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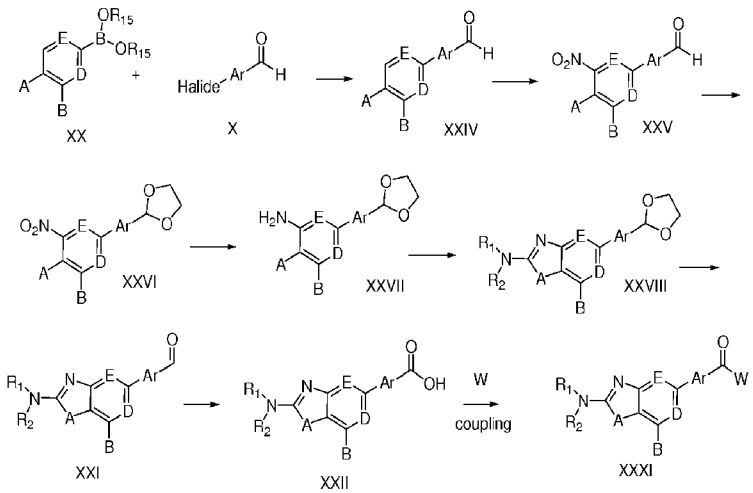
[Continued on next page]

(54) **Title**: NOVEL SUBSTITUTED BIARYLHETEROCYCLE DERIVATIVES AS PROTEIN KINASE INHIBITORS FOR THE TREATMENT OF CANCER AND OTHER DISEASES

Figure 7



(57) **Abstract**: The present invention provides a new patentable class of substituted benzoxazole derivative compounds that exhibit protein kinase (PK) inhibition activity or modulating ability, as well as compositions and methods of using such compounds, for example, to prevent or treat various diseases and disorders in human and non-human animals.

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INTERNATIONAL PATENT APPLICATION

NOVEL SUBSTITUTED BIARYLHETEROCYCLE DERIVATIVES AS PROTEIN KINASE INHIBITORS FOR THE TREATMENT OF CANCER AND OTHER DISEASES

Related Application

This patent application claims the benefit of and priority to U.S. provisional patent application serial number 61/512,882, filed on 28 July 2011, which is incorporated herein in its entirety for any and all purposes.

BACKGROUND OF THE INVENTION

1. Introduction.

The following description includes information that may be useful in understanding the present invention. It is not an admission that any such information is prior art, or relevant, to the presently claimed inventions, or that any publication specifically or implicitly referenced is prior art or even particularly relevant to the presently claimed invention.

2. Background.

Protein kinases play a crucial role in signal transduction and control many important biological processes, including cell proliferation, differentiation, and cell death. Aberrant expression and activity of protein kinases has been linked to carcinogenesis, and the inhibition of such kinases that are often hyper-activated in cancer has attracted significant interest in developing novel signal transduction-based anticancer therapies. With over 500 protein kinases present in the human kinome, combined with their critical roles in important signal transduction pathways, it is noteworthy that more than 100 kinases have been linked to cancer and/or other diseases. In addition, an increasing number of kinases have now been validated as targets or candidate targets for anticancer drug development, and are being targeted with antibodies or small molecule inhibitors.

The approval of Gleevec® (Imatinib mesylate) in 2001 for the treatment of Chronic Myelogenous Leukemia (CML) represented a hallmark in cancer treatment, proving the principle of targeted drug development and encouraged further research on small molecules as novel targeted therapies. Gleevec was first identified as an inhibitor of Bcr-Abl tyrosine kinase, and later found to inhibit cKIT and PDGFR as well. Inhibition of cKIT and PDGFR was the basis for the subsequent accelerated approval of Gleevec for advanced gastrointestinal tumors (GISTs). Several other small molecule kinase inhibitors have since been approved for the treatment of various solid tumors, including the EGFR inhibitors Iressa® and Tarceva® and the multikinase inhibitors Nexavar® and Sutent®.

Despite the significant number of protein kinase inhibitors reported to efficiently inhibit cancer cell growth *in vitro* and in preclinical studies, together with numerous compounds that have been evaluated in clinical trials during the last few

years, new targeted drugs are still being approved at only a slow pace and only for a limited number of cancer types. One problem of the early kinase inhibitors may be their relative non-selectiveness, which can lead to undesirable side effects and limit effective dosing. As part of this invention, the inventors descibe a scaffold for small molecule kinase inhibitors that can yield highly selective inhibitors, including molecules useful for treating certain cases of Acute Myelogeneous Leukemia (AML) as well as various solid tumors.

Approximately 10,000 new cases of AML are diagnosed each year in the U.S., and 200,000 cases worldwide. The FLT-3 (FMS-like tyrosine kinase 3) kinase is necessary for disease progression and hence is an attractive target for the development of novel therapies (Levis, et al., Blood, 2002, vol. 99(11): 3885-3891). FLT-3 is a receptor tyrosine kinase that catalyzes the phosphorylation of hydroxy groups on tyrosine residues of proteins. Receptor tyrosine kinases comprise a large family of transmembrane receptors with diverse biological activity. At present, at least nineteen (19) distinct subfamilies of receptor tyrosine kinases have been identified. FLT-3 is a member of the Platelet Derived Growth Factor Receptor (PDGFR) tyrosine kinase subfamily and shares the structural features of KIT, FMS, and PDGFR. Structurally, FLT-3 has five immunoglobulin-like domains in the extracellular region, a single transmembrane sequence, and an intracellular short juxtamembrane portion followed by the kinase domain (Blume-Jensen and Hunter, Nature, 2001, vol. 411: 355-365). Its activation signals are transduced through phosphorylation of itself and cytoplasmic proteins in biochemical signaling pathways that promote uncontrolled cell growth and inhibit apoptosis.

Aberrant expression of FLT-3 occurs in the majority of AML patients (Birg, et al., Blood, 1992 vol. 80:2584-2593; Carow, et al. Blood, 1996, vol. 87:1089-1096). Moreover, up to 40% of AML patients have a mutated FLT-3 kinase such that the enzyme is constitutively active, resulting in the activation of downstream signaling molecules and uncontrolled growth of bone marrow stem cells. There are two main types of FLT-3 mutations in AML patients. The first type is an internal tandem duplication (ITD) within the juxtamembrane domain is the most common mutation and is found in over 30% of AML patients (Nakao, et al, Leukemia, 1996, vol. 10(12):1911-1918). The second type are point mutations, with mutations at residue D835 within the kinase domain occuring most frequently (~7%) (Yamamoto, et al., Blood, 2001, vol. 97(8):2434-2439; Abu-Duhier, et al. Br J Haematol , 2001, vol. 113(4):983-988). Both ITD and D835 mutations render FLT-3 constitutively active in the absence of FLT-3 ligand and patients carrying these mutations have a very poor prognosis (Abu-Duhier, et al., Br. J Haematol , 2000, vol. 111:190-195). Additional point mutations have been found at lower rates. This lethal blood cancer carries a grim prognosis with survival duration of five years for only 14% of patients. Consequently, there is a need for effective agents to treat both early and late stage diseases of AML.

The present invention relates to a novel class of kinase inhibitors that are substituted benzoxazole derivatives that inhibit FLT-3 mutants with high efficacy and specifically kill leukemic cells that carry the FLT-3 ITD mutation *in vitro* and *in vivo*. In addition, these compounds efficiently inhibit the related kinase c-KIT (including Gleevec resistant mutants), and/or RET, and/or PDGFRα/β in *in vitro* tests, and can therefore be expected to also be useful for treating cancers in which these kinases play a proliferative role. The general chemical structures and specific examples shown in this specification cover molecules that belong to a new class of very selective kinase inhibitors that can serve as "targeted anticancer" agents and function by defined mechanisms, inhibiting specific kinases, very differently from drugs that are currently

available for the treatment of myeloid leukemia and other cancers. Therefore, the heterocyclic compounds disclosed herein are useful in the treatment of diseases of uncontrolled proliferation including AML, gastrointestinal stromal cancers (GISTs), melanoma, and thyroid cancer, as well as other cancers and other diseases, including inflammation and atherosclerosis. Furthermore, these patentable new compounds are selective kinase inhibitors with good oral bio-availability. The structures described and claimed herein can thus reasonably be expected to have limited side effects such that one or more of these compounds can be developed into medicines for the treatment of various types of cancers in humans as well as other non-human mammals. This invention thus also relates to the use of such compounds for the treatment of solid tumor cancers, including, but not limited to, GISTs, certain forms of medullary thyroid cancer and renal cancer, as well as other diseases. Pharmaceutical compositions comprising these compounds, methods of treating diseases and methods of preparing them, are also described.

3. Definitions.

Before describing the instant invention in detail, several terms used in the context of the present invention will be defined. In addition to these terms, others are defined elsewhere in the specification, as necessary. Unless otherwise expressly defined herein, terms of art used in this specification will have their art-recognized meanings.

The term "combination therapy" refers to a therapeutic regimen that involves the provision of at least two distinct therapies to achieve an indicated therapeutic effect. For example, a combination therapy may involve the administration of two or more chemically distinct active ingredients, for example, a substituted benzoxazole derivative according to the invention and another chemotherapeutic agent. Combination therapy may, alternatively, involve administration of a substituted benzoxazole derivative according to the invention with the delivery of another treatment, such as radiation therapy and/or surgery. Further, a combination therapy may involve administration of a substituted benzoxazole derivative according to the invention together with one or more other biological agents (e.g., anti-VEGF, TGFβ, PDGF, or bFGF agent), chemotherapeutic agents, and another treatment such as radiation and/or surgery. In the context of combination therapy using two or more chemically distinct active ingredients, it is understood that the active ingredients may be administered as part of the same composition or as different compositions. When administered as separate compositions, the compositions comprising the different active ingredients may be administered at the same or different times, by the same or different routes, using the same of different dosing regimens, all as the particular context requires and as determined by the attending physician. Similarly, when one or more compounds of the invention are administered, alone or in conjunction with one or more other chemotherapeutic agents and/or radiation and/or surgery, the drug(s) may be delivered before or after surgery or radiation treatment.

"Monotherapy" refers to a treatment regimen based on the delivery of one therapeutically effective compound, whether administered as a single dose or several doses over time.

A "patentable" composition, process, machine, or article of manufacture according to the invention means that the subject matter satisfies all statutory requirements for patentability at the time the analysis is performed. For example, with regard to novelty, non-obviousness, or the like, if later investigation reveals that one or more claims encompass one or more embodiments that would negate novelty, non-obviousness, *etc.*, the claim(s), being limited by definition to "patentable" embodiments, specifically exclude the unpatentable embodiment(s). Also, the claims appended hereto are to be interpreted both to provide the broadest reasonable scope, as well as to preserve their validity. Furthermore, the claims are to be interpreted in a way that (1) preserves their validity and (2) provides the broadest reasonable interpretation under the circumstances, if one or more of the statutory requirements for patentability are amended or if the standards change for assessing whether a particular statutory requirement for patentability is satisfied from the time this application is filed or issues as a patent to a time the validity of one or more of the appended claims is questioned.

A "plurality" means more than one.

The term "pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the agents and compounds of this invention and which are not biologically or otherwise undesirable. In many cases, the agents and compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of charged groups, for example, charged amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids, while pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. For a review of pharmaceutically acceptable salts (see Berge, *et al.* (1977) J. Pharm. Sci., vol. 66, 1-19).

The terms "separated," "purified," "isolated," and the like mean that one or more components of a sample contained in a sample-holding vessel are or have been physically removed from, or diluted in the presence of, one or more other sample components present in the vessel. Sample components that may be removed or diluted during a separating or purifying step include, chemical reaction products, unreacted chemicals, proteins, carbohydrates, lipids, and unbound molecules.

The term "species" is used herein in various contexts, *e.g.*, a particular species of chemotherapeutic agent. In each context, the term refers to a population of molecules, chemically indistinguishable from each other, of the sort referred in the particular context.

A "subject" or "patient" refers to an animal in which treatment can be effected by molecules of the invention. The animal may have, be at risk for, or be believed to have or be at risk for a disease or condition that can be treated by compositions and/or methods of the present invention. Animals that can be treated in accordance with the invention include vertebrates, with mammals such as bovine, canine, equine, feline, ovine, porcine, and primate (including humans and non-human primates) animals being particularly preferred examples.

A "therapeutically effective amount" (or "effective amount") refers to an amount of an active ingredient, *e.g.*, a substituted benzoxazole derivative according to the invention, sufficient to effect treatment when administered to a subject or patient. Accordingly, what constitutes a therapeutically effective amount of a composition according to the invention may be readily determined by one of ordinary skill in the art. Of course, the therapeutically effective amount will vary depending upon the particular subject and condition being treated, the weight and age of the subject, the severity of the disease condition, the particular compound chosen, the dosing regimen to be followed, timing of administration, the manner of administration and the like, all of which can readily be determined by one of ordinary skill in the art. It will be appreciated that in the context of combination therapy, what constitutes a therapeutically effective amount of a particular active ingredient may differ from what constitutes a therapeutically effective amount of the active ingredient when administered as a monotherapy (ie., a therapeutic regimen that employs only one chemical entity as the active ingredient).

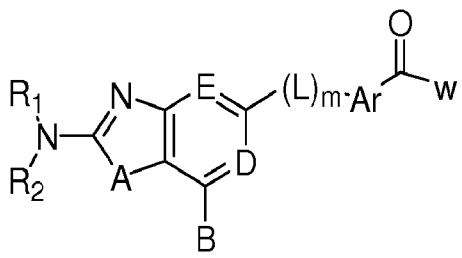
The term "treatment" or "treating" of a disease or disorder includes preventing or protecting against the disease or disorder (that is, causing the clinical symptoms not to develop); inhibiting the disease or disorder (*i.e.*, arresting or suppressing the development of clinical symptoms; and/or relieving the disease or disorder (*i.e.*, causing the regression of clinical symptoms). As will be appreciated, it is not always possible to distinguish between "preventing" and "suppressing" a disease or disorder since the ultimate inductive event or events may be unknown or latent. Accordingly, the term "prophylaxis" will be understood to constitute a type of "treatment" that encompasses both "preventing" and "suppressing." The term "treatment" thus includes "prophylaxis".

The term "therapeutic regimen" means any treatment of a disease or disorder using chemotherapeutic drugs, radiation therapy, surgery, gene therapy, DNA vaccines and therapy, antisense-based therapies including siRNA therapy, anti-angiogenic therapy, immunotherapy, bone marrow transplants, aptamers and other biologics such as antibodies and antibody variants, receptor decoys and other protein-based therapeutics.

SUMMARY OF THE INVENTION

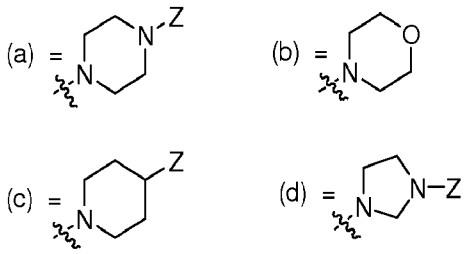
The present invention is directed to a patentable new class of substituted benzoxazole derivatives that exhibit protein kinase (PK) inhibition activity or modulating ability and are therefore useful in treating diseases and disorders related to abnormal PK activity.

Thus, one aspect of the invention concerns compounds of Formula (1):



in which

W is



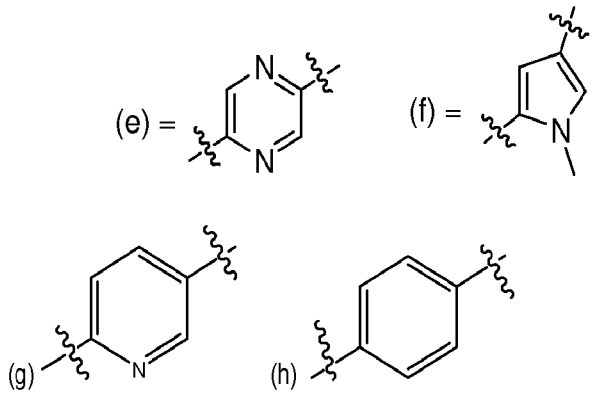
A is $–CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S- ;

B is $–OR_{24}$,$-SR_{25}$, $-NR_{28}R_{29}$;

D and E are together or independently $–CR_{30}$-, or –N-;

L is $–CH_2$-;

Ar is



m is 0 to 1

z= H or R1

R_1, R_2, R_3,R_{11},R_{12} R_{21},R_{22},R_{23},R_{24},R_{25},R_{28},R_{29} and R_{30} are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide; cycloalkyl (three, four, five, six, and seven membered cyclic ring system),

or an isomer, metabolite, polymorph, prodrug, or salt of any such compound.

A related aspect of the invention provide methods of synthesizing the compounds of the invention.

In another related aspect, this invention relates to pharmaceutical compositions comprising a compound described herein in admixture with one or more pharmaceutically acceptable excipients.

In another aspect, this invention relates to the use of the compounds described herein for inhibiting uncontrolled cellular proliferation such as various forms of cancer and leukemias, as well as for treating inflammatory diseases or atherosclerosis. Typically, such methods involve administering to a mammal diagnosed as having a disease of uncontrolled cellular proliferation or a composition comprising a compound according to the invention. .

These and other aspects and embodiments of the invention are discussed in greater detail in the sections that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

This application contains at least one figure executed in color. Copies of this application with color drawing(s) will be provided upon request and payment of the necessary fee. A brief summary of each of the figures is provided below.

FIGURE 1 illustrates the effect of Compounds 1, 2, and 3 on the growth of MV4-11 cells, which carry a FLT-3 ITD mutation. Cells were treated for 48 hours with increasing concentrations of compounds and the percentage of cell growth was calculated with respect to control cells grown in the presence of 0.1% solvent (DMSO).

FIGURE 2 depicts the selectivity of Compound 1 for FLT-3 mutant cells (MV4-11). In contrast, leukemia (AML) cells harboring wild type FLT-3 (HL-60 and HEL 92.1.7.) were not killed by Compound 1.

FIGURE 3 shows the pharmacokinetic profile of Compound 1 in a rat study. Three rats were given a single oral dose of 5 mg/kg of Compound 1 and blood samples were obtained at different periods of time up to 24 h. Plasma concentrations of Compound 1 (in nM) are given as a function of time.

FIGURE 4 illustrates the efficacy of Compound 1 in inhibiting tumor growth in an athymic mouse model of AML in which MV4-11 tumors are grown subcutaneously in nude mice. Mice were given a daily dose of vehicle or 10 mg/kg. At day 21 (arrow), the dosing schedule was increased to twice daily, with an 8 hours span between doses.

FIGURE 5 shows that Compound 1 had no significant effect on body weight during the length of treatment (38 days), indicating no major toxicity.

FIGURE 6 illustrates the size (A) and weight (B) of MV4-11 tumors isolated from nude mice after 38 days of treatment with Compound 1. Tumors in animals treated with Compound 1 were clearly smaller in size and weighed an average of 44% relative to tumors isolated from vehicle-treated animals.

FIGURE 7 shows a representative scheme of the synthetic pathway for the compounds disclosed herein in Formula 1, wherein m is 0.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds that are useful, for example, to prevent, alleviate or otherwise treat cancer and in particular AML, gastro intestinal cancer – including Gleevec resistant GISTs- and certain thyroid cancer in humans and other mammals. In addition, compounds of the invention have demonstrated oral bioavailability as exhibited by their high blood levels after oral dosing, either alone or in the presence of an excipient. Oral bioavailability allows oral dosing for use in chronic diseases, with the advantage of self-administration and decreased cost over other means of administration.

Before describing the compounds of the invention in detail, it will be understood that in the specification, the appended claims, and the formulae set forth herein the following terms will be understood to be defined as indicated.

The term "alkyl" denotes a radical containing 1 to 12 carbons, straight or branched chain group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, t-butyl, amyl, t-amyl, n-pentyl and the like. The term "alkenyl" denotes a straight or branched chain hydrocarbon radical containing 1 to 12 carbons and a carbon-carbon double bond, such as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexanyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl and the like. The term "alkenyl" includes dienes and trienes of straight and branch chains. The term "alkynyl" denotes a straight or branched chain hydrocarbon radical containing 1 to 12 carbons and a carbon-carbon triple bond such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl and the like. The term "alkynyl" includes di- and tri-ynes.

The term "substituted alkyl" denotes a radical containing 1 to 12 carbons of the above definitions that are substituted with one or more groups, but preferably one, two or three groups, selected from hydroxyl, holagen, cycloalkyl, amino, mono- substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is present then they may be the same or different.

The term "substituted alkeny1" denotes a radical containing 1 to 12 carbons of the above definitions that are substituted with one or more groups, but preferably one, two or three groups, selected from halogen, hydroxyl, cycloalkyl, amino, mono-substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is present then they may be the same or different.

The term "substituted alkynyl" denotes a radical containing 1 to 8 carbons of the above definitions that are substituted with one or more groups, but preferably one or two groups, selected from halogen, hydroxyl, cycloalkyl, amino, mono-substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, sub- stituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy.

The term "cycloalkyl" denotes a cyclic alkyl moiety containing 3 to 8 carbons, wherein alkyl is defined above, to include such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclopenyl, cyclohexyl, cycloheptyl and the like. The term "substituted cycloalkyl" denotes a cycloalkyl as defined above that is further substituted with one or more groups, selected from halogen, alkyl, hydroxyl, alkoxy, substituted alkoxy, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, amino, mono-substituted amino or di-substituted amino. When the cycloalkyl is substituted with more than one group, they may be the same or different.

The term "cycloalkenyl" denotes a radical containing 3 to 8 carbons, such as cyclopropenyl, l-cyclobutenyl, 2-cyclobutenyl, l-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, l-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl and the like. The term "substituted cycloalkenyl" denotes a cycloalkenyl as defined above further substituted with one or more groups selected from halogen, alkyl, hydroxyl, alkoxy, substituted alkoxy, haloalkoxy, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted. dialkylcarboxamide, amino, mono-substituted amino or di-substituted amino. When the cycloalkenyl is substituted with more than one group, they may be the same or different.

The term "alkoxy" as used herein denotes a radical alkyl, defined above, attached directly to an oxygen such as, methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, t-butoxy, iso-butoxy and the like. The term "substituted alkoxy" denotes a radical alkoxy of the above definition that is substituted with one or more groups, but preferably one or two groups, selected from, hydroxyl, cycloalkyl, amino, mono-substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, thioalkyl, thiohaloalkyl, alkoxy, substituted alkoxy or haloalkoxy. When more than one group is present then they may be the same or different. The term "mono-substituted amino" denotes an amino substituted with one group selected from alkyl, substituted alkyl or arylalkyl wherein the terms have the same defini- tions found throughout.

The term "di-substituted amino" denotes an amino sub- stituted with two radicals that may be same or different selected from aryl, substituted aryl, alkyl, substituted alkyl or arylalkyl wherein the terms have the same definitions found throughout. Some examples include dimethylamino, methylethylamino, diethylamino and the like.

The term "haloalkyl" denotes a radical alkyl, defined above, substituted with one or more halogens, preferably fluorine, such as a trifiuoromethyl, pentafluoroethyl and the like.

The term "haloalkoxy" denotes a haloalkyl as defined above, that is directly attached to an oxygen to form trifluoromethoxy, pentafluoroethoxy and the like. The term "acyl" denotes a radical containing 1 to 8 carbons such as formyl, acetyl, propionyl, butanoyl, iso- le butanoyl, pentanoyl. hexanoyl, heptanoyl, benzoyl and the like. The term "acyloxy" denotes a radical containing 1 to 8 carbons of an acyl group defined above directly attached to an oxygen such as acetyloxy, propionyloxy, butanoyloxy, iso-butanoyloxy, benzoyloxy and the like. The term "aryl" denotes an aromatic ring radical containing 6 to 10 carbons that include phenyl and naphthyl. The term "substituted aryl" denotes an aromatic radical as defined above that is substituted with one or more selected from hydroxyl, cycloalkyl, aryl, substituted aryl,

heteroaryl, heterocyclic ring, substituted heterocyclic ring, amino, 1 mono-substituted amino, di-substituted amino, acyloxy, nitro, cyano, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted l dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, alkylthio, l alkoxy, substituted alkoxy or haloalkoxy, wherein the terms are defined herein. The term "halo" or "halogen" refers to a fluoro, chloro, bromo or iodo group.

The term "thioalkyl" denotes a sulfide radical containing 1 to 8 carbons, linear or branched. Examples include methyl sulfide, ethyl sulfide, isopropyl sulfide and the like. The term "thiohaloalkyl" denotes a thioalkyl radical substituted with one or more halogens. Examples include trifluoromethylthio, 1,1-difluoroethylthio, 2,2,2- trifluoroethylthio and the like.

The term "carboalkoxy" refers to an alkyl ester of a carboxylic acid, wherein alkyl has the same definition as found above. Examples include carbomethoxy, carboethoxy, carboisopropoxy and the like. The term "alkylcarboxamide" denotes a single alkyl group attached to the amine of an amide, wherein alkyl has the same definition as found above. Examples include N-methylcarboxamide, N-ethylcarboxamide, N-isopropylcarboxamide and the like. The term "substituted alkylcarboxamide" denotes a single "substituted alkyl" group, as defined above, attached to the amine of an amide.

The term "dialkylcarboxamide" denotes two alkyl or arylalkyl groups that are the same or different attached to the amine of an amide, wherein alkyl has the same definition as found above. Examples of a dialkylcarboxamide include N,N -dimethylcarboxamide, N -methyl-N -ethyl carboxamide and the like.

The term substituted "dialkylcarboxamide" denotes two alkyl groups attached to the amine of an amide, where one or both groups are a "substituted alkyl", as defined above. It is understood that these groups may be the same or different. Examples include N,N-dibenzylcarboxamide, N-benzyl-N-methylcarboxamide and the like.

The term "alkylamide" denotes an acyl radical attached to an amine or monoalkylamine, wherein the term acyl has the same definition as found above. Examples of "alkylamide" include acetamido, propionamido and the like.

The term "arylalky1" defines an alkylene, such as -CH2- for example, which is substituted with an aryl group that may be substituted or unsubstituted as defined above. Examples of an "arylalkyl" include benzyl, phenethylene and the like.

The term "residue of a chemical species", as used in the specification and appended claims, refers to a moiety that is the resulting product of the chemical species in a particular reaction scheme or subsequent formulation or chemical product, regardless of whether the moiety is actually obtained from the chemical species. Thus, an ethylene glycol residue in a polyester refers to one or more $-OCH_2CH_2O-$ repeat units in the polyester, regardless of whether ethylene glycol is used to prepare the polyester.

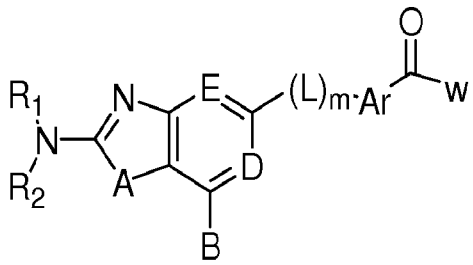
As those in the art will appreciate, where any variable, moiety, group, or the like occurs more than one time in any variable or structure of compound of the invention, its definition at each occurrence is independent of its definition at every other occurrence. All percentages, ratios, and proportions used herein are by weight unless otherwise specified. Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only, and they do not exclude

other defined values or other values within defined ranges for the radicals and substituents. The compounds of the invention are patentable compounds of formula I having any combination of the values, specific values, more specific values, and preferred values described herein.

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an aromatic compound" includes mixtures of aromatic compounds.

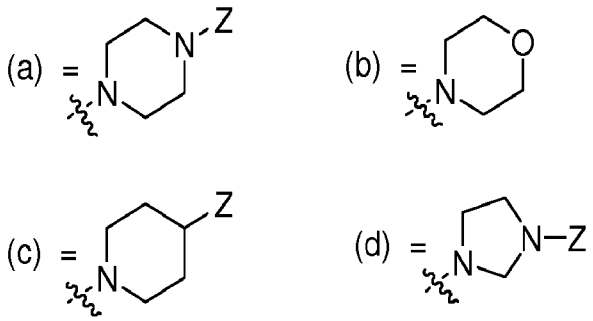
Compositions

Some disclosed embodiments of the invention relate to the Formula (1):



in which

W is (a) or (b) or (c) or (d)



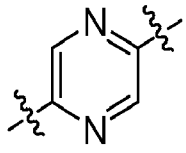
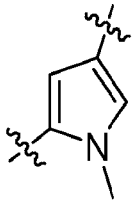
A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S- ;

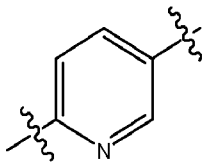
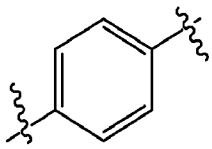
B is $-OR_{24}$,$-SR_{25}$, $-NR_{28}R_{29}$;

D and E are together or independently $-CR_{30}$-, or –N-;

L is $-CH_2$-;

Ar is formula (e), or (f) or (g) or (h)

(e) =  (f) = 

(g)  (h) 

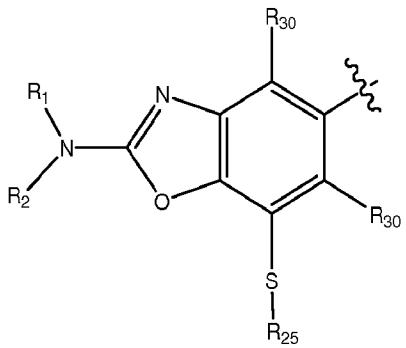
m is 0 to 1

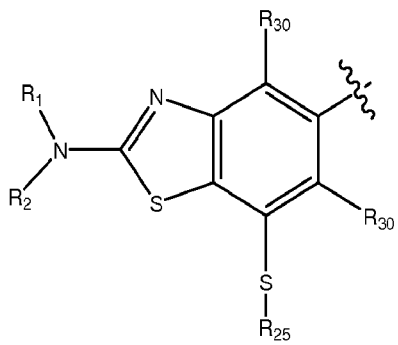
Z= H or R1

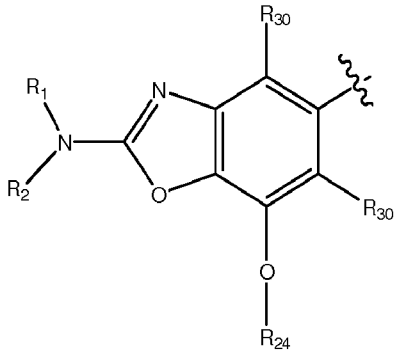
R_1,R_2, R_3,R_{11},R_{12} R_{21},R_{22},R_{23},R_{24},R_{25}, R_{28},R_{29} and R_{30} are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide; cycloalkyl (three, four, five, six and seven membered cyclic ring system);

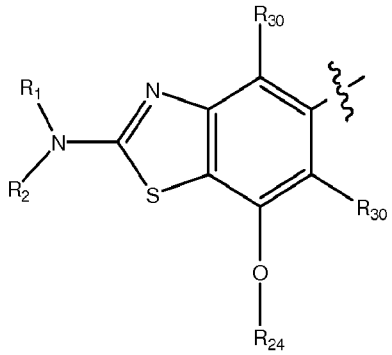
or an isomer, metabolite, polymorph, prodrug, or salt of any such compound.

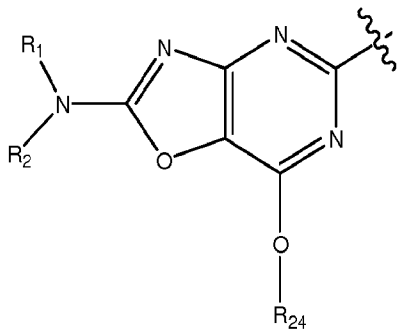
In another embodiment, A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S- ; B is $-OR_{24}$,$-SR_{25}$, $-NR_{28}R_{29}$, D and E are together or independently $-CR_{30}$-, or –N-. Preferred heterobicyclic residues may be selected from

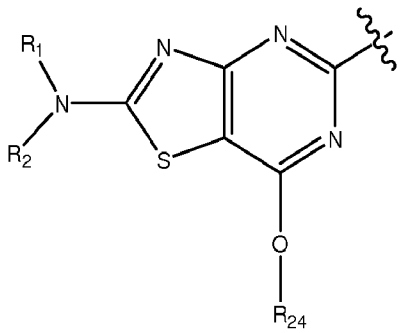


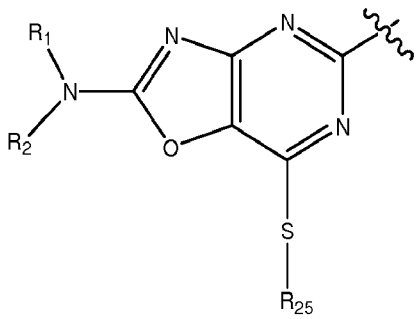


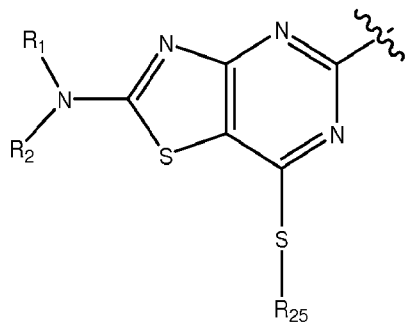


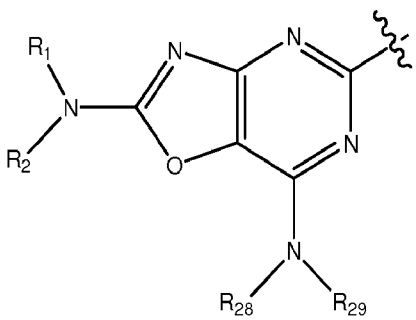


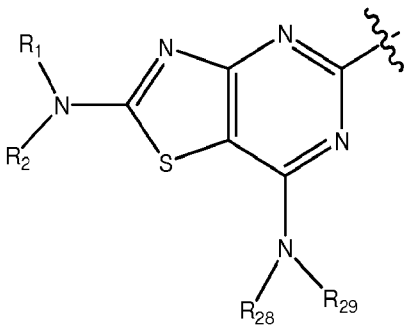


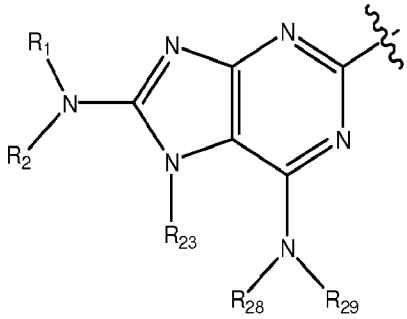


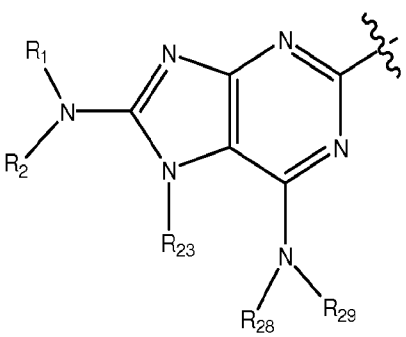




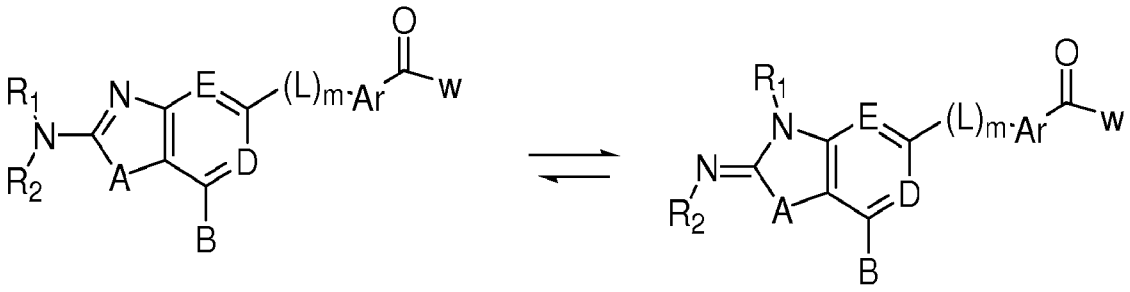






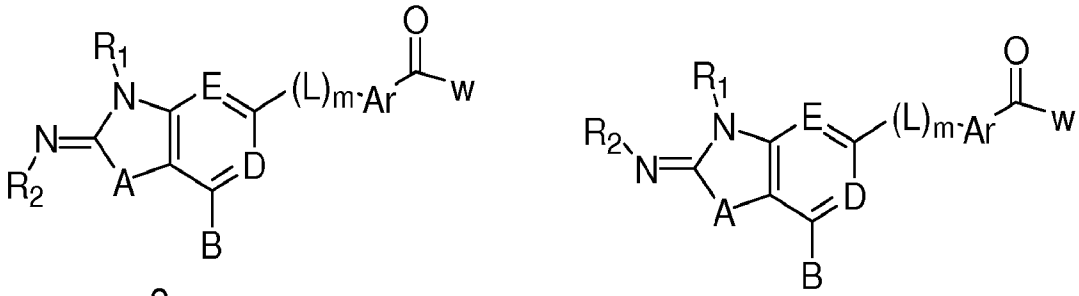


Some embodiments of this invention, compounds of formula (1) disclosed herein may exist in the form of tautomers (1) and (2), which are within the scope of the invention.



(1) (2)

Further 2 can exist in Z or E form in some embodiments



2 2a

The compounds disclosed herein may also include salts of the compounds. The term "salt" refers to a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many salts are known in the art. Preferred cationic salts include the alkali metal salts (such as, for example, sodium and potassium), alkaline earth metal salts (such as, for example, magnesium and calcium), and organic salts. Preferred anionic salts include the halides (such as, for example, chloride salts). For instance, one or more compounds disclosed herein may include salts formed by reaction of a nitrogen contained within the compound, such as an amine, aniline, substituted aniline, pyridyl and the like, with an acid, such as HCl, carboxylic acid and the like. Therefore, all possible salt forms in relationship to the tautomers and a salt formed from the reaction between a nitrogen and acid are within the scope of the invention. When intended for administration to a subject, such salts should be appropriate for such use. Thus, the term "pharmaceutically acceptable" means suitable for use in humans, whereas "veterinarily acceptable" means suitable for use in non-human animals, particularly non-human mammals.

The term "pharmaceutically acceptable salt" refers to salts which retain the biological effectiveness and properties of the compounds of the invention and which are not biologically or otherwise undesirable. In many cases, the compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic

acids, while pharmaceutically acceptable base addition salts can be prepared from inorganic and organic bases. For a review of pharmaceutically acceptable salts, *see*, *e.g.*, Berge, *et al.* ((1977) *J. Pharm. Sci.*, vol. 66, 1).

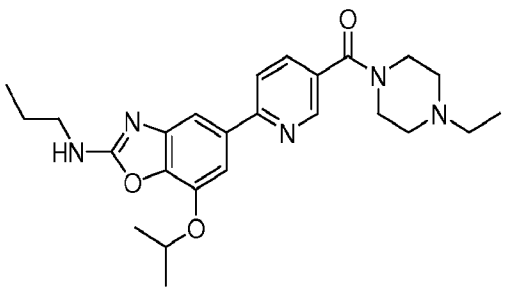
The expression "non-toxic pharmaceutically acceptable salts" non-toxic salts formed with nontoxic, pharmaceutically acceptable inorganic or organic acids or inorganic or organic bases. For example, the salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, fumaric, methanesulfonic, trifluoromethanesulfonic, and toluenesulfonic acid and the like. Salts also include those from inorganic bases, such as ammonia, sodium hydroxide, potassium hydroxide, and hydrazine. Suitable organic bases include methylamine, ethylamine, propylamine, dimethylamine, diethylamine, diethanolamine, trimethylamine, triethylamine, triethanolamine, ethylenediamine, hydroxyethylamine, morpholine, piperazine, and guanidine.

The present invention also includes other forms of the compounds of the invention, including prodrug forms. Here, a "prodrug" is a compound that contains one or more functional groups that can be removed or modified *in vivo* to result in a molecule that can exhibit therapeutic utility *in vivo*. [Magnus, if you are aware of any prodrug example sof the compounds of the invention, it may be useful to provide an exemplary structure after the structures for compounds 1-10.]

The present invention provides, but is not limited to, the specific compounds set forth in the Examples as well as those set forth below, and a pharmaceutically acceptable salt thereof:

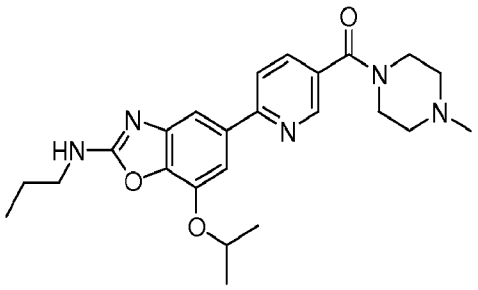
m is 0:

Compound 1



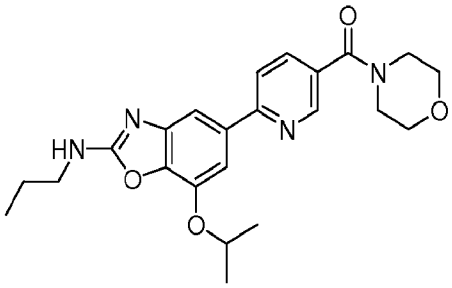
(4ethylpiperzine-1-yl)(6-(7-isopropoxy2-(propylamino)benzo[d]oxazole-5-yl)pyridine-3-yl)methanone

Compound 2



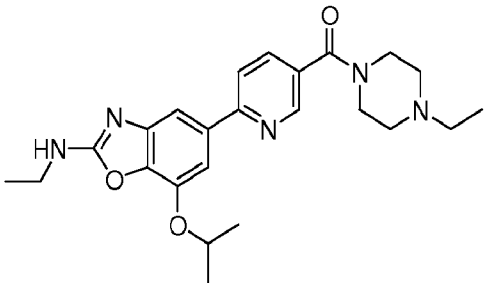
(6-(7-isopropoxy-2-(propylamino)benzo[d]oxazole-5-yl)pyridine-3-yl)(4-methylpiperzine)methanone

Compound 3



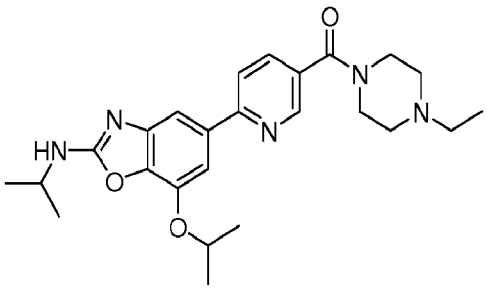
(6-(7-isopropoxy-2-(propylamino)benzo[d]oxazole-5-yl)pyridine-3-yl)(morpholino)methanone

Compound 4



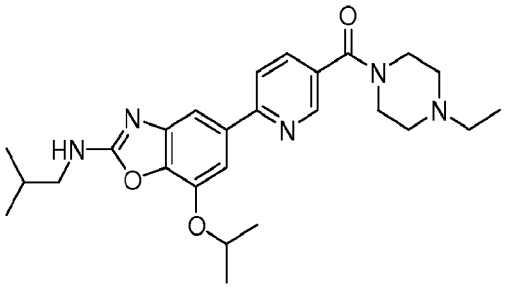
(6-(2-(ethylamino)-7-isopropoxybenzo[d]oxazol-5-yl)pyridine-3-yl)(4-ethylpiperazine-1-yl)methanone

Compound 5



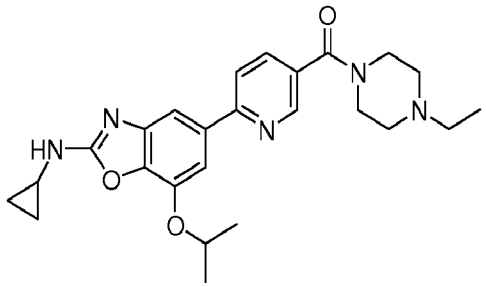
(4-ethylpiperazine-1-yl)(6-(7-isopropoxy-2-(isopropylamino)benzo[d]oxazole-5-yl)pyridine-3-yl)methanone

Compound 6



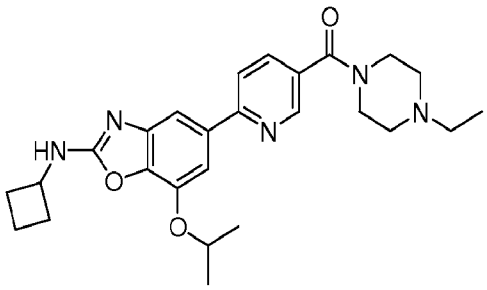
(4-ethylpiperazine-1-yl)(6-(2-(isobutylamino)-7-isopropoxybenzo[d]oxazole-5-yl)pyridine-3-yl)methanone

Compound 7



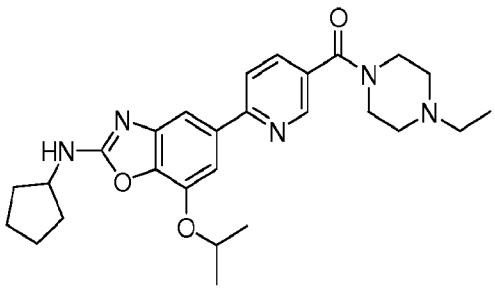
(6-(2-(cyclopropylamino)-7-isopropoxybenzo[d]oxazole-5-yl)pyridine-3-yl)(4-ethylpiperazine-1-yl)methanone

Compound 8



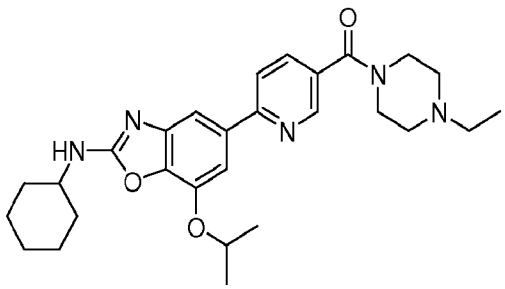
(6-(2-(cyclobutylamino)-7-isopropoxybenzo[d]oxazole-5-yl)pyridine-3-yl)(4-ethylpiperazine-1-yl)methanone

Compound 9



(6-(2-(cyclopentylamino)-7-isopropoxybenzo[d]oxazole-5-yl)pyridine-3-yl)(4-ethylpiperazine-1-yl)methanone

Compound 10



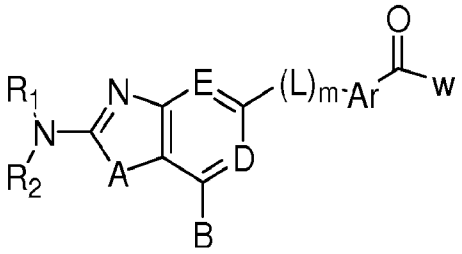
(6-(2-(cyclohexylamino)-7-isopropoxybenzo[d]oxazole-5-yl)pyridine-3-yl)(4-ethylpiperazine-1-yl)methanone

Making the Compounds of the Invention

The compounds of the invention can be synthesized by any suitable method. A representative scheme of the synthetic pathway in the production of the compounds of the invention is shown in FIG. 7, and is described below. Synthetically, a boronic acid or boron pinacolate ester of Formula (XX, RI5=H) or formula (XXX), may be coupled with aryl halide of Formula (X) containing a carbonyl group, to give biaryl (XXIV). Coupling reaction such as that described for the formation of Biaryl (XXIV) may be conducted using boronic esters, such as where RI5 together with the boron form a

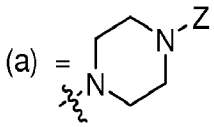
pinacol borate ester (formation of pinacol esters: Ishiyama, et al.,J. *Org. Chem.*, 1995, vol. 60,7508-7510, Ishiyama, et al., *Tetrahedron Letters*, 1997, vol. 38, 3447-3450; coupling pinacol esters: Firooznia, et al., *Tetrahedron Letters*, 1999, vol. 40,213-216, Manickam, et al., *Synthesis*, 2000, vol:__:442-446). Biaryl (XXI) may subsequently be converted into corresponding acid and coupled with cylic amine to give amide (XXII)

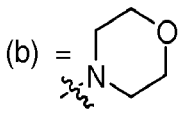
Some embodiments of the invention provide a process for the preparation of a compound of the Formula (XXII):

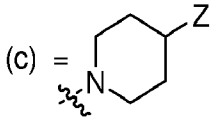


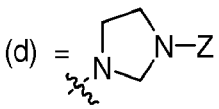
wherein

W is (a),(b),(c),or (d)







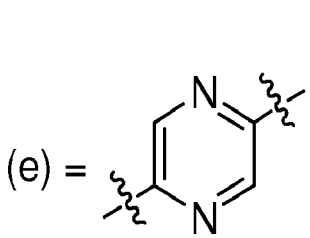


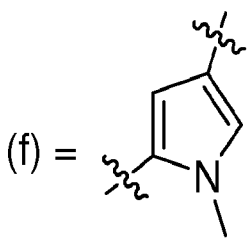
A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S- ;

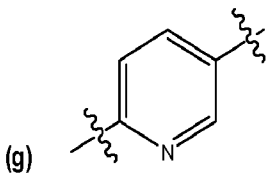
B is $-OR_{24}$,$-SR_{25}$, $-NR_{28}R_{29}$;

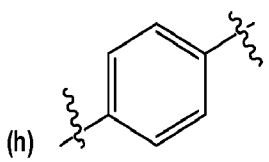
D and E are together or independently $-CR_{30}$-, or –N-;

Ar is formula (e) or (f) or (g) or (h)



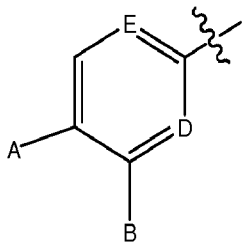




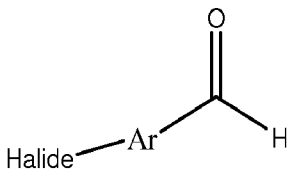


R_1, R_2, R_3, R_{21}, R_{22},R_{23},R_{24},R_{25},R_{26},R_{29} and R_{30} are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide, cycloalkyl (three, four , five and six membered cyclic ring system).

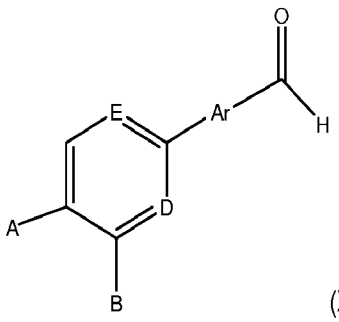
1) **Comprising the steps of:** coupling a first aryl residue with a second aryl residue to give a biaryl carbonyl containing compound; wherein the first aryl residue comprises a substituted or unsubstituted residue having the structure:



and wherein the second aryl residue has a carbonyl group having the structure (X):

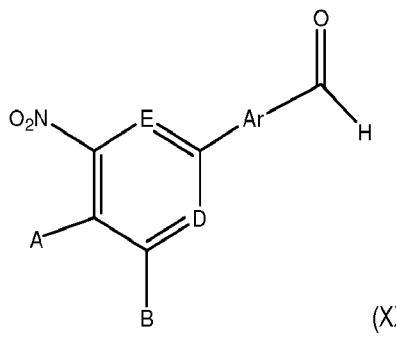


and wherein the biaryl carbonyl containing compound having the structure (XXIV):



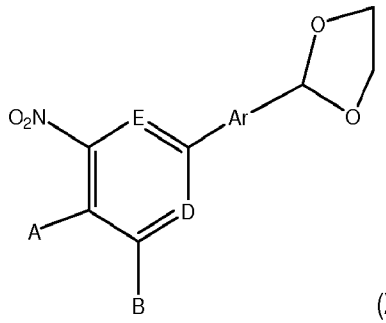
(XXIV)

2) Upon nitration of (XXIV), the condensed product is of the structure (XXV):



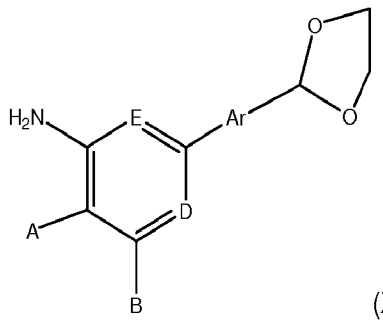
(XXV)

3) Protecting carbonyl group with ethylene glycol, the protected product is of the structure (XXVI):



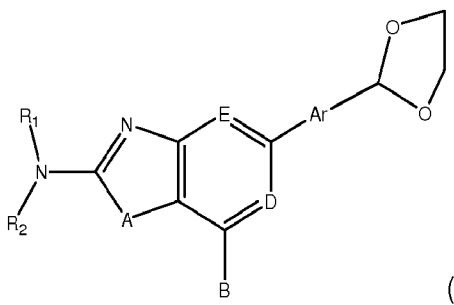
(XXVI)

4) Reducing nitro group to amino group with ammonium formate in the presence of palladium on active carbon to give the structure (XXVII):



(XXVII)

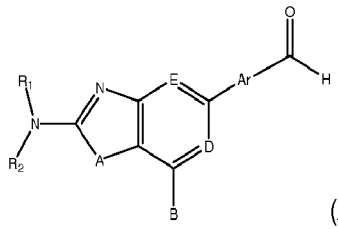
5) Cyclizing with alkylisothiocyanate, the product is of the formula (XXVIII).



(XXVIII)

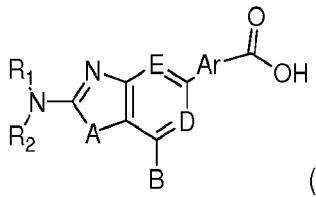
Where R1 is linear alkyl chain or branched alkyl chain or cyclic alkyl group

6 Upon hydrolysis, the product is of the formula (XXI).



(XXI)

7 Oxidizing the biaryl carbony containing compound (XXI) to acid (XXII) by methods



(XXII)

that are known to those of skill in the art, and those methods may be applied in the methods of the present invention.

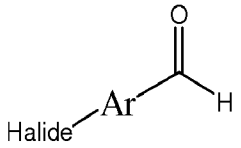
The various organic group transformations utilized herein may be performed by a number of procedures other than those described above. References for other synthetic procedures that may be utilized for the synthetic steps leading to the compounds described herein may be found in, for example, March, J., *Advanced Organic Chemistry, 4th Edition,* Weiley-Interscience (1992); or Larock, R. C., *Comprehensive Organic Transformations, A Guide to Functional Group Preparations,* VCH Publishers, Inc. (1989).

One embodiment of the invention relates to the processes for making compounds of Formula I, which comprises coupling two aromatic rings to give a biaryl wherein one of the aryl rings contains a carbonyl moiety, preferably an aldehyde. The resulting biaryl aldehyde can be converted to biaryl acid and condense with amines in presence of coupling reagents

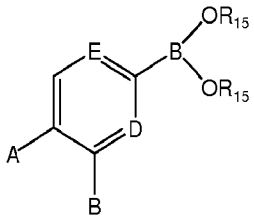
Coupling of two aryl rings may be conducted using an aryl boronic acid or esters with an aryl halide (such as, iodo, bromo, or chloro), triflate or diazonium tetrafluoroborate; as described respectively in Suzuki, *Pure & Applied Chem., 66:213-222 (1994), Miyaura and Suzuki, Chem. Rev. 95:2457-2483 (1995), Watanabe, Miyaura and Suzuki, Syn- lett.* 207-210 (1992), Littke and *Fu,Angew. Chem. Int. Ed., 37:3387-3388 (1998), Indolese, Tetrahedron Letters, 38:3513-3516 (1997), Firooznia, et. al., Tetrahedron Letters 40:213-216 (1999), and Darses, et al., Butt. Soc. Chim. F7: 133: 1095-1102 (1996); all incorporated herein by reference.*

According to this coupling reaction, precursors such as (X), (XX) and (XXX) may be employed:

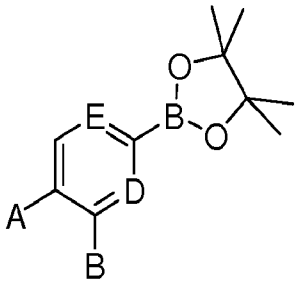
(X)



(XX)

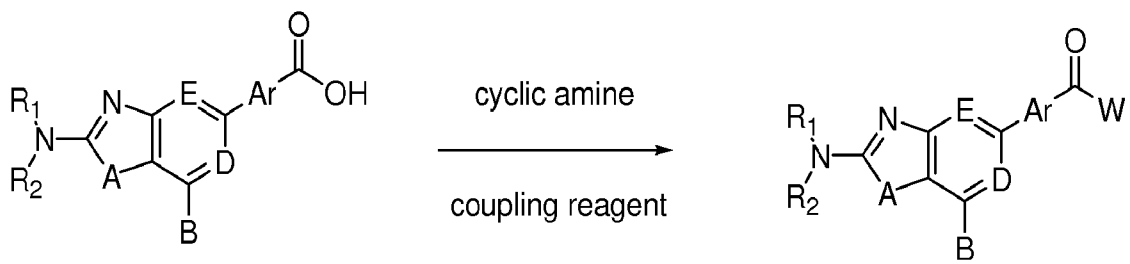


or (XXX)



Where:

(X) is either a triflate, a halide (such as, iodo, bromo, or chloro), or diazonium tet- rafluoroborate or hydrogen and R15 is either alkyl or hydrogen . Alternately, it is understood that the coupling groups may be reversed. The above mentioned precursors may be prepared by methods readily available to those skilled in the art. For example, the boronic ester may be prepared from an aryl halide by conversion into the corresponding aryl lithium, followed by treatment with a trialkyl borate. Preferably, the boronic ester is hydrolyzed to the boronic acid. The coupling reaction may also be conducted between an arylzinc halide and an aryl halide or triflate. Alternately, the coupling reaction may also be executed using an aryl trialkyltin derivative and an aryl halide or triflate. These coupling methods are reviewed by Stanforth, *Tetrahedron* 65 54:263-303 (1998) and incorporated herein by reference. In general, the utilization of a specific coupling procedure is selected with respect to available precursors, chemoselectivity, regioselectivity and steric considerations.



The acid compounds (XXII) can be coupled with cyclic amine in presence of coupling reagents, DCC, HOBT, EDC.HCl or HATU and tertiary amine as the base

The coupling can be carried out using combination of EDC.HCl and HOBT, or HATU. Preferreble HATU, in presence of Diisopropylethyl amine as preferred based.

Using the Compositions

The compounds of the present invention have been found to be potent compounds in a number of biological assays, both *in vitro* and *in vivo*, that correlate to, or are representative of, human diseases. For instance, the compounds that inhibit FLT-3 kinase are cytotoxic to leukemic cells. Compound 1 has a highly specific kinase binding profile when tested against approximately 442 different kinases, including mutated kinases as for instance in the case of FLT3 and KIT (see Table 1), as measured using the Ambit kinase screening platform (Fabian, et al., Nature Biotechnology, 2005, vol. 23:329-336).

Table 1. Kinase binding inhibition profile of 10 μM Compound 1 (from a total of 442 kinases tested).

Ambit Gene Symbol	Entrez Gene Symbol	Percent Control	Ambit Gene Symbol	Entrez Gene Symbol	Percent Control
ABL1(E255K)-phosphorylated	ABL1	15	JAK2(JH1domain-catalytic)	JAK2	33
ABL1(F317L)-phosphorylated	ABL1	17	JAK3(JH1domain-catalytic)	JAK3	35
ABL1(H396P)-nonphosphorylated	ABL1	2	**KIT**	**KIT**	**0**
ABL1(H396P)-phosphorylated	ABL1	24	**KIT(D816H)**	**KIT**	**35**
ABL1(M351T)-phosphorylated	ABL1	20	**KIT(D816V)**	**KIT**	**6**
ABL1(Q252H)-nonphosphorylated	ABL1	3	**KIT(L576P)**	**KIT**	**0**
ABL1(Q252H)-phosphorylated	ABL1	11	**KIT(V559D)**	**KIT**	**0**
ABL1(T315I)-nonphosphorylated	ABL1	14	**KIT(V559D,T670I)**	**KIT**	**0**
ABL1(T315I)-phosphorylated	ABL1	6	**KIT(V559D,V654A)**	**KIT**	**2**
ABL1(Y253F)-phosphorylated	ABL1	24	LCK	LCK	32
ABL1-nonphosphorylated	ABL1	20	LOK	STK10	1
ABL1-phosphorylated	ABL1	25	MAP3K2	MAP3K2	0
ALK	ALK	13	MAP3K3	MAP3K3	1
ARK5	NUAK1	16	MAP4K2	MAP4K2	8
AURKA	AURKA	31	MARK4	MARK4	16
AURKC	AURKC	33	MERTK	MERTK	17
AXL	AXL	2	MKNK2	MKNK2	14
BIKE	BMP2K	16	NEK7	NEK7	14
BLK	BLK	27	PAK1	PAK1	29
CLK1	CLK1	22	**PDGFRA**	**PDGFRA**	**0**
CLK4	CLK4	24	**PDGFRB**	**PDGFRB**	**0**
CSF1R	CSF1R	0	**RET**	**RET**	**0**
DDR1	DDR1	6	**RET(M918T)**	**RET**	**0**
DRAK1	STK17A	22	**RET(V804L)**	**RET**	**0**
FGFR1	FGFR1	25	**RET(V804M)**	**RET**	**0**
FGFR2	FGFR2	27	RIPK5	DSTKY	25
FGFR3	FGFR3	8	RSK2(Kin.Dom.1-N-terminal)	RPS6KA3	35
FGFR3(G697C)	FGFR3	10	SIK	SIK1	35
FGR	FGR	32	SIK2	SIK2	32
FLT1	FLT1	0	SLK	SLK	2
FLT3	**FLT3**	**0**	SRC	SRC	23
FLT3(D835H)	**FLT3**	**1**	STK16	STK16	28
FLT3(D835Y)	**FLT3**	**0**	STK33	STK33	18
FLT3(ITD)	**FLT3**	**0**	TAK1	MAP3K7	7
FLT3(K663Q)	**FLT3**	**0**	TRKA	NTRK1	2
FLT3(N841I)	**FLT3**	**0**	TRKB	NTRK2	3
FLT3(R834Q)	**FLT3**	**34**	TRKC	NTRK3	3
FLT4	FLT4	1	TXK	TXK	7
GAK	GAK	3	VEGFR2	KDR	2
GCN2(Kin.Dom.2,S808G)	EIF2AK4	18	YSK4	YSK4	4

Only nine (9) of all the 386 non-mutant kinases kinases were inhibited by 99% or more (0.023 selectivity score S-1) and 24 kinases were inhibited by more than 90% (selectivity score 0.062 S-10) (see Table 2).

Table 2. Kinase Selectivity of Compound 1 (10 μM, 386 total non-mutated kinases).

Selectivity Score Type	Number of Hits	Selectivity Score
S(35)	50	0.13
S(10)	24	0.062
S(1)	9	0.023

Table 3, below, depicts the binding constants (Kd) for Compound 1 with the most relevant kinases. Of note is a Kd value of 28 nM observed with FLT-3 ITD mutant that is most frequently found in AML patients.

Table 3. Binding constants for Compound 1 and relevant kinases.

Ambit Gene Symbol	Kd (nM)
FLT3(ITD)	28
KIT(V559D,T670I)	58
PDGFRB	64
RET(M918T)	100
CSF1R	120
MAP3K2	160

These test results show that structures described here can inhibit a number of relevant protein kinases, while at the same time being highly selective.

The selective biological response of inhibition of FLT-3 was tested in a cell proliferation assay with MV4-11 cells. These human AML cells, which express FLT-3 ITD mutant, were aliquoted into 96-well plates each with different concentrations of Compound 1, 2, or 3. Cell proliferation assays using 3-4,5-dimethylthiazol-2,5-diphenyltetrazoilum (MTT) were conducted to measure inhibition of cell proliferation and cell killing of the human AML cell line MV4-11. Compounds 1, 2, and 3, dramatically inhibited cellular proliferation (cell growth below 100%) at low concentrations and killed (growth percentage shown as negative values) MV4-11 cells at concentrations of 1 μM or higher (Figure 1). The specificity of cell killing was demonstrated in Figure 2 wherein compound 1 specifically killed leukemic cells bearing FLT-3 mutant ITD (MV4-11 cells), but not cells with wild type FLT-3 (such as HL-60 or HEL 92.1.7 cells) and in Table 4, below,

were compounds 1, 2, and 3 were tested against a panel of 60 cell lines from a variety of cancer types (NCI-60 screen) (Shoemaker, R.H., Nat Rev. Cancer, 2006, vol. 6:813-823).

Table 4. Effect of Compounds 1, 2, and 3 on cell growth of a cancer cell panel (NCI 60 panel) after 48 h of treatment with 10 μM.

	Compound 1	Compound 2	Compound 3
Leukemia			
CCRF-CEM	108.54	94.69	101.47
HL-60	73.43	63.42	87.79
K-562	61.98	72.39	88.85
MOLT-4	81.61	82.54	94.93
RPMI-8226	n.t.	96.57	112.33
SR	74.75	74.49	88.27
Non-Small Cell Lung Cancer			
A549	87.10	82.75	90.43
EKVX	83.06	83.62	224.05
HOP-62	70.80	66.01	85.14
NCI-H226	64.34	65.63	83.78
NCI-H23	80.29	75.32	85.52
NCI-H322M	53.99	**46.27**	73.79
NCI-H460	68.53	72.89	93.33
NCI-H522	59.55	53.90	65.81
Colon Cancer			
COLO 205	77.41	79.35	101.59
HCC-2998	87.24	93.22	96.57
HCT-116	67.15	62.28	81.85
HCT-15	56.49	65.01	80.28
HT29	75.56	79.35	91.70
KM12	**25.37**	**26.51**	**29.47**
SW-620	71.76	63.63	85.00
CNS Cancer			
SF-268	84.41	87.74	91.56
SF-295	89.37	138.01	n.t.
SF-539	60.85	67.47	78.70
SNB-19	82.55	86.93	91.61
SNB-75	78.87	73.41	94.46
U251	68.41	73.57	72.34
Prostate Cancer			
PC-3	69.84	70.15	86.97
DU-145	75.44	80.45	94.46
Melanoma			
LOX IMVI	56.62	53.58	67.81
MALME-3M	77.88	72.69	95.59
MDA-MB-435	78.89	72.25	104.05
SK-MEL-2	**39.87**	**25.60**	**50.37**
SK-MEL-28	102.97	100.62	107.87
SK-MEL-5	69.28	66.15	93.24
UACC-257	126.08	71.48	77.29
UACC-62	75.32	73.21	81.91
Ovarian Cancer			
IGROV1	**32.32**	**23.54**	80.05
OVCAR-3	90.12	91.14	104.04
OVCAR-5	69.78	68.69	92.44
OVCAR-8	86.38	85.56	100.59
NCI/ADR-RES	85.29	86.52	88.93
SK-OV-3	52.98	58.44	93.85
Renal Cancer			
786-0	90.37	89.89	99.36
A498	**38.80**	**43.09**	65.05
ACHN	**48.03**	**47.00**	65.23
CAKI-1	**-3.30**	**-6.44**	n.t.
RXF 393	66.91	63.62	86.35
SN12C	66.91	70.66	84.27
TK-10	60.39	58.19	71.16
UO-31	**38.95**	**32.80**	**49.26**
Breast Cancer			
MCF7	79.84	63.51	85.58
MDA-MB-231	84.38	88.67	109.72
HS 578T	61.06	63.88	79.37
BT-549	83.56	78.69	89.21
T-47D	89.18	85.44	99.41
MDA-MB-468	96.27	93.49	108.67
Mean	**71.14**	**70.17**	**88.25**
Delta	74.44	76.61	58.78
Range	129.38	144.45	194.58

Table 4 illustrates that compounds 1, 2, and 3 do not inhibit the growth of any leukemia cells containing wild type FLT-3 and only a few cancer cell lines were dramatically affected by a high concentration (10 μM) of the compounds. Thus, only Caki-1 renal cancer cells and KM-12 colon carcinoma cells were most significantly growth inhibited by

compounds 1, 2, and 3. These compounds inhibited MV4-11 cells with IC_{50} values between 0.2 and 0.45 μM, whereas KM-12 cells were inhibited with IC_{50} values between 1.1 and 1.5 μM (see Table 5, below).

Table 5. IC_{50} values (in μM) for Compounds 1, 2, and 3 against MV4-11 (AML) and KM-12 (colon carcinoma) cell lines obtained after 48 h of treatment.

	MV4-11	KM-12
Compound 1	0.202	1.116
Compound 2	0.301	1.375
Compound 3	0.456	1.515

Taken together these data suggest that Compound 1 is a selective FLT-3 inhibitor with potent cell killing effects on FLT-3 ITD mutant MV4-11 cells.

To measure bioavailability, a single oral dose of 5 mg/Kg of Compound 1 was given to 3 rats. Blood samples were removed at various time points for analysis of drug levels. The single oral dose of compound 1 produced plasma drug concentration of about 1 μM within 1 hour and reached a maximal concentration (C_{max}) of 1.4 μM within 2 hours and an overall peak that extended for 8 hours (see Figure 3). The maintenance of high plasma drug levels for several hours and good bioavailability suggest that compound 1 could be administered orally twice a day for a more effective dosing.

A subcutaneous tumor xenograft model was used to assess the effects of Compound 1 *in vivo*. Athymic nude mice injected with cells expressing constitutively activated FLT-3 (FLT-3 ITD) is a proven model of leukemia (O'Farrell, et al., Blood, 2003, vol. 101: 3597-3605). These mice typically sicken and die within a few weeks following subcutaneous injection of MV4-11 cells, with large spleens full of leukemic cells. MV4-11, a human leukemia cell line that expresses a FLT-3-ITD mutation were harvested during exponential growth and were resuspended in matrigel (BD Biosciences, Bedford, MA). Athymic nude mice were injected with 5 x 10^6 MV4-11 cells near the hind flank on day 0. The therapeutic effects of daily oral administration of Compound 1 were evaluated in this animal model. Two weeks after tumor initiation, and when tumors were established in the animals with an average size of 125 mm^3, animals were separated in two groups with 10 animals per group. One group of mice was treated with 10 mg/kg of Compound 1 administered orally once a day and a second group was treated with vehicle (placebo). Tumor volumes were measured twice/week using vernier caliper for the duration of treatment and volumes were calculated as ellipsoid volumes (Tomayko and Reynolds, Cancer Chemother Pharmacol,, 1989, vol. 24(3):148-154). Figure 4 demonstrates that Compound 1 significantly inhibited tumor growth in this model. Because the pharmacokinetic profile observed in Figure 3 demonstrates that compound 1 is cleared from the system soon after 8 h, we increased the dosing schedule of compound 1 to twice daily after day 21 (as indicated with an arrow in Figure 4). Figure 5 shows that body weight was not significantly affected by compound 1. Overall, a dramatic effect of tumor growth inhibition was observed with Compound 1, with no overt signs of toxicity.

At the end of the experiment, when tumors in control, vehicle treated, animals reached a size larger than 1500 mm^3, tumors were excised and weighed. Figure 6 shows that tumors in the group that received compound 1 where significantly smaller than those isolated from control animals and the average tumor weight of the compound 1-treated group was

~40% of that of the control vehicle-treated group.

A preferred embodiment of the invention relates to the use of the compounds disclosed herein. The compounds disclosed herein may be either used singularly or plurally, and pharmaceutical compositions thereof for the treatment of mammalian diseases, particularly those related to humans. Compounds disclosed herein and compositions thereof may be administered by various methods including, for example, orally, enterally, parentally, topically, nasally, vaginally, ophthalinically, sublingually or by inhalation for the treatment of leukemic and other cancers including AML and certain solid tumors. Routes of administration and dosages known in the art may be found in comprehensive medicinal chemistry, volume S, Hanscb, C. Pergamon Press, 1990 [Magnus, this citation needs to be completed]. The compositions may also be used as regulator in diseases of uncontrolled proliferation. A representative but non-limiting list of cancers is myeloid leukemia, GISTs, medullar thyroid cancer, renal cancer, lymphoma, Hodgkin's disease, bladder cancer, brain cancer, head and neck cancer, kidney cancer, lung cancers such as small cell lung cancer and non-small cell lung cancer, myeloma, neuroblastoma glioblastoma, ovarian cancer, pancreatic cancer, prostate cancer, skin cancer, liver cancer, melanoma, colon cancer, cervical carcinoma, breast cancer, and skin cancer. Although the compounds described herein may be administered as pure chemicals, it is preferable to present the active ingredient as a pharmaceutical composition. Thus, another embodiment of is the use of a pharmaceutical composition comprising one or more compounds and/or a pharmaceutically acceptable salt thereof, together without more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the composition and not overly deleterious to the recipient thereof.

Pharmaceutical compositions include those suitable for oral, enteral, parental (including intramuscular, subcutaneous and intravenous), topical, nasal, vaginal, ophthalinical, sublingually or by inhalation administration. The compositions may, where appropriate, be conveniently presented in discrete unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with liquid carriers, solid matrices, semi- solid carrier, finely divided solid carrier or combination thereof, and then, if necessary, shaping the product into the desired delivery system. Pharmaceutical compositions suitable for oral administration may be presented in a discrete unit dosage form; such as hard or soft gelatin capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or as granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art, e.g., with enteric coatings.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solution, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or one or more preservative.

The compounds may also be formulated for parenteral administration (e.g., by injection, for example, bolus injection or continuous infusion) and may be presented in unit dose form in ampules, pre-filled syringes, small bolus infusion containers or in multi-does containers with an added preservative. The composition may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g., sterile, pyrogen-free water, before use. For topical administration to the epidermis, the com- pounds may be formulated as ointments, creams or lotion, or as the active ingredient of a transdermal patch. Suitable transdermal delivery systems are disclosed, for example, in Fisher, et al. (U.S. Pat. No. 4,788,603) or Bawas, et al. (U.S. Pat. Nos. 4,931,279, 4,668, 504 and 4,713,224). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition or suitable thickening and/or gelling agents. Lotion may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. The active ingredient may also be delivered via iontophoresis, e.g., as disclosed in U.S. Pat. Nos. 4,140,122, 4383,529, or 4,051,842. Compositions suitable for topical administration in the mouth include unit dosage forms such as lozenges comprising active ingredient in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; mucoadherent gels, and mouthwashes comprising the active ingredient in a suitable liquid carrier. When desired, the above-described compositions may be adapted to provide sustained release of the active ingredient employed, e.g., by combination thereof with certain hydrophilic polymer matrices, e.g., comprising natural gels, synthetic polymer gels or mixtures thereof. The pharmaceutical compositions according to the invention may also contain other adjuvants such as flavorings, coloring, antimicrobial agents, or preservatives. It will be further appreciated that the amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician. In general, one of skill in the art understands how to extrapolate in vivo data obtained in a model organism, such as an athymic nude mouse, to another mammal, such as a human. These extrapolations are not simply based on the weights of the two organisms, but rather incorporate differences in metabolism, differences in pharmacological delivery, and administrative routes. Based on these types of considerations, a suitable dose will, in alternative embodiments, typically be in the range of from about 0.5 to about 100 mg/kg/day, from about 1 to about 75 mg/kg of body weight per day, from about 3 to about 50 mg per kilogram body weight of the recipient per day, or in the range of 6 to 90 mg/kg/day. The compound is conveniently administered in unit dosage form; for example, in alternative embodiments, containing 0.5 to 5000 mg, 5 to 750 mg, most conveniently, or 10 to 500 mg of *active ingredient per unit dosage form.*

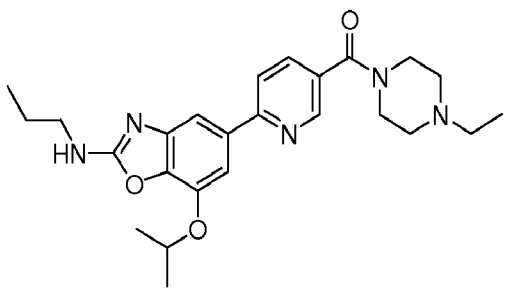
One skilled in the art will recognize that dosage and dosage forms outside these typical ranges can be tested and, where appropriate, be used in the methods of this invention. In separate embodiments, the active ingredient may be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μM, about: 1 to 50 μM, or about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 0.5-500 mg of the

active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredients. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye. While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

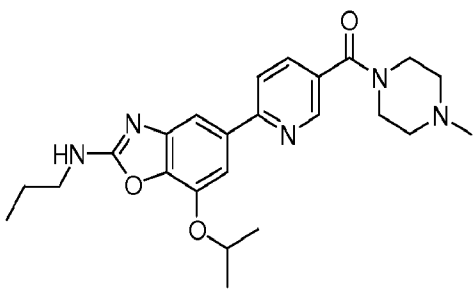
EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Compound 1



Compound 2



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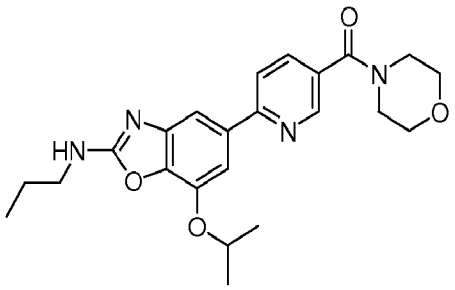
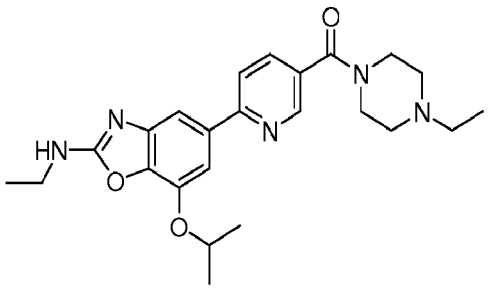
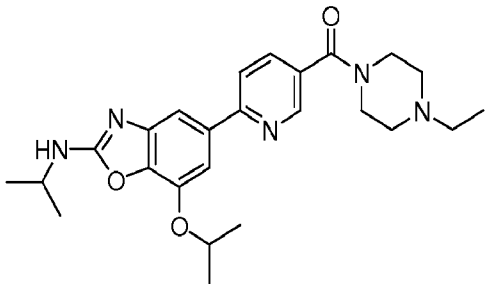


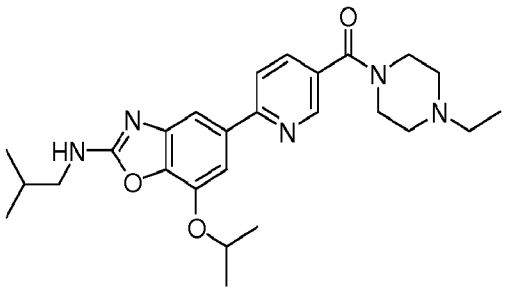
Compound 4



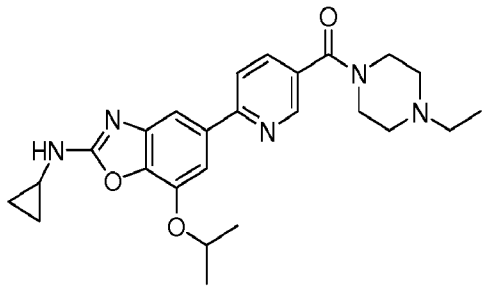
Compound 5



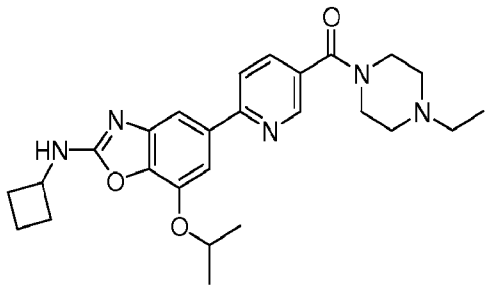
Compound 6



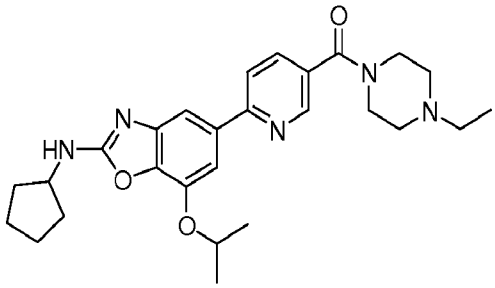
Compound 7



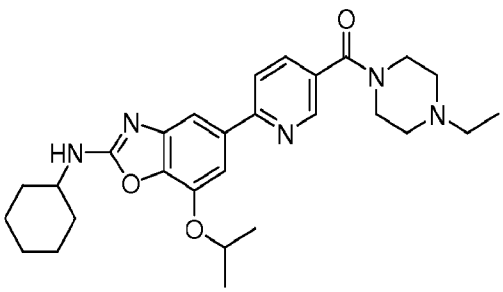
Compound 8



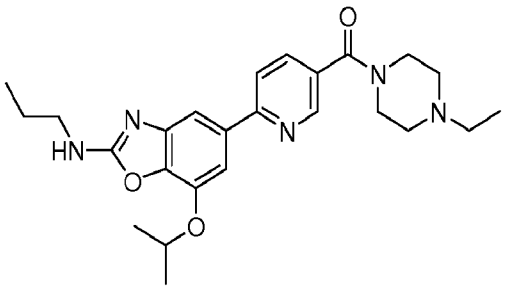
Compound 9



Compound 10

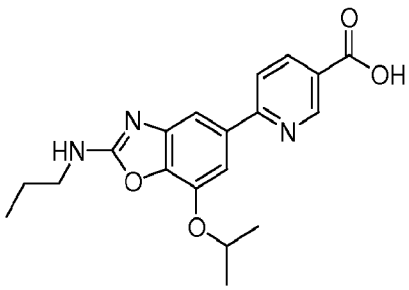


Synthesis of compound 1



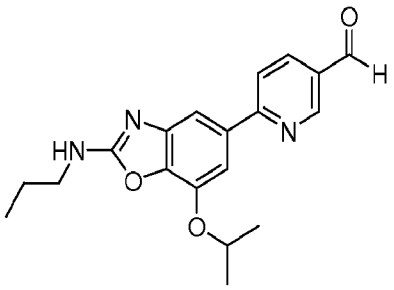
(1-ethylpiperzine-4-yl)(6-(7-isopropoxy-2-(propylamino)benzo[d]oxazole-5-yl)pyridine-3-yl)methanone (1)

To stirred solution of 6-(7-isopropoxy-2-propylamino-benzooxazole-5-yl)-nicotinic acid (1 g, 0.0028 moles) in acetonitrile (20 ml) was added diisopropylethylamine (1 g, 0.0084 moles). To this mixture was also added HATU (1.3 g, 0.003 moles) and N-ethylpiperzine (0.0084 moles), the resulting mixture was stirred at room temperature for overnight. Acetonitrile was evaporated and the resulting crude was diluted with MDC (50 ml). Washed MDC layer with sat sodium bicarbonate (25 ml x 2), followed by water wash and dried over anhydrous sodium sulfate. Solvent was evaporated to get crude compound, which was column purified using methanol chloroform mixture to get 400 mg (50%, white solid); purity by HPLC 97.67%; mp>230 oC (uncorrected); **1H NMR (300 MHz,CDCl3):** δ 8.70 (s, 1H), 7.74-7.83(m, 2H), 7.52(d 2H), 4.97-5.01(m, 1H), 4.84-4.92(m, 1H) 3.74-3.93 (brs, 4H) 3.44-3.51(q, 2H), 2.55-2.80(brs, 4H), 1.68-1.76 (m, 2H), 1.43 (d, 6H), 1.23-1.25(m, 3H), 0.99-1.04(t, 3H)



The intermediate 6-(7-isopropoxy-2-propylamino-benzooxazole-5-yl)-nicotinic acid was prepared as follows

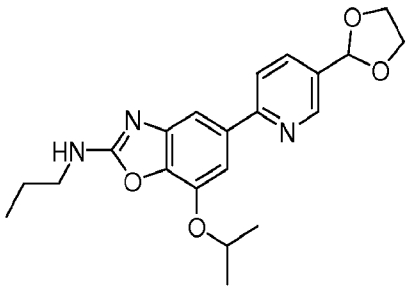
To a stirred solution of 6-(7-isopropoxy-2-propylamino-benzooxazole-5-yl)-pyridine-3-carbaldehyde (1 g, 0.0029 moles) in t-butanol (80 ml) was added 2-methyl-2-butene and the mixture was stirred at room temperature for 10 minutes. Subsequently, added mixture of sodium chlorite (3.67 g, 0.0406 moles) and sodium dihydrogen phosphate (4.75 g, 0.0304 moles) in water (30 ml) over a period of 30 minutes. This mixture was stirred at room temperature for 30 minutes. The reaction mass was diluted with water and extracted with 10% MeOH/CHCl3 mixture (200 mlX2). Organic layer was filtered through celite pad and washed with sat sodium hydrogen carbonate (200 mlX3). The basic aq layer was neutralized with dil HCl (100 ml) at 10•C and extracted with 10% MeOH/CHCl3 mixture (100 ml X 3). The combined organic layer was washed with water (50 ml) and dried over anhydrous sodium sulfate, followed by concentrated to get required compound 1.1 g (95%, Solid); LCMS: 356(m+1) ;**1H NMR (400 MHz $CDCl_3$):** δ 9.10 (s, 1H), 8.25(dd, 1H), 7.65-7.80(m, 2H), 7.55 (s, 1H), 7.50 (s, 1H), 4.70-4.85 (m, 1H), 3.35 (m, 2H) 1.50-1.70 (m, 2H), 1.30(d, 6H), 0.8-0.95 (t, 3H).



The intermediate 6-(7-isopropoxy-2-propylamino-benzooxazole-5-yl)-pyridine-3-carbaldehyde was prepared as follows

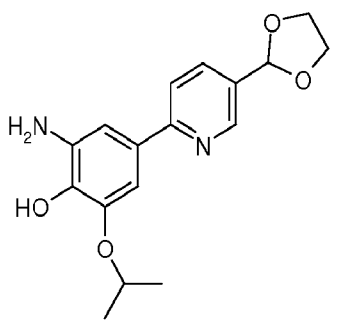
The solution of [5-(5-[1,3]dioxolan-2-yl)-7-isopropoxy-benzooxazol-2-yl]-propyl-amine (1.5 g ,0.0039 moles) in 0.5 N HCl (25 ml) was stirred at room temperature for 16 h. Reaction mixture was diluted with water (30 ml) and extracted with Ethyl acetate (50 ml X 2). Aqueous layer pH was adjusted to 8 using sodium bicarbonate (20 ml) and extracted with 5% methanol MDC mixture (30 ml X 3). Combined organic layer was washed with water, followed by brine. Dried over anhydrous sodium sulfate and filtered. Upon evaporation of solvent obtained; 1.1 g (85%, solid) of required compound:

LCMS: 340(m+1); **1H NMR (400 MHz $CDCl_3$):** δ 10.25(s, 1H), 9.20 (s, 1H), 8.20-8.30 (2dd, 2H), 8.10 (t, 1H), 7.68 (s, 1H) 7.58(s, 1H) δ 4.80 (m, 1H), 3.25-3.45 (m, 2H), 1.55-1.60 (m, 2H), 1.45 (d, 6H), 1.08 (t, 3H)



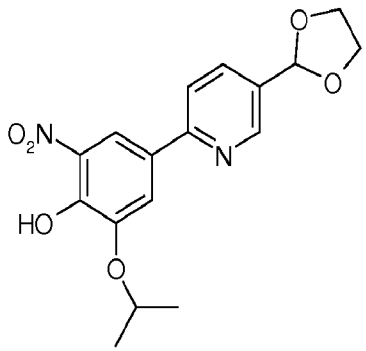
The intermediate [5-(5-[1,3]dioxolan-2-yl)-7-isopropoxy-benzooxazol-2-yl]-propyl-amine was prepared as follows:

To a stirred solution of 2-amino-4-(5-[1,3]dioxolan-2-yl)-6-isopropoxy-phenol (2 g, 0.0069 moles) in Ethanol (30 ml) was added the propyl isothiocyanate (1 g, 0.010 moles) and the mixture was refluxed for 65 h. Solvent was evaporated and the crude material was triturated with MTBE followed by filteration to get the required compound:1.5 g (62%, solid); LCMS: 384(m+1).



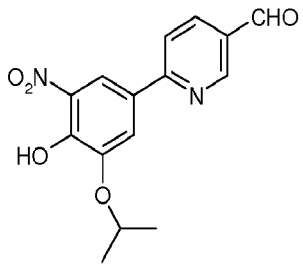
The intermediate 2-amino-4- (5-[1,3] dioxolan-2-yl-pyridin-2-yl)-6-isopropoxy-phenol was prepared as follows:

To a mixture of 4-(5-[1,3] dioxolan-2-yl-pyridin-2-yl)-2-isopropoxy-6-nitro-phenol (1.596g, 4.96 mmol), in anhydrous ethanol (80 ml) was added ammonium formate (1.45g, 23.0 mmol), followed by palladium, 10% wt on activated carbon (0.23g). The resulting mixture was then stirred and brought to reflux under argon for 1.25 hours. The completed reaction mixture cooled to 23°C and filtered through celite. The filtrate was concentrated under reduced pressure and diluted with with ethyl acetate (150 ml), and H_2O (50 ml). The aqueous phase was separated and extracted with ethyl acetate (3x15 ml). Organic phases combined and washed with H_2O (50 ml), brine (50 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel (eluent: ethyl acetate/ hexane, 3:2) to give 1.273g of 2-Amino-4- (5-[1,3] dioxolan-2-yl-pyridin-2-yl)-6-isopropoxy-phenol (87% yield). ^{1}H NMR (500MHz; DMSO-d_6): 1.29(d, J= 5.97 Hz, 6H); 3.97(m,2H); 4.08(m, 2H); 4.57(m, 1H); 4.68 (br s, 2H); 5.81(s, 1H); 7.01(d, J= 2.05 Hz, 1H); 7.09(d, J1= 2.12 Hz, 1H); 7.78(m, 2H); 8.58 (d, J= 1.77 Hz, 1H).



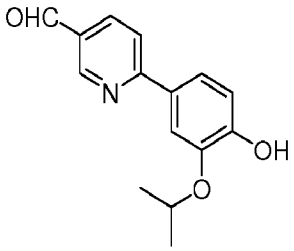
The intermediate 4-(5-[1,3] Dioxolan-2-yl-pyridin-2-yl)-2-isopropoxy-6-nitro-phenol was prepared as follows:

To a mixture of 6-(4-Hydroxy-3-isopropoxy-5-nitro-phenyl)-pyridine-3-carbaldehyde (1.507g, 4.99 mmol), in anhydrous toluene (30 ml) was added ethylene glycol (5.6 ml, 99.7 mmol), followed by P-toluenesulfonic acid monohydrate (57 mg, 0.3 mmol). The resulting mixture was then stirred and brought to reflux using a dean-stark trap under argon for 5 hours. The completed reaction mixture cooled to 23°C and brought to pH~7 with a solution of 10% K_2CO_3 then diluted with ethyl acetate (30 ml), and H_2O (20 ml). The aqueous phase was separated and extracted with ethyl acetate (3 x 15 ml). Organic phases combined and washed with H_2O (30 ml), brine (30 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel (eluent: ethyl acetate/ hexane, 3:7) to give 1.596g of 4-(5-[1,3] dioxolan-2-yl-pyridin-2-yl)-2-isopropoxy-6-nitro-phenol (92% yield). ^{1}H NMR (500MHz; DMSO-d_6): 1.46 (d, J= 6.22 Hz, 6H); 4.09(m, 2H); 4.15(m, 2H); 4.78(m, 1H); 5.90(s, 1H); 7.74(d, J= 8.47 Hz, 1H); 7.87(dd, J1= 2.19 Hz, J2=8.21 Hz, 1H); 8.01(d, J1= 2.03 Hz, 1H); 8.30 (d, J= 2.1 Hz, 1H); 8.75(d, J= 2.03 Hz, 1H); 10.76 (br s, 1H).



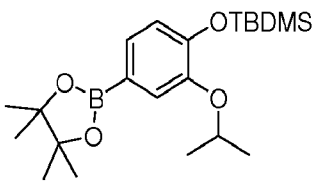
The intermediate 6-(4-Hydroxy-3-isopropoxy-5-nitro-phenyl)-pyridine-3-carbaldehyde was prepared as follows:

To a mixture of 6-(4-Hydroxy-3-isopropoxy-phenyl)-pyridine-3-carbaldehyde (2.864g, 11.13 mmol), in trifluoroacetic acid (30 ml) at 0°C was added potassium nitrate (1.18g, 11.69 mmol). The resulting mixture was then stirred at 0°C under argon for 45 minutes. The completed reaction mixture was poured into ice and allowed to stir for 3 hrs. The solution was extracted with ethyl acetate (30 ml). Aqueous was neutralized to pH ~ 7 with solid sodium bicarbonate and extracted from ethyl acetate again (30 ml). Organic phases combined and washed with H_2O (30 ml), brine (30 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel (eluent: ethyl acetate/ hexane, 2:3) to give 2.621g 6-(4-Hydroxy-3-isopropoxy-5-nitro-phenyl)-pyridine-3-carbaldehyde (78% yield). ^{1}H NMR (500MHz; DMSO-d_6): 1.47 (d, J= 6.12 Hz, 6H); 4.80(m, 1H); 7.91(d, J= 8.3 Hz, 1H); 8.09(d, J= 2.0 Hz, 1H); 8.25(dd, J1= 2.05 Hz, J2= 8.3 Hz, 1H); 8.40 (d, J= 2.1 Hz, 1H); 9.11(d, J= 1.90 Hz, 1H); 10.08 (s, 1H); 10.86 (s, 1H).



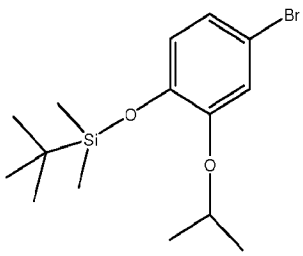
The intermediate 6-(4-hydroxy-3-isopropoxy-phenyl)- pyridine-3-carbaldehyde was prepared as follows:

To a solution of 2-chloro-5-formylpyridine (34 g, 0.241 moles) in ACN (500 ml), was added compound 4 (99 g, 0.253 moles), Palladium acetate (1.35 g, 0.006 moles), Dppf (6 g, 0.010 moles) and potassium carbonate (100 g, 0.723 moles). Additionally, water (140 ml) and ACN (250 ml) were added, followed by refluxed for 4 h under nitrogen. Acetonitrile was evaporated and diluted the crude material with water. Extracted with DCM and combined organic layer was dried over anhydrous sodium sulfate. After concentration, crude material was column purified using ethyl acetate and hexane mixture to get pure compound (55g, 89% yield). **1H NMR (300 MHz $CDCl_3$):** δ 10.05 (s, 1H), 9.00 (s, 1H), 8.05-8.20 (dd, 1H), 7.78-7.85(m, 2H), 7.45-7.65 (dd, 1H),7.00 (dd,1H), 6.85(brs, 1H), 4.65-4.85(m, 1H), 1.40(d,6H).



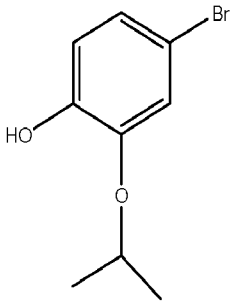
The intermediate 2-[4-tert-butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-4,4,5,5-tetramethyl[1,3,2]dioxaborolane was prepared as follows

To a suspension of bispinacolatodiborane (154 g, 0.608 moles) in toluene (1 L) was added potassium acetate (170 g, 1.73 moles) and [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium (II) (2 g, 4 mol%). This mixture was thoroughly de-evacuated and stirred at room temperature while dry nitrogen was bubbled into the mixture. Compound (4-bromo-2-isopropoxy-phenoxy)-tert-butyl-dimethylsilane (200 g, 0.579 moles) was dissolved in toluene (300 ml) and added to the above mixture. Reaction mixture was refluxed for over night under nitrogen bubbling. Reaction mass was filtered through celite pad and washed thoroughly with ethylacetate, concentrated to get crude material. Pure compound was isolated after column purification, using ethyl acetate and hexane mixture to get 185 g (82%, pale yellow solid) of title compound. **1H NMR (400 MHz $CDCl_3$):** δ 7.20 (m, 2H), 6.80 (d, 1H), 4.55-4.65 (m, 1H), 1.20-1.25(m, 18H), 1.00 (s, 9H), 0.20 (s,6H).



The intermediate (4-Bromo-2-isopropoxy-phenoxy)-tert-butyl-dimethyl-silane was prepared as follows:

Tert-butyl-dimethyl silylchloride (21.4 g, 0.142 mol), 4-N-dimethylamininopyridine (0.461 g, 0.004 mol) and triethylamine (19.8 ml, 0.142 mol) were added to a solution of 4-Bromo-2-isopropoxy-phenol (23.5 g, 0.102 mol) in 160 ml DMF. The resulting mixture was stirred for 17 hrs at room temperature. The reaction mixture was diluted with ethyl acetate (200 ml) and washed with water (150 ml), brine (150 ml) and dried over anhydrous magnesium sulfate. After filtering off magnesium sulfate, the filtrate was evaporated. The residue was chromatographed on silica gel (eluent: hexane) to give 32.3 g of (4-Bromo-2-isopropoxy-phenoxy)-tert-butyl-dimethyl-silane.



The intermediate 4-Bromo-2-isopropoxy-phenol was prepared as follows:

To a suspension of pyridinium tribromide (116g, 0.362 mol) in 250 ml dichloromethane, was added 2-isopropoxyphenol (50 g, 0.329 mol) in 150 ml dichloromethane. The mixture was stirred at room temperature for 6 hrs. The reaction mixture was quenched with aqueous HCl (1N, 200ml). After separation, the organic phase was washed with

saturated sodium thiosulfate (150 ml), and brine (150 ml), and dried over anhydrous magnesium sulfate. After filtering off magnesium sulfate, the filtrate was evaporated to give 71g 4-Bromo-2-isopropoxy-phenol (94% yield).

Example 2: Kinase Binding Profile Assay

As a primary screen, compounds were tested at 10 μM against a panel of 442 kinases. This collection of kinases included the most common FLT-3, cKIT, and RET mutations found in cancer patients. Kinase assays and binding constant measurements were done as described in Fabian *et al* (A small molecule-kinase interaction map for clinical kinase inhibitors. Nature Biotechnology, 2005, 23:329-336). Briefly, the human kinases are tagged with T7 bacteriophage DNA, which is combined with immobilized active-site directed ligand and the free test compounds. The amount of T7-tagged protein bound to the solid support via the immobilized ligand is measured via quantitative PCR of the DNA tag. If the free test compound binds to and occludes the ATP site of the kinase, fewer protein molecules will bind the immobilized ligand on the solid support, resulting in lower PCR product. For each kinase, compounds are scored initially as a 'hit' or 'no hit' in the primary screen. The hits were scored quantitatively and reported as 'percent of control' obtained in the absence of test compound. The results summarized in Table 1 indicate that Compound 1 bound to several kinases with high efficiency, as shown by the reduced binding of tagged-protein to the solid support (of the 442 kinases tested, only those that are inhibited by 65% or more are shown). Compound 1 completely inhibited protein kinases that are most relevant to cancer (wild type and mutants FLT-3, cKIT, PDGFR, and RET with few exceptions) (0% binding) Table 2 illustrates the selectivity score for compound 1. This score represents a quantitative measure of compound selectivity and is calculated taking into account the total number of distinct kinases, not considering mutant forms. For example compound 1 inhibits 24 kinases out of 386 by 90% or more and therefore the S(10) value is 0.062 (or 6.2% of all kinases). Nine (9) kinases are inhibited by 99% or more, which translates into a S(1) of 0.023.

Secondary assays were performed to determine the binding constants (Kd) of Compound 1 for some selected kinases that are highly relevant to cancer. The results in Table 3 indicate that Compound 1 is a potent inhibitor of FLT-3 ITD mutant (Kd 28 nM), cKIT V559D,T670I (Kd 58 nM), and PDGFRB (64 nM). In addition, Compound 1 also bound RET M918T, CSFR1, and MAP3K2 with nanomolar affinities (Kd 100, 120, and 160 respectively). It is important to note here that inhibition of cKIT mutants by Compound 1, including V559D,T670I, is highly relevant for the treatment of Gleevec resistant GIST patients, as T670I mutation confers resistance to the clinical cKIT inhibitor Gleevec (Negri et al, T670X KIT mutations in gastrointestinal stromal tumors: making sense of missesnse; J Natl Cancer Inst, 2009, 101: 194-204). PDGFR mutations have also been found in GISTs (Heinrich et al, PDGRFA activating mutations in gastrointestinal stromal tumors; Science, 2003, 299:708-710), whereas RET activating mutants are found in patients with medullary thyroid carcinoma (Phay and Shah, Targeting RET receptor tyrosine kinase activation in cancer; Clin Cancer Res, 2010, 16:5936-5941).

Example 3: Cellular proliferation inhibition assays

The biological response of FLT-3 inhibition was tested in a cell proliferation assay with the human AML cell line MV4-11. This cell line carries the most frequent human FLT-3 mutation, FLT-3 ITD and does not express wild type FLT-3. The

selectivity of cell killing was tested by comparing the effect of compounds on the MV4-11 cell line with their effects on the proliferation of two other leukemia cells bearing wild type FLT-3 (HL-60 and HEL 92.1.7). Cell proliferation was measured using 3-4,5-dimethylthiazol-2,5- diphenyltetrazoilum (MTT) assay. Briefly, cells were aliquoted into 96 well plates. MV4-11, HL-60, and HEL 92.1.7 cells were grown in RPMI medium containing 4500 mg/L glucose; 4 mM L-glutamine; 10 U/ml Pen-G; 10 mcg/ml and 10% heat-inactivated fetal bovine serum (FBS). Cells were seeded at 40,000 cells/well in 96-well tissue culture plates and maintained at 5% CO_2 and 37°C. Cells were treated with test compounds or vehicle for two days. The percentage of surviving cells and cell proliferation were then measured colorimetrically. The assay is based on the cleavage of the yellow tetrazolium salt MTT to purple formazan crystals by dehydrogenase activity in active mitochondria. Therefore, this conversion only occurs in living cells with intact/functional mitochondria. The formazan crystals formed are solubilized and the resulting colored solution is quantified using a scanning multiwell spectrophotometer at 595 nm. Briefly, 10 µl of 5 mg/ml MTT dye are added to each well and incubated for 4 hours and the reaction was stopped by adding 100 µl/well of solubilization solution, consisting of 10% Sodium Dodecyl Sulfate (SDS) and 10 mM HCl. To determine cell growth, the MTT colorimetric reaction (readings at 595 nm) was also taken at time 0 in a duplicate plate and the difference between 48 h and time 0 was normalized to 100% as percentage control growth. Cell killing by test compounds is thus visualized as negative growth values in such representation.

Compounds 1-3 strongly inhibited cellular growth and killed MV4-11 cells in a dose dependent manner (Figure 1); interestingly, this cell killing was FLT-3 ITD mutant specific, as HL-60 and HEL 92.1.7 cells were not growth inhibited by Compound 1 (Figure 2). The growth inhibitory activity of compounds 1-3 was further investigated against the NCI-60 cancer cell panel. Developed by the Developmental Therapeutics Program (DTP) of the NCI, the NCI60 Human Tumor Cell Line anticancer drug screen has been used to evaluate the growth inhibitory activity of Compounds 1-3 against a panel of 60 cancer cell lines representing nine distinct tumor types, including leukemia, lung, colon, CNS, prostate, breast, ovarian, renal, and melanoma (Shoemaker,R.H. The NCI60 human tumour cell line anticancer drug screen. Nat Rev. Cancer, 2006; *6*, 813-823). In a typical screen, anticancer drugs are initially tested at a single concentration of 10 µM. Cells are incubated with the drug for 48 h, when TCA-fixed cells are stained with sulforhodamine B; following solubilization, the amount of bound dye is then measured by absorbance at a wavelength of 515 nm using a microplate reader. For each cell line and drug concentration, the absorbances at times zero and 48 h and that of control cells without drug are used to calculate the growth percent. The results shown in Table 4 demonstrate that compounds 1, 2, and 3 have no broad anticancer activity, with mean growth percents of 71, 70, and 88, respectively. None of the leukemia cell lines in the NCI60 panel was significantly affected by compounds 1-3, as anticipated due to the presence of wild type FLT-3. In contrast, Compounds 1 and 2 efficiently killed Caki-1 renal cancer cells, whereas the growth of other renal cancer cells (UO-31, A498, and ACHN), colon (KM-12), ovarian (IGROV-1), and melanoma cancers (SK-MEL-2) was significantly inhibited by those compounds. Detailed titration studies were performed with compounds 1-3 on MV4-11 and KM-12 cells. Table 5 illustrates that all three compounds exhibited IC_{50} values in the sub-micromolar range for MV4-11 cells or in the low micromolar with KM-12.

Example 4: Pharmacokinetic measurements

To measure bioavailability, a single oral dose of 5 mg/Kg of compound 1 was given to 3 Sprague Dawley rats. Blood samples were removed at various time points (0.5, 1, 1.5, 2, 4, 6, 8, and 24 hours) for analysis of drug levels in plasma. Figure 3 demonstrates that Compound 1 showed good bioavailability. The single dose of 5 mg/Kg of Compound 1 administration produced plasma drug concentration above 1 μM within 1.5 hours and reached a maximal concentration (C_{max}) of 627 ± 106 ng/L (1.39 ± 0.24 μM) at 2 h, with an overall peak that extended over 6 hours. The half time of compound 1 was 2.02 h and the mean residence time [MRT(0-∞)] was 4.23 h. The maximum accumulated amount [AUC(0-∞)] of compound 1 was 3245 ± 360 ng/L*h (7.19 ± 0.8 μM). Compound 1 was below detection limits at the 24 h time point. The maintenance of high plasma drug levels for several hours and good oral bioavailability suggest that compound 1 could be administered orally once a day, although a twice daily dosing could also be more beneficial.

Example 5: Oral administration of compound 1 in the treatment of AML tumors in an animal model

A subcutaneous tumor xenograft model was used to assess the anticancer activity of compound 1 *in vivo*. Athymic nude mice injected subcutaneously with MV4-11 cells, expressing constitutively activated FLT-3 ITD mutant, served as a model for leukemia [O'Farrell *et al.* SU11248 is a novel FLT-3 tyrosine kinase inhibitor with potent activity *in vitro* and *in vivo*. Blood 101:3597-3605 (2003)]. MV4-11 cells were harvested during exponential growth and were resuspended in Matrigel (BD Biosciences, Bedford, MA). Athymic nude mice were injected with 10 million MV4-11 cells near the hind flank. Around two weeks later, when tumors were measured with a vernier caliper as having an average volume of approximately 125 mm^3, animals were allocated into two separate groups of 10 animals per group. One group received vehicle (control group); the second group received a single oral daily dose of 10 mg/kg compound 1 (treatment group). Tumor volumes were measured twice/week using vernier caliper for the duration of treatment, and volumes were calculated as ellipsoid volumes according to the formula V = (length x $width^2$) / 2 (Tomayko MM and Reynolds CP, Determination of subcutaneous tumor size in athymic nude mice. Cancer Chemother Pharmacol, 1989, 124:148-54). Animals were also weighted every day and observed for clinical symptoms of illness and general reaction to the treatment that could indicate toxicity.

Figure 4 illustrates that Compound 1 significantly inhibited the growth of MV4-11 tumors in nude mice. After 21 days of treatment, and taking into consideration the pharmacokinetic data depicted in figure 3, we increased the dosing schedule of Compound 1 to twice/day administration, with an 8 h separation between doses. This 10 mg/kg twice daily schedule was kept until the end of the experiment at day 38 after grouping and initiation of treatment. Figure 5 demonstrates that Compound 1 had no significant effect on body weight, suggesting the lack of major toxicity. This was corroborated by daily observations of the animals. The experiment was ended and animals were sacrificed when tumor volume reached an average size over 1500 mm^3 and tumor burden in the control untreated group was affecting the quality of life. Tumors were isolated and weighted. Figure 6 illustrates that tumors in the drug treated group were significantly smaller compared to tumors in the vehicle control group. The average weight of tumors in compound 1-treated animals was about 40% that of vehicle-treated group. This experiment demonstrates that compound 1 efficiently inhibits tumor growth in a MV4-11 xenograft model with no overt signs of toxicity. Improved efficacy could be obtained with enhanced

doses of compound 1 and/or additional dosing schedules from the beginning of treatment.

* * *

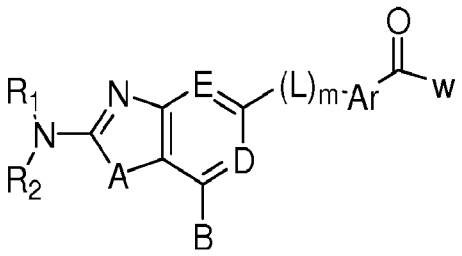
All patents, patent applications, and publications mentioned in the specification are indicative of the levels of those of ordinary skill in the art to which the invention pertains. Each patent, patent application, and publication cited herein is hereby incorporated by reference in its entirety for all purposes regardless of whether it is specifically indicated to be incorporated by reference in the particular citation.

All of the compounds, compositions, and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. Moreover, it is intended to obtain rights which include alternative and/or equivalent embodiments to the extent permitted, including alternate, interchangeable, and/or equivalent structures, functions, ranges, or steps to those claimed, whether or not such alternate, interchangeable and/or equivalent structures, functions, ranges, or steps are disclosed herein, and without intending to publicly dedicate any patentable subject matter, as it is intended that all patentable subject matter disclosed herein eventually be the subject of patent claims.

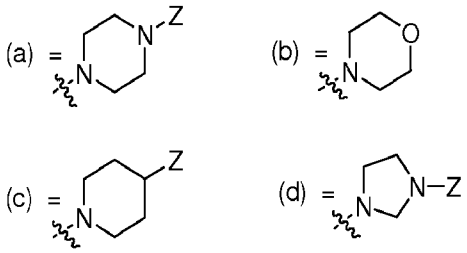
The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Also, the invention illustratively described herein suitably may be practiced in the absence of any element(s) not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of", and "consisting of" may be replaced with either of the other two terms. Furthermore, while the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and methods and in the steps or in the sequence of steps of the method described herein without departing from the spirit and scope of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention as defined by the appended claims.

We claim:

1. A compound of the formula:



whereibn W is (a) or (b) or (c) or (d)



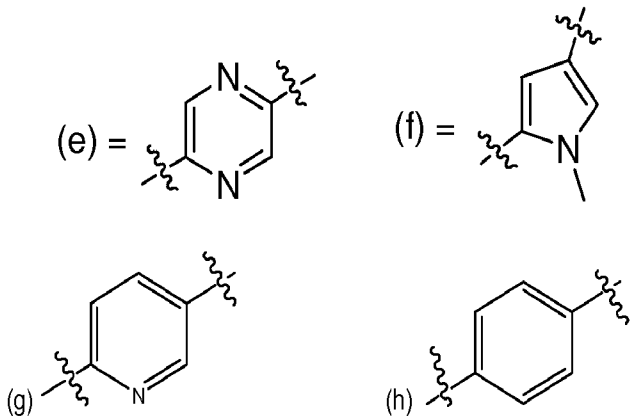
wherein:

A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S-;

B is $-OR_{24}$,$-SR_{25}$, $-NR_{28}R_{29}$;

D and E are together or independently $-CR_{30}$-, or –N-;

wherein Ar is (e) or (f) or (g) or (h)

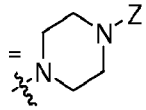


and wherein R_1, R_2, R_3, R_{11}, R_{12}, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{28}, R_{29} and R_{30} are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide;

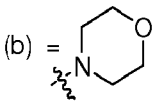
or an isomer, metabolite, polymorph, prodrug, or salt of any such compound.

2. A compound according to claim 1 wherein Rl and R2 are independently or together hydrogen,alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substi- tuted alkoxy, acyl, mono-substituted amino, di-substituted amino, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, substituted dialkylcarboxamide or haloalkoxy.

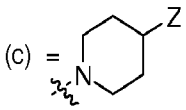
3. A compound according to claim 2 wherein R_l and R_2 are independently hydrogen, alkyl, substituted alkyl, arylalkyl, substituted aryalkyl, a disubstituted amino group or branched alkyl group with 2 to 10 carbon atoms or acycloalkyl, (with ring size of 3-7 carbon atoms)– A compound according to claim 1 wherein W is (a)



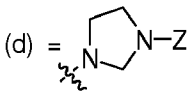
4. A compound according to claim 1 wherein W (b)



5. A compound according to claim 1 wherein W is (c)



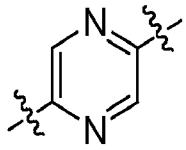
6. A compound according to claim 1 wherein W is (d)

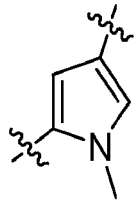


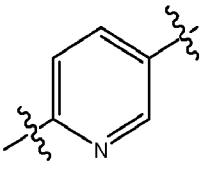
7. The compounds of claim 4, 5, 6, or 7 wherein R11 and R12 are independently or together alky group.selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl,n-butyl, sec-butyl,t-butyl, amyl, t-amyl, and n-pentyl.

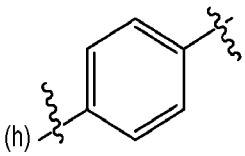
8. A compound according to claim 1 wherein R_1 and R_2 are idependently or together hydrogen or alkyl.

9. A compound according to claim 1 wherein Ar is either Formula (e) or (f) or (g) or (h)

(e) = 

(f) = 

(g) 

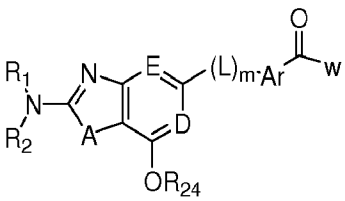
(h) 

10. A compound according to claim 2 wherein R_2 is hydrogen.

11. A compound according to claim 2 wherein R2 is hydrogen and R1 is propyl.

12. A compound according to claim 2 wherein R3 is hydrogen, methyl, or ethyl.

13. A compound of Formula (II):



wherein:

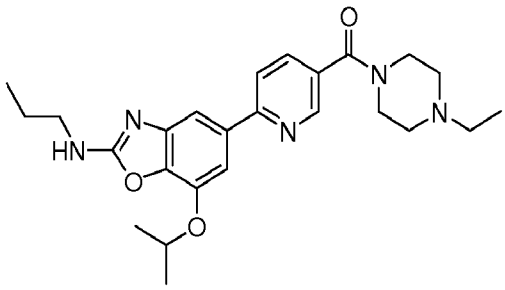
R_1 is hydrogen.

R_2 and R_{24} are independently or together alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide substituted dialkylcarboxamide, or cyclo alkyl with ring size of 3-7 carbon atoms,

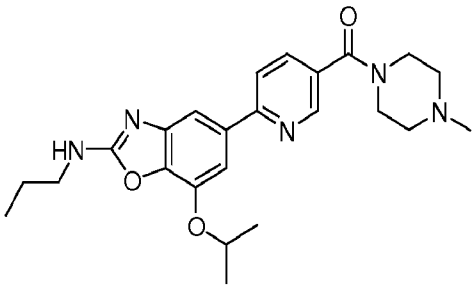
or an isomer, metabolite, polymorph, prodrug, or salt of any such compound.

14. A compound according to claim 1 selected from the group consisting of:

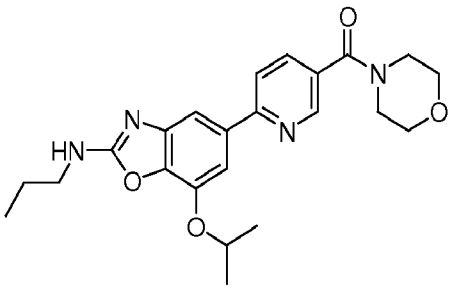
. Compound 1



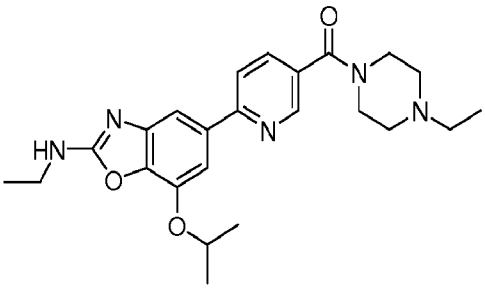
Compound 2



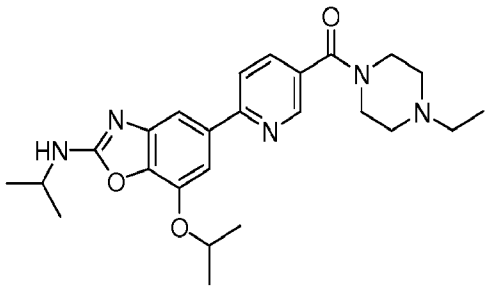
Compound 3



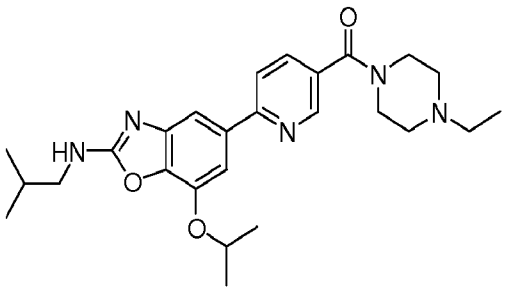
Compound 4



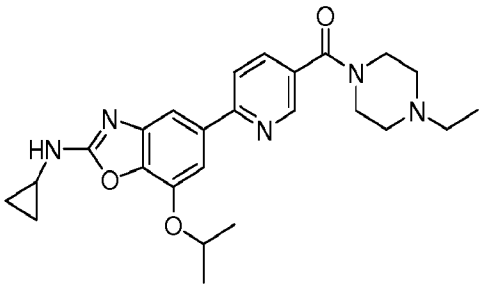
Compound 5



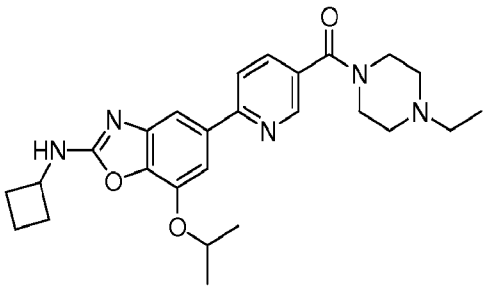
Compound 6



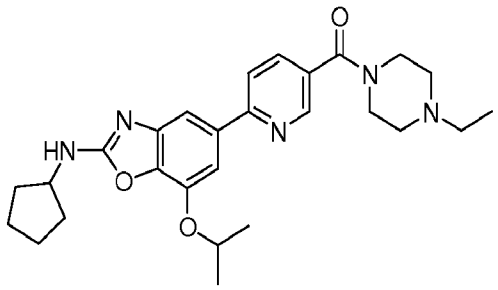
Compound 7



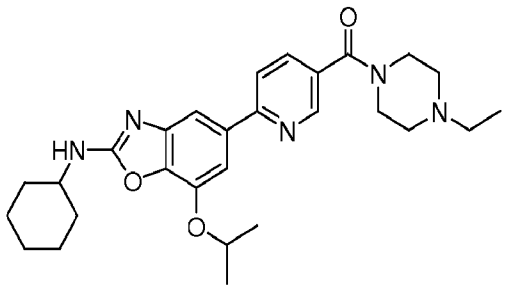
Compound 8



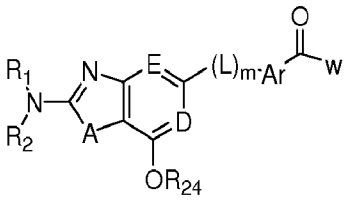
Compound 9



Compound 10

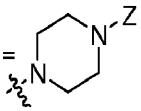
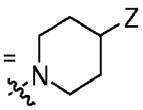
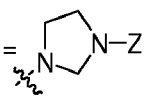


15. A compound of Formula (III)



wherein:

W is (a) or (c) or (d)

(a) =  (c) =  (d) = 

R_1 is hydrogen;

R_2 and R_{24} are independently or together alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide or substituted dialkylcarboxamide; and

R11 and R12 are independently or together alky group selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl,n-butyl, sec-butyl,t-butyl, amyl, t-amyl, and n-pentyl,

or an isomer, metabolite, polymorph, prodrug, or salt of any such compound.

16. A pharmaceutical composition, comprising a compound according to any one of claims 1 through 15 and a pharmaceutically acceptable carrier or excipient.

17. A method for the modulation or inhibition of the catalytic activity of a protein kinase, comprising contacting said protein kinase with a compound or salt of any one of claims 1 through 15.

18. A method according to claim 17, wherein said protein kinase is selected from the group consisting of a receptor tyrosine kinase, a non-receptor tyrosine kinase, and a serine-threonine kinase.

19. A method according to claim 17, wherein said protein kinase related disorder is selected from the group consisting of an EGFR related disorder, a PDGFR related disorder, a cKIT related disorder, a RET related disorder, and a FLT-3 related disorder.

20 . A method according to claim 17, wherein said protein kinase related disorder is a cancer selected from the group consisting of squamous cell carcinoma, astrocytoma, Kaposi's sarcoma, glioblastoma, lung cancer, bladder cancer, head and neck cancer, melanoma, ovarian cancer, prostate cancer, breast cancer, thyroid cancer, kidney cancer, small-cell lung cancer, leukemia, glioma, colorectal cancer, genitourinary cancer, and gastrointestinal cancer.

21. A method according to claim 17, wherein said protein kinase related disorder is selected from the group consisting of diabetes, an autoimmune disorder, a hyperproliferation disorder, restenosis, fibrosis, psoriasis, von Heppel-Lindau disease, osteoarthritis, rheumatoid arthritis, angiogenesis, an inflammatory disorder, an immunological disorder, and a cardiovascular disorder.

22. A method according to claim 17, wherein said organism is a human.

23. A method according to claim 18, wherein said kinase is a mutated form of FLT-3 in a patient with AML and or cKit (KIT) or a mutated form of cKit in a patient with gastro intestinal cancer or other cancer.

Figure 1

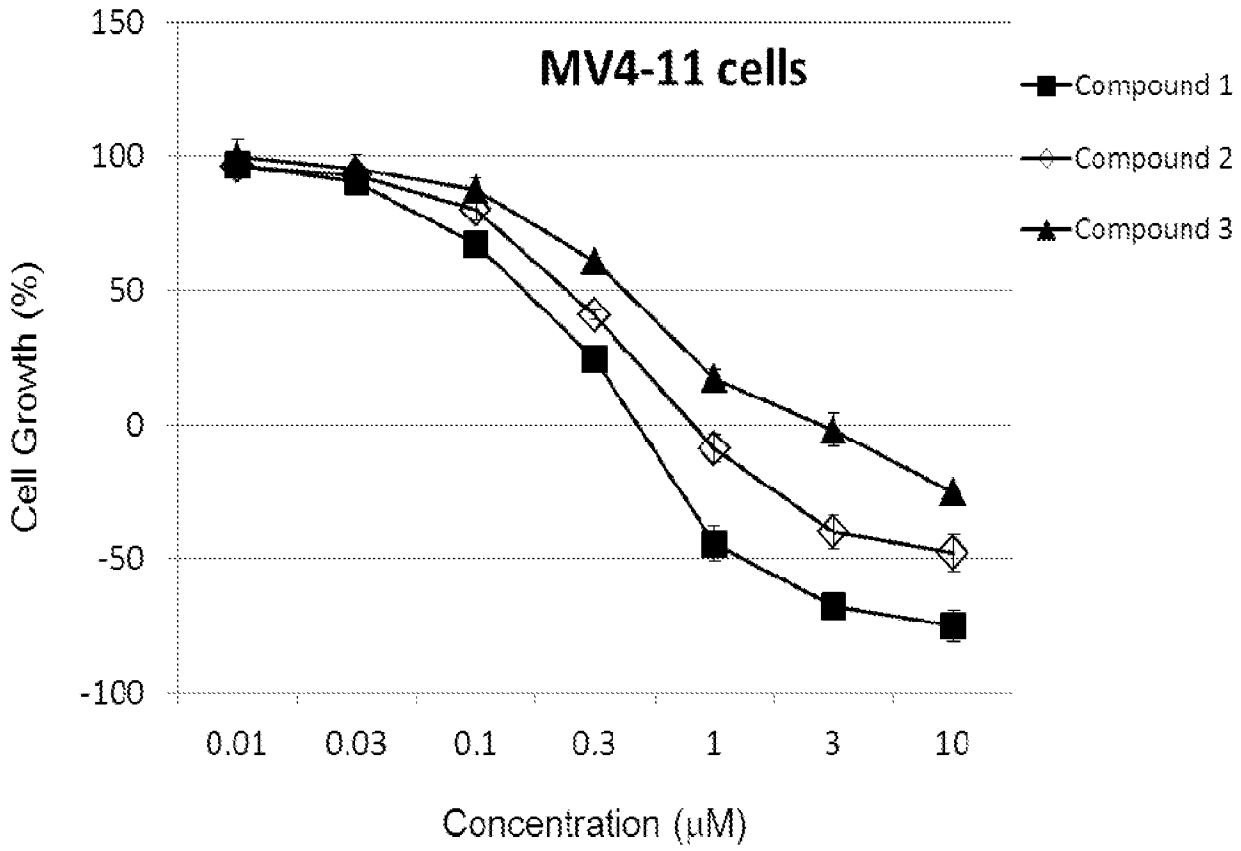

MV4-11 cells
Compound 1
Compound 2
Compound 3
Cell Growth (%)
150
100
50
0
-50
-100
0.01
0.03
0.1
0.3
1
3
10
Concentration (μM)

Figure 2

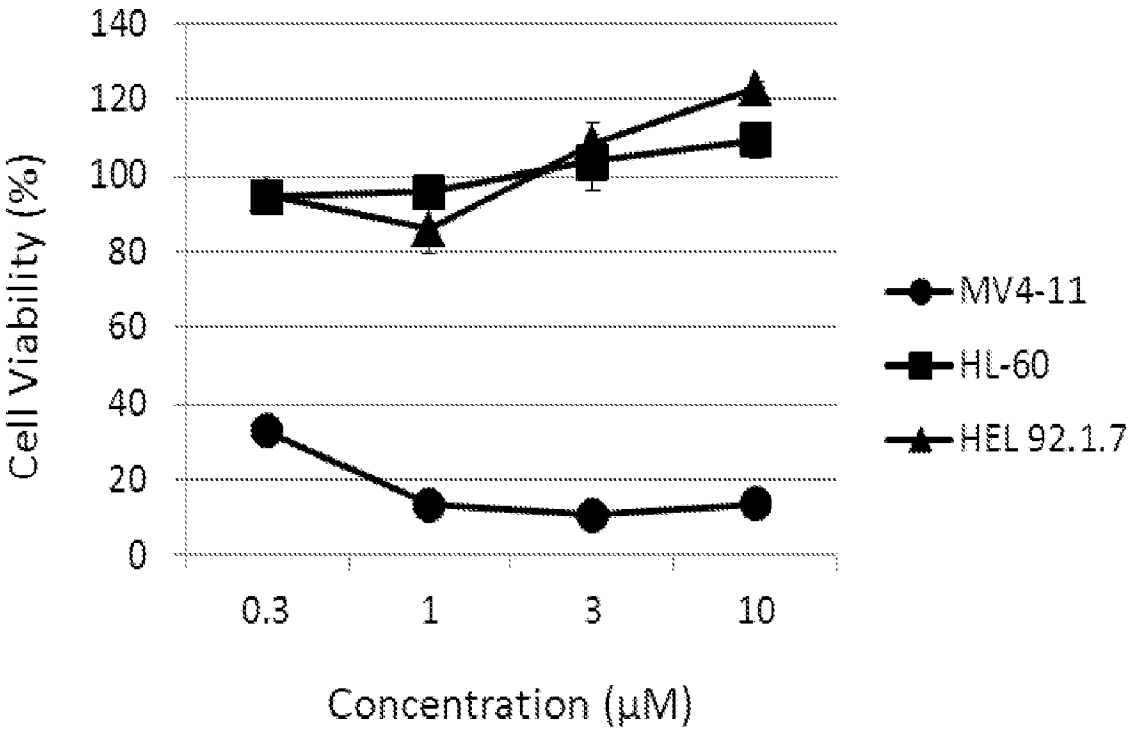

140
120
100
80
60
40
20
0
Cell Viability (%)
0.3
1
3
10
Concentration (µM)
MV4-11
HL-60
HEL 92.1.7

Figure 3

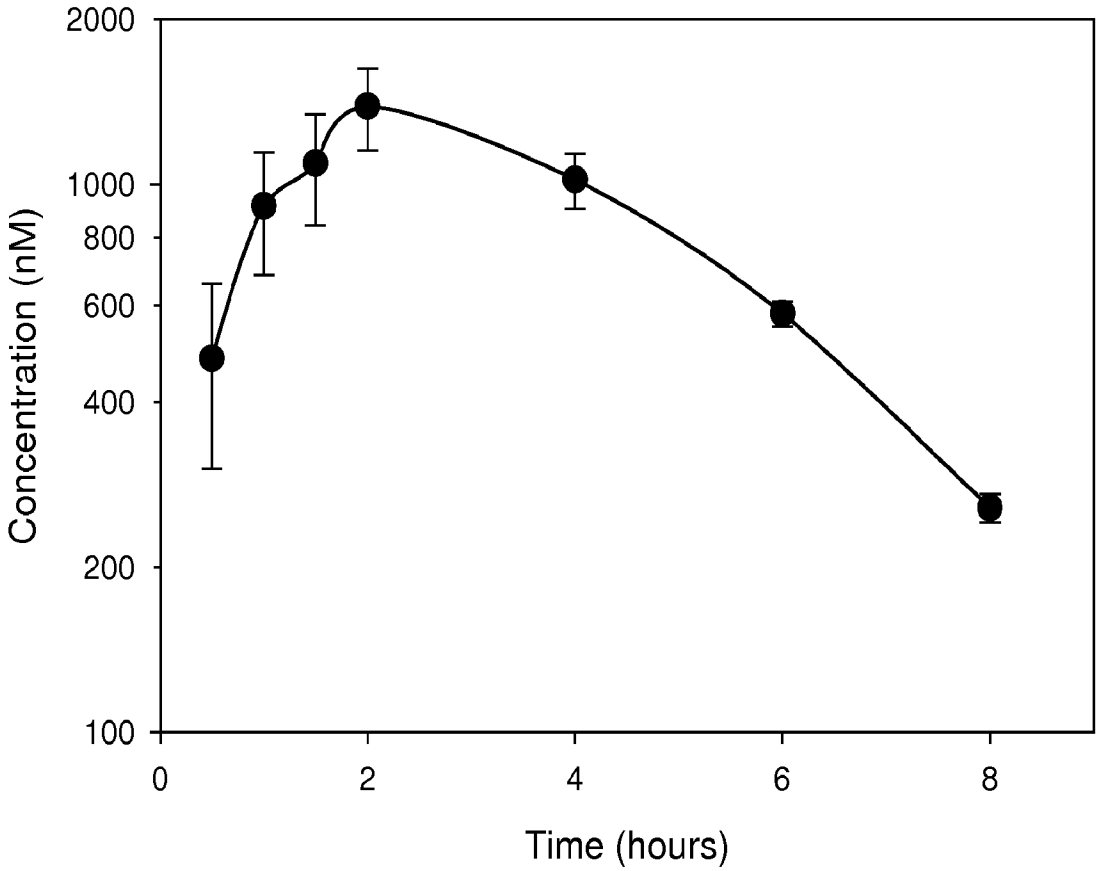

2000
1000
800
600
400
200
100
Concentration (nM)
0
2
4
6
8
Time (hours)

Figure 4

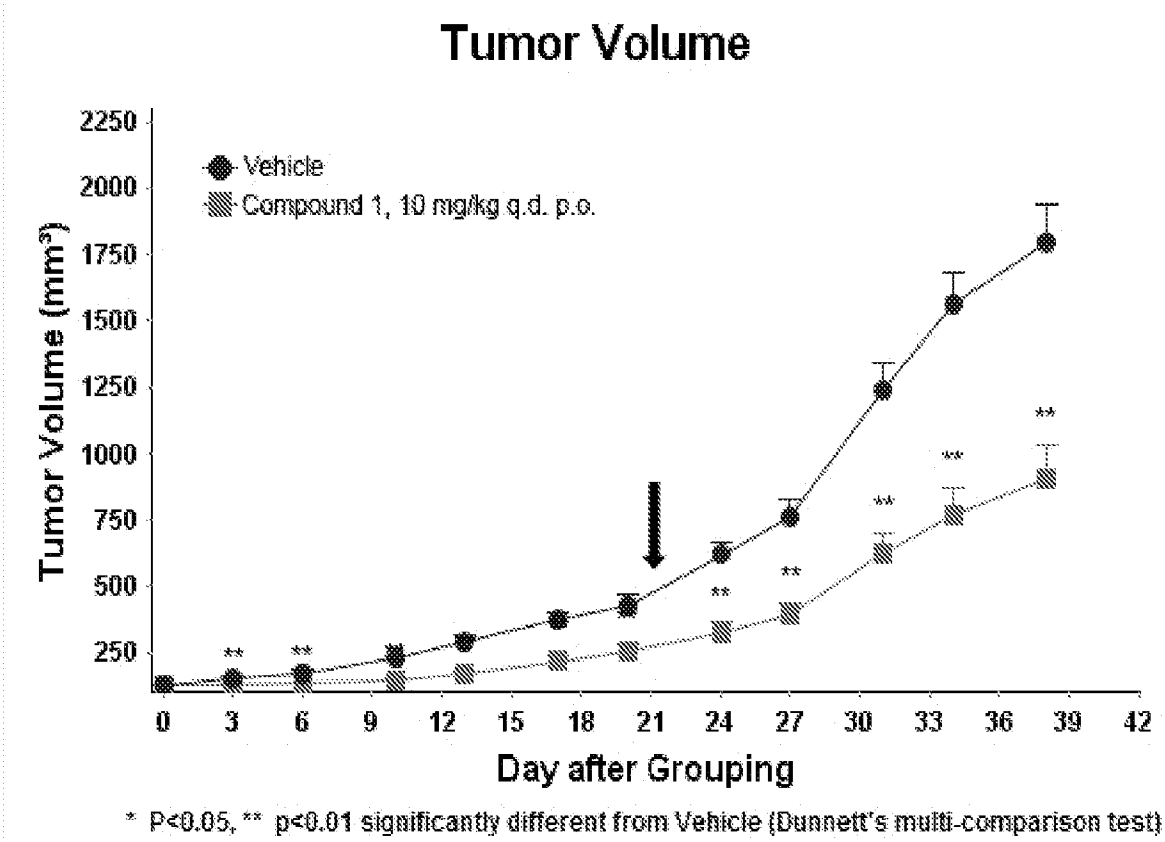

Tumor Volume
Vehicle
Compound 1, 10 mg/kg q.d. p.o.
Tumor Volume (mm³)
2250
2000
1750
1500
1250
1000
750
500
250
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
Day after Grouping
* P<0.05, ** p<0.01 significantly different from Vehicle (Dunnett's multi-comparison test)

Figure 5

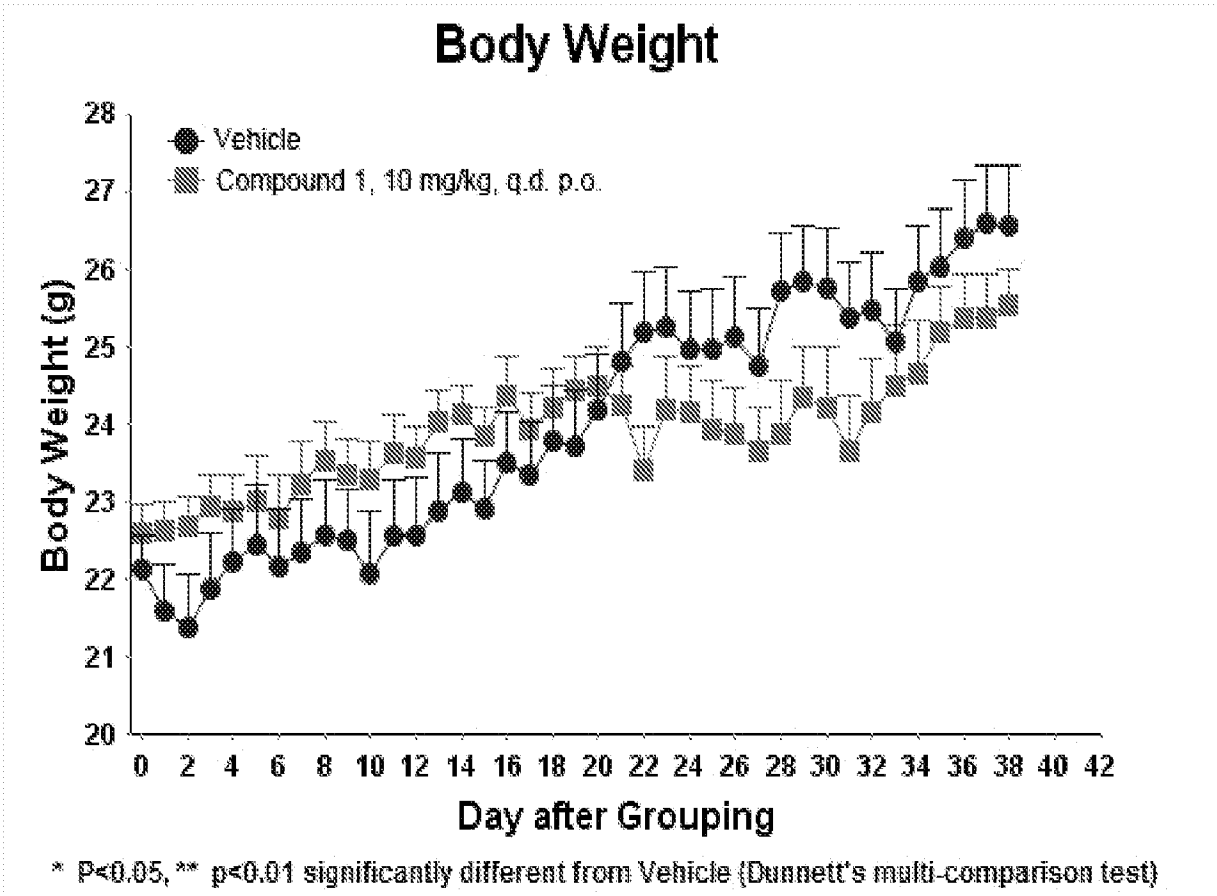
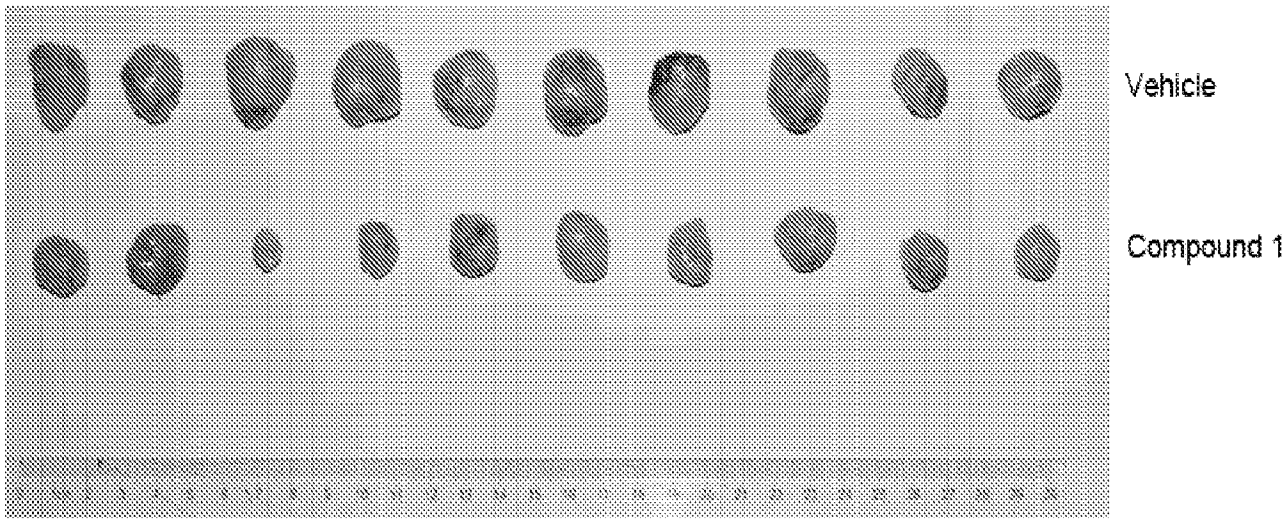

Body Weight
Vehicle
Compound 1, 10 mg/kg, q.d. p.o.
Body Weight (g)
28
27
26
25
24
23
22
21
20
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42
Day after Grouping
* P<0.05, ** p<0.01 significantly different from Vehicle (Dunnett's multi-comparison test)

Figure 6

A)



B)

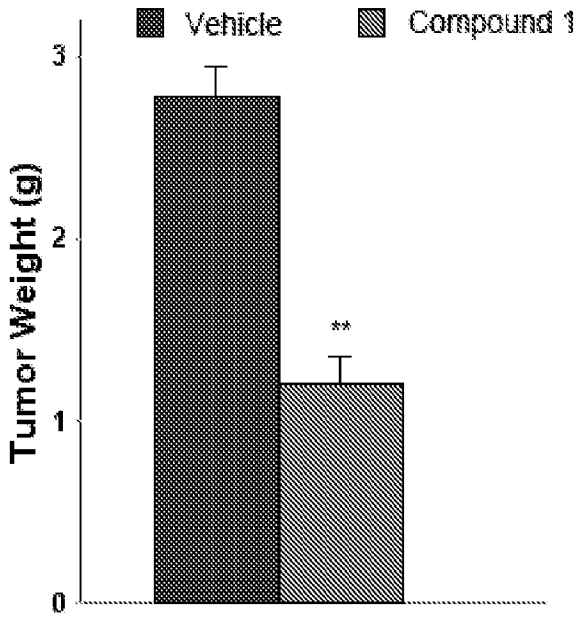
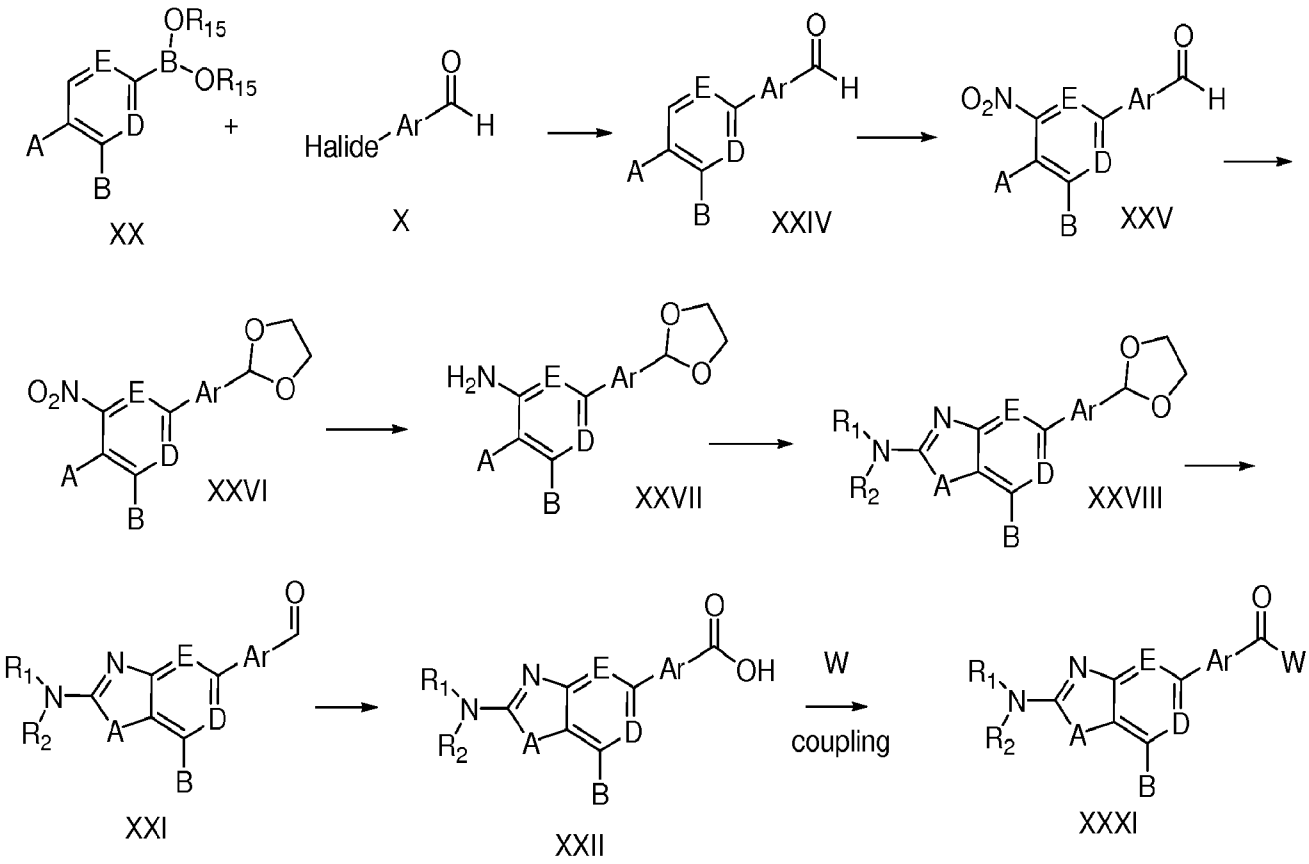


Figure 7


OR15
B
OR15
E
D
A
B
+
XX
Halide
Ar
O
H
X
E
Ar
O
H
D
A
B
XXIV
O2N
E
Ar
O
H
D
A
B
XXV
O2N
E
Ar
O
O
D
A
B
XXVI
H2N
E
Ar
O
O
D
A
B
XXVII
R1
N
R2
N
E
Ar
O
O
D
A
B
XXVIII
R1
N
R2
N
E
Ar
O
D
A
B
XXI
R1
N
R2
N
E
Ar
O
OH
D
A
B
XXII
W
coupling
R1
N
R2
N
E
Ar
O
W
D
A
B
XXXI