Gly Tyr Gly Cys Ala Ala Asp Arg Ala Glu Glu Gln Arg Arg		
435	440	445
His Gln Asp Gly Leu Pro Tyr Ile Asp Asp Ser Pro Ser Ser Ser Pro		
450	455	460
His Leu Ser Ser Lys Gly Arg Gly Ser Arg Asp Ala Leu Val Ser Gly		
465	470	475
Ala Leu Lys Ser Thr Lys Ala Ser Glu Leu Asp Leu Glu Lys Gly Leu		
485	490	495
Glu Met Arg Lys Trp Val Leu Ser Gly Ile Leu Ala Ser Glu Glu Thr		
500	505	510
Tyr Leu Ser His Leu Glu Ala Leu Leu Pro Met Lys Pro Leu Lys		
515	520	525
Ala Ala Ala Thr Thr Ser Gln Pro Val Leu Thr Ser Gln Gln Ile Glu		
530	535	540
Thr Ile Phe Phe Lys Val Pro Glu Leu Tyr Glu Ile His Lys Glu Ser		
545	550	555
Tyr Asp Gly Leu Phe Pro Arg Val Gln Gln Trp Ser His Gln Gln Arg		
565	570	575
Val Gly Asp Leu Phe Gln Lys Leu Ala Ser Gln Leu Gly Val Tyr Arg		
580	585	590
Ala Phe Val Asp Asn Tyr Gly Val Ala Met Glu Met Ala Glu Lys Cys		
595	600	605
Cys Gln Ala Asn Ala Gln Phe Ala Glu Ile Ser Glu Asn Leu Arg Ala		
610	615	620
Arg Ser Asn Lys Asp Ala Lys Asp Pro Thr Thr Lys Asn Ser Leu Glu		
625	630	635
640		
Thr Leu Leu Tyr Lys Pro Val Asp Arg Val Thr Arg Ser Thr Leu Val		
645	650	655
Leu His Asp Leu Leu Lys His Thr Pro Ala Ser His Pro Asp His Pro		
660	665	670
Leu Leu Gln Asp Ala Leu Arg Ile Ser Gln Asn Phe Leu Ser Ser Ile		
675	680	685
Asn Glu Glu Ile Thr Pro Arg Arg Gln Ser Met Thr Val Lys Lys Gly		
690	695	700
Glu His Arg Gln Leu Leu Lys Asp Ser Phe Met Val Glu Leu Val Glu		
705	710	715
720		
Gly Ala Arg Lys Leu Arg His Val Phe Leu Phe Thr Asp Leu Leu Leu		
725	730	735

---

-continued

---

Cys Thr Lys Leu Lys Lys Gln Ser Gly Gly Lys Thr Gln Gln Tyr Asp  
740 745 750

Cys Lys Trp Tyr Ile Pro Leu Thr Asp Leu Ser Phe Gln Met Val Asp  
755 760 765

Glu Leu Glu Ala Val Pro Asn Ile Pro Leu Val Pro Asp Glu Glu Leu  
770 775 780

Asp Ala Leu Lys Ile Lys Ile Ser Gln Ile Lys Ser Asp Ile Gln Arg  
785 790 795 800

Glu Lys Arg Ala Asn Lys Gly Ser Lys Ala Thr Glu Arg Leu Lys Lys  
805 810 815

Lys Leu Ser Glu Gln Glu Ser Leu Leu Leu Met Ser Pro Ser Met  
820 825 830

Ala Phe Arg Val His Ser Arg Asn Gly Lys Ser Tyr Thr Phe Leu Ile  
835 840 845

Ser Ser Asp Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln  
850 855 860

Gln Lys Lys Cys Phe Arg Ser Phe Ser Leu Thr Ser Val Glu Leu Gln  
865 870 875 880

Met Leu Thr Asn Ser Cys Val Lys Leu Gln Thr Val His Ser Ile Pro  
885 890 895

Leu Thr Ile Asn Lys Glu Asp Asp Glu Ser Pro Gly Leu Tyr Gly Phe  
900 905 910

Leu Asn Val Ile Val His Ser Ala Thr Gly Phe Lys Gln Ser Ser Lys  
915 920 925

Ala Leu Gln Arg Pro Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser  
930 935 940

Glu Ala Ala Arg Trp Asn Ser Lys Glu Asn Leu Ala Gly Pro Ser  
945 950 955 960

Glu Asn Asp Pro Asn Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser  
965 970 975

Gly Asp Asn Thr Leu Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu  
980 985 990

Gly Tyr Asn His Asn Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly  
995 1000 1005

Gln Gly Trp Val Pro Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu  
1010 1015 1020

Glu Lys His Ser Trp Tyr His Gly Pro Val Ser Arg Asn Ala Ala  
1025 1030 1035

Glu Tyr Pro Leu Ser Ser Gly Ile Asn Gly Ser Phe Leu Val Arg  
1040 1045 1050

Glu Ser Glu Ser Ser Pro Ser Gln Arg Ser Ile Ser Leu Arg Tyr  
1055 1060 1065

Glu Gly Arg Val Tyr His Tyr Arg Ile Asn Thr Ala Ser Asp Gly  
1070 1075 1080

Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe Asn Thr Leu Ala Glu  
1085 1090 1095

Leu Val His His His Ser Thr Val Ala Asp Gly Leu Ile Thr Thr  
1100 1105 1110

Leu His Tyr Pro Ala Pro Lys Arg Asn Lys Pro Thr Val Tyr Gly  
1115 1120 1125

-continued

---

Val	Ser	Pro	Asn	Tyr	Asp	Lys	Trp	Glu	Met	Glu	Arg	Thr	Asp	Ile
1130														1140
Thr	Met	Lys	His	Lys	Leu	Gly	Gly	Gly	Gln	Tyr	Gly	Glu	Val	Tyr
1145						1150								1155
Glu	Gly	Val	Trp	Lys	Lys	Tyr	Ser	Leu	Thr	Val	Ala	Val	Lys	Thr
1160														1170
Leu	Lys	Glu	Asp	Thr	Met	Glu	Val	Glu	Glu	Phe	Leu	Lys	Glu	Ala
1175						1180								1185
Ala	Val	Met	Lys	Glu	Ile	Lys	His	Pro	Asn	Leu	Val	Gln	Leu	Leu
1190														1200
Gly	Val	Cys	Thr	Arg	Glu	Pro	Pro	Phe	Tyr	Ile	Ile	Thr	Glu	Phe
1205														1215
Met	Thr	Tyr	Gly	Asn	Leu	Leu	Asp	Tyr	Leu	Arg	Glu	Cys	Asn	Arg
1220														1230
Gln	Glu	Val	Asn	Ala	Val	Val	Leu	Leu	Tyr	Met	Ala	Thr	Gln	Ile
1235														1245
Ser	Ser	Ala	Met	Glu	Tyr	Leu	Glu	Lys	Lys	Asn	Phe	Ile	His	Arg
1250														1260
Asp	Leu	Ala	Ala	Arg	Asn	Cys	Leu	Val	Gly	Glu	Asn	His	Leu	Val
1265														1275
Lys	Val	Ala	Asp	Phe	Gly	Leu	Ser	Arg	Leu	Met	Thr	Gly	Asp	Thr
1280														1290
Tyr	Thr	Ala	His	Ala	Gly	Ala	Lys	Phe	Pro	Ile	Lys	Trp	Thr	Ala
1295														1305
Pro	Glu	Ser	Leu	Ala	Tyr	Asn	Lys	Phe	Ser	Ile	Lys	Ser	Asp	Val
1310														1320
Trp	Ala	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Ala	Thr	Tyr	Gly	Met
1325														1335
Ser	Pro	Tyr	Pro	Gly	Ile	Asp	Arg	Ser	Gln	Val	Tyr	Glu	Leu	Leu
1340														1350
Glu	Lys	Asp	Tyr	Arg	Met	Lys	Arg	Pro	Glu	Gly	Cys	Pro	Glu	Lys
1355														1365
Val	Tyr	Glu	Leu	Met	Arg	Ala	Cys	Trp	Gln	Trp	Asn	Pro	Ser	Asp
1370														1380
Arg	Pro	Ser	Phe	Ala	Glu	Ile	His	Gln	Ala	Phe	Glu	Thr	Met	Phe
1385														1395
Gln	Glu	Ser	Ser	Ile	Ser	Asp	Glu	Val	Glu	Lys	Glu	Leu	Gly	Lys
1400														1410
Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu	Leu	Gln	Ala	Pro	Glu
1415														1425
Leu	Pro	Thr	Lys	Thr	Arg	Thr	Ser	Arg	Arg	Ala	Ala	Glu	His	Arg
1430														1440
Asp	Thr	Thr	Asp	Val	Pro	Glu	Met	Pro	His	Ser	Lys	Gly	Gln	Gly
1445														1455
Glu	Ser	Asp	Pro	Leu	Asp	His	Glu	Pro	Ala	Val	Ser	Pro	Leu	Leu
1460														1470
Pro	Arg	Lys	Glu	Arg	Gly	Pro	Pro	Glu	Gly	Leu	Asn	Glu	Asp	
1475														1485
Glu	Arg	Leu	Leu	Pro	Lys	Asp	Lys	Lys	Thr	Asn	Leu	Phe	Ser	Ala
1490														1500
Leu	Ile	Lys	Lys	Lys	Lys	Thr	Ala	Pro	Thr	Pro	Pro	Lys	Arg	

---

-continued

---

1505	1510	1515
Ser Ser Ser Phe Arg Glu Met Asp Gly Gln Pro Glu Arg Arg Gly		
1520	1525	1530
Ala Gly Glu Glu Glu Gly Arg Asp Ile Ser Asn Gly Ala Leu Ala		
1535	1540	1545
Phe Thr Pro Leu Asp Thr Ala Asp Pro Ala Lys Ser Pro Lys Pro		
1550	1555	1560
Ser Asn Gly Ala Gly Val Pro Asn Gly Ala Leu Arg Glu Ser Gly		
1565	1570	1575
Gly Ser Gly Phe Arg Ser Pro His Leu Trp Lys Lys Ser Ser Thr		
1580	1585	1590
Leu Thr Ser Ser Arg Leu Ala Thr Gly Glu Glu Glu Gly Gly Gly		
1595	1600	1605
Ser Ser Ser Lys Arg Phe Leu Arg Ser Cys Ser Val Ser Cys Val		
1610	1615	1620
Pro His Gly Ala Lys Asp Thr Glu Trp Arg Ser Val Thr Leu Pro		
1625	1630	1635
Arg Asp Leu Gln Ser Thr Gly Arg Gln Phe Asp Ser Ser Thr Phe		
1640	1645	1650
Gly Gly His Lys Ser Glu Lys Pro Ala Leu Pro Arg Lys Arg Ala		
1655	1660	1665
Gly Glu Asn Arg Ser Asp Gln Val Thr Arg Gly Thr Val Thr Pro		
1670	1675	1680
Pro Pro Arg Leu Val Lys Lys Asn Glu Glu Ala Ala Asp Glu Val		
1685	1690	1695
Phe Lys Asp Ile Met Glu Ser Ser Pro Gly Ser Ser Pro Pro Asn		
1700	1705	1710
Leu Thr Pro Lys Pro Leu Arg Arg Gln Val Thr Val Ala Pro Ala		
1715	1720	1725
Ser Gly Leu Pro His Lys Glu Glu Ala Trp Lys Gly Ser Ala Leu		
1730	1735	1740
Gly Thr Pro Ala Ala Ala Glu Pro Val Thr Pro Thr Ser Lys Ala		
1745	1750	1755
Gly Ser Gly Ala Pro Arg Gly Thr Ser Lys Gly Pro Ala Glu Glu		
1760	1765	1770
Ser Arg Val Arg Arg His Lys His Ser Ser Glu Ser Pro Gly Arg		
1775	1780	1785
Asp Lys Gly Lys Leu Ser Lys Leu Lys Pro Ala Pro Pro Pro Pro		
1790	1795	1800
Pro Ala Ala Ser Ala Gly Lys Ala Gly Gly Lys Pro Ser Gln Arg		
1805	1810	1815
Pro Gly Gln Glu Ala Ala Gly Glu Ala Val Leu Gly Ala Lys Thr		
1820	1825	1830
Lys Ala Thr Ser Leu Val Asp Ala Val Asn Ser Asp Ala Ala Lys		
1835	1840	1845
Pro Ser Gln Pro Ala Glu Gly Leu Lys Lys Pro Val Leu Pro Ala		
1850	1855	1860
Thr Pro Lys Pro His Pro Ala Lys Pro Ser Gly Thr Pro Ile Ser		
1865	1870	1875
Pro Ala Pro Val Pro Leu Ser Thr Leu Pro Ser Ala Ser Ser Ala		
1880	1885	1890

---

-continued

---

Leu Ala Gly Asp Gln Pro Ser Ser Thr Ala Phe Ile Pro Leu Ile  
 1895 1900 1905  
 Ser Thr Arg Val Ser Leu Arg Lys Thr Arg Gln Pro Pro Glu Arg  
 1910 1915 1920  
 Ala Ser Gly Ala Ile Thr Lys Gly Val Val Leu Asp Ser Thr Glu  
 1925 1930 1935  
 Ala Leu Cys Leu Ala Ile Ser Gly Asn Ser Glu Gln Met Ala Ser  
 1940 1945 1950  
 His Ser Ala Val Leu Glu Ala Gly Lys Asn Leu Tyr Thr Phe Cys  
 1955 1960 1965  
 Val Ser Tyr Val Asp Ser Ile Gln Gln Met Arg Asn Lys Phe Ala  
 1970 1975 1980  
 Phe Arg Glu Ala Ile Asn Lys Leu Glu Asn Asn Leu Arg Glu Leu  
 1985 1990 1995  
 Gln Ile Cys Pro Ala Ser Ala Gly Ser Gly Pro Ala Ala Thr Gln  
 2000 2005 2010  
 Asp Phe Ser Lys Leu Leu Ser Ser Val Lys Glu Ile Ser Asp Ile  
 2015 2020 2025  
 Val Gln Arg  
 2030

<210> SEQ ID NO 4  
 <211> LENGTH: 2006  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens  
 <400> SEQUENCE: 4

Met Val Asp Pro Val Gly Phe Ala Glu Ala Trp Lys Ala Gln Phe Pro  
 1 5 10 15  
 Asp Ser Glu Pro Pro Arg Met Glu Leu Arg Ser Val Gly Asp Ile Glu  
 20 25 30  
 Gln Glu Leu Glu Arg Cys Lys Ala Ser Ile Arg Arg Leu Glu Gln Glu  
 35 40 45  
 Val Asn Gln Glu Arg Phe Arg Met Ile Tyr Leu Gln Thr Leu Leu Ala  
 50 55 60  
 Lys Glu Lys Lys Ser Tyr Asp Arg Gln Arg Trp Gly Phe Arg Arg Ala  
 65 70 75 80  
 Ala Gln Ala Pro Asp Gly Ala Ser Glu Pro Arg Ala Ser Ala Ser Arg  
 85 90 95  
 Pro Gln Pro Ala Pro Ala Asp Gly Ala Asp Pro Pro Pro Ala Glu Glu  
 100 105 110  
 Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro  
 115 120 125  
 Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp  
 130 135 140  
 Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg  
 145 150 155 160  
 Ile Arg Lys Gly His Gly Gln Pro Gly Ala Asp Ala Glu Lys Pro Phe  
 165 170 175  
 Tyr Val Asn Val Glu Phe His His Glu Arg Gly Leu Val Lys Val Asn  
 180 185 190  
 Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met

---

-continued

---

195	200	205
Gln Met Glu Arg Lys Lys Ser Gln His Gly Ala Gly Ser Ser Val Gly		
210	215	220
Asp Ala Ser Arg Pro Pro Tyr Arg Gly Arg Ser Ser Glu Ser Ser Cys		
225	230	235
240		
Gly Val Asp Gly Asp Tyr Glu Asp Ala Glu Leu Asn Pro Arg Phe Leu		
245	250	255
Lys Asp Asn Leu Ile Asp Ala Asn Gly Gly Ser Arg Pro Pro Trp Pro		
260	265	270
Pro Leu Glu Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Ile Met		
275	280	285
Glu Gly Glu Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu		
290	295	300
Gln Glu Lys Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser		
305	310	315
320		
Phe Glu Asp Cys Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu		
325	330	335
Asn Leu Thr Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg		
340	345	350
Val Ser Pro Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg		
355	360	365
Ser Pro Ser Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro		
370	375	380
Thr Pro Gln Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser		
385	390	395
400		
Glu Ala Thr Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn		
405	410	415
Asp Asp Glu Gly Ala Phe His Gly Asp Ala Asp Gly Ser Phe Gly Thr		
420	425	430
Pro Pro Gly Tyr Gly Cys Ala Ala Asp Arg Ala Glu Glu Gln Arg Arg		
435	440	445
His Gln Asp Gly Leu Pro Tyr Ile Asp Asp Ser Pro Ser Ser Ser Pro		
450	455	460
His Leu Ser Ser Lys Gly Arg Gly Ser Arg Asp Ala Leu Val Ser Gly		
465	470	475
480		
Ala Leu Lys Ser Thr Lys Ala Ser Glu Leu Asp Leu Glu Lys Gly Leu		
485	490	495
Glu Met Arg Lys Trp Val Leu Ser Gly Ile Leu Ala Ser Glu Glu Thr		
500	505	510
Tyr Leu Ser His Leu Glu Ala Leu Leu Pro Met Lys Pro Leu Lys		
515	520	525
Ala Ala Ala Thr Thr Ser Gln Pro Val Leu Thr Ser Gln Gln Ile Glu		
530	535	540
Thr Ile Phe Phe Lys Val Pro Glu Leu Tyr Glu Ile His Lys Glu Ser		
545	550	555
560		
Tyr Asp Gly Leu Phe Pro Arg Val Gln Gln Trp Ser His Gln Gln Arg		
565	570	575
Val Gly Asp Leu Phe Gln Lys Leu Ala Ser Gln Leu Gly Val Tyr Arg		
580	585	590
Ala Phe Val Asp Asn Tyr Gly Val Ala Met Glu Met Ala Glu Lys Cys		
595	600	605

---

-continued

---

Cys Gln Ala Asn Ala Gln Phe Ala Glu Ile Ser Glu Asn Leu Arg Ala  
610 615 620

Arg Ser Asn Lys Asp Ala Lys Asp Pro Thr Thr Lys Asn Ser Leu Glu  
625 630 635 640

Thr Leu Leu Tyr Lys Pro Val Asp Arg Val Thr Arg Ser Thr Leu Val  
645 650 655

Leu His Asp Leu Leu Lys His Thr Pro Ala Ser His Pro Asp His Pro  
660 665 670

Leu Leu Gln Asp Ala Leu Arg Ile Ser Gln Asn Phe Leu Ser Ser Ile  
675 680 685

Asn Glu Glu Ile Thr Pro Arg Arg Gln Ser Met Thr Val Lys Lys Gly  
690 695 700

Glu His Arg Gln Leu Leu Lys Asp Ser Phe Met Val Glu Leu Val Glu  
705 710 715 720

Gly Ala Arg Lys Leu Arg His Val Phe Leu Phe Thr Asp Leu Leu Leu  
725 730 735

Cys Thr Lys Leu Lys Lys Gln Ser Gly Gly Lys Thr Gln Gln Tyr Asp  
740 745 750

Cys Lys Trp Tyr Ile Pro Leu Thr Asp Leu Ser Phe Gln Met Val Asp  
755 760 765

Glu Leu Glu Ala Val Pro Asn Ile Pro Leu Val Pro Asp Glu Glu Leu  
770 775 780

Asp Ala Leu Lys Ile Lys Ile Ser Gln Ile Lys Ser Asp Ile Gln Arg  
785 790 795 800

Glu Lys Arg Ala Asn Lys Gly Ser Lys Ala Thr Glu Arg Leu Lys Lys  
805 810 815

Lys Leu Ser Glu Gln Glu Ser Leu Leu Leu Met Ser Pro Ser Met  
820 825 830

Ala Phe Arg Val His Ser Arg Asn Gly Lys Ser Tyr Thr Phe Leu Ile  
835 840 845

Ser Ser Asp Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln  
850 855 860

Gln Lys Lys Cys Phe Arg Ser Phe Ser Leu Thr Ser Val Glu Leu Gln  
865 870 875 880

Met Leu Thr Asn Ser Cys Val Lys Leu Gln Thr Val His Ser Ile Pro  
885 890 895

Leu Thr Ile Asn Lys Glu Glu Ala Leu Gln Arg Pro Val Ala Ser Asp  
900 905 910

Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp Asn Ser Lys Glu  
915 920 925

Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp Pro Asn Leu Phe Val Ala  
930 935 940

Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys  
945 950 955 960

Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn Gly Glu Trp Cys  
965 970 975

Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro Ser Asn Tyr Ile  
980 985 990

Thr Pro Val Asn Ser Leu Glu Lys His Ser Trp Tyr His Gly Pro Val  
995 1000 1005

-continued

---

Ser	Arg	Asn	Ala	Ala	Glu	Tyr	Pro	Leu	Ser	Ser	Gly	Ile	Asn	Gly
1010					1015							1020		
Ser	Phe	Leu	Val	Arg	Glu	Ser	Glu	Ser	Ser	Pro	Ser	Gln	Arg	Ser
1025					1030							1035		
Ile	Ser	Leu	Arg	Tyr	Glu	Gly	Arg	Val	Tyr	His	Tyr	Arg	Ile	Asn
1040					1045							1050		
Thr	Ala	Ser	Asp	Gly	Lys	Leu	Tyr	Val	Ser	Ser	Glu	Ser	Arg	Phe
1055					1060							1065		
Asn	Thr	Leu	Ala	Glu	Leu	Val	His	His	His	Ser	Thr	Val	Ala	Asp
1070					1075							1080		
Gly	Leu	Ile	Thr	Thr	Leu	His	Tyr	Pro	Ala	Pro	Lys	Arg	Asn	Lys
1085					1090							1095		
Pro	Thr	Val	Tyr	Gly	Val	Ser	Pro	Asn	Tyr	Asp	Lys	Trp	Glu	Met
1100					1105							1110		
Glu	Arg	Thr	Asp	Ile	Thr	Met	Lys	His	Lys	Leu	Gly	Gly	Gly	Gln
1115					1120							1125		
Tyr	Gly	Glu	Val	Tyr	Glu	Gly	Val	Trp	Lys	Lys	Tyr	Ser	Leu	Thr
1130					1135							1140		
Val	Ala	Val	Lys	Thr	Leu	Lys	Glu	Asp	Thr	Met	Glu	Val	Glu	Glu
1145					1150							1155		
Phe	Leu	Lys	Glu	Ala	Ala	Val	Met	Lys	Glu	Ile	Lys	His	Pro	Asn
1160					1165							1170		
Leu	Val	Gln	Leu	Leu	Gly	Val	Cys	Thr	Arg	Glu	Pro	Pro	Phe	Tyr
1175					1180							1185		
Ile	Ile	Thr	Glu	Phe	Met	Thr	Tyr	Gly	Asn	Leu	Leu	Asp	Tyr	Leu
1190					1195							1200		
Arg	Glu	Cys	Asn	Arg	Gln	Glu	Val	Asn	Ala	Val	Val	Leu	Leu	Tyr
1205					1210							1215		
Met	Ala	Thr	Gln	Ile	Ser	Ser	Ala	Met	Glu	Tyr	Leu	Glu	Lys	Lys
1220					1225							1230		
Asn	Phe	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Cys	Leu	Val	Gly
1235					1240							1245		
Glu	Asn	His	Leu	Val	Lys	Val	Ala	Asp	Phe	Gly	Leu	Ser	Arg	Leu
1250					1255							1260		
Met	Thr	Gly	Asp	Thr	Tyr	Thr	Ala	His	Ala	Gly	Ala	Lys	Phe	Pro
1265					1270							1275		
Ile	Lys	Trp	Thr	Ala	Pro	Glu	Ser	Leu	Ala	Tyr	Asn	Lys	Phe	Ser
1280					1285							1290		
Ile	Lys	Ser	Asp	Val	Trp	Ala	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile
1295					1300							1305		
Ala	Thr	Tyr	Gly	Met	Ser	Pro	Tyr	Pro	Gly	Ile	Asp	Arg	Ser	Gln
1310					1315							1320		
Val	Tyr	Glu	Leu	Leu	Glu	Lys	Asp	Tyr	Arg	Met	Lys	Arg	Pro	Glu
1325					1330							1335		
Gly	Cys	Pro	Glu	Lys	Val	Tyr	Glu	Leu	Met	Arg	Ala	Cys	Trp	Gln
1340					1345							1350		
Trp	Asn	Pro	Ser	Asp	Arg	Pro	Ser	Phe	Ala	Glu	Ile	His	Gln	Ala
1355					1360							1365		
Phe	Glu	Thr	Met	Phe	Gln	Glu	Ser	Ser	Ile	Ser	Asp	Glu	Val	Glu
1370					1375							1380		
Lys	Glu	Leu	Gly	Lys	Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu

---

-continued

---

1385	1390	1395
Leu Gln Ala Pro Glu Leu Pro Thr Lys Thr Arg Thr Ser Arg Arg		
1400	1405	1410
Ala Ala Glu His Arg Asp Thr Thr Asp Val Pro Glu Met Pro His		
1415	1420	1425
Ser Lys Gly Gln Gly Glu Ser Asp Pro Leu Asp His Glu Pro Ala		
1430	1435	1440
Val Ser Pro Leu Leu Pro Arg Lys Glu Arg Gly Pro Pro Glu Gly		
1445	1450	1455
Gly Leu Asn Glu Asp Glu Arg Leu Leu Pro Lys Asp Lys Lys Thr		
1460	1465	1470
Asn Leu Phe Ser Ala Leu Ile Lys Lys Lys Lys Thr Ala Pro		
1475	1480	1485
Thr Pro Pro Lys Arg Ser Ser Ser Phe Arg Glu Met Asp Gly Gln		
1490	1495	1500
Pro Glu Arg Arg Gly Ala Gly Glu Glu Glu Gly Arg Asp Ile Ser		
1505	1510	1515
Asn Gly Ala Leu Ala Phe Thr Pro Leu Asp Thr Ala Asp Pro Ala		
1520	1525	1530
Lys Ser Pro Lys Pro Ser Asn Gly Ala Gly Val Pro Asn Gly Ala		
1535	1540	1545
Leu Arg Glu Ser Gly Gly Ser Gly Phe Arg Ser Pro His Leu Trp		
1550	1555	1560
Lys Lys Ser Ser Thr Leu Thr Ser Ser Arg Leu Ala Thr Gly Glu		
1565	1570	1575
Glu Glu Gly Gly Ser Ser Ser Lys Arg Phe Leu Arg Ser Cys		
1580	1585	1590
Ser Val Ser Cys Val Pro His Gly Ala Lys Asp Thr Glu Trp Arg		
1595	1600	1605
Ser Val Thr Leu Pro Arg Asp Leu Gln Ser Thr Gly Arg Gln Phe		
1610	1615	1620
Asp Ser Ser Thr Phe Gly Gly His Lys Ser Glu Lys Pro Ala Leu		
1625	1630	1635
Pro Arg Lys Arg Ala Gly Glu Asn Arg Ser Asp Gln Val Thr Arg		
1640	1645	1650
Gly Thr Val Thr Pro Pro Pro Arg Leu Val Lys Lys Asn Glu Glu		
1655	1660	1665
Ala Ala Asp Glu Val Phe Lys Asp Ile Met Glu Ser Ser Pro Gly		
1670	1675	1680
Ser Ser Pro Pro Asn Leu Thr Pro Lys Pro Leu Arg Arg Gln Val		
1685	1690	1695
Thr Val Ala Pro Ala Ser Gly Leu Pro His Lys Glu Glu Ala Trp		
1700	1705	1710
Lys Gly Ser Ala Leu Gly Thr Pro Ala Ala Ala Glu Pro Val Thr		
1715	1720	1725
Pro Thr Ser Lys Ala Gly Ser Gly Ala Pro Arg Gly Thr Ser Lys		
1730	1735	1740
Gly Pro Ala Glu Glu Ser Arg Val Arg Arg His Lys His Ser Ser		
1745	1750	1755
Glu Ser Pro Gly Arg Asp Lys Gly Lys Leu Ser Lys Leu Lys Pro		
1760	1765	1770

---

-continued

---

Ala Pro Pro Pro Pro Pro Ala Ala Ser Ala Gly Lys Ala Gly Gly  
 1775 1780 1785  
 Lys Pro Ser Gln Arg Pro Gly Gln Glu Ala Ala Gly Glu Ala Val  
 1790 1795 1800  
 Leu Gly Ala Lys Thr Lys Ala Thr Ser Leu Val Asp Ala Val Asn  
 1805 1810 1815  
 Ser Asp Ala Ala Lys Pro Ser Gln Pro Ala Glu Gly Leu Lys Lys  
 1820 1825 1830  
 Pro Val Leu Pro Ala Thr Pro Lys Pro His Pro Ala Lys Pro Ser  
 1835 1840 1845  
 Gly Thr Pro Ile Ser Pro Ala Pro Val Pro Leu Ser Thr Leu Pro  
 1850 1855 1860  
 Ser Ala Ser Ser Ala Leu Ala Gly Asp Gln Pro Ser Ser Thr Ala  
 1865 1870 1875  
 Phe Ile Pro Leu Ile Ser Thr Arg Val Ser Leu Arg Lys Thr Arg  
 1880 1885 1890  
 Gln Pro Pro Glu Arg Ala Ser Gly Ala Ile Thr Lys Gly Val Val  
 1895 1900 1905  
 Leu Asp Ser Thr Glu Ala Leu Cys Leu Ala Ile Ser Gly Asn Ser  
 1910 1915 1920  
 Glu Gln Met Ala Ser His Ser Ala Val Leu Glu Ala Gly Lys Asn  
 1925 1930 1935  
 Leu Tyr Thr Phe Cys Val Ser Tyr Val Asp Ser Ile Gln Gln Met  
 1940 1945 1950  
 Arg Asn Lys Phe Ala Phe Arg Glu Ala Ile Asn Lys Leu Glu Asn  
 1955 1960 1965  
 Asn Leu Arg Glu Leu Gln Ile Cys Pro Ala Ser Ala Gly Ser Gly  
 1970 1975 1980  
 Pro Ala Ala Thr Gln Asp Phe Ser Lys Leu Leu Ser Ser Val Lys  
 1985 1990 1995  
 Glu Ile Ser Asp Ile Val Gln Arg  
 2000 2005

<210> SEQ ID NO 5  
 <211> LENGTH: 1530  
 <212> TYPE: PRT  
 <213> ORGANISM: Homo sapiens  
 <400> SEQUENCE: 5

Met	Val	Asp	Pro	Val	Gly	Phe	Ala	Glu	Ala	Trp	Lys	Ala	Gln	Phe	Pro	
1																15
Asp	Ser	Glu	Pro	Pro	Arg	Met	Glu	Leu	Arg	Ser	Val	Gly	Asp	Ile	Glu	
						20		25						30		
Gln	Glu	Leu	Glu	Arg	Cys	Lys	Ala	Ser	Ile	Arg	Arg	Leu	Glu	Gln	Glu	
						35		40						45		
Val	Asn	Gln	Glu	Arg	Phe	Arg	Met	Ile	Tyr	Leu	Gln	Thr	Leu	Leu	Ala	
							50		55					60		
Lys	Glu	Lys	Lys	Ser	Tyr	Asp	Arg	Gln	Arg	Trp	Gly	Phe	Arg	Arg	Ala	
						65		70		75				80		
Ala	Gln	Ala	Pro	Asp	Gly	Ala	Ser	Glu	Pro	Arg	Ala	Ser	Ala	Ser	Arg	
						85		90						95		
Pro	Gln	Pro	Ala	Pro	Ala	Asp	Gly	Ala	Asp	Pro	Pro	Ala	Glu	Glu		

---

-continued

---

100	105	110
Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro		
115	120	125
Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp		
130	135	140
Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg		
145	150	155
Ile Arg Lys Gly His Gln Pro Gly Ala Asp Ala Glu Lys Pro Phe		
165	170	175
Tyr Val Asn Val Glu Phe His His Glu Arg Gly Leu Val Lys Val Asn		
180	185	190
Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met		
195	200	205
Gln Met Glu Arg Lys Lys Ser Gln His Gly Ala Gly Ser Ser Val Gly		
210	215	220
Asp Ala Ser Arg Pro Pro Tyr Arg Gly Arg Ser Ser Glu Ser Ser Cys		
225	230	235
Gly Val Asp Gly Asp Tyr Glu Asp Ala Glu Leu Asn Pro Arg Phe Leu		
245	250	255
Lys Asp Asn Leu Ile Asp Ala Asn Gly Gly Ser Arg Pro Pro Trp Pro		
260	265	270
Pro Leu Glu Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Ile Met		
275	280	285
Glu Gly Glu Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu		
290	295	300
Gln Glu Lys Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser		
305	310	315
Phe Glu Asp Cys Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu		
325	330	335
Asn Leu Thr Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg		
340	345	350
Val Ser Pro Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg		
355	360	365
Ser Pro Ser Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro		
370	375	380
Thr Pro Gln Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser		
385	390	395
Glu Ala Thr Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn		
405	410	415
Asp Asp Glu Gly Ala Phe His Gly Asp Ala Glu Ala Leu Gln Arg Pro		
420	425	430
Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp		
435	440	445
Asn Ser Lys Glu Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp Pro Asn		
450	455	460
Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu		
465	470	475
Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn		
485	490	495
Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro		
500	505	510

-continued

Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu Glu Lys His Ser Trp Tyr  
 515 520 525  
 His Gly Pro Val Ser Arg Asn Ala Ala Glu Tyr Pro Leu Ser Ser Gly  
 530 535 540  
 Ile Asn Gly Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro Ser Gln  
 545 550 555 560  
 Arg Ser Ile Ser Leu Arg Tyr Glu Gly Arg Val Tyr His Tyr Arg Ile  
 565 570 575  
 Asn Thr Ala Ser Asp Gly Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe  
 580 585 590  
 Asn Thr Leu Ala Glu Leu Val His His His Ser Thr Val Ala Asp Gly  
 595 600 605  
 Leu Ile Thr Thr Leu His Tyr Pro Ala Pro Lys Arg Asn Lys Pro Thr  
 610 615 620  
 Val Tyr Gly Val Ser Pro Asn Tyr Asp Lys Trp Glu Met Glu Arg Thr  
 625 630 635 640  
 Asp Ile Thr Met Lys His Lys Leu Gly Gly Gln Tyr Gly Glu Val  
 645 650 655  
 Tyr Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr Val Ala Val Lys Thr  
 660 665 670  
 Leu Lys Glu Asp Thr Met Glu Val Glu Glu Phe Leu Lys Glu Ala Ala  
 675 680 685  
 Val Met Lys Glu Ile Lys His Pro Asn Leu Val Gln Leu Leu Gly Val  
 690 695 700  
 Cys Thr Arg Glu Pro Pro Phe Tyr Ile Ile Thr Glu Phe Met Thr Tyr  
 705 710 715 720  
 Gly Asn Leu Leu Asp Tyr Leu Arg Glu Cys Asn Arg Gln Glu Val Asn  
 725 730 735  
 Ala Val Val Leu Leu Tyr Met Ala Thr Gln Ile Ser Ser Ala Met Glu  
 740 745 750  
 Tyr Leu Glu Lys Lys Asn Phe Ile His Arg Asp Leu Ala Ala Arg Asn  
 755 760 765  
 Cys Leu Val Gly Glu Asn His Leu Val Lys Val Ala Asp Phe Gly Leu  
 770 775 780  
 Ser Arg Leu Met Thr Gly Asp Thr Tyr Thr Ala His Ala Gly Ala Lys  
 785 790 795 800  
 Phe Pro Ile Lys Trp Thr Ala Pro Glu Ser Leu Ala Tyr Asn Lys Phe  
 805 810 815  
 Ser Ile Lys Ser Asp Val Trp Ala Phe Gly Val Leu Leu Trp Glu Ile  
 820 825 830  
 Ala Thr Tyr Gly Met Ser Pro Tyr Pro Gly Ile Asp Arg Ser Gln Val  
 835 840 845  
 Tyr Glu Leu Leu Glu Lys Asp Tyr Arg Met Lys Arg Pro Glu Gly Cys  
 850 855 860  
 Pro Glu Lys Val Tyr Glu Leu Met Arg Ala Cys Trp Gln Trp Asn Pro  
 865 870 875 880  
 Ser Asp Arg Pro Ser Phe Ala Glu Ile His Gln Ala Phe Glu Thr Met  
 885 890 895  
 Phe Gln Glu Ser Ser Ile Ser Asp Glu Val Glu Lys Glu Leu Gly Lys  
 900 905 910

-continued

---

Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu	Leu	Gln	Ala	Pro	Glu	Leu
915						920					925				
Pro	Thr	Lys	Thr	Arg	Thr	Ser	Arg	Arg	Ala	Ala	Glu	His	Arg	Asp	Thr
930						935					940				
Thr	Asp	Val	Pro	Glu	Met	Pro	His	Ser	Lys	Gly	Gln	Gly	Glu	Ser	Asp
945						950			955				960		
Pro	Leu	Asp	His	Glu	Pro	Ala	Val	Ser	Pro	Leu	Leu	Pro	Arg	Lys	Glu
965						970			975						
Arg	Gly	Pro	Pro	Glu	Gly	Leu	Asn	Glu	Asp	Glu	Arg	Leu	Leu	Pro	
980						985			990						
Lys	Asp	Lys	Lys	Thr	Asn	Leu	Phe	Ser	Ala	Leu	Ile	Lys	Lys	Lys	Lys
995						1000			1005						
Lys	Thr	Ala	Pro	Thr	Pro	Pro	Lys	Arg	Ser	Ser	Ser	Phe	Arg	Glu	
1010						1015			1020						
Met	Asp	Gly	Gln	Pro	Glu	Arg	Arg	Gly	Ala	Gly	Glu	Glu	Glu	Gly	
1025						1030			1035						
Arg	Asp	Ile	Ser	Asn	Gly	Ala	Leu	Ala	Phe	Thr	Pro	Leu	Asp	Thr	
1040						1045			1050						
Ala	Asp	Pro	Ala	Lys	Ser	Pro	Lys	Pro	Ser	Asn	Gly	Ala	Gly	Val	
1055						1060			1065						
Pro	Asn	Gly	Ala	Leu	Arg	Glu	Ser	Gly	Gly	Ser	Gly	Phe	Arg	Ser	
1070						1075			1080						
Pro	His	Leu	Trp	Lys	Lys	Ser	Ser	Thr	Leu	Thr	Ser	Ser	Arg	Leu	
1085						1090			1095						
Ala	Thr	Gly	Glu	Glu	Gly	Gly	Gly	Ser	Ser	Ser	Lys	Arg	Phe		
1100						1105			1110						
Leu	Arg	Ser	Cys	Ser	Val	Ser	Cys	Val	Pro	His	Gly	Ala	Lys	Asp	
1115						1120			1125						
Thr	Glu	Trp	Arg	Ser	Val	Thr	Leu	Pro	Arg	Asp	Leu	Gln	Ser	Thr	
1130						1135			1140						
Gly	Arg	Gln	Phe	Asp	Ser	Ser	Thr	Phe	Gly	Gly	His	Lys	Ser	Glu	
1145						1150			1155						
Lys	Pro	Ala	Leu	Pro	Arg	Lys	Arg	Ala	Gly	Glu	Asn	Arg	Ser	Asp	
1160						1165			1170						
Gln	Val	Thr	Arg	Gly	Thr	Val	Thr	Pro	Pro	Pro	Arg	Leu	Val	Lys	
1175						1180			1185						
Lys	Asn	Glu	Glu	Ala	Ala	Asp	Glu	Val	Phe	Lys	Asp	Ile	Met	Glu	
1190						1195			1200						
Ser	Ser	Pro	Gly	Ser	Ser	Pro	Pro	Asn	Leu	Thr	Pro	Lys	Pro	Leu	
1205						1210			1215						
Arg	Arg	Gln	Val	Thr	Val	Ala	Pro	Ala	Ser	Gly	Leu	Pro	His	Lys	
1220						1225			1230						
Glu	Glu	Ala	Trp	Lys	Gly	Ser	Ala	Leu	Gly	Thr	Pro	Ala	Ala	Ala	
1235						1240			1245						
Glu	Pro	Val	Thr	Pro	Thr	Ser	Lys	Ala	Gly	Ser	Gly	Ala	Pro	Arg	
1250						1255			1260						
Gly	Thr	Ser	Lys	Gly	Pro	Ala	Glu	Glu	Ser	Arg	Val	Arg	Arg	His	
1265						1270			1275						
Lys	His	Ser	Ser	Glu	Ser	Pro	Gly	Arg	Asp	Lys	Gly	Lys	Leu	Ser	
1280						1285			1290						
Lys	Leu	Lys	Pro	Ala	Pro	Pro	Pro	Pro	Ala	Ala	Ser	Ala	Gly		

---

-continued

---

1295	1300	1305
Lys Ala Gly Gly Lys Pro Ser Gln Arg Pro Gly Gln Glu Ala Ala		
1310	1315	1320
Gly Glu Ala Val Leu Gly Ala Lys Thr Lys Ala Thr Ser Leu Val		
1325	1330	1335
Asp Ala Val Asn Ser Asp Ala Ala Lys Pro Ser Gln Pro Ala Glu		
1340	1345	1350
Gly Leu Lys Lys Pro Val Leu Pro Ala Thr Pro Lys Pro His Pro		
1355	1360	1365
Ala Lys Pro Ser Gly Thr Pro Ile Ser Pro Ala Pro Val Pro Leu		
1370	1375	1380
Ser Thr Leu Pro Ser Ala Ser Ser Ala Leu Ala Gly Asp Gln Pro		
1385	1390	1395
Ser Ser Thr Ala Phe Ile Pro Leu Ile Ser Thr Arg Val Ser Leu		
1400	1405	1410
Arg Lys Thr Arg Gln Pro Pro Glu Arg Ala Ser Gly Ala Ile Thr		
1415	1420	1425
Lys Gly Val Val Leu Asp Ser Thr Glu Ala Leu Cys Leu Ala Ile		
1430	1435	1440
Ser Gly Asn Ser Glu Gln Met Ala Ser His Ser Ala Val Leu Glu		
1445	1450	1455
Ala Gly Lys Asn Leu Tyr Thr Phe Cys Val Ser Tyr Val Asp Ser		
1460	1465	1470
Ile Gln Gln Met Arg Asn Lys Phe Ala Phe Arg Glu Ala Ile Asn		
1475	1480	1485
Lys Leu Glu Asn Asn Leu Arg Glu Leu Gln Ile Cys Pro Ala Ser		
1490	1495	1500
Ala Gly Ser Gly Pro Ala Ala Thr Gln Asp Phe Ser Lys Leu Leu		
1505	1510	1515
Ser Ser Val Lys Glu Ile Ser Asp Ile Val Gln Arg		
1520	1525	1530

&lt;210&gt; SEQ ID NO 6

&lt;211&gt; LENGTH: 2031

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

&lt;400&gt; SEQUENCE: 6

Met Val Asp Pro Val Gly Phe Ala Glu Ala Trp Lys Ala Gln Phe Pro			
1	5	10	15
Asp Ser Glu Pro Pro Arg Met Glu Leu Arg Ser Val Gly Asp Ile Glu			
20	25	30	
Gln Glu Leu Glu Arg Cys Lys Ala Ser Ile Arg Arg Leu Glu Gln Glu			
35	40	45	
Val Asn Gln Glu Arg Phe Arg Met Ile Tyr Leu Gln Thr Leu Leu Ala			
50	55	60	
Lys Glu Lys Lys Ser Tyr Asp Arg Gln Arg Trp Gly Phe Arg Arg Ala			
65	70	75	80
Ala Gln Ala Pro Asp Gly Ala Ser Glu Pro Arg Ala Ser Ala Ser Arg			
85	90	95	
Pro Gln Pro Ala Pro Ala Asp Gly Ala Asp Pro Pro Pro Ala Glu Glu			
100	105	110	

-continued

---

```

Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro
115          120          125

Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp
130          135          140

Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg
145          150          155          160

Ile Arg Lys Gly His Gly Gln Pro Gly Ala Asp Ala Glu Lys Pro Phe
165          170          175

Tyr Val Asn Val Glu Phe His His Glu Arg Gly Leu Val Lys Val Asn
180          185          190

Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met
195          200          205

Gln Met Glu Arg Lys Lys Ser Gln His Gly Ala Gly Ser Ser Val Gly
210          215          220

Asp Ala Ser Arg Pro Pro Tyr Arg Gly Arg Ser Ser Glu Ser Ser Cys
225          230          235          240

Gly Val Asp Gly Asp Tyr Glu Asp Ala Glu Leu Asn Pro Arg Phe Leu
245          250          255

Lys Asp Asn Leu Ile Asp Ala Asn Gly Gly Ser Arg Pro Pro Trp Pro
260          265          270

Pro Leu Glu Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Ile Met
275          280          285

Glu Gly Glu Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu
290          295          300

Gln Glu Lys Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser
305          310          315          320

Phe Glu Asp Cys Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu
325          330          335

Asn Leu Thr Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg
340          345          350

Val Ser Pro Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg
355          360          365

Ser Pro Ser Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro
370          375          380

Thr Pro Gln Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser
385          390          395          400

Glu Ala Thr Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn
405          410          415

Asp Asp Glu Gly Ala Phe His Gly Asp Ala Asp Gly Ser Phe Gly Thr
420          425          430

Pro Pro Gly Tyr Gly Cys Ala Ala Asp Arg Ala Glu Glu Gln Arg Arg
435          440          445

His Gln Asp Gly Leu Pro Tyr Ile Asp Asp Ser Pro Ser Ser Ser Pro
450          455          460

His Leu Ser Ser Lys Gly Arg Gly Ser Arg Asp Ala Leu Val Ser Gly
465          470          475          480

Ala Leu Lys Ser Thr Lys Ala Ser Glu Leu Asp Leu Glu Lys Gly Leu
485          490          495

Glu Met Arg Lys Trp Val Leu Ser Gly Ile Leu Ala Ser Glu Glu Thr
500          505          510

Tyr Leu Ser His Leu Glu Ala Leu Leu Leu Pro Met Lys Pro Leu Lys

```

---

-continued

---

515	520	525
Ala Ala Ala Thr Thr Ser Gln Pro Val Leu Thr Ser Gln Gln Ile Glu		
530	535	540
Thr Ile Phe Phe Lys Val Pro Glu Leu Tyr Glu Ile His Lys Glu Ser		
545	550	555
Tyr Asp Gly Leu Phe Pro Arg Val Gln Gln Trp Ser His Gln Gln Arg		
565	570	575
Val Gly Asp Leu Phe Gln Lys Leu Ala Ser Gln Leu Gly Val Tyr Arg		
580	585	590
Ala Phe Val Asp Asn Tyr Gly Val Ala Met Glu Met Ala Glu Lys Cys		
595	600	605
Cys Gln Ala Asn Ala Gln Phe Ala Glu Ile Ser Glu Asn Leu Arg Ala		
610	615	620
Arg Ser Asn Lys Asp Ala Lys Asp Pro Thr Thr Lys Asn Ser Leu Glu		
625	630	635
Thr Leu Leu Tyr Lys Pro Val Asp Arg Val Thr Arg Ser Thr Leu Val		
645	650	655
Leu His Asp Leu Leu Lys His Thr Pro Ala Ser His Pro Asp His Pro		
660	665	670
Leu Leu Gln Asp Ala Leu Arg Ile Ser Gln Asn Phe Leu Ser Ser Ile		
675	680	685
Asn Glu Glu Ile Thr Pro Arg Arg Gln Ser Met Thr Val Lys Lys Gly		
690	695	700
Glu His Arg Gln Leu Leu Lys Asp Ser Phe Met Val Glu Leu Val Glu		
705	710	715
720		
Gly Ala Arg Lys Leu Arg His Val Phe Leu Phe Thr Asp Leu Leu Leu		
725	730	735
Cys Thr Lys Leu Lys Lys Gln Ser Gly Gly Lys Thr Gln Gln Tyr Asp		
740	745	750
Cys Lys Trp Tyr Ile Pro Leu Thr Asp Leu Ser Phe Gln Met Val Asp		
755	760	765
Glu Leu Glu Ala Val Pro Asn Ile Pro Leu Val Pro Asp Glu Glu Leu		
770	775	780
Asp Ala Leu Lys Ile Lys Ile Ser Gln Ile Lys Ser Asp Ile Gln Arg		
785	790	795
800		
Glu Lys Arg Ala Asn Lys Gly Ser Lys Ala Thr Glu Arg Leu Lys Lys		
805	810	815
Lys Leu Ser Glu Gln Glu Ser Leu Leu Leu Met Ser Pro Ser Met		
820	825	830
Ala Phe Arg Val His Ser Arg Asn Gly Lys Ser Tyr Thr Phe Leu Ile		
835	840	845
Ser Ser Asp Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln		
850	855	860
Gln Lys Lys Cys Phe Arg Ser Phe Ser Leu Thr Ser Val Glu Leu Gln		
865	870	875
880		
Met Leu Thr Asn Ser Cys Val Lys Leu Gln Thr Val His Ser Ile Pro		
885	890	895
Leu Thr Ile Asn Lys Glu Asp Asp Glu Ser Pro Gly Leu Tyr Gly Phe		
900	905	910
Leu Asn Val Ile Val His Ser Ala Thr Gly Phe Lys Gln Ser Ser Lys		
915	920	925

---

-continued

---

Ala Leu Gln Arg Pro Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser  
 930 935 940  
 Glu Ala Ala Arg Trp Asn Ser Lys Glu Asn Leu Leu Ala Gly Pro Ser  
 945 950 955 960  
 Glu Asn Asp Pro Asn Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser  
 965 970 975  
 Gly Asp Asn Thr Leu Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu  
 980 985 990  
 Gly Tyr Asn His Asn Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly  
 995 1000 1005  
 Gln Gly Trp Val Pro Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu  
 1010 1015 1020  
 Glu Lys His Ser Trp Tyr His Gly Pro Val Ser Arg Asn Ala Ala  
 1025 1030 1035  
 Glu Tyr Pro Leu Ser Ser Gly Ile Asn Gly Ser Phe Leu Val Arg  
 1040 1045 1050  
 Glu Ser Glu Ser Ser Pro Ser Gln Arg Ser Ile Ser Leu Arg Tyr  
 1055 1060 1065  
 Glu Gly Arg Val Tyr His Tyr Arg Ile Asn Thr Ala Ser Asp Gly  
 1070 1075 1080  
 Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe Asn Thr Leu Ala Glu  
 1085 1090 1095  
 Leu Val His His His Ser Thr Val Ala Asp Gly Leu Ile Thr Thr  
 1100 1105 1110  
 Leu His Tyr Pro Ala Pro Lys Arg Asn Lys Pro Thr Val Tyr Gly  
 1115 1120 1125  
 Val Ser Pro Asn Tyr Asp Lys Trp Glu Met Glu Arg Thr Asp Ile  
 1130 1135 1140  
 Thr Met Lys His Lys Leu Gly Gly Gly Gln Tyr Gly Glu Val Tyr  
 1145 1150 1155  
 Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr Val Ala Val Lys Thr  
 1160 1165 1170  
 Leu Lys Glu Asp Thr Met Glu Val Glu Glu Phe Leu Lys Glu Ala  
 1175 1180 1185  
 Ala Val Met Lys Glu Ile Lys His Pro Asn Leu Val Gln Leu Leu  
 1190 1195 1200  
 Gly Val Cys Thr Arg Glu Pro Pro Phe Tyr Ile Ile Ile Glu Phe  
 1205 1210 1215  
 Met Thr Tyr Gly Asn Leu Leu Asp Tyr Leu Arg Glu Cys Asn Arg  
 1220 1225 1230  
 Gln Glu Val Asn Ala Val Val Leu Leu Tyr Met Ala Thr Gln Ile  
 1235 1240 1245  
 Ser Ser Ala Met Glu Tyr Leu Glu Lys Lys Asn Phe Ile His Arg  
 1250 1255 1260  
 Asp Leu Ala Ala Arg Asn Cys Leu Val Gly Glu Asn His Leu Val  
 1265 1270 1275  
 Lys Val Ala Asp Phe Gly Leu Ser Arg Leu Met Thr Gly Asp Thr  
 1280 1285 1290  
 Tyr Thr Ala His Ala Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala  
 1295 1300 1305

-continued

---

Pro	Glu	Ser	Leu	Ala	Tyr	Asn	Lys	Phe	Ser	Ile	Lys	Ser	Asp	Val
1310														1320
Trp	Ala	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Ala	Thr	Tyr	Gly	Met
1325														1335
Ser	Pro	Tyr	Pro	Gly	Ile	Asp	Arg	Ser	Gln	Val	Tyr	Glu	Leu	Leu
1340														1350
Glu	Lys	Asp	Tyr	Arg	Met	Lys	Arg	Pro	Glu	Gly	Cys	Pro	Glu	Lys
1355														1365
Val	Tyr	Glu	Leu	Met	Arg	Ala	Cys	Trp	Gln	Trp	Asn	Pro	Ser	Asp
1370														1380
Arg	Pro	Ser	Phe	Ala	Glu	Ile	His	Gln	Ala	Phe	Glu	Thr	Met	Phe
1385														1395
Gln	Glu	Ser	Ser	Ile	Ser	Asp	Glu	Val	Glu	Lys	Glu	Leu	Gly	Lys
1400														1410
Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu	Leu	Gln	Ala	Pro	Glu
1415														1425
Leu	Pro	Thr	Lys	Thr	Arg	Thr	Ser	Arg	Arg	Ala	Ala	Glu	His	Arg
1430														1440
Asp	Thr	Thr	Asp	Val	Pro	Glu	Met	Pro	His	Ser	Lys	Gly	Gln	Gly
1445														1455
Glu	Ser	Asp	Pro	Leu	Asp	His	Glu	Pro	Ala	Val	Ser	Pro	Leu	Leu
1460														1470
Pro	Arg	Lys	Glu	Arg	Gly	Pro	Pro	Glu	Gly	Gly	Leu	Asn	Glu	Asp
1475														1485
Glu	Arg	Leu	Leu	Pro	Lys	Asp	Lys	Lys	Thr	Asn	Leu	Phe	Ser	Ala
1490														1500
Leu	Ile	Lys	Lys	Lys	Lys	Thr	Ala	Pro	Thr	Pro	Pro	Lys	Arg	
1505														1515
Ser	Ser	Ser	Phe	Arg	Glu	Met	Asp	Gly	Gln	Pro	Glu	Arg	Arg	Gly
1520														1530
Ala	Gly	Glu	Glu	Glu	Gly	Arg	Asp	Ile	Ser	Asn	Gly	Ala	Leu	Ala
1535														1545
Phe	Thr	Pro	Leu	Asp	Thr	Ala	Asp	Pro	Ala	Lys	Ser	Pro	Lys	Pro
1550														1560
Ser	Asn	Gly	Ala	Gly	Val	Pro	Asn	Gly	Ala	Leu	Arg	Glu	Ser	Gly
1565														1575
Gly	Ser	Gly	Phe	Arg	Ser	Pro	His	Leu	Trp	Lys	Lys	Ser	Ser	Thr
1580														1590
Leu	Thr	Ser	Ser	Arg	Leu	Ala	Thr	Gly	Glu	Glu	Gly	Gly	Gly	
1595														1605
Ser	Ser	Ser	Lys	Arg	Phe	Leu	Arg	Ser	Cys	Ser	Val	Ser	Cys	Val
1610														1620
Pro	His	Gly	Ala	Lys	Asp	Thr	Glu	Trp	Arg	Ser	Val	Thr	Leu	Pro
1625														1635
Arg	Asp	Leu	Gln	Ser	Thr	Gly	Arg	Gln	Phe	Asp	Ser	Ser	Thr	Phe
1640														1650
Gly	Gly	His	Lys	Ser	Glu	Lys	Pro	Ala	Leu	Pro	Arg	Lys	Arg	Ala
1655														1665
Gly	Glu	Asn	Arg	Ser	Asp	Gln	Val	Thr	Arg	Gly	Thr	Val	Thr	Pro
1670														1680
Pro	Pro	Arg	Leu	Val	Lys	Lys	Asn	Glu	Glu	Ala	Ala	Asp	Glu	Val

---

-continued

---

1685	1690	1695
Phe Lys Asp Ile Met Glu Ser Ser Pro Gly Ser Ser Pro Pro Asn		
1700	1705	1710
Leu Thr Pro Lys Pro Leu Arg Arg Gln Val Thr Val Ala Pro Ala		
1715	1720	1725
Ser Gly Leu Pro His Lys Glu Glu Ala Trp Lys Gly Ser Ala Leu		
1730	1735	1740
Gly Thr Pro Ala Ala Ala Glu Pro Val Thr Pro Thr Ser Lys Ala		
1745	1750	1755
Gly Ser Gly Ala Pro Arg Gly Thr Ser Lys Gly Pro Ala Glu Glu		
1760	1765	1770
Ser Arg Val Arg Arg His Lys His Ser Ser Glu Ser Pro Gly Arg		
1775	1780	1785
Asp Lys Gly Lys Leu Ser Lys Leu Lys Pro Ala Pro Pro Pro Pro		
1790	1795	1800
Pro Ala Ala Ser Ala Gly Lys Ala Gly Gly Lys Pro Ser Gln Arg		
1805	1810	1815
Pro Gly Gln Glu Ala Ala Gly Glu Ala Val Leu Gly Ala Lys Thr		
1820	1825	1830
Lys Ala Thr Ser Leu Val Asp Ala Val Asn Ser Asp Ala Ala Lys		
1835	1840	1845
Pro Ser Gln Pro Ala Glu Gly Leu Lys Lys Pro Val Leu Pro Ala		
1850	1855	1860
Thr Pro Lys Pro His Pro Ala Lys Pro Ser Gly Thr Pro Ile Ser		
1865	1870	1875
Pro Ala Pro Val Pro Leu Ser Thr Leu Pro Ser Ala Ser Ser Ala		
1880	1885	1890
Leu Ala Gly Asp Gln Pro Ser Ser Thr Ala Phe Ile Pro Leu Ile		
1895	1900	1905
Ser Thr Arg Val Ser Leu Arg Lys Thr Arg Gln Pro Pro Glu Arg		
1910	1915	1920
Ala Ser Gly Ala Ile Thr Lys Gly Val Val Leu Asp Ser Thr Glu		
1925	1930	1935
Ala Leu Cys Leu Ala Ile Ser Gly Asn Ser Glu Gln Met Ala Ser		
1940	1945	1950
His Ser Ala Val Leu Glu Ala Gly Lys Asn Leu Tyr Thr Phe Cys		
1955	1960	1965
Val Ser Tyr Val Asp Ser Ile Gln Gln Met Arg Asn Lys Phe Ala		
1970	1975	1980
Phe Arg Glu Ala Ile Asn Lys Leu Glu Asn Asn Leu Arg Glu Leu		
1985	1990	1995
Gln Ile Cys Pro Ala Ser Ala Gly Ser Gly Pro Ala Ala Thr Gln		
2000	2005	2010
Asp Phe Ser Lys Leu Leu Ser Ser Val Lys Glu Ile Ser Asp Ile		
2015	2020	2025
Val Gln Arg		
2030		

&lt;210&gt; SEQ ID NO 7

&lt;211&gt; LENGTH: 2006

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Homo sapiens

---

-continued

---

&lt;400&gt; SEQUENCE: 7

Met Val Asp Pro Val Gly Phe Ala Glu Ala Trp Lys Ala Gln Phe Pro  
1 5 10 15

Asp Ser Glu Pro Pro Arg Met Glu Leu Arg Ser Val Gly Asp Ile Glu  
20 25 30

Gln Glu Leu Glu Arg Cys Lys Ala Ser Ile Arg Arg Leu Glu Gln Glu  
35 40 45

Val Asn Gln Glu Arg Phe Arg Met Ile Tyr Leu Gln Thr Leu Leu Ala  
50 55 60

Lys Glu Lys Lys Ser Tyr Asp Arg Gln Arg Trp Gly Phe Arg Arg Ala  
65 70 75 80

Ala Gln Ala Pro Asp Gly Ala Ser Glu Pro Arg Ala Ser Ala Ser Arg  
85 90 95

Pro Gln Pro Ala Pro Ala Asp Gly Ala Asp Pro Pro Pro Ala Glu Glu  
100 105 110

Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro  
115 120 125

Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp  
130 135 140

Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg  
145 150 155 160

Ile Arg Lys Gly His Gly Gln Pro Gly Ala Asp Ala Glu Lys Pro Phe  
165 170 175

Tyr Val Asn Val Glu Phe His His Glu Arg Gly Leu Val Lys Val Asn  
180 185 190

Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met  
195 200 205

Gln Met Glu Arg Lys Lys Ser Gln His Gly Ala Gly Ser Ser Val Gly  
210 215 220

Asp Ala Ser Arg Pro Pro Tyr Arg Gly Arg Ser Ser Glu Ser Ser Cys  
225 230 235 240

Gly Val Asp Gly Asp Tyr Glu Asp Ala Glu Leu Asn Pro Arg Phe Leu  
245 250 255

Lys Asp Asn Leu Ile Asp Ala Asn Gly Gly Ser Arg Pro Pro Trp Pro  
260 265 270

Pro Leu Glu Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Ile Met  
275 280 285

Glu Gly Glu Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu  
290 295 300

Gln Glu Lys Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser  
305 310 315 320

Phe Glu Asp Cys Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu  
325 330 335

Asn Leu Thr Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg  
340 345 350

Val Ser Pro Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg  
355 360 365

Ser Pro Ser Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro  
370 375 380

Thr Pro Gln Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser

---

-continued

---

385	390	395	400
Glu Ala Thr Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn			
405	410	415	
Asp Asp Glu Gly Ala Phe His Gly Asp Ala Asp Gly Ser Phe Gly Thr			
420	425	430	
Pro Pro Gly Tyr Gly Cys Ala Ala Asp Arg Ala Glu Glu Gln Arg Arg			
435	440	445	
His Gln Asp Gly Leu Pro Tyr Ile Asp Asp Ser Pro Ser Ser Ser Pro			
450	455	460	
His Leu Ser Ser Lys Gly Arg Gly Ser Arg Asp Ala Leu Val Ser Gly			
465	470	475	480
Ala Leu Lys Ser Thr Lys Ala Ser Glu Leu Asp Leu Glu Lys Gly Leu			
485	490	495	
Glu Met Arg Lys Trp Val Leu Ser Gly Ile Leu Ala Ser Glu Glu Thr			
500	505	510	
Tyr Leu Ser His Leu Glu Ala Leu Leu Pro Met Lys Pro Leu Lys			
515	520	525	
Ala Ala Ala Thr Thr Ser Gln Pro Val Leu Thr Ser Gln Gln Ile Glu			
530	535	540	
Thr Ile Phe Phe Lys Val Pro Glu Leu Tyr Glu Ile His Lys Glu Ser			
545	550	555	560
Tyr Asp Gly Leu Phe Pro Arg Val Gln Gln Trp Ser His Gln Gln Arg			
565	570	575	
Val Gly Asp Leu Phe Gln Lys Leu Ala Ser Gln Leu Gly Val Tyr Arg			
580	585	590	
Ala Phe Val Asp Asn Tyr Gly Val Ala Met Glu Met Ala Glu Lys Cys			
595	600	605	
Cys Gln Ala Asn Ala Gln Phe Ala Glu Ile Ser Glu Asn Leu Arg Ala			
610	615	620	
Arg Ser Asn Lys Asp Ala Lys Asp Pro Thr Thr Lys Asn Ser Leu Glu			
625	630	635	640
Thr Leu Leu Tyr Lys Pro Val Asp Arg Val Thr Arg Ser Thr Leu Val			
645	650	655	
Leu His Asp Leu Leu Lys His Thr Pro Ala Ser His Pro Asp His Pro			
660	665	670	
Leu Leu Gln Asp Ala Leu Arg Ile Ser Gln Asn Phe Leu Ser Ser Ile			
675	680	685	
Asn Glu Glu Ile Thr Pro Arg Arg Gln Ser Met Thr Val Lys Lys Gly			
690	695	700	
Glu His Arg Gln Leu Leu Lys Asp Ser Phe Met Val Glu Leu Val Glu			
705	710	715	720
Gly Ala Arg Lys Leu Arg His Val Phe Leu Phe Thr Asp Leu Leu Leu			
725	730	735	
Cys Thr Lys Leu Lys Lys Gln Ser Gly Gly Lys Thr Gln Gln Tyr Asp			
740	745	750	
Cys Lys Trp Tyr Ile Pro Leu Thr Asp Leu Ser Phe Gln Met Val Asp			
755	760	765	
Glu Leu Glu Ala Val Pro Asn Ile Pro Leu Val Pro Asp Glu Glu Leu			
770	775	780	
Asp Ala Leu Lys Ile Lys Ile Ser Gln Ile Lys Ser Asp Ile Gln Arg			
785	790	795	800

---

-continued

---

Glu Lys Arg Ala Asn Lys Gly Ser Lys Ala Thr Glu Arg Leu Lys Lys  
   805               810               815  
 Lys Leu Ser Glu Gln Glu Ser Leu Leu Leu Met Ser Pro Ser Met  
   820               825               830  
 Ala Phe Arg Val His Ser Arg Asn Gly Lys Ser Tyr Thr Phe Leu Ile  
   835               840               845  
 Ser Ser Asp Tyr Glu Arg Ala Glu Trp Arg Glu Asn Ile Arg Glu Gln  
   850               855               860  
 Gln Lys Lys Cys Phe Arg Ser Phe Ser Leu Thr Ser Val Glu Leu Gln  
   865               870               875               880  
 Met Leu Thr Asn Ser Cys Val Lys Leu Gln Thr Val His Ser Ile Pro  
   885               890               895  
 Leu Thr Ile Asn Lys Glu Glu Ala Leu Gln Arg Pro Val Ala Ser Asp  
   900               905               910  
 Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp Asn Ser Lys Glu  
   915               920               925  
 Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp Pro Asn Leu Phe Val Ala  
   930               935               940  
 Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu Ser Ile Thr Lys  
   945               950               955               960  
 Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn Gly Glu Trp Cys  
   965               970               975  
 Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro Ser Asn Tyr Ile  
   980               985               990  
 Thr Pro Val Asn Ser Leu Glu Lys His Ser Trp Tyr His Gly Pro Val  
   995               1000              1005  
 Ser Arg Asn Ala Ala Glu Tyr Pro Leu Ser Ser Gly Ile Asn Gly  
   1010              1015              1020  
 Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro Ser Gln Arg Ser  
   1025              1030              1035  
 Ile Ser Leu Arg Tyr Glu Gly Arg Val Tyr His Tyr Arg Ile Asn  
   1040              1045              1050  
 Thr Ala Ser Asp Gly Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe  
   1055              1060              1065  
 Asn Thr Leu Ala Glu Leu Val His His Ser Thr Val Ala Asp  
   1070              1075              1080  
 Gly Leu Ile Thr Thr Leu His Tyr Pro Ala Pro Lys Arg Asn Lys  
   1085              1090              1095  
 Pro Thr Val Tyr Gly Val Ser Pro Asn Tyr Asp Lys Trp Glu Met  
   1100              1105              1110  
 Glu Arg Thr Asp Ile Thr Met Lys His Lys Leu Gly Gly Gly Gln  
   1115              1120              1125  
 Tyr Gly Glu Val Tyr Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr  
   1130              1135              1140  
 Val Ala Val Lys Thr Leu Lys Glu Asp Thr Met Glu Val Glu Glu  
   1145              1150              1155  
 Phe Leu Lys Glu Ala Ala Val Met Lys Glu Ile Lys His Pro Asn  
   1160              1165              1170  
 Leu Val Gln Leu Leu Gly Val Cys Thr Arg Glu Pro Pro Phe Tyr  
   1175              1180              1185

-continued

---

Ile	Ile	Ile	Glu	Phe	Met	Thr	Tyr	Gly	Asn	Leu	Leu	Asp	Tyr	Leu
1190			1195							1200				
Arg	Glu	Cys	Asn	Arg	Gln	Glu	Val	Asn	Ala	Val	Val	Leu	Leu	Tyr
1205						1210					1215			
Met	Ala	Thr	Gln	Ile	Ser	Ser	Ala	Met	Glu	Tyr	Leu	Glu	Lys	Lys
1220						1225					1230			
Asn	Phe	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Cys	Leu	Val	Gly
1235						1240					1245			
Glu	Asn	His	Leu	Val	Lys	Val	Ala	Asp	Phe	Gly	Leu	Ser	Arg	Leu
1250						1255					1260			
Met	Thr	Gly	Asp	Thr	Tyr	Thr	Ala	His	Ala	Gly	Ala	Lys	Phe	Pro
1265						1270					1275			
Ile	Lys	Trp	Thr	Ala	Pro	Glu	Ser	Leu	Ala	Tyr	Asn	Lys	Phe	Ser
1280						1285					1290			
Ile	Lys	Ser	Asp	Val	Trp	Ala	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile
1295						1300					1305			
Ala	Thr	Tyr	Gly	Met	Ser	Pro	Tyr	Pro	Gly	Ile	Asp	Arg	Ser	Gln
1310						1315					1320			
Val	Tyr	Glu	Leu	Leu	Glu	Lys	Asp	Tyr	Arg	Met	Lys	Arg	Pro	Glu
1325						1330					1335			
Gly	Cys	Pro	Glu	Lys	Val	Tyr	Glu	Leu	Met	Arg	Ala	Cys	Trp	Gln
1340						1345					1350			
Trp	Asn	Pro	Ser	Asp	Arg	Pro	Ser	Phe	Ala	Glu	Ile	His	Gln	Ala
1355						1360					1365			
Phe	Glu	Thr	Met	Phe	Gln	Glu	Ser	Ser	Ile	Ser	Asp	Glu	Val	Glu
1370						1375					1380			
Lys	Glu	Leu	Gly	Lys	Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu
1385						1390					1395			
Leu	Gln	Ala	Pro	Glu	Leu	Pro	Thr	Lys	Thr	Arg	Thr	Ser	Arg	Arg
1400						1405					1410			
Ala	Ala	Glu	His	Arg	Asp	Thr	Thr	Asp	Val	Pro	Glu	Met	Pro	His
1415						1420					1425			
Ser	Lys	Gly	Gln	Gly	Glu	Ser	Asp	Pro	Leu	Asp	His	Glu	Pro	Ala
1430						1435					1440			
Val	Ser	Pro	Leu	Leu	Pro	Arg	Lys	Glu	Arg	Gly	Pro	Pro	Glu	Gly
1445						1450					1455			
Gly	Leu	Asn	Glu	Asp	Glu	Arg	Leu	Leu	Pro	Lys	Asp	Lys	Lys	Thr
1460						1465					1470			
Asn	Leu	Phe	Ser	Ala	Ile	Lys	Lys	Lys	Lys	Thr	Ala	Pro		
1475						1480					1485			
Thr	Pro	Pro	Lys	Arg	Ser	Ser	Ser	Phe	Arg	Glu	Met	Asp	Gly	Gln
1490						1495					1500			
Pro	Glu	Arg	Arg	Gly	Ala	Gly	Glu	Glu	Glu	Gly	Arg	Asp	Ile	Ser
1505						1510					1515			
Asn	Gly	Ala	Leu	Ala	Phe	Thr	Pro	Leu	Asp	Thr	Ala	Asp	Pro	Ala
1520						1525					1530			
Lys	Ser	Pro	Lys	Pro	Ser	Asn	Gly	Ala	Gly	Val	Pro	Asn	Gly	Ala
1535						1540					1545			
Leu	Arg	Glu	Ser	Gly	Gly	Ser	Gly	Phe	Arg	Ser	Pro	His	Leu	Trp
1550						1555					1560			
Lys	Lys	Ser	Ser	Thr	Leu	Thr	Ser	Ser	Arg	Leu	Ala	Thr	Gly	Glu

---

-continued

---

1565	1570	1575
Glu Glu Gly Gly Ser Ser Ser Lys Arg Phe Leu Arg Ser Cys		
1580	1585	1590
Ser Val Ser Cys Val Pro His Gly Ala Lys Asp Thr Glu Trp Arg		
1595	1600	1605
Ser Val Thr Leu Pro Arg Asp Leu Gln Ser Thr Gly Arg Gln Phe		
1610	1615	1620
Asp Ser Ser Thr Phe Gly Gly His Lys Ser Glu Lys Pro Ala Leu		
1625	1630	1635
Pro Arg Lys Arg Ala Gly Glu Asn Arg Ser Asp Gln Val Thr Arg		
1640	1645	1650
Gly Thr Val Thr Pro Pro Arg Leu Val Lys Lys Asn Glu Glu		
1655	1660	1665
Ala Ala Asp Glu Val Phe Lys Asp Ile Met Glu Ser Ser Pro Gly		
1670	1675	1680
Ser Ser Pro Pro Asn Leu Thr Pro Lys Pro Leu Arg Arg Gln Val		
1685	1690	1695
Thr Val Ala Pro Ala Ser Gly Leu Pro His Lys Glu Glu Ala Trp		
1700	1705	1710
Lys Gly Ser Ala Leu Gly Thr Pro Ala Ala Ala Glu Pro Val Thr		
1715	1720	1725
Pro Thr Ser Lys Ala Gly Ser Gly Ala Pro Arg Gly Thr Ser Lys		
1730	1735	1740
Gly Pro Ala Glu Glu Ser Arg Val Arg Arg His Lys His Ser Ser		
1745	1750	1755
Glu Ser Pro Gly Arg Asp Lys Gly Lys Leu Ser Lys Leu Lys Pro		
1760	1765	1770
Ala Pro Pro Pro Pro Ala Ala Ser Ala Gly Lys Ala Gly Gly		
1775	1780	1785
Lys Pro Ser Gln Arg Pro Gly Gln Glu Ala Ala Gly Glu Ala Val		
1790	1795	1800
Leu Gly Ala Lys Thr Lys Ala Thr Ser Leu Val Asp Ala Val Asn		
1805	1810	1815
Ser Asp Ala Ala Lys Pro Ser Gln Pro Ala Glu Gly Leu Lys Lys		
1820	1825	1830
Pro Val Leu Pro Ala Thr Pro Lys Pro His Pro Ala Lys Pro Ser		
1835	1840	1845
Gly Thr Pro Ile Ser Pro Ala Pro Val Pro Leu Ser Thr Leu Pro		
1850	1855	1860
Ser Ala Ser Ser Ala Leu Ala Gly Asp Gln Pro Ser Ser Thr Ala		
1865	1870	1875
Phe Ile Pro Leu Ile Ser Thr Arg Val Ser Leu Arg Lys Thr Arg		
1880	1885	1890
Gln Pro Pro Glu Arg Ala Ser Gly Ala Ile Thr Lys Gly Val Val		
1895	1900	1905
Leu Asp Ser Thr Glu Ala Leu Cys Leu Ala Ile Ser Gly Asn Ser		
1910	1915	1920
Glu Gln Met Ala Ser His Ser Ala Val Leu Glu Ala Gly Lys Asn		
1925	1930	1935
Leu Tyr Thr Phe Cys Val Ser Tyr Val Asp Ser Ile Gln Gln Met		
1940	1945	1950

---

-continued

---

Arg Asn Lys Phe Ala Phe Arg Glu Ala Ile Asn Lys Leu Glu Asn  
1955 1960 1965

Asn Leu Arg Glu Leu Gln Ile Cys Pro Ala Ser Ala Gly Ser Gly  
1970 1975 1980

Pro Ala Ala Thr Gln Asp Phe Ser Lys Leu Leu Ser Ser Val Lys  
1985 1990 1995

Glu Ile Ser Asp Ile Val Gln Arg  
2000 2005

<210> SEQ ID NO 8

<211> LENGTH: 1530

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Val Asp Pro Val Gly Phe Ala Glu Ala Trp Lys Ala Gln Phe Pro  
1 5 10 15

Asp Ser Glu Pro Pro Arg Met Glu Leu Arg Ser Val Gly Asp Ile Glu  
20 25 30

Gln Glu Leu Glu Arg Cys Lys Ala Ser Ile Arg Arg Leu Glu Gln Glu  
35 40 45

Val Asn Gln Glu Arg Phe Arg Met Ile Tyr Leu Gln Thr Leu Leu Ala  
50 55 60

Lys Glu Lys Lys Ser Tyr Asp Arg Gln Arg Trp Gly Phe Arg Arg Ala  
65 70 75 80

Ala Gln Ala Pro Asp Gly Ala Ser Glu Pro Arg Ala Ser Ala Ser Arg  
85 90 95

Pro Gln Pro Ala Pro Ala Asp Gly Ala Asp Pro Pro Pro Ala Glu Glu  
100 105 110

Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro  
115 120 125

Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp  
130 135 140

Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg  
145 150 155 160

Ile Arg Lys Gly His Gly Gln Pro Gly Ala Asp Ala Glu Lys Pro Phe  
165 170 175

Tyr Val Asn Val Glu Phe His His Glu Arg Gly Leu Val Lys Val Asn  
180 185 190

Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met  
195 200 205

Gln Met Glu Arg Lys Lys Ser Gln His Gly Ala Gly Ser Ser Val Gly  
210 215 220

Asp Ala Ser Arg Pro Pro Tyr Arg Gly Arg Ser Ser Glu Ser Ser Cys  
225 230 235 240

Gly Val Asp Gly Asp Tyr Glu Asp Ala Glu Leu Asn Pro Arg Phe Leu  
245 250 255

Lys Asp Asn Leu Ile Asp Ala Asn Gly Gly Ser Arg Pro Pro Trp Pro  
260 265 270

Pro Leu Glu Tyr Gln Pro Tyr Gln Ser Ile Tyr Val Gly Gly Ile Met  
275 280 285

Glu Gly Glu Gly Lys Gly Pro Leu Leu Arg Ser Gln Ser Thr Ser Glu

-continued

290	295	300
Gln Glu Lys Arg Leu Thr Trp Pro Arg Arg Ser Tyr Ser Pro Arg Ser		
305	310	315
Phe Glu Asp Cys Gly Gly Tyr Thr Pro Asp Cys Ser Ser Asn Glu		
325	330	335
Asn Leu Thr Ser Ser Glu Glu Asp Phe Ser Ser Gly Gln Ser Ser Arg		
340	345	350
Val Ser Pro Ser Pro Thr Thr Tyr Arg Met Phe Arg Asp Lys Ser Arg		
355	360	365
Ser Pro Ser Gln Asn Ser Gln Gln Ser Phe Asp Ser Ser Ser Pro Pro		
370	375	380
Thr Pro Gln Cys His Lys Arg His Arg His Cys Pro Val Val Val Ser		
385	390	395
Glu Ala Thr Ile Val Gly Val Arg Lys Thr Gly Gln Ile Trp Pro Asn		
405	410	415
Asp Asp Glu Gly Ala Phe His Gly Asp Ala Glu Ala Leu Gln Arg Pro		
420	425	430
Val Ala Ser Asp Phe Glu Pro Gln Gly Leu Ser Glu Ala Ala Arg Trp		
435	440	445
Asn Ser Lys Glu Asn Leu Leu Ala Gly Pro Ser Glu Asn Asp Pro Asn		
450	455	460
Leu Phe Val Ala Leu Tyr Asp Phe Val Ala Ser Gly Asp Asn Thr Leu		
465	470	475
Ser Ile Thr Lys Gly Glu Lys Leu Arg Val Leu Gly Tyr Asn His Asn		
485	490	495
Gly Glu Trp Cys Glu Ala Gln Thr Lys Asn Gly Gln Gly Trp Val Pro		
500	505	510
Ser Asn Tyr Ile Thr Pro Val Asn Ser Leu Glu Lys His Ser Trp Tyr		
515	520	525
His Gly Pro Val Ser Arg Asn Ala Ala Glu Tyr Pro Leu Ser Ser Gly		
530	535	540
Ile Asn Gly Ser Phe Leu Val Arg Glu Ser Glu Ser Ser Pro Ser Gln		
545	550	555
Arg Ser Ile Ser Leu Arg Tyr Glu Gly Arg Val Tyr His Tyr Arg Ile		
565	570	575
Asn Thr Ala Ser Asp Gly Lys Leu Tyr Val Ser Ser Glu Ser Arg Phe		
580	585	590
Asn Thr Leu Ala Glu Leu Val His His Ser Thr Val Ala Asp Gly		
595	600	605
Leu Ile Thr Thr Leu His Tyr Pro Ala Pro Lys Arg Asn Lys Pro Thr		
610	615	620
Val Tyr Gly Val Ser Pro Asn Tyr Asp Lys Trp Glu Met Glu Arg Thr		
625	630	635
Asp Ile Thr Met Lys His Lys Leu Gly Gly Gln Tyr Gly Glu Val		
645	650	655
Tyr Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr Val Ala Val Lys Thr		
660	665	670
Leu Lys Glu Asp Thr Met Glu Val Glu Glu Phe Leu Lys Glu Ala Ala		
675	680	685
Val Met Lys Glu Ile Lys His Pro Asn Leu Val Gln Leu Leu Gly Val		
690	695	700

---

-continued

---

Cys Thr Arg Glu Pro Pro Phe Tyr Ile Ile Ile Glu Phe Met Thr Tyr  
705 710 715 720

Gly Asn Leu Leu Asp Tyr Leu Arg Glu Cys Asn Arg Gln Glu Val Asn  
725 730 735

Ala Val Val Leu Leu Tyr Met Ala Thr Gln Ile Ser Ser Ala Met Glu  
740 745 750

Tyr Leu Glu Lys Lys Asn Phe Ile His Arg Asp Leu Ala Ala Arg Asn  
755 760 765

Cys Leu Val Gly Glu Asn His Leu Val Lys Val Ala Asp Phe Gly Leu  
770 775 780

Ser Arg Leu Met Thr Gly Asp Thr Tyr Thr Ala His Ala Gly Ala Lys  
785 790 795 800

Phe Pro Ile Lys Trp Thr Ala Pro Glu Ser Leu Ala Tyr Asn Lys Phe  
805 810 815

Ser Ile Lys Ser Asp Val Trp Ala Phe Gly Val Leu Leu Trp Glu Ile  
820 825 830

Ala Thr Tyr Gly Met Ser Pro Tyr Pro Gly Ile Asp Arg Ser Gln Val  
835 840 845

Tyr Glu Leu Leu Glu Lys Asp Tyr Arg Met Lys Arg Pro Glu Gly Cys  
850 855 860

Pro Glu Lys Val Tyr Glu Leu Met Arg Ala Cys Trp Gln Trp Asn Pro  
865 870 875 880

Ser Asp Arg Pro Ser Phe Ala Glu Ile His Gln Ala Phe Glu Thr Met  
885 890 895

Phe Gln Glu Ser Ser Ile Ser Asp Glu Val Glu Lys Glu Leu Gly Lys  
900 905 910

Gln Gly Val Arg Gly Ala Val Thr Thr Leu Leu Gln Ala Pro Glu Leu  
915 920 925

Pro Thr Lys Thr Arg Thr Ser Arg Arg Ala Ala Glu His Arg Asp Thr  
930 935 940

Thr Asp Val Pro Glu Met Pro His Ser Lys Gly Gln Gly Glu Ser Asp  
945 950 955 960

Pro Leu Asp His Glu Pro Ala Val Ser Pro Leu Leu Pro Arg Lys Glu  
965 970 975

Arg Gly Pro Pro Glu Gly Gly Leu Asn Glu Asp Glu Arg Leu Leu Pro  
980 985 990

Lys Asp Lys Lys Thr Asn Leu Phe Ser Ala Leu Ile Lys Lys Lys Lys  
995 1000 1005

Lys Thr Ala Pro Thr Pro Pro Lys Arg Ser Ser Ser Phe Arg Glu  
1010 1015 1020

Met Asp Gly Gln Pro Glu Arg Arg Gly Ala Gly Glu Glu Glu Gly  
1025 1030 1035

Arg Asp Ile Ser Asn Gly Ala Leu Ala Phe Thr Pro Leu Asp Thr  
1040 1045 1050

Ala Asp Pro Ala Lys Ser Pro Lys Pro Ser Asn Gly Ala Gly Val  
1055 1060 1065

Pro Asn Gly Ala Leu Arg Glu Ser Gly Gly Ser Gly Phe Arg Ser  
1070 1075 1080

Pro His Leu Trp Lys Lys Ser Ser Thr Leu Thr Ser Ser Arg Leu  
1085 1090 1095

-continued

---

Ala	Thr	Gly	Glu	Glu	Glu	Gly	Gly	Ser	Ser	Ser	Lys	Arg	Phe	
1100			1105					1110						
Leu	Arg	Ser	Cys	Ser	Val	Ser	Cys	Val	Pro	His	Gly	Ala	Lys	Asp
1115					1120				1125					
Thr	Glu	Trp	Arg	Ser	Val	Thr	Leu	Pro	Arg	Asp	Leu	Gln	Ser	Thr
1130					1135			1140						
Gly	Arg	Gln	Phe	Asp	Ser	Ser	Thr	Phe	Gly	Gly	His	Lys	Ser	Glu
1145					1150				1155					
Lys	Pro	Ala	Leu	Pro	Arg	Lys	Arg	Ala	Gly	Glu	Asn	Arg	Ser	Asp
1160					1165			1170						
Gln	Val	Thr	Arg	Gly	Thr	Val	Thr	Pro	Pro	Pro	Arg	Leu	Val	Lys
1175					1180				1185					
Lys	Asn	Glu	Glu	Ala	Ala	Asp	Glu	Val	Phe	Lys	Asp	Ile	Met	Glu
1190					1195				1200					
Ser	Ser	Pro	Gly	Ser	Ser	Pro	Pro	Asn	Leu	Thr	Pro	Lys	Pro	Leu
1205					1210			1215						
Arg	Arg	Gln	Val	Thr	Val	Ala	Pro	Ala	Ser	Gly	Leu	Pro	His	Lys
1220					1225			1230						
Glu	Glu	Ala	Trp	Lys	Gly	Ser	Ala	Leu	Gly	Thr	Pro	Ala	Ala	Ala
1235					1240			1245						
Glu	Pro	Val	Thr	Pro	Thr	Ser	Lys	Ala	Gly	Ser	Gly	Ala	Pro	Arg
1250					1255			1260						
Gly	Thr	Ser	Lys	Gly	Pro	Ala	Glu	Glu	Ser	Arg	Val	Arg	Arg	His
1265					1270			1275						
Lys	His	Ser	Ser	Glu	Ser	Pro	Gly	Arg	Asp	Lys	Gly	Lys	Leu	Ser
1280					1285			1290						
Lys	Leu	Lys	Pro	Ala	Pro	Pro	Pro	Pro	Ala	Ala	Ser	Ala	Gly	
1295					1300			1305						
Lys	Ala	Gly	Gly	Lys	Pro	Ser	Gln	Arg	Pro	Gly	Gln	Glu	Ala	Ala
1310					1315			1320						
Gly	Glu	Ala	Val	Leu	Gly	Ala	Lys	Thr	Lys	Ala	Thr	Ser	Leu	Val
1325					1330			1335						
Asp	Ala	Val	Asn	Ser	Asp	Ala	Ala	Lys	Pro	Ser	Gln	Pro	Ala	Glu
1340					1345			1350						
Gly	Leu	Lys	Lys	Pro	Val	Leu	Pro	Ala	Thr	Pro	Lys	Pro	His	Pro
1355					1360			1365						
Ala	Lys	Pro	Ser	Gly	Thr	Pro	Ile	Ser	Pro	Ala	Pro	Val	Pro	Leu
1370					1375			1380						
Ser	Thr	Leu	Pro	Ser	Ala	Ser	Ser	Ala	Leu	Ala	Gly	Asp	Gln	Pro
1385					1390			1395						
Ser	Ser	Thr	Ala	Phe	Ile	Pro	Leu	Ile	Ser	Thr	Arg	Val	Ser	Leu
1400					1405			1410						
Arg	Lys	Thr	Arg	Gln	Pro	Pro	Glu	Arg	Ala	Ser	Gly	Ala	Ile	Thr
1415					1420			1425						
Lys	Gly	Val	Val	Leu	Asp	Ser	Thr	Glu	Ala	Leu	Cys	Leu	Ala	Ile
1430					1435			1440						
Ser	Gly	Asn	Ser	Glu	Gln	Met	Ala	Ser	His	Ser	Ala	Val	Leu	Glu
1445					1450			1455						
Ala	Gly	Lys	Asn	Leu	Tyr	Thr	Phe	Cys	Val	Ser	Tyr	Val	Asp	Ser
1460					1465			1470						
Ile	Gln	Gln	Met	Arg	Asn	Lys	Phe	Ala	Phe	Arg	Glu	Ala	Ile	Asn

---

-continued

---

1475	1480	1485
Lys Leu Glu Asn Asn Leu Arg	Glu Leu Gln Ile Cys	Pro Ala Ser
1490	1495	1500
Ala Gly Ser Gly Pro Ala Ala	Thr Gln Asp Phe Ser	Lys Leu Leu
1505	1510	1515
Ser Ser Val Lys Glu Ile Ser	Asp Ile Val Gln Arg	
1520	1525	1530
 <210> SEQ_ID NO 9		
<211> LENGTH: 676		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
 <400> SEQUENCE: 9		
Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro Thr Arg Leu Leu		
1	5	10
15		
Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu Tyr Glu Arg Asp		
20	25	30
Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu Gly Leu Glu Phe		
35	40	45
Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys Leu Thr Gln Ser		
50	55	60
Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn Met Leu Gly Gly		
65	70	75
80		
Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu Gly Ala Val Asp		
85	90	95
Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser Lys Asp Phe Glu Thr		
100	105	110
Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu Met Leu Lys Met Phe		
115	120	125
Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn Gly Asp His Val Thr		
130	135	140
His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp Val Val Leu Tyr Met		
145	150	155
160		
Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu Val Cys Phe Lys Lys		
165	170	175
Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr Leu Lys Ser Ser Lys		
180	185	190
Tyr Ile Trp Pro Leu Gln Gly Trp Gln Ala Thr Phe Gly Gly Asp		
195	200	205
His Pro Pro Lys Ser Asp Leu Val Pro Arg His Asn Gln Thr Ser Leu		
210	215	220
Tyr Lys Lys Ala Gly Ser Ala Ala Val Leu Glu Glu Asn Leu Tyr		
225	230	235
240		
Phe Gln Gly Thr Tyr Lys Tyr Leu Gln Lys Pro Met Tyr Glu Val Gln		
245	250	255
Trp Lys Val Val Glu Glu Ile Asn Gly Asn Asn Tyr Val Tyr Ile Asp		
260	265	270
Pro Thr Gln Leu Pro Tyr Asp His Lys Trp Glu Phe Pro Arg Asn Arg		
275	280	285
Lys Ser Phe Gly Lys Thr Leu Gly Ala Gly Ala Phe Gly Lys Val Val		
290	295	300

---

-continued

---

Glu Ala Thr Ala Tyr Gly Leu Ile Lys Ser Asp Ala Ala Met Thr Val  
 305 310 315 320  
 Ala Val Lys Met Leu Lys Pro Ser Ala His Leu Thr Glu Arg Glu Ala  
 325 330 335  
 Leu Met Ser Glu Leu Lys Val Leu Ser Tyr Leu Gly Asn His Met Asn  
 340 345 350  
 Ile Val Asn Leu Leu Gly Ala Cys Thr Ile Gly Gly Pro Thr Leu Val  
 355 360 365  
 Ile Thr Glu Tyr Cys Cys Tyr Gly Asp Leu Leu Asn Phe Leu Arg Arg  
 370 375 380  
 Lys Arg Asp Ser Phe Ile Cys Ser Lys Gln Glu Asp His Ala Glu Ala  
 385 390 395 400  
 Ala Leu Tyr Lys Asn Leu Leu His Ser Lys Glu Ser Ser Cys Ser Asp  
 405 410 415  
 Ser Thr Asn Glu Tyr Met Asp Met Lys Pro Gly Val Ser Tyr Val Val  
 420 425 430  
 Pro Thr Lys Ala Asp Lys Arg Arg Ser Val Arg Ile Gly Ser Tyr Ile  
 435 440 445  
 Glu Arg Asp Val Thr Pro Ala Ile Met Glu Asp Asp Glu Leu Ala Leu  
 450 455 460  
 Asp Leu Glu Asp Leu Leu Ser Phe Ser Tyr Gln Val Ala Lys Gly Met  
 465 470 475 480  
 Ala Phe Leu Ala Ser Lys Asn Cys Ile His Arg Asp Leu Ala Ala Arg  
 485 490 495  
 Asn Ile Leu Leu Thr His Gly Arg Ile Thr Lys Ile Cys Asp Phe Gly  
 500 505 510  
 Leu Ala Arg Asp Ile Lys Asn Asp Ser Asn Tyr Val Val Lys Gly Asn  
 515 520 525  
 Ala Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ser Ile Phe Asn Cys  
 530 535 540  
 Val Tyr Thr Phe Glu Ser Asp Val Trp Ser Tyr Gly Ile Phe Leu Trp  
 545 550 555 560  
 Glu Leu Phe Ser Leu Gly Ser Ser Pro Tyr Pro Gly Met Pro Val Asp  
 565 570 575  
 Ser Lys Phe Tyr Lys Met Ile Lys Glu Gly Phe Arg Met Leu Ser Pro  
 580 585 590  
 Glu His Ala Pro Ala Glu Met Tyr Asp Ile Met Lys Thr Cys Trp Asp  
 595 600 605  
 Ala Asp Pro Leu Lys Arg Pro Thr Phe Lys Gln Ile Val Gln Leu Ile  
 610 615 620  
 Glu Lys Gln Ile Ser Glu Ser Thr Asn His Ile Tyr Ser Asn Leu Ala  
 625 630 635 640  
 Asn Cys Ser Pro Asn Arg Gln Lys Pro Val Val Asp His Ser Val Arg  
 645 650 655  
 Ile Asn Ser Val Gly Ser Thr Ala Ser Ser Ser Gln Pro Leu Leu Val  
 660 665 670  
 His Asp Asp Val  
 675

<210> SEQ ID NO 10  
 <211> LENGTH: 474  
 <212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Ser Tyr Tyr His His His His His Asp Tyr Asp Ile Pro Thr  
1 5 10 15

Thr Glu Asn Leu Tyr Phe Gln Gly Ala Met Leu Val Pro Arg Gly Ser  
20 25 30

Pro Trp Ile Pro Phe Thr Met Lys Lys Arg Lys Gln Ile Lys Asp Leu  
35 40 45

Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg Val His Thr Pro His Leu  
50 55 60

Asp Arg Leu Val Ser Ala Arg Ser Val Ser Pro Thr Thr Glu Met Val  
65 70 75 80

Ser Asn Glu Ser Val Asp Tyr Arg Ala Thr Phe Pro Glu Asp Gln Phe  
85 90 95

Pro Asn Ser Ser Gln Asn Gly Ser Cys Arg Gln Val Gln Tyr Pro Leu  
100 105 110

Thr Asp Met Ser Pro Ile Leu Thr Ser Gly Asp Ser Asp Ile Ser Ser  
115 120 125

Pro Leu Leu Gln Asn Thr Val His Ile Asp Leu Ser Ala Leu Asn Pro  
130 135 140

Glu Leu Val Gln Ala Val Gln His Val Val Ile Gly Pro Ser Ser Leu  
145 150 155 160

Ile Val His Phe Asn Glu Val Ile Gly Arg Gly His Phe Gly Cys Val  
165 170 175

Tyr His Gly Thr Leu Leu Asp Asn Asp Gly Lys Lys Ile His Cys Ala  
180 185 190

Val Lys Ser Leu Asn Arg Ile Thr Asp Ile Gly Glu Val Ser Gln Phe  
195 200 205

Leu Thr Glu Gly Ile Ile Met Lys Asp Phe Ser His Pro Asn Val Leu  
210 215 220

Ser Leu Leu Gly Ile Cys Leu Arg Ser Glu Gly Ser Pro Leu Val Val  
225 230 235 240

Leu Pro Tyr Met Lys His Gly Asp Leu Arg Asn Phe Ile Arg Asn Glu  
245 250 255

Thr His Asn Pro Thr Val Lys Asp Leu Ile Gly Phe Gly Leu Gln Val  
260 265 270

Ala Lys Gly Met Lys Tyr Leu Ala Ser Lys Lys Phe Val His Arg Asp  
275 280 285

Leu Ala Ala Arg Asn Cys Met Leu Asp Glu Lys Phe Thr Val Lys Val  
290 295 300

Ala Asp Phe Gly Leu Ala Arg Asp Met Tyr Asp Lys Glu Tyr Tyr Ser  
305 310 315 320

Val His Asn Lys Thr Gly Ala Lys Leu Pro Val Lys Trp Met Ala Leu  
325 330 335

Glu Ser Leu Gln Thr Gln Lys Phe Thr Thr Lys Ser Asp Val Trp Ser  
340 345 350

Phe Gly Val Leu Leu Trp Glu Leu Met Thr Arg Gly Ala Pro Pro Tyr  
355 360 365

Pro Asp Val Asn Thr Phe Asp Ile Thr Val Tyr Leu Leu Gln Gly Arg  
370 375 380

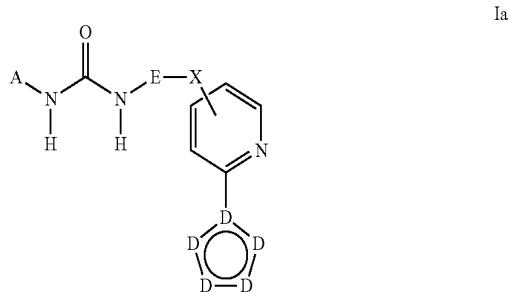
-continued

---

Arg	Leu	Leu	Gln	Pro	Glu	Tyr	Cys	Pro	Asp	Pro	Leu	Tyr	Glu	Val	Met
385					390						395				400
Leu	Lys	Cys	Trp	His	Pro	Lys	Ala	Glu	Met	Arg	Pro	Ser	Phe	Ser	Glu
	405						410						415		
Leu	Val	Ser	Arg	Ile	Ser	Ala	Ile	Phe	Ser	Thr	Phe	Ile	Gly	Glu	His
	420					425						430			
Tyr	Val	His	Val	Asn	Ala	Thr	Tyr	Val	Asn	Val	Lys	Cys	Val	Ala	Pro
	435					440						445			
Tyr	Pro	Ser	Leu	Leu	Ser	Ser	Glu	Asp	Asn	Ala	Asp	Asp	Glu	Val	Asp
	450					455						460			
Thr	Arg	Pro	Ala	Ser	Phe	Trp	Glu	Thr	Ser						
	465					470									
<210> SEQ_ID NO 11															
<211> LENGTH: 12															
<212> TYPE: PRT															
<213> ORGANISM: Unknown															
<220> FEATURE:															
<223> OTHER INFORMATION: Abl kinase peptide substrate															
<400> SEQUENCE: 11															
Glu Ala Ile Tyr Ala Ala Pro Phe Ala Lys Lys Lys															
1		5		10											

---

1. A method of modulating a kinase activity of a wild-type kinase species, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing, comprising the step of contacting said species with a compound of formula Ia:



wherein the pyridine ring may be optionally substituted with one or more R20 moieties;  
 each D is individually taken from the group consisting of C, CH, C—R20, N—Z3, and N, such that the resultant ring is a pyrazole;  
 wherein E is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl;  
 E may be optionally substituted with one or two R16 moieties;  
 wherein A is a ring system selected from the group consisting of phenyl, naphthyl, cyclopentyl, cyclohexyl, G1, G2, and G3;  
 G1 is a heteroaryl taken from the group consisting of pyrrolyl, furyl, thieryl, oxazolyl, thiazolyl, isoxazol-4-yl, isoxazol-5-yl, isothiazolyl, imidazolyl, pyrazolyl, oxa-

diazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl, pyridinyl, and pyrimidinyl;

G2 is a fused bicyclic heteroaryl taken from the group consisting of indolyl, indolinyl, isoindolyl, isoindolinyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzoxazolonyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazonopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazolonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazonopyrimidinyl, thiazolopyrimidinyl, thiazolonopyrimidinyl, oxazolopyrimidinyl, oxazolonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, and benzoxazepinyl;

G3 is a heterocycl taken from the group consisting of oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, imidazolonyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl;

the A ring may be optionally substituted with one or two R2 moieties;

X is selected from the group consisting of —O—, —S(CH<sub>2</sub>)<sub>n</sub>—, —N(R3)(CH<sub>2</sub>)<sub>n</sub>—, —(CH<sub>2</sub>)<sub>p</sub>—, and wherein the carbon atoms of —(CH<sub>2</sub>)<sub>n</sub>—, —(CH<sub>2</sub>)<sub>p</sub>—, of X may be further substituted by oxo or one or more C1-C6alkyl moieties;

when A, G1, G2 or G3 has one or more substitutable sp<sub>2</sub>-hybridized carbon atoms, each respective sp<sub>2</sub> hybridized carbon atom may be optionally substituted with a Z1 substituent;

when A, G1, G2 or G3 has one or more substitutable sp<sub>3</sub>-hybridized carbon atoms, each respective sp<sub>3</sub> hybridized carbon atom may be optionally substituted with a Z2 substituent;

when A, G1, G2 or G3 has one or more substitutable nitrogen atoms, each respective nitrogen atom may be optionally substituted with a Z4 substituent;

each Z1 is independently and individually selected from the group consisting of C1-6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, halogen, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, cyano, C1-C6alkoxy, fluoroC1-C6alkoxy wherein the alkyl moiety can be partially or fully fluorinated, —(CH<sub>2</sub>)<sub>n</sub>OH, oxo, C1-C6alkoxyC1-C6alkyl, (R4)<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>—, (R3)<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>—, (R4)<sub>2</sub>N(CH<sub>2</sub>)<sub>q</sub>N(R4)(CH<sub>2</sub>)<sub>n</sub>—, (R4)<sub>2</sub>N(CH<sub>2</sub>)<sub>q</sub>O(CH<sub>2</sub>)<sub>n</sub>—, (R3)<sub>2</sub>NC(O)—, (R4)<sub>2</sub>NC(O)—, (R4)<sub>2</sub>NC(O)C1-C6alkyl-, —(R4)NC(O)R8, C1-C6alkoxycarbonyl-, -carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, (R3)<sub>2</sub>NSO<sub>2</sub>—, —SOR3, (R4)<sub>2</sub>NSO<sub>2</sub>—, —N(R4)SO<sub>2</sub>R8, —O(CH<sub>2</sub>)<sub>q</sub>OC1-C6alkyl, —SO<sub>2</sub>R3, —SOR4, —C(O)R8, —C(O)R6, —C(=NOH)R6, —C(=NOR3)R6, —(CH<sub>2</sub>)<sub>n</sub>N(R4)C(O)R8, —N(R3)(CH<sub>2</sub>)<sub>q</sub>O-alkyl, —N(R3)(CH<sub>2</sub>)<sub>q</sub>N(R4)<sub>2</sub>, nitro, —CH(OH)CH(OH)R4, —C(=NH)N(R4)<sub>2</sub>, —C(=NOR3)N(R4)<sub>2</sub>, —NHC(=NH)R8, R17 substituted G3, R17 substituted pyrazolyl and R17 substituted imidazolyl;

in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z2 is independently and individually selected from the group consisting of aryl, C1-C6alkyl, C3-C8cycloalkyl, branched C3-C7alkyl, hydroxyl, hydroxyC1-C6alkyl-, cyano, (R3)<sub>2</sub>N—, (R4)<sub>2</sub>N—, (R4)<sub>2</sub>NCI—C6alkyl-, (R4)<sub>2</sub>NC2-C<sub>6</sub>alkylN(R4)(CH<sub>2</sub>)<sub>n</sub>—, (R4)<sub>2</sub>NC2-C6alkylO(CH<sub>2</sub>)<sub>n</sub>—, (R3)<sub>2</sub>NC(O)—, (R4)<sub>2</sub>NC(O)—, (R4)<sub>2</sub>NC(O)C1-C6alkyl-, carboxyl, -carboxyC1-C6alkyl, C1-C6alkoxycarbonyl-, C1-C6alkoxycarbonylC1-C6alkyl-, (R3)<sub>2</sub>NSO<sub>2</sub>—, (R4)<sub>2</sub>NSO<sub>2</sub>—, —SO<sub>2</sub>R8, —(CH<sub>2</sub>)<sub>n</sub>N(R4)C(O)R8, —C(O)R8, =O, =NOH, and =N(OR6);

in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, hydroxyC2-C6alkyl-, C1-C6alkoxycarbonyl-, —C(O)R8, R5C(O)(CH<sub>2</sub>)<sub>n</sub>—, (R4)<sub>2</sub>NC(O)—, (R4)<sub>2</sub>NC(O)C1-C6alkyl-, R8C(O)N(R4)(CH<sub>2</sub>)<sub>q</sub>—, (R3)<sub>2</sub>NSO<sub>2</sub>—, (R4)<sub>2</sub>NSO<sub>2</sub>—, —(CH<sub>2</sub>)<sub>q</sub>N(R3)<sub>2</sub>, and —(CH<sub>2</sub>)<sub>q</sub>N(R4)<sub>2</sub>;

each Z4 is independently and individually selected from the group consisting of C1-C6alkyl, branched

C3-7alkyl, hydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, (R4)<sub>2</sub>N—C2-C6alkyl-, (R4)<sub>2</sub>N—C2-C6alkylN(R4)-C2-C6alkyl-, (R4)<sub>2</sub>N—C2-C6alkyl-O—C2-C6alkyl-(R4)<sub>2</sub>NC(O)C1-C6alkyl-, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, —C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)-, —SO<sub>2</sub>R8, and —COR8;

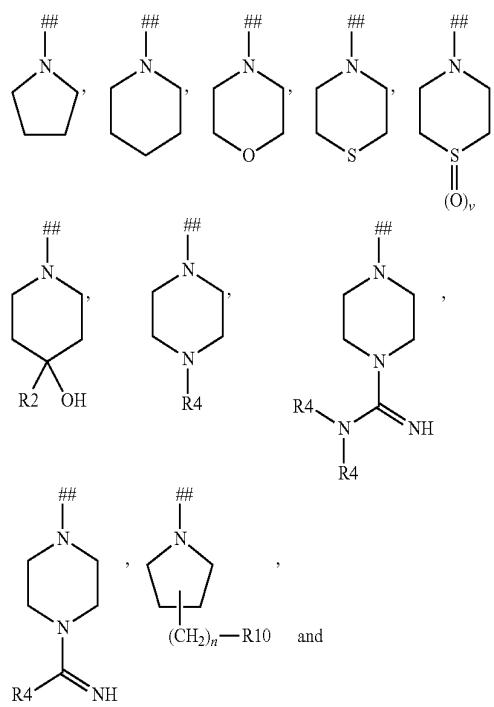
in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each R2 is selected from the group consisting of H, C1-C6alkyl, branched C3-C8alkyl, R19 substituted C3-C8cycloalkyl-, fluoroC1-C6alkyl- wherein the alkyl is fully or partially fluorinated, halogen, cyano, C1-C6alkoxy-, and fluoroC1-C6alkoxy- wherein the alkyl group is fully or partially fluorinated, hydroxyl substituted C1-C6alkyl-, hydroxyl substituted branched C3-C8alkyl-, cyano substituted C1-C6alkyl-, cyano substituted branched C3-C8alkyl-, (R3)<sub>2</sub>NC(O)C1-C6alkyl-, and (R3)<sub>2</sub>NC(O)C3-C8 branched alkyl-;

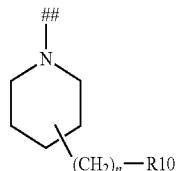
wherein each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, and C3-C8cycloalkyl;

each R4 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6alkyl-, dihydroxyC1-C6alkyl-, C1-C6alkoxyC1-C6alkyl-, branched C3-C7alkyl, branched hydroxyC1-C6alkyl-, branched C1-C6alkoxyC1-C6alkyl-, branched dihydroxyC1-C6alkyl-, —(CH<sub>2</sub>)<sub>p</sub>N(R7)<sub>2</sub>, —(CH<sub>2</sub>)<sub>p</sub>C(O)N(R7)<sub>2</sub>, —(CH<sub>2</sub>)<sub>p</sub>C(O)OR3, and R19 substituted C3-C8cycloalkyl-;

each R5 is independently and individually selected from the group consisting of



-continued



;

and wherein the symbol (##) is the point of attachment to Z3;  
each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8cycloalkyl-; each R7 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC2-C6alkyl-, dihydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, branched C3-C7alkyl, branched hydroxyC2-C6alkyl-, branched C1-C6alkoxyC2-C6alkyl-, branched dihydroxyC2-C6alkyl-, —(CH<sub>2</sub>)<sub>n</sub>C(O)OR3, R19 substituted C3-C8cycloalkyl- and —(CH<sub>2</sub>)<sub>n</sub>R17; each R8 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, fluoroC1-C6alkyl- wherein the alkyl moiety is partially or fully fluorinated, R19 substituted C3-C8cycloalkyl-, —OH, C1-C6alkoxy, —N(R3)<sub>2</sub>, and —N(R4)<sub>2</sub>; each R10 is independently and individually selected from the group consisting of —CO<sub>2</sub>H, —CO<sub>2</sub>C1-C6alkyl, —C(O)N(R4)<sub>2</sub>, OH, C1-C6alkoxy, and —N(R4)<sub>2</sub>; each R16 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or fully fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)<sub>2</sub>, —N(R4)<sub>2</sub>, R3 substituted C2-C3alkynyl- and nitro; each R17 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or fully fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)<sub>2</sub>, —N(R4)<sub>2</sub>, and nitro; each R19 is independently and individually selected from the group consisting of H, OH and C1-C6alkyl; each R20 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or fully fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)<sub>2</sub>, —N(R4)<sub>2</sub>, —N(R3)C(O)R3, —C(O)N(R3)<sub>2</sub> and nitro and wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl-, and alkoxyalkyl and attached to the same nitrogen heteroatom may cyclize to form a C3-C7 heterocycl ring;  
k is 0 or 1; n is 0-6; p is 1-4; q is 2-6; r is 0 or 1; t is 1-3; v is 1 or 2; m is 0-2;

or a pharmaceutically acceptable salt, a stereoisomer, a regioisomer, or a tautomer of such compounds.

**2.** A method of treating mammalian disease wherein the disease etiology or progression is at least partially mediated by the kinase activity of c-ABL kinase, BCR-ABL kinase, FLT-3 kinase, VEGFR-2 kinases, c-MET kinase, PDGFR-alpha kinase, PDGFR-beta kinase, HER-1 kinase, HER-2 kinase, HER-3 kinase, HER-4 kinase, FGFR kinases, c-KIT kinase, RET kinase, c-FMS kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing, comprising the step of administering to the mammal a therapeutically effective amount of a pharmaceutical composition comprising a compound of formula Ia.

**3.** A method of claim 2 wherein said kinase is selected from the group consisting of BCR-ABL fusion protein kinases p210, BCR-ABL fusion protein kinases p190, BCR-ABL fusion protein kinases bearing the T315I gatekeeper mutant in the ABL kinase domain of p210, BCR-ABL fusion protein kinases bearing the T315I gatekeeper mutant in the ABL kinase domain of p190, and other BCR-ABL polymorphs of any of the foregoing kinases.

**4.** The method of claim 3, wherein said BCR-ABL fusion protein kinases p210 have Seq. IDs 3 & 4, wherein said BCR-ABL fusion protein kinase p190 has Seq. ID 5, wherein said BCR-ABL fusion protein kinases p210 bearing the T315I mutation in the ABL kinase domain have Seq. IDs 6 & 7, and wherein said BCR-ABL fusion protein kinase p190 bearing the T315I mutation in the ABL kinase domain has Seq. ID 8.

**5.** The method of claim 2 wherein said kinase is selected from the group consisting of c-KIT protein kinase, PDGFR-alpha kinase, PDGFR-beta kinase, c-FMS kinase, and any fusion protein, mutation and polymorph of any of the foregoing.

**6.** The method of claim 2 wherein said kinase is selected from the group consisting of c-MET protein kinase, RET kinase, FGFR kinases, HER kinases, and any fusion protein, mutation and polymorph of any of the foregoing.

**7.** A method of treating an individual suffering from a condition selected from the group consisting of cancer, secondary cancer growth arising from metastasis, hyperproliferative diseases, diseases characterized by hyper-vascularization, inflammation, osteoarthritis, rheumatoid arthritis, respiratory diseases, stroke, systemic shock, immunological diseases, autoimmune diseases, bone resorptive diseases, cardiovascular disease and diseases characterized by angiogenesis, comprising the step of administering to such individual a therapeutically effective amount of a pharmaceutical composition comprising a compound of formula Ia.

**8.** A method of treating an individual suffering from a disease caused by c-ABL kinase, oncogenic forms thereof, aberrant fusion proteins thereof including BCR-ABL kinase and polymorphs thereof; a disease caused by FLT-3 kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof; a disease caused by cMET kinase, oncogenic forms thereof, aberrant fusion proteins thereof including TPR-MET; a disease caused by KDR kinase or PDGFR kinases; a disease caused by HER kinases, oncogenic forms thereof and polymorphs thereof; a disease caused by RET kinase, oncogenic forms thereof, aberrant fusion proteins thereof; a disease caused by c-FMS kinase, oncogenic forms thereof and polymorphs thereof; a disease caused by a c-KIT kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof; and diseases caused by any

of the foregoing kinases, oncogenic forms thereof, and aberrant fusion proteins thereof, including but not limited to, chronic myelogenous leukemia, acute lymphocytic leukemia, acute myeloid leukemia, other myeloproliferative disorders, a disease caused by metastasis of primary solid tumors to secondary sites, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, mesothelioma, hyper-eosinophilic syndrome, a disease caused or maintained by pathological vascularization, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies, i.e. diabetic retinopathy and age-related macular degeneration, non small cell lung cancer, breast cancers, kidney cancers, colon cancers, cervical carcinomas, papillary thyroid carcinoma, melanomas, autoimmune diseases including rheumatoid arthritis, multiple sclerosis, lupus, asthma, human inflammation, rheumatoid spondylitis, ostero-arthritis, asthma, gouty arthritis, sepsis, septic shock, endotoxic shock, Gram-negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, stroke, reperfusion injury, neural trauma, neural ischemia, psoriasis, restenosis, chronic obstructive pulmonary disease, bone resorptive diseases, bone cancer, graft-versus-host reaction, Chron's disease, ulcerative colitis, inflammatory bowel disease, pyresis, gastrointestinal stromal tumors, mastocytosis, mast cell leukemia, and combinations thereof, comprising the step of administering to such individual a therapeutically effective amount of a pharmaceutical composition comprising a compound of formula Ia.

**9.** The method of claim **8**, said compound being administered by a method selected from the group consisting of oral, parenteral, inhalation, and subcutaneous.

**10.** The method of claim **7 or 8**, wherein the pharmaceutical composition further comprises at least one other therapeutic agent.

**11.** The method of claim **10**, wherein the at least one other therapeutic agent is useful for treating cancer.

**12.** The method of claim **11**, wherein the other therapeutic agent is selected from the group consisting of imatinib, nilotinib, dasatinib, and bosutinib.

**13.** The method of claim **12**, wherein the other therapeutic agent is imatinib.

**14.** The method of claim **10**, wherein the at least one other therapeutic agent is useful for treating autoimmune diseases or inflammatory diseases.

**15.** The method of claim **14**, wherein the other therapeutic agent is selected from the group consisting of methotrexate or other anti-folate agent.

**16.** The method of claim **14**, wherein the other therapeutic agent is an anti-TNF agent.

**17.** The method of claim **16**, wherein the other therapeutic agent is selected from the group consisting of Humira®, Enbrel®, and Remicade®.

\* \* \* \* \*