(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2006 (07.12.2006)

PCT

(10) International Publication Number
WO 2006/130613 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/US2006/020986

(22) International Filing Date: 30 May 2006 (30.05.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/686,062 31 May 2005 (31.05.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

Kinase Inhibition Profile of Compound 1

Binding Constants Kd (nM)	
Kinase Target	Compound I
ABL1 (T315I)	371
AURKA	232
CSF1R	80
FGFR3	271
FLT3	204
FLT3(D835H)	145
FLT3(ITD)	133
FLT3(N841I)	276
JAK2	388
KIT	451
KIT(V559D,T670I)	714
PDGFRB	333
RET	134
VEGFR	4000

Pfahl M et al

Substituted Biaryl heterocycle derivatives....other diseases

(57) Abstract: The present invention is directed to certain patentable substituted benzoxazole derivatives that exhibit protein kinase (PK) inhibition activity or modulating ability. Pharmaceutical compositions comprising these compounds, and methods for preparing and using them, are also described. For example, these heterocyclic compounds are useful in treating disorders related to abnormal PK activity, including diseases and disorders involving aberrant cell proliferation, for example, AML, CML, gastrointestinal stromal cancers, thyroid cancer, other cancers and leukemias, as well as other diseases such as inflammation and atherosclerosis.

WO 2006/130613 A2

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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

BACKGROUND OF THE INVENTION

The clinical success of c-Abl tyrosine kinase inhibitor, STI571 (Gleevec or Imanitib, Novartis Pharma) for the treatment of Chronic Myeloid Leukemias (CML) has promoted development of protein kinase inhibitors (PKIs) as targeted therapy for other types of leukemia as well as for solid tumors. CML is a rare, malignant, myeloproliferative disorder that is characterized by the acquisition of the reciprocal (9:22) (q34;q11) chromosomal translocation (Philadelphia chromosome) in hematopoietic stem cells and constitutive activation of protein tyrosine kinase Bcr-Abl (Heisterkamp N, Stam K, Groffen J, de Klein A and Grosveld G 1985 Structural organization of the bcr gene and its role in the Ph' translocation. Nature 315:758-61; Barila D and Superti-Furga G 1998. This chromosomal defect is seen in about 95% of all patients with CML as well as in 30% -50% of adult patients with acute lymphoblastic leukemia. An intramolecular SH3-domain interaction regulates c-Abl activity. Nature Genetics 18:280-2). CML comprises 0.4% of all malignancies and prevalent is 3-5 per 100,000 of the population (Baker DE 2002 Imatinib Mesylate. New Drug Review. Reviews in Gastroenterological disorders. 2:75-86).

Inhibition of Abl tyrosine kinase by Gleevec is effective for the treatment of CML but there are no targeted therapies available for the treatment of the more common Acute Myeloid Leukemia (AML). Morevoer, Gleevec while effective in treating accelerated and blast crisis, the emergence of drug resistance is a problem. AML, a more common disease, accounts for a high percent of all adult leukemia cases and claims about 7,200 victims per year in U.S. and a much larger number worldwide (Seppa N 2002 Smart drugs: Leukemia treatments nearing prime time. Science 161: 2-4).

Approximately 10,000 new cases of AML are diagnosed each year in the U.S., from 200,000 cases worldwide. Forty percent of AML patients have a mutated Flt-3 kinase such that the enzyme is constitutively active, resulting in the activation of tyrosine kinases and uncontrolled growth of bone marrow stem cells (Abu-Duhier FM, Goodeve AC, Wilson GA et al. 2000). Flt-3 internal tandem duplication mutations in adult AML define a high risk group (Br. J Haematol 111:190-195). 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 FLT-3 kinase is necessary for disease progression and hence is an attractive target for the development of novel therapies.

FLT-3 (FMS-like tyrosine kinase 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, intracellularly, a short juxtamembrane portion followed by an intracellular kinase domain (Levis M, Allebach J,, Tse K-F, Zheng R, Baldwin BR, Douglas Smith B, Jones-Bolin S, Ruggeri B, Dionne C and Small D (2002).

A FLT-3-targeted tyrosine kinase inhibitor is cytotoxic to leukemia cells in vitro and in vivo. Blood 99(11): 3885-3891). Its activation signals are transduced through phosphorylation of itself and cytoplasmic proteins in biochemical signaling pathways that promote uncontrolled cell growth and inhibit apoptosis. On binding to FLT-3 ligand, the wild type receptor dimerizes, activating its tyrosine kinase domain with resultant phosphorylation. RAS-GAP, PLC□, PI3-kinase, STAT5, and ERK1/2 are important signaling proteins linked to activation of FLT-3.

Other subfamilies of the receptor tyrosine kinase families include EGF receptor tyrosine kinases, insulin receptor tyrosine kinases, and FGF receptor tyrosine kinases. EGF receptor kinase for example is overexpressed in many cancers such as lung and breast cancers. Several agents such as Astrazeneca's Iressa, Genentech's Herceptin (for HER2-positive metastatic breast cancer), and OSI-Genentech's Tarceva (for nonsmall cell lung cancer) specifically target the EGFR receptor pathway. A number of other small molecule receptor tyrosine kinase inhibitors that are in clinical development include: SU5416, SU6668 and SU11248 (Sugen-Pfizer), ZD-6474 (Astrazeneca), andPTK787/ZK 222584 (Novartis), and inhibit a wide range of kinases such as VEGFR, FGFR, PDGFR, and c-kit. In addition, other attempts have been made to identify small molecules that act as protein kinase inhibitors. For example, bis-monocylic, bicyclic and heterocyclic aryl compounds (PCT WO 92/20642), vinyleneazaindole derivatives (PCT WO 94/14808) and 1-cyclopropyl-4-pyridyl-quinolinones (U.S. Pat. No. 5,330,992) and styryl compounds I (U.S. Pat. No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Pat. No. 5,302,606), quinazoline derivatives (EP App. No.0566 266 A1), selenaindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660), and benzylphosphonic acid compounds (PCT WO 91/15495) have all been described as protein tyrosine kinase inhibitors potentially useful in the treatment of cancer. In addition, benzoxazole, benzothiazole, and benzimidazole derivative (PCT WO 02/072543 A2) have also been reported useful for the treatment of cancer and other diseases as well but have not been shown to be suitable targeted inhibitors of specific kinases, which is also the case for many other herocyclic compounds described in many patents.

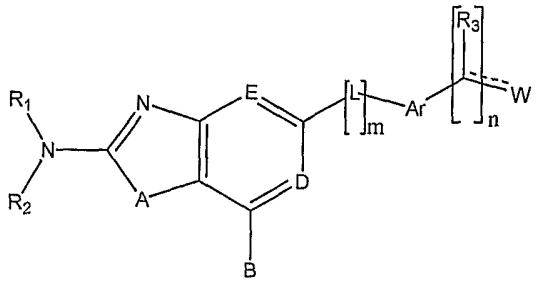
The present invention relates to a patentable class of kinase inhibitors with certain substituted benzoxazole derivatives that inhibit Flt-3 with high efficacy, and specifically kill leukemic cells that carry Flt-3 mutation *in vitro* and *in vivo*. In addition, these compounds

inhibited effectively c-Kit (including Gleevec-resistant mutants), and/or RET, and/or PDGFR□ (platelet derived growth factor receptor beta) in *in vitro* tests and can therefore be expected to be useful for the treatment of cancers in which these kinases play a role for the proliferation of these cancers. These compounds are structurally distinct from the broad species of benzoxazole derivatives disclosed in PCT WO 02/072543 A2. Those compounds reportedly have broad anti-cancer activities associated with significant toxicities. The compounds described here have very selective anticancer activities in that they, for instance, kill a human leukemia cell line that carries a FLT3 kinase mutation, but not other cell lines that were tested. Thus the compounds described here are structurally, and, because of their selective anticancer activity, different from compounds reported in PCT WO 02/072543 A2. Having only targeted anti-cancer activity and not broad anti-cancer activity is a major advantage since such compounds can be expected to have minimum side effects and toxicity. Described in particular are compounds that inhibit FLT-3 *in vitro* and which *in vivo* are inhibitors of the growth and progression of human AML tumors that carry Flt-3 mutation. Furthermore, some of these heterocyclic compounds also appear to be potent inhibitors of other kinases, including c-Abl, PDGFR, and c-Kit and/or RET known to be involved in CML, gastrointestinal stromal tumors, and/or thyroid cancer. Additional kinases that were observed to be inhibited with high affinity *in vitro* were AURKA, FGFR3, JAK2, PDGFR□RET, and VEGFR. Thus, the general structures and specific examples shown in this application cover molecules that belong to a new class of kinase inhibitors that can serve as "targeted anticancer" agents and function by defined mechanisms, inhibiting specific kinases, and thus markedly differ from drugs that are currently available for the treatment of myeloid leukemia and other cancers. Therefore, the heterocyclic compounds described herein are useful in the treatment of diseases of uncontrolled proliferation including AML, CML, gastrointestinal stromal cancers, and thyroid cancer, as well as other cancers and other diseases including inflammation and atherosclerosis. Furthermore, since the compounds analyzed here were selective kinase inhibitors with good oral bio-availability, these compounds can thus be expected to have limited side-effects and be suitable for the treatment of many cancers, alone or in combination with other cancer therapies. This invention thus also relates to the usage of such compounds for the treatment of solid tumor cancers and other diseases. Pharmaceutical compositions comprising these compounds, methods of treating diseases, and methods of preparing them are also described.

SUMMARY OF THE INVENTION

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

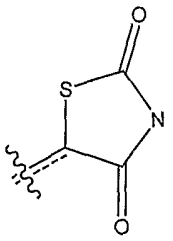
One aspect of this invention concerns compounds of Formula (1):



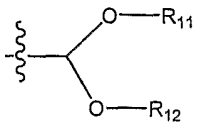
in which

W is

(a)



(b)



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

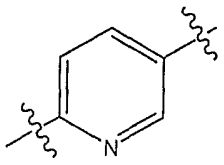
B is $-OR_{24}$, $-SR_{25}$, or $-NR_{28}R_{29}$;

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

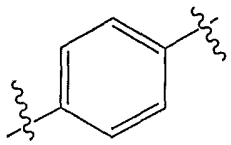
L is $-CH_2$-;

Ar is

(c)



(d)



m is 0 to 1;

n is 1 to 2; and

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, and substituted alkylcarboxamide, dialkylcarboxamide, or substituted dialkylcarboxamide; or an isomer, metabolite, polymorph, prodrug, or salt thereof.

Another aspect of the invention provides methods of synthesizing such compounds.

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 the treatment inflammatory diseases or atherosclerosis. This invention also relates to methods for inhibiting uncontrolled cellular proliferation, e.g., a cancer or leukemia, by administering to a mammal, preferably a human, diagnosed as needing such an inhibitor. The invention also provides for methods of treatment for diseases of uncontrolled cellular proliferation, such as cancer and leukemias, comprising administering an effective amount of a compound of the invention to a mammal diagnosed as having such a disease, as well as of methods of treating an inflammatory disease comprising administering to a mammal diagnosed as having an inflammatory disease an effective amount of a compound of the invention.

In another aspect, this invention relates to pharmaceutical compositions comprising a compound described herein in admixture with one or more pharmaceutically acceptable carriers, excipients, etc. A related aspect concerns kits, which comprise, for example, a unit dosage of a pharmaceutical composition according to the invention packaged in a suitable container (e.g., a glass vial), which may optionally be packaged in a box or the like for shipment and storage prior to use. In preferred embodiments, such kits typically further include a package insert providing details on the particular compound, its administration, and use.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the kinase inhibition profile of compound 1.

FIGURE 2 shows killing of MV4;11 human AML cell line by compounds 2, 3, 4, and 5.

FIGURE 3 shows selectivity of cell killing. Compound 1 specifically kills AML (MV4;11) but not prostate (PC-3) and pancreatic (Bx-PC-3) cells.

FIGURE 4 shows the kinase inhibition profiles of compounds 2, 5, and 8.

FIGURE 5 shows oral bioavailability and pharmacokinetics profile of compound 2 in rats.

FIGURE 6 shows prevention of AML tumor progression in the athymic nude mouse model by compound 2.

FIGURE 7 shows inhibition of large established AML tumors in the nude mouse model by compound 2.

FIGURE 8 shows selectivity of cell killing by compound 5.

FIGURE 9 shows oral bioavailability and pharmacokinetics profile of compound 5 in rats.

FIGURE 10 shows efficacy studies in nude mouse model by compound 5.

FIGURE 11 shows comparison of compound 2 and compound 5 in reducing tumor growth in nude mouse model.

FIGURE 12 shows inhibition of large established tumors in nude mouse model by compound 5.

FIGURE 13 shows a representative scheme of the synthetic pathway for the compounds disclosed herein in Formula 1, wherein m is 0 and n is 1.

DETAILED DESCRIPTION

The present invention provides compounds that are useful, for example, to prevent, alleviate, or otherwise treat cancer, and in particular AML and gastro-intestinal cancer – including Gleevec resistant mutants- 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.

Definitions

In the specification and Formulae described herein the following terms are hereby 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.

An "agent" refers to an active ingredient delivered to achieve an intended therapeutic benefit.

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 branched 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 alkenyl" 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 moieties 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 "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 agents, for example, a compound according to the invention and another chemotherapeutic agent. Alternatively, a combination therapy may involve the administration of one or more agents according to the invention, alone or in conjunction with another agent as well as the delivery of another therapy, e.g., surgery, radiation, etc. In the context of the administration of two or more chemically distinct agents, 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 agents are combined with, for example, psychoanalysis, the drug(s) may be delivered before, during, and/or after the period the subject is in therapy. In contrast, "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.

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 definitions found throughout.

The term "di-substituted amino" denotes an amino substituted 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 I dialkylcarboxamide, alkylsulfonyl, alkylsulfinyl, alkylthio, I 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 "arylalkyl" 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.

A residue of a chemical species, as used in the specification and concluding claims, refers to the 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. Similarly, a 2,4-thiazolidinedione residue in a chemical compound refers to one or more -2,4-thiazolidinedione moieties of the compound, regardless of whether the residue was obtained by reacting 2,4-thiazolidinedione to obtain the compound.

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

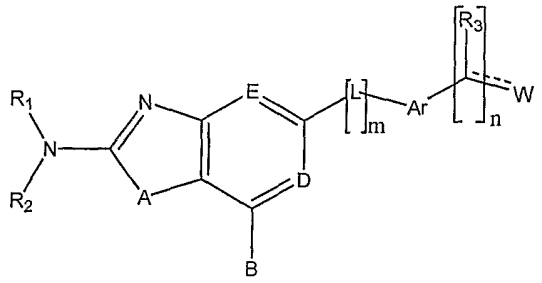
well as to preserve their validity. Furthermore, if one or more of the statutory requirements for patentability are amended or if the standards change for assessing whether a particular statutory requirement for patentability is satisfied from the time this application is filed or issues as a patent to a time the validity of one or more of the appended claims is questioned, the claims are to be interpreted in a way that (1) preserves their validity and (2) provides the broadest reasonable interpretation under the circumstances.

A "subject" or "patient" refers to an animal in need of treatment that can be effected by molecules of the 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-humans primates) animals being particularly preferred examples.

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

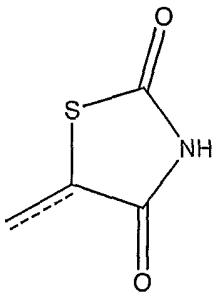
Some disclosed embodiments of the invention relate to the Formula (1):



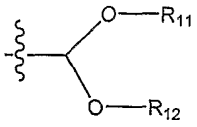
in which

W is

(a)



(b)



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

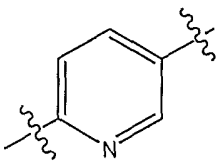
B is $-OR_{24}$, $-SR_{25}$, $-NR_{28}R_{29}$;

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

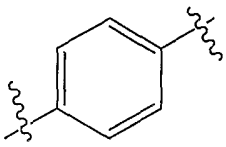
L is $-CH_2$-;

Ar is formula (C) or (d)

(c)



(d)



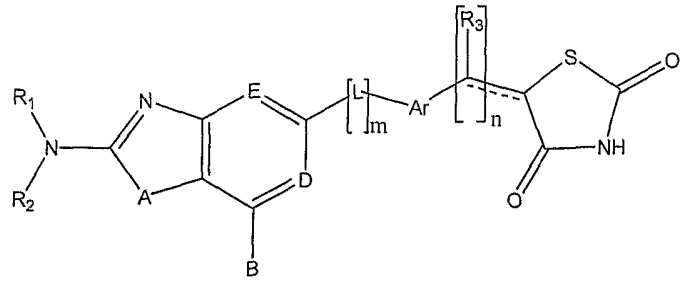
m is 0 to 1;

n is 1 to 2;

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 thereof. 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. A "polymorph" refers to a compound that has an identical chemical composition (i.e., it is of the same compound species) as compared to another compound but that differs in crystal structure.

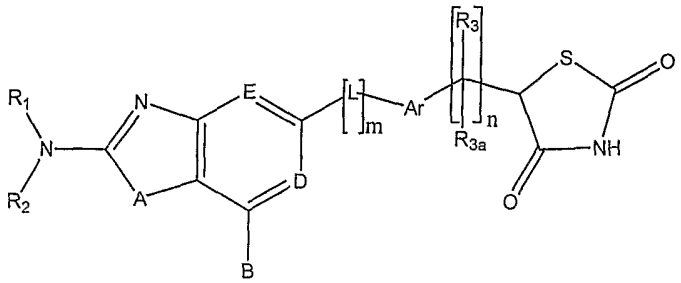
In some embodiments when W is 2,4-thiazolidinedione and "-----" is present, the compound is a benzilidine compound having the structural Formula:

(E)

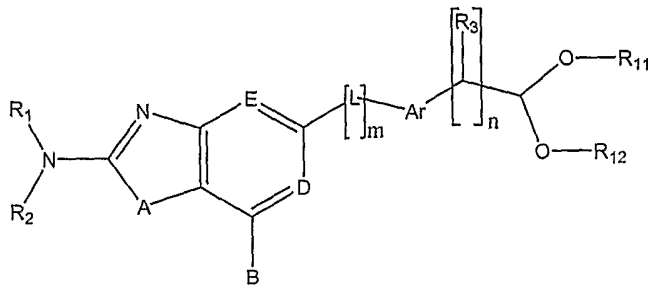


In some embodiments when W is 2,4-thiazolidinedione and "-----" is absent, the compound is a benzyl compound having the structural Formula:

(F)

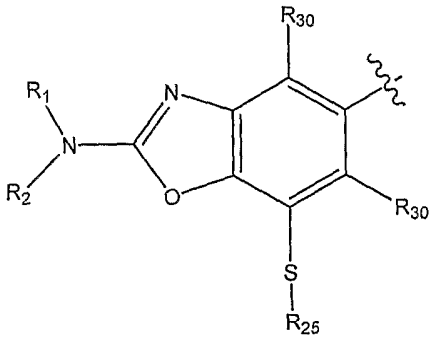


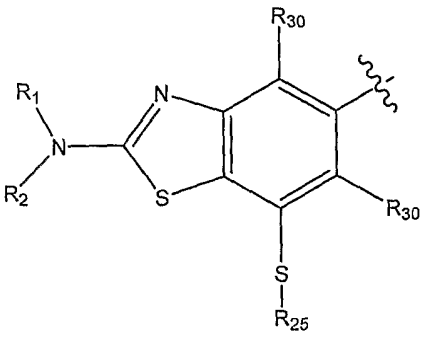
In another embodiment of the invention, when W is (b), the compound an alkylacetal having the structural formula:

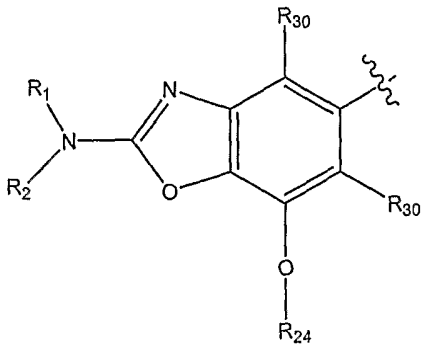


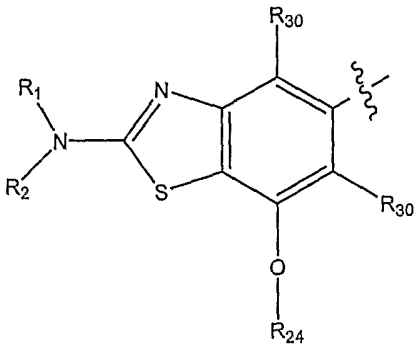
wherein R_{11} and R_{12} are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyl, substituted acyl, acyloxy, amino, mono-substituted amino, di-substituted amino, alkylsulfonamide, arylsulfonamide, alkylurea, arylurea, alkylcarbamate, arylcarbamate, heteroaryl, alkoxy, substituted alkoxy, haloalkoxy, thioalkyl, thiohaloalkyl, carboxy, carboalkoxy, alkylcarboxamide, substituted alkylcarboxamide, dialkylcarboxamide, or substituted dialkylcarboxamide

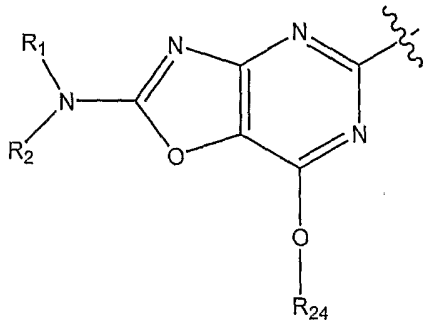
In another embodiment, A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S- ; B is $-OR_{24}$, $-SR_{25}$, $-NR_{28}R_{29}$, D and E are together or independently $-CR_{30}$-, or –N-. Preferred heterobicyclic residues may be selected from

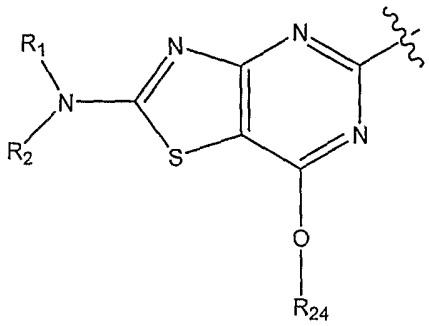












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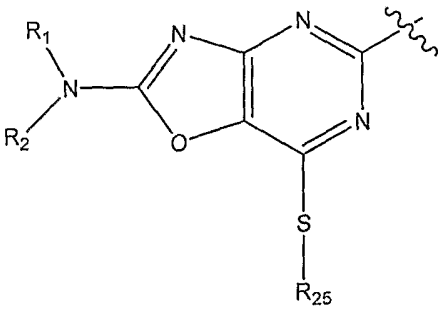

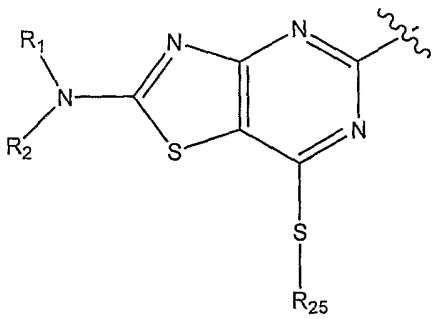

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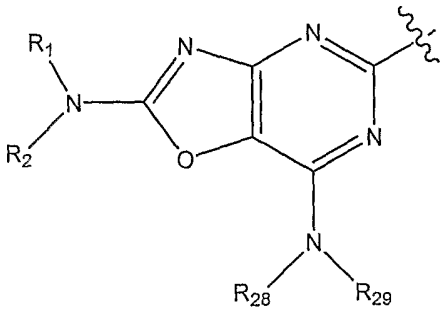

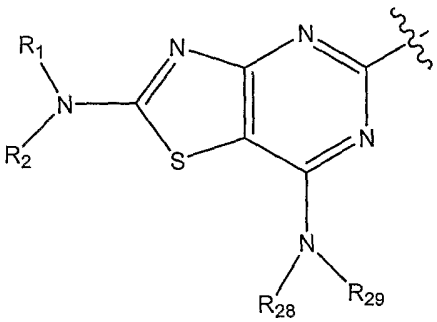

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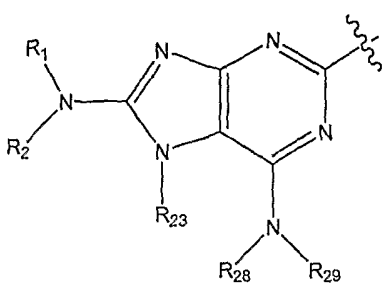
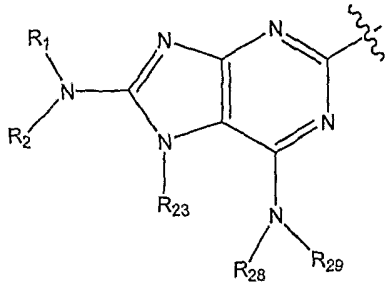
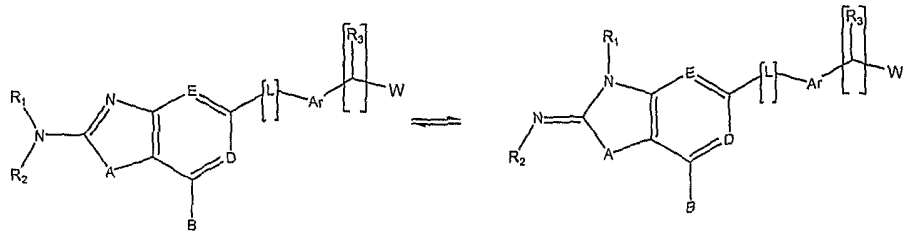


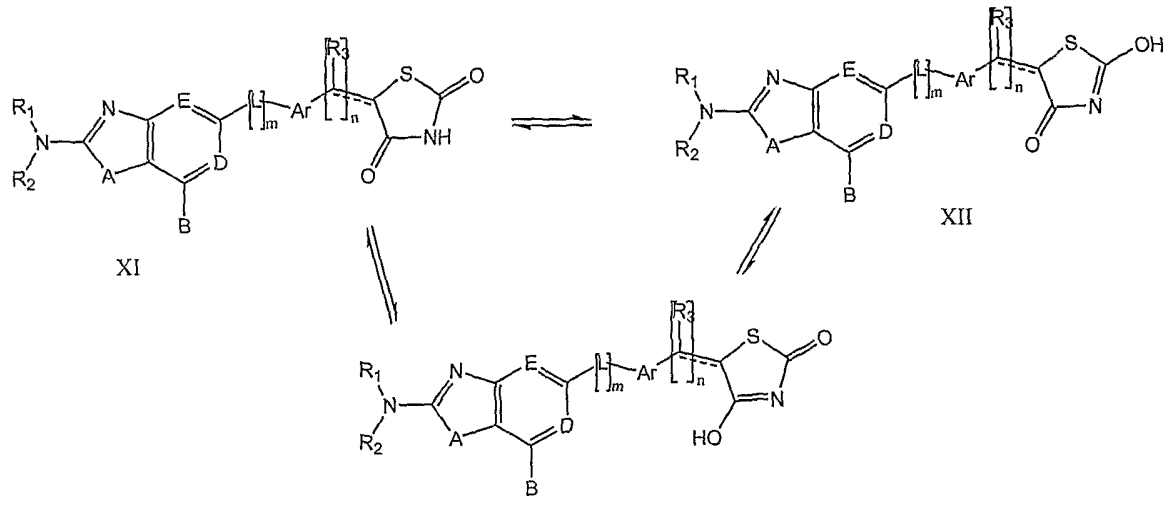


Some embodiments of this invention, compounds of formula (1) disclosed herein may exist in the form of tautomers (1) and (2), which are within the scope of the invention.



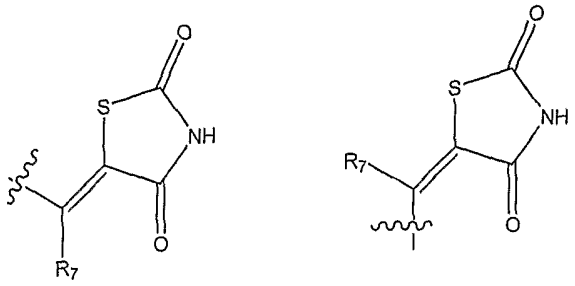
(1) (2)

In some embodiments of this invention, 2, 4-thiazolidinedione-containing compounds disclosed herein may exist in the form of tautomers (XI) ((XII), and (XIII), which are within the scope of the invention.



XI XII XIII

When "-----" is present, both Z and E configurations of the 2, 4-thiazolidinedione-containing compounds disclosed herein are within the scope of the invention both Z and E configurations formula may have the following structures, respectively:

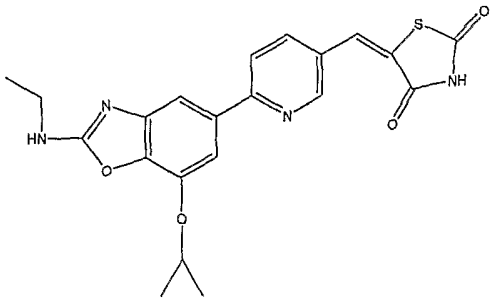


The compounds disclosed herein may also include salts of the compounds, such as salts with cations. Cations with which the compounds of the invention may form pharmaceutically acceptable salts include alkali metals, such as sodium or potassium; alkaline earth metals, such as calcium; and trivalent metals, such as aluminum. The only constraint with respect to the selection of the cation is that it should not unacceptably increase the toxicity. Due to the tautomerism described above for the compounds, mono-, di-, or tri-salts may be possible depending on the corresponding alkali metal. Also, 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.

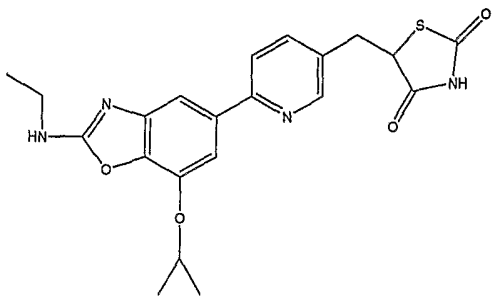
The present invention provides, but is not limited to, the specific compounds set forth in the Examples as well as those set forth below, and a pharmaceutically acceptable salt thereof:

Where

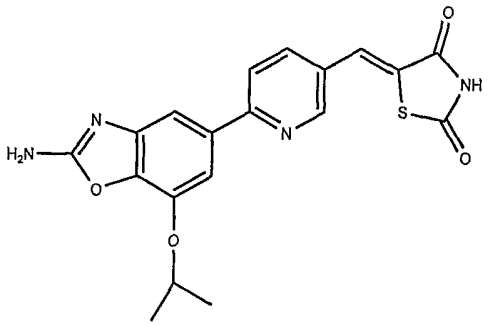
"-----" is absent or present; m is 0, and n is 1



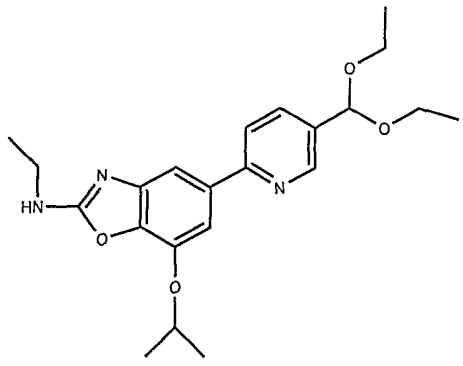
5-[6-(2-Ethylamino-7-isopropoxy-benzoxazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione



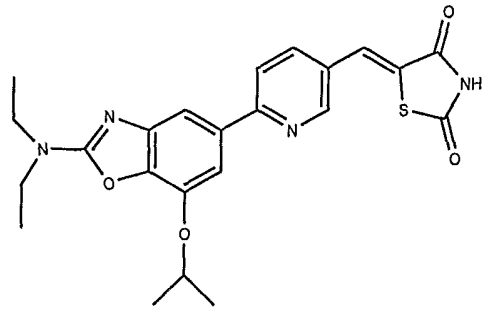
5-[6-(2-Ethylamino-7-isopropoxy-benzoxazol-5-yl)-pyridin-3-ylmethyl]-thiazolidine-2,4-dione



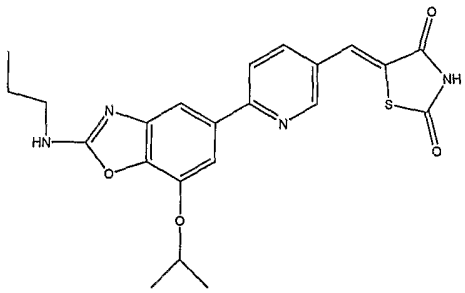
5-[6-(2-Amino-7-isopropoxy-benzoxazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione



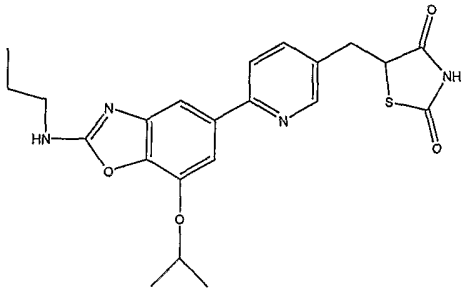
[5-(5-Diethoxymethyl-pyridin-2-yl)-7-isopropoxy-benzoxazol-2-yl]-ethyl-amine



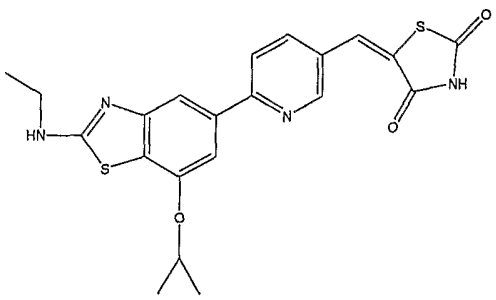
5-[6-(2-Diethylamino-7-isopropoxy-benzoxazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dion



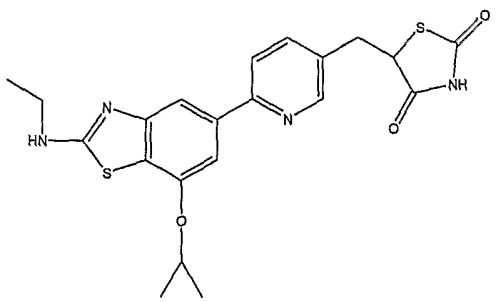
5-[6-(7-Isopropoxy-2-propylamino-benzoxazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione



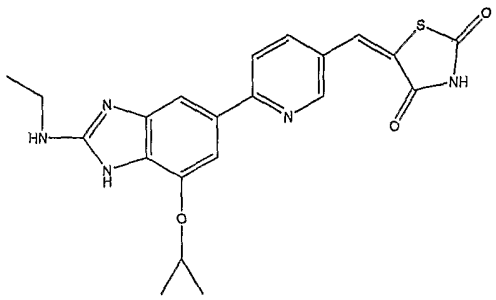
5-[6-(7-Isopropoxy-2-propylamino-benzoxazol-5-yl)-pyridin-3-ylmethyl]-thiazolidine-2,4-dione



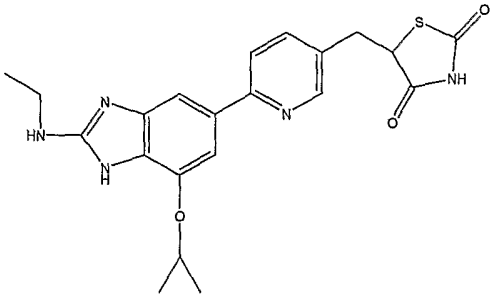
5-[6-(2-Ethylamino-7-isopropoxy-benzothiazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione



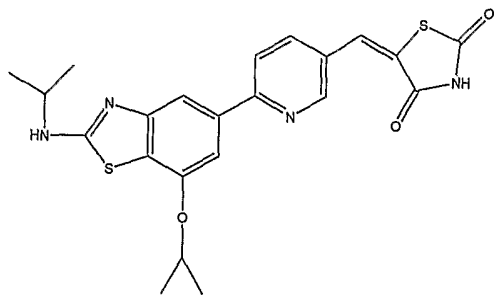
5-[6-(2-Ethylamino-7-isopropoxy-benzothiazol-5-yl)-pyridin-3-ylmethyl]-thiazolidine-2,4-dione.



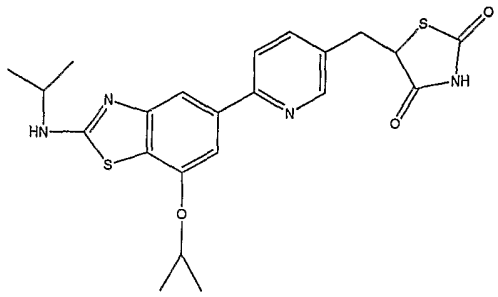
5-[6-(2-Ethylamino-7-isopropoxy-1H-benzoimidazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione



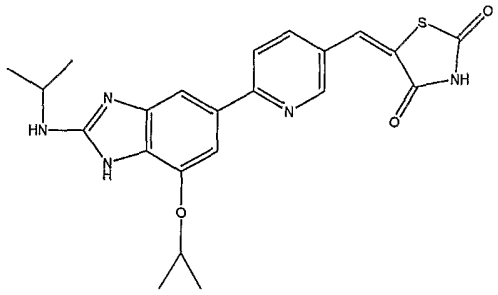
5-[6-(2-Ethylamino-7-isopropoxy-1H-benzoimidazol-5-yl)-pyridin-3-ylmethyl]-thiazolidine-2,4-dione



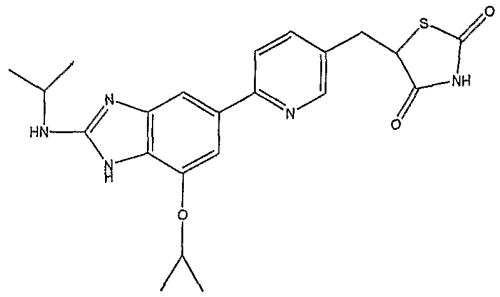
5-[6-(7-Isopropoxy-2-isopropylamino-benzothiazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione



5-[6-(7-Isopropoxy-2-isopropylamino-benzothiazol-5-yl)-pyridin-3-ylmethyl]-thiazolidine-2,4-dione



5-[6-(7-Isopropoxy-2-isopropylamino-1H-benzoimidazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione

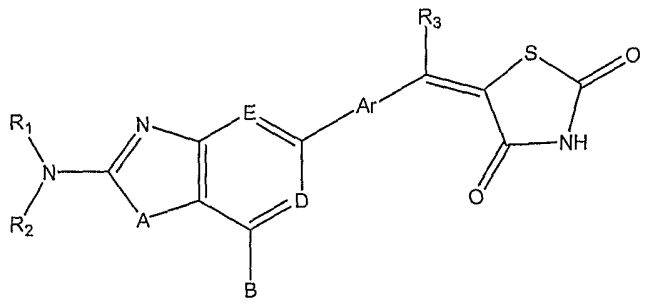


5-[6-(7-Isopropoxy-2-isopropylamino-1H-benzoimidazol-5-yl)-pyridin-3-ylmethyl]-thiazolidine-2,4-dione

Making the Compositions

A representative scheme of the synthetic pathway in the production of the compounds disclosed herein is shown in FIG. 13. Synthetically, a boronic acid of Formula (XX), R15=H, may be coupled with anaryl 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 R15 together with the boron form a pinacol borate ester (formation of pinacol esters: Ishiyama T., et al.,J. *Org. Chem.* 1995,60,7508-7510, Ishiyama T., et al., *Tetrahedron Letters* 1997, 38, 3447-3450; coupling pinacol esters: Firooznia, F. et al., *Tetrahedron Letters* 1999, 40,213-216, Manickam, G. et al., *Synthesis* 2000,442-446; all four citations incorporated herein by reference). Biaryl (XXI) may subsequently be condensed with 2,4-thiazolidinedione forming benzylidine (XXII).

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



.

wherein

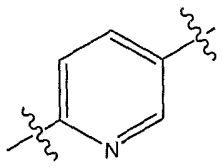
A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S- ;

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

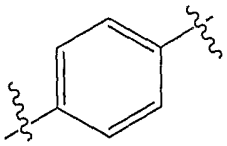
D and E are together or independently $-CR_{30}$-, or –N-;

Ar is formula (c) or (d)

(c)



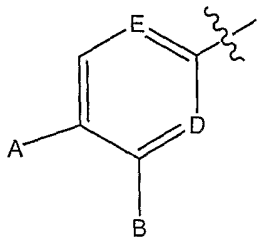
(d)



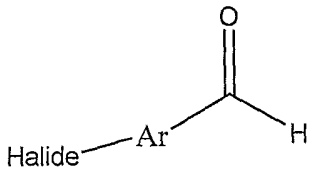
R_1, R_2, R_3, R_{21}, R_{22}, R_{23}, R_{24}, R_{25}, R_{28}, R_{29}, and R_{30} are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halogen, cyano, nitro, hydroxyl, acyl, substituted acyl, acyloxy, amino, mono-substituted 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

Comprising the steps of:

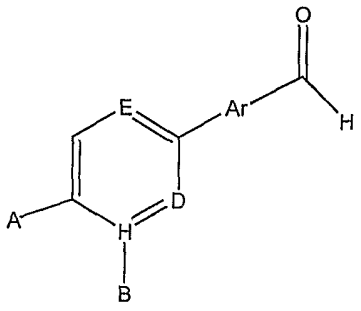
1) coupling a first aryl residue with a second aryl residue to give a biaryl carbonyl containing compound; wherein the first aryl residue comprises a substituted or unsubstituted residue having the structure:



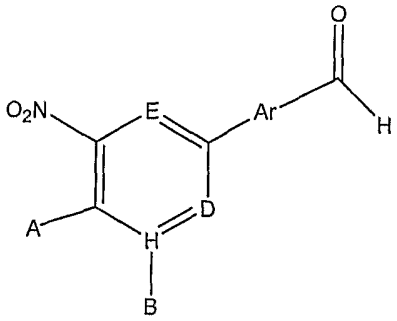
and wherein the second aryl residue has a carbonyl group having the structure (X):



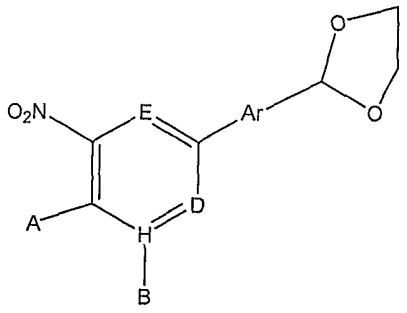
and wherein the biaryl carbonyl containing compound having the structure (XXIV):



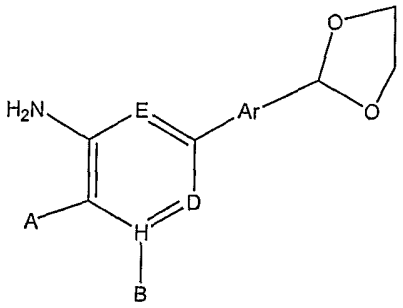
2) Upon nitration of (XXIV), the condensed product is of the structure (XXV):



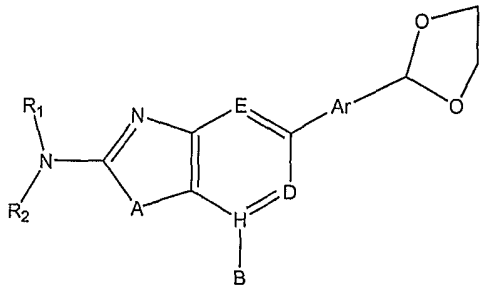
3) Protecting carbonyl group with ethylene glycol, the protected product is of the structure (XXVI):



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

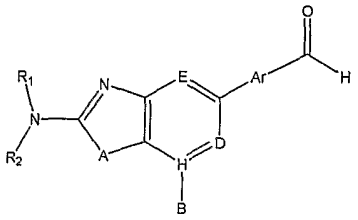


5) Cyclizing with cyanogen bromide, the product is of the formula (XXVIII).

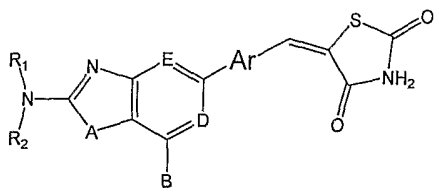


Where R_1 and R_2 are hydrogen. For R_1 to be an alkyl group, the above product (XXVIII) can be alkylated with alkyl halide in the presence of NaH.

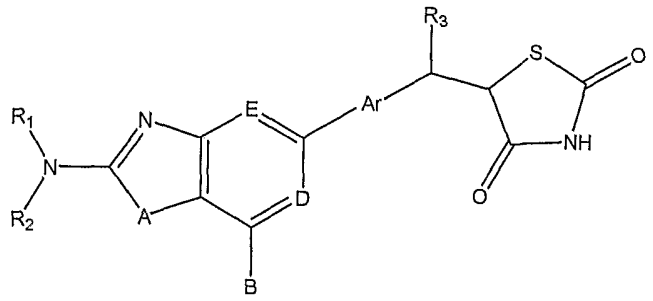
5) Upon hydrolysis, the product is of the formula (XXI).



6) condensing the biaryl carbonyl containing compound (XXI) with 2,4-thiazolidinedione, the product is of the structure (XXII):



In another embodiments of the invention provides a process further comprising the step of reducing the benzylidene of Formula (XXII) to form the benzyl compound of Formula (XXIII):



A number of methods suitable for reducing benzylidene compounds to benzyl compounds (including hydrogenation, reaction with metal hydride reagents, or dissolving metal reductions) are known to those of skill in the art, and those methods may be applied in the methods of the instant invention.

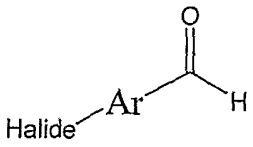
The various organic group transformations utilized herein may be performed by a number of procedures other than those described above. References for other synthetic procedures that may be utilized for the synthetic steps leading to the compounds disclosed herein may be found in, for example, March,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

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 product may be subsequently condensed with an active methylene compound, such as 2,4-thiazolidinedione to give a benzylidene compound of Formula (1) where"-----" is present. In an optional step, the benzylidene compound may be reduced to give a benzyl compound of Formula (1) where "-----" is absent.

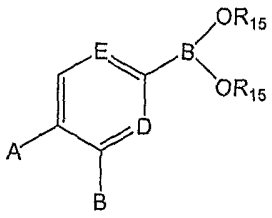
Coupling of two aryl rings may be conducted using an aryl boronic acid or esters with an aryl halide (such as, iodo, bromo, or chloro), triflate or diazonium tetrafluoroborate; as described respectively in Suzuki, *Pure & Applied Chem., 66:213-222 (1994), Miyaura and Suzuki, Chem. Rev. 95:2457-2483 (1995), 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., TetrahedronLetters 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) and (XX) may be employed:

(X)



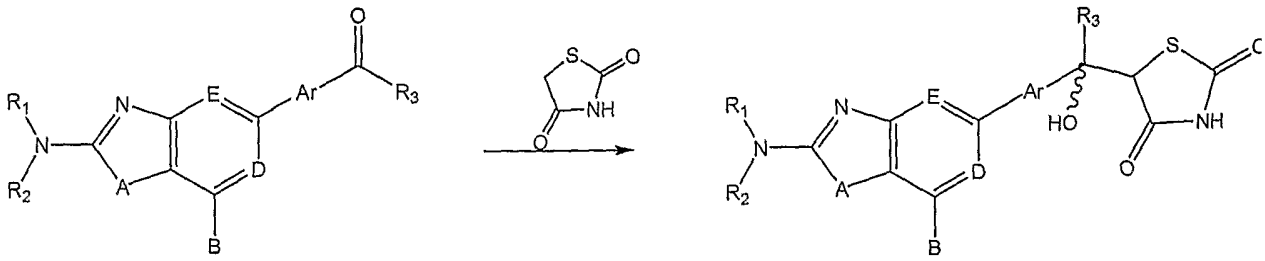
(XX)



Where

(X) is either a triflate, a halide (such as, iodo, bromo, or chloro), or diazonium tetrafluoroborate 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.

Condensation of the biaryl carbonyl containing derivatives (e.g., FIG. 13, compound (XXI) with a suitable active methylene compound, such as, 2,4-thiazolidinedione, may be accomplished by the use of methods known in the art. For example, the biaryl carbonyl product from the coupling reaction may be condensed with an active methylene compound to give a benzylidene compound of Formula (I) (i.e., "-----" is present) as described by Tietze and Beifuss, *Compre- hensive Organic Synthesis* (Pergamon Press), 2:341-394, (1991), incorporated herein by reference. It is understood by those of skill in the art that intermediates having hydroxyl groups bound thereto may be formed during condensation of a biaryl carbonyl containing derivative and an active methylene compound, as shown below.



The hydroxyl groups of such intermediates are often eliminated (as water) during the condensation reaction, to form the desired benzylidene compound. Nevertheless, the conditions of the reaction may be modified for the isolation or further use of hydroxyl containing intermediates, and such embodiments are within the scope of the invention. The reaction shown above depicts the formation of the condensation intermediate for the reaction between compound (XXI) and an active methylene compound. Effective catalysts for the condensation may be selected from ammonia, primary, secondary, and tertiary amines, either as the free base or the amine salt with an organic acid, such as acetic acid. Examples of catalysts include pyrrolidine, piperidine, pyridine, diethylamine, and the acetate salts, thereof. Inorganic catalysts may also be used for the condensation. Inorganic, catalysts include, but are not limited to, titanium tetrachloride and a tertiary base, such as pyridine; and magnesium oxide or zinc oxide in an inert solvent system. This type of condensation can be strongly solvent- dependent and it is understood that routine experimentation may be necessary to identify the optimal solvent with a particular catalyst, preferable solvents include ethanol, tetrahydrofuran, dioxane, or toluene; or mixtures thereof. The active methylene compound of the present invention is 2,4-thiazolidinedione. The resulting benzylidene (e.g., FIG. 13, compound (XXII) may be reduced, if desired, to a compound of Formula (I) wherein "----"is absent (e.g., FIG. 13, compound (XXIII).

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 specific kinase inhibition profile when tested against approximately 180 different kinases including mutated kinases as for instance in the case of FLT3 and KIT. Only six of all the kinases were inhibited with inhibition constants (or binding constants Kd) in the sub micro molar range (see Figure 1), as measured using the Ambit kinase screening test (M.A. Fabian et al., Nature Biotechnology, 23 pp.329- 336, March 2005). These test results show that structures described here can inhibit a variety of protein kinases, while at the same time being 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 mutated FLT-3) were aliquoted into 96-well plates each with different concentrations of Compound 1,2, 3, or 4. Cell proliferation assays using 3-4,5-dimethylthiazol-2,5-diphenyltetrazoilum (MTT) were conducted to measure inhibition of proliferation and cell killing of the human AML cell line MV4;11. Compounds 1, 2, 3, and 4 dramatically inhibited cellular proliferation and killed MV4;11 cells in a dose dependent manner (Figure 2). The specificity of cell killing was demonstrated in Figure 3 wherein, compound 1 specifically killed leukemic cells but not prostate (PC-3) and pancreatic (Bx-PC-3) cancer cell lines. Taken together these data indicate that compound 1 is a selective Flt-3 inhibitor with cell killing effects on Flt-3 mutated MV4;11 cells. Compound 2 showed selective anticancer cell activity *in vitro* and a more specific kinase inhibition profile than compound 1. Results shown in Figure 4 demonstrate that when tested against approximately 180 kinases, using the Ambit test, compound 2 inhibits only 3 different kinases and some of their mutated forms at or near micro molar concentrations. To measure bioavailability, a single oral dose of 10 mg/Kg of compound 2 was given to three rats. Blood samples were removed at various time points for analysis of drug levels. The single oral dose of compound 2 produced plasma drug concentration of more than 2 □M within 2 hours and reached a maximal concentration (C_{max}) of 3 □M within 10 hours and an overall peak that extended over 24 hours (Figure 5). The maintenance of high plasma drug levels for several hours and good bioavailability suggest that compound 2 could be administered orally once a day.

A subcutaneous tumor xenograft model was used to assess the effects of compound 2 *in vivo*. Athymic nude mice injected with cells expressing constitutively activated Flt-3 is a proven model of leukemia (O'Farrell A-M, Abrams TJ, Yuen HA, Ngail TJ, Louie SG, Yee KWH, Wong LM, Hong W, Lee LB, Town A, Smolich BD, Manning WC, Murray LJ, Heinrich MC and Cherrington JM (2003) SU11248 is a novel Flt-3 tyrosine kinase inhibitor with potent activity *in vitro* and *in vivo*. Blood 101: 3597-3605). These mice typically sicken and die, with large spleens full of leukemic cells, within a few weeks following injection. MV4;11, a human leukemia cell lines that expresses a Flt-3-internal tandem repeat 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 2 were evaluated in two different experiments.

Prevention of AML tumor progression in athymic mouse

Nude mice were injected subcutaneously with MV4:11 cells. Two weeks after tumor initiation, and when tumors were established in the animals, one group of mice was treated with 30 mg/kg of compound 2 administered orally once a day for 8 and 14 days, a second group was treated with placebo. Tumor volumes were measured twice/week using a vernier caliper for the

duration of treatment and volumes were calculated as ellipsoid volumes (Tomayko MM, Reynolds CP (1989) Determination of subcutaneous tumor size in athymic nude mice. Cancer Chemother Pharmacol 24(3):148-54) determined from the size of the subcutaneous tumors grown as xenografts. Bars represent five animals/group. It was found that compound 2 dramatically inhibited the growth of human leukemia MV4:11 xenografts at 30 mg/Kg given orally once/day (Figure 6). After an additional week the difference between treated and untreated animals were even more pronounced. Data were plotted for 8 and 14 days of treatment in Figure 6. Overall, a dramatic effect of tumor growth inhibition was observed with compound 2. This effect was still the same at 24 days when this experiment was terminated.

Treatment of large pre-existing tumors

In another series of studies, nude mice were injected subcutaneously with about 5,000,000 MV4;11 cells. After 3 weeks, when the tumors had reached a size of approximately 100 mm^3, mice were divided into 2 groups (6 animals/group). One group was treated with 50 mg/kg of compound 2 administered orally once a day for two weeks, the other group was given placebo. Tumors were then grouped as non-detectable/regressed, static or progressed based on the tumor sizes. Tumors in placebo treated mice progressed to a size of 1000 mm^3 within two weeks, whereas 66% of the mice that were treated with compound 2 (50 mg/kg) showed an effect on the tumor size. Of those mice that responded, 50% showed tumors that were static and in the remaining 50% tumors were completely eliminated (Figure 7).

Compound 5 selectively killed MV4;11 leukemic cells but not prostate and pancreatic cells. In these latter two tumor cell lines FLT-3 is not required for cell proliferation (Figure 8). Moreover, compound 5 showed a selective Flt-3 kinase inhibition profile in the kinase inhibition assay, including effective inhibition of all tested FLT-3 mutations. Compound 5 also inhibited RET kinase at sub micro molar concentrations. RET is known to contribute to the proliferation of thyroid cancer cells (Figure 4). In rats, compound 5 showed a good pharmacokinetic profile: A single oral dose of 12 mg/Kg of compound 5 produced plasma drug concentrations of more than 14 □M within 2 hours and overall high plasma drug levels were maintained for up to 15 hours (Figure 9). In the nude mouse model, compound 5, when administered orally at 15 mg/Kg twice a day, inhibited the growth of human leukemic xenografts (Figure 10). In Figure 11, individual tumor volumes were measured to compare the efficacies of compound 2 and compound 5 with placebo in the nude mouse model. Groups of 5-8 animals were treated with placebo or compound 2 (30 mg/Kg once a day) or compound 5 (15 mg/Kg twice a day) for ten days. Both compounds reduced tumor growth when compared to placebo. In addition compound 5 showed significant improvement over compound 2 in reducing tumor growth (Figure 11). Treatment of nude mice that had large established AML tumors with compound 5 at 50 mg/Kg showed also a significant reduction on the tumor growth (Figure 12).

Another aspect of the invention relates to the use of the compounds described herein. These compounds may be either used singularly or plurally, and pharmaceutical compositions thereof for the treatment of mammalian diseases, particularly those that occur in humans. Compounds described herein and compositions that contain them 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, CML, and 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; incorporated herein by reference. The compositions may also be used as regulator in diseases of uncontrolled proliferation. A representative but non-limiting list of cancers is lymphoma, Hodgkin's disease, myeloid leukemia, 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 epithelial 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 aspect of the invention concerns 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, transmucosally, nasal, vaginal, ophthalinical, sublingually, bucally, 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; or as a solution, suspension, or 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, incorporated herein by reference) or Bawas et al. (U.S. Pat. Nos. 4,931,279, 4,668,504 and 4,713,224; all incorporated herein by reference). 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; incorporated herein by reference. 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.

In preferred embodiments of this and other aspects of the inventions, the agent is part of composition, which includes at least a carrier and an amount of such compound sufficient to achieve the desired effect for which it is to be administered in at least a subset of the population of subjects to whom it is administered (i.e., an "effective amount" of the particular compound or

other active agent, as the case may be). Here, a "therapeutically effective amount" refers to an amount of an agent sufficient to effect treatment when administered to a subject in need of such treatment. In the context of cancer treatment, a "therapeutically effective amount" is one that produces an objective response in evaluable patients. Determination of therapeutically effective dosages of a composition comprising a compound according to the invention may be readily made by those of ordinary skill in the art.

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 □M, about: 1 to 50 □M, or about 2 to about 30 □M. 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.

The term "treatment" or "treating" means any treatment of a disease or disorder, including preventing or protecting against the disease or disorder (that is, causing the clinical symptoms

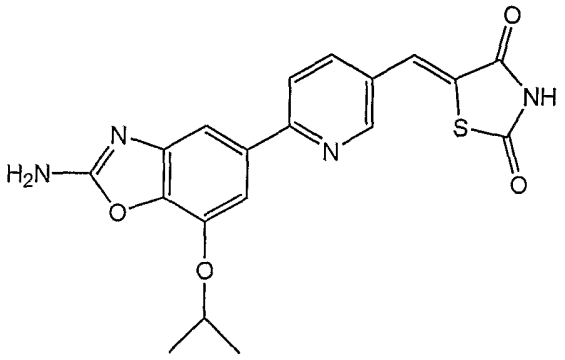
not to develop); inhibiting the disease or disorder (i.e., arresting or suppressing the development of clinical symptoms; and/or relieving the disease or disorder (i.e., causing the regression of clinical symptoms). As will be appreciated, it is not always possible to distinguish between "preventing" 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 "protection" thus includes "prophylaxis".

EXAMPLES

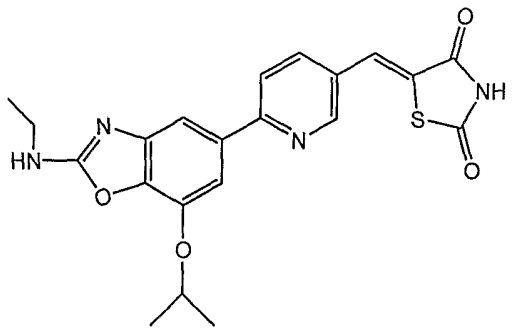
The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Example 1: Representative compounds and their synthesis

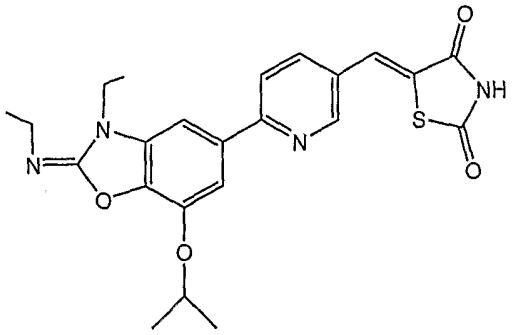
Compound 1



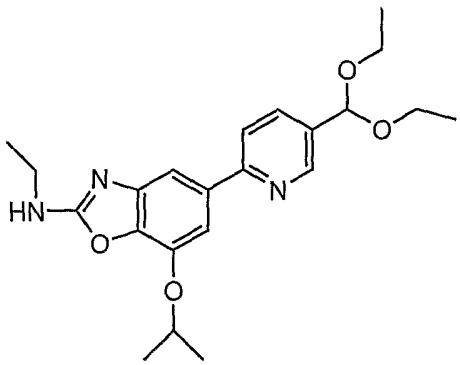
Compound 2



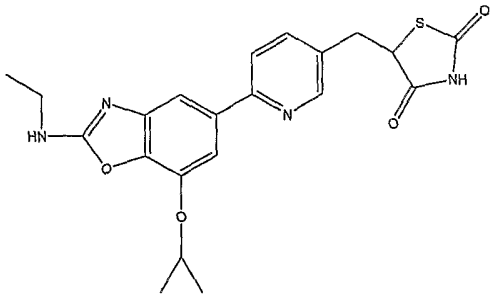
Compound 3



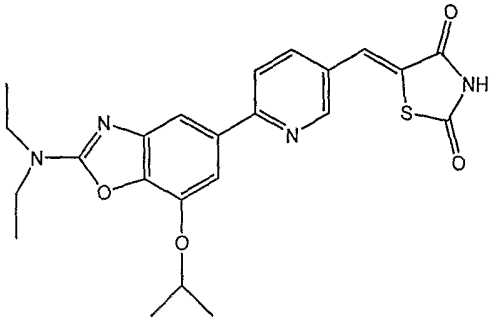
Compound 4



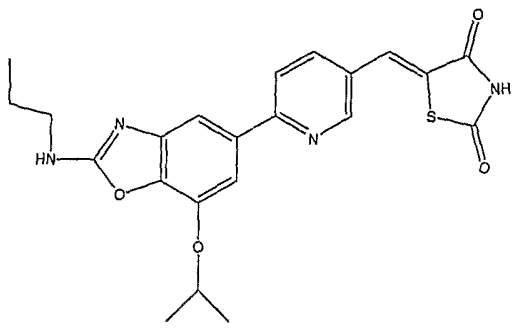
Compound 5



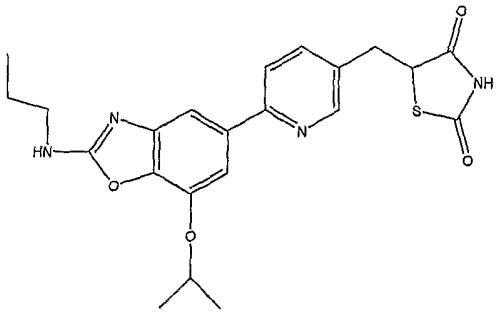
Compound 6



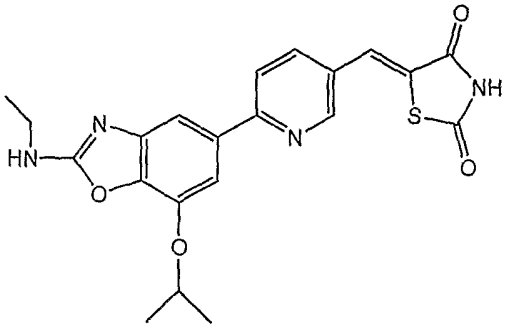
Compound 7



Compound 8

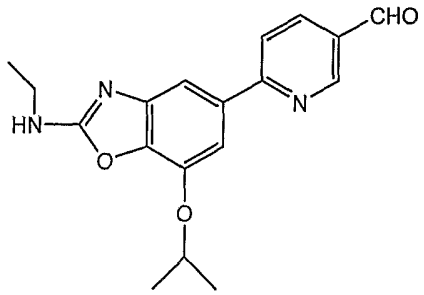


Synthesis of compound 2



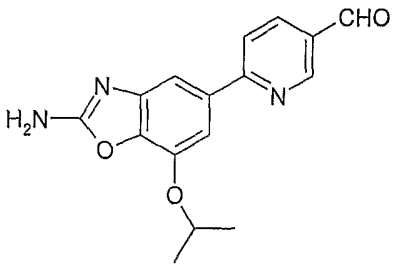
To a solution of 6-(2-Ethylamino-7-isopropoxy-benzoxazol-5-yl)-pyridine-3-carbaldehyde (0.385 g, 1.183 mmol) in toluene(2 ml) was added a solution of piperidine(23 ul, 0.237 mmol) and acetic acid (23 ul, 0.237 mmol) in toluene(2 ml). Thiazolidine-2,4-dione(0.139 g, 1.183 mmol) was added. The reaction mixture was heated to reflux for 4 hours. The product precipitated, was filtered and dried to give 0.395 g of 5-[6-(2-Ethylamino-7-isopropoxy-benzooxazol-5-yl)-pyridin-3-ylmethylene]-thiazolidine-2,4-dione as a yellow solid(78.7% yield); purity by HPLC 99.59% (355 nm); 99.40% (225nm); mp 280 °C – 281 °C. ^{1}H NMR

(500 MHz, DMSO-d_6):□ï2□t, J= 7.26 Hz, 3H);1.34(d, J= 6.04 Hz, 6H); 3.35(m, 2H); 4.87(m, 1H); 7.54(d, J= 1.24 Hz, 1H); 7.64(d, J= 1.17 Hz, 1H); 7.86(s, 1H); 7.97(dd, J1= 2.39 Hz, J2= 8.52 Hz, 1H); 8.03(t, J= 5.63 Hz, 1H); 8.14(d, J= 8.50 Hz, 1H); 8.88(d, J= 2.30 Hz, 1H); 12.7 (br s, 1H).



The intermediate 6-(2-Ethylamino-7-isopropoxy-benzooxazol-5-yl)-pyridine-3-carbaldehyde was prepared as follows:

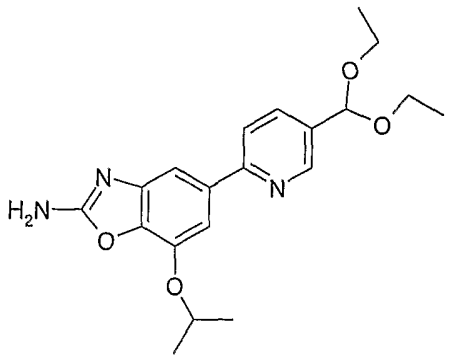
The mixture of 6-(2-Amino-7-isopropoxy-benzoxazol-5-yl)-pyridine-3-carbaldehyde (0.860 g, 2.893 mmol) and K_2CO_3 (0.960 g, 6.942 mmol) in DMF 20 ml) was stirred at room temperature for 1 1/2 hours. Iodoethane (278 □l, 3.472 mmol) was added. The reaction was stirred at room temperature for 3 days. The solution was diluted with ethyl acetate (20 ml) and washed successively with water (2x30 ml) and brine (30 ml), dried over anhydrous magnesium sulfate, filtered and evaporated. The residue was chromatographed on silica gel (eluent: 100% ethyl acetate) to give 0.385 g of 6-(2-Ethylamino-7-isopropoxy-benzoxazol-5-yl)-pyridine-3-carbaldehyde as a yellow solid (41% yield). ^{1}H NMR (500 MHz; DMSO-d_6): □1.98 (t, J=7.31 Hz, 3H); 1.35(d, J=6.09 Hz, 6H); 3.36(m, 2H); 4.88(m, 1H); 7.57(d, J=1.35 Hz, 1H); 7.69(d, J=1.4 Hz, 1H); 8.01(t, J=5.6 Hz, 1H); 8.21(d, J= 8.35 Hz, 1H); 8.26(dd, J1=2.2 Hz, J2=8.35 Hz, 1H); 9.12(d, J=1.65 Hz, 1H); 10.12(s, 1H).



The intermediate 6-(2-Amino-7-isopropoxy-benzoxazol-5-yl)-pyridine-3-carbaldehyde was prepared as follows:

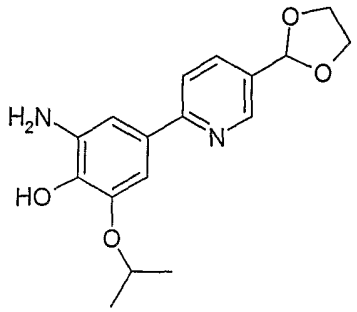
A mixture of 5-(5-Diethoxymethyl-pyridin-2-yl)-7-isopropoxy-benzooxazol-2-ylamine (1.00 g, 2.69 mmol), in 0.5N HCl was stirred and brought to 80°C for 30 minutes. The product

precipitated, was filtered, and washed with H_2O. The filtrate was brought to pH ~7 with saturated $NaHCO_3$ and extracted from ethyl acetate (3 x 15 ml). Organic phase combined and washed with H_2O (50 ml), brine (50 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was combined with filtered product and dried to give 0.860 g of 6-(2-Amino-7-isopropoxy-benzooxazol-5-yl)-pyridine-3-carbaldehyde (quantitative yield). ^1H NMR (500MHz; DMSO-d_6): □1.35 (d, J= 6.00 Hz, 6H); 4.90(m, 1H); 7.59(d, J=1.44 Hz, 1H); 7.66 (d, J=1.5 Hz, 1H); 7.78(br s, 2H); 8.25 (m, 2H); 9.12 (m, 1H); 10.12 (s, 1H).



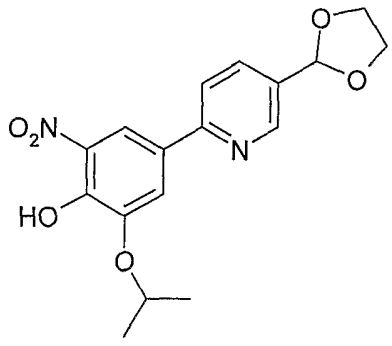
The intermediate 5-(5-Diethoxymethyl-pyridin-2-yl)-7-isopropoxy-benzoxazol-2-ylamine was prepared as follows:

To a mixture of 2-Amino-4- (5-[1,3] dioxolan-2-yl-pyridin-2-yl)-6-isopropoxy-phenol (1.273g, 4.02 mmol), in anhydrous ethanol (60 ml) was added cyanogen bromide 5M in acetonitrile (2.41 ml, 12.07 mmol) drop-wise. The resulting mixture was then stirred and brought to reflux under argon for 1.5 hours. The completed reaction mixture was concentrated under reduced pressure and diluted with with ethyl acetate (50 ml), and H_2O (20 ml). The aqueous phase was separated and extracted with ethyl acetate (2 x 20 ml). The aqueous phase was brought to pH ~7 with saturated $NaHCO_3$ and extracted from ethyl acetate (15 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, 4:1) to give 1.118g of 5-(5-Diethoxymethyl-pyridin-2-yl)-7-isopropoxy-benzoxazol-2-ylamine (81% yield). ^1H NMR (500MHz; DMSO-d_6): □ĩ15 (t, J=7.01 Hz, 6H); 1.31(d, J= 6.03, Hz, 6H); 3.50(m, 2H); 3.57(m, 2H); 4.82(m, 1H); 5.58(s, 1H); 7.41(m, 1H); 7.43 (s, 2H); 7.76(dd, J1= 2.20 Hz, J2=8.30 Hz, 1H); 7.93 (m, 1H); 8.59 (d, J=2.18 Hz, 1H).



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

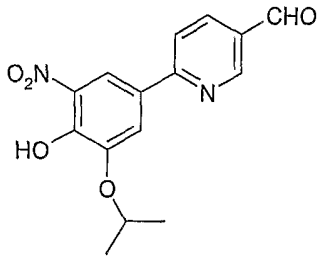
To a mixture of 4-(5-[1,3] dioxolan-2-yl-pyridin-2-yl)-2-isopropoxy-6-nitro-phenol (1.596g, 4.96 mmol), in anhydrous ethanol (80 ml) was added ammonium formate (1.45g, 23.0 mmol), followed by palladium, 10% wt on activated carbon (0.23g). The resulting mixture was then stirred and brought to reflux under 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:

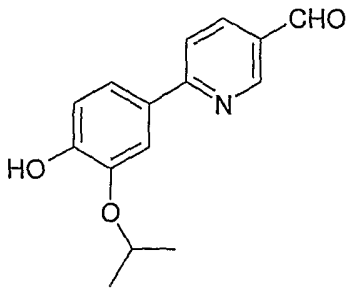
To a mixture of 6-(4-Hydroxy-3-isopropoxy-5-nitro-phenyl)-pyridine-3-carbaldehyde (1.507g, 4.99 mmol), in anhydrous toluene (30 ml) was added ethylene glycol (5.6 ml, 99.7

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).



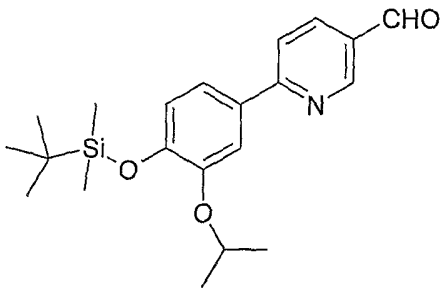
The intermediate 6-(4-Hydroxy-3-isopropoxy-5-nitro-phenyl)-pyridine-3-carbaldehyde was prepared as follows:

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:

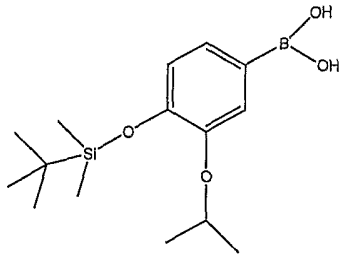
To a mixture of 6-[4-(tert-Butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-pyridine-3-carbaldehyde (3.0g, 8.07 mmol), dissolved into anhydrous THF (60ml) was added Tetrabutylammonium fluoride (1.0M in THF, 9.69 ml, 9.69 mmol) drop-wise. The resulting mixture was then stirred at 23°C under argon for 1.5 hrs. The solution was diluted with ethyl acetate (30 ml), and H_2O (30 ml). The aqueous phase was separated and extracted with ethyl acetate (2 x 20 ml). The combined organics phase were washed with water (15 ml), 0.1N HCl (22 ml), and brine (15 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel (eluent: ethyl acetate/ hexane, 1:4) to give 1.90 g 6-(4-Hydroxy-3-isopropoxy-phenyl)-pyridine-3-carbaldehyde (91% yield). ^1H NMR (500MHz; DMSO-d_6): □1.41 (d, J= 6.04 Hz, 6H); 4.79(m, 1H); 6.15 (br s, 1H); 7.02(d, J= 8.35 Hz, 1H); 7.55(dd, J1= 2.0 Hz, J2= 8.35 Hz, 1H); 7.79 (m, 2H); 8.16(dd, J1= 2.10 Hz, J2= 8.35 Hz, 1H); 9.04 (d, J= 2.15 Hz, 1H); 10.08 (s, 1H).



The intermediate 6-[4-(tert-Butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-pyridine-3-carbaldehyde was prepared as follows:

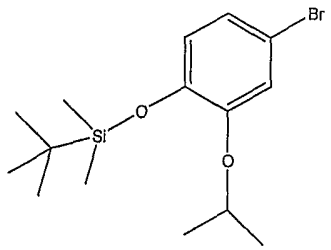
A mixture of 6-Bromo-pyridine-3-carbaldehyde (4.70 g, 25.2 mmol), [4-(tert-Butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-boronic acid (11.72 g, 37.80 mmol) and potassium carbonate (6.97 g, 50.4 mmol) in toluene (100 ml), ethanol (17ml) and water (15 ml) was degassed with argon at room temperature for 20 minutes. Tetrakis(triphenylphosphine) palladium (0) (1.46 g, 1.26 mmol) was added, then the mixture was brought to reflux and stirred

under argon for 16 hours. The solution was cooled to room temperature, diluted with ethyl acetate (75 ml) and washed successively with water (40 ml) and brine (40 ml), dried over anhydrous $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel (eluent: ethyl acetate/ hexane, 1:4) to give 11.403 g of 6-[4-(tert-Butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-pyridine-3-carbaldehyde (95% yield).



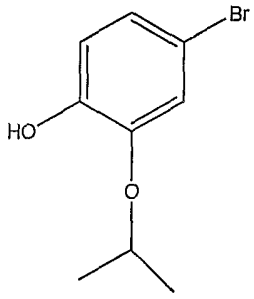
The intermediate [4-(tert-Butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-boronic acid was prepared as follows:

80 ml of 2.5 M *n*-BuLi in hexane 0.33 mol) was placed in a 2 liter three necks round bottom flask equipped with an overhead air-driven stirrer, and cooled the solution in dry ice acetone bath to -78 °C. To this solution under argon at–78°C was added (4-Bromo-2-isopropoxy-phenoxy)-tert-butyl-dimethyl-silane (76 g, 0.22 mol) in THF (60ml) drop-wisely. The reaction mixture was stirred for 1 hour and then triisopropylborate (152 ml, 0.660 mol) was added drop-wisely. The mixture was stirred at 0°C for 2 hours. Saturated aqueous NH_4Cl (80 ml) was slowly added to the reaction mixture. The quenched mixture was extracted with ethyl acetate (200ml). The organic layer was 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: ethyl acetate/ hexane, 5:95) to give 38.5 g of [4-(tert-Butyl-dimethyl-silanyloxy)-3-isopropoxy-phenyl]-boronic acid (56% yield).



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 Inhibition Profile Assay

As a primary screen, compounds were tested at 10 uM against a panel of 180 kinases. This collection of kinases included the most common FLT-3 and cKit mutations. 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 23:329-36 (2005). Briefly, the human kinases are expressed as T7 bacteriphage fusion protein and a small set of immobilized probe ligand is combined with the free test compounds. If the free test compound binds and occlude the ATP site, fewer protein molecules bind the immobilized ligand on the solid support. The results are read out by quantifying the amount of fusion protein bound to the solid support. For each kinase, compounds were scored initially as a 'hit' or 'no hit' in the primary screen. The hits were scored quantitatively and reported as 'percent of control'. The results summarized in Figure 1 indicate that Compound I inhibited several kinases whereas

Compound 2, 5 and 8 gained significant specificity and bound specifically only to very few kinase targets.

Secondary assays were performed on compounds 2, 3, 5. and 8 to determine the binding constants (Kd) of the compounds for the selected kinases as described in Fabian *et al* (A small molecule-kinase interaction map for clinical kinase inhibitors. Nature Biotechnology 23:329-36 (2005). The results indicate that compound I is a potent inhibitor of FLT-3 (Kd 100-200 nM) had a broad kinase inhibition profile inhibiting Abl and PDGFR□, FGFR3, CSF1R, RET, Kit, JAK2, and Aurka kinases with affinities between 80 nM to 714 nM (Figure 1). Thus compound I can likely serve as lead structure for a larger series of more selective kinase inhibitors. Altering selected residues on the structure of compound I resulted in very selective compounds 2, 5, and 8, which are highly selective kinase inhibitors that bind specifically only to very few kinase targets. A comparison of their ability to inhibit FLT-3, KIT, PDGFR□ and RET are presented in Figure 4. Compound 5 specifically inhibited FLT-3 and important FLT-3 mutants (Kd 333-975 nM) but also RET (binding constant 770 nM) and compound 8 specifically inhibited FLT-3, KIT and PDGFR□ (Kd between 95 and 740 nM). It is important to note here that compound 8 inhibited also effectively the KIT double mutation V559D/T670I. This mutation is resistant to the clinical cKit inhibitor Gleevec. Thus compound 8 could serve for the treatment of Gleevec resistant GIST patients.

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. The selectivity of cell killing was tested by comparing the effect of compounds on the MV4;11 cells with their effects on proliferation of the prostate cancer cell line (PC-3) and pancreatic cancer cell line (Bx-PC3) cells. Cell proliferation was measured using 3-4,5-dimethylthiazol-2,5-diphenyltetrazoilum (MTT) assay. Briefly, cells were aliquoted into 96 well plates. MV4;11 cells were grown in RPMI medium containing 4500 mg/L glucose; 4 mM L-glutamine; 10 U/ml Pen-G; 10 mcg/ml and 20% fetal bovine serum (FBS). PC-3 and Bx-PC3 cells were grown in RPMI medium 1640 containing 2 mM L-glutamine; 10 U/ml Pen-G; 10 mcg/ml Streptomycin and 10% FBS. Cells were seeded at 300-500 cells/well in 96-well tissue culture plates and maintained at 6% CO_2 and 37°C. Cells were treated with kinase inhibitors or vehicle for three days. The percentage of surviving cells was 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 □l of 5 mg/ml MTT dye are added to each well and incubated for 4 hours

and the reaction was stopped by adding 100 □l/well of solubilization solution, consisting of 10% Sodium Dodecyl Sulfate (SDS) and 10 mM HCl].

Compound 1-5 strongly inhibited cellular proliferation and killed MV4;11 cells in a dose dependent manner and compound 1 did not inhibit the proliferation of PC-3 and Bx-PC-3 cancer cell lines (Figure 2 and 3).

Example 4: Pharmacokinetic measurements

To measure bioavailability, a single oral dose of 10 mg/Kg of compound 2 was given to three rats. Blood samples were removed at various time points (1 hr, 2 hrs, 4 hrs, 7 hrs, 10 hrs, 12 hrs, and 24 hrs) for analysis of drug levels. Compound 2 showed good bioavailability. The single dose of 10 mg/Kg of compound 2 administration produced plasma drug concentration of more than 2 □M within two hours and reached a maximal concentration (C_{max}) of 3 □M within 10 hours and an overall peak that extended over 24 hours. The maintenance of high plasma drug levels for several hours and good oral bioavailability suggest that compound 2 could be administered orally once a day (Figure 5).

A single dose of compound 5 when given at 12 mg/Kg produced plasma drug concentrations of more than 10 □M within 1 hour and reached a Cmax of 14 □M within 3 hours and an overall peak that extended over 10 hours. Overall, compound 5 showed approximately 3 to 4 fold increased bioavailability over compound 2 (Figure 9).

Example 5: Oral administration of compound 2 and compound 5 in the treatment of AML tumors in an animal model

A subcutaneous tumor xenograft model was used to assess the effects of compounds 2 and 5 *in vivo*. Athymic nude mice injected subcutaneously with MV4;11 cells, expressing constitutively activated FLT-3 , 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 (a human leukemia cell lines that expresses the most frequent 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 million MV4;11 cells near the hind flank on day 0. The therapeutic effects of daily oral administration of compounds 2 and 5 were evaluated in prevention of AML tumors and the treatment of large pre-existing tumors in the athymic mouse. Typically, nude mice were injected subcutaneously with 5 million MV4:11 cells. Two weeks after tumor injection one group of mice was treated with 30 mg/kg of compound 2 administered orally once a day for 8 and 14 days (Figure 6). Tumor volumes were measured twice/week using vernier caliper for the duration of treatment, and volumes were calculated as ellipsoid volumes (Tomayko MM and Reynolds CP 1989 Determination of subcutaneous tumor size in athymic nude mice. Cancer Chemother Pharmacol 124:148-54). Bars represent 5 animals/group. Compound 2 dramatically inhibited the growth

of FLT3- ITD mutation xenografts at 30 mg/Kg.

In another series of studies, nude mice were injected subcutaneously with 5 million MV4:11 cells. After the tumors had reached a size of approximately 100 mm^3, mice were divided into 2 groups (6 animals/group). One group was treated with 50 mg/kg of compound 2, the other group was treated with placebo, administered orally once a day for two weeks. Tumors were then grouped as non-detectable/regressed, static or progressed based on the tumor sizes in placebo treated group (Figure 7). Tumors in placebo treated mice progressed to a size of 1000 mm^3 within two weeks, whereas, 66% of the mice that were treated with MC-2002 (50 mg/kg) showed an effect on the tumor size. Of those mice that responded, 50% showed tumors that were static and in the remaining 50% tumors were completely eliminated (data not shown).

Compound 5 was administered orally twice a day at 15 mg/Kg to nude mice injected with MV4;11 cells. Eighteen days after tumor initiation animals were sorted based on tumor sizes into two groups (7-9 animals per group) and treated with vehicle or15 mg/kg of compound 5. Tumor sizes were measured at the start of treatment and after 5 and 10 days. Animals treated with 15 mg/Kg of compound 5 showed a significant inhibition of the growth of AML xenografts (Figure 10).

Another experiment was conducted to compare the *in vivo* efficacies of compound 2 and compound 5. Eighteen days after tumor initiation, animals were sorted based on tumor sizes into three groups. They were treated with vehicle, 30 mg/Kg of compound 2 (once a day) or 15 mg/kg of compound 5 (twice a day) administered orally for 10 days. Tumor volumes were measured and individual tumors were plotted for each group (n= 5-8 animals/group). The tumors in vehicle treated group grew faster. Both compound 2 and compound 5 showed strong inhibition of tumor growth. Compound 5 showed a significant improvement over compound 2 in reducing tumor sizes (Figure 11).

In another experiment, three weeks after tumor cell injection, animals with large AML tumors were sorted based on tumor sizes into two groups. Animals were then treated with vehicle or 50 mg/kg of compound 5 (twice a day) administered orally for 3 and 6 days. Tumor volumes of each individual tumor were plotted. Compound 5 showed significant inhibition of the growth of large tumors (Figure 12).

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.

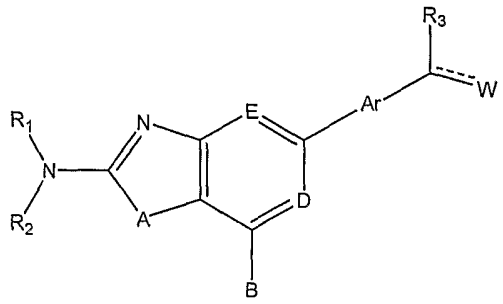
While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to

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.

5

We claim:

1. A compound of the formula:

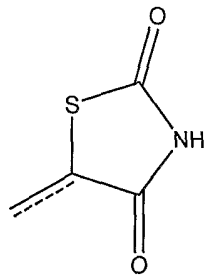


wherein:

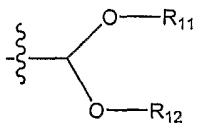
"-------" is present or absent;

W is (a) or (b)

(a)



(b)



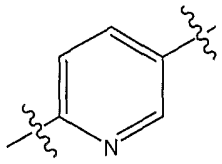
A is $-CR_{21}R_{22}$-, $-NR_{23}$-, -O-, or –S-;

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

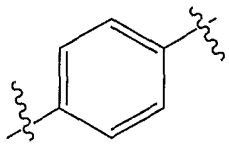
D and E are together or independently $-CR_{30}$-, or –N-;

Ar is (c) or (d)

(c)



(d)



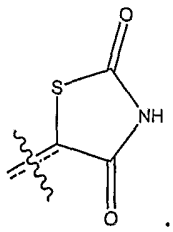
and

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 thereof.

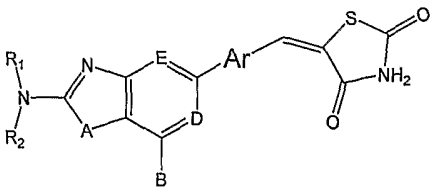
2. The compound of claim 1 wherein Rl and R2 are independently or together hydrogen, alkyl, substituted alkyl, haloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substi- tuted alkoxy, acyl, mono-substituted amino, di-substituted amino, carboxy, carboalkoxy, alkylcarboxamide,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

3. The compound of claim 2 wherein R_1 and R_2 are independently hydrogen, alkyl, substituted alkyl, arylalkyl, substituted aryalkyl, a disubstituted amino group, or abranched alkyl group with 2 to 10 carbon atoms.

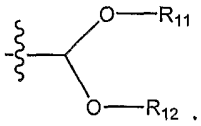
4. The compound of claim 1 wherein W is



5. The compound of claim 4 wherein R_3 is hydrogen, and "-----" represents a bond present.



6. The compound of claim 1 wherein W is

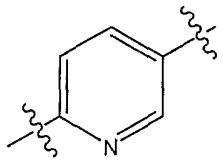


7. The compound of claim 6 wherein R11 and R12 are independently or together selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl,n-butyl, sec-butyl,t-butyl, amyl, t-amyl, and n-pentyl.

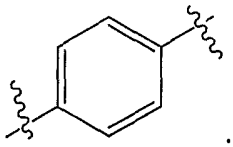
8. The compound of claim 1 wherein R_1 and R_2 are idependently or together hydrogen or alkyl.

9. The compound of claim 1 wherein Ar is either Formula (c) or (d):

(c)



(d)

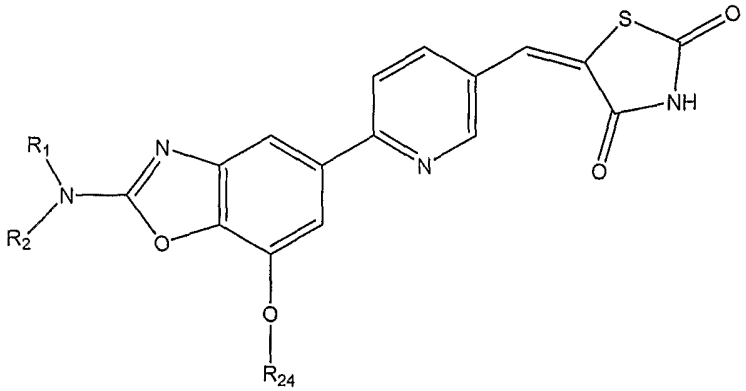


10. The compound of claim 2 wherein R_2 is hydrogen.

11. The compound of claim 2 wherein"-----" represents a bond present.

12. A compound of claim 2 wherein R_3 is hydrogen, methyl, or ethyl.

13. A compound of Formula (II):



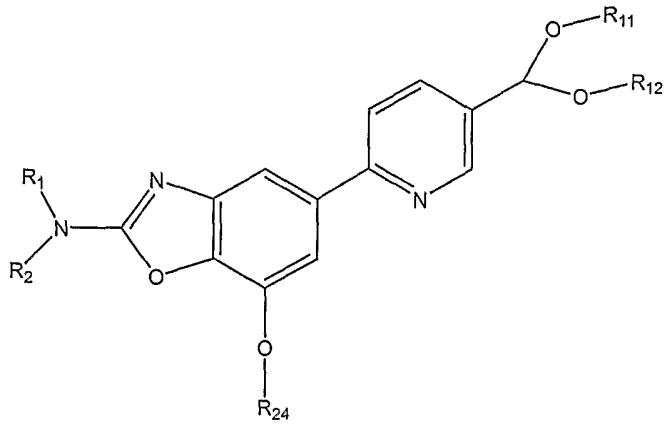
wherein:

R_1 is hydrogen; and

R_2 and R_{24} are each 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; or an isomer, metabolite, polymorph, prodrug, or salt thereof.

14. A compound selected from the group consisting of compounds 2, 5, and 8.

15. A compound of Formula (III):



wherein:

R_1 is hydrogen;

R_2 and R_{24} are each 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 each independently or together alky group.selected from the group consisiting 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 thereof.

16. A pharmaceutical composition, comprising a compound of any 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 anyone of claim 1 through 15.

18. The method of 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. The method of 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. The method of 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. The method of 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. The method of claim 17, wherein said modulation or inhibition occurs in a mammal, optionally in a human.

23. The method of 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 gastrointestinal cancer or other cancer.

24. The method of claim 23, wherein said modulation or inhibition occurs in a mammal, optionally in a human, having a cancer, optionally AML or gastrointestinal cancer.

Figure 1: Kinase Inhibition Profile of Compound 1

Binding Constants Kd (nM)	
Kinase Target	Compound I
ABL1 (T315I)	371
AURKA	232
CSF1R	80
FGFR3	271
FLT3	204
FLT3(D835H)	145
FLT3(ITD)	133
FLT3(N841I)	276
JAK2	388
KIT	451
KIT(V559D,T670I)	714
PDGFRB	333
RET	134
VEGFR	4000

Figure 2: MV4;11 cell killing by compounds 2, 3, 4 and 5

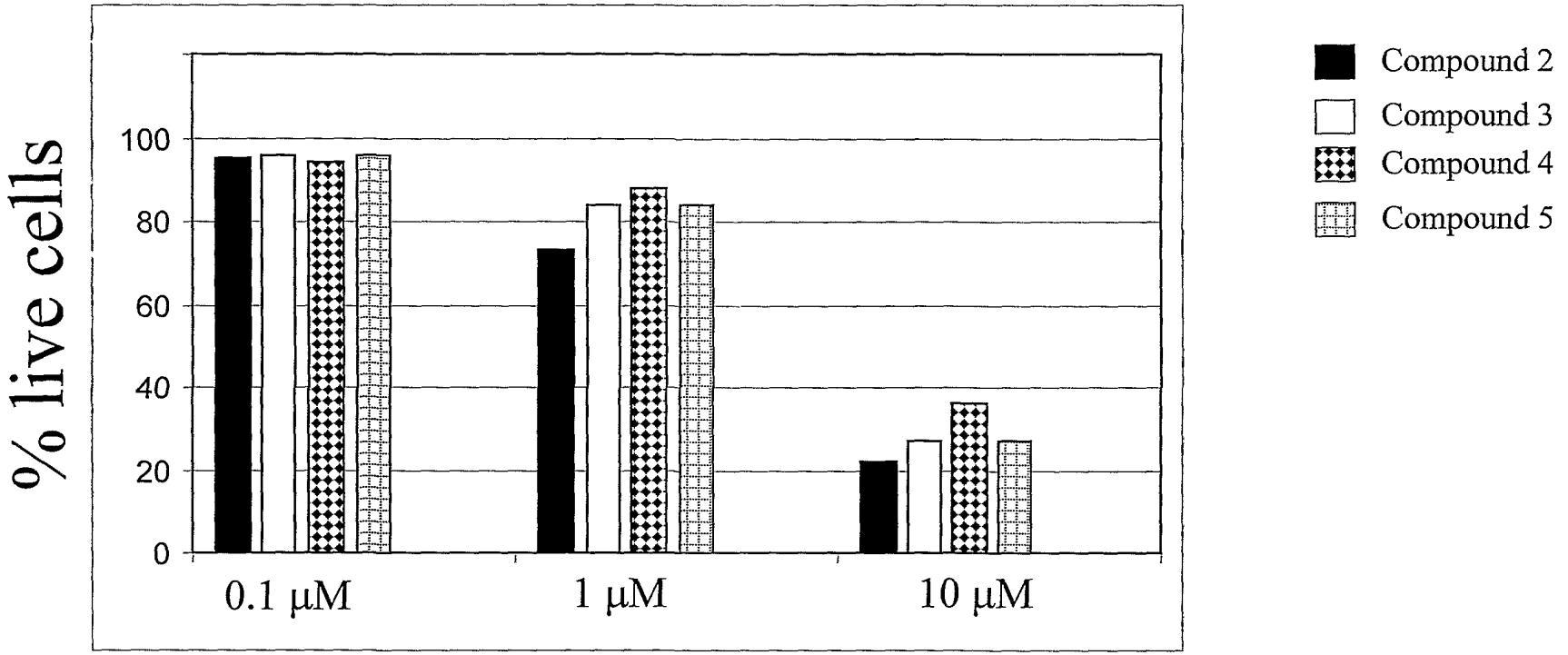


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Figure 3: Selectivity of cancer cell killing by Compound 1

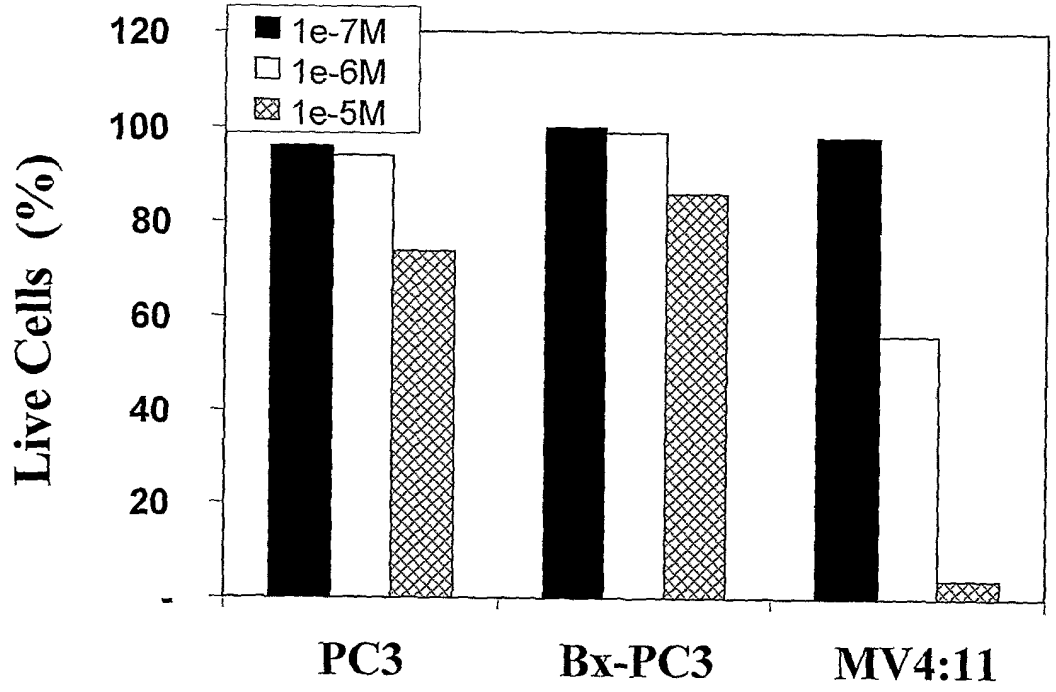

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Figure 4: Selectivity of kinase inhibition profile for Compounds 2, 5 and 8

Binding Constants Kd (nM)			
Kinase Target	**compound 2**	**Compound 5**	**Compound 8**
FLT3	488	332	95
FLT3(D835H)	1020	540	505
FLT3(ITD)	738	369	364
FLT3(N841I)	1140	975	526
KIT	1510	989	603
KIT(V559D,T670I)	1850	1650	740
PDGFRB	1190	1430	369
RET	1470	771	1240

Figure 5: Pharmacokinetic profiles of Compound 2

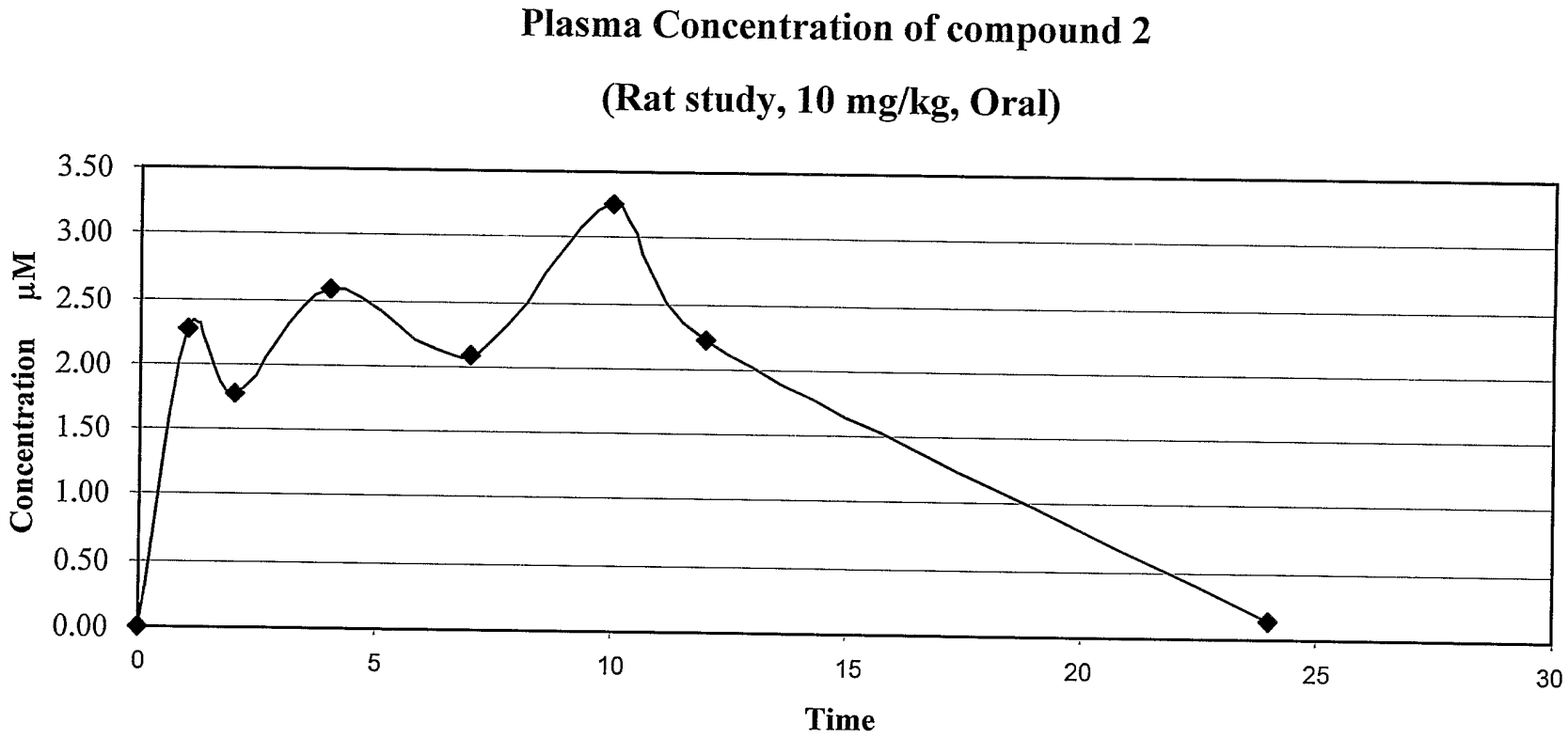

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Figure 6: Prevention of AML Tumor Progression in Athymic Mouse by Compound 2

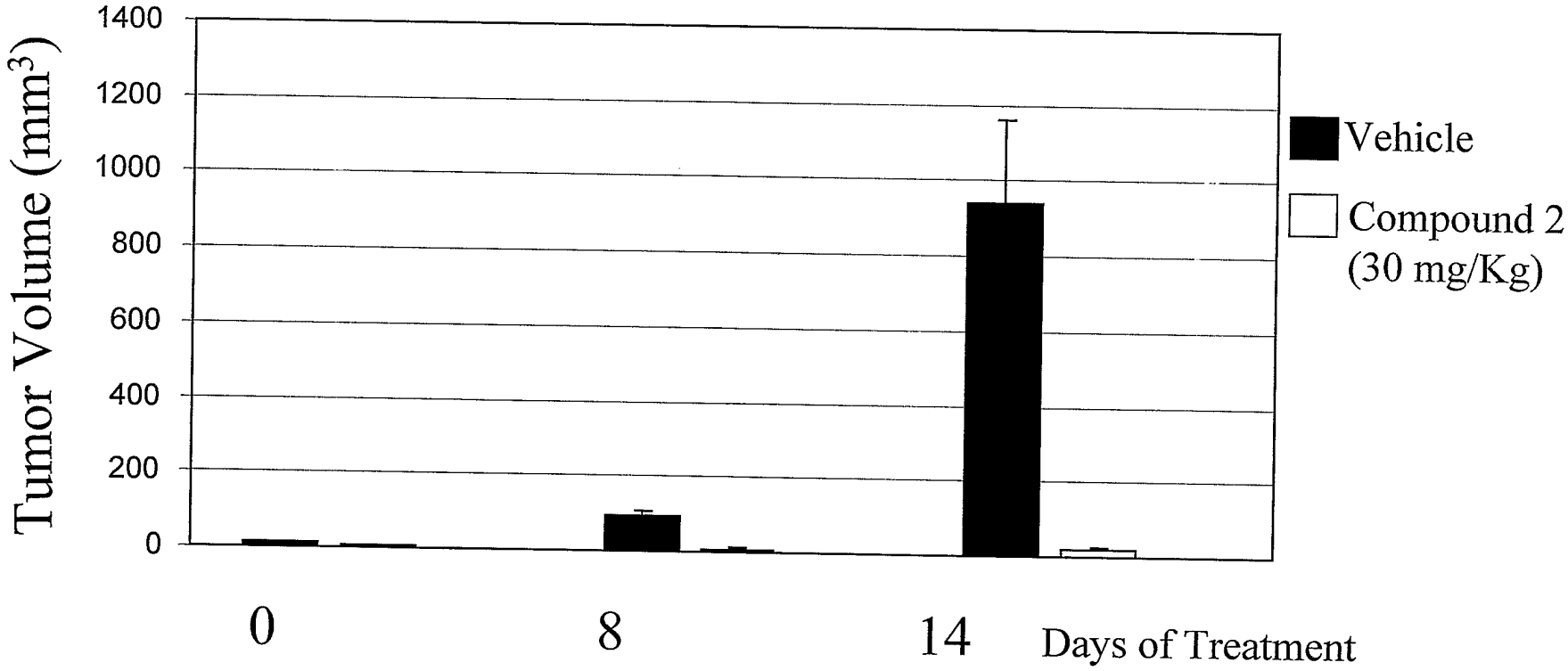

Figure 7: Regression of large AML tumors by compound 2 in nude mouse model

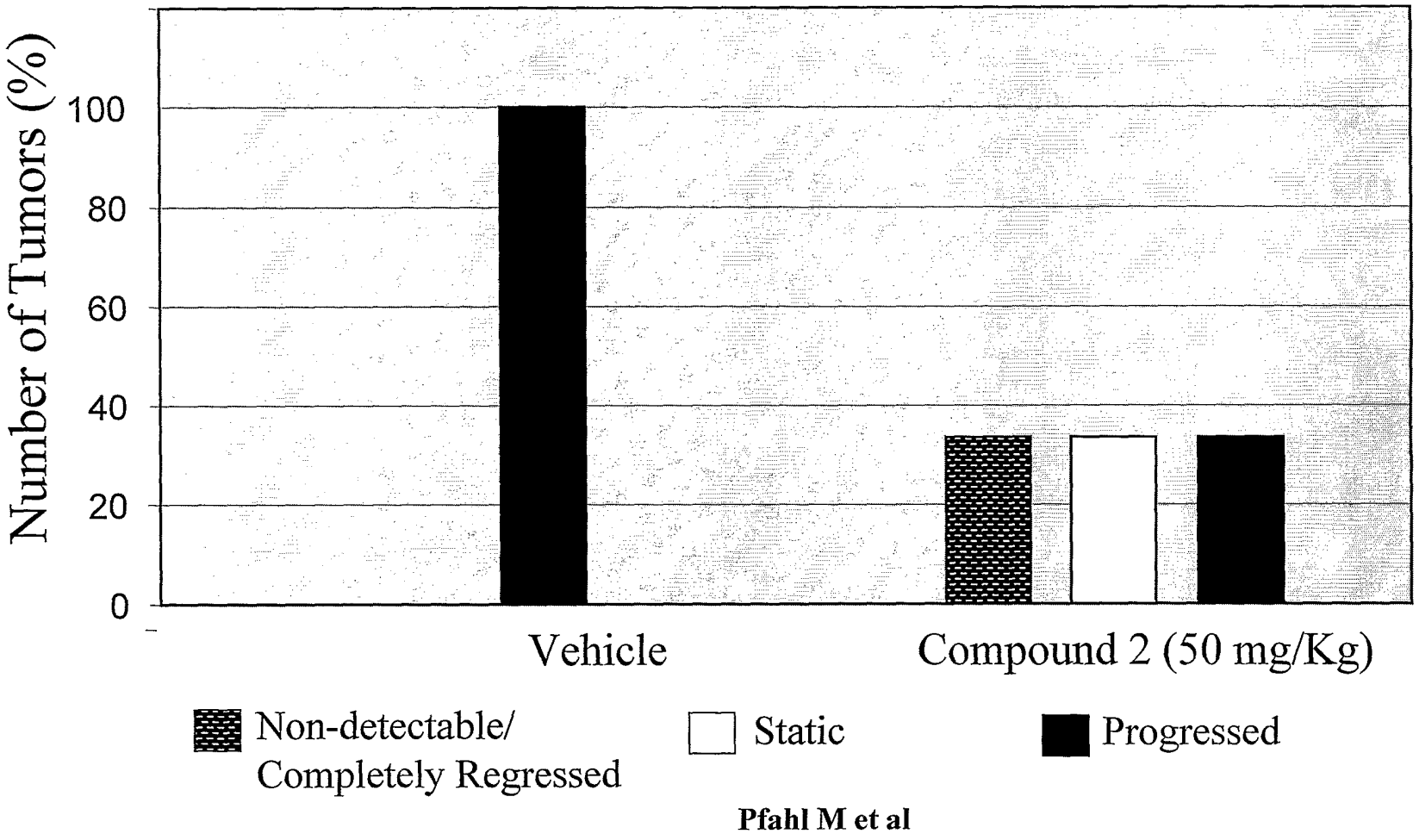

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Figure 8: Cell killing selectivity and kinase inhibition profile by compound 5

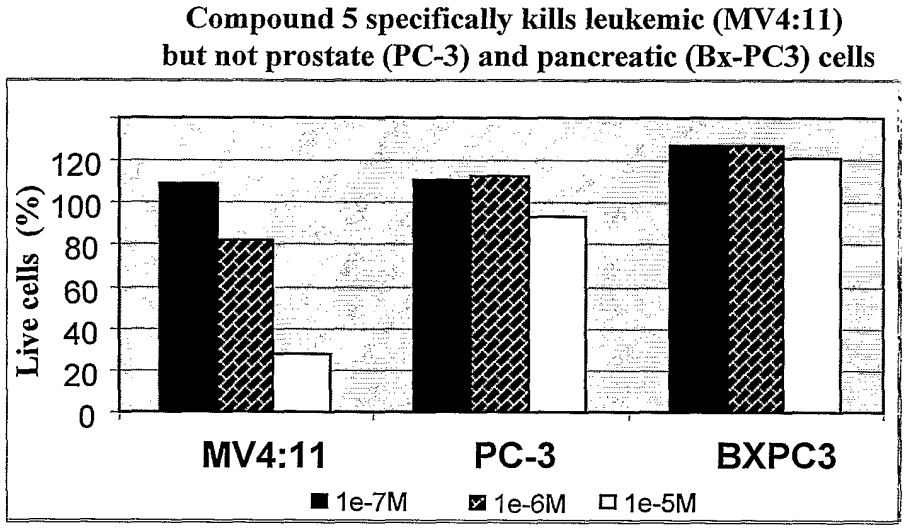

Figure 9: Pharmacokinetic profile of compound 5

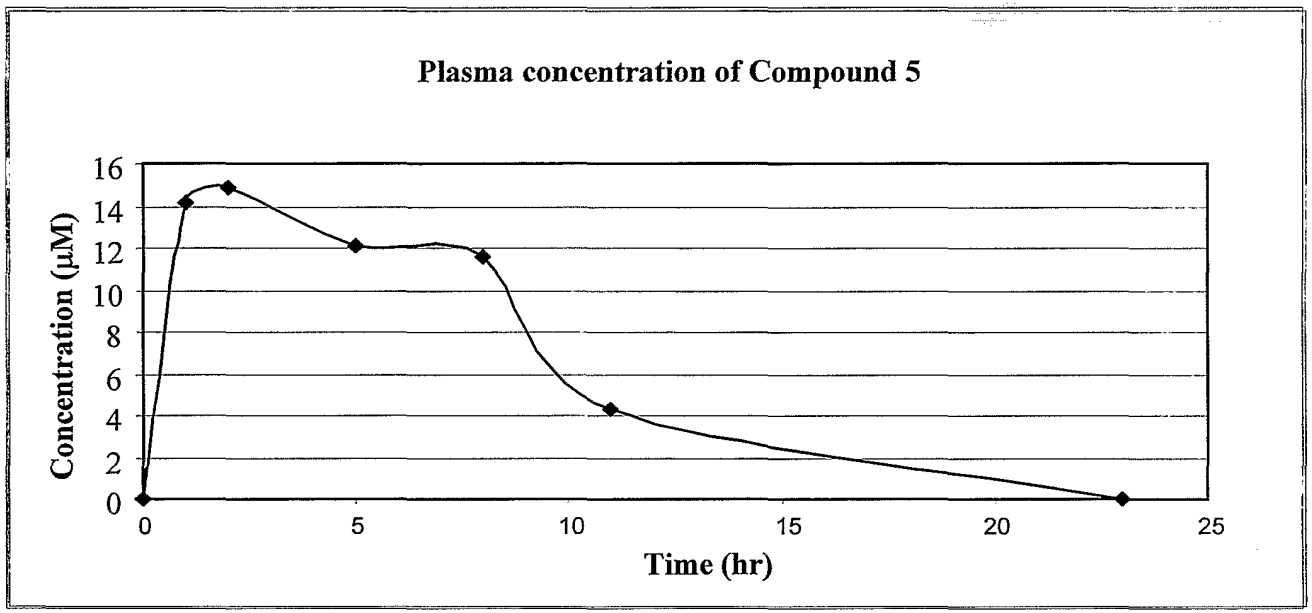

Figure 10: Efficacy of compound 5 in nude mouse model

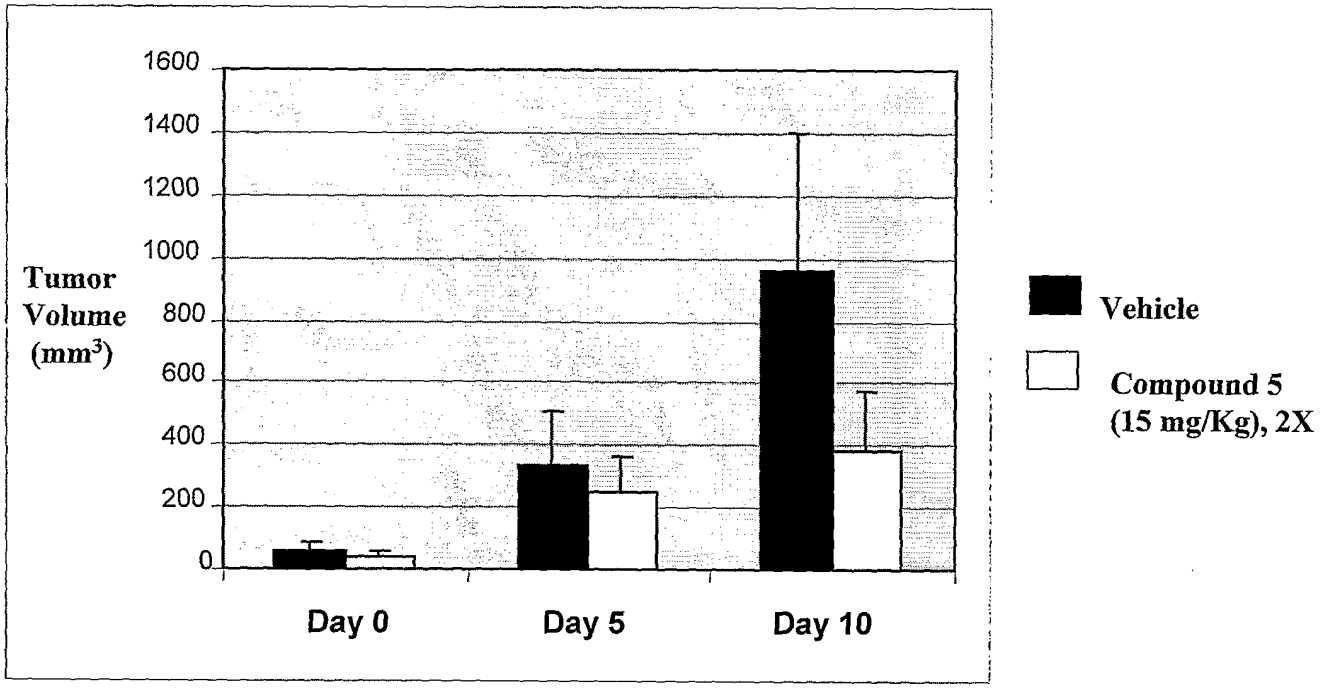

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Figure 11: Comparison of compound 2 and 5 in nude mouse model

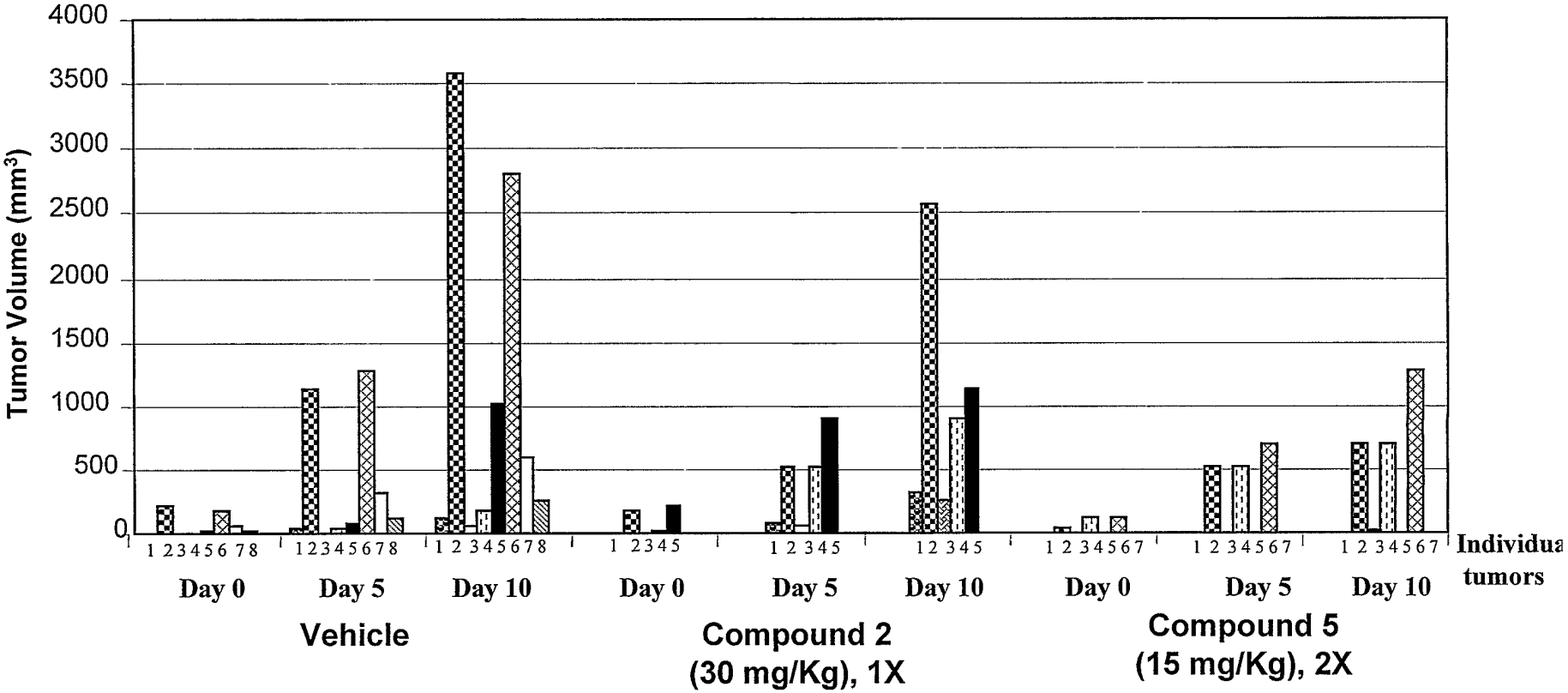

Figure 12: Inhibition of large established tumors in nude mouse by compound 5

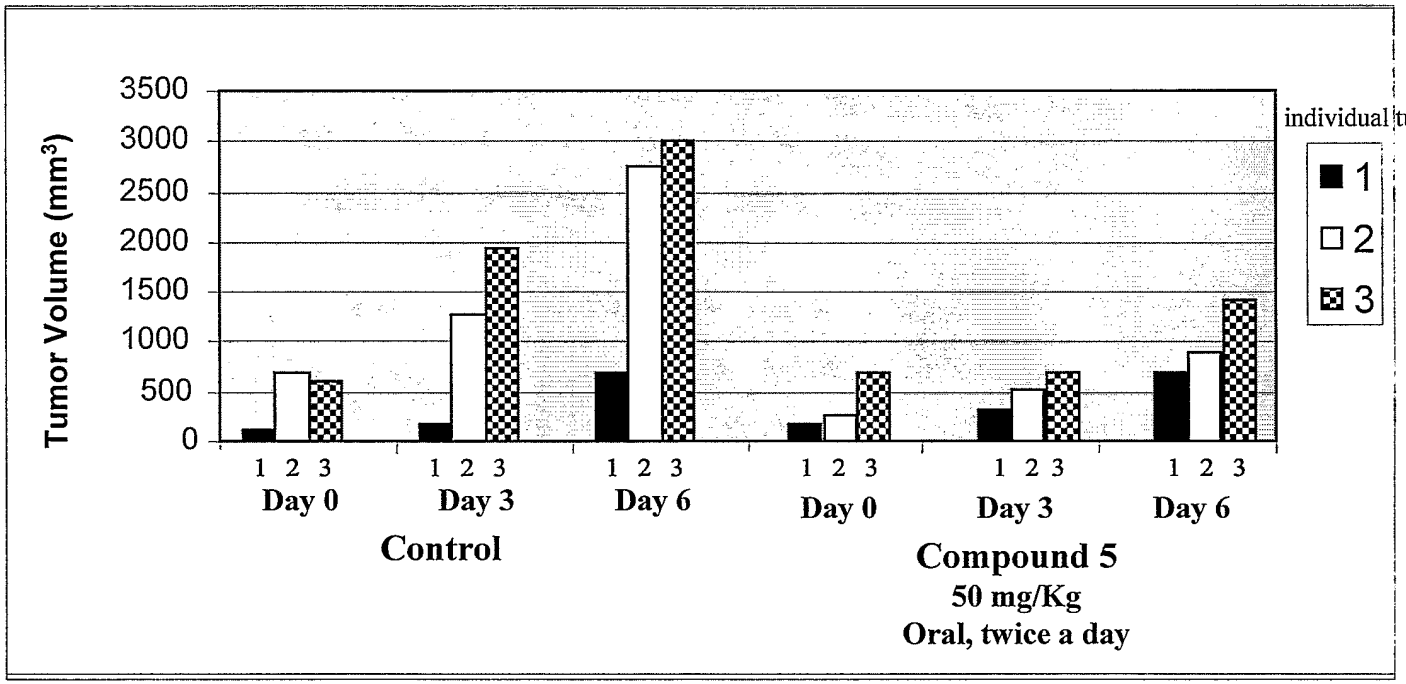

Figure 13

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