



US 20080261961A1

(19) **United States**(12) **Patent Application Publication**
Flynn et al.(10) **Pub. No.: US 2008/0261961 A1**(43) **Pub. Date: Oct. 23, 2008**(54) **KINASE INHIBITORS USEFUL FOR THE
TREATMENT OF MYELOPROLIFIC
DISEASES AND OTHER PROLIFERATIVE
DISEASES**(75) Inventors: **Daniel L. Flynn**, Lawrence, KS
(US); **Peter A. Petillo**, Lawrence,
KS (US); **Michael D. Kaufman**,
Lawrence, KS (US)Correspondence Address:
HOVEY WILLIAMS LLP
10801 Mastin Boulevard, Suite 1000
Overland Park, KS 66210 (US)(73) Assignee: **Deciphera Pharmaceuticals, LLC**,
Lawrence, KS (US)(21) Appl. No.: **12/105,376**(22) Filed: **Apr. 18, 2008****Related U.S. Application Data**(60) Provisional application No. 60/913,216, filed on Apr.
20, 2007.**Publication Classification**(51) **Int. Cl.**
A61K 31/4439 (2006.01)
C07D 401/12 (2006.01)
C07D 413/12 (2006.01)
C07D 417/12 (2006.01)**A61K 31/541** (2006.01)
A61P 27/02 (2006.01)
A61P 11/00 (2006.01)
A61P 19/02 (2006.01)
A61P 35/00 (2006.01)
A61K 31/5377 (2006.01)
A61K 31/496 (2006.01)
A61K 31/4545 (2006.01)(52) **U.S. Cl.** **514/227.8**; 546/275.4; 546/279.1;
546/271.1; 546/272.4; 546/193; 544/131;
544/361; 544/56; 514/235.5; 514/253.01;
514/318; 514/342; 514/343; 514/341; 514/340(57) **ABSTRACT**

Compounds of the present invention find utility in the treatment of mammalian cancers and especially human cancers including but not limited to malignant, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases, leukemias, papillary thyroid carcinoma, non small cell lung cancer, mesothelioma, hypereosinophilic syndrome, gastrointestinal stromal tumors, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, mastocytosis, mast cell leukemia, a disease caused by c-Abl kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof, or a disease caused by c-Kit kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof.

KINASE INHIBITORS USEFUL FOR THE TREATMENT OF MYELOPROLIFIC DISEASES AND OTHER PROLIFERATIVE DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of Provisional Application 60/913,216 filed Apr. 20, 2007. This provisional application is incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] This application contains a Sequence Listing in both paper and computer readable format in accordance with 37 C.F.R. 1.821 (c) and (e), the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0003] 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, kinase/compound adducts, 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 kinases, Flt-3, c-Met, FGFR, the HER family and disease polymorphs thereof.

BACKGROUND OF THE INVENTION

[0004] 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, PDGF receptor kinase; VEGF receptor kinases; and Flt-3 kinase.

[0005] 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 myristoylation 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 e1a2 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.

[0006] 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, 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 KIT and its association with substrates such as phosphatidylinositol 3-kinase (PI3K). Tyrosine phosphorylation by protein tyrosine kinases is of particular importance in cellular signalling and can mediate signals for major cellular processes, such as proliferation, differentiation, apoptosis, attachment, and migration. Defects in 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 KIT are found in most gastrointestinal stromal tumors and mastocytosis. Further, almost all gonadal seminomas/dysgerminomas exhibit 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). KIT defects have also been associated with testicular tumors including germ cell tumors (GCT) and testicular germ cell tumors (TGCT).

[0007] The role of c-kit expression has been studied in hematologic and solid tumours, 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, STI571, 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 con-

ventional 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.

[0008] 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 paucity 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.

[0009] 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 acts to activate 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 (Ponzetto 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 β -catenin expression, and provides good prognostic and predictive factors in breast cancer patients.

[0010] 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. Other inhibitors have been shown to bind to a separate hydrophobic region of the protein known as the "DFG-in-conformation" pocket wherein such a binding mode by the inhibitor causes the kinase to adopt the "DFG-out" conformation, and still others have been shown to bind to both the ATP domain and the "DFG-in-conformation" pocket again causing the kinase to adopt the "DFG-out" conformation. Examples specific to inhibitors of Raf kinases can be found in Lowinger et al, *Current Pharmaceutical Design* (2002) 8: 2269; Dumas, J. et al., *Current Opinion in Drug Discovery & Development* (2004) 7: 600; 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.

[0011] 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. 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)

SUMMARY OF THE INVENTION

[0012] Compounds of the present invention find utility in the treatment of mammalian cancers and especially human cancers including but not limited to malignant, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases, leukemias, papillary thyroid carcinoma, non small cell lung cancer, mesothelioma, hypereosinophilic syndrome, gastrointestinal stromal tumors, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies, rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder, a disease caused by c-Abl kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof, or a disease caused by c-Kit, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof.

SECTION 1—DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0013] The following descriptions refer to various compounds, stereo-, regioisomers and tautomers of such compounds and individual moieties of the compounds thereof.

[0014] Cycloalkyl refers to monocyclic saturated carbon rings taken from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctanyl;

[0015] Aryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized π 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;

[0016] Heteroaryl refers to monocyclic or fused bicyclic ring systems characterized by delocalized π 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, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazolopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolopyrimidinyl, thiazolopyrimidinyl, thiazolonopyrimidinyl, oxazolopyrimidinyl, oxazonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl,

quinoxaliny, quinazoliny, quinoliny, isoquinoliny, phthalaziny, benzodioxyl, benzisothiazoline-1,1,3-trionyl, dihydroquinoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, benzoazepiny, benzodiazepiny, benzoxapiny, and benzoxazepiny;

[0017] Heterocyclyl refers to monocyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms; heterocyclyl rings include, but are not limited to, oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidiny, oxazoliny, oxazolidiny, thiazoliny, thiazolidiny, pyranly, thiopyranly, tetrahydropyranly, dioxaliny, piperidiny, morpholiny, thiomorpholiny, thiomorpholiny S-oxide, thiomorpholiny S-dioxide, piperaziny, azepiny, oxepiny, diazepiny, tropanly, and homotropanly;

[0018] Poly-aryl refers to two or more monocyclic or fused aryl bicyclic ring systems characterized by delocalized π electrons (aromaticity) shared among the ring carbon atoms of at least one carbocyclic ring wherein the rings contained therein are optionally linked together;

[0019] Poly-heteroaryl refers to two or more monocyclic or fused bicyclic systems characterized by delocalized π 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 heterocyclyl as defined broadly above;

[0020] Poly-heterocyclyl 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 π 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 heterocyclyl as defined broadly above and the other rings are taken from either aryl, heteroaryl, or heterocyclyl as defined broadly above;

[0021] Alkyl refers to straight or branched chain C1-C6alkyls;

[0022] Halogen refers to fluorine, chlorine, bromine, and iodine;

[0023] Alkoxy refers to —O-(alkyl) wherein alkyl is defined as above;

[0024] Alkoxyalkyl refers to -(alkyl)-O-(alkyl) wherein alkyl is defined as above;

[0025] Alkoxy carbonyl refers to —C(O)O-(alkyl) wherein alkyl is defined as above;

[0026] Carboxyl C1-C6alkyl refers to —C(O)-alkyl wherein alkyl is defined as above;

[0027] 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.

[0028] 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 heterocyclyl 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, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, 3-hydroxybutyric, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable salts of free acid-containing compounds of Formula I 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, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine(N-methylglucamine) and procaine.

[0029] 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: 2393 and Lorenzi et. al, *J. Pharm. Exp. Therapeutic* (2005) 883 for reviews.

[0030] 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:

[0031] 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.

[0032] Regioisomers or structural isomers are defined as isomers involving the same atoms in different arrangements.

[0033] Enantiomers are defined as one of a pair of molecular entities which are mirror images of each other and non-superimposable.

[0034] Diastereomers or diastereoisomers are defined as stereoisomers other than enantiomers. Diastereomers or diastereoisomers are stereoisomers not related as mirror images.

[0035] Diastereoisomers are characterized by differences in physical properties, and by some differences in chemical behavior towards achiral as well as chiral reagents.

[0036] Tautomerism is defined as isomerism of the general form

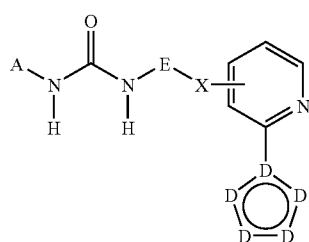


[0037] where the isomers (called tautomers) are readily interconvertible; the atoms connecting the groups X,Y,Z are

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 H^+ , is also known as "prototropy".

[0038] Tautomers are defined as isomers that arise from tautomerism, independent of whether the isomers are isolable.

[0039] 1. First Aspect of the Invention—Compounds, Methods, Preparations and Adducts



Ia

[0040] and wherein the pyridine ring may be optionally substituted with one or more R20 moieties;

[0041] each D is individually taken from the group consisting of C, CH, C—R20, N—Z3, N, O and S, such that the resultant ring is taken from the group consisting of triazolyl, isoxazolyl, isothiazolyl, oxazolyl, and thiadiazolyl;

[0042] wherein E is selected from the group consisting of phenyl, pyridyl, and pyrimidinyl;

[0043] E may be optionally substituted with one or two R16 moieties;

[0044] wherein A is a ring system selected from the group consisting of phenyl, naphthyl, cyclopentyl, cyclohexyl, G1, G2, and G3;

[0045] G1 is a heteroaryl taken from the group consisting of pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazol-4-yl, isoxazol-5-yl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl, pyridinyl, and pyrimidinyl;

[0046] G2 is a fused bicyclic heteroaryl taken from the group consisting of indolyl, indolinyl, isoindolyl, isoindolinyl, indazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzothiazolonyl, benzoxazolyl, benzoxazolonyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazolopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolopyrimidinyl, thiazolopyrimidinyl, thiazolonopyrimidinyl, oxazolopyrimidinyl, oxazonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinyl, 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;

[0047] G3 is a heterocyclyl taken from the group consisting of oxetanyl, azetadanyl, tetrahydrofuranyl, pyrrolidinyl, oxazoliny, oxazolidinyl, imidazolonyl, pyranyl, thiopyranyl,

tetrahydropyranyl, dioxaliny, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl;

[0048] the A ring may be optionally substituted with one or two R2 moieties;

[0049] X is selected from the group consisting of —O—, —S(CH₂)_n—, —N(R3)(CH₂)_n—, —(CH₂)_p—, and wherein the carbon atoms of —(CH₂)_n—, —(CH₂)_p—, of X may be further substituted by oxo or one or more C1-C6alkyl moieties;

[0050] 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;

[0051] 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;

[0052] 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;

[0053] 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, —(CH₂)_nOH, oxo, C1-C6alkoxyC1-C6alkyl, (R4)₂N(CH₂)_n—, (R3)₂N(CH₂)_n—, (R4)₂N(CH₂)_qN(R4)(CH₂)_n—, (R4)₂N(CH₂)_qO(CH₂)_n—, (R3)₂NC(O)—, (R4)₂NC(O)—, (R4)₂NC(O)C1-C6alkyl—, —(R4)NC(O)R8, C1-C6alkoxycarbonyl-, -carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, (R3)₂NSO₂—, —SOR3, (R4)₂NSO₂—, —N(R4)SO₂R8, —O(CH₂)_qOC1-C6alkyl, —SO₂R3, —SOR4, —C((O)R8, —C(O)R6, —C(=NOH)R6, —C(=NOR3)R6, —(CH₂)_nN(R4)C(O)R8, —N(R3)(CH₂)_qO-alkyl, —N(R3)(CH₂)_qN(R4)₂, nitro, —CH(OH)CH(OH)R4, —C(=NH)N(R4)₂, —C(=NOR3)N(R4)₂, —NHC(=NH)R8, R17 substituted G3, R17 substituted pyrazolyl and R17 substituted imidazolyl;

[0054] in the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0055] 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)₂N—, (R4)₂N—, (R4)₂NC1-C6alkyl-, (R4)₂NC2-C6alkylN(R4)(CH₂)_n—, (R4)₂NC2-C6alkylO(CH₂)_n—, (R3)₂NC(O)—, (R4)₂NC(O)—, (R4)₂NC(O)—C1-C6alkyl-, carboxyl-, -carboxyC1-C6alkyl, C1-C6alkoxycarbonyl-, C1-C6alkoxycarbonylC1-C6alkyl-, (R3)₂NSO₂—, (R4)₂NSO₂—, —SO₂R8, —(CH₂)_nN(R4)C(O)R8, —C(O)R8, —O, —NOH, and —N(OR6);

[0056] in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0057] 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)(CH₂)_n—, (R4)₂NC(O)—, (R4)₂NC(O)C1-

C6alkyl-, $R_8C(O)N(R_4)(CH_2)_q-$, $(R_3)_2NSO_2-$, $(R_4)_2NSO_2-$, $-(CH_2)_qN(R_3)_2$, and $-(CH_2)_qN(R_4)_2$;

[0058] each Z4 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, hydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, $(R_4)_2N-C2-C6alkyl-$, $(R_4)_2N-C2-C6alkylN(R_4)-C2-C6alkyl-$, $(R_4)_2N-C2-C6alkyl-O-C2-C6alkyl-(R_4)_2NC(O)C1-C6alkyl-$, carboxyC1-C6alkyl-, C1-C6alkoxycarbonylC1-C6alkyl-, $-C2-C6alkylN(R_4)C(O)R_8$, $R_8-C(=NR_3)-$, $-SO_2R_8$, and $-COR_8$;

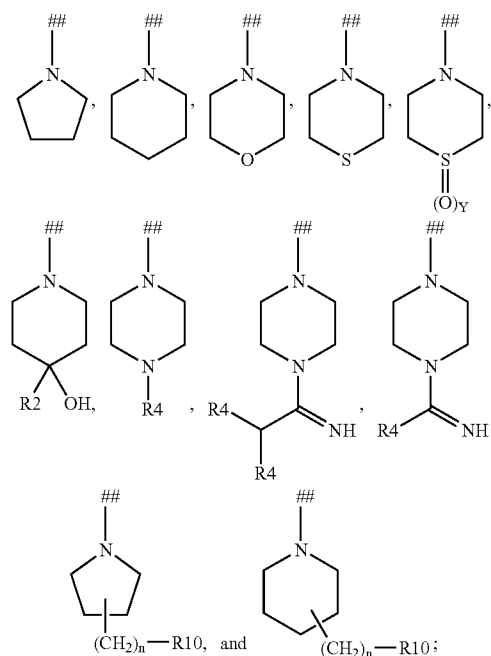
[0059] in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0060] 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-, $(R_3)_2NC(O)C1-C6alkyl-$, and $(R_3)_2NC(O)C3-C8$ branched alkyl-;

[0061] wherein each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, and C3-C8cycloalkyl;

[0062] 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-, $-(CH_2)_pN(R_7)_2$, $-(CH_2)_pC(O)N(R_7)_2$, $-(CH_2)_pC(O)OR_3$, and R19 substituted C3-C8cycloalkyl-;

[0063] each R5 is independently and individually selected from the group consisting of



[0064] and wherein the symbol (##) is the point of attachment to Z3;

[0065] each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8cycloalkyl-;

[0066] 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-, $-(CH_2)_mC(O)OR_3$, R19 substituted C3-C8cycloalkyl- and $-(CH_2)_mR_{17}$;

[0067] 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, $-N(R_3)_2$, and $-N(R_4)_2$;

[0068] each R10 is independently and individually selected from the group consisting of $-CO_2H$, $-CO_2C1-C6alkyl$, $-C(O)N(R_4)_2$, OH , C1-C6alkoxy, and $-N(R_4)_2$;

[0069] 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, $-N(R_3)_2$, $-N(R_4)_2$, R3 substituted C2-C3alkynyl- and nitro;

[0070] 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, $-N(R_3)_2$, $-N(R_4)_2$, and nitro;

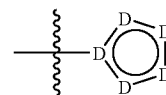
[0071] each R19 is independently and individually selected from the group consisting of H, OH and C1-C6alkyl;

[0072] 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, $-N(R_3)_2$, $-N(R_4)_2$, $-N(R_3)C(O)R_3$, $-C(O)N(R_3)_2$, 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 heterocyclyl ring;

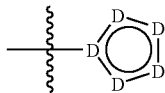
[0073] k is 0 or 1; n is 0-6; p is 1-4; q is 2-6; r is 0 or 1; t is 1-3; v is 1 or 2; m is 0-2;

[0074] and stereo-, regioisomers and tautomers of such compounds.

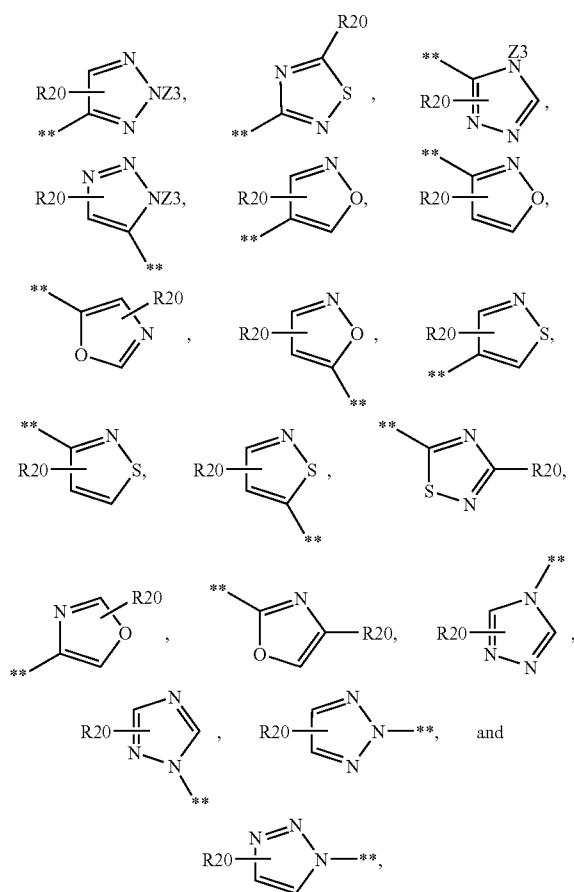
[0075] 1.1 Compounds of Formula Ia which Exemplify Referred D Moieties



[0076] In a preferred embodiment of compounds of formula Ia, said compounds have preferred



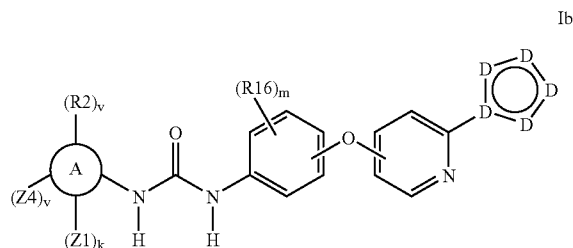
[0077] moieties of the formula:



[0078] wherein the symbol (**) indicates the point of attachment to the pyridine ring.

[0079] 1.1.1 Compounds of Formula Ia which Exemplify Preferred A Moieties

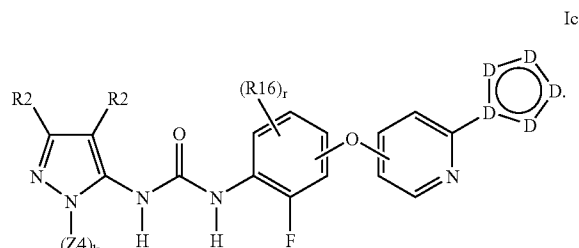
[0080] In a preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ib



[0081] wherein A is any possible isomer of pyrazole.

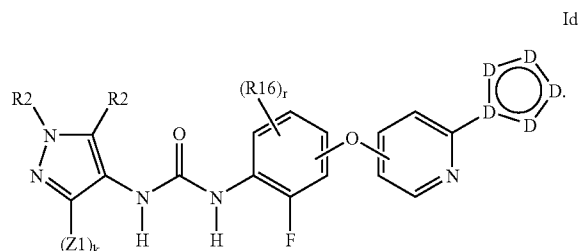
[0082] 1.1.2 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0083] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Ic



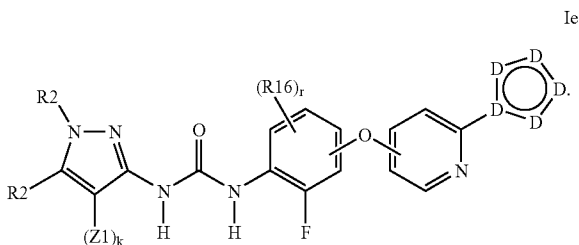
[0084] 1.1.3 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0085] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Id



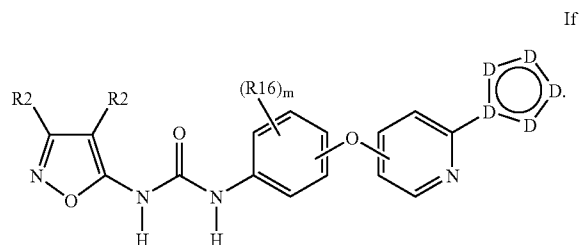
[0086] 1.1.4 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0087] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Ie



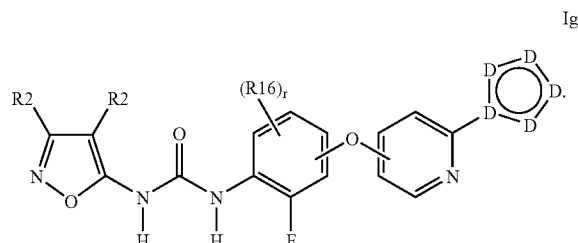
[0088] 1.1.5 Compounds of Formula Ia which Exemplify Preferred A Moieties

[0089] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula If



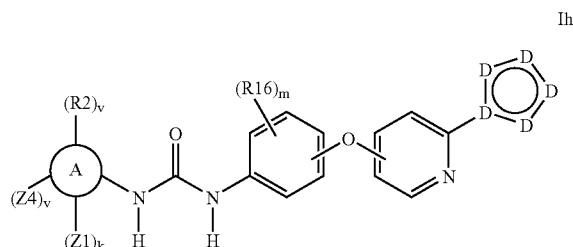
[0090] 1.1.6 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0091] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ig



[0092] 1.1.7 Compounds of Formula Ia which Exemplify Preferred A Moieties

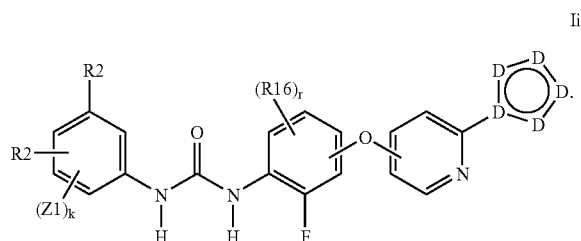
[0093] In a preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ih



[0094] wherein A is selected from the group consisting of any possible isomer of phenyl and pyridine.

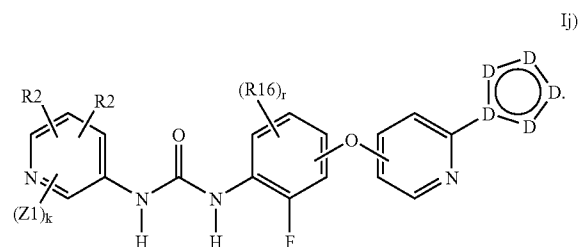
[0095] 1.1.8 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0096] In a more preferred embodiment of compounds of formula Ih, said compounds have structures of formula Ii



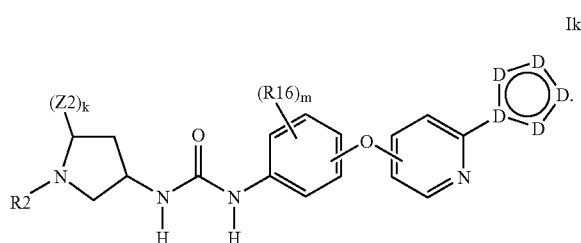
[0097] 1.1.9 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0098] In a more preferred embodiment of compounds of formula Ih, said compounds have structures of formula Ij



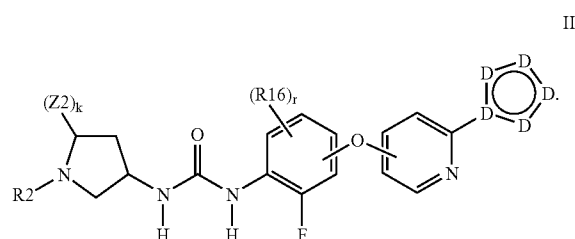
[0099] 1.1.10 Compounds of Formula Ia which Exemplify Preferred A Moieties

[0100] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ik



[0101] 1.1.11 Compounds of Formula Ia which Exemplify Preferred A and R16 Moieties

[0102] In a more preferred embodiment of compounds of formula Ik, said compounds have structures of formula II



[0103] 1.1.12 Most Preferred Compounds of Formula Ia

[0104] 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-(2-(1H-1,2,3-triazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(4-(2-(1H-1,2,4-triazol-1-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea and 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-2-yl)pyridin-4-yloxy)phenyl)urea.

[0105] 1.2 Methods

[0106] 1.2a Methods of Protein Modulation

[0107] 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 and the HER family of kinases. 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 phosphorylation, 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.

[0108] 1.2b Treatment Methods

[0109] 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, malignant melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary tumor secondary sites, myeloproliferative diseases, leukemias, papillary thyroid carcinoma, non small cell lung cancer, mesothelioma, hypereosinophilic syndrome, gastrointestinal stromal tumors, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including various retinopathies including diabetic retinopathy and age-related macular degeneration, rheumatoid arthritis, asthma, chronic obstructive pulmonary disorder, mastocytosis, mast cell leukemia, a disease caused by c-Abl kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof, or a disease caused by a c-Kit kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof. The administration method is not critical, and may be from the group consisting of oral, parenteral, inhalation, and subcutaneous.

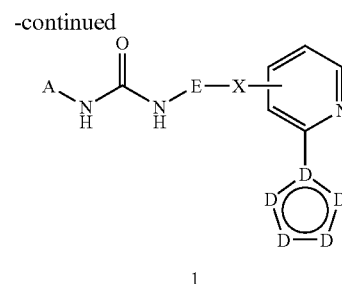
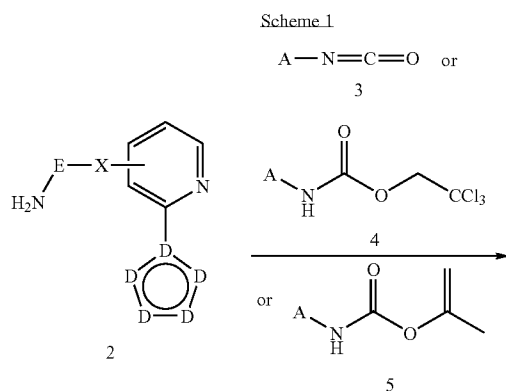
[0110] 1.3 Pharmaceutical Preparations

[0111] 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 pharmaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stabilizers.

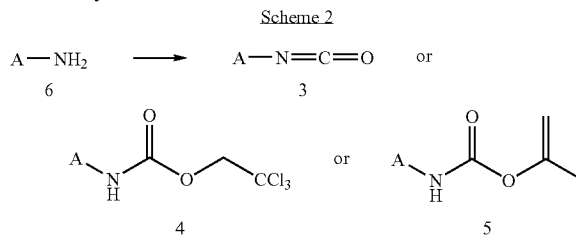
SECTION 2. SYNTHESIS OF COMPOUNDS OF THE PRESENT INVENTION

[0112] 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.

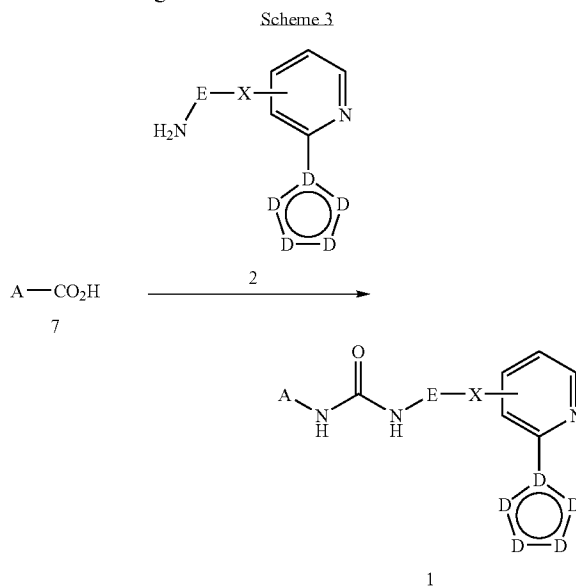
[0113] As indicated in Scheme 1, ureas of general formula 1 can be readily prepared by the union of amines of general formula 2 with isocyanates 3 or isocyanate surrogates, for example trichloroethyl carbamates (4) or isopropenyl carbamates (5). Preferred conditions for the preparation of compounds of 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.



[0114] As shown in Scheme 2, isocyanates 3 can be prepared from amines A-NH₂ 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-NH₂, (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.



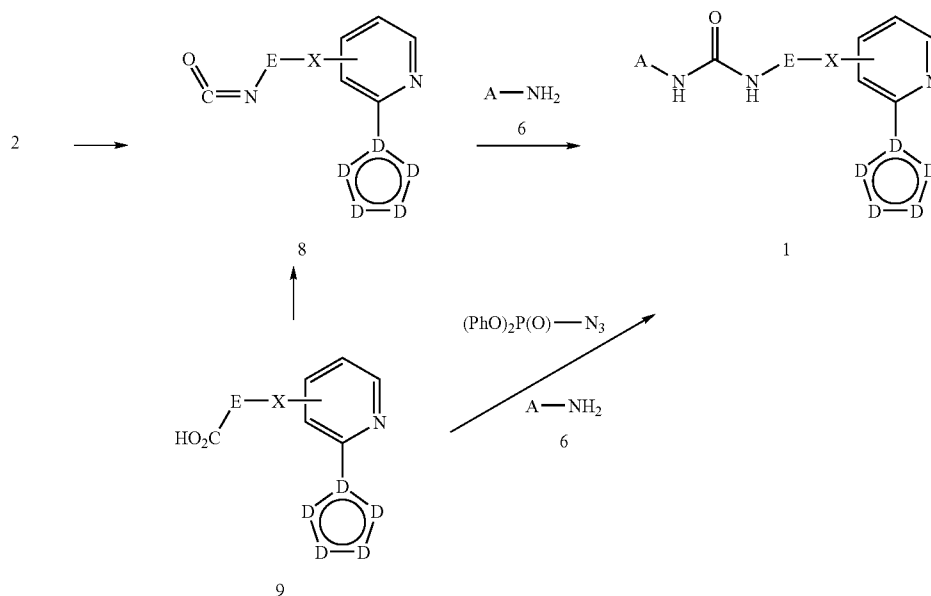
[0115] Additionally, compounds of formula 1 can also be prepared from carboxylic acids 7 by the intermediacy of in-situ generated acyl azides (Curtius rearrangement) as indicated in Scheme 3. Preferred conditions for Scheme 3 include the mixing of acid 7 with amine 2 and diphenylphosphoryl azide in a 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.



[0116] 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-NH₂

solvent, for example dioxane. Heating said mixture to a temperature of between 80 and 120° C. provides the compounds of formula 1.

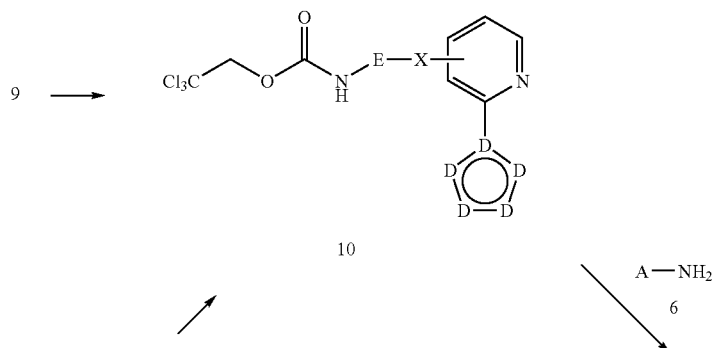
Scheme 4

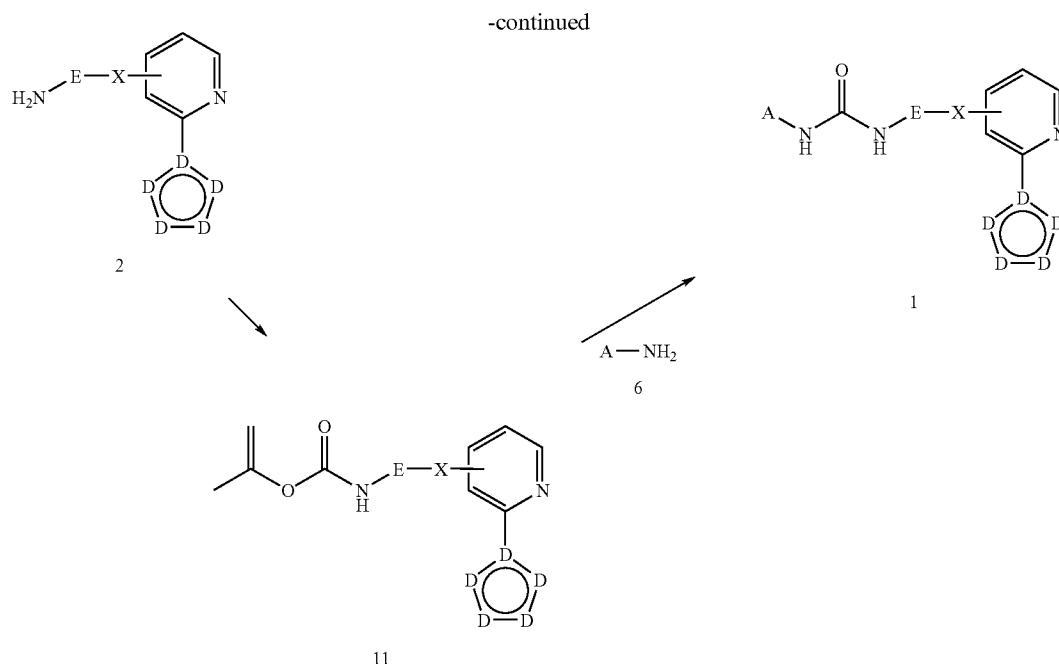


6 with isocyanates 8 (Scheme 4). Isocyanates 8 can be prepared from general amines 2 by standard synthetic methods. Suitable methods for example, include reaction of 2 with phosgene, or a phosgene equivalent such as diphosgene, triphosgene, or N,N-dicarbonylimidazole. In addition to the methods above 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-NH₂ 6, diphenylphosphoryl azide and a suitable base, for example triethylamine, in an aprotic

[0117] 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-NH₂ 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

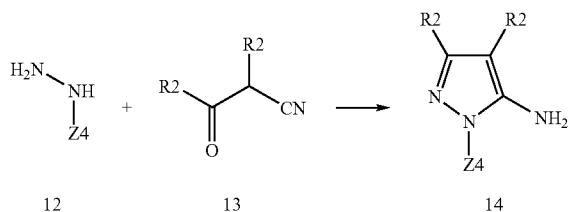




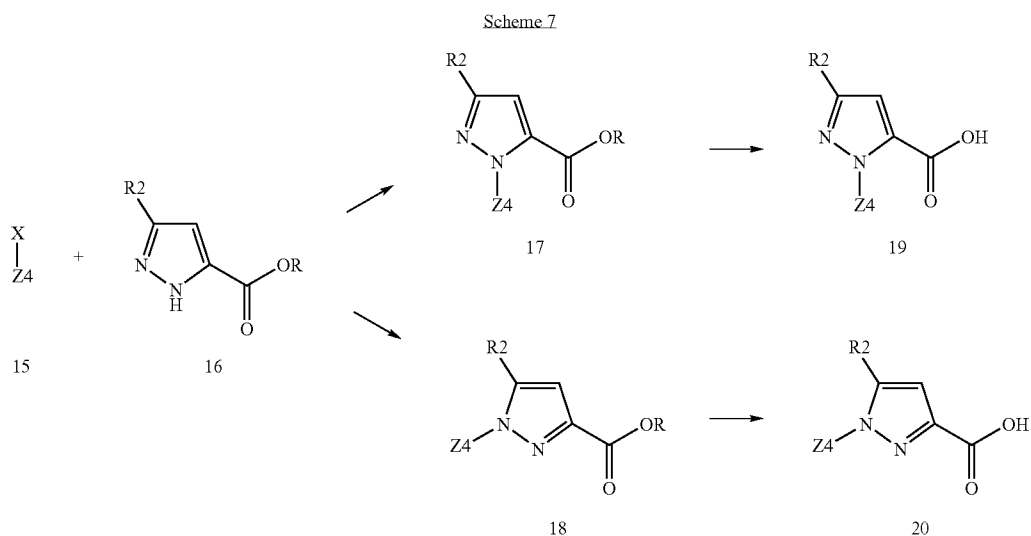
[0118] Many methods exist for the preparation of amines $A-NH_2$ 6 and acids $A-CO_2H$ 7, depending on the nature of the A-moiety. Indeed, many such amines (6) and acids (7) useful for the preparation of compounds of formula 1 are available from commercial vendors. Some non-limiting preferred synthetic methods for the preparation of amines 6 and acids 7 are outlined in the following schemes and accompanying examples.

[0119] As illustrated in Scheme 6, Z4-substituted pyrazol-5-yl amines 14 (a preferred aspect of $A-NH_2$ 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.

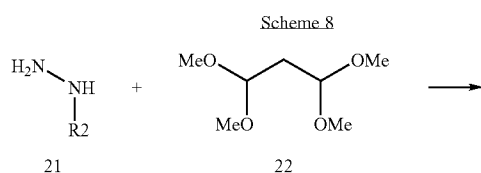
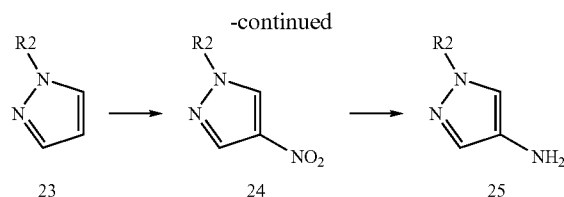
Scheme 6



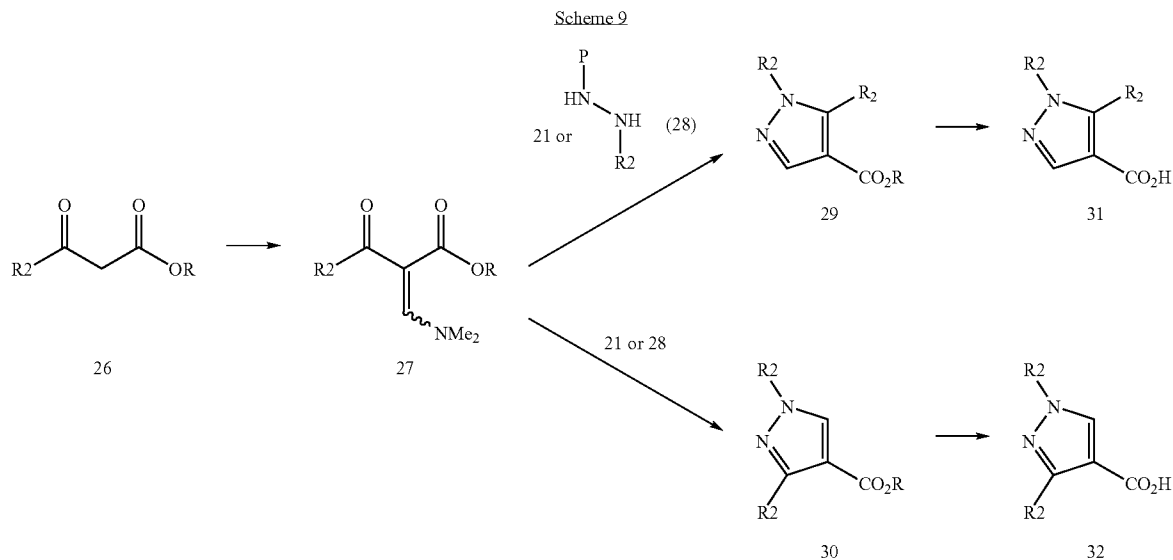
[0120] Another preferred method for constructing Z4-substituted pyrazoles is illustrated by the general preparation of pyrazole acids 19 and 20. (Scheme 7), aspects of of general acid $A-CO_2H$ 7 (Scheme 3). As indicated in Scheme 7, pyrazole 5-carboxylic esters 17 and 18 can be prepared by the alkylation 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.



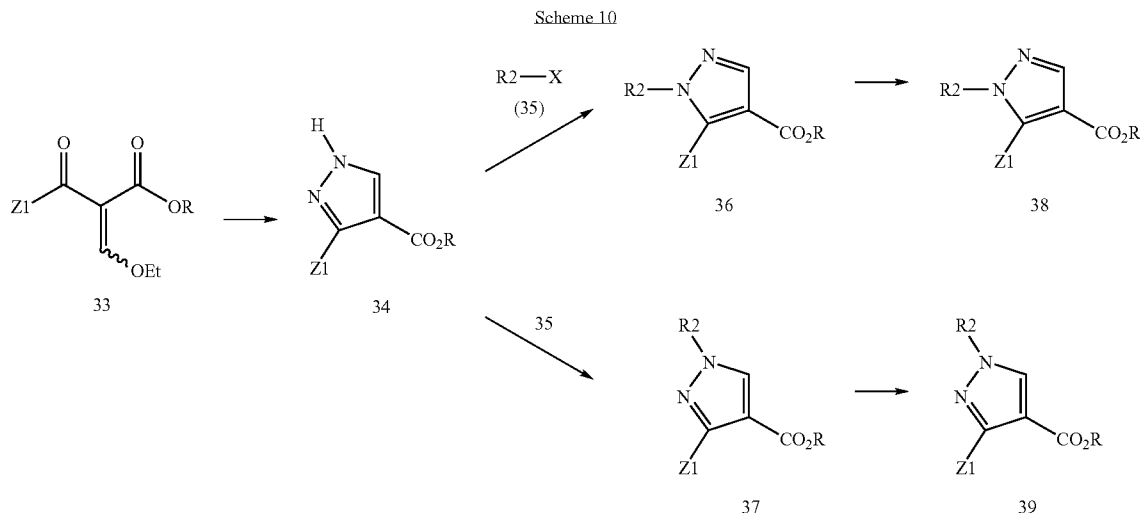
[0121] Scheme 8 illustrates the preparation of pyrazole amine 25, a further example of general amine A-NH₂ 6. Acid-catalyzed condensation of R₂-substituted hydrazine 21 with 1,1,3,3-tetramethoxypropane 22 provides R₂-substituted pyrazole 23. Those skilled in the art will further recognize that R₂-substituted 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-NH₂ 6.



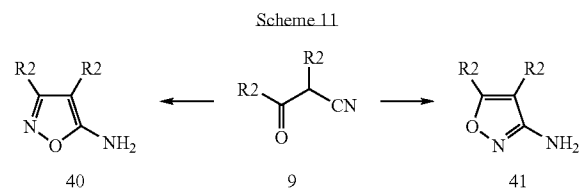
[0122] Additional pyrazoles useful for the synthesis of compounds of formula 1 can be prepared as described in Scheme 9. Thus, keto-ester 26 can be reacted with N,N-dimethylformamide dimethyl acetal to provide 27. Reaction of 27 with either 21 or 28 (wherein P is an acid-labile protecting group) in the 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 previously described in Scheme 7.



[0123] 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 R²-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 above in Scheme 7.



[0124] 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 15 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 15 and 100° C.



[0125] 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 partici-

pates 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,

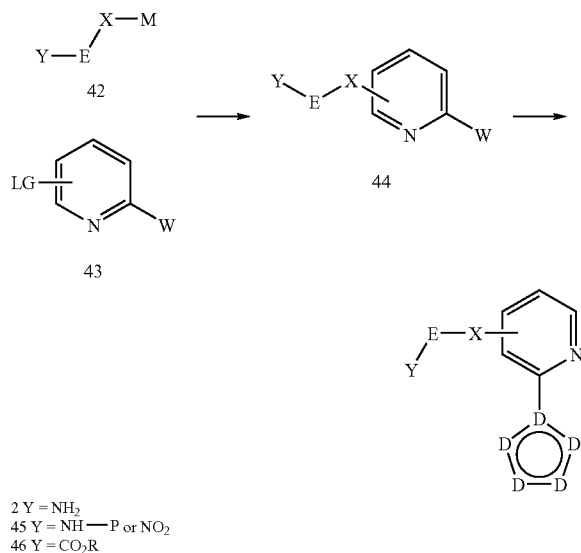
aluminum, magnesium, lithium, silicon, etc.) on a carbon atom of the X₂ moiety that can undergo a transition-metal-mediated coupling with monocycle 43.

[0126] 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), benzyloxycarbonyl (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.

[0127] 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

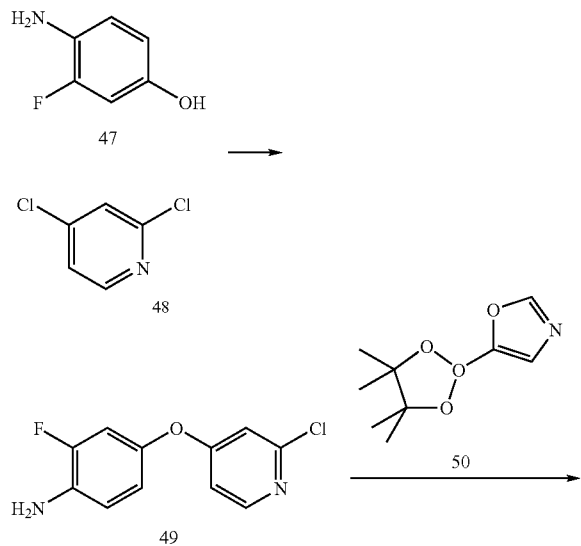
either a single reaction or a reaction sequence. Additionally, the “W” group of 44 may represent a leaving group (halogen or triflate) that can be displaced by a nucleophilic nitrogen atom of a pyrazole ring.

Scheme 12

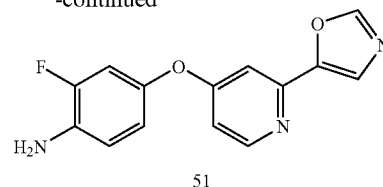


[0128] Some non-limiting examples of general Scheme 12 are illustrated in the Schemes below. Scheme 13 illustrates the preparation of pyrazole 51, an example of general amine 2. In Scheme 13, commercially available 3-fluoro-4-aminophenol (47) is reacted with potassium tert-butoxide and 2,4-dichloropyridine 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 oxazole-4-boronic acid pinacol ester 50 in the presence of a palladium catalyst, preferably tetrakis(triphenylphosphine)palladium, provides oxazole amine 51.

Scheme 13

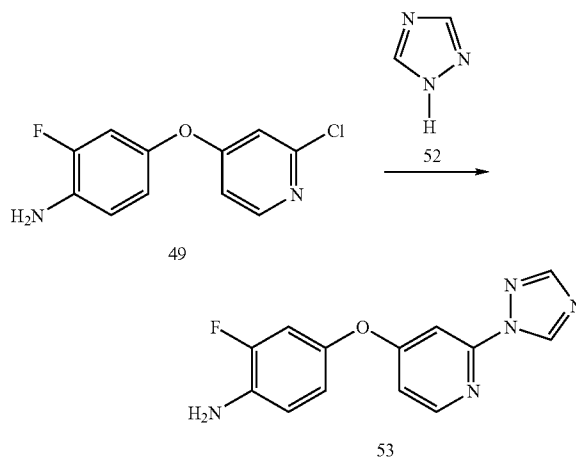


-continued

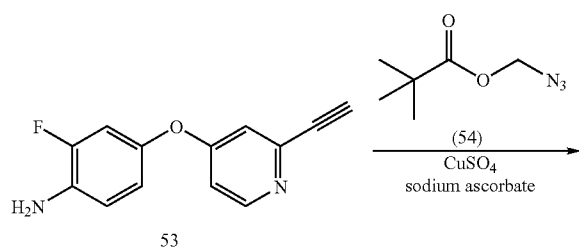
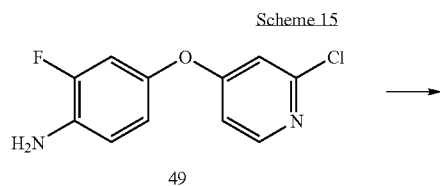


[0129] Scheme 14 illustrates a non-limiting example of Scheme 12 wherein the “W” group is a leaving group for nucleophilic aromatic substitution. Thus, amine 53, an example of general amine 2, can be prepared from general intermediate 49 by reaction with 1,2,4-triazole (52). Preferred conditions include 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. Those skilled in the art will recognize that the general methods of scheme 14 can be used to prepare additional triazole isomers by employing either 1,2,4-triazole 52, or alternatively, by employing 1,2,3-triazole in place of 52.

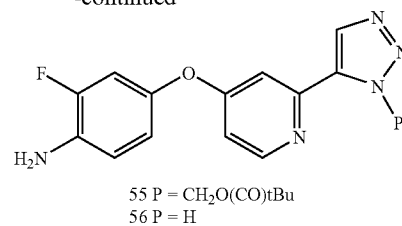
Scheme 14



[0130] Scheme 15 illustrates the preparation of amine 55 and 56, non-limiting examples of 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 azidomethyl pivalate (54) in the presence of copper sulfate and sodium ascorbate provides the N-pivaloylmethyl triazole amine 55. (see Loren, et. al. *Synlett*, (2005), 2847). Deprotection under standard conditions, preferably dilute aqueous sodium hydroxide, provides 56. Alternatively, the amine 55 can be used directly to produce ureas of formula 1 prior to the removal of the N-pivaloylmethyl protecting group.

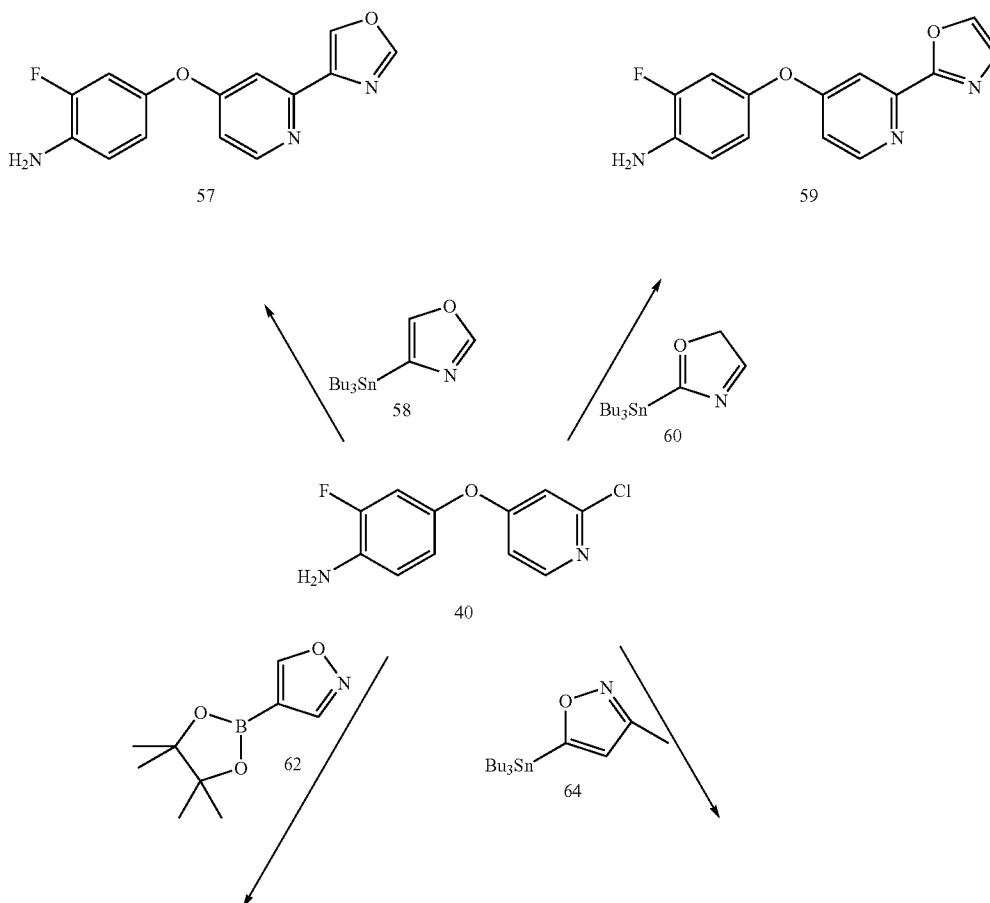


-continued

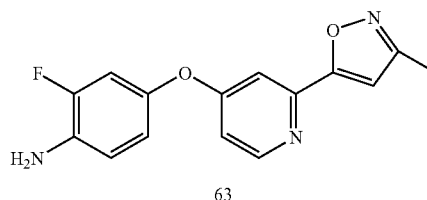
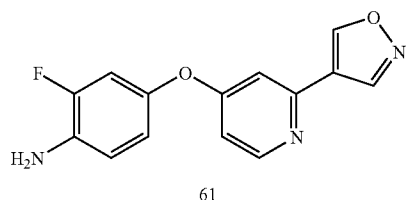


[0131] Additional examples of general amines of formula 2 can be prepared as illustrated in Scheme 16. Thus, by analogy to Scheme 12, the general intermediate 40 can be converted by palladium-mediated Stille-coupling into oxazoles 57 or 59 by reaction with the tributylstannanes 58 (see: Cheng et al., *Biorg. Med. Chem. Lett.*, 2006, 2076) or 60 (Aldrich Chemical). Preferred palladium catalysts for the Stille reactions include dichlorobis(triphenylphosphine)palladium, dichloro [11'-bis(diphenylphosphino)ferrocene]palladium and tetrakis(triphenylphosphine)palladium. Similarly, isoxazoles 61 and 63 can be obtained by the palladium-catalyzed reaction of 40 with 4-isoxazoleboronic acid pinacol ester 62 (Frontier Scientific) or tributylstannane 64 (see: Sakamoto, et al. *Tetrahedron*, 1991, 5111).

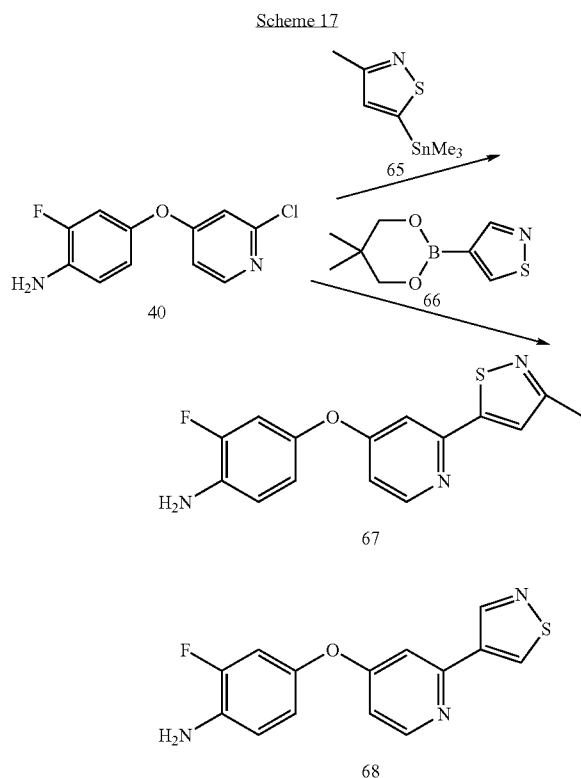
Scheme 16



-continued



[0132] As an extension of Schemes 12, 13 and 16, amines of general formula 2 containing an isothiazole ring can also be prepared by the methods described above. Scheme 17 shows a non-limiting example wherein a palladium-catalyzed Stille reaction of trimethylstannane 65 (see: Wentland, et al. *J. Med. Chem.*, 1993, 1580) with 40 can provide isothiazole 67. In a similar fashion, palladium-catalyzed Suzuki-cross coupling between 40 and the boronate ester 66 (see: Blackaby, et al., U.S. Pat. No. 7,030,128) gives rise to isothiazole amine 68.



[0133] Additional preferred synthetic methods for the preparation of compounds of formula 1 are found in the following examples.

SECTION 3. EXAMPLES

[0134] General Method A: 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 (MgSO₄) and concentrated. The residue was purified by chromatography to afford the target compound.

[0135] General Method B: To a solution of the starting pyrazole amine (1 eq) in EtOAc were added 2,2,2-trichloroethylchloroformate (1.1 eq) and saturated NaHCO₃ (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 (Na₂SO₄) and concentrated under vacuum to yield the crude TROC carbamate of the pyrazole amine.

[0136] 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 (Na₂SO₄) and concentrated to yield crude product, which was purified by column chromatography to yield the target compound.

Example A1

[0137] 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 (MgSO₄), concentrated in vacuo and purified by silica gel column chromatography to give 4-(2-chloro-pyridin-4-yloxy)-2-fluorophenylamine (11 g, 86% yield). ¹H NMR (300 MHz, DMSO-d₆), δ 8.24 (d, J=5.7 Hz, 1 H), 7.00 (dd, J=9.0, 2.7 Hz, 1 H), 6.89-6.73 (m, 4 H), 5.21 (br s, 2 H); MS (ESI) m/z: 239.2 (M+H⁺).

[0138] To a degassed solution of 4-(2-chloropyridin-4-yloxy)-2-fluorobenzenamine (0.801 g, 3.36 mmol) in DMF (2 mL) and TEA (2 mL) was added ethynyltrimethylsilane (0.929 mL, 6.71 mmol), trans-dichloro-bis(triphenyl phosphine)palladium(0) (0.236 g, 0.336 mmol) and copper (I) iodide (0.064 g, 0.336 mmol) and the mixture was stirred at 90° C. for 16 h. Water (60 mL) was added to the mixture, product was extracted with EtOAc (2×45 mL) and the combined organics were washed with brine, dried (Na₂SO₄) concentrated to afford crude product. The product was dissolved in methanol (10 mL), K₂CO₃ (0.5 g) was added and the mixture was stirred at RT for 2 h. Solvent was removed, to the crude residue was added water (60 mL) and EtOAc (40 mL),

the layers were separated and the aqueous layer was extracted with EtOAc (1×30 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated to afford crude product which was purified by column chromatography (ethylacetate/hexane) to afford 4-(2-ethynylpyridin-4-yloxy)-2-fluorobenzenamine as a thick residue (0.56 g, 73% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.37 (d, J=6.0 Hz, 1H), 6.98 (dd, J=8.0 Hz, 2.4 Hz, 1H), 6.95 (d, J=6.0 Hz, 1H), 6.87 (dd, J=6.0 Hz, 2.4 Hz, 1H), 6.81-6.73 (m, 2H), 5.20 (brs, 2H), 4.03 (s, 1H); MS (ESI) m/z: 229.1 (M+H⁺).

[0139] Sodium azide (1.942 g, 29.9 mmol) was added to a suspension of chloromethyl pivalate (3.00 g, 19.92 mmol) in water (5 mL) and stirred vigorously at 90° C. for 16 h. The reaction mixture was diluted with water (20 mL) and EtOAc (20 mL). The organic layer was washed with brine, dried (Na₂SO₄) and concentrated to afford azidomethyl pivalate as a liquid (2 g, 64% yield). ¹H NMR (400 MHz, Acetone-d₆): δ 5.23 (s, 2H), 1.22 (s, 9H).

[0140] To a suspension of azidomethyl pivalate (0.075 g, 0.477 mmol), 4-(2-ethynylpyridin-4-yloxy)-2-fluorobenzenamine (0.109 g, 0.477 mmol) in t-butanol (0.6 mL) and water (0.6 mL) was added sodium ascorbate (0.021 g, 0.095 mmol). Copper(II)sulfate in water (0.048 mL, 0.048 mmol) was added to the above suspension and the dark red mixture was stirred for 3 h at RT. It was diluted with water (30 mL) and EtOAc (20 mL), the layers were separated and the aqueous layer was extracted with EtOAc (2×15 mL). The combined organics were washed with brine, dried (Na₂SO₄) and concentrated to afford (4-(4-(4-amino-3-fluorophenoxy)pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl pivalate as a red solid. (0.165 g, 90% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.54 (s, 1H), 8.46 (brs, 1H), 7.60 (s, 1H), 6.98 (d, J=8.8 Hz, 1H), 6.94 (d, J=3.6 Hz, 1H), 6.83-6.81 (m, 2H), 6.42 (s, 2H), 4.78 (s, 2H), 1.17 (s, 9H); MS (ESI) m/z: 386.1 (M+H⁺).

Example A2

[0141] To a solution of 4-(2-chloropyridin-4-yloxy)-2-fluorobenzenamine from Example A1 (1.0 g, 4.2 mmol) in NMP (10 mL) was added DBU (0.94 mL, 6.3 mmol) and 1,2,4-triazol sodium salt (0.57 g, 6.3 mmol) and the mixture was heated overnight under argon atmosphere at 160° C. The reaction mixture cooled to RT, diluted with water (100 mL) and the solution was extracted with EtOAc (3×). The organics were combined and washed with LiCl solution and brine (2×), dried (Na₂SO₄) and concentrated in vacuo. The residue was slurried in EtOAc (5 mL), the solid was filtered and washed with EtOAc to obtain a mixture of product and SM. The filtrate was concentrated in vacuo, the residue was slurried in CH₂Cl₂, filtered and washed with CH₂Cl₂ to obtain 4-(2-(1H-1,2,4-triazol-1-yl)pyridin-4-yloxy)-2-fluorobenzenamine (0.35 g). MS (ESI) m/z: 272.2 (M+H⁺).

Example A3

[0142] 4-(2-Chloropyridin-4-yloxy)-2-fluorobenzenamine from Example A1 (150 mg, 0.629 mmol), 2-(tri-n-butylstannyl)oxazole (0.132 mL, 0.629 mmol) and PdCl₂(dppf)·CH₂Cl₂ (51.3 mg, 0.063 mmol) were combined in DMF (3 mL) under Ar and stirred with heating at 90° C. After 3 h, the completed reaction was cooled to RT and treated with satd. aq. KF (5 mL; prepared from equal portions of KF·H₂O and H₂O) and stirred at RT for 1 h. The suspension was diluted with EtOAc and filtered through Celite®, rinsing forward with EtOAc. The filtrate was diluted with H₂O and the layers

were separated. The aqueous was extracted with EtOAc (2×). The combined organics were washed with brine (2×), dried (MgSO₄), concentrated in vacuo and purified by flash column chromatography (EtOAc/hexanes) to afford 80 mg of 2-fluoro-4-(2-(oxazol-2-yl)pyridin-4-yloxy)benzenamine (0.295 mmol, 47% yield) as an oil that solidified on standing. ¹H NMR (400 MHz, DMSO-d₆): δ 8.52 (d, J=5.8 Hz, 1H), 8.26 (s, 1H), 7.40 (d, J=2.3 Hz, 1H), 7.38 (s, 1H), 7.05-7.02 (m, 2H), 6.88-6.78 (m, 2H), 5.23 (s, 2H); MS (ESI) m/z: 272.1 (M+H⁺).

Example A4

[0143] In a 3:1 mix of DMF:H₂O (6 mL) was placed 4-(2-chloropyridin-4-yloxy)-2-fluorobenzenamine from example A1 (245 mg, 1.026 mmol), cesium carbonate (1.337 g, 4.10 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (300 mg, 1.538 mmol) and tetrakis(triphenyl)phosphine Pd(0) (178 mg, 0.154 mmol). The mix was degassed, placed under Ar, warmed to 80° C. and stirred overnight. The reaction was cooled to RT, diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with brine, dried (Na₂SO₄) and concentrated in vacuo to give 2-fluoro-4-(2-(oxazol-5-yl)pyridin-4-yloxy)benzenamine (415 mg, 149% yield) as a dark oil. LC and LCMS shows mostly desired product as well as triphenylphosphine oxide as a by product. Used as is. MS (ESI) m/z: 272.1 (M+H⁺).

Example A5

[0144] In a microwave reaction vial, 4-(2-ethynylpyridin-4-yloxy)-2-fluorobenzenamine from Example A1 (0.201 g, 0.881 mmol) was dissolved in THF (4 mL). Acetaldoxime (0.078 g, 1.321 mmol), triethylamine (0.246 mL, 1.761 mmol), and 1-chloropyrrolidine-2,5-dione (0.176 g, 1.321 mmol) were added and the mixture was stirred at 130° C. for 45 min under microwave irradiation. An additional 1.5 eq each of acetaldoxime and 1-chloropyrrolidine-2,5-dione were added and microwave heating was heated for an additional 45 min at 130° C. This process repeated one more time. The mixture was poured into a biphasic solution of water (40 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×20 mL). The combined organics were washed with brine, dried (Na₂SO₄) and concentrated. The residue was purified by silica gel chromatography to afford 2-fluoro-4-(2-(3-methylisoxazol-5-yl)pyridin-4-yloxy)benzenamine (58 mg, 23% yield) as light red colored residue. MS (ESI) m/z: 286.1 (M+H⁺).

Example B1

[0145] 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 pivaloylacetone nitrile (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). ¹H NMR (DMSO-d₆) δ 6.41 (brs, 2H), 4.85 (s, 1H), 1.18 (s, 9H); LC-MS (ES, m/z, M+H) 141.3.

Example 1

[0146] Using General Method A, 3-tert-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (0.054 g, 0.3 mmol), Example

A1 (0.1 g, 0.25 mmol), triethylamine (0.76 g, 0.75 mmol) and DPPA (0.137 g, 0.5 mmol) were combined and purified by column chromatography (ethylacetate/hexanes) to afford 1-(4-(4-(3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)ureido)-3-fluorophenoxy)pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl pivalate as a white solid (0.115 g, 82% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.89 (s, 1H), 8.84 (s, 1H), 8.68 (s, 1H), 8.50 (d, J=5.6 Hz, 1H), 8.19 (t, J=8.8 Hz, 1H), 7.46 (d, J=2.4 Hz, 1H), 7.33 (dd, J=12.0 Hz, 2.8 Hz, 1H), 7.06 (dd, J=8.8 Hz, 1.6 Hz, 1H), 6.97 (dd, J=5.6 Hz, 2.4 Hz, 1H), 6.35 (s, 2H), 6.07 (s, 1H), 3.60 (s, 3H), 1.19 (s, 9H), 1.10 (s, 9H); MS (ESI) m/z: 565.2 (M+H⁺).

[0147] To a solution of 1-(4-(4-(3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)ureido)-3-fluorophenoxy)pyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl pivalate (0.11 g, 0.195 mmol) in MeOH (1 mL) was added 2M NaOH (0.4 mL) and the mixture was stirred for 30 min at RT. Solvent was removed, crude residue was diluted with water (5 mL) and neutralized with 50% aqueous acetic acid (1 mL). The resultant solid was filtered and dried to afford 1-(4-(2-(1H-1,2,3-triazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea as a white solid (75 mg, 85% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.89 (s, 1H), 8.84 (s, 1H), 8.68 (s, 1H), 8.49 (d, J=6.0 Hz, 1H), 8.36 (brs, 1H), 8.19 (t, J=9.2 Hz, 1H), 7.42 (s, 1H), 7.33 (dd, J=11.6 Hz, 2.4 Hz, 1H), 7.06-7.04 (m, 1H), 6.94 (dd, J=5.6 Hz, 2.0 Hz, 1H), 6.07 (s, 1H), 3.60 (s, 3H), 1.19 (s, 9H); MS (ESI) m/z: 451.1 (M+H⁺).

Example 2

[0148] To a solution of 2,2,2-trichloroethyl 3-tert-butylisoxazol-5-ylcarbamate (0.080 g, 0.25 mmol), formed via General method B from Example B1, in dioxane (3 mL) was added Example A2 (70 mg, 0.25 mmol) and 1-methylpyrrolidine (22 mg, 0.25 mmol). The reaction mixture was heated overnight at 65° C. The reaction mixture cooled to RT, concentrated in vacuo, DCM (2 mL) was added and the slurry was stirred for 1 hour. The solid was filtered and air dried to obtain 1-(4-(2-(1H-1,2,4-triazol-1-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea. ¹H NMR (400 MHz, DMSO-d₆): δ 10.3 (s, 1H), 9.56 (s, 1H), 8.70 (s, 1H), 8.34 (s, 1H), 8.29 (d, J=6.0 Hz, 1H), 8.03 (t, J=9.2 Hz, 1H), 7.68 (dd, J=2.0, and 5.6 Hz, 1H), 7.57 (d, J=1.2 Hz, 1H), 7.26 (dd, J=2.8, and 12.0 Hz, 1H), 7.03 (m, 1H), 6.05 (s, 1H), 1.24 (s, 9H); MS (ESI) m/z: 438.1 (M+H⁺).

Example 3

[0149] To a solution of 3-(t-butyl)-1-methyl-1H-pyrazole-5-carboxylic acid (0.054 g, 0.295 mmol) in dioxane (3 mL) was added TEA (0.123 mL, 0.885 mmol) followed by DPPA (0.095 mL, 0.442 mmol). The mixture was stirred at RT for 30 min and then treated with a solution of Example A3 (0.080 g, 0.295 mmol) in dioxane (3.00 mL). The reaction was then placed in an oil bath preheated to 100° C. and stirred with heating overnight. The completed reaction was cooled to RT. Without aqueous workup, the reaction mixture was purified directly by reverse phase chromatography (MeCN (w/0.1% TFA)/H₂O (w/0.1% TFA)) to afford 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-2-yl)pyridin-4-yloxy)phenyl)urea of 96.8% purity. MS (ESI) m/z: 451.1 (M+H⁺).

Example 4

[0150] Using General Method A, 3-tert-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (205 mg, 1.127 mmol), tri-

ethylamine (415 mg, 4.10 mmol), Example A4 [max theoretical yield from previous reaction] (278 mg, 1.025 mmol) and DPPA (338 mg, 1.23 mmol) were combined and purified by reverse phase chromatography (acetonitrile/water/-0.1% TFA) to give a residue which was treated with 10% potassium carbonate (10 mL) and extracted with ethyl acetate (3×25 mL). The combined organic phases were washed with brine (25 mL), dried (Na₂SO₄) and concentrated in vacuo to give 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-5-yl)pyridin-4-yloxy)phenyl)urea (131 mg, 28% yield) as a film. ¹H NMR (400 MHz, DMSO-d₆): δ 1.15 (s, 9H), 3.60 (s, 3H), 6.07 (s, 1H), 6.91-6.93 (m, 1H), 7.04-7.07 (m, 1H), 7.23 (d, 1H), 7.30-7.34 (m, 1H), 7.78 (s, 1H), 8.18 (t, 1H), 8.48-8.51 (m, 2H), 8.85 (d, 1H), 8.90 (s, 1H); MS (ESI) m/z: 451.1 (M+H⁺).

Example 5

[0151] Using general method A, 3-tert-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (0.042 g, 0.23 mmol), Example A5 (0.51 g, 0.18 mmol), triethylamine (0.54 g, 0.53 mmol) and DPPA (0.1 g, 0.35 mmol) were combined and purified by column chromatography using (EtOAc/hexanes) to afford 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methylisoxazol-5-yl)pyridin-4-yloxy)phenyl)urea as white solid (0.015 g, 18% yield). ¹H NMR (400 MHz, DMSO-d₆): δ 8.89 (s, 1H), 8.85 (s, 1H), 8.56 (d, J=6.0 Hz, 1H), 8.20 (t, J=8.8 Hz, 1H), 7.38 (d, J=2.4 Hz, 1H), 7.34 (dd, J=12.0 Hz, 2.4 Hz, 1H), 7.08-7.05 (m, 1H), 7.03-7.00 (m, 1H), 6.97 (s, 1H), 6.07 (s, 1H), 3.60 (s, 3H), 2.82 (s, 3H), 1.19 (s, 9H); MS (ESI) m/z: 465.1 (M+H⁺).

[0152] Using the synthetic procedures and methods described herein and methods known to those skilled in the art, the following compounds are made: 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(4-methyloxazol-2-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methyl-1,2,4-thiadiazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(isoxazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-(2-(4H-1,2,4-triazol-4-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(isothiazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methyl-1H-1,2,4-triazol-1-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(isothiazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(isothiazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(4-methyl-2H-1,2,3-triazol-2-yl)pyridin-4-yloxy)phenyl)urea, 1-(5-tert-butylisoxazol-3-yl)-3-(2-fluoro-4-(2-(4-methyl-4H-1,2,4-triazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(2-methyl-2H-1,2,3-triazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(5-methyl-1,2,4-thiadiazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(4-methyl-4H-1,2,4-triazol-3-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methyl-3H-1,2,3-triazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(isoxazol-3-yl)

pyridin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(3-methylisoxazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(3-methylisothiazol-5-yl)pyridin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-imidazol-4-yl)pyridin-4-yloxy)phenyl)urea, 1-(4-(2-(1H-1,2,4-triazol-1-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(4-(2-(4H-1,2,4-triazol-3-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(2-(1H-1,2,3-triazol-1-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(2-(1,3,4-thiadiazol-2-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(2-(1H-1,2,4-triazol-1-yl)pyridin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, and 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-2-yl)pyridin-4-yloxy)phenyl)urea.

SECTION 4. BIOLOGICAL DATA

[0153] Abl Kinase (SEQ ID NO:1) Assay

[0154] Activity of 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_{340nm}) was continuously monitored spectrophotometrically. The reaction mixture (100 μ l) contained Abl kinase (1 nM, Abl from deCode Genetics), peptide substrate (EAIYAAPFAKKK, 0.2 mM), $MgCl_2$ (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.298 mM) in 90 mM Tris buffer containing 0.2% octyl-glucoside and 3.5% DMSO, pH 7.5. Test compounds were incubated with Abl (SEQ ID NO:1) and other reaction reagents at 30° C. for 2 h before ATP (500 μ 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_{50} 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.

Abl kinase (SEQ ID NO: 1)
 GTSMDPSSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKYSLTVAVK
 TLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCRTREPPFYIIIEFMTYG
 NLLDYLRECNQEVNAVVLVLYMATQISSAMEYLEKKNFIIHRDLAARNCLV
 GENHLVKVADFGLSRLMTGDTYTAHAGAKFPIKWTAPELAYNKFSIKSD
 VWAFGVLLWEIATYGMSPYFGIDLSQVYELLEKDYRMERPEGCPEKVYEL
 MRACQWNPSPDRPSFAEIHQAFETMFQE

[0155] Abl Kinase (SEQ ID NO:2) Assay

[0156] Activity of T3 151 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_{340nm}) was continuously monitored spectrophotometrically. The reaction mixture (100 μ l) contained Abl kinase (4.4 nM, M3151 Abl from deCode Genetics), peptide substrate (EAIYAAPFAKKK, 0.2 mM), $MgCl_2$ (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 T3151 Abl (SEQ ID NO:2) and other reaction reagents at 30° C. for 1 h before ATP (500 μ 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_{50} 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.

Abl T3151 kinase (SEQ ID NO: 2)
 GTSMDPSSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKYSLTVAVK
 TLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCRTREPPFYIIIEFMTYG
 NLLDYLRECNQEVNAVVLVLYMATQISSAMEYLEKKNFIIHRDLAARNCLV
 GENHLVKVADFGLSRLMTGDTYTAHAGAKFPIKWTAPELAYNKFSIKSD
 VWAFGVLLWEIATYGMSPYFGIDLSQVYELLEKDYRMERPEGCPEKVYEL
 MRACQWNPSPDRPSFAEIHQAFETMFQE
 BCR-Abl p210-e14a2 (SEQ ID NO: 3)
 MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLQEVRN
 QERFRMIYLTLLAKEKKS YDRQWGFRAAQAQFDGASEPRASASRPQPA
 PADGADPPPAEPEARPDGEGSPGKARPGTARRPGAAASGERDDRGPAS
 VAALRSNFERIRKGGHQPADAEPFYVNVFHHHRLVKNVNDKEVSDRI
 SSLGSQAMQMERKKSQHAGGSSVGDASRPYPYGRSSSESSCGVDGDYEDAE
 LNPRFLKDNLDANGGSRPPWPPLEYQPYQSIYVVGIMEGEGKGPLLRQS
 STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQS
 SRVSPSPPTTYRMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVS
 EATIVGVKRTGQIWPNDDEGAFHGDADGSFGTPPGYGCAADRAEEQRRHQ
 DGLPYIDDSPPSSPHLSSKGRGSRDALVSGALKSTKASELDLEKGLEMRK
 VWLSGILASEETYLSHLEALLLPMPKPLKAAATTSQPVLTSQQIETIFFVK
 PELYEIHKESYDGLFPRVQQWQSHQQRVGDLPQKLASQLGVYAFVDNYGV
 AMEMAEEKCCQANAQFAEISENLRARSNKDAKPTTKNSLETLLYKPVDRV
 TRSTLVLDLHKHTPASHPDHPLLDALRISQNFLLSSINEEITPRRQSMT
 VKKGHEHRLKDSFMVELVEGARKLRHVFLFTDLLLCTKLKKQSGGKTQQ
 YDCKWYIPLTDLFSQMVDELEAVPNIPLVPDEELDALKIKISQIKSDIQR
 EKRANKGSKATERLKKKLSQESLLLLMSPSMAFRVHSRNGKSYTFLISS
 DYERAEWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTIN

-continued

KEDDESPGLYGLNVIVHSATGFKQSSKALQRPVASFEPQGLSEAAARNW
SKENLLAGPSENDPNLFVALYDFVASGDNTLSITKGEKLRVLGYNHNGEW
CEAQTKNGQGWPVPSNYITPVNSLEKHSWYHGPVSRNAAEYPLSSGINGSF
LVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSSRFNTLAEVLV
HHHSTVADGLITTLHYPAKRNKPTVYGVSPNYDKWEMERTDITMKHKL
GGQYGEVYEGVWKKYSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLV
QLLGVCCTREPPFYIITEFMTYGNLLDYLRNCRQEVNAVVLVLYMATQISS
AMEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGA
KFPPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDRSQVY
ELLEKDYMRKPEGCPEKVYELMRACWQWNPSPDRPSFAEIHQAFETMFQ
SSISDEVEKELGKQGVRGAVTTLLQAPELPTKTRTSRRAAEHRDITDVP
MPHSGKGQGESDPLDHEPAVSPLLPRKERGPPEGLNEDERLLPKDKKTNL
FSALIKKKKTAPTTPKRSSSFREMDGQPERRGAGEEGRDISNGALFT
PLDTADPAKSPKPSNGAGVPNGALRESGGSGFRSPHLWKKSTLTSSRLA
TGEEEGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTLPRDLQSTGRQFDS
STFGGHKSEKPAIPRKRAGENRSQVTRGTVTTPPRLVKKNEEADEVFK
DIMESSPGSSPPNLTTPKPLRRQVTVAPASGLPHKEEAWKGSALGTPAAAE
PVTPTSKAGSGAPRGTSKGPAAESRVRHKKHSSSPGRDKGKLSKLPAP
PPPPAASAGKAGGKPSQRPQGEAAGEAVLGAKTKATSLVDVNSDAAKPS
QPAEGLKKPVLPAATPKPHPAKPSGTPISPAPVPLSTLPSASSALAGDQPS
STAFIPLISTRVSLRKTRQPPERASGAIKGVVLDSTEALCLAISGNSEQ
MASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQI
CPASAGSGPAATQDFSKLLSSVKEISDIVQR
BCR-Abl p210-e13a2 (SEQ ID NO: 4)
MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLQE
QERFRMIYLTLLAKEKKS YDRQWRGFRRAAQAPDGASEPRASASRPQPA
PADGADPPPAEPEARPDGEGSPGKARPGTARRPGAAASGERDDRGPPAS
VAALRSNFERIRKGGHQPADAEPFYVNVFHHHERGLVKVNDKEVSDRI
SSLGSQAMQMERKKSQHGAGSSVGDA SRPPYRGRSSESSCGVDGDYEDAE
LNPRFLKDNLDANGGSRPPWPPLYQPYQSIYVG GIMEGEGKGPLLRSQ
STSEQEKRLTWPRRSYSPRSFEDCGGYTPDCSSNENLTSSEEDFSSGQS
SRVSPSPPTTYRMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVS
EATIVGVRKTGQIWPNDDEGAFHGADAGSGFTPGYGCAADRAEQRPHQ
DGLPYIDDSPSSPHLSSKGRGSRDALVSGALKSTKASELDLEKGLEMRK
WVLSGILASEETYLSHLEALLPMKPLKAAATTSQPVLTSSQIETIFFKV
PELYEIHKESYDGLFPRVQWQSHQQRVGDLFQKLASQLGVYRAFDNYGV
AMEMAEEKCCQANAQFAEISENLRARSNKDAKDPPTKNSLETLLYKPVDRV
TRSTLVLDLHLLKHTPASHDPHLLQDALRISQNFLSSINEEITPRRQSM
VKKGEHRQLLDKDSFMVELVEGARKLRHVLFDTDLLCTKLKQSGGKTQ

-continued

YDCKWYIPLTDL SFQMVDELEAVPNIPLPVDEELDALKIKISQIKSDIQ
EKRANKGSKATERLKKKLESEQESLLLLMSPSMAFRVHSRNGKSYTFLISS
DYERAEWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPETIN
KEEALQRPVASFEPQGLSEAAARNW SKENLLAGPSENDPNLFVALYDFVA
SGDNTLSITKGEKLRVLGYNHNGEWCEAQTKNGQGWPVPSNYITPVNSLEK
HSWYHGPVSRNAAEYPLSSGINGSFLVRESESSPSQRSISLRYEGRVYHY
RINTASDGKLYVSSSRFNTLAEVLHHHSTVADGLITTLHYPAKRNKPT
VYGVSPNYDKWEMERTDITMKHKLGGQYGEVYEGVWKKYSLTVAVKTLK
EDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCCTREPPFYIITEFMTYGNLL
DYLRNCRQEVNAVVLVLYMATQISSAMEYLEKKNFIHRDLAARNCLVGEN
HLVKVADFGLSRLMTGDTYTAHAGAKFPPIKWTAPESLAYNKFSIKSDVWA
FGVLLWEIATYGMSPYPGIDRSQVYELLEKDYMRKPEGCPEKVYELMRA
CWQWNPSPDRPSFAEIHQAFETMFQESSISDEVEKELGKQGVRGAVTTLLQ
APELPTKTRTSRRAAEHRDITDVPMPHSGKGQGESDPLDHEPAVSPLLPR
KERGPPEGLNEDERLLPKDKKTNLFSALIKKKKTAPTTPKRSSSFRE
MDGQPERRGAGEEGRDISNGALFTPLDTADPAKSPKPSNGAGVPNGALR
ESGGSGFRSPHLWKKSTLTSSRLATGEEEGGSSSKRFLRSCSVSCVPH
GAKDTEWRSVTLPRDLQSTGRQFDSSTFGGHKSEKPAIPRKRAGENRSQ
VTRGTVTTPPRLVKKNEEADEVFKDIMESSPGSSPPNLTTPKPLRRQVTV
APASGLPHKEEAWKGSALGTPAAAEFVTPTSKAGSGAPRGTSKGPAAESR
VRRHKKHSSSPGRDKGKLSKLPAPPPPAASAGKAGGKPSQRPQGEAAG
EAVLGAKTKATSLVDVNSDAAKPSQPAEGLKKPVLPAATPKPHPAKPSGT
PISPAPVPLSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPPERAS
GAIKGVVLDSTEALCLAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSI
QQMRNKFAFREAINKLENNLRELQICPASAGSGPAATQDFSKLLSSVKEI
SDIVQR
BCR-Abl p190-e1a2 (SEQ ID NO: 5)
MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLQE
QERFRMIYLTLLAKEKKS YDRQWRGFRRAAQAPDGASEPRASASRPQPA
PADGADPPPAEPEARPDGEGSPGKARPGTARRPGAAASGERDDRGPPAS
VAALRSNFERIRKGGHQPADAEPFYVNVFHHHERGLVKVNDKEVSDRI
SSLGSQAMQMERKKSQHGAGSSVGDA SRPPYRGRSSESSCGVDGDYEDAE
LNPRFLKDNLDANGGSRPPWPPLYQPYQSIYVG GIMEGEGKGPLLRSQ
STSEQEKRLTWPRRSYSPRSFEDCGGYTPDCSSNENLTSSEEDFSSGQS
SRVSPSPPTTYRMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVS
EATIVGVRKTGQIWPNDDEGAFHGDAEALQRPVASFEPQGLSEAAARNW
KENLLAGPSENDPNLFVALYDFVASGDNTLSITKGEKLRVLGYNHNGEW
EAQTKNGQGWPVPSNYITPVNSLEKHSWYHGPVSRNAAEYPLSSGINGSFL
VRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSSRFNTLAEVLH

-continued

HHSTVADGLITTLHYPAKRNKPTVYGVSPNYDKWEMERTDITMKHKLGG
 GQYGEVYEGVWKYSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQ
 LLGVCTREPPFYIIIEFTMTYGNLLDYLRECNRQEVNAVVLVLYMATQISSA
 MEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAK
 FPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDRSQVYE
 LLEKDYMRKREPGCEKQVYELMRACWQWNPDRPSFAEIHQAFETMFQES
 SISDEVEKELGKQGVRCVTTLLQAPELPTKTRTSRRAAEHRDITDVP
 PHSKGQGESDPLDHEPAVSPLLPKRGEPPEGLNEDERLLPKDKKTNLF
 SALIKKKKTAPTTPKRSSSFREMDGQPERRGAGEEGRDISNGALAFTP
 LDADPAKSPKPSNGAGVPNGALRESGGSGFRSPHLWKKSSTLTSSRLAT
 GEEEGGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTLPRDLQSTGRQFDS
 TFGGHKSEKPAKPRKAGENRSDQVTRGTVTTPPRLVKKNEEADEVFKD
 IMESSPGSSPPNLTTPKPLRRQVTVAPASGLPHKREAWKGSALGTAAAEP
 VTPTSKAGSGAPRGTSKGPAAESRVRHKKHSSSPGRDRGKLSKLPAP
 PPPAASAGKAGGKPSQRPQGEAAGEAVLGAKTKATSLVDVNSDAKPSQ
 PAEGLKKPVLPAKPKHPAKPSGTPISPAPVPLSTLPSASSALAGDQPS
 TAFIPLISTRVSLRKTRQPPERASGAIKGVVLDSTEALCLAISGNSEQM
 ASHAVLEAGKNLYTFCVSVYDSIQQMRNKFAFREAINKLENNLRELQIC
 PASAGSGPAATQDFSKLLSSVKEISDIVQR
 BCR-Abl p210-e14a2 T315I (SEQ ID NO: 6)
 MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRLEQEVN
 QERFRMIYQLTLLAKEKKS YDRQWGFRRAAQAPDGASEPRASASRPQPA
 PADGADPPPAEPEARPDEGSGPGKARPGTARRPGAAASGERDDRGPPAS
 VAALRSNFERIRKGGHQPADAEPFYVNVFHHHERGLVKVNDKEVSDRI
 SSLGSQAMQMERKKSQHAGSSVGDASRPPYRGRSSSESSCGVDGDYEDAE
 LNPRFLKDNLDANGSRPPWPPLYQPYQSIYVGGIMEGEGKGPLLRSQ
 STSEQEKRLTWPRRSYSRPSFEDCGGYTPDCSSNENLTSSEEDFSSGQS
 SRVSPSPPTTYRMFRDKSRSPSQNSQSFSSPPTPQCHKRHRHCPVVVS
 EATIVGRKGTQIWPNDDEGAFHGDADGSGFTPPGYCAADRAEEQRRHQ
 DGLPYIDDSPPSSPHLSSKGRGSRDALVSGALKSTKASELDLEKGLEMRK
 WVLSGILASEETYLSHLEALLPMKPLKAAATTSQPVLTSQQIETIFFKV
 PELYEIHKESYDGLFPRVQWQSHQQRVGDLPQKLASQLGVYRAFVDNYGV
 AMEMAEEKCCQANAQFAEISENLRARSNKDAKDPPTKNSLETLLYKPVDRV
 TRSTLVLDLHKHTPASHPDHPLLDALRISQNFSSINEEITPRRQSM
 VKKGEHRQLLKDSFMVELVEGARKLRHVFLFTDLLCTKLKQSGGKTQQ
 YDCKWYIPLTDLFSQMVELEAVPNIPVLPDEELDALKIKISQIKSDIQR
 EKRANKGSKATERLKKKLSQESLLLLMSPSMAFRVHSRNGKSYTFLISS
 DYERAEWRENIREQQKKCFRFSLSVELQMLTNSCVKLQTVHSIPLTIN
 KEDDESPLYGFLNVIHVSATGFKQSSKALQRPVASFEPQGLSEARWN

-continued

SKENLLAGPSENDPNLFVALYDFVASGDNTLSITKGEKLRVLGYNHNGEW
 CEAQTKNGQGWVPSNYITPVNSLEKHSWYHGPVSRNAEYPLSSGINGSF
 LVRESSESPSQRSISLRYEGRVYHYRINTASDGKLYVSSSESRENTLAELV
 HHHSTVADGLITTLHYPAKRNKPTVYGVSPNYDKWEMERTDITMKHKLGG
 GGQYGEVYEGVWKYSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLV
 QLLGVCTREPPFYIIIEFTMTYGNLLDYLRECNRQEVNAVVLVLYMATQISS
 AMEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGA
 KFPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDRSQVY
 ELLEKDYMRKREPGCEKQVYELMRACWQWNPDRPSFAEIHQAFETMFQE
 SSISDEVEKELGKQGVRCVTTLLQAPELPTKTRTSRRAAEHRDITDVP
 MPHSGKQGESDPLDHEPAVSPLLPKRGEPPEGLNEDERLLPKDKKTNLF
 FSALIKKKKTAPTTPKRSSSFREMDGQPERRGAGEEGRDISNGALAFTP
 PLDTADPAKSPKPSNGAGVPNGALRESGGSGFRSPHLWKKSSTLTSSRLA
 TGEEGGGGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTLPRDLQSTGRQFDS
 STFGGHKSEKPAKPRKAGENRSDQVTRGTVTTPPRLVKKNEEADEVFK
 DIMESSPGSSPPNLTTPKPLRRQVTVAPASGLPHKEAWKGSALGTAAAEP
 PVTPTS KAGSGAPRGTSKGPAAESRVRHKKHSSSPGRDRGKLSKLPAP
 PPPAASAGKAGGKPSQRPQGEAAGEAVLGAKTKATSLVDVNSDAKPS
 QPAEGLKKPVLPAKPKHPAKPSGTPISPAPVPLSTLPSASSALAGDQPS
 STAFIPLISTRVSLRKTRQPPERASGAIKGVVLDSTEALCLAISGNSEQ
 MASHAVLEAGKNLYTFCVSVYDSIQQMRNKFAFREAINKLENNLRELQI
 CPASAGSGPAATQDFSKLLSSVKEISDIVQR
 BCR-Abl p210-e13a2 T315I (SEQ ID NO: 7)
 MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRLEQEVN
 QERFRMIYQLTLLAKEKKS YDRQWGFRRAAQAPDGASEPRASASRPQPA
 PADGADPPPAEPEARPDEGSGPGKARPGTARRPGAAASGERDDRGPPAS
 VAALRSNFERIRKGGHQPADAEPFYVNVFHHHERGLVKVNDKEVSDRI
 SSLGSQAMQMERKKSQHAGSSVGDASRPPYRGRSSSESSCGVDGDYEDAE
 LNPRFLKDNLDANGSRPPWPPLYQPYQSIYVGGIMEGEGKGPLLRSQ
 STSEQEKRLTWPRRSYSRPSFEDCGGYTPDCSSNENLTSSEEDFSSGQS
 SRVSPSPPTTYRMFRDKSRSPSQNSQSFSSPPTPQCHKRHRHCPVVVS
 EATIVGRKGTQIWPNDDEGAFHGDADGSGFTPPGYCAADRAEEQRRHQ
 DGLPYIDDSPPSSPHLSSKGRGSRDALVSGALKSTKASELDLEKGLEMRK
 WVLSGILASEETYLSHLEALLPMKPLKAAATTSQPVLTSQQIETIFFKV
 PELYEIHKESYDGLFPRVQWQSHQQRVGDLPQKLASQLGVYRAFVDNYGV
 AMEMAEEKCCQANAQFAEISENLRARSNKDAKDPPTKNSLETLLYKPVDRV
 TRSTLVLDLHKHTPASHPDHPLLDALRISQNFSSINEEITPRRQSM
 VKKGEHRQLLKDSFMVELVEGARKLRHVFLFTDLLCTKLKQSGGKTQQ
 YDCKWYIPLTDESQMVELEAVPNIPVLPDEELDALKIKISQIKSDIQR

-continued

EKRANKGSKATERLKKKLSSEQESLLLLMSPSMAFRVHSRNGKSYTFLISS
 DYERAEWRENIREQQKKCFRSPSLTSVELQMLTNSCVKLQTVHSIPLTIN
 KEEALQRPVASDFEPQGLSEAAPWNSKENLLAGPSENDPNLFVALYDFVA
 SQDNTLSITKGEKLRVLGYNHNGEWCEAQTNGQGWPVSNYITPVNSLEK
 HSWYHGPVSRNAEYPLSSGINGSFLVRESESSPSQRSISLRYEGRVYHY
 RINTASDGKLYVSSSERFNTLAEVLVHHHSTVADGLITTLHYPAKRNKPT
 VYGVSPNYDKWEMERTDITMKHKLGGQYGEVYEGVWKYSLTVAVKTLK
 EDTMEVEEFLKEAAVMKEIKHPNLVQLLVCTREPPFYIIIEFMTYGNLL
 DYLRECNRQEVNAVVLVLYMATQISSAMEYLEKKNFIHRDLAARNCLVGEN
 HLKVKVADFGLSRLMTGDTYTAHAGAKFPIKWTAFESLAYNKFSIKSDVWA
 FGVLWEIATYGMSPYPGIDRSQVYELLEKDYRMKRPEGCEPKVYELMRA
 CWQWNPDRPSFAEIHQAFETMFQESSISDEVEKELGKQGVRAVTTLLQ
 APELPTKTRTSRRAAEHRDITDVPMPHSGQGESDPLDHEPAVSPLLR
 KERGPPEGGLNEDERLLPKDKKTNLFSAIIKKKKKTAPTTPKRSSSFREM
 DGQFERRGAGEEEGRDISNGALFTPLDTADPAKSFKPSNGAGVPNGALR
 ESGSGGFRSPHLWKSSLTSSRLATGEEEGGSSSKRFLRSCSVSCVPH
 GAKDTEWRSVTLPRDLQSTGRQFDSSTFGGHKSEKALPRKRAGENRSDQ
 VTRGTVTTPPRLVKNEEADEVFKDIMESSPGSSPPLTPKPLRRQVTV
 APASGLPHKEEAWKGSALGTPAAAEPTPTSKAGSGAPRGTSKGAPEESR
 VRRHKHSSSPGRDKGLSKLKPAPPPPPAASAGKAGKPSQRPQGEAAG
 EAVLGAKTKATSLVDVANSDAAKPSQPAEGLKPPVLPATPKHPAKPSGT
 PISPAPVPLSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTQPPERAS
 GAITKGVLDSTEALCLAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSI
 QQMRNKFAPREAINKLENNLRELQICPASAGSGPAATQDFSLLSSVKEI
 SDIVQR
 BCR-Abl p190-e1a2 (SEQ ID NO: 8)
 MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLQEVEN
 QERFRMIYLQTLTLLAKEKSYDRQWGFRRAAQAFDGASEPRASASRPQPA
 PADGADPPPAEEPEARPDGEGSPGKARPGTARRPQAAASGERDDRGPPAS
 VAALRSNFERIRKGHGQPGADAEPFYVNVFHHHERGLVKVNDKEVSDRI
 SSLGSQAMQMERKKSQHAGSSVGDASRPYPYRGRSSSESSCGVDGDYEDAE
 LNPFRFLKNDLIDANGSRPPWFPLEYQPYQSIYVGGIMEGEGKPLLRQ
 STSEQEKLRLTWPRRSYSRPFEDCGGYTPDCSSNENLTSSSEDFSSGQS
 SRVSPSPPTTYRMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVS
 EATIVGRKTGQIWPNDDEGAHFGDAEALQRPVASFEPQGLSEARWNS
 KENLLAGPSENDPNLFVALYDFVAGDNTLSITKGEKLRVLGYNHNGEWCE
 EAQTNGQGWPVSNYITPVNSLEKHSWYHGPVSRNAEYPLSSGINGSFL
 VRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSSERFNTLAEVLH
 HHSTVADGLITTLHYPAKRNRPVYGVSPNYDKWEMERTDITMKHKLGG

-continued

GQYGEVYEGVWKYSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQ
 LLGVCTREPPFYIIIEFMTYGNLLDYLRECNRQEVNAVVLVLYMATQISSA
 MEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAK
 FPIKWTAPESLAYNKFSIKSDVWAFVLLWEIATYGMSPYPGIDRSQVYE
 LLEKDYRMKRPEGCEPKVYELMPACWQWNPDRPSFAEIHQAFETMFQES
 SISDEVEKELGKQGVRAVTTLLQAPLPTKTRTSRRAAEHRDITDVPME
 PHSKGQGESDPLDHEPAVSFLLPRKERGPPEGGLNEDERLLPKDKKTNLF
 SALIKKKKKKTAPTTPKRSSSFREMDGQPERRGAGEEGRDISNGALAFTP
 LDADPAKSPKPSNGAGVPNGALRESGGSGFRSPHLWKSSLTSSRLAT
 GEEEGGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTLPRDLQSTGRQFDS
 TFGGHKSEKALPRKRAGENRSDQVTRGTVTTPPRLVKNEEADEVFKD
 IMESSPGSSPPLTPKPLRRQVTVAPASGLPHKEEAWKGSALGTPAAAE
 VTPTSKAGSGAPRGTSKGAPEESRVRHKKHSSSPGRDKGLSKLKPAP
 PPPAASAGKAGKPSQRPQGEAAGEAVLGAKTKATSLVDVANSDAAKPSQ
 PAEGLKPPVLPATPKHPAKPSGTPISPAPVPLSTLPSASSALAGDQPS
 TAFIPLISTRVSLRKTQPPERASGAITKGVLDSTEALCLAISGNSEQM
 ASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAPREAINKLENNLRELQIC
 PASAGSGPAATQDFSLLSSVKEISDIVQR

C-Kit kinase (SEQ ID NO: 9) assay

[0157] 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 μ l) contained c-Kit (cKIT residues T544-V976, from ProKinase, 5.4 nM), polyE4Y (1 mg/ml), MgCl₂ (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 μ M) 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). IC₅₀ 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)
 LGYWKIKGLVQPTLRLLEYLEEKYEEHLVERDEBGDKWRNKKFELGLEFPN
 LPYYIDGDVVKLTQSMALIRYIADKHNMLGGCPKERAIEISMLEGAVDIRYG
 VSRIAYSKDFETLKVDFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDMFL
 YDALDVVLYMDPMCLDAFPKLVCFKKRIEAIPIQIDKYLKSSKYIWLQGW

-continued

QATFGGGDHPKSDLVPRHNQTSLYKKAGSAAVLEENLYFQGTYYKYLQK
 PMYEVQWKVVEEINGNNYVYIDPTQLPYDHKWEFPRNRLSFGKTLGAGAF
 GKVVEATAYGLIKSDAAMTVAVKMLKPSAHLTEREALMSELKVLSYLGNH
 MNIVNLLGACTTGGPTLVITEYCCYGDLLNFLRRKRDSFICSKQEDHAEA
 ALYKNLLHSKESSCSDSTNEYMDMKPGVSVVPTKADKRRSVRIGSYIER
 DVTPTAIMEDELALDLEDLLSFSYQVAKGMAFLASKNCIHRDLAARNIL
 THGRITKICDFGLARDIKNDSNYVVGKGNARLPVKWMAPEISFNCVYTFES
 DVWSYGIFLWELFSLGSSPYPGMPVDISKFYKMIKEGFRMLSFEHAPAEMY
 DIMKTCWDADPLKRPFTFKQIVQLIEKQISESTNHIYSNLANCSPNRQKPV
 VDHSVRINSVGSTASSSQPLLVDHDDV

[0158] C-Met Kinase (SEQ ID NO:10) Assay

[0159] 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 μ l) contained C-Met (c-Met residues: 956-1390, from Invitrogen, catalogue #PV3143, 6 nM), polyE4Y (1 mg/ml), MgCl₂ (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 μ 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), IC₅₀ 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.

cMet Kinase (SEQ ID NO: 10)
 MSYYHHHHHDYDIPTTENLYFQGAMLVPRGSPWIPFTMKKRKQIKDLGS
 ELVRYDARVHTPHLDRLVSARSVSPTTEMVSNESVDYRATFPEDQFPNSS
 QNGSCRQVQYPLTDMSPILTSGDSIDISSPLLQNTVHIDLSALNPELVQAV
 QHVVGPSLIVHFNEVIGRGHFGCVYHGTLDDNDGKKIHCAVKSLNRIT
 DIGEVSQFLTEGIIMKDFSHPNVLSLLGICLRSECSPLVVLPYMKHGDLR
 NFIRNETHNPTVKDLIGFGLQVAKGMKYLASKKFVHRDLAARNCMLEKDF
 TVKVADFGGLARDMYDKEYYSVHNKTGAKLPVKWMALESLOTQKFTTKSDV
 WSGVLLWELMTRGAPPYPDVNTFDITVYLLQGRRLQPEYCPDPLYEVM
 LKCWHPKAEMRPSFSELVSRIASIFSTFGEHYHVHNATYVNVKCVAPYP
 SLLSSEDNADDEVDTTPASFWETS

[0160] The biochemical IC₅₀ Values of other compounds disclosed herein are at least 10 μ M against Abl enzyme.

Cell Culture

[0161] 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% CO₂, 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

[0162] A serial dilution of test compound was dispensed into a 96 well black clear bottom plate (Coming, Coming, 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% CO₂, 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% CO₂, 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.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 10

<210> SEQ ID NO 1

<211> LENGTH: 278

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> 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 Gly Gln Tyr
 20 25 30

Gly Glu Val Tyr Glu Gly Val Trp Lys Lys Tyr Ser Leu Thr Val Ala

-continued

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

-continued

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
 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

-continued

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	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	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	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

-continued

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
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	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	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

-continued

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	Thr	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				
Pro Glu	Ser	Leu	Ala	Tyr	Asn	Lys	Phe	Ser	Ile	Lys	Ser	Asp	Val	
1310					1315					1320				
Trp Ala	Phe	Gly	Val	Leu	Leu	Trp	Glu	Ile	Ala	Thr	Tyr	Gly	Met	
1325					1330					1335				
Ser Pro	Tyr	Pro	Gly	Ile	Asp	Arg	Ser	Gln	Val	Tyr	Glu	Leu	Leu	
1340					1345					1350				
Glu Lys	Asp	Tyr	Arg	Met	Lys	Arg	Pro	Glu	Gly	Cys	Pro	Glu	Lys	
1355					1360					1365				
Val Tyr	Glu	Leu	Met	Arg	Ala	Cys	Trp	Gln	Trp	Asn	Pro	Ser	Asp	
1370					1375					1380				

-continued

Arg	Pro	Ser	Phe	Ala	Glu	Ile	His	Gln	Ala	Phe	Glu	Thr	Met	Phe
1385						1390					1395			
Gln	Glu	Ser	Ser	Ile	Ser	Asp	Glu	Val	Glu	Lys	Glu	Leu	Gly	Lys
1400						1405					1410			
Gln	Gly	Val	Arg	Gly	Ala	Val	Thr	Thr	Leu	Leu	Gln	Ala	Pro	Glu
1415						1420					1425			
Leu	Pro	Thr	Lys	Thr	Arg	Thr	Ser	Arg	Arg	Ala	Ala	Glu	His	Arg
1430						1435					1440			
Asp	Thr	Thr	Asp	Val	Pro	Glu	Met	Pro	His	Ser	Lys	Gly	Gln	Gly
1445						1450					1455			
Glu	Ser	Asp	Pro	Leu	Asp	His	Glu	Pro	Ala	Val	Ser	Pro	Leu	Leu
1460						1465					1470			
Pro	Arg	Lys	Glu	Arg	Gly	Pro	Pro	Glu	Gly	Gly	Leu	Asn	Glu	Asp
1475						1480					1485			
Glu	Arg	Leu	Leu	Pro	Lys	Asp	Lys	Lys	Thr	Asn	Leu	Phe	Ser	Ala
1490						1495					1500			
Leu	Ile	Lys	Lys	Lys	Lys	Lys	Thr	Ala	Pro	Thr	Pro	Pro	Lys	Arg
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			

-continued

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														

<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				

-continued

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	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	

-continued

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	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
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	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				

-continued

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
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 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

-continued

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	Leu	Ile	Lys	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	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			
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</											

-continued

```

<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          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 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

```

-continued

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	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					480
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					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	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

-continued

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		
Ala Thr Gly Glu 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		

-continued

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 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
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 6
 <211> LENGTH: 2031

-continued

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> 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

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 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

```

-continued

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
	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				

-continued

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	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	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					

-continued

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

-continued

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		
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		

-continued

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 7

<211> LENGTH: 2006

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> 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
					310					315					320
Phe	Glu	Asp	Cys	Gly	Gly	Gly	Tyr	Thr	Pro	Asp	Cys	Ser	Ser	Asn	Gln
			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
					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
					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
		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
					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	G							

-continued

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	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	

-continued

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 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

-continued

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	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	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			
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			

-continued

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 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	15
Asp Ser Glu Pro Pro Arg Met Glu Leu Arg Ser Val Gly Asp Ile Glu	
20	30
Gln Glu Leu Glu Arg Cys Lys Ala Ser Ile Arg Arg Leu Glu Gln Glu	
35	45
Val Asn Gln Glu Arg Phe Arg Met Ile Tyr Leu Gln Thr Leu Leu Ala	
50	60
Lys Glu Lys Lys Ser Tyr Asp Arg Gln Arg Trp Gly Phe Arg Arg Ala	
65	80
Ala Gln Ala Pro Asp Gly Ala Ser Glu Pro Arg Ala Ser Ala Ser Arg	
85	95
Pro Gln Pro Ala Pro Ala Asp Gly Ala Asp Pro Pro Pro Ala Glu Glu	
100	110
Pro Glu Ala Arg Pro Asp Gly Glu Gly Ser Pro Gly Lys Ala Arg Pro	
115	125
Gly Thr Ala Arg Arg Pro Gly Ala Ala Ala Ser Gly Glu Arg Asp Asp	
130	140
Arg Gly Pro Pro Ala Ser Val Ala Ala Leu Arg Ser Asn Phe Glu Arg	
145	160

-continued

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
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	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

-continued

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	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	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

-continued

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			
Ala	Thr	Gly	Glu	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	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			

-continued

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

<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

-continued

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	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	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								
Leu	Ser	Phe	Gly	Lys	Thr	Leu	Gly	Ala	Gly	Ala	Phe	Gly	Lys	Val	Val					
	290					295					300									
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						

-continued

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
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Ser Tyr Tyr His 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

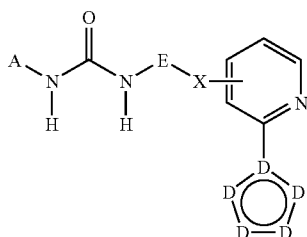
Ser Leu Leu Gly Ile Cys Leu Arg Ser Glu Gly Ser Pro Leu Val Val
225 230 235 240

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

-continued

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					
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					
Arg	Leu	Leu	Gln	Pro	Glu	Tyr	Cys	Pro	Asp	Pro	Leu	Tyr	Glu	Val	Met			
385								390					395					
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										

1. 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, N, O and S, such that the resultant ring is taken from the group consisting of triazolyl, isoxazolyl, isothiazolyl, oxazolyl, and thiadiazolyl;

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, thienyl, 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, benzisothiazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazolopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazolopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolopyrimidinyl, thiazolopyrimidinyl, thiazolonopyrimidinyl, oxazolopyrimidinyl, oxazolopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolonyl,

quinoxaliny, quinazoliny, quinoliny, isoquinoliny, phthalaziny, benzodioxyl, benzisothiazoline-1,1,3-trionyl, dihydroquinoliny, tetrahydroquinoliny, dihydroisoquinoliny, tetrahydroisoquinoliny, benzoazepiny, benzodiazepiny, benzoxapiny, and benzoxazepiny;

G3 is a heterocyclyl taken from the group consisting of oxetanyl, azetadiny, tetrahydrofuranyl, pyrrolidiny, oxazoliny, oxazolidiny, imidazolonyl, pyranly, thiopyranly, tetrahydropyranly, dioxaliny, piperidiny, morpholiny, thiomorpholiny, thiomorpholiny S-oxide, thiomorpholiny S-dioxide, piperaziny, azepiny, oxepiny, diazepiny, 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, $(\text{R}4)_2\text{N}(\text{CH}_2)_n-$, $(\text{R}3)_2\text{N}(\text{CH}_2)_n-$, $(\text{R}4)_2\text{N}(\text{CH}_2)_q\text{O}(\text{CH}_2)_n-$, $(\text{R}4)_2\text{N}(\text{CH}_2)_q\text{O}(\text{CH}_2)_n-$, $(\text{R}3)_2\text{NC}(\text{O})-$, $(\text{R}4)_2\text{NC}(\text{O})-$, $(\text{R}4)_2\text{NC}(\text{O})\text{C1-C6alkyl-}$, $-(\text{R}4)\text{NC}(\text{O})\text{R}8$, C1-C6alkoxycarbonyl-, -carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, $(\text{R}3)_2\text{NSO}_2-$, $-\text{SOR}3$, $(\text{R}4)_2\text{NSO}_2-$, $-\text{N}(\text{R}4)\text{SO}_2\text{R}8$, $-\text{O}(\text{CH}_2)_q\text{OC1-C6alkyl-}$, $-\text{SO}_2\text{R}3$, $-\text{SOR}4$, $-\text{C}(\text{O})\text{R}8$, $-\text{C}(\text{O})\text{R}6$, $-\text{C}(=\text{NOH})\text{R}6$, $-\text{C}(=\text{NOR}3)\text{R}6$, $-(\text{CH}_2)_n\text{N}(\text{R}4)\text{C}(\text{O})\text{R}8$, $-\text{N}(\text{R}3)(\text{CH}_2)_q\text{O-alkyl-}$, $-\text{N}(\text{R}3)(\text{CH}_2)_q\text{N}(\text{R}4)_2$, nitro, $-\text{CH}(\text{OH})\text{CH}(\text{OH})\text{R}4$, $-\text{C}(=\text{NH})\text{N}(\text{R}4)_2$, $-\text{C}(=\text{NOR}3)\text{N}(\text{R}4)_2$, $-\text{NHC}(=\text{NH})\text{R}8$, 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;

each Z2 is independently and individually selected from the group consisting of aryl, C1-C6alkyl, C3-C8cycloalkyl, branched C3-C7alkyl, hydroxyl, hydroxyC1-C6alkyl-, cyano, $(\text{R}3)_2\text{N}-$, $(\text{R}4)_2\text{N}-$, $(\text{R}4)_2\text{NC1-C6alkyl-}$, $(\text{R}4)_2\text{NC2-C6alkylN}(\text{R}4)(\text{CH}_2)_n-$, $(\text{R}4)_2\text{NC2-C6alkylO}(\text{CH}_2)_n-$, $(\text{R}3)_2\text{NC}(\text{O})-$, $(\text{R}4)_2\text{NC}(\text{O})-$, $(\text{R}4)_2\text{NC}(\text{O})\text{C1-C6alkyl-}$, carboxyl, -carboxyC1-C6alkyl, C1-C6alkoxycarbonyl-, C1-C6alkoxycarbonylC1-C6alkyl-, $(\text{R}3)_2\text{NSO}_2-$,

$(\text{R}4)_2\text{NSO}_2-$, $-\text{SO}_2\text{R}8$, $-(\text{CH}_2)_n\text{N}(\text{R}4)\text{C}(\text{O})\text{R}8$, $-\text{C}(\text{O})\text{R}8$, $=\text{O}$, $=\text{NOH}$, and $=\text{N}(\text{OR}6)$;

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-, $-\text{C}(\text{O})\text{R}8$, $\text{R}5\text{C}(\text{O})(\text{CH}_2)_n-$, $(\text{R}4)_2\text{NC}(\text{O})-$, $(\text{R}4)_2\text{NC}(\text{O})\text{C1-C6alkyl-}$, $\text{R}8\text{C}(\text{O})\text{N}(\text{R}4)(\text{CH}_2)_q-$, $(\text{R}3)_2\text{NSO}_2-$, $(\text{R}4)_2\text{NSO}_2-$, $-(\text{CH}_2)_q\text{N}(\text{R}3)_2$, and $-(\text{CH}_2)_q\text{N}(\text{R}4)_2$;

each Z4 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-7alkyl, hydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, $(\text{R}4)_2\text{N}-\text{C}2-\text{C6alkyl-}$, $(\text{R}4)_2\text{N}-\text{C}2-\text{C6alkylN}(\text{R}4)-\text{C}2-\text{C6alkyl-}$, $(\text{R}4)_2\text{N}-\text{C}2-\text{C6alkylO}-\text{C}2-\text{C6alkyl-}$, $(\text{R}4)_2\text{NC}(\text{O})\text{C1-C6alkyl-}$, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, $-\text{C}2-\text{C6alkylN}(\text{R}4)\text{C}(\text{O})\text{R}8$, $\text{R}8-\text{C}(=\text{NR}3)-$, $-\text{SO}_2\text{R}8$, and $-\text{COR}8$;

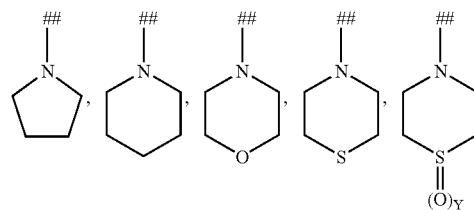
in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

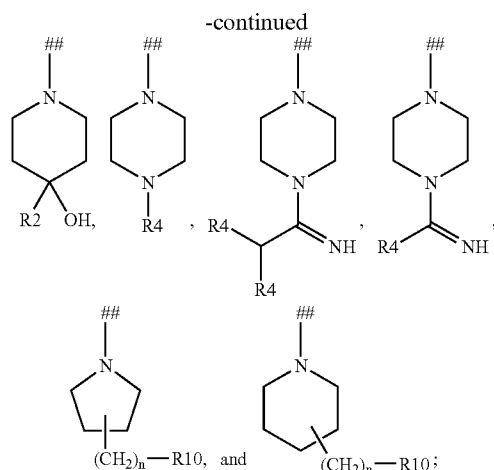
each R2 is selected from the group consisting of H, C1-C6alkyl, branched C3-C8alkyl, R19 substituted C3-C8cycloalkyl-, fluoroC1-C6alkyl- wherein the alkyl is fully or partially fluorinated, halogen, cyano, C1-C6alkoxy-, and fluoroC1-C6alkoxy- wherein the alkyl group is fully or partially fluorinated, hydroxyl substituted C1-C6alkyl-, hydroxyl substituted branched C3-C8alkyl-, cyano substituted C1-C6alkyl-, cyano substituted branched C3-C8alkyl-, $(\text{R}3)_2\text{NC}(\text{O})\text{C1-C6alkyl-}$, and $(\text{R}3)_2\text{NC}(\text{O})\text{C}3-\text{C}8$ 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-, $-(\text{CH}_2)_p\text{N}(\text{R}7)_2$, $-(\text{CH}_2)_p\text{C}(\text{O})\text{N}(\text{R}7)_2$, $-(\text{CH}_2)_n\text{C}(\text{O})\text{OR}3$, and R19 substituted C3-C8cycloalkyl-;

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





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-, —(CH₂)_nC(O)OR3, R19 substituted C3-C8cycloalkyl- and —(CH₂)_nR17;

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)₂, and —N(R4)₂;

each R10 is independently and individually selected from the group consisting of —CO₂H, —CO₂C1-C6alkyl, —C(O)N(R4)₂, OH, C1-C6alkoxy and —N(R4)₂;

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)₂, —N(R4)₂, 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)₂, —N(R4)₂, and nitro;

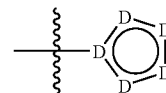
each R19 is independently and individually selected from the group consisting of H, OH and C1-C6alkyl;

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,

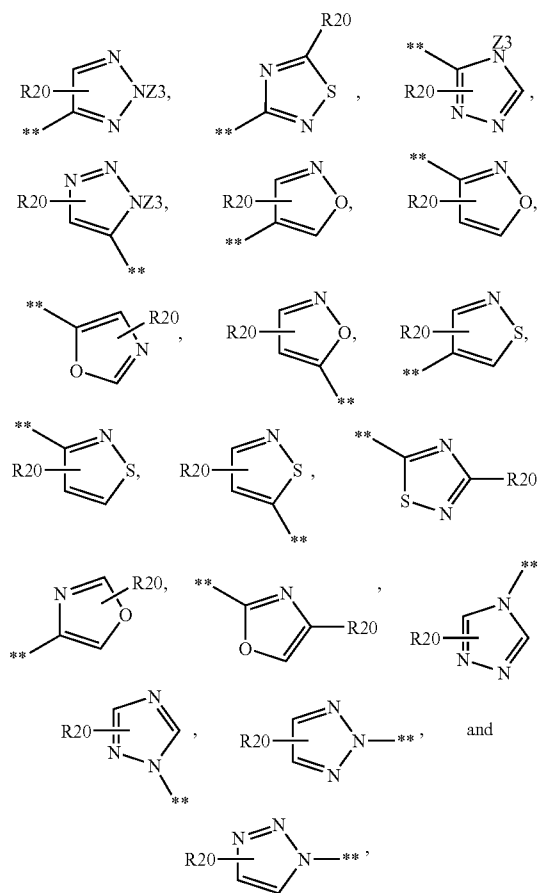
C1-C6alkoxy, fluoroC1-C6alkoxy- wherein the alkyl moiety can be partially or fully fluorinated, —N(R3)₂, —N(R4)₂, —N(R3)C(O)R3, —C(O)N(R3)₂ and nitro and wherein two R4 moieties independently and individually taken from the group consisting of C1-C6alkyl, branched C3-C6alkyl, hydroxyalkyl-, and alkoxyalkyl 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;

and stereo-, regioisomers and tautomers of such compounds.

2. Compounds of claim 1 wherein

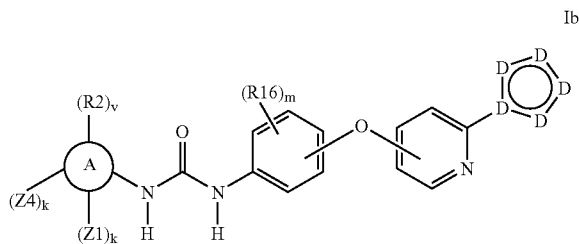


is selected from the group consisting of



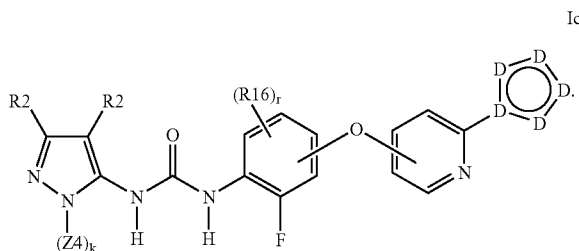
wherein the symbol (**) indicates the point of attachment to the pyridine ring.

3. Compounds of claim 2 having the formula Ib

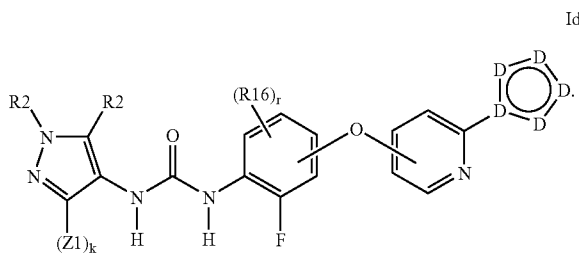


wherein A is any possible isomer of pyrazole.

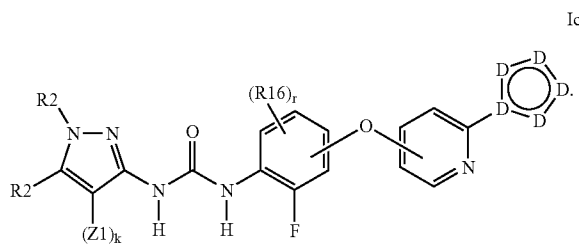
4. Compounds of claim 3 having formula Ic



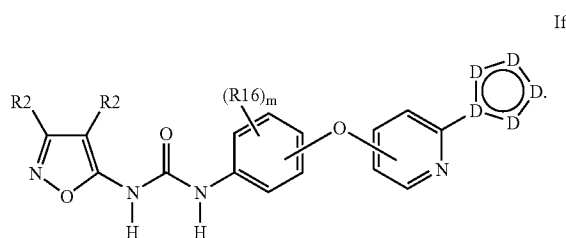
5. Compounds of claim 3 having formula Id



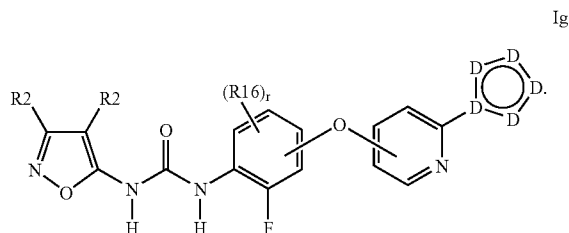
6. Compounds of claim 3 having formula Ie



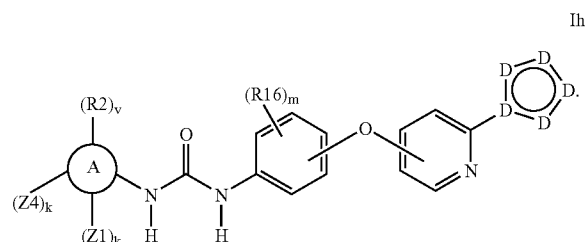
7. Compounds of claim 2 having the formula If



8. Compounds of claim 7 having formula Ig

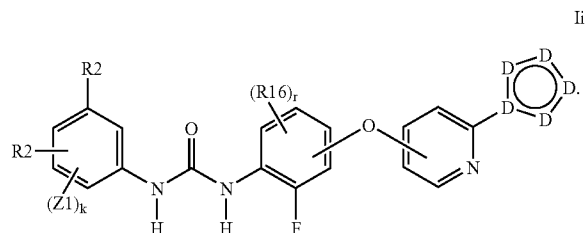


9. Compounds of claim 2 having the formula Ih

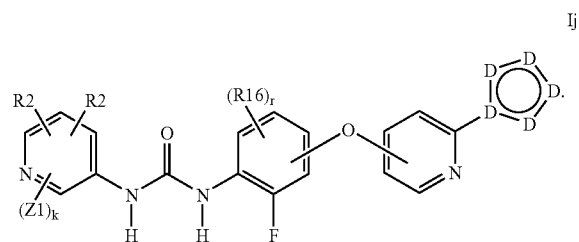


wherein A is selected from the group consisting of any possible isomer of phenyl and pyridine.

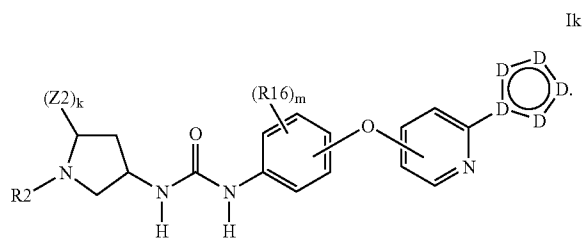
10. Compounds of claim 9 having formula Ii



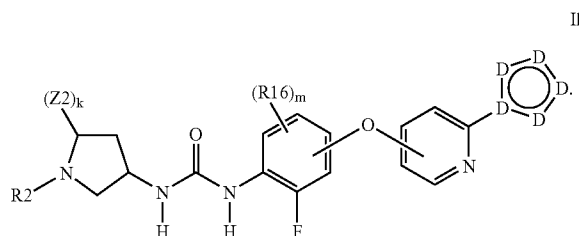
11. Compounds of claim 9 having formula Ij



12. Compounds of claim 2 having the formula Ik



13. Compounds of claim 12 having formula II



14. 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 kinase mutants, c-Met, PDGFR-alpha kinase, PDGFR-beta kinase, HER-1, HER-2, HER-3, HER-4, FGFR, c-Kit, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs of any of the foregoing, comprising the step of administering to the mammal a compound of claim 1.

15. A method of claim 14 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.

16. The method of claim 15, wherein said bcr-Abl fusion protein kinases p210 having SEQ ID NO:3 & SEQ ID NO:4, wherein said bcr-Abl fusion protein kinase p190 has SEQ ID NO:5, wherein said bcr-Abl fusion protein kinases p210 bearing the T315I mutation in the Abl kinase domain has SEQ ID NO:6 & SEQ ID NO:7, and wherein said bcr-Abl fusion protein kinase p190 bearing the T315I mutation in the Abl kinase domain has SEQ ID NO:8.

17. A method of claim 14 wherein said kinase is selected from the group consisting of ckit protein kinase, PDGFR-alpha kinase, and any fusion protein, mutation and polymorphs of any of the foregoing.

18. A method of claim 14 wherein said kinase is selected from the group consisting of c-Met protein kinase, and any fusion protein, mutation and polymorphs of any of the foregoing.

19. A pharmaceutical composition comprising a compound of claim 1, together with a pharmaceutically acceptable carrier, optionally containing an additive selected from the group including adjuvants, excipients, diluents, and stabilizers.

20. A method of treating an individual suffering from a condition selected from the group consisting of cancer, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, or diseases characterized by angiogenesis, such as solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases, chronic myelogenous leukemia, leukemias, papillary thyroid carcinoma, non-small cell lung cancer, mesothelioma, hypereosinophilic syndrome, gastrointestinal stromal tumors, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including retinopathies, diabetic retinopathy, age-related macular degeneration and hypereosinophilic syndrome, rheumatoid arthritis, asthma, chronic obstructive pulmonary, mastocytosis, mast cell leukemia, or disease a disease caused by c-Kit kinase, oncogenic forms thereof, aberrant fusion proteins thereof and polymorphs thereof, comprising the step of administering to such individual a compound of claim 1.

21. The method of claim 20, said compound being administered by a method selected from the group consisting of oral, parenteral, inhalation, and subcutaneous.

* * * * *