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(54) **KINASE INHIBITORS USEFUL FOR THE TREATMENT OF MYLEOPROLIFIC DISEASES AND OTHER PROLIFERATIVE DISEASES**

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(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 MYLEOPROLIFIC 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. Preferrably, 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 causing 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 myleoproliferative 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 pathogensis 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 myristolyl 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 ber-Abl (C. 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 myristolylation 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, ST1571, Novartis Pharma AG Basel, Switzerland) that specifically inhibits tyrosine kinase receptors (Lefevre G. et al. *J Biol Chem* (2004) 279(30):31769). Moreover, a clinically relevant breakthrough has been the finding of anti-tumor effects of this compound in GIST, a group of tumors regarded as being generally resistant to 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 panoply of tumor types for which c-Met mediated growth has been implicated suggests this is a target ideally suited for modulation by specific c-MET small molecule inhibitors.

[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_r 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 activated 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 tie 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 "DGF-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 activation 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, mycloproliferative 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, cycloheptanyl 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, benzisotlilazolyl, benzimidazolyl, benzimidazolonyl, benztriazolyl, imidazopyridinyl, pyrazolopyridinyl, imidazolonopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazolonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolonopyrimidinyl, thiazolopyridiminyl, thiazolonopyrimidinyl, oxazolopyridiminyl, oxazolonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl,

phthalazinyl, benzodioxyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, and benzoxazepinyl;

[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, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholiniyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl;

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

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

[0026] CarboxylC1-C6alkyl refers to -(C1-C6alkyl)-CO_2H 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, aiithranilic, 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, chloroprocaine, 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. Therpeutics* (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] Enatiomers 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. Diastereoisomers are characterized by differences in physical properties, and by some differences in chemical behavior towards achiral as well as chiral reagents

[0035] Tautomerism is defined as isomerism of the general form

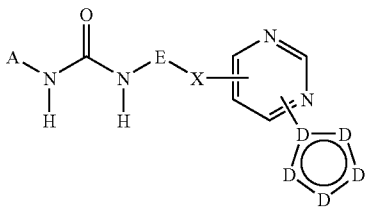
$$G\text{-}X\text{—}Y{=}Z \rightleftharpoons X{=}Y\text{—}Z\text{-}G$$

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".

[0036] Tautomers are defined as isomers that arise from tautomerism, independent of whether the isomers are isolable.

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

[0037]



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[0038] and wherein the pyrimidine ring may be optionally substituted with one or more R20 moieties;

[0039] 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 pyrazolyl, triazolyl, isoxazolyl, isothiazolyl, oxazolyl, imidazoyl, and thiadiazolyl;

[0040] wherein E is selected from the group consisting phenyl, pyridyl, and pyrimidinyl;

[0041] E may be optionally substituted with one or two R16 moieties;

[0042] wherein A is a ring system selected from the group consisting of cyclopentyl, cyclohexyl, G1, G2, and G3;

[0043] 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, and tetrazolyl;

[0044] 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, imidazolonopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazolonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolonopyrimidinyl, thiazolopyridiminyl, thiazolonopyrimidinyl, oxazolopyridiminyl, oxazolonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, and benzoxazepinyl;

[0045] G3 is a heterocyclyl taken from the group consisting of oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, imidazolonyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl;

[0046] the A ring may be optionally substituted with-one or two R2 moieties;

[0047] X is selected from the group consisting of —O—, —S(CH—))—, —N(R3)$(CH_2)_n$—, —$(CH_2)_p$—, and wherein the carbon atoms of —$(CH_2)_n$—, —$(CH_2)_p$—, of X may be flier substituted by oxo or one or more C1-C6alkyl moieties;

[0048] when A, G1, G2 or G6 has one or more substitutable sp2-hybridized carbon atoms, each respective sp2 hybridized carbon atom may be optionally substituted with a Z1 substituent;

[0049] 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;

[0050] each Z1 is independently and individually selected from the group consisting of C1-6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, halogen, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, cyano, C1-C6alkoxy, fluoroC1-C6alkoxy wherein the alkyl moiety can be partially or fully fluorinated, —$(CH_2)_n$OH, oxo, C1-C6alkoxyC1-C6alkyl, $(R4)_2N(CH_2)_n$—, $(R3)_2N(CH_2)_n$—, $(R4)_2N(CH_2)_qN(R4)(CH_2)_n$—, $(R4)_2N(CH_2)_qO(CH_2)_n$—, $(R3)_2NC(O)$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)$C1-C6alkyl-, —(R4)NC(O)R8, C1-C6alkoxycarbonyl-, -carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, $(R3)_2NSO_2$—, —SOR3, $(R4)_2NSO_2$—, —N(R4)SO_2R8, —$O(CH_2)_q$OC1-C6alkyl, —SO_2R3, —SOR4, —C(O)R8, —C(O)R6, —C(═NOH)R6, —C(═NOR3)R6, —$(CH_2)_n$N(R4)C(O)R8, —N(R3)$(CH_2)_q$O-alkyl, —N(R3)$(CH_2)_q$N$(R4)_2$, 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;

[0051] In the event that Z1 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0052] 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)$(CH_2)_n$—, $(R4)_2NC2$-C6alkylO$(CH_2)_n$—, $(R3)_2NC(O)$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)$-C1-C6alkyl-, carboxyl, -carboxyC1-C6alkyl, C1-C6alkoxycarbonyl-, C1-C6alkoxycarbonylC1-C6alkyl-, $(R3)_2NSO_2$—, $(R4)_2NSO_2$—, —SO_2R8, —$(CH_2)_n$N(R4)C(O)R8, —C(O)R8, ═O, ═NOH, and ═N(OR6);

[0053] in the event that Z2 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0054] each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, hydroxyC2-C6alkyl-, C1-C6alkoxycarbonyl-, —C(O)R8, R5C(O)$(CH_2)_n$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)$C1-C6alkyl-, R8C(O)N(R4)$(CH_2)_q$-, $(R3)_2NSO_2$—, $(R4)_2NSO_2$—, —$(CH_2)_q$N$(R3)_2$, and —$(CH_2)_q$N$(R4)_2$;

[0055] each Z4 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-7alkyl, hydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, $(R4)_2$N-C2-C6alkyl-, $(R4)_2$N-C2-C6alkylN(R4)-C2-

C6alkyl-, $(R4)_2N$-C2-C6alkyl-O-C2-C6alkyl-$(R4)_2NC(O)$ C1-C6alkyl-, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, -C2-C6alkylN(R4)C(O) R8, R8-C(=NR3)—, $—SO_2R8$, and —COR8;

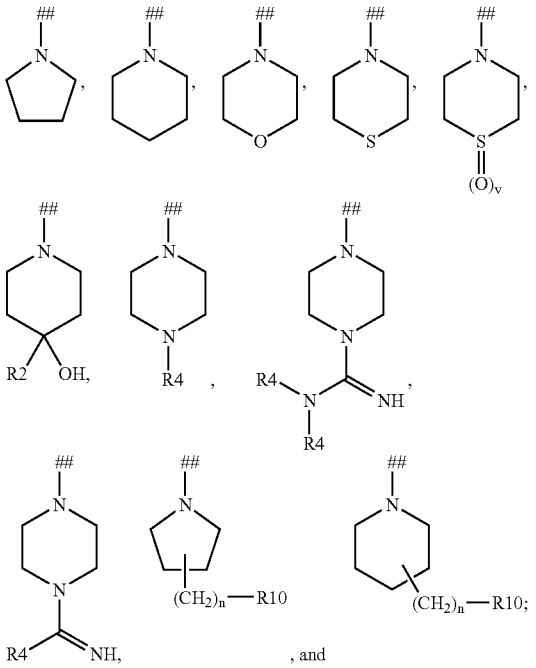
[0056] in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

[0057] each R2 is selected from the group consisting of H, C1-C6alkyl, branched C3-C8alkyl, R19 substituted C3-C8cycloalkyl-, fluoroC1-C6alkyl- wherein the alkyl is fully or partially fluorinated, halogen, cyano, C1-C6alkoxy-, and fluoroC1-C6alkoxy- wherein the alkyl group is fully or partially fluorinated, hydroxyl substituted C1-C6alkyl-, hydroxyl substituted branched C3-C8alkyl-, cyano substituted C1-C6alkyl-, cyano substituted branched C3-C8alkyl-, $(R3)_2NC(O)$C1-C6alkyl-, and $(R3)_2NC(O)$C3-C8 branched alkyl-;

[0058] wherein each R3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, and C3-C8cycloalkyl;

[0059] 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-, $—(CH_2)_pN(R7)_2$, $—(CH_2)_pC(O)N(R7)_2$, $—(CH_2)_nC(O)OR3$, and R19 substituted C3-C8cycloalkyl-;

[0060] each R5 is independently and individually selected from the group consisting of



[0061] and wherein the symbol (##) is the point of attachment to Z3;

[0062] each R6 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, and R19 substituted C3-C8cycloalkyl-;

[0063] 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-, $—(CH_2)_nC(O)OR3$, R19 substituted C3-C8cycloalkyl- and $—(CH_2)_nR17$;

[0064] 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 $—N(R4)_2$;

[0065] each R10 is independently and individually selected from the group consisting of $—CO_2H$, $—CO_2$C1-C6alkyl, $—C(O)N(R4)_2$, OH, C1-C6alkoxy, and $—N(R4)_2$;

[0066] 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;

[0067] 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;

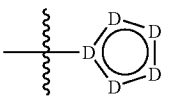
[0068] each R19 is independently and individually selected from the group consisting of H, OH and C1-C6alkyl;

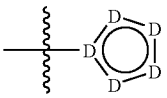
[0069] each R20 is independently and individually selected from the group consisting of C1-C6alkyl, branched C3-C7alkyl, R19 substituted C3-C8cycloalkyl-, halogen, fluoroC1-C6alkyl- wherein the alkyl moiety can be partially or filly fluorinated, cyano, hydroxyl, C1-C6alkoxy, fluoroC1-C6alkoxy- wherein 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 heterocyclyl ring;

[0070] 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; x is 0-2;

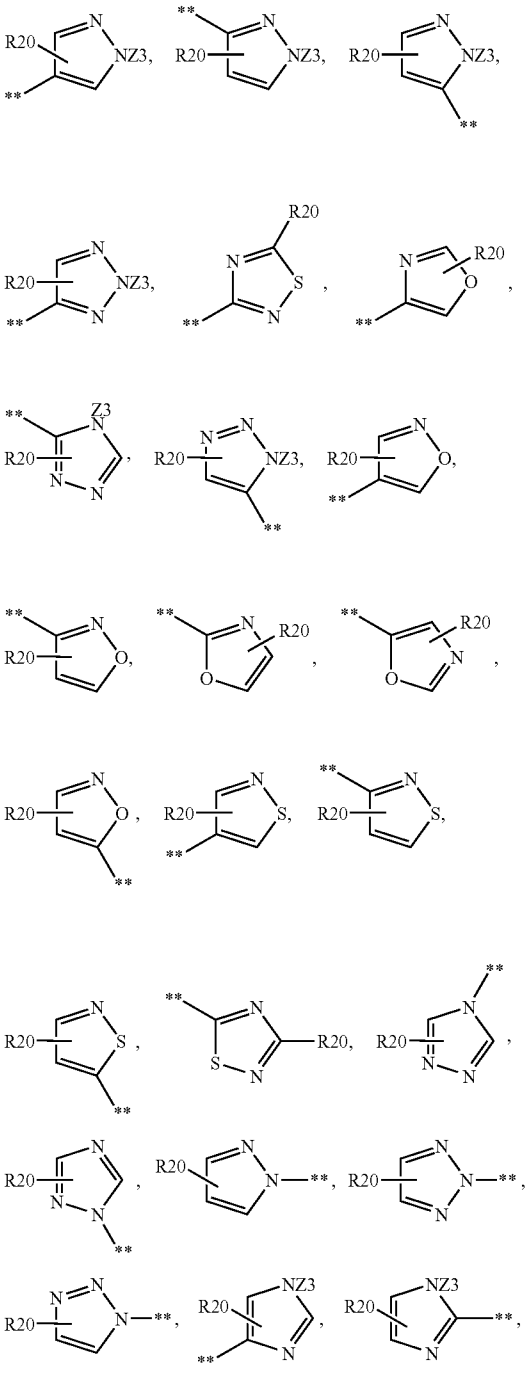
[0071] and stereo-, regioisomers and tautomers of such compounds.

1.1 Compounds of Formula Ia which Exemplify Preferred D Moieties





moieties of the formula:



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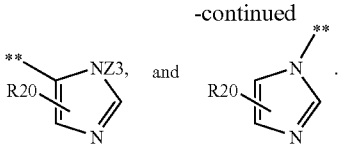
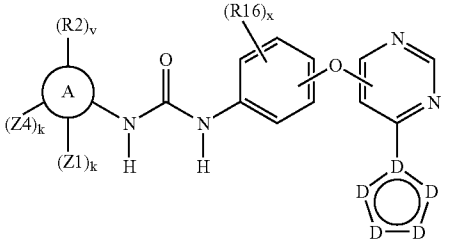


wherein the symbol (**) indicates the point of attachment to the pyrimidine ring.

1.1.1 Compounds of Formula Ia which Exemplify Preferred A Moieties

[0073] In a preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ib

Ib

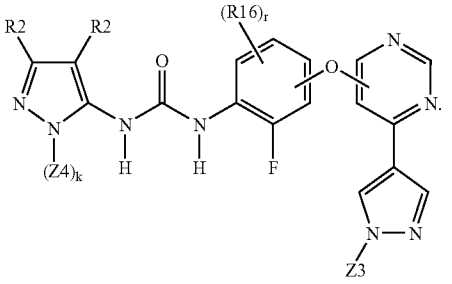


wherein A is any possible isomer of pyrazole.

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

[0074] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Ic

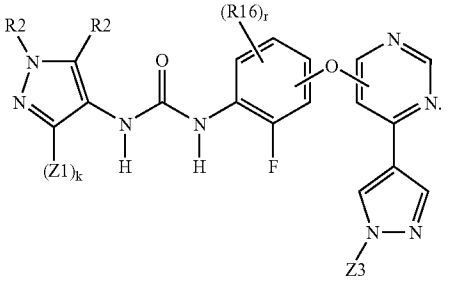
Ic



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

[0075] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Id

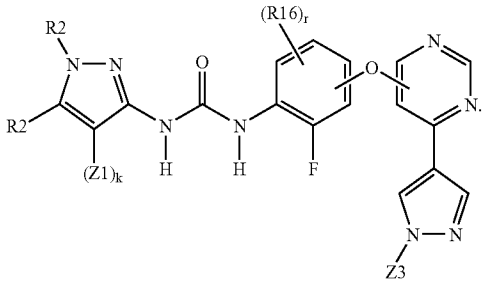
Id



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

[0076] In a more preferred embodiment of compounds of formula Ib, said compounds have structures of formula Ie

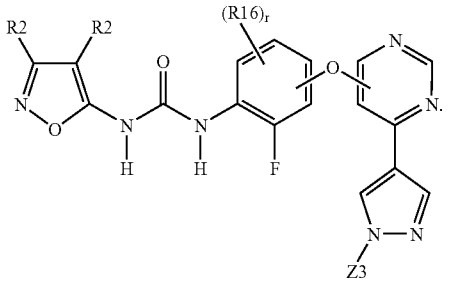
Ie



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

[0077] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula If

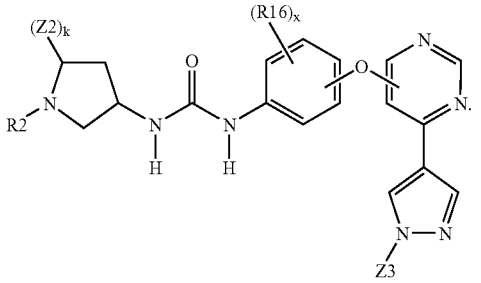
If



Compounds of Formula Ia which Exemplify Preferred A and D Moieties

[0078] In a more preferred embodiment of compounds of formula Ia, said compounds have structures of formula Ig

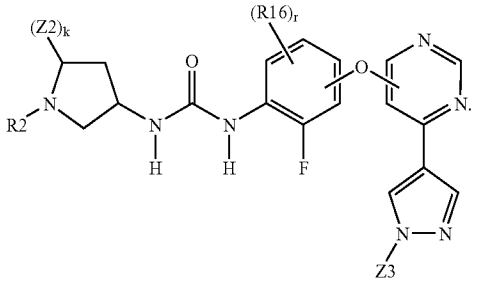
Ig



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

[0079] In a more preferred embodiment of compounds of formula Ig, said compounds have structures of formula Ih

Ih



1.1.8 Most Preferred Compounds of Formula Ia

[0080] 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy) phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl) urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl) pyrimidin-2-yloxy)phenyl)urea, and 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea.

1.2 Methods

1.2a Methods of Protein Modulation

[0081] 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 phosphorylations, sulfation, fatty acid acylations glycosylations, nitrosylation, cystinylation (i.e. proximal cysteine residues in the kinase react with each other to form a disulfide bond) or oxidation. The kinase activity may be selected from the group consisting of catalysis of phospho transfer reactions, inhibition of phosphorylation, oxidation or nitrosylation of said kinase by another enzyme, enhancement of dephosphorylation, reduction or denitrosylation of said kinase by another enzyme, kinase cellular localization, and recruitment of other proteins into signaling complexes through modulation of kinase conformation.

1.2b Treatment Methods

[0082] 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, mycloproliferative 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.

1.3 Pharmaceutical Preparations

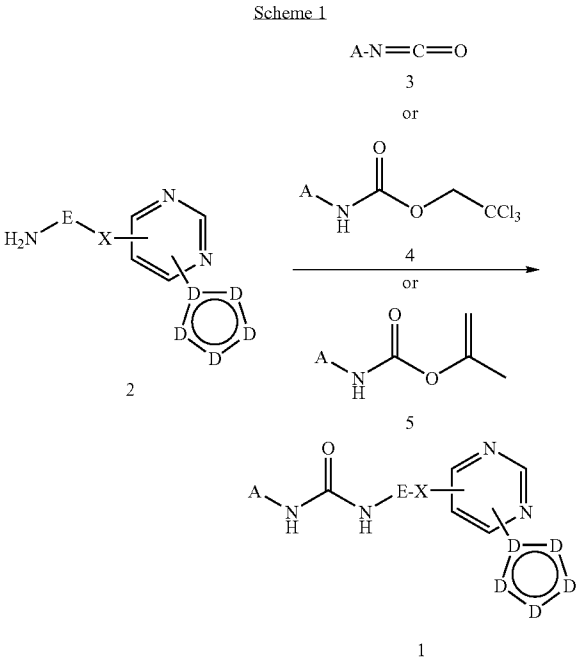
[0083] The compounds of the invention, especially those of section 1 may form a part of a pharmaceutical composition by combining one or more such compounds with a pharamaceutically acceptable carrier. Additionally, the compositions may include an additive selected from the group consisting of adjuvants, excipients, diluents, and stablilizers.

Section 2. Synthesis of Compounds of the Present Invention

[0084] The compounds of the invention are available by the general synthetic methods illustrated in the Schemes below and the accompanying examples.

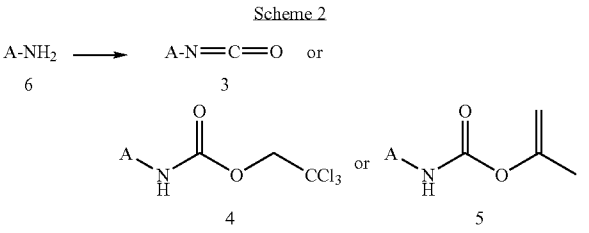
[0085] As indicated in Scheme 1, ureas of general formula 1 can be readily prepared by the union of amines of general formula 2 with isocyanates 3 or isocyanate surrogates 4 (trichloroethyl carbamates) or 5 (isopropenyl carbamates). Preferred conditions for the preparation of compounds of general formula 1 involve heating a solution of 4 or 5 with 2 in the presence of a tertiary base such as diisopropylethylamine, triethylamine or N-methylpyrrolidine in a solvent such as dimethylformamide, dimethylsulfoxide, tetrahydrofuran or 1,4-dioxane at a temperature between 50 and 100° C. for a period of time ranging from 1 hour to 2 days.

Scheme 1



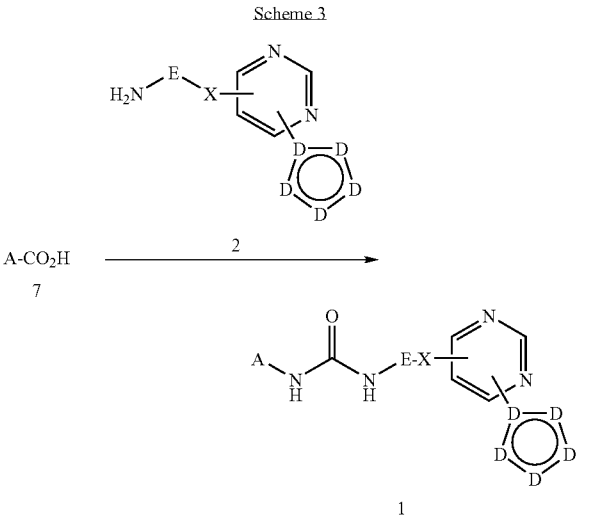
[0086] As shown in Scheme 2, isocyanates 3 can be prepared from amines A-NH_2 6 with phosgene, or a phosgene equivalent such as diphosgene, triphosgene, or N,N-dicarbonylimidazole. Trichloroethyl carbamates 4 and isopropenyl carbamates 5 are readily prepared from amines A-NH_2 (6) by reaction with trichloroethyl chloroformate or isopropenyl chloroformate by standard conditions familiar to those skilled in the art. Preferred conditions for the preparation of 4 and 5 include include treatment of compound 6 with the appropriate chloroformate in the presence of pyridine in an aprotic solvent such as dichloromethane or in the presence of aqueous hydroxide or carbonate in a biphasic aqueous/ethyl acetate solvent system.

Scheme 2



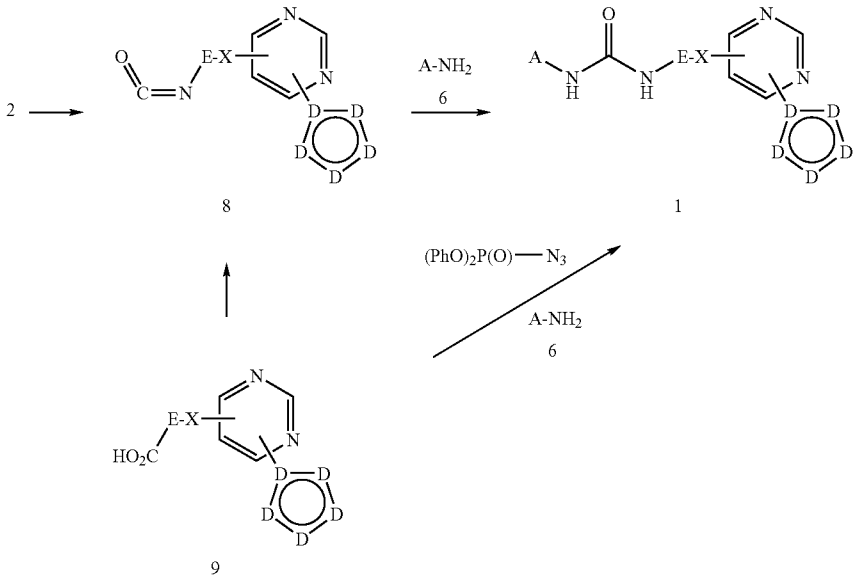
[0087] Additionally, compounds of formula 1 can also be prepared from carboxylic acids 7 by the intermediacy of in-situ generated acyl azides (Curtius rearrangement) as indicated in Scheme 3. Preferred conditions for Scheme 3 include the mixing of acid 7 with amine 2 and diphenylphosphoryl azide in a solvent such as 1,4-dioxane or dimethylformamide in the presence of base, such as triethylamine, and raising the temperature of the reaction to about 80-120° C. to affect the Curtius rearrangement.

Scheme 3



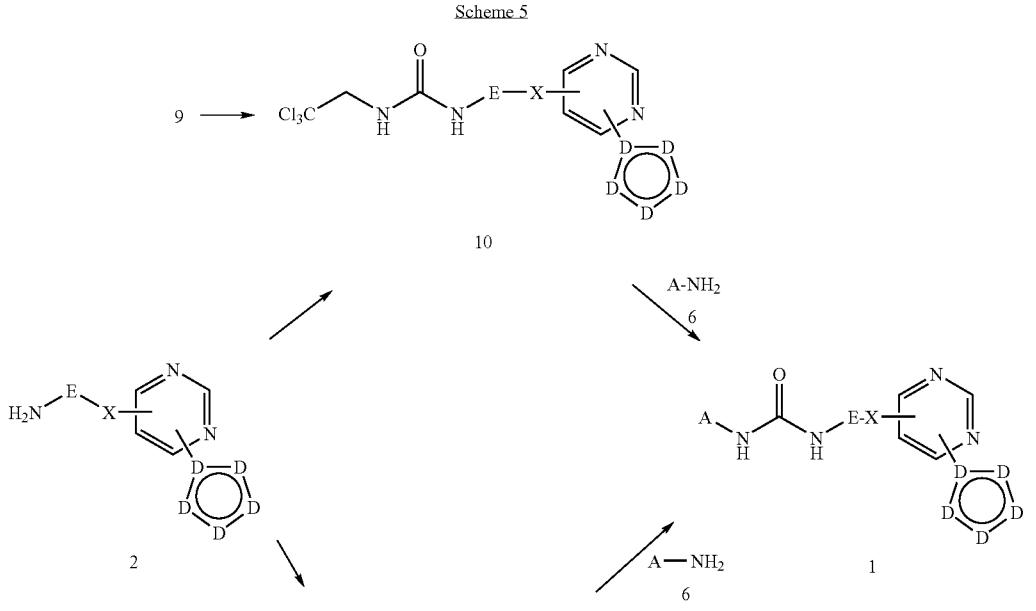
[0088] By analogy to Schemes 1 and 3 above, it will be recognized by those skilled in the art that the compounds of formula 1 can also be prepared by the union of amines A-NH_2 6 with isocyanates 8 (Scheme 4). Isocyanates 8 can be prepared from general amines 2 by standard synthetic methods. Suitable 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 isocycanates 8 need not be isolated, but may be simply generated in situ. Accordingly, acid 9 can be converted to compounds of formula I either with or without isolation of 8. Preferred conditions for the direct conversion of acid 9 to compounds of formula 1 involve the mixing of acid 9, amine A-NH_2 6, diphenylphosphoryl azide and a suitable base, for example triethylamine, in an aprotic solvent, for example dioxane. Heating said mixture to a temperature of between 80 and 120° C. provides the compounds of formula 1.

Scheme 4



[0089] Additionally, compounds of formula 1 can also be prepared from amines 2 by first preparing stable isocyanate equivalents, such as carbamates (Scheme 5). Especially preferred carbamates include trichloroethyl carbamates (10) and isopropenyl carbamates (11) which are readily prepared from amine 2 by reaction with trichloroethyl chloroformate or isopropenyl chloroformate respectively using standard conditions familiar to those skilled in the art. Further reaction of carbamates 10 or 11 with amine A-NH_2 6 provides compounds of formula 1. Those skilled in the art will farther 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



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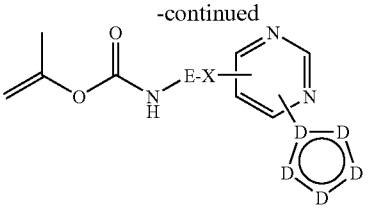

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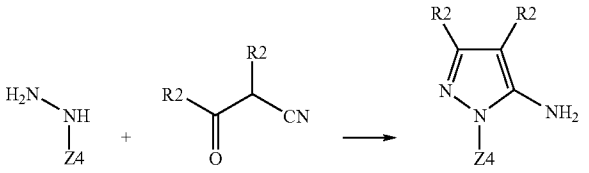
[0090] Many methods exist for the preparation of amines A-NH_2 6 and acids A-CO_2H 7, depending on the nature of the A-moiety. Indeed, many such amines (6) and acids (7) useful for the preparation of compounds of formula 1 are available from commercial vendors. Some non-limiting preferred synthetic methods for the preparation of amines 6 and acids 7 are outlined in the following schemes and accompanying examples.

[0091] 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 nitrites 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.

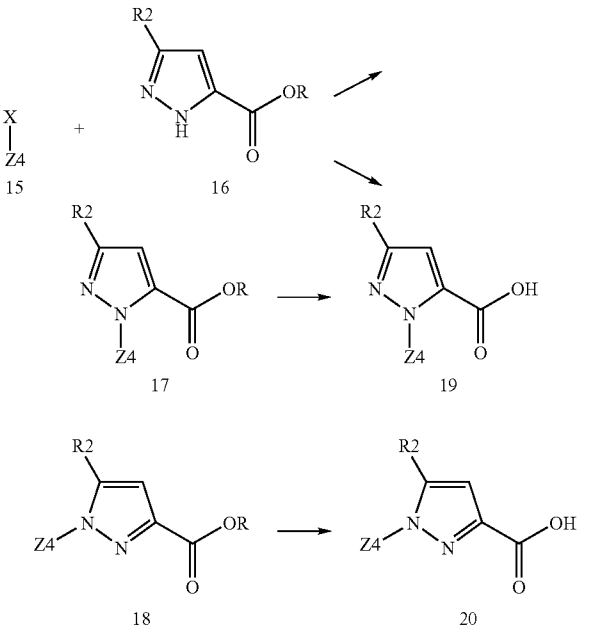
Scheme 6



12 13 14

[0092] 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 15D 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 solovents such as dimethylsulfoxide, dimethylformamide or tetrahydrofuran. Z4-substituted pyrazoles 17 and 18 are isomers of one another and can both be prepared in the same reactions vessel and separated by purification methods familiar to those skilled in the art. The esters 17 and 18 in turn can be converted to acids 19 and 20 using conditions familiar to those skilled in the art, for example saponification in the case of ethyl esters, hydrogenation in the case of benzyl esters or acidic hydrolysis in the case of tert-butyl esters.

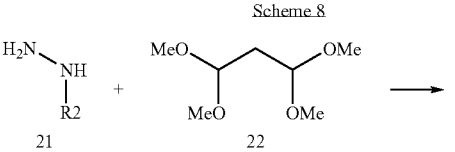
Scheme 7



15 16 17 18 19 20

[0093] Scheme 8 illustrates the preparation of pyrazole amine 25, a further example of general amine A-NH_2 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 farther recognize that R2-substituted pyrazole 23 can also be prepared by direct alkylation of pyrazole. Pyrazole 23 can be regioselectively nitrated to provide nitro-pyrazole 24 by standard conditions familiar to those skilled in the art. Finally, hydrogenation of nitro-pyrazole 24 employing a hydrogenation catalyst such as palladium or nickel provides pyrazole amine 25, an example of general amine A-NH_2 6.

Scheme 8



21 22

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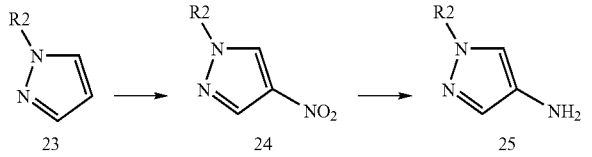
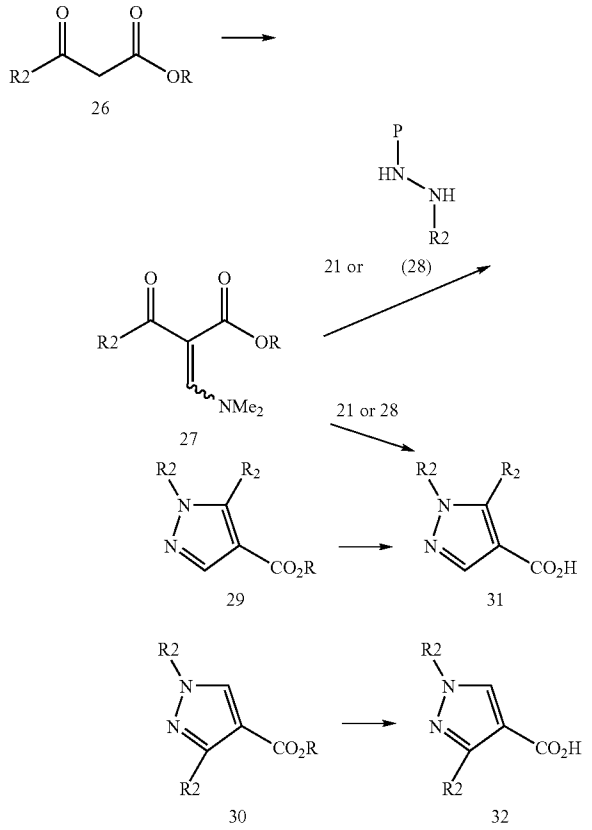


23 24 25

[0094] 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.

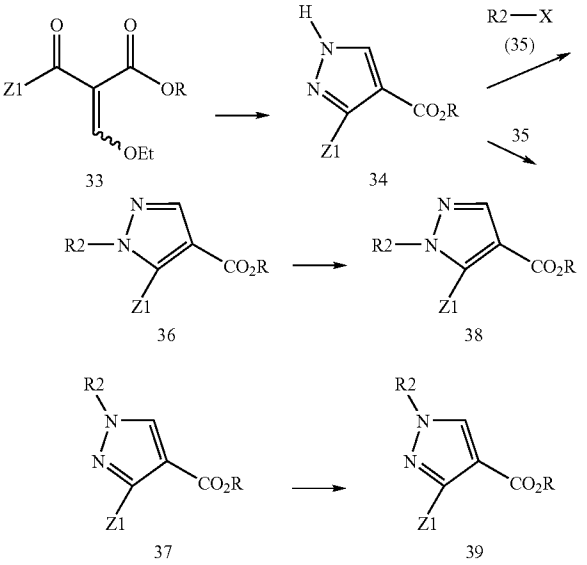
Scheme 9



26 27 29 30 31 32

[0095] 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.

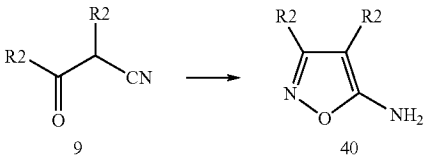
Scheme 10



33 34 35 36 37 38 39

[0096] 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 the 5-aminoisoxazole 40. Preferred conditions for the formation of 5-aminoisoxazole 40 include the treatment of 9 with hydroxylamine in the presence of aqueous sodium hydroxide, optionally in the presence of an alcoholic co-solvent at a temperature between 0 and 100° C.

Scheme 11



9 40

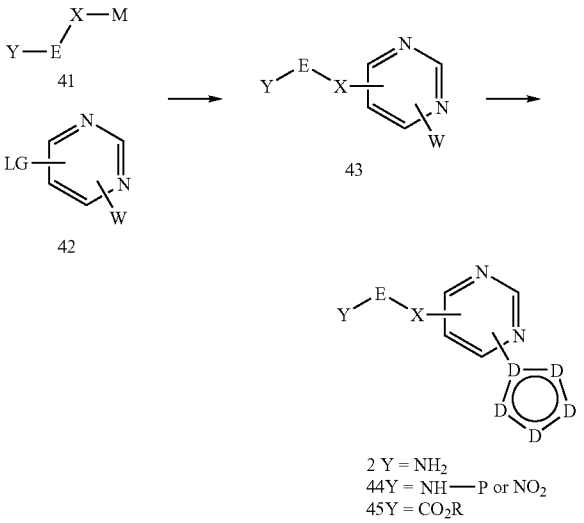
[0097] Amines 2 useful for the invention can be synthesized according to methods commonly known to those skilled in the art. Amines of general formula 2 contain three rings and can be prepared by the stepwise union of three monocyclic subunits as illustrated in the following non-limiting Schemes. Scheme 12 illustrates one mode of assembly in which an E-containing subunit 41 is combined with the central pyridine ring 42 to provide the bicyclic intermediate 43. In one aspect this general Scheme, the "M" moiety of 41, represents a hydrogen atom of a heteroatom on the X linker that participates in a nucleophilic aromatic substitution reaction with monocycle 42. Such reactions may be facilitated by the presence of bases (for example, potassium tert-butoxide), thus M may also represent a suitable counterion (for example potassium, sodium, lithium, or cesium) within an alkoxide, sulfide or amide moiety. Alternately, the "M" group can represent a metallic species (for example, copper, boron, tin, zirconium, aluminum, magnesium, lithium, silicon, etc.) on a carbon

atom of the X moiety that can undergo a transition-metal-mediated coupling with monocycle 42.

[0098] The "Y" group of monocyclic species 41 is an amine or an amine surrogate, such as an amine masked by a protecting group ("P" in formula 44), 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 41 is not an amine, the products of Scheme 12 will be amine surrogates such as 44 or 45 that can be converted to amine 2 by a deprotection, reduction or rearrangement (for example, Curtius rearrangement) familiar to those skilled in the art.

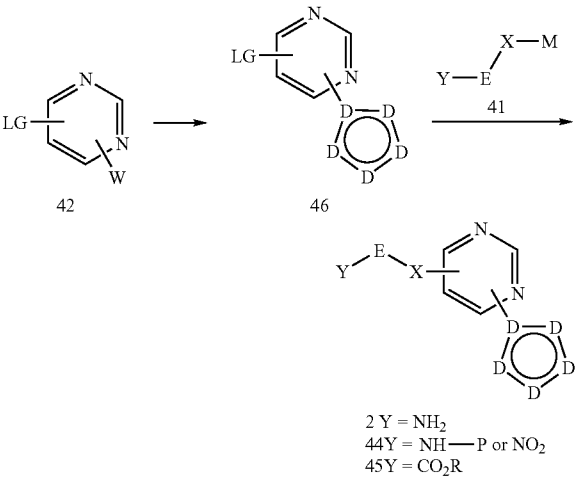
[0099] In these instances, the "LG" of monocycle 42 represents a moiety that can either be directly displaced in a nucleophilic substitution reaction (with or without additional activation) or can participate in a transition-mediated union with fragment 41. The W group of monocycle 42 or bicycle 43 represents 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 42 and 43 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 five-membered heterocycle 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 12 may represent either a single reaction or a reaction sequence. Additionally, the "W" group of 43 may represent a leaving group (halogen or triflate) that can be displaced by a nucleophilic nitrogen atom of a pyrazole, triazole or imidazole ring.

Scheme 12



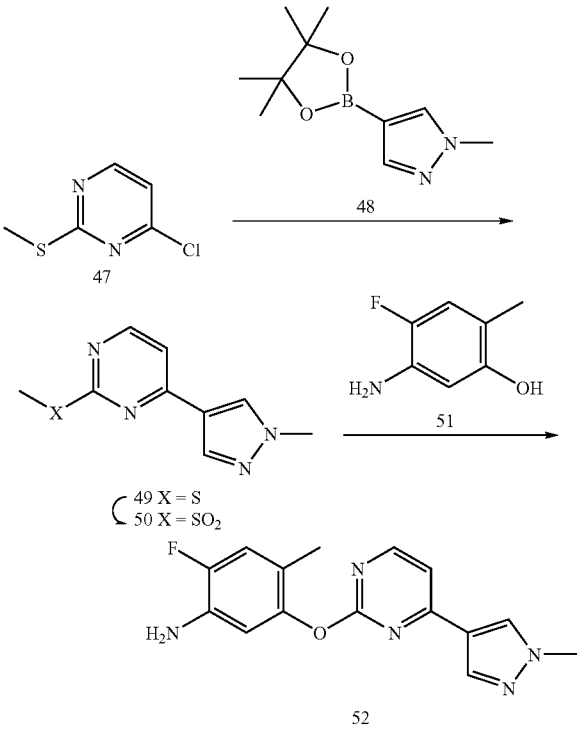
[0100] Scheme 13 illustrates another general method of preparing amines 2 by first attaching the 5-membered heterocycle to the pyrimidine ring (42). As before, the "LG" of monocycle 42 represents a moiety that can either be directly displaced in a nucleophilic substitution reaction (with or without additional activation) or can participate in a transition-mediated union with fragment 41. The "W" group of monocycle 42 represents a moiety that allows the attachment of a 5-membered heterocycle. 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 42 represents a functional group that can be converted to a five-membered heterocycle by an annulation reaction. Additionally, the "W" group of 42 may represent a leaving group (halogen or triflate) that can be displaced by a nucleophilic nitrogen atom of a pyrazole, triazole or imidazole ring. After conversion of 49 to 46, the "LG" moiety can be replaced with an "X" linkage to the E-sub-unit to provide the tricylic amine 2, as described above in Scheme 12. Those skilled in the art will recognize that amines 2 may be accessed directly from the union of 46 and 41 or may arise indirectly via the intermediacy of 44 or 45, as described previously.

Scheme 13



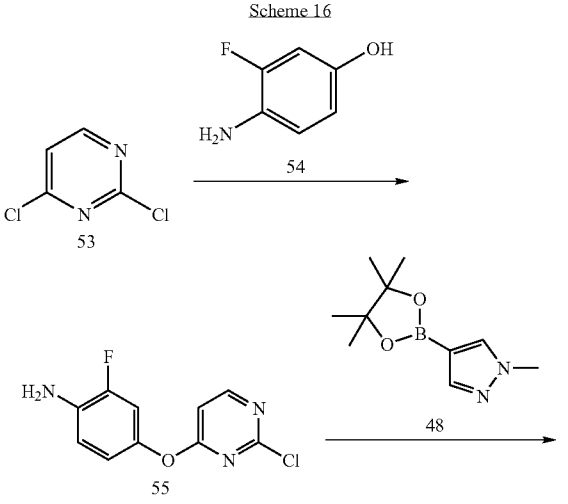
[0101] A specific example of Scheme 13 is illustrated by the preparation of amine 55 in Scheme 14. Thus, commercially available pyrimidine 47, an example of general intermediate 42, undergoes a palladium-catalyzed coupling with the commercially available pyrazole boronate 48 to provide the bicycle 49, an example of general intermediate 46. Oxidation of the sulfide moiety of 49 (The "LG" group of general intermediate 46) with m-chloroperbenzoic acid firer activates this moiety toward nucleophilic displacement and gives rise to intermediate 50. Treatment of sulfone 50 with phenol 51 in the presence of a base provides tricylic amine 52, an example of general amine 2. Preferred bases for the later transformation include potassium carbonate and potassium tert-butoxide in polar aprotic solvents such as dimethylformamide or dimethylacetamide.

Scheme 15



[0102] Similarly, Scheme 16 illustrates the preparation amine 56 as a non-limiting example of general Scheme 12. Thus, 2,4-dichloropyrimidine (53) can be reacted with phenol 54 in the presence of a base to provide 55. an example of general intermediate 43 (Scheme 12). Further reaction of chloropyrimidine 55 with pyrazole boronate 48 in the presence of palladium catalyst provides amine 56, an example of general amine 2.

Scheme 16



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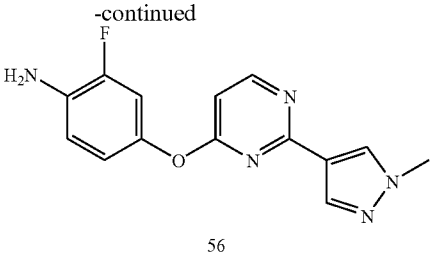
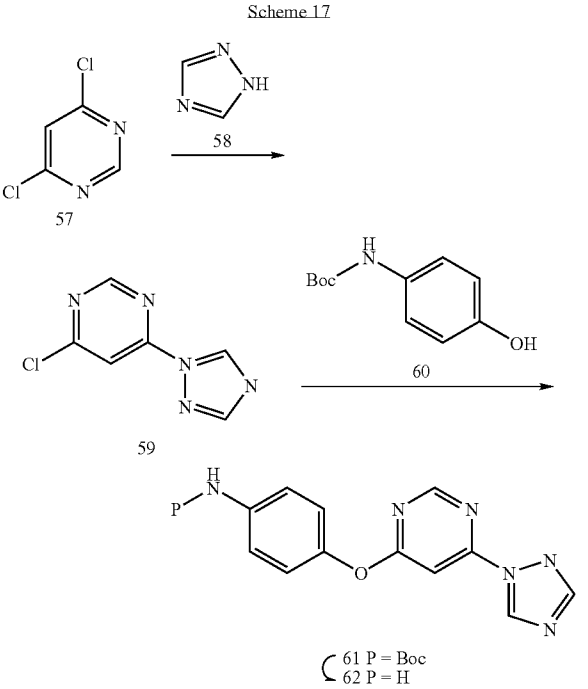


[0103] As an additional example of general Scheme 13, Scheme 17 illustrates the preparation of amine 62, an additional example of general amine 2. In this instance, 4,6-dichloropyrimidine (57), an example of general pyrimidine 42 (Scheme 13) wherein "W" is chloro, is reacted with 1,2, 4-triazole 58 to provide 59, an example of general intermediate 46 (Scheme 13) wherein "LG" is chloro. Further reaction of 59 with phenol 60 provides the Boc-protected amine 61, corresponding to general intermediate 44 (Scheme 13 wherein "P" is tert-butoxycarbonyl [Boc]). Treatment of 61 with an acid, for example trifluoracetic acid, provides amine 61, an example of general amine 2.

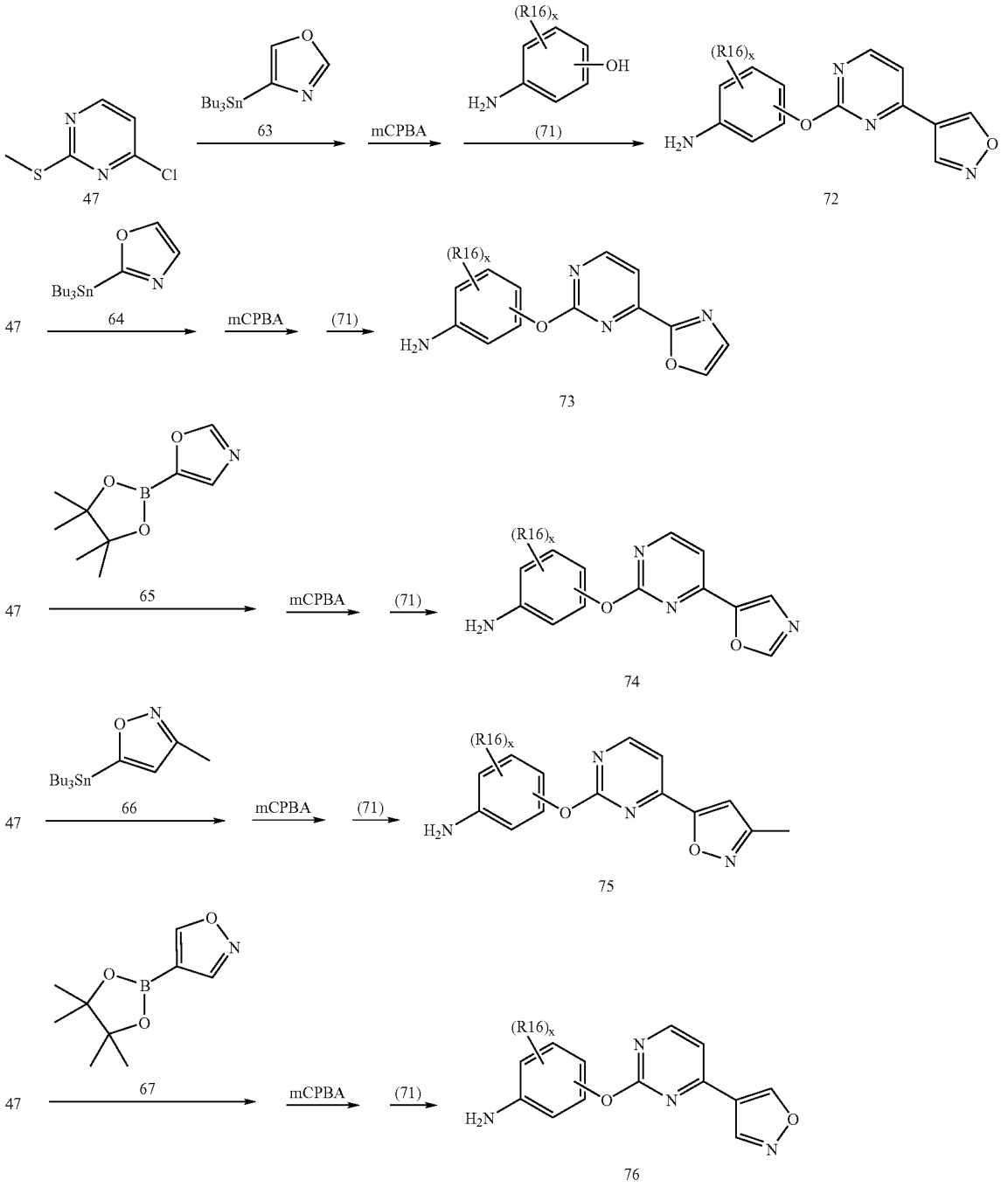
Scheme 17



[0104] As indicated in Scheme 18, additional non-limiting examples of general amine 2 can also be prepared from chloropyrimidine 47 by the three step sequence of Scheme 15 (Step 1: palladium-catalyzed cross-coupling reaction; Step 2: Sulfide oxidation to sulfone; Step 3: Displacement of sulfone with phenol 71, wherein R16 is an optional substituent as described above and x is 0-2). Suzuki cross-coupling reactions using readily available boronates or Stille cross-coupling reactions using readily available stannanes are interchangeable for Step 1. Thus, in a 3-step sequence as indicated

in Scheme 18, chloropyrimidine 47, can be combined with tributylstannane 63 (see: Cheng et al., *Biorg. Med. Chem Lett.,* 2006, 2076), stannane 64 (Aldrich Chemical), boronate 65 (BoroPharm), tributylstannane 66 (see: Sakamoto, et al. *Tetrahedron,* 1991, 5111), boronate 67 (Frontier Scientific), boronate 68 (see: Blackaby, et al., U.S. Pat. No. 7,030,128), trimethylstannane 69 (see: Wentland, et al. *J. Med. Chem.,* 1993, 1580) or stannane 70 (see: Nicolaou, et. al., *Chem. Med. Chem.,* 2006, 41) to provide general amines 72-79 respectively.

Scheme 18



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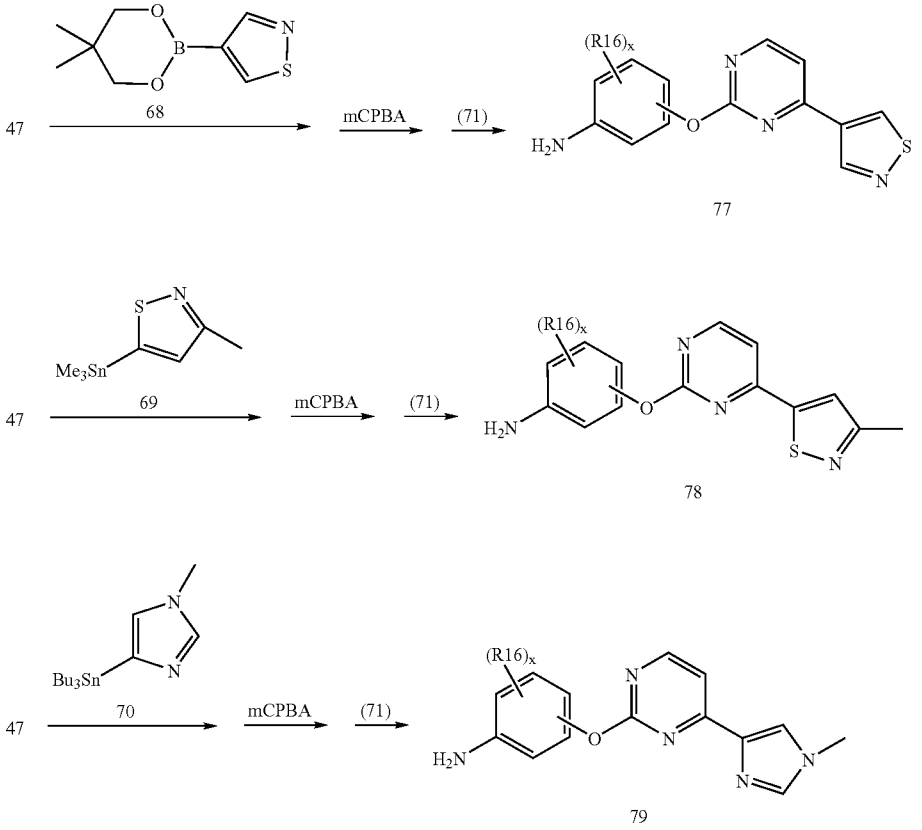
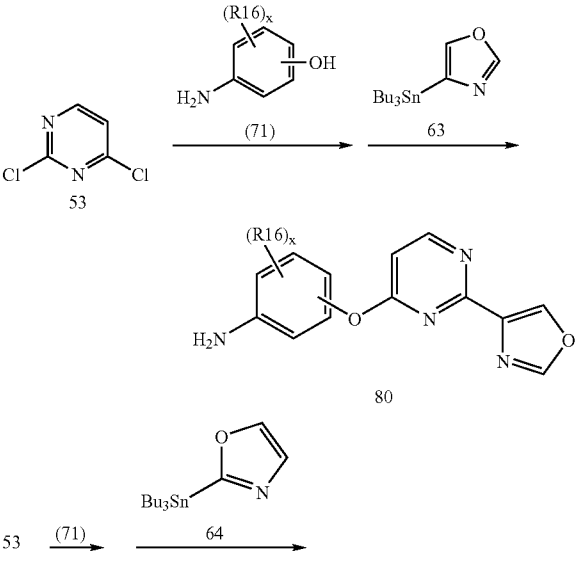
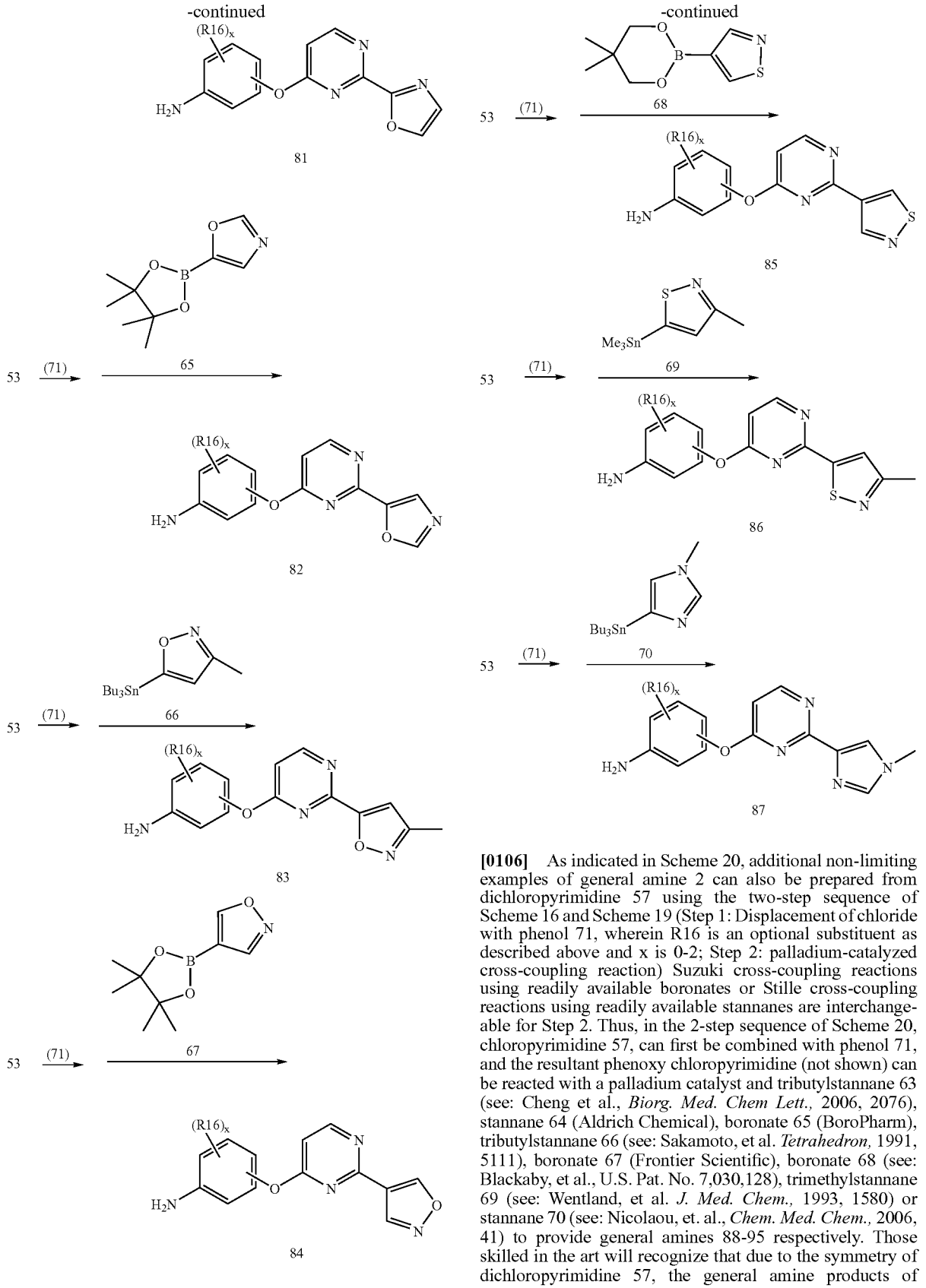


[0105] As indicated in Scheme 19, additional non-limiting examples of general amine 2 can also be prepared from dichloropyrimidine 53 by the two-step sequence of Scheme 16 (Step 1: Displacement of chloride with phenol 71, wherein R16 is an optional substituent as described above and x is 0-2; Step 2: palladium-catalyzed cross-coupling reaction). Suzuki cross-coupling reactions using readily available boronates or Stille cross-coupling reactions using readily available stannanes are interchangeable for Step 2. Thus, in the 2-step sequence of Scheme 19, chloropyrimidine 53, can first be combined with phenol 71, and the resultant phenoxy chloropyrimidine (not shown) can be reacted with a palladium catalyst and tributylstannane 63 (see: Cheng et al., *Biorg. Med Chem Lett.,* 2006, 2076), stannane 64 (Aldrich Chemical), boronate 65 (BoroPharm), tributylstannane 66 (see: Sakamoto, et al. *Tetrahedron,* 1991, 5111), boronate 67 (Frontier Scientific), boronate 68 (see: Blackaby, et al., U.S. Pat. No. 7,030,128), trimethylstannane 69 (see: Wentland, et al. *J. Med. Chem.,* 1993, 1580) or stannane 70 (see: Nicolaou, et. al., *Chem. Med. Chem.,* 2006, 41) to provide general amines 80-87 respectively.

Scheme 19

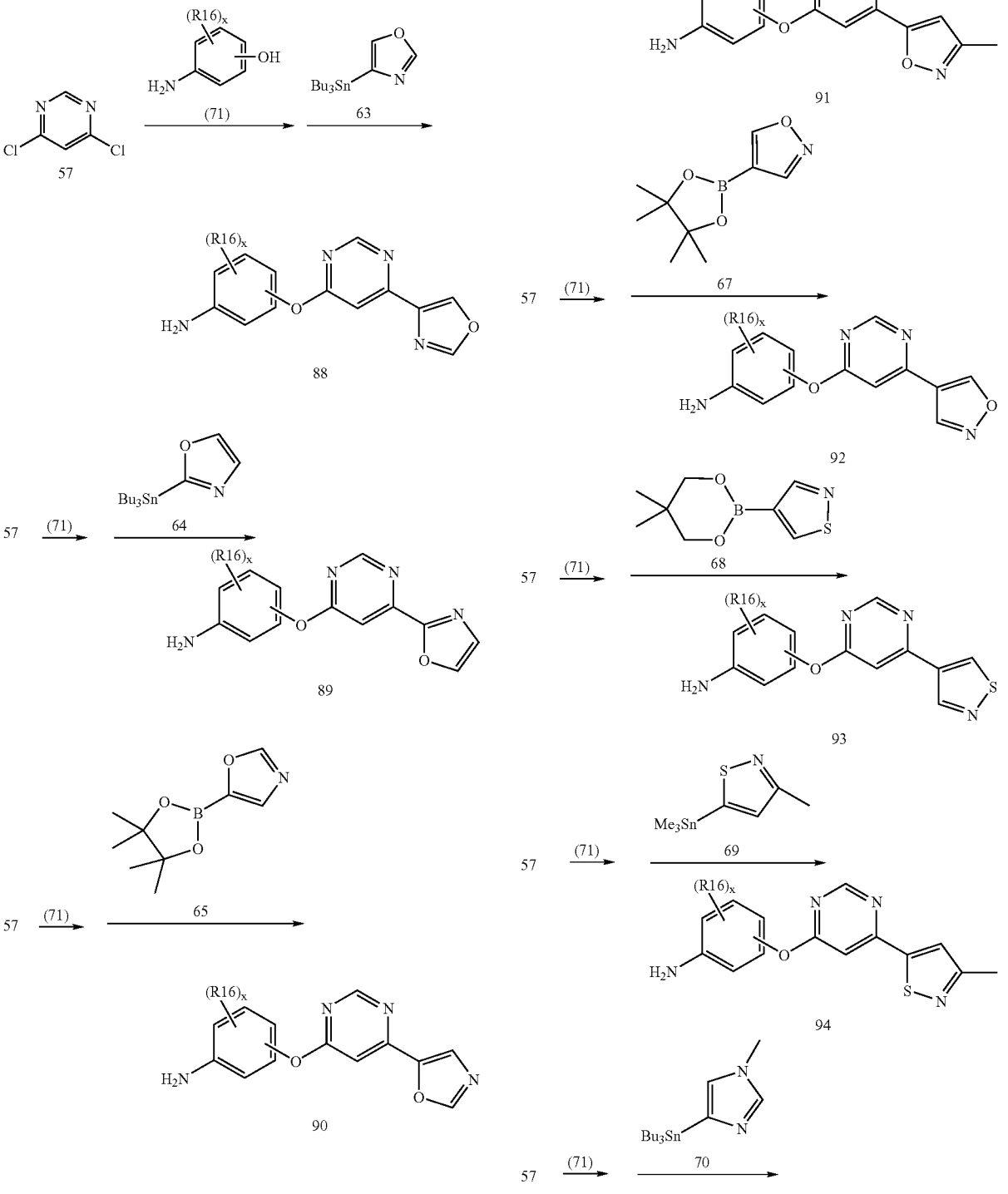




[0106] As indicated in Scheme 20, additional non-limiting examples of general amine 2 can also be prepared from dichloropyrimidine 57 using the two-step sequence of Scheme 16 and Scheme 19 (Step 1: Displacement of chloride with phenol 71, wherein R16 is an optional substituent as described above and x is 0-2; Step 2: palladium-catalyzed cross-coupling reaction) Suzuki cross-coupling reactions using readily available boronates or Stille cross-coupling reactions using readily available stannanes are interchangeable for Step 2. Thus, in the 2-step sequence of Scheme 20, chloropyrimidine 57, can first be combined with phenol 71, and the resultant phenoxy chloropyrimidine (not shown) can be reacted with a palladium catalyst and tributylstannane 63 (see: Cheng et al., *Biorg. Med. Chem Lett.,* 2006, 2076), stannane 64 (Aldrich Chemical), boronate 65 (BoroPharm), tributylstannane 66 (see: Sakamoto, et al. *Tetrahedron,* 1991, 5111), boronate 67 (Frontier Scientific), boronate 68 (see: Blackaby, et al., U.S. Pat. No. 7,030,128), trimethylstannane 69 (see: Wentland, et al. *J. Med. Chem.,* 1993, 1580) or stannane 70 (see: Nicolaou, et. al., *Chem. Med. Chem.,* 2006, 41) to provide general amines 88-95 respectively. Those skilled in the art will recognize that due to the symmetry of dichloropyrimidine 57, the general amine products of

Scheme 20 can also be prepared by reversing the order of the 2-step sequence (Step 1: Palladium-catalyzed cross-coupling reaction of 57 with 63-70; Step 2: Displacement of chloride with phenol 71).

Scheme 20



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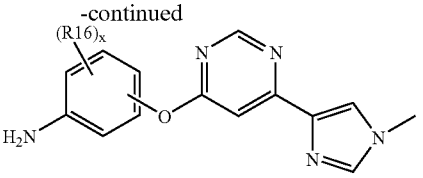

95

[0107] Additional synthetic methods for the preparation of compounds of formula 1 are found in the following examples.

Section 3

EXAMPLES

General Method A

[0108] To a stirring solution of the carboxylic acid (0.24 mmol) and TEA (1.2 mmol) in 1,4-dioxane (4.5 mL) at RT was added DPPA (0.29 mmol). After stirring for 0.5 h at RT, the appropriate amine (0.71 mmol) was added and the reaction was stirred with heating at 100° C. for 2 h. The reaction was cooled to RT, diluted with brine (15 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography to afford the target compound.

Example A1

[0109] 4-Fluoro-2-methyl-phenol (25 g, 0.2 mol) was added to a solution of sodium hydroxide (9.7 g, 0.24 mol) in water (160 mL) and the resultant solution was cooled to 0° C. Methyl chloroformate (24.2 g, 0.26 mol) was added dropwise at 0° C. At the completion of the reaction, the pH was adjusted to pH 8 with saturated aqueous Na_2CO_3 and then mixture was extracted with ethyl acetate (3×300 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and were concentrated under reduced pressure to provide carbonic acid 4-fluoro-2-methyl-phenyl ester methyl ester (30 g, 82% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.22-7.13 (m, 2 H), 7.05 (m, 1H), 3.81 (s, 1H), 2.12 (s, 3H).

[0110] To a solution of carbonic acid 4-fluoro-2-methyl-phenyl ester methyl ester (15 g, 81.5 mmol) in conc. sulfuric acid (100 mL) at 0° C. was added powdered KNO_3 (8.3 g, 82.2 mmol) in several portions. The reaction mixture was stirred for 1 hour at 0° C. and was then poured into ice water and extracted with ethyl acetate (3×100 mL). The extracts were washed with water and brine, dried ($MgSO_4$), concentrated in vacuo and purified by silica gel chromatography to provide carbonic acid 4-fluoro-2-methyl-5-nitro-phenyl ester methyl ester (2.0 g, 11% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.14 (d, J=6.9, 1H), 7.60 (d, J=12.0 Hz, 1H), 3.86 (s, 3H), 2.25 (s, 3H).

[0111] To a solution of aqueous sodium hydroxide (1.2 N, 20 mL, 24 mmol) was added 4-fluoro-2-methyl-5-nitro-phenyl ester methyl ester (2.0 g, 8.7 mmol), then the resultant mixture was refluxed for 2 hours. The reaction was cooled to RT and partitioned between EtOAc and water. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to provide 4-fluoro-2-methyl-5-nitro-phenol (1.4 g, 93% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 7.45 (d, J=6.6, 1H), 7.32 (d, J=12.3 Hz, 1H), 2.19 (s, 3H).

[0112] A mixture of 4-fluoro-2-methyl-5-nitro-phenol (1.4 g, 8.2 mmol) and 10% Pd/C (0.3 g, 20%/w) in MeOH (80 mL) was stirred under H_2 (30 psi) for 2 h. The Pd/C was removed by filtration and the filtrate was concentrated to give 5-amino-4-fluoro-2-methyl-phenol (0.68 g, 62% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.75 (s, 1H), 6.62 (d, J=12.0 Hz, 1H), 6.21 (d, J=8.1 Hz, 1H), 4.69 (s, 2H), 1.93 (s, 3H).

[0113] The mixture of 2-methanesulfonyl-4-(1-methyl-1H-pyrazol-4-yl)-pyrimidine and 2-methanesulfinyl-4-(1-methyl-1H-pyrazol-4-yl)-pyrimidine from Example A10 (1 g, 4.2 mmol), 5-amino-4-fluoro-2-methylphenol (1.2 g, 8.5 mmol) and K_2CO_3 (1.2 g, 8.6 mmol) were combined in DMF (10 mL) using a procedure analogous to Example A10 to provide 2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl) pyrimidin-2-yloxy)benzenamine (420 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (d, J=5.2 Hz, 1H), 8.39 (s, 1H), 8.07 (s, 1H), 7.40 (d, J=5.2 Hz, 1H), 6.90 (d, J=9.6 Hz, 1H), 6.47 (d, J=8.4 Hz, 1H), 5.02 (br s, 2H), 3.88 (s, 3H), 1.88 (s, 3H); MS (ESI) m/z: 300.2 ($M+H^+$).

Example A2

[0114] Methyl chloroformate (77.3 g, 0.82 mol) was added dropwise to a −10° C. solution of 2-chloro-4-fluorophenol (100 g, 0.68 mol) and sodium hydroxide (32.8 g, 0.82 mol) in water (550 mL). After complete addition, the precipitated solid was collected by filtration and washed with water to give 2-chloro-4-fluorophenyl methyl carbonate (110 g, 79% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (dd, J=8.1, 2.7 Hz, 1H), 7.50 (dd, J=9.0, 5.4 Hz, 1H), 7.30 (td, J=8.1, 3.0 Hz, 1H), 3.86 (s, 3H); MS (ESI) m/z: 205.2 ($M+H^+$).

[0115] To a suspension of 2-chloro-4-fluorophenyl methyl carbonate (110 g, 0.54 mol) in conc. H_2SO_4 (50 mL) was slowly added a mixture comprised of conc. H_2SO_4 (40 mL) and fuming HNO_3 (40.8 mL, 0.89 mol). The resultant mixture was stirred for 30 min at 0° C. The reaction mixture was poured into ice water and the precipitated solid was collected by filtration and washed with water to rive 2-chloro-4-fluoro-5-nitrophenyl methyl carbonate (120 g, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (d, J=7.2 Hz, 1H), 8.12 (d, J=10.8 Hz, 1H), 3.89 (s, 3H); MS (ESI) m/z: 250.1 ($M+H^+$).

[0116] 2-Chloro-4-fluoro-5-nitrophenyl methyl carbonate (120 g 0.48 mol) was combined with a solution of sodium hydroxide (22.7 g, 0.57 mol) in water (300 mL) and the resultant mixture was refluxed for 4 h. The insoluble solids were removed by filtration and the filtrate was acidified with dilute HCl. The precipitated solid was collected by filtration and washed with water to give 2-chloro-4-fluoro-5-nitrophenol (90 g, 98% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.18 (s, 1H), 8.10 (d, J=10.4 Hz, 1H), 7.62 (d, J=7.2 Hz, 1H); MS (ESI) m/z: 192.1 ($M+H^+$).

[0117] 2-Chloro-4-fluoro-5-nitrophenol (85 g, 0.45 mol) and 10% Pd/C (25 g, 0.023 mol) were combined in EtOH and hydrogenated (50 psi) for 12 h. The reaction mixture was filtered. The filtrate was concentrated in vacuo and purified by silica gel chromatography to provide 3-amino-4-fluorophenol (40 g 70%, yield). ^{1}H NMR (400 MHz, DMSO-d_6). δ 8.87 (s, 1H), 6.70 (dd, J=11.2, 8.8 Hz, 1H), 6.14 (dd, J=7.8, 2.4 Hz, 1H), 5.84 (m, 1H), 4.92 (s, 2H); MS (ESI) m/z: 128.2 ($M+H^+$).

[0118] 4-Chloro-2-methylsulfanyl-pyrimidine (1.4 g, 8.8 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (2.0 g, 1.1 eq), Na_2CO_3 (2.8 g, 3 eq) and $Pd(PPh_3)_4$ (500 mg, 0.43 mmol) were combined in a solvent comprised of toluene/EtOH/H_2O (4/4/1, 20 mL). The

reaction mixture was purged with argon and heated to 100° C. overnight. The reaction was filtered to remove insolubles and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography to provide 4-(1-methyl-1H-pyrazol-4-yl)-2-(methylthio)pyrimidine contaminated with triphenylphoshine oxide (2.0 g, >100% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.49 (d, J=5.1 Hz, 1H), 8.46 (s, 1H), 8.12 (s, 1H), 7.38 (d, J=5.1 Hz, 1H), 3.89 (s, 3H), 2.52 (s, 3H).

[0119] A solution of 4-(1-methyl-1H-pyrazol-4-yl)-2-methylsulfanyl-pyrimidine (2.0 g crude, 8.8 mmol) in dichloromethane (20 mL) was treated with m-CPBA (3.0 g, 17.4 mmol) portionwise at RT. The reaction was stirred 2 h and was quenched with saturated aqueous NaS_2SO_3 (3 mL). The mixture was partitioned with saturated aq Na_2CO_3 and the organics were washed with brine, dried (Na_2SO_4), and concentrated to provide a mixture (2.0 g) of 2-methanesulfonyl-4-(1-methyl-1H-pyrazol-4-yl)-pyrimidine and 2-methanesulfinyl-4-(1-methyl-1H-pyrazol-4-yl)-pyrimidine with a molar ratio of 1:0.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.83 (d, J=5.2 Hz, 1H), 8.82 (d, J=5.2 Hz, 0.24 H), 8.57 (s, 1H), 8.57 (s, 0.24H), 8.21 (s, 1H), 8.21 (s, 0.23H), 7.80 (d, J=5.6 Hz, 1H), 7.80 (d, J=5.6 Hz, 0.25H), 3.48 (s, 3H), 2.88 (s, 0.7H).

[0120] The above mixture of 2-methanesulfonyl-4-(1-methyl-1H-pyrazol-4-yl)-pyrimidine and 2-methanesulfinyl-4-(1-methyl-1 H-pyrazol-4-yl)-pyrimidine (1 g, 4.2 mmol), 4-amino-3-fluoro-phenol (1.1 g, 8.6 mmol) and K_2CO_3 (1.2 g, 8.6 mmol) in DMF (10 mL) was heated at 100° C. for 12 h. The reaction was partitioned between H_2O and EtOAc (3×50 mL). The combined organics were dried (Na_2SO4), concentrated in vacuo and chromatographed to 2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)benzenamine (402 mg). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.44 (d, J=5.2 Hz, 1H), 8.39 (s, 1H), 8.07 (s, 1H), 7.41 (d, J=5.2 Hz, 1H), 6.98 (t, J=9.6 Hz, 1H), 6.53 (dd, J=5.6, 2.0 Hz, 1H), 6.28 (d, J=8.4 Hz, 1H), 5.25 (br s, 2H), 3.88 (s, 3H). MS (ESI) m/z: 286.2 (M+H$^+$).

Example B1

[0121] t-Butylhydrazine and 1,1,1,3-tetramethoxypropane were combined according to literature procedures to yield 1-t-butyl-1H-pyrazol-4-amine. See Ger. Offen., DE3332270, 21 Mar. 1985.

Example 1

[0122] To a biphasic solution of Example A1 (0.071 g, 0.23 mmol) in EtOAc (5 ml) and $NaHCO_3$ (10 ml) was added prop-1-en-2-yl carbonochloridate (0.043 g, 0.35 mmol) and the mixture was stirred for 2 h at RT. The layers were separated and the aqueous layer was extracted with EtOAc (1×5 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to afford prop-1-en-2-yl 2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenylcarbamate as an off-white solid. MS (ESI) m/z: 384.2 (M+H$^+$).

[0123] A solution of prop-1-en-2-yl 2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenylcarbamate, Example B1 (0.033 g, 0.237 mmol) and DBU (catalytic) was dissolved in THF (2 ml) and stirred at 55° C. for 6 h. Solvents were removed and the crude residue was purified by column chromatography (methanol/CH_2Cl_2) to afford 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea as a white solid. (0.089 mg, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.50 (d, J=1.6 Hz, 1H), 8.44 (d, J=5.2 Hz, 1H), 8.42 (s, 1H), 8.09 (s, 1H), 7.91 (d, J=7.2 Hz, 1H), 7.77 (s, 1H), 7.44 (d, J=5.2 Hz, 1H), 7.36 (s, 1H), 7.18 (d, J=12.0 Hz, 1H), 3.87 (s, 3H), 2.01 (s, 3H), 1.46 (s, 9H); MS (ESI) m/z: 465.3 (M+H$^+$).

Example 2

[0124] To a biphasic solution of Example A1 (0.075 g, 0.26 mmol) in EtOAc (5 ml) and $NaHCO_3$ (10 ml) was added prop-1-en-2-yl carbonochloridate (0.048 g, 0.35 mmol) and the mixture was stirred for 2 h at RT. The layers were separated and the aqueous layer was extracted with EtOAc (1×5 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to afford prop-1-en-2-yl 2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenylcarbamate as an off-white solid. MS (ESI) m/z: 370.2 (M+H$^+$).

[0125] A solution of prop-1-en-2-yl 2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenylcarbamate, Example B1 (0.037 g, 0.26 mmol), DBU (catalytic) in THF (2 ml) was stirred at 55° C. for 6 h. Solvents were removed and the crude residue was purified by column chromatography (methanol/CH_2Cl_2) to afford 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea as a white solid. (0.089 mg, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.73 (s, 1H), 8.61 (d, J=2.4 Hz, 1H), 8.46 (d, J=5.2 Hz. 1H), 8.42 (s, 1H), 8.10 (s, 1H), 8.04 (dd, J=7.2 Hz, 2.8 Hz, 1H), 7.79 (s, 1H) 7.45 (d, J=5.2 Hz, 1H), 7.38 (s, 1H), 7.26 (dd, J=10.8 Hz, 8.8 Hz, 1H), 6.81-6.78 (m, 1H), 3.87 (s, 3H), 1.46 (s, 9H); MS (ESI) m/z: 451.2 (M+H$^+$).

Example 3

[0126] Using General Method A, 3-tert-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (0.074 g, 0.4 mmol), Example A1 (0.081 g, 0.27 mmol), triethylamine (0.0892 g, 0.8 mmol) and DPPA (0.15 g, 0.54 mmol) were combined and purified via chromatography (EtOAc/hexanes) to afford 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea as white solid (0.07 g, 54% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.88 (s, 1H), 8.82 (d, J=2.4 Hz, 1H), 8.44 (d, J=4.8 Hz, 1H), 8.42 (s, 1H), 8.08 (s, 1H), 7.89 (d, J=7.6 Hz, 1H), 7.44 (d, J=5.2 Hz, 1H), 7.22 (d, J=11.6 Hz, 1H), 6.02 (s, 1H), 3.87 (s, 3H), 3.57 (s, 3H), 2.02 (s, 3H), 1.15 (s, 9H); MS (ESI) m/z: 479.3 (M+H$^+$).

Example 4

[0127] Using General Method A, 3-tert-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (0.072 g, 0.39 mmol), Example A2 (0.075 g, 0.26 mmol), triethylamine (0.08 g, 0.79 mmol) and DPPA (0.14 g, 0.52 mmol) were combined and purified via chromatography (EtOAc/hexanes) to afford 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea as white solid (0.062 g, 51% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.93 (d, J=2.0 Hz, 1H), 8.46 (d, J=5.2 Hz, 1H), 8.42 (s, 1H), 8.08 (s, 1H), 8.02 (dd, J=6.8 Hz, 2.8 Hz, 1H), 7.45 (d, J=5.2 Hz, 1H), 7.30 (dd, J=11.2 Hz, 2 Hz, 1H), 6.87-6.83 (m, 1H), 6.04 (s, 1H), 3.87 (s, 3H), 3.58 (s, 3H), 1.16 (s, 9H); MS (ESI) m/z: 465.3 (M+H$^+$).

[0128] Using the synthetic procedures and methods described herein and methods known to those skilled in the art, the following compounds are made:

[0129] 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-4-methylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-4-methylisoxazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-cyclohexyl-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-cyclohexyl-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea. 1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-imidazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-imidazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butylpyrrolidin-3-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butylpyrrolidin-3-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-chloro-2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,4-difluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2,4-difluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, 1-(3-tert-butyl-4-methylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-4-chloro-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2,4-difluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-4-chloro-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,4-difluoro-5-(4-(oxazol-5-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(oxazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(oxazol-5-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-1-(2-fluoro-5-(4-(oxazol-2-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(oxazol-5-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, (3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-3-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-cyclohexyl-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-cyclohexyl-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-imidazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-imidazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butylpyrrolidin-3-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butylpyrrolidin-3-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(4-chloro-2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,4-difluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(1-tert-butyl-5-methyl-1H-pyrazol-4-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2,4-difluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, 1-3-tert-butyl-4-methylisoxazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-4-chloro-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2,4-difluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-4-chloro-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2,4-difluoro-5-(4-(oxazol-5-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(oxazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-methyl-5-(4-(oxazol-5-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(oxazol-2-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(oxazol-5-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-

1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(3-methylisoxazol-5-yl) pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(isoxazol-4-yl) pyrimidin-2-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-imidazol-4-yl) pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-1,2,4-triazol-1-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(4-(isothiazol-4-yl)pyrimidin-2-yloxy) phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(4-(3-methylisothiazol-5-yl)pyrimidin-2-yloxy) phenyl)urea, 1-(5-(4-(4H-1,2,4-triazol-3-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl) urea, 1-(5-(4-(1H-1,2,3-triazol-1-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(4-(1,3,4-thiadiazol-2-yl)pyrimidin-2-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-5-(2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(5-(2-(1H-pyrazol-4-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(5-(2-(1H-pyrazol-3-yl)pyrimidin-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-5-(2-(oxozol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(2-(oxazol-2-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(2-(oxazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(2-(3-methylisoxazol-5-yl pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(2-(isoxazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(2-(isothiazol-4-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(2-(3-methylisothiazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(2-(1-methyl-1H-imidazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(5-(2-(1H-1,2,4-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(2-(4H-1,2,4-triazol-3-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(2-(1H-1,2,3-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(2-(1,3,4-thiadiazol-2-yl) pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(4-(2-(1H-pyrazol-4-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(4-(2-(1H-pyrazol-3-yl)pyrimidin-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-(oxazol-4-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-2-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(oxazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(3-methylisoxazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-isoxazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(2-(isothiazol-4-yl) pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(2-(3-methylisothiazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-4-(2-(1-methyl-1H-imidazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(4-(2-(1H-1,2,4-triazol-1-yl) pyrimidin-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)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(2-(1H-1,2,3-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl) urea, 1-(4-(2-(1,3,4-thiadiazol-2-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(6-(1H-pyrazol-4-yl)pyrimidin-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-5-(6-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(5-(6-(1H-pyrazol-3-yl)pyrimidin-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-5-(6-(1-methyl-1H-pyrazol-4-yl) pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(6-(oxazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-1-(2-fluoro-5-(6-(oxazol-2-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(6-(oxazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(6-(3-methylisoxazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(6-(isoxazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(6-(isothiazol-4-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(3-tert-butylisoxazol-5-yl)-3-(2-fluoro-5-(6-(3-methylisothiazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(6-(1-methyl-1H-imidazol-4-yl)pyrimidin-4-yloxy)phenyl) urea, 1-(5-(6-(1H-1,2,4-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(6-(4H-1,2,4-triazol-3-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-5-(6-(1H-1,2,3-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(5-(6-(1,3,4-thiadiazol-2-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-5-(6-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(4-(6-(1H-pyrazol-4-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(4-(6-(1H-pyrazol-3-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yloxy) phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(6-(oxazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl3-(2-fluoro-4-(6-(oxazol-2-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(6-(oxazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3-(2-fluoro-4-(6-(3-methylisoxazol-5-yl) pyrimidin-4-yloxy)phenyl)urea, 1-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)-3(2-fluoro-4-(6-(isoxazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(6-(isothiazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(6-(3-methylisothiazol-5-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(6-(1-methyl-1H-imi-

dazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-(6-(1-methyl-1H-1,2,3-triazol-4-yl)pyrimidin-4-yloxy)phenyl)urea, 1-(4-(6-(1H-1,2,4-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(6-(4H-1,2,4-triazol-3-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(6-(1H-1,2,3-triazol-1-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(4-(6-(1,3,4-thiadiazol-2-yl)pyrimidin-4-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-4-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(3-tert-butylisoxazol-5-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-pyrazol-3-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(5-tert-butylthiophen-3-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(1-tert-butyl-1H-imidazol-4-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluorophenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-3-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-tert-butylthiophen-3-yl)-3-(2-fluoro-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(3-tert-butyl-1-methyl-1H-pyrazol-5-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(3-tert-butylisoxazol-5-yl)urea, H-pyrazol-4-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(1-tert-butyl-1H-pyrazol-3-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(5-tert-butylthiophen-3-yl)urea, 1-(5-(4-(1H-pyrazol-4-yl)pyrimidin-2-yloxy)-2-fluoro-4-methylphenyl)-3-(1-tert-butyl-1H-imidazol-4-yl)urea, 1-(1-tert-butyl-1H-pyrazol-4-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, 1-(1-tert-butyl-1H-pyrazol-3-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea, and 1-(5-tert-butyltriophen-3-yl)-3-(2-fluoro-4-methyl-5-(4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yloxy)phenyl)urea.

Section 4. Biological Data

Abl Kinase (SEQ ID NO: 1) Assay

[0130] 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 $A_{340\ nm}$) was continuously monitored spectrophometrically. The reaction mixture (100 μl) contained Abl kinase (1 μM, Abl from deCode Genetics), peptide substrate (EAIYAAPFAKKK, 0.2 mM), MgCl, (10 mM), pyruvate kinase (4 units), lactate dehydrogenase (0.7 units), phosphoenol pyruvate (1 mM), and NADH (0.28 mM) in 90 mM Tris buffer containing 0.2% octyl-glucoside and 3.5% DMSO, pH 7.5. Test compounds were incubated with Abl (SEQ ID NO:1) and other reaction reagents at 30° C. for 2 h before ATP (500 μM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC_{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

TLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIITEFMTYG

NLLDYLRECNRQEVNAVVLLYMATQISSAMEYLEKKNFIHRDLAARNCLV

GENHLVKVADFGLSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIKSD

VWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRMERPEGCPEKVYEL

MRACWQWNPSDRPSFAEIHQAFETMFQE

Abl Kinase (SEQ ID NO:2) Assay

[0131] Activity of T315I Abl kinase (SEQ ID NO:2) was determined by following the production of ADP from the kinase reaction through coupling with the pyruvate kinase/lactate dehydrogenase system (e.g., Schindler, et al. Science (2000) 289, 1938-1942). In this assay, the oxidation of NADH (thus the decrease at $A_{340\ nm}$) was continuously monitored spectrophometrically. The reaction mixture (100 μl) contained Abl kinase (4.4 nM. M315I 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 T315I Abl (SEQ ID NO:2) and other reaction reagents at 30° C. for 1 h before ATP (500 μM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). IC_{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 T315I kinase

(SEQ ID NO:2)

GTSMDPSSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKYSLTVAVKTLKEDTMEVE

EFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIIIEFMTYGNLLDYLRECNRQEVNAVVLL

YMATQISSAMEYLEKKNFIHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAKF

PIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGIDLSQVYELLEKDYRMERP

-continued

EGCPEKVYELMRACWQWNPSDRPSFAEIHQAFETMFQE

BCR-Abl p210-e14a2

(SEQ ID NO:3)

MVDPVGFAEAWKAQFPDSEPPRMELRSVGDIEQELERCKASIRRLEQEVNQERFRMIYLQ

TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQPAPADGADPPPAEEPEARPDGE

GSPGKARPGTARRPGAAASGERDDRGPPASVAALRSNFERIRKGHGQPGADAEKPFYVNV

EFHHERGLVKVNDKEVSDRISSLGSQAMQMERKKSQHGAGSSVGDASRPPYRGRSSESSC

GVDGDYEDAELNPRFLKDNLIDANGGSRPPWPPLEYQPYQSIYVGGIMEGEGKGPLLRSQ

STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY

RMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVSEATIVGVRKTGQIWPNDDEG

AFHGDADGSFGTPPGYGCAADRAEEQRRHQDGLPYIDDSPSSSPHLSSKGRGSRDALVSG

ALKSTKASELDLEKGLEMRKWVLSGILASEETYLSHLEALLLPMKPLKAAATTSQPVLTS

QQIETIFFKVPELYEIHKESYDGLFPRVQQWSHQQRVGDLFQKLASQLGVYRAFVDNYGV

AMEMAEKCCQANAQFAEISENLRARSNKDAKDPTTKNSLETLLYKPVDRVTRSTLVLHDL

LKHTPASHPDHPLLQDALRISQNFLSSINEEITPRRQSMTVKKGEHRQLLKDSFMVELVE

GARKLRHVFLFTDLLLCTKLKKQSGGKTQQYDCKWYIPLTDLSFQMVDELEAVPNIPLVP

DEELDALKIKISQIKSDIQREKRANKGSKATERLKKKLSEQESLLLLMSPSMAFRVHSRN

GKSYTFLISSDYERAEWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTIN

KEDDESPGLYGFLNVIVHSATGFKQSSKALQRPVASDFEPQGLSEAARWNSKENLLAGPS

ENDPNLFVALYDFVASGDNTLSITKGEKLRVLGYNHNGEWCEAQTKNGQGWVPSNYITPV

NSLEKHSWYHGPVSRNAAEYPLSSGINGSFLVRESESSPSQRSISLRYEGRVYHYRINTA

SDGKLYVSSESRFNTLAELVHHHSTVADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMER

TDITMKHKLGGGQYGEVYEGVWKKYSLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLV

QLLGVCTREPPFYIITEFMTYGNLLDYLRECNRQEVNAVVLLYMATQISSAMEYLEKKNF

IHRDLAARNCLVGENHLVKVADFGLSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIK

SDVWAFGVLLWEIATYGMSPYPGIDRSQVYELLEKDYRMKRPEGCPEKVYELMRACWQWN

PSDRPSFAEIHQAFETMFQESSISDEVEKELGKQGVRGAVTTLLQAPELPTKTRTSRRAA

EHRDTTDVPEMPHSKGQGESDPLDHEPAVSPLLPRKERGPPEGGLNEDERLLPKDKKTNL

FSALIKKKKKTAPTPPKRSSSFREMDGQPERRGAGEEEGRDISNGALAFTPLDTADPAKS

PKPSNGAGVPNGALRESGGSGFRSPHLWKKSSTLTSSRLATGEEEGGGSSSKRFLRSCSV

SCVPHGAKDTEWRSVTLPRDLQSTGRQFDSSTFGGHKSEKPALPRKRAGENRSDQVTRGT

VTPPPRLVKKNEEAADEVFKDIMESSPGSSPPNLTPKPLRRQVTVAPASGLPHKEEAWKG

SALGTPAAAEPVTPTSKAGSGAPRGTSKGPAEESRVRRHKHSSESPGRDKGKLSKLKPAP

PPPPAASAGKAGGKPSQRPGQEAAGEAVLGAKTKATSLVDAVNSDAAKPSQPAEGLKKPV

LPATPKPHPAKPSGTPISPAPVPLSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQP

PERASGAITKGVVLDSTEALCLAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSIQQMRN

KFAFREAINKLENNLRELQICPASAGSGPAATQDFSKLLSSVKEISDIVQR

BCR-Abl p210-e13a2

(SEQ ID NO:4)

MVDPVGFAEAWKAQFPDSEPPEMELRSVGDIEQELERCKASIRRLEQEVNQERFRMIYLQ

-continued

TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQPAPADGADPPPAEEPEARPDGE

GSPGKARPGTARRPGAAASGERDDRGPPASVAALRSNFERIRKGHGQPGADAEKPFYVNV

EFHHERGLVKVNDKEVSDRISSLGSQAMQMERKKSQHGAGSSVGDASRPPYRGRSSESSC

GVDGDYEDAELNPRFLKDNLIDANGGSRPPWPPLEYQPYQSIYVGGIMEGEGKGPLLRSQ

STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY

RMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVSEATIVGVRKTGQIWPNDDEG

AFHGDADGSFGTPPGYGCAADRAEEQRRHQDGLPYIDDSPSSSPHLSSKGRGSRDALVSG

ALKSTKASELDLEKGLEMRKWVLSGILASEETYLSHLEALLLPMKPLKAAATTSQPVLTS

QQIETIFFKVPELYEIHKESYDGLFPRVQQWSHQQRVGDLFQKLASQLGVYRAFVDNYGV

AMEMAEKCCQANAQFAEISENLRARSNKDAKDPTTKNSLETLLYKPVDRVTRSTLVLHDL

LKHTPASHPDHPLLQDALRISQNFLSSINEEITPRRQSMTVKKGEHRQLLKDSFMVELVE

GARKLRHVFLFTDLLLCTKLKKQSGGKTQQYDCKWYIPLTDLSFQMVDELEAVPNIPLVP

DEELDALKIKISQIKSDIQREKRANKGSKATERLKKKLSEQESLLLLMSPSMAFRVHSRN

GKSYTFLISSDYERAEWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTIN

KEEALQRPVASDFEPQGLSEAARWNSKENLLAGPSENDPNLFVALYDFVASGDNTLSITK

GEKLRVLGYNHNGEWCEAQTKNGQGWVPSNYITPVNSLEKHSWYHGPVSRNAAEYPLSSG

INGSFLVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSESRFNTLAELVHHHST

VADGLITTLHYPAPKRNKPTVYGVSPNYDKWEMERTDITMKHKLGGGQYGEVYEGVWKKY

SLTVAVKTLKEDTMEVEEFLKEAAVMKEIKHPNLVQLLGVCTREPPFYIITEFMTYGNLL

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SRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPYPGID

RSQVYELLEKDYRMKRPEGCPEKVYELMRACWQWNPSDRPSFAEIHQAFETMFQESSISD

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EPAVSPLLPRKERGPPEGGLNEDERLLPKDKKTNLFSALIKKKKKTAPTPPKRSSSFREM

DGQPERRGAGEEEGRDISNGALAFTPLDTADPAKSPKPSNGAGVPNGALRESGGSGFRSP

HLWKKSSTLTSSRLATGEEEGGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTLPRDLQSTG

RQFDSSTFGGHKSEKPALPRKRAGENRSDQVTRGTVTPPPRLVKKNEEAADEVFKDIMES

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TSKGPAEESRVRRHKHSSESPGRDKGKLSKLKPAPPPPPAASAGKAGGKPSQRPGQEAAG

EAVLGAKTKATSLVDAVNSDAAKPSQPAEGLKKPVLPATPKPHPAKPSGTPISPAPVPLS

TLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPPERASGAITKGVVLDSTEALCLAIS

GNSEQMASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQICPASA

GSGPAATQDFSKLLSSVKEISDIVQR

BCR-Abl p190-e1a2

(SEQ ID NO:5)

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TLLAKEKKSYDRQRWGFRRAAQAPDGASEPRASASRPQPAPADGADPPPAEEPEARPDGE

GSPGKARPGTARRPGAAASGERDDRGPPASVAALRSNFERIRKGHGQPGADAEKPFYVNV

EFHHERGLVKVNDKEVSDRISSLGSQAMQMERKKSQHGAGSSVGDASRPPYRGRSSESSC

GVDGDYEDAELNPRFLKDNLIDANGGSRPPWPPLEYQPYQSIYVGGIMEGEGKGPLLRSQ

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STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY

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BCR-Abl p210-e14a2 T315I

(SEQ ID NO:6)

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QQIETIFFKVPELYEIHKESYDGLFPRVQQWSHQQRVGDLFQKLASQLGVYRAFVDNYGV

AMEMAEKCCQANAQFAEISENLRARSNKDAKDPTTKNSLETLLYKPVDRVTRSTLVLHDL

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GKSYTFLISSDYERAEWRENIREQQKKCFRSFSLTSVELQMLTNSCVKLQTVHSIPLTIN

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LPATPKPHPAKPSGTPISPAPVPLSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQP

PERASGAITKGVVLDSTEALCLAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSIQQMRN

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BCR-Abl p210-e13a2 T315I

(SEQ ID NO:7)

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EFHHERGLVKVNDKEVSDRISSLGSQAMQMERKKSQHGAGSSVGDASRPPYRGRSSESSC

GVDGDYEDAELNPRFLKDNLIDANGGSRPPWPPLEYQPYQSIYVGGIMEGEGKGPLLRSQ

STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY

RMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVSEATIVGVRKTGQIWPNDDEG

AFHGDADGSFGTPPGYGCAADRAEEQRRHQDGLPYIDDSPSSSPHLSSKGRGSRDALVSG

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QQIETIFFKVPELYEIHKESYDGLFPRVQQWSHQQRVGDLFQKLASQLGVYRAFVDNYGV

AMEMAEKCCQANAQFAEISENLRARSNKDAKDPTTKNSLETLLYKPVDRVTRSTLVLHDL

LKHTPASHPDHPLLQDALRISQNFLSSINEEITPRRQSMTVKKGEHRQLLKDSFMVELVE

GARKLRHVFLFTDLLLCTKLKKQSGGKTQQYDCKWYIPLTDLSFQMVDELEAVPNIPLVP

DEELDALKIKISQIKSDIQREKRANKGSKATERLKKKLSEQESLLLLMSPSMAFRVHSRN

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INGSFLVRESESSPSQRSISLRYEGRVYHYRINTASDGKLYVSSESRFNTLAELVHHHST

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TLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPPERASGAITKGVVLDSTEALCLAIS

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BCR-Abl p190-e1a2

(SEQ ID NO:8)

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GSPGKARPGTARRPGAAASGERDDRGPPASVAALRSNFERIRKGHGQPGADAEKPFYVNV

EFHHERGLVKVKDKEVSDRISSLGSQAMQMERKKSQHGAGSSVGDASRPPYRGRSSESSC

GVDGDYEDAELNPRFLKDNLIDANGGSRPPWPPLEYQPYQSIYVGGIMEGEGKGPLLRSQ

STSEQEKRLTWPRRSYSPRSFEDCGGGYTPDCSSNENLTSSEEDFSSGQSSRVSPSPTTY

RMFRDKSRSPSQNSQQSFDSSSPPTPQCHKRHRHCPVVVSEATIVGVRKTGQIWPNDDEG

AFHGDAEALQRPVASDFEPQGLSEAARWNSKENLLAGPSENDPNLFVALYDFVASGDNTL

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DFGLSRLMTGDTYTAHAGAKFPIKWTAPESLAYNKFSIKSDVWAFGVLLWEIATYGMSPY

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PLDHEPAVSPLLPRKERGPPEGGLNEDERLLPKDKKTNLFSALIKKKKKTAPTPPKRSSS

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FRSPHLWKKSSTLTSSRLATGEEEGGGSSSKRFLRSCSVSCVPHGAKDTEWRSVTLPRDL

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APRGTSKGPAEESRVRRHKHSSESPGRDKGKLSKLKPAPPPPPAASAGKAGGKPSQRPGQ

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VPLSTLPSASSALAGDQPSSTAFIPLISTRVSLRKTRQPPERASGAITKGVVLDSTEALC

LAISGNSEQMASHSAVLEAGKNLYTFCVSYVDSIQQMRNKFAFREAINKLENNLRELQIC

PASAGSGPAATQDESKLLSSVKEISDIVQR

C-Kit Kinase (SEQ ID NO:9) Assay

[0132] 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 spectrophometrically. The reaction mixture (100 μl) contained c-Kit (cKIT residues T544-V976, from ProQinase, 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 μM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 0.5 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 0 to 0.5 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). 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)

LGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPN

LPYYIDGDVKLTQSMAIIRYIADKHNMLGGCPKERAEISMLEGAVDIRYG

VSRIAYSKDFETLKVDFLSKLPEMLKMFEDRLCHKTYLNGDHVTHPDFML

YDALDVVLYMDPMCLDAFPKLVCFKKRIEAIPQIDKYLKSSKYIWPLQGW

QATFGGGDHPPKSDLVPRHNQTSLYKKAGSAAAVLEENLYFQQTYKYLQK

PMYEVQWKVVEEINGNNYVYIDPTQLPYDHKWEFPPNRLSFGKTLGAGAF

GKVVEATAYGLIKSDAAMTVAVKMLKPSAHLTEREALMSELKVLSYLGNH

MNIVNLLGACTIGGPTLVITEYCCYGDLLNFLRRKRDSFICSKQEDHAEA

ALYKNLLHSKESSCSDSTNEYMDMKPGVSYVVPTKADKRRSVRIGSYIER

DVTPAIMEDDELALDLEDLLSFSYQVAKGMAFLASKNCIHRDLAARNILL

THGRITKICDFGLARDIKNDSNYVVKGNARLPVKWMAPESIFNCVYTFES

DVWSYGIFLWELFSLGSSPYPGMPVDSKFYKMIKEGFRMLSPEHAPAEMY

DIMKTCWDADPLKRPTFKQIVQLIEKQISESTNHIYSNLANCSPNRQKPV

VDHSVRINSVGSTASSSQPLLVHDDV

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

[0133] 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 spectrophometrically. The reaction mixture (100 μl) 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 μM) was added to start the reaction. The absorption at 340 nm was monitored continuously for 2 hours at 30° C. on Polarstar Optima plate reader (BMG). The reaction rate was calculated using the 1.0 to 2.0 h time frame. Percent inhibition was obtained by comparison of reaction rate with that of a control (i.e. with no test compound). 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)

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QNGSCRQVQYPLTDMSPILTSGDSDISSPLLQNTVHIDLSALNPELVQAV

QHVVIGPSSLIVHFNEVIGRGHFGCVYHGTLLDNDGKKIHCAVKSLNRIT

DIGEVSQFLTEGIIMKDFSHPNVLSLLGICLRSEGSPLVVLPYMKHGDLR

NFIRNETHNPTVKDLIGFGIQVAKGMKYLASKKFVHRDLAARNCMLDEKF

TVKVADFGLARDMYDKEYYSVHNKTGAKLPVKWMALESLQTQKFTTKSDV

WSFGVLLWELMTRGAPPYPDVNTFDITVYLLQGRRLLQPEYCPDPLYEVM

LKCWHPKAEMRPSFSELVSRISAIFSTFIGEHYVHVNATYVNVKCVAPYP

SLLSSEDNADDEVDTRPASFWETS

[0134] The biochemical IC_{50} values of other compounds disclosed herein are at least 10 μM against Abl enzyme.

Cell Culture

[0135] BaF3 cells (parental or transfected with the following: wild type p210 BCR-Abl and T315I p210 BCR-Abl was obtained from Professor Richard Van Etten (New England Medical Center, Boston, Mass.). Briefly, cells were grown in RPMI 1640 supplemented with 10% characterized fetal bovine serum (HyClone, Logan, Utah) at 37 degrees Celsius, 5% CO,, 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

[0136] A serial dilution of test compound was dispensed into a 96 well black clear bottom plate (Corning, Corning,

N.Y.). For each cell line, three thousand cells were added per well in complete growth medium. Plates were incubated for 72 hours at 37 degrees Celsius, 5% CO_2, 95% humidity. At the end of the incubation period Cell Titer Blue (Promega, Madison, Wis.) was added to each well and an additional 4.5 hour incubation at 37 degrees Celsius, 5% CO_2, 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

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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

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

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

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

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

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

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

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

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

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
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Glu Thr Met Phe Gln Glu
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35 40 45

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

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

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

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

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

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

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

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

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

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

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

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

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

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
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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

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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

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
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    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

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
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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
    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
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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

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
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    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

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
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Asp Phe  Ser Lys Leu Leu Ser  Ser Val Lys Glu Ile  Ser Asp Ile
    2015                2020                2025

Val Gln  Arg
    2030


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

<400> SEQUENCE: 4

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

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

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

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

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

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

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

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

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

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

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

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

Asp Lys Glu Val Ser Asp Arg Ile Ser Ser Leu Gly Ser Gln Ala Met
        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
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               325                 330                 335

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

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

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

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

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

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

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

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

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

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

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

Tyr Leu Ser His Leu Glu Ala Leu Leu Leu Pro Met Lys Pro Leu Lys
        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
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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
    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
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Tyr Gly  Glu Val Tyr Glu Gly  Val Trp Lys Lys Tyr  Ser Leu Thr
    1130                1135                1140

Val Ala  Val Lys Thr Leu Lys  Glu Asp Thr Met Glu  Val Glu Glu
    1145                1150                1155

Phe Leu  Lys Glu Ala Ala Val  Met Lys Glu Ile Lys  His Pro Asn
    1160                1165                1170

Leu Val  Gln Leu Leu Gly Val  Cys Thr Arg Glu Pro  Pro Phe Tyr
    1175                1180                1185

Ile Ile  Thr Glu Phe Met Thr  Tyr Gly Asn Leu Leu  Asp Tyr Leu
    1190                1195                1200

Arg Glu  Cys Asn Arg Gln Glu  Val Asn Ala Val Val  Leu Leu Tyr
    1205                1210                1215

Met Ala  Thr Gln Ile Ser Ser  Ala Met Glu Tyr Leu  Glu Lys Lys
    1220                1225                1230

Asn Phe  Ile His Arg Asp Leu  Ala Ala Arg Asn Cys  Leu Val Gly
    1235                1240                1245

Glu Asn  His Leu Val Lys Val  Ala Asp Phe Gly Leu  Ser Arg Leu
    1250                1255                1260

Met Thr  Gly Asp Thr Tyr Thr  Ala His Ala Gly Ala  Lys Phe Pro
    1265                1270                1275

Ile Lys  Trp Thr Ala Pro Glu  Ser Leu Ala Tyr Asn  Lys Phe Ser
    1280                1285                1290

Ile Lys  Ser Asp Val Trp Ala  Phe Gly Val Leu Leu  Trp Glu Ile
    1295                1300                1305

Ala Thr  Tyr Gly Met Ser Pro  Tyr Pro Gly Ile Asp  Arg Ser Gln
    1310                1315                1320

Val Tyr  Glu Leu Leu Glu Lys  Asp Tyr Arg Met Lys  Arg Pro Glu
    1325                1330                1335

Gly Cys  Pro Glu Lys Val Tyr  Glu Leu Met Arg Ala  Cys Trp Gln
    1340                1345                1350

Trp Asn  Pro Ser Asp Arg Pro  Ser Phe Ala Glu Ile  His Gln Ala
    1355                1360                1365

Phe Glu  Thr Met Phe Gln Glu  Ser Ser Ile Ser Asp  Glu Val Glu
    1370                1375                1380

Lys Glu  Leu Gly Lys Gln Gly  Val Arg Gly Ala Val  Thr Thr Leu
    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
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    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
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Gln Pro  Pro Glu Arg Ala Ser  Gly Ala Ile Thr Lys  Gly Val Val
    1895                 1900                 1905

Leu Asp  Ser Thr Glu Ala Leu  Cys Leu Ala Ile Ser  Gly Asn Ser
    1910                 1915                 1920

Glu Gln  Met Ala Ser His Ser  Ala Val Leu Glu Ala  Gly Lys Asn
    1925                 1930                 1935

Leu Tyr  Thr Phe Cys Val Ser  Tyr Val Asp Ser Ile  Gln Gln Met
    1940                 1945                 1950

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

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

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

Glu Ile  Ser Asp Ile Val Gln  Arg
    2000                 2005


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

<400> SEQUENCE: 5

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

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
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    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
<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
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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

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

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

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

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

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

Val Ser  Pro Asn Tyr Asp Lys  Trp Glu Met Glu Arg  Thr Asp Ile
    1130                 1135                 1140

Thr Met  Lys His Lys Leu Gly  Gly Gly Gln Tyr Gly  Glu Val Tyr
    1145                 1150                 1155

Glu Gly  Val Trp Lys Lys Tyr  Ser Leu Thr Val Ala  Val Lys Thr
    1160                 1165                 1170

Leu Lys  Glu Asp Thr Met Glu  Val Glu Glu Phe Leu  Lys Glu Ala
    1175                 1180                 1185

Ala Val  Met Lys Glu Ile Lys  His Pro Asn Leu Val  Gln Leu Leu
    1190                 1195                 1200

Gly Val  Cys Thr Arg Glu Pro  Pro Phe Tyr Ile Ile  Ile Glu Phe
    1205                 1210                 1215

Met Thr  Tyr Gly Asn Leu Leu  Asp Tyr Leu Arg Glu  Cys Asn Arg
    1220                 1225                 1230

Gln Glu  Val Asn Ala Val Val  Leu Leu Tyr Met Ala  Thr Gln Ile
    1235                 1240                 1245

Ser Ser  Ala Met Glu Tyr Leu  Glu Lys Lys Asn Phe  Ile His Arg
    1250                 1255                 1260

Asp Leu  Ala Ala Arg Asn Cys  Leu Val Gly Glu Asn  His Leu Val
    1265                 1270                 1275

Lys Val  Ala Asp Phe Gly Leu  Ser Arg Leu Met Thr  Gly Asp Thr
    1280                 1285                 1290

Tyr Thr  Ala His Ala Gly Ala  Lys Phe Pro Ile Lys  Trp Thr Ala
    1295                 1300                 1305

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
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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

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
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    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 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
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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

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

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

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

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

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

Ser Arg  Asn Ala Ala Glu Tyr  Pro Leu Ser Ser Gly  Ile Asn Gly
    1010                1015                1020

Ser Phe  Leu Val Arg Glu Ser  Glu Ser Ser Pro Ser  Gln Arg Ser
    1025                1030                1035

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

Thr Ala  Ser Asp Gly Lys Leu  Tyr Val Ser Ser Glu  Ser Arg Phe
    1055                1060                1065

Asn Thr  Leu Ala Glu Leu Val  His His 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
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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
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    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 Gln Asp Phe  Ser Lys Leu Leu Ser  Ser Val Lys
    1985                1990                1995

Glu Ile  Ser Asp Ile Val Gln  Arg
    2000                2005


<210> SEQ ID NO 8
<211> LENGTH: 1530
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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

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
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            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 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
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```
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

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
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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 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
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Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu Gly Leu Glu Phe
        35                  40                  45

Pro Asn Leu Pro Tyr Tyr Ile Asp Gly Asp Val Lys Leu Thr Gln Ser
    50                  55                  60

Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn Met Leu Gly Gly
65                  70                  75                  80

Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu Gly Ala Val Asp
                85                  90                  95

Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser Lys Asp Phe Glu Thr
            100                 105                 110

Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu Met Leu Lys Met Phe
        115                 120                 125

Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn Gly Asp His Val Thr
    130                 135                 140

His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp Val Val Leu Tyr Met
145                 150                 155                 160

Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu Val Cys Phe Lys Lys
                165                 170                 175

Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr Leu Lys Ser Ser Lys
            180                 185                 190

Tyr Ile Trp Pro Leu Gln Gly Trp Gln Ala Thr Phe Gly Gly 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
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Pro Thr Lys Ala Asp Lys Arg Arg Ser Val Arg Ile Gly Ser Tyr Ile
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Glu Arg Asp Val Thr Pro Ala Ile Met Glu Asp Asp Glu Leu Ala Leu
    450                 455                 460

Asp Leu Glu Asp Leu Leu Ser Phe Ser Tyr Gln Val Ala Lys Gly Met
465                 470                 475                 480

Ala Phe Leu Ala Ser Lys Asn Cys Ile His Arg Asp Leu Ala Ala Arg
                485                 490                 495

Asn Ile Leu Leu Thr His Gly Arg Ile Thr Lys Ile Cys Asp Phe Gly
            500                 505                 510

Leu Ala Arg Asp Ile Lys Asn Asp Ser Asn Tyr Val Val Lys Gly Asn
        515                 520                 525

Ala Arg Leu Pro Val Lys Trp Met Ala Pro Glu Ser Ile Phe Asn Cys
    530                 535                 540

Val Tyr Thr Phe Glu Ser Asp Val Trp Ser Tyr Gly Ile Phe Leu Trp
545                 550                 555                 560

Glu Leu Phe Ser Leu Gly Ser Ser Pro Tyr Pro Gly Met Pro Val Asp
                565                 570                 575

Ser Lys Phe Tyr Lys Met Ile Lys Glu Gly Phe Arg Met Leu Ser Pro
            580                 585                 590

Glu His Ala Pro Ala Glu Met Tyr Asp Ile Met Lys Thr Cys Trp Asp
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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
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His Asp Asp Val
        675


<210> SEQ ID NO 10
<211> LENGTH: 474
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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            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
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-continued

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Arg Leu Leu Gln Pro Glu Tyr Cys Pro Asp Pro Leu Tyr Glu Val Met
385                 390                 395                 400

Leu Lys Cys Trp His Pro Lys Ala Glu Met Arg Pro Ser Phe Ser Glu
                405                 410                 415

Leu Val Ser Arg Ile Ser Ala Ile Phe Ser Thr Phe Ile Gly Glu His
            420                 425                 430

Tyr Val His Val Asn Ala Thr Tyr Val Asn Val Lys Cys Val Ala Pro
        435                 440                 445

Tyr Pro Ser Leu Leu Ser Ser Glu Asp Asn Ala Asp Asp Glu Val Asp
    450                 455                 460

Thr Arg Pro Ala Ser Phe Trp Glu Thr Ser
465                 470
```
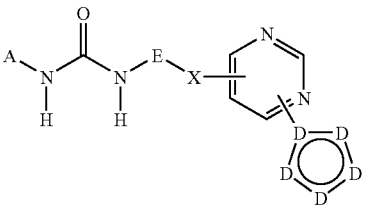

1. Compounds of the formula Ia

Ia



and wherein the pyrimidine 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 pyrazolyl, triazolyl, isoxazolyl, isothiazolyl, oxazolyl, imidazoyl, and thiadiazolyl;

wherein E is selected from the group consisting 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 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, and tetrazolyl;

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, imidazolonopyridinyl, thiazolopyridinyl, thiazolonopyridinyl, oxazolopyridinyl, oxazolonopyridinyl, isoxazolopyridinyl, isothiazolopyridinyl, triazolopyridinyl, imidazopyrimidinyl, pyrazolopyrimidinyl, imidazolonopyrimidinyl, thiazolopyridiminyl, thiazolonopyrimidinyl, oxazolopyridiminyl, oxazolonopyrimidinyl, isoxazolopyrimidinyl, isothiazolopyrimidinyl, triazolopyrimidinyl, dihydropurinonyl, pyrrolopyrimidinyl, purinyl, pyrazolopyrimidinyl, phthalimidyl, phthalimidinyl, pyrazinylpyridinyl, pyridinopyrimidinyl, pyrimidinopyrimidinyl, cinnolinyl, quinoxalinyl, quinazolinyl, quinolinyl, isoquinolinyl, phthalazinyl, benzodioxyl, benzisothiazoline-1,1,3-trionyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolyl, tetrahydroisoquinolinyl, benzoazepinyl, benzodiazepinyl, benzoxapinyl, and benzoxazepinyl;

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

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

X is selected from the group consisting of —O—, —S$(CH_2)_n$—, —N(R3)$(CH_2)_n$—, —$(CH_2)_p$—, and wherein the carbon atoms of —$(CH_2)_n$—, —$(CH_2)_p$—, 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, —$(CH_2)_n$OH, oxo, C1-C6alkoxyC1-C6alkyl, $(R4)_2N(CH_2)_n$—, $(R3)_2N(CH_2)_n$—, $(R4)_2N(CH_2)_qN(R4)(CH_2)_n$—, $(R4)_2N(CH_2)_qO(CH_2)_n$—, $(R3)_2NC(O)$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)$C1-C6alkyl-, —(R4)NC(O)R8, C1-C6alkoxycarbonyl-, -carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, $(R3)_2NSO_2$—, —SOR3, $(R4)_2NSO_2$—, —N(R4)SO_2R8, —O(CH2)$_q$OC1-C6alkyl, —SO_3R3, —SOR4, —C(O)R8, —C(O)R6, —C(═NOH)R6, —C(═NOR3)R6, —$(CH_2)_n$N(R4)C(O)R8, —N(R3)$(CH_2)_q$O-alkyl, —N(R3)$(CH_2)_q$N$(R4)_2$, nitro, —CH(OH)CH(OH)R4, —C(═NH)N$(R4)_2$, —C(═NOR3)N$(R4)_2$, and —NHC(═NH)R8, R17 substituted G3, R17 substituted pyrazolyl and R17 substituted imidazolyl;

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

each Z2 is independently and individually selected from the group consisting of aryl, C1-C6alkyl, C3-C8cycloalkyl, branched C3-C7alkyl, hydroxyl, hydroxyC1-C6alkyl-, cyano, $(R3)_2N$—, $(R4)_2N$—, $(R4)_2NC1$-C6alkyl-, $(R4)_2NC2$-C6alkylN(R4)$(CH_2)_n$—, $(R4)_2NC2$-C6alkylO$(CH_2)_n$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)$-C1-C6alkyl-, carboxyl, -carboxyC1-C6alkyl, C1-C6alkoxycarbonyl-, C1-C6alkoxycarbonylC1-C6alkyl-, $(R3)_2NSO_2$—, $(R4)_2NSO_2$—, —SO_2R8, —$(CH_2)_n$N(R4)C(O)R8, —C(O)R8, ═O, ═NOH, and ═N(OR6);

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

each Z3 is independently and individually selected from the group consisting of H, C1-C6alkyl, branched C3-C7alkyl, C3-C8cycloalkyl, fluoroC1-C6alkyl wherein the alkyl moiety can be partially or fully fluorinated, hydroxyC2-C6alkyl-, C1-C6alkoxycarbonyl-, —C(O)R8, R5C(O)$(CH_2)_n$—, $(R4)_2NC(O)$—, $(R4)_2NC(O)C1$-C6alkyl-, R8C(O)N(R4)$(CH_2)_q$—, $(R3)_2NSO_2$—, $(R4)_2NSO_2$—, —$(CH_2)_qN(R3)_2$, and —$(CH_2)_qN(R4)_2$;

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

C3-7alkyl, hydroxyC2-C6alkyl-, C1-C6alkoxyC2-C6alkyl-, $(R4)_2N$-C2-C6alkyl-, $(R4)_2N$-C2-C6alkylN(R4)-C2-C6alkyl-, $(R4)_2N$-C2-C6alkyl-O-C2-C6alkyl-, $(R4)_2NC(O)C1$-C6alkyl-, carboxyC1-C6alkyl, C1-C6alkoxycarbonylC1-C6alkyl-, -C2-C6alkylN(R4)C(O)R8, R8-C(=NR3)—, $—SO_2R8$, and —COR8;

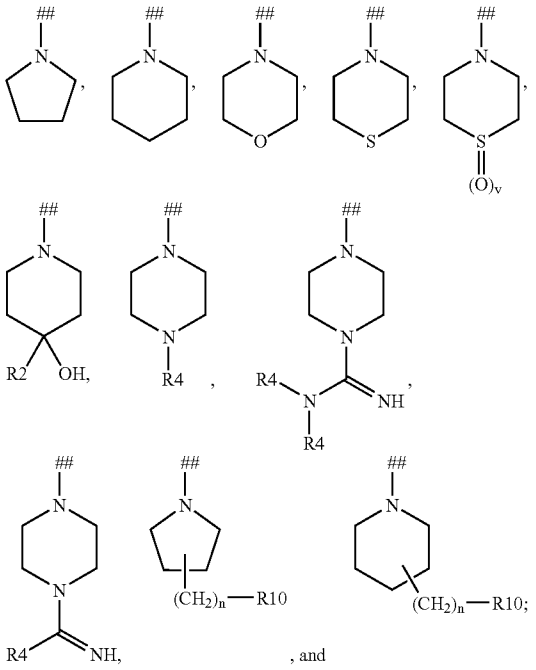
in the event that Z4 contains an alkyl or alkylene moiety, such moieties may be further substituted with one or more C1-C6alkyls;

each R2 is selected from the group consisting of H, C1-C6alkyl, branched C3-C8alkyl, R19 substituted C3-C8cycloalkyl-, fluoroC1-C6alkyl- wherein the alkyl is fully or partially fluorinated, halogen, cyano, C1-C6alkoxy-, and fluoroC1-C6alkoxy- wherein the alkyl group is fully or partially fluorinated, hydroxyl substituted C1-C6alkyl-, hydroxyl substituted branched C3-C8alkyl-, cyano substituted C1-C6alkyl-, cyano substituted branched C3-C8alkyl-, $(R3)_2NC(O)C1$-C6alkyl- and $(R3)_2NC(O)C3$-C8 branched alkyl-;

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

each R4 is independently and individually selected from the group consisting of H, C1-C6alkyl, hydroxyC1-C6alkyl-, dihydroxyC1-C6alkyl-, C1-C6alkoxyC1-C6alkyl-, branched C3-C7alkyl, branched hydroxyC1-C6alkyl-, branched C1-C6alkoxyC1-C6alkyl-, branched dihydroxyC1-C6alkyl-, $—(CH_2)_pN(R7)_2$, $—(CH_2)_pC(O)N(R7)_2$, $—(CH_2)_nC(C)OR3$, 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-, $—(CH_2)_nC(O)OR3$, R19 substituted C3-C8cycloalkyl- and $—(CH_2)_nR17$;

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 $—CO_2H$, $—CO_2C1$-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;

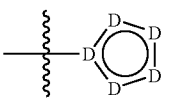
each R19 is independently and individually selected from the group consisting of H, OH and C1-C6alkyl;

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 heterocyclyl ring;

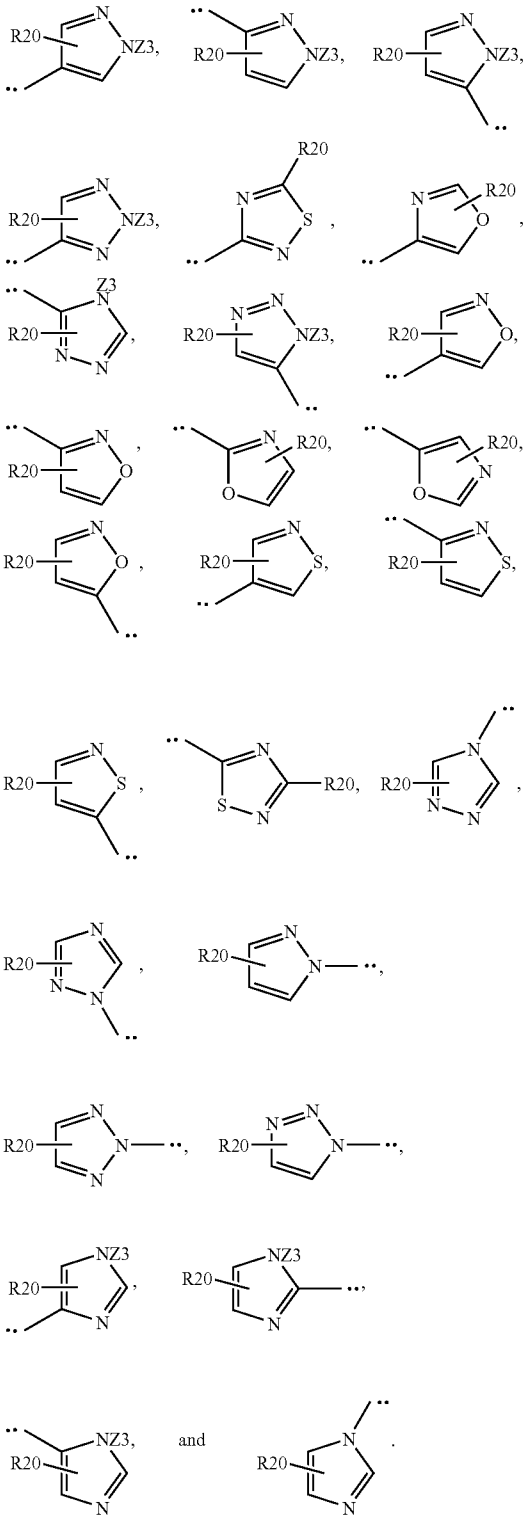
k is 0 or 1; n is 0-6; p is 1-4; q is 2-6; r is 0 or 1; t is 1-3; v is 1 or2; x is 0-2;

and stereo-, regioisomers and tautomers of such compounds.

2. Compounds of claim **1** wherein

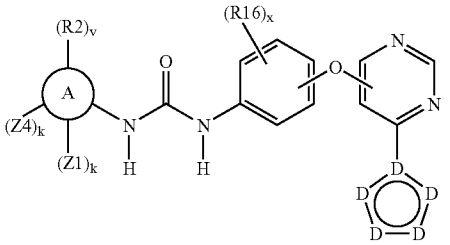


is selected from the group consisting of



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

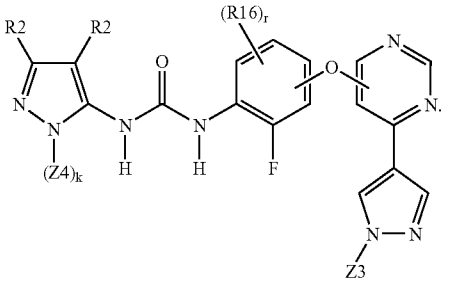
3. Compounds of claim **2** having formula Ib



Ib

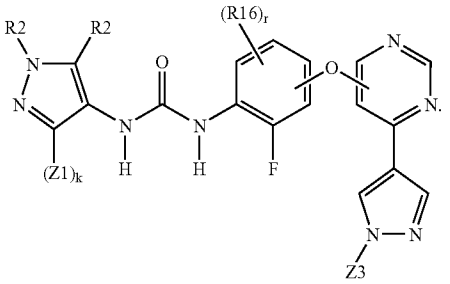
wherein A is any possible isomer of pyrazole.

4. Compounds of claim **3** having formula Ic



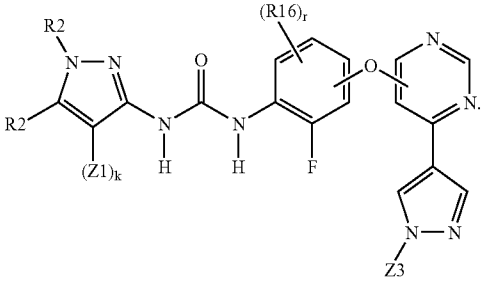
Ic

5. Compounds of claim having formula Id



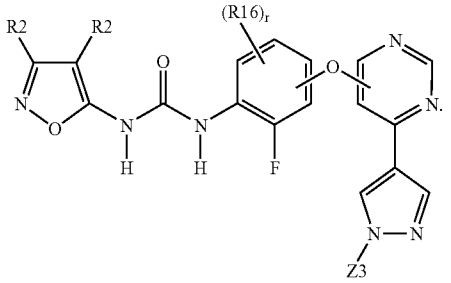
Id

6. Compounds of claim **3** having formula Ie



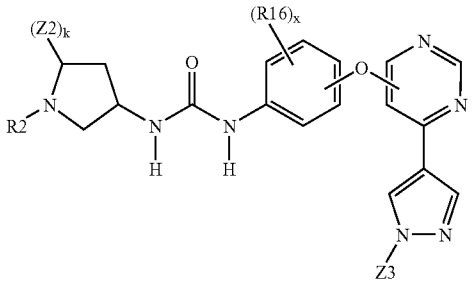
Ie

7. Compounds of claim **2** having formula If



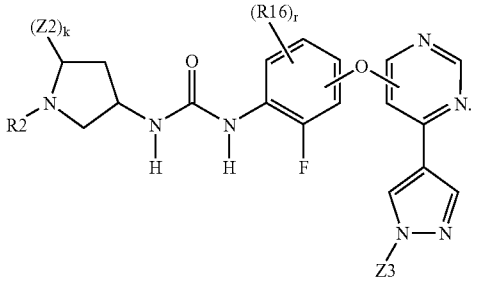
If

8. Compounds of claim **2** having formula Ig



Ig

9. Compounds of claim **8** having formula Ih



Ih

10. 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**.

11. A method of claim **10** wherein said kinase is selected from the group consisting of bcr-Abl fusion protein kinases p210, ber-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.

12. The method of claim **11**, 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.

13. A method of claim **10** 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.

14. A method of claim **10** 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.

15. 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.

16. 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**.

17. The method of claim **16**, said compound being administered by a method selected from the group consisting of oral, parenteral, inhalation, and subcutaneous.

* * * * *