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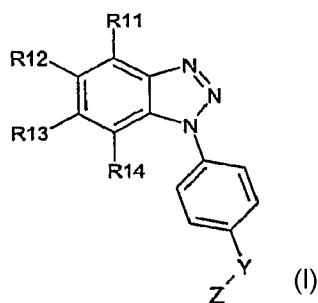
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(54) Title: N-PHENYLBENZOTRIAZOLYL C-KIT INHIBITORS



(57) Abstract: Compounds represented by Formula (I); or a pharmaceutically acceptable salt or N-oxide thereof, are useful in the treatment of cancer.

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TITLE OF THE INVENTION

N-PHENYLBENZOTRIAZOLYL C-KIT INHIBITORS

BACKGROUND OF THE INVENTION

[1] The present invention is directed to N-phenylbenzotriazolyl compounds. In particular, the present invention is directed to N-phenylbenzotriazolyl compounds that are inhibitors of the c-Kit proto-oncogene (also known as KIT, CD-117, stem cell factor receptor, mast cell growth factor receptor). The present invention is also directed to N-phenylbenzotriazolyl compounds that are inhibitors of c-Kit.

[2] The c-Kit proto-oncogene is believed to be important in embryogenesis, melanogenesis, hematopoiesis, and the pathogenesis of mastocytosis, gastrointestinal tumors, and other solid tumors, as well as certain leukemias, including AML. Accordingly, it would be desirable to develop novel compounds that are inhibitors of the c-Kit receptor.

[3] Many of the current treatment regimes for hyperproliferative disorders (cancer) utilize compounds that inhibit DNA synthesis. Such compounds' mechanism of operation is to be toxic to cells, particularly to rapidly dividing tumor cells. Thus, their broad toxicity can be a problem to the subject patient. However, other approaches to anti-cancer agents that act other than by the inhibition of DNA synthesis have been explored to try to enhance the selectivity of the anti-cancer action and thereby reduce adverse side-effects.

[4] It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e. a gene which, on activation, leads to the formation of malignant tumor cells). Many oncogenes encode proteins that are aberrant protein-tyrosine kinases capable of causing cell transformation. By a different route, the overexpression of a normal proto-oncogenic tyrosine kinase can also result in proliferative disorders, sometimes resulting in a malignant phenotype. Alternatively, co-expression of a receptor tyrosine kinase and its cognate ligand within the same cell type may also lead to malignant transformation.

[5] Receptor tyrosine kinases are large enzymes which span the cell membrane and possess i) an extracellular binding domain for growth factors such as KIT ligand (also known as stem cell factor (SCF), Steel factor (SLF) or mast cell growth factor (MGF)), ii) a transmembrane domain, and iii) an intracellular portion which functions as a kinase to phosphorylate specific tyrosine residues in proteins. Binding of KIT ligand to KIT tyrosine kinase results in receptor homodimerization, the activation of KIT tyrosine kinase activity, and the subsequent phosphorylation of a variety of protein substrates, many of which are effectors of intracellular signal transduction. These events can lead to enhanced cell proliferation or promote enhanced cell survival. With some receptor kinases, receptor heterodimerization can also occur.

[6] It is known that such kinases are frequently aberrantly expressed in common human cancers such as breast cancer, head and neck cancers, gastrointestinal cancer such as colon, rectal or stomach cancer, leukemia, and ovarian, bronchial, lung or pancreatic cancer. KIT kinase expression has been documented in a wide variety of human malignancies such as mastocytosis/ mast cell leukemia, gastrointestinal stromal tumors (GIST), small cell lung carcinoma (SCLC), sinonasal natural killer/T-cell lymphoma, testicular cancer (seminoma), thyroid carcinoma, malignant melanoma, ovarian carcinoma, adenoid

cystic carcinoma, acute myelogenous leukemia (AML), breast carcinoma, pediatric T-cell acute lymphoblastic leukemia, angiosarcoma, anaplastic large cell lymphoma, endometrial carcinoma, and prostate carcinoma. The kinase activity of KIT has been implicated in the pathophysiology of several of these - and additional tumors - including breast carcinoma, SCLC, GIST, germ cell tumors, mast cell leukemia, neuroblastoma, AML, melanoma and ovarian carcinoma.

[7] Several mechanisms of KIT activation in tumor cells have been reported, including activating mutations, autocrine and paracrine activation of the receptor kinase by its ligand, loss of protein-tyrosine phosphatase activity, and cross activation by other kinases. The transforming mechanisms initiated by the activating mutations are thought to include dimer formation and increased intrinsic activity of the kinase domain, both of which result in constitutive ligand-independent kinase activation, and possibly altered substrate specificity. More than thirty activating mutations of the Kit protein have been associated with highly malignant tumors in humans.

[8] Accordingly, it has been recognized that inhibitors of receptor tyrosine kinases are useful as selective inhibitors of the growth of mammalian cancer cells. For example, Gleevec™ (also known as imatinib mesylate, or STI571), a 2-phenylpyrimidine tyrosine kinase inhibitor that inhibits the kinase activity of the BCR-ABL fusion gene product, was recently approved by the U.S. Food and Drug Administration for the treatment of CML. Gleevec™, in addition to inhibiting BCR-ABL kinase, also inhibits the KIT kinase and PDGF receptor kinase, although it is not effective against all mutant isoforms of the KIT kinase. Kit ligand-stimulated growth of MO7e human leukemia cells is inhibited by Gleevec™, which also induces apoptosis under these conditions. By contrast, GM-CSF stimulated growth of MO7e human leukemia cells is not affected by Gleevec™. Further, in recent clinical studies using Gleevec™ to treat patients with GIST, a disease in which KIT kinase is involved in transformation of the cells, many of the patients showed marked improvement.

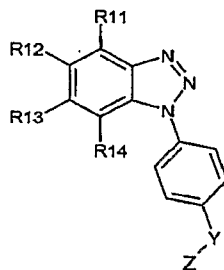
[9] These studies demonstrate how KIT kinase inhibitors can treat tumors whose growth is dependent on KIT kinase activity. Other kinase inhibitors show even greater kinase selectivity. For example, the 4-anilinoquinazoline compound Tarceva™ inhibits only EGF receptor kinase with high potency, although it can inhibit the signal transduction of other receptor kinases, probably by virtue of the fact that these receptors heterodimerize with EGF receptor.

[10] Although anti-cancer compounds such as those described above make a significant contribution to the art, there is a continuing need for improved anti-cancer pharmaceuticals, and it would be desirable to develop new compounds with better selectivity or potency, or with reduced toxicity or side effects.

[11] European patent EP293978 describes benzotriazole derivatives as aromatase inhibitors and German patent DE 3129447 describes benzotriazoles and their use as drugs.

SUMMARY OF THE INVENTION

[12] Compounds represented by Formula (I):

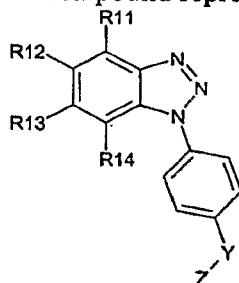


(I)

or a pharmaceutically acceptable salt or N-oxide thereof, are useful in the treatment of tumors.

DETAILED DESCRIPTION OF THE INVENTION

[13] The present invention is directed to a compound represented by Formula (I):



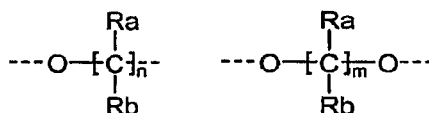
(I)

or a pharmaceutically acceptable salt or N-oxide thereof, wherein

R12 is $-\text{NR}^3\text{COR}^{31}$, $-\text{NR}^3\text{CONR}^{32}\text{R}^{31}$, $-\text{NR}^3\text{SO}_2\text{R}^{31}$, $-\text{CO}_2\text{R}^3$, $-\text{CO}_2\text{H}$, $-\text{C}_{0-8}\text{alkylNR}^3\text{R}^{31}$, $-\text{C}_{0-8}\text{alkylSO}_2\text{NR}^3\text{R}^{31}$, $-\text{C}_{0-8}\text{alkylSO}_2\text{R}^3$, heterocyclyl, hetaryl, or $-\text{CONR}^3\text{R}^{31}$;

R11, R13 and R14 are independently F, Cl, $\text{C}_{0-3}\text{alkyl}$, or $\text{C}_{0-8}\text{alkoxy}$;

Y is



Ra and Rb are each independently $\text{C}_{0-8}\text{alkyl}$ or $\text{C}_{3-8}\text{cycloalkyl}$;

or Ra and Rb taken together with the C to which they are attached form a saturated or partially unsaturated 3-10 membered ring optionally containing 0-4 N, O, S, SO, or SO_2 at the ring nodes, provided that no N, O or S atoms are placed adjacent to each other at ring nodes;

m is 2, 3, 4 or 5;

n is 1, 2, 3, 4 or 5;

Z is a cyclyl or heterocyclyl group, optionally substituted with 1-5 independent halogen, $-\text{NR}^{34}\text{R}^{35}$, $-\text{NR}^{34}\text{COR}^{35}$, $-\text{NR}^{34}\text{C(O)OR}^{35}$, $-\text{NR}^{34}\text{SO}_2\text{R}^{35}$, $-\text{OR}^{34}$, $-\text{SR}^{34}$, $-\text{SO}_2\text{R}^{34}$, $-\text{SO}_2\text{NR}^{34}\text{R}^{35}$, $-\text{C(O)OR}^{34}$, $-\text{CO}_2\text{H}$, $-\text{CONR}^{34}\text{R}^{35}$, $\text{C}_{0-8}\text{alkyl}$, $\text{C}_{2-8}\text{alkenyl}$, $\text{C}_{2-8}\text{alkynyl}$, CN, CF_3 , NO_2 , oxo, cyclyl or heterocyclyl substituents;

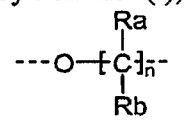
R^3 , R^{31} , R^{32} , R^{33} , R^{34} and R^{35} are independently $\text{C}_{0-8}\text{alkyl}$ optionally substituted with a heterocyclyl, CHF_2 , or OH substituent; $-\text{C}_{0-8}\text{alkyl}-\text{C}_{3-8}\text{cycloalkyl}$, CF_3 , $-\text{C}_{0-8}\text{alkyl}-\text{O}-\text{C}_{0-8}\text{alkyl}$, $-\text{C}_{0-}$

$\text{alkyl-N}(\text{C}_{0-8}\text{alkyl})(\text{C}_{0-8}\text{alkyl})$, $-\text{C}_{0-8}\text{alkyl-S}(\text{O})_{0-2}-\text{C}_{0-8}\text{alkyl}$; or heterocyclyl optionally substituted with $\text{C}_{0-8}\text{alkyl}$, cyclyl or substituted cyclyl substituent; or benzyl optionally substituted with $-\text{SO}_2-\text{NH}_2$.

[14] In one aspect, the present invention is directed to a compound represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{NR}^3\text{COR}^{31}$, $-\text{NR}^3\text{CONR}^{32}\text{R}^{31}$, $-\text{NR}^3\text{SO}_2\text{R}^{31}$, $-\text{CO}_2\text{R}^3$, $-\text{CO}_2\text{H}$, $-\text{C}_{0-8}\text{alkylNR}^3\text{R}^{31}$ or $-\text{CONR}^3\text{R}^{31}$; and the other variables are as described above for Formula (I).

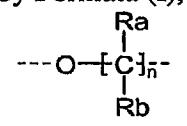
[15] In another aspect, the present invention is directed to a compound represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$; and the other variables are as described above for Formula (I).

[16] In an embodiment, the present invention is directed to a compound represented by Formula (I), or



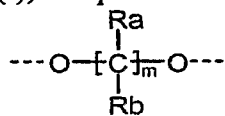
a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$; Y is Z is cyclyl; and the other variables are as described above for Formula (I).

[17] In an embodiment, the present invention is directed to a compound represented by Formula (I), or



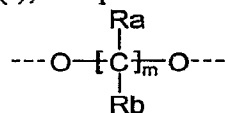
a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$; Y is Z is heterocyclyl; and the other variables are as described above for Formula (I).

[18] In another embodiment, the present invention is directed to a compound represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$; Y is



; Z is cyclyl; and the other variables are as described above for Formula (I).

[19] In another embodiment, the present invention is directed to a compound represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$; Y is



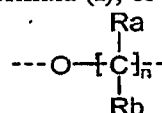
; Z is heterocyclyl; and the other variables are as described above for Formula (I).

[20] Thus, the invention includes compounds represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$.

[21] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$, and Z is cyclyl.

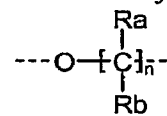
[22] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$ and Z is heterocyclyl.

[23] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable



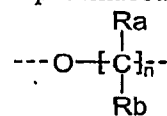
salt or N-oxide thereof, wherein R12 is $-\text{CONR}^3\text{R}^{31}$ and Y is

[24] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable



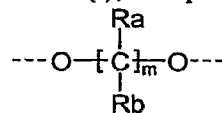
salt or N-oxide thereof, wherein R12 is -CONR³R³¹, Z is heterocyclyl, and Y is

[25] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable



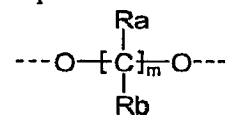
salt or N-oxide thereof, wherein R12 is -CONR³R³¹, Z is cyclyl, and Y is

[26] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable



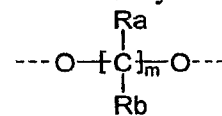
salt or N-oxide thereof, wherein R12 is -CONR³R³¹ and Y is

[27] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable



salt or N-oxide thereof, wherein R12 is -CONR³R³¹, Z is cyclyl, and Y is

[28] The invention includes compounds represented by Formula (I), or a pharmaceutically acceptable



salt or N-oxide thereof, wherein R12 is -CONR³R³¹, Z is heterocyclyl, and Y is

[29] Compounds of the invention include

N-(Pyridin-2-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-(Tetrahydro-2*H*-pyran-4-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-Methyl-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-(2-Hydroxyethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-Isopropyl-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

or a pharmaceutically acceptable salt, or *N*-oxide, thereof.

[30] As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanyl, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

[31] As used herein, "C₀₋₄alkyl" is used to mean an alkyl having 0-4 carbons – that is, 0, 1, 2, 3, or 4 carbons in a straight or branched configuration. An alkyl having no carbon is hydrogen when the alkyl is a terminal group. An alkyl having no carbon is a direct bond when the alkyl is a bridging (connecting) group.

[32] The terms "cycloalkyl", "carbocyclic ring", "cyclic", or "cyclyl" mean 3-10 membered mono or polycyclic aromatic, partially aromatic or non-aromatic ring carbocycles containing no heteroatoms, and

include mono-, bi-, and tricyclic saturated carbocycles, as well as fused and bridged systems. Such fused ring systems can include one ring that is partially or fully unsaturated, such as a benzene ring, to form fused ring systems, such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl and carbocyclic rings include C_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and decahydronaphthalene, adamantane, indanyl, 1,2,3,4-tetrahydronaphthalene and the like.

[33] The term "halogen" includes fluorine, chlorine, bromine, and iodine atoms.

[34] The term "carbamoyl" unless specifically described otherwise means $-C(O)-NH-$ or $-NH-C(O)-$.

[35] The term "aryl" is well known to chemists. The preferred aryl groups are phenyl and naphthyl.

[36] The term "hetaryl" is well known to chemists. The term includes 5- or 6-membered heteroaryl rings containing 1–4 heteroatoms chosen from oxygen, sulfur, and nitrogen in which oxygen and sulfur are not next to each other. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. The term "hetaryl" includes hetaryl rings with fused carbocyclic ring systems that are partially or fully unsaturated, such as a benzene ring, to form a benzofused hetaryl. For example, benzimidazole, benzoxazole, benzothiazole, benzofuran, quinoline, isoquinoline, quinoxaline, and the like.

[37] Unless otherwise stated, the terms "heterocyclic ring", "heterocycle", "heterocyclic", and "heterocyclyl" are equivalent, and is defined as for cyclic but also contains one or more atoms chosen independently from N, O, and S (and the N and S oxides), provided such derivatives exhibit appropriate and stable valencies and excludes moieties containing O-O, $S(O)_n-S(O)_n$, $S(O)_n-O$ bonds where $n=0-2$. The terms include 4–8-membered saturated rings containing one or two heteroatoms chosen from oxygen, sulfur, and nitrogen. Examples of heterocyclic rings include azetidine, oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, thiazolidine, oxazolidine, oxazetidine, pyrazolidine, isoxazolidine, isothiazolidine, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, homopiperazine, morpholine, thiomorpholine, and the like. Other examples of heterocyclic rings include the oxidized forms of the sulfur-containing rings. Thus, tetrahydrothiophene-1-oxide, tetrahydrothiophene-1,1-dioxide, thiomorpholine-1-oxide, thiomorpholine-1,1-dioxide, tetrahydrothiopyran-1-oxide, tetrahydrothiopyran-1,1-dioxide, thiazolidine-1-oxide, and thiazolidine-1,1-dioxide are also considered to be heterocyclic rings. The term "heterocyclic" also includes fused ring systems, including het-het fused systems, and can include a carbocyclic ring that is partially or fully unsaturated, such as a benzene ring, to form benzofused heterocycles. For example, 3,4,-dihydro-1,4-benzodioxine, tetrahydroquinoline, tetrahydroisoquinoline and the like.

[38] Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to

prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

[39] The invention also encompasses a pharmaceutical composition that is comprised of a compound of Formula I in combination with a pharmaceutically acceptable carrier.

[40] Preferably, the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of Formula I as described above (or a pharmaceutically acceptable salt or *N*-oxide thereof).

[41] Moreover, within this preferred embodiment, the invention encompasses a pharmaceutical composition for the treatment of disease by the inhibition of the c-Kit kinase, which may be a wild-type or mutant form of the protein, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above (or a pharmaceutically acceptable salt or *N*-oxide thereof).

[42] The compounds and compositions of the present invention are effective for treating mammals such as, for example, humans.

[43] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, *N*',*N*'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[44] When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, *p*-toluenesulfonic acid and the like. Particularly preferred are citric, hydrochloric, maleic, phosphoric, sulfuric, methanesulfonic, and tartaric acids.

[45] The pharmaceutical compositions of the present invention comprise a compound represented by formula I (or a pharmaceutically acceptable salt or *N*-oxide thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including

subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

[46] In practice, the compounds represented by Formula I, or pharmaceutically acceptable salts or N-oxides thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration. E.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or a pharmaceutically acceptable salt or N-oxide thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[47] Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt or N-oxide of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts or N-oxides thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

[48] The pharmaceutical compositions of this invention include a pharmaceutically acceptable liposomal formulation containing a compound of Formula I or a pharmaceutically acceptable salt or N-oxide thereof.

[49] The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[50] In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

[51] A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be

prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent or other such excipient. These excipients may be, for example, inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer time. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be used.

[52] In hard gelatin capsules, the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. In soft gelatin capsules, the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

[53] For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material, which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

[54] Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

[55] Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[56] Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or a pharmaceutically acceptable salt or N-oxide thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

[57] Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

[58] In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts or N-oxides thereof, may also be prepared in powder or liquid concentrate form.

[59] Generally, dosage levels on the order of from about 0.01mg/kg to about 750mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 75g per patient per day. For example, breast cancer, head and neck cancers, and gastrointestinal cancer such as colon, rectal or stomach cancer may be effectively treated by the administration of from about 0.01 to 500mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 50g per patient per day.

[60] Similarly, leukemia, ovarian, bronchial, lung, and pancreatic cancer may be effectively treated by the administration of from about 0.01 to 500mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 50g per patient per day.

[61] Mastocytosis/ mast cell leukemia, gastrointestinal stromal tumors (GIST), small cell lung carcinoma (SCLC), sinonasal natural killer/T-cell lymphoma, testicular cancer (seminoma), thyroid carcinoma, malignant melanoma, ovarian carcinoma, adenoid cystic carcinoma, acute myelogenous leukemia (AML), breast carcinoma, pediatric T-cell acute lymphoblastic leukemia, angiosarcoma, anaplastic large cell lymphoma, endometrial carcinoma, and prostate carcinoma may be effectively treated by the administration of from about 0.01 to 500mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 50g per patient per day.

[62] It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

[63] The compounds of the present invention, or pharmaceutically acceptable salts or N-oxides thereof, can also be effectively administered in conjunction with other cancer therapeutic compounds. For example, cytotoxic agents and angiogenesis inhibiting agents can be advantageous co-agents with the compounds of the present invention. Accordingly, the present invention includes compositions comprising the compounds represented by Formula I, or a pharmaceutically acceptable salt or N-oxide thereof, and a cytotoxic agent or an angiogenesis-inhibiting agent. The amounts of each can be therapeutically effective alone – in which case the additive effects can overcome cancers resistant to treatment by monotherapy. The amounts of any can also be subtherapeutic – to minimize adverse effects, particularly in sensitive patients.

[64] It is understood that the treatment of cancer depends on the type of cancer. For example, lung cancer is treated differently as a first line therapy than are colon cancer or breast cancer treated. Even within lung cancer, for example, first line therapy is different from second line therapy, which in turn is different from third line therapy. Newly diagnosed patients might be treated with cisplatin containing regimens. Were that to fail, they move onto a second line therapy such as a taxane. Finally, if that failed, they might get a tyrosine kinase EGFR inhibitor as a third line therapy. Further, The regulatory approval process differs from country to country. Accordingly, the accepted treatment regimens can differ from country to country. Nevertheless, the compounds of the present invention, or pharmaceutically acceptable salts or *N*-oxides thereof, can be beneficially co-administered in conjunction or combination with other such cancer therapeutic compounds. Such other compounds include, for example, a variety of cytotoxic agents (alkylators, DNA topoisomerase inhibitors, antimetabolites, tubulin binders); inhibitors of angiogenesis; and different other forms of therapies including kinase inhibitors such as Tarceva, monoclonal antibodies, and cancer vaccines. Other such compounds that can be beneficially co-administered with the compounds of the present invention include doxorubicin, vincristine, cisplatin, carboplatin, gemcitabine, and the taxanes. Thus, the compositions of the present invention include a compound according to Formula I, or a pharmaceutically acceptable salt or *N*-oxide thereof, and an anti-neoplastic, anti-tumor, anti-angiogenic, or chemotherapeutic agent.

[65] The compounds of the present invention, or pharmaceutically acceptable salts or *N*-oxides thereof, can also be effectively administered in conjunction with other therapeutic compounds, aside from cancer therapy. For example, therapeutic agents effective to ameliorate adverse side-effects can be advantageous co-agents with the compounds of the present invention.

[66] **Assay for inhibition of c-Kit in intact cells**

[67] The ability of compounds to inhibit the tyrosine kinase activity of c-Kit was determined in a cell-based ELISA assay using the H526 cell line (ATCC # CRL-5811), which was originally derived from a human small cell lung cancer. The assay determines the ability of compounds to block ligand-stimulated tyrosine phosphorylation of the wild-type c-Kit receptor protein that is endogenously expressed in H526 cells. Cells are pre-incubated with compounds at various concentrations prior to addition of stem cell factor (SCF), the ligand for the c-Kit receptor tyrosine kinase. Cell lysates are then prepared and the c-Kit protein is captured onto a c-Kit antibody-coated 96-well ELISA plate. The phosphotyrosine content of the receptor protein is then monitored by quantitation of the degree of binding of an antibody that recognizes only the phosphorylated tyrosine residues within the captured protein. The antibody used has a reporter enzyme (e.g. horseradish peroxidase, HRP) covalently attached, such that binding of antibody to phosphorylated c-Kit can be determined quantitatively by incubation with an appropriate HRP substrate.

[68] The stock reagents used are as follows:

Cell lysis buffer:

50 mM Tris-HCl, pH 7.4
150 mM NaCl
10% Glycerol
1% Triton X-100
0.5 mM EDTA

1 $\mu\text{g/mL}$ leupeptin

1 $\mu\text{g/mL}$ aprotinin

1 mM Sodium orthovanadate

[69] Anti c-Kit antibody:

0.5 $\mu\text{g/mL}$ anti c-Kit Ab-3 (Lab Vision, catalog #MS289P1) in 50mM Sodium bicarbonate, pH 9.

[70] ELISA Assay plates:

ELISA assay plates are prepared by addition of 100 μL of anti c-Kit antibody to each well of a 96-well Microlite-2 plate (Dynex, catalog # 7417), followed by incubation at 37°C for 2h. The wells are then washed twice with 300 μL wash buffer.

[71] Plate wash buffer:

PBS containing 0.5% Tween-20 (PBST)

[72] Cell assay medium:

RPMI with 0.1% BSA

[73] pY20-HRP:

25ng/mL pY20-HRP (Calbiochem, catalog # 525320) in PBS, containing 0.5% Tween-20, 5% BSA, 1 mM Sodium orthovanadate

[74] HRP substrate:

Chemoluminescent detection reagent (Pierce, catalog # 37075)

[75] Assay protocol:

[76] Cultures of H526 cells, growing in RPMI with 10% fetal calf serum, were collected by centrifugation, washed twice with PBS, and suspended in cell assay medium. Cells were then distributed into a V-bottom 96-well plate at 7.5×10^4 cells per well in 100 μL cell assay medium.

[77] Compound dilutions were prepared from 10mM DMSO stocks by dilution in cell assay medium, the final concentration of DMSO in the assay being 0.1%. To compound incubation wells, 50 μL of the test compound was added (compounds are assayed at concentrations between 0.1nM and 100 μM); to positive and negative control wells, 50 μL cell assay medium containing 0.1% DMSO was added. The cells were then incubated with compound at 37°C for 3h. SCF (R&D Systems, catalog #255-SC-010) was then added in order to stimulate the Kit receptor and induce its tyrosine phosphorylation. Then, 10 μL of a 1.6 $\mu\text{g/mL}$ solution of SCF in cell assay medium was added to all wells apart from the negative control wells, and the cells were incubated for an additional 15min at 37°C. Following the addition of ice-cold PBS, the plate was centrifuged at 1000rpm for 5min, the medium removed by aspiration, and the cell pellet lysed by the addition of 120 μL ice-cold cell lysis buffer per well. The plate was kept on ice for 20min and 100 μL of the cell lysates from each well were then transferred to the wells of an ELISA assay plate and incubated at 4°C for 16h.

[78] Following incubation of the cell lysates in the ELISA plate, the wells were washed 4 times with 300 μL wash buffer, then 100 μL of the phosphotyrosine detection antibody pY20-HRP was added to each well and the plate incubated at rt for 2h. The wells were then washed 4 times with 300 μL wash buffer. Then, 50 μL of the chemiluminescent HRP substrate was added to each well for luminometric quantitation of the amount of antiphosphotyrosine-HRP conjugate bound to the plate.

[79] Comparison of the assay signals obtained in the presence of compound with those of the positive and negative controls (cells incubated in the presence or absence of SCF, with no compound added),

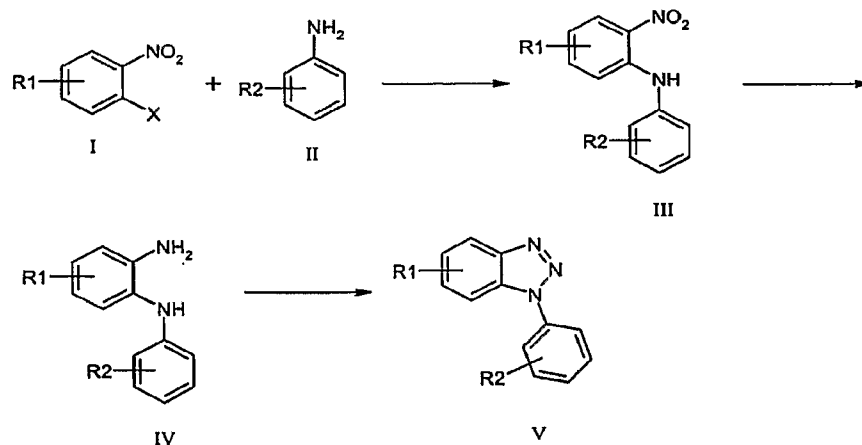
allows the degree of inhibition of c-Kit receptor tyrosine phosphorylation to be determined over a range of compound concentrations. These inhibition values were fitted to a sigmoidal dose-response inhibition curve to determine the IC_{50} values (i.e. the concentration of compound that inhibits SCF-induced tyrosine phosphorylation of the c-Kit protein by 50%).

[80] The **EXAMPLES** of this invention reduced the level of SCF-induced tyrosine phosphorylation of Kit in intact H526 cells as determined in the above assay with IC_{50} values between than $4\mu M$ and $0.04\mu M$.

EXPERIMENTAL

[81] The **EXAMPLES** of the present invention were prepared according to the following procedures by the methods illustrated in the following schemes. Appropriate solvents, temperatures, pressures and other reaction conditions may be readily selected by one of ordinary skill in the art. Similarly, suitable starting materials may be commercially obtained or readily prepared by one skilled in the art.

Scheme 1



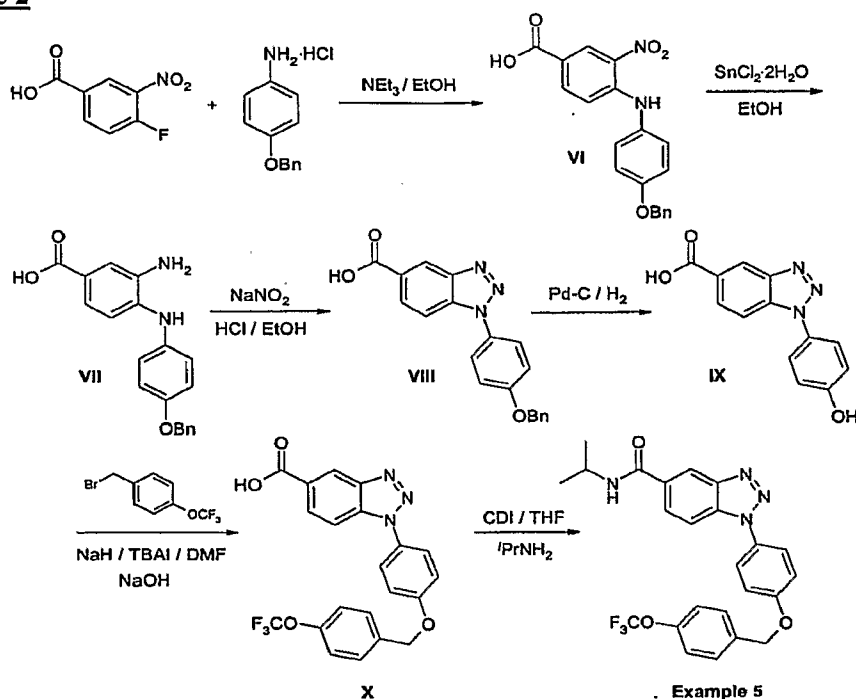
[82] In Scheme 1, diarylamines (III) may be produced from the condensation of nitrobenzenes (I, X = F, OMS, OTs) with substituted anilines (II). Coupling of the anilines (II) may also be achieved where X = I, Br, Cl, OTf by utilisation of Pd(0) mediated Buchwald-Hartwig-type conditions (such as those described in *J. Organic Chem.*, (1996), 61(21), 7240) or with Cu(I) catalysts and base (e.g. K_2CO_3). Reduction of III to give the phenylenediamines (IV) may be achieved using for example, hydrogen in the presence of a suitable transition metal catalyst (palladium, platinum, ruthenium, nickel), iron, zinc or tin under acidic conditions, with sodium hydrosulphite or with tin(II)chloride dihydrate. Cyclisation of IV to the benzotriazoles (V) may be achieved by reaction with a suitable nitrite derivative such as sodium nitrite.

[83] Functionalities R1 and R2, may be included into the target molecules through appropriate choice of starting materials, e.g. of type I, II, and VI. Where the final functionality is not available directly through this process, or where such functionality may be compromised during the subsequent chemistry to build the final molecule, alternative functionalities may be used and subsequently transformed into the final desired functionality by methods, and at points in the sequence, readily determined by one skilled in the art.

[84] For example, a non-exhaustive list of such transformations includes the conversions: OMe→OH (BBr₃), NH₂→Cl (NaNO₂, CuCl), Br→CN (Pd₂(dba)₃, Zn(CN)₂, DPPF), Me→CO₂H (KMnO₄), CO₂H→CO₂Me (MeOH, H₂SO₄), OH→OAlkyl (Alkyl halide, base), CO₂H→CONR'R'' (EDC, HOAt, DIPEA, HNR'R''), Br→CO₂Me (Pd₂(dba)₃, DPPF, CO(g), MeOH), Br→CO₂H (t-BuLi, CO₂), Ar-H→Ar-Br (NBS), CN→CO₂H (conc. H₂SO₄), Br→NR'R'' (Pd₂(dba)₃, DPPF, HNR'R'').

[85] A representative example of the synthesis of a target molecule and the incorporation of such functionality is shown below in Scheme 2.

Scheme 2



[86] Condensation of 4-benzyloxylaniline hydrochloride with 4-fluoro-3-nitrobenzoic acid occurs through heating in ethanol in the presence of triethylamine to give VI which may be reduced with tin chloride in ethanol to give the phenylenediamine VII. Cyclization to the benzotriazole (VIII) and removal of the benzyl protecting group is achieved by reaction with sodium nitrite and hydrochloric acid, and hydrogenation over 10% Pd/C, respectively. The resulting phenol (IX) can then be alkylated, for example, with a suitable benzyl halide derivative in the presence of sodium hydride to give intermediate X, which can then be coupled with a suitable amine such as isopropylamine in the presence of CDI to give the target molecule (EXAMPLE 5).

[87] Definitions: EDC = ethyl dimethylaminopropylcarbodiimide hydrochloride, HOAt = 1-hydroxyazabenzotriazole, HOBt = 1-hydroxybenzotriazole, CDI = 1,1'-carbonyldiimidazole, TBTU = O-benzotriazole-N,N,N',N'-tetramethyluronium tetrafluoroborate, HATU = azabenzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate, DIPEA = diisopropylethylamine, TEA = triethylamine, DMF = N,N-dimethylformamide, NMP = N-methylpyrrolidinone, DCM = dichloromethane, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid, Boc = t-butoxycarbonyl, Fmoc = fluorenylmethyloxycarbonyl, DMSO = dimethylsulphoxide, OMs = OSO₂Me, OTs = OSO₂-(4-Me)Ph, OTf = OSO₂CF₃, DPPF = 1,1'-bis(diphenylphosphino)ferrocene, NBS = N-bromosuccinimide, HCl (aq)

= aqueous hydrochloric acid, DMA = N,N-dimethylacetamide, MeOH = methanol, EtOH = ethanol, EtOAc = ethyl acetate, DCM = dichloromethane, THF = tetrahydrofuran, HOAc = acetic acid, DMF = N,N-dimethylformamide, HPLC = high performance liquid chromatography, rt = room temp.

EXAMPLE 1

N-(Pyridin-3-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1H-benzotriazole-5-carboxamide

4-{[4-(Benzyloxy)phenyl]amino}-3-nitrobenzoic acid

[88] A solution of 4-fluoro-3-nitrobenzoic acid (10.0g, 54.0mmol), 4-benzyloxyaniline hydrochloride (12.7g, 54.0mmol) and Et₃N (7.5mL, 54.0mmol) in EtOH (54mL) was heated at reflux under N₂ overnight. The reaction was then cooled to rt and acidified with aq HCl (4mL, few drops) to afford 4-{[4-(benzyloxy)phenyl]amino}-3-nitrobenzoic acid as a red solid which was collected by filtration.

3-Amino-4-{[4-(benzyloxy)phenyl]amino}benzoic acid

[89] A solution of SnCl₂·2H₂O (9.29g, 41.2mmol) and 4-{[4-(benzyloxy)phenyl]amino}-3-nitrobenzoic acid (3.00g, 8.23mmol) in EtOH (36mL) was heated at reflux under N₂ for 5.5h. The mixture was then cooled to rt, treated with 2M aq NaOH to pH 11 and filtered through Celite. The Celite pad was rinsed with excess MeOH and the combined filtrate was stripped of the organic solvents under reduced pressure. The aqueous residue was acidified to pH 5 (2M aq HCl), extracted with DCM (2x 50mL), and the combined organic layers washed with brine, dried (MgSO₄) and concentrated under reduced pressure to afford 3-amino-4-{[4-(benzyloxy)phenyl]amino}benzoic acid.

1-[4-(Benzyloxy)phenyl]-1H-benzotriazole-5-carboxylic acid

[90] A suspension of 3-amino-4-{[4-(benzyloxy)phenyl]amino}benzoic acid (1.0g, 2.9mmol) in EtOH (29mL) was briefly sonicated and then treated with concentrated aq HCl (0.72mL) at 0°C. NaNO₂ (0.22g, 3.2mmol) was added in portions over 40min with stirring at 0°C, then the stirring was continued for 15min at rt. The reaction mixture was diluted with water (100mL) and then extracted with DCM (2 x 40mL). The combined extracts were washed with brine (3 x 20mL) and concentrated under reduced pressure. The aqueous layer was further extracted with EtOAc (2 x 40mL) and the extracts dried (Na₂SO₄) and concentrated under reduced pressure. The materials from both DCM and EtOAc, extractions were combined to provide 1-[4-(benzyloxy)phenyl]-1H-benzotriazole-5-carboxylic acid as a light purple solid.

1-(4-Hydroxyphenyl)-1H-benzotriazole-5-carboxylic acid

[91] A mixture of 1-[4-(benzyloxy)phenyl]-1H-benzotriazole-5-carboxylic acid (0.77g, 2.2mmol) and Pd (on activated carbon: 10% wt, 50% H₂O, 24mg, 0.11mmol) in THF (108mL) was stirred under H₂ (1atm) at rt overnight. The reaction mixture was then filtered through a pad of Celite and concentrated under reduced pressure to afford 1-(4-hydroxyphenyl)-1H-benzotriazole-5-carboxylic acid as a brown-purple solid.

1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1H-benzotriazole-5-carboxylic acid

[92] NaH (60% dispersion in mineral oil, 0.253g, 6.3mmol) and TBAI (0.078g, 0.21mmol) were added in one portion to a solution of 1-(4-hydroxyphenyl)-1H-benzotriazole-5-carboxylic acid (0.54g, 2.1mmol) in anhydrous DMF (33mL) at 0°C. After stirring for 15min, 1-(bromomethyl)-4-(trifluoromethoxy)benzene (1.20mL, 7.5mmol) was added. The reaction was allowed to warm to rt and

stirring was continued overnight. Aqueous NaOH (2.0M, 2.1mL, 4.2mmol) was then added and the reaction was stirred for 6h at rt. The reaction was partitioned between water and EtOAc, the aqueous layer separated and acidified to pH 5, then extracted with EtOAc. The organic extracts were dried (Na₂SO₄) and concentrated under reduced pressure to 1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxylic acid.

***N*-(Pyridin-3-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide**

[93] A solution of 1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxylic acid (54mg, 0.13mmol) and CDI (41mg, 0.25mmol) in THF (5mL) was heated at 60°C for 3h. 1-Pyridin-3-ylmethanamine (0.026mL, 0.25mmol) was then added and the mixture was heated for a further 2days. The reaction solution was then concentrated *in vacuo*, the residue dissolved in EtOAc (30mL) and this resulting solution washed with brine (3 x 10mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude product thus isolated was purified by mass-directed preparative HPLC to afford *N*-(pyridin-3-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide. ¹H NMR (400 MHz, CD₃OD): δ = 4.68 (s, 2H), 5.26 (s, 2H), 7.28-7.30 (m, 4H), 7.45 (dd, J = 7.6 Hz, 5.2 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 9.2 Hz, 2H), 7.88 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 8.13 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 8.46 (br, 1H), 8.55 (s, 1H) and 8.60-8.61 (m, 2H). MS (ES⁺): *m/z* 520.5 (100) [MH⁺].

EXAMPLE 2

***N*-(Tetrahydro-2*H*-pyran-4-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide**

[94] Prepared according to the procedure described above for Example 1, except using 1-(tetrahydro-2*H*-pyran-4-yl)methanamine in place of 1-pyridin-3-ylmethanamine. MS (ES⁺): *m/z* 527.6 [MH⁺].

EXAMPLE 3

***N*-methyl-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide**

[95] Prepared according to the procedure described above for Example 1, except using methylamine in place of 1-pyridin-3-ylmethanamine. MS (ES⁺): *m/z* 443.4 [MH⁺].

EXAMPLE 4

***N*-(2-Hydroxyethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide**

[96] Prepared according to the procedure described above for Example 1, except using 2-aminoethanol in place of 1-pyridin-3-ylmethanamine. MS (ES⁺): *m/z* 473.5 [MH⁺].

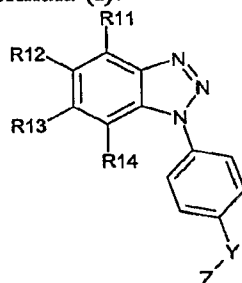
EXAMPLE 5

***N*-Isopropyl-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide**

[97] Prepared according to the procedure described above for Example 1, except using isopropylamine in place of 1-pyridin-3-ylmethanamine. MS (ES⁺): *m/z* 471.5 [MH⁺].

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I):



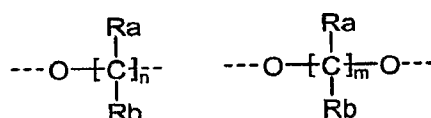
(I)

or a pharmaceutically acceptable salt or N-oxide thereof, wherein

R12 is $-\text{NR}^3\text{COR}^{31}$, $-\text{NR}^3\text{CONR}^{32}\text{R}^{31}$, $-\text{NR}^3\text{SO}_2\text{R}^{31}$, $-\text{CO}_2\text{R}^3$, $-\text{CO}_2\text{H}$, $-\text{C}_{0-8}\text{alkylNR}^3\text{R}^{31}$, $-\text{C}_{0-8}\text{alkylSO}_2\text{NR}^3\text{R}^{31}$, $-\text{C}_{0-8}\text{alkylSO}_2\text{R}^3$, heterocyclyl, hetaryl, or $-\text{CONR}^3\text{R}^{31}$;

R11, R13 and R14 are independently F, Cl, $\text{C}_{0-3}\text{alkyl}$, or $\text{C}_{0-8}\text{alkoxy}$;

Y is



Ra and Rb are each independently $\text{C}_{0-8}\text{alkyl}$ or $\text{C}_{3-8}\text{cycloalkyl}$;

or Ra and Rb taken together with the C to which they are attached form a saturated or partially unsaturated 3-10 membered ring optionally containing 0-4 N, O, S, SO, or SO_2 at the ring nodes, provided that no N, O or S atoms are placed adjacent to each other at ring nodes;

m is 2, 3, 4 or 5;

n is 1, 2, 3, 4 or 5;

Z is a cyclyl or heterocyclyl group, optionally substituted with 1-5 independent halogen, $-\text{NR}^{34}\text{R}^{35}$, $-\text{NR}^{34}\text{COR}^{35}$, $-\text{NR}^{34}\text{C(O)OR}^{35}$, $-\text{NR}^{34}\text{SO}_2\text{R}^{35}$, $-\text{OR}^{34}$, $-\text{SR}^{34}$, $-\text{SO}_2\text{R}^{34}$, $-\text{SO}_2\text{NR}^{34}\text{R}^{35}$, $-\text{C(O)OR}^{34}$, $-\text{CO}_2\text{H}$, $-\text{CONR}^{34}\text{R}^{35}$, $\text{C}_{0-8}\text{alkyl}$, $\text{C}_{2-8}\text{alkenyl}$, $\text{C}_{2-8}\text{alkynyl}$, CN, CF_3 , NO_2 , oxo, cyclyl or heterocyclyl substituents;

R^3 , R^{31} , R^{32} , R^{33} , R^{34} and R^{35} are independently $\text{C}_{0-8}\text{alkyl}$ optionally substituted with a heterocyclyl, CHF_2 , or OH substituent; $-\text{C}_{0-8}\text{alkyl}-\text{C}_{3-8}\text{cycloalkyl}$, CF_3 , $-\text{C}_{0-8}\text{alkyl}-\text{O}-\text{C}_{0-8}\text{alkyl}$, $-\text{C}_{0-8}\text{alkyl}-\text{N}(\text{C}_{0-8}\text{alkyl})(\text{C}_{0-8}\text{alkyl})$, $-\text{C}_{0-8}\text{alkyl}-\text{S(O)}_{0-2}-\text{C}_{0-8}\text{alkyl}$; or heterocyclyl optionally substituted with $\text{C}_{0-8}\text{alkyl}$, cyclyl or substituted cyclyl substituent; or benzyl optionally substituted with $-\text{SO}_2-\text{NH}_2$.

2. The compound according to claim 1, or a pharmaceutically acceptable salt or N-oxide thereof, wherein

R12 is $-\text{NR}^3\text{COR}^{31}$, $-\text{NR}^3\text{CONR}^{32}\text{R}^{31}$, $-\text{NR}^3\text{SO}_2\text{R}^{31}$, $-\text{CO}_2\text{R}^3$, $-\text{CO}_2\text{H}$, $-\text{C}_{0-8}\text{alkylNR}^3\text{R}^{31}$ or $-\text{CONR}^3\text{R}^{31}$.

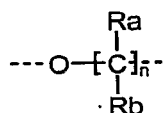
3. The compound according to claim 1, or a pharmaceutically acceptable salt or N-oxide thereof, wherein

R12 is -CONR³R³¹.

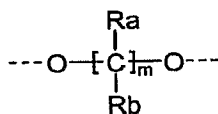
4. The compound according to claim 3, or a pharmaceutically acceptable salt or N-oxide thereof, wherein Z is cyclyl.

5. The compound according to claim 4, or a pharmaceutically acceptable salt or N-oxide thereof, wherein Z is heterocyclyl.

6. The compound according to claim 4, or a pharmaceutically acceptable salt or N-oxide thereof, wherein Y is



7. The compound according to claim 4, or a pharmaceutically acceptable salt or N-oxide thereof, wherein Y is



8. A composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt or N-oxide thereof, and a pharmaceutically acceptable carrier.

9. A composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt or N-oxide thereof; and
an anti-neoplastic, anti-tumor, anti-angiogenic, or chemotherapeutic agent.

10. A composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt or N-oxide thereof, and a cytotoxic cancer therapeutic agent.

11. A composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt or N-oxide thereof, and an angiogenesis inhibiting cancer therapeutic agent.

12. A compound consisting of
N-(Pyridin-2-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-(Tetrahydro-2H-pyran-4-ylmethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-Methyl-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-(2-Hydroxyethyl)-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide;

N-Isopropyl-1-(4-{[4-(trifluoromethoxy)benzyl]oxy}phenyl)-1*H*-benzotriazole-5-carboxamide; or a pharmaceutically acceptable salt, or *N*-oxide, thereof.

13. A method of treatment of hyperproliferative disorder comprising a step of administering an effective amount of the compound according to claim 1.

14. The method of claim 139, further comprising the step of administering an anti-neoplastic, anti-tumor, anti-angiogenic, or chemotherapeutic agent.

15. The method of claim 19 wherein the hyperproliferative disorder is breast cancer, head cancer, or neck cancer.

16. The method of claim 13 wherein the hyperproliferative disorder is gastrointestinal cancer.

17. The method of claim 13 wherein the hyperproliferative disorder is leukemia.

18. The method of claim 13 wherein the hyperproliferative disorder is ovarian, bronchial, lung, or pancreatic cancer.

19. The method of claim 13 wherein the hyperproliferative disorder is small cell lung or colon cancer.

20. The method of claim 13 wherein the hyperproliferative disorder is sinonasal natural killer/T-cell lymphoma, testicular cancer (seminoma), thyroid carcinoma, malignant melanoma, adenoid cystic carcinoma, angiosarcoma, anaplastic large cell lymphoma, endometrial carcinoma, or prostate carcinoma.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/003073

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D249/18 C07D401/12 C07D405/12 A61P35/00 A61K31/4192

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2005/021531 A (OSI PHARM INC [US]; BOLGER JOSHUA [US]; CASTELHANO ARLINDO L [US]; CRE) 10 March 2005 (2005-03-10) claim 1	1-20
A	WO 2005/021537 A (OSI PHARM INC [US]; BOLGER JOSHUA [US]; CASTELHANO ARLINDO L [US]; CRE) 10 March 2005 (2005-03-10) claim 1	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 June 2007

Date of mailing of the international search report

20/06/2007

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Authorized officer

De Jong, Bart

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/003073

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/003073

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005021531 A	10-03-2005	AU 2004268949 A1	10-03-2005
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