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(54) Title: SUBSTITUTED BENZIMIDAZOLES FOR NEUROFIBROMATOSIS

(57) Abstract: The present invention relates to the use of BENZIMIDAZOLE DERIVATIVES for the preparation of a drug for the treatment of neurofibromatosis.

SUBSTITUTED BENZIMIDAZOLES FOR NEUROFIBROMATOSIS

Summary of the invention

The present invention relates to the use of substituted benzimidazoles for the treatment of, and preparation of a drug for the treatment of, non-cancerous, benign brain tumors, especially for the curative and/or prophylactic treatment of meningiomas, schwannomas, craniopharyngiomas, dermoids, epidermoids, hemangioblastomas, choroid plexus papillomas and pineal region tumors; espceially those tumors associated with neurofibromatosis types 1 and 2, and tumors occurring along the skull base.

Background of the Invention

Neurofibromatosis (NF) is a genetic disorder that affects the bone, soft tissue, skin and nervous system. It is classified into neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2), occuring in about 1 in 3,000 and 1 in 50,000 births, respectively. The disorders occur as a result of genetic defects, with NF1 resulting from a mutation on a gene located on chromosome 17 and NF2 on chromosome 22.

NF1, also known as von Recklinghausen Disease, is a hereditary disease seen in approximately 1 in 4,000 live births in the U.S. NF1 is characterized by a triad of café-au-lait spots (skin discolorations), cutaneous neurofibromata and iris Lisch nodules. Other features of the disorder may include skeletal dysplasia, vascular dysplasias, learning disabilities, seizures and other tumors of the neural crest origin, such as pheochromocytomas. In addition, about 10-15% of NF1 patients have low-grade astrocytomas, and less commonly, ependymoas or meningiomas.

NF2, is characterized by bilateral vestibular schwannomas with associated symptoms of tinnitus, hearing loss and balance dysfunction. Other findings include schwannomas of other cranial and peripheral nerves, meningiomas and juvenile posterior subcapsular contaract.

Both forms of NF are characterized by the growth of benign tumors called neurofibromas. These tumors can grow anywhere in the body where there are nerve cells. This includes nerves just under the surface of the skin, as well as nerves deeper within the body, spinal cord and/or brain. Neurofibromas usually originate in peripheral nerve fibres.

In NF1, neurofibromas most commonly grow on the skin or on the nerve to the eye. A tumor that grows on the nerve to the eye is called an optic glioma, and if it grows large enough can cause problems with vision, including blindness.

If untreated, a neurofibroma can cause severe nerve damage leading to loss of function to the area stimulated by that nerve, such as malformation of the long bones, curvature of the spine, short stature and growth hormone deficiency. Tumors on the optic nerve can cause visual loss, on the gastrointestinal tract may cause bleeding or obstruction, on the brain may lead to learning difficulties (speech problems), behavioural problems (learning disabilities or mental retaration), hearing problems, increased risk of epilepsy.

The Ras family of proto-oncogenes (N-Ras, K-Ras and H-Ras) serve as signal transduction mediators promoting cell growth, differentiation, and survival signals. Activated Ras exists in a GTP-bound state, and inactivation occurs upon hydrolysis of GTP to GDP. Ras mutations are associated with several human malignancies and result in a decreased rate of GTP hydrolysis, leading to sustained activation.

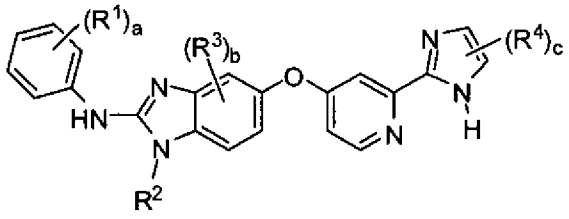
The NF1 genes encode a GTPase activating protein (GAP) which functions as a negative regulator of Ras. Thus, loss of NFI leads to enhanced activation of Ras and downstream signal transduction pathways, such as the Raf/MEK/ERK pathway and the PI3K/AKT pathway. Therapeutic interventions targeting these downstream signaling pathways represent an potential approach to treating this disease.

Benzamidazoles as described in U.S. Patent No. 7,071,216 and U.S. Patent Application No. 11/513,959 are small molecule inhibitors of Raf kinase that has been shown to preferentially inhibit the Raf/MEK/ERK signaling pathway in tumor cells which express mutant, activated forms of Ras or B-Raf.

As an inhibitor of Raf/MEK/ERK signaling pathway, benzimidazole derivatives have the potential to be of benefit in the treatment of NF.

Summary of the Invention

The present invention relates to the use of benzimidazoles of formula (I), hereinafter "BENZIMIDAZOLE DERIVATIVES").



(I)

wherein,

each R^1 is independently selected from hydroxy, halo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)sulfanyl, (C_{1-6} alkyl)sulfonyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl;

R^2 is C_{1-6} alkyl or halo(C_{1-6} alkyl);

each R^3 is independently selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each R^4 is independently selected from hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, carboxyl, (C_{1-6} alkoxy)carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, carbonitrile, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, phenyl and heteroaryl;

wherein R^1, R^2, R^3, and R^4 may be optionally substituted with one or more substituents independently selected from hydroxy, halo, C_{1-6} alkyl, halo(C_{1-6} alkyl), C_{1-6} alkoxy and halo(C_{1-6} alkoxy);

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

b is 0, 1, 2 or 3; and

c is 1 or 2;

or a tautomer or stereoisomer, thereof or a pharmaceutically acceptable salt of the compound, tautomer, or stereoisomer for use in treating or preventing conditions caused by neurofibromatosis (NF).

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated.

In yet other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II) or (III) effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer. A number of suitable anticancer agents to be used as combination

therapeutics are contemplated for use in the methods of the present invention. Indeed, the present invention contemplates, but is not limited to, administration of numerous anticancer agents, such as agents that induce apoptosis; polynucleotides, e.g., ribozymes; polypeptides, e.g., enzymes; drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers, e.g., interferons, e.g., IFN-a, etc.; and interleukins, e.g., IL-2, etc., adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation, e.g., all-trans-retinoic acid, etc.; gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for coadministration with the disclosed compounds of formula (I), (II) or (III) are known to those skilled in the art.

In preferred embodiments, anticancer agents to be used in combination with compounds of the present invention comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation; kinase inhibitors, e.g., epidermal growth factor receptor (EGFR) kinase inhibitor, vascular growth factor receptor (VGFR) kinase inhibitor, fibroblast growth factor receptor (FGFR) kinase inhibitor, platelet-derived growth factor receptor (PGFR) I kinase inhibitor, and Bcr-Abl kinase inhibitors, such as STI-571, Gleevec, and Glivec; antisense molecules; antibodies, e.g., herceptin and rituxan; anti-estrogens, e.g., raloxifene and tamoxifen; anti-androgens, e.g., flutamide, bicalutamide, finasteride, amino-glutethamide, ketoconazole and corticosteroids; cyclooxygenase 2 (COX-2) inhibitors, e.g., celecoxib, meloxicam, NS-398 and non-steroidal antiinflammatory drugs (NSAIDs); and cancer chemotherapeutic drugs, e.g., irinotecan (camptosar), CPT-11, fludarabine (fludara), dacarbazine (DTIC), dexamethasone, mitoxantrone, mylotarg, VP-16, cisplatinum, 5-FU, doxrubicin, taxotere or taxol; cellular signaling molecules; ceramides and cytokines; and staurosprine, and the like.

In other aspects, the present invention provides pharmaceutical compositions comprising at least one compound or a pharmaceutically acceptable salt thereof of formula (I), (II) or (III) together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

"Raf inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to Raf kinase activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the Raf/Mek Filtration Assay described generally hereinbelow. Preferred isoforms of Raf Kinase in which the compounds of the present invention will be shown to inhibit, include A-Raf, B-Raf, and C-Raf (Raf-1). "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme, e.g., Raf kinase, to half-maximal level. Representative compounds of the present invention have been discovered to exhibit inhibitory activity against Raf. Compounds of the present invention preferably exhibit an IC_{50} with respect to Raf of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM, and most preferably, not more than about 200 nM, as measured in the Raf kinase assays described herein.

"Alkyl" refers to saturated hydrocarbyl groups that do not contain heteroatoms and includes straight chain alkyl groups, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. Alkyl also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)-CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$ and others. Thus alkyl groups include primary alkyl groups, secondary alkyl groups and tertiary alkyl groups. The phrase "C_{1-12} alkyl" refers to alkyl groups having from one to twelve carbon atoms. The phrase "C_{1-6} alkyl" refers to alkyl groups having from one to six carbon atoms.

"Alkoxy" refers to RO-, wherein R is an alkyl group. The phrase "C_{1-6} alkoxy", as used herein, refers to RO-, wherein R is a C_{1-6} alkyl group. Representative examples of C_{1-6} alkoxy groups include methoxy, ethoxy, *t*-butoxy and the like.

"(C_{1-6} alkoxy)carbonyl" refers to ester –C(=O)–OR, wherein R is C_{1-6} alkyl.

"Aminocarbonyl" refers herein to the group $-C(O)-NH_2$.

"C_{1-6} alkylaminocarbonyl" refers to the group –C(O)-NRR', where R is C_{1-6} alkyl and R' is selected from hydrogen and C_{1-6} alkyl.

"Carbonyl" refers to the divalent group –C(O)-.

"Carboxyl" refers to –C(=O)–OH.

"Cyano", "carbonitrile" or "nitrile" refers to –CN.

"Carbonitrile(C_{1-6} alkyl)" refers to C_{1-6} alkyl substituted with –CN.

"Cycloalkyl" refers to a mono- or polycyclic alkyl substituent. Typical cycloalkyl groups have from 3 to 8 carbon ring atoms. Representative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

"Halogen" or "halo" refers to chloro, bromo, fluoro and iodo groups.

"Halo(C_{1-6} alkyl)" refers to a C_{1-6} alkyl radical substituted with one or more halogen atoms, preferably one to five halogen atoms. A more preferred halo(C_{1-6} alkyl) group is trifluoromethyl.

"Halo(C_{1-6} alkyl)phenyl" refers to a phenyl group substituted with a halo(C_{1-6} alkyl) group.

"Halo(C_{1-6} alkoxy)" refers to an alkoxy radical substituted with one or more halogen atoms, preferably one to five halogen atoms. A more preferred halo(C_{1-6} alkoxy) group is trifluoromethoxy.

"Halo(C_{1-6} alkyl)sulfonyl" and "halo(C_{1-6} alkyl)sulfanyl" refer to substitution of sulfonyl and sulfanyl groups with halo(C_{1-6} alkyl) groups, wherein sulfonyl and sulfanyl are as defined herein.

"Heteroaryl" refers to an aromatic group having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen and sulfur, wherein the nitrogen and sulfur atoms may be optionally oxidized. Exemplary heteroaryl groups have 5 to 14 ring atoms and include, e.g., benzimidazolyl, benzothiazolyl, benzoxazolyl, diazapinyl, furanyl, pyrazinyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrroyl, oxazolyl, isoxazolyl, imidazolyl, indolyl, indazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, thiazolyl, thienyl and triazolyl.

"Heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 2 heteroatoms in the ring structure. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen and sulfur, wherein the nitrogen

and sulfur atoms may be optionally oxidized. Representative heterocycloalkyl moieties include, e.g., morpholino, piperazinyl, piperidinyl and the like.

"(C_{1-6} alkyl)Heterocycloalkyl" refers to a heterocycloalkyl group substituted with a C_{1-6} alkyl group.

"Heterocycloalkyl(C_{1-6} alkyl)" refers to C_{1-6} alkyl substituted with heterocycloalkyl.

"Heterocycloalkylcarbonyl" refers herein to the group $-C(O)-R^{10}$, where R^{10} is heterocycloalkyl.

"(C_{1-6} alkyl)Heterocycloalkylcarbonyl" refers to the group $-C(O)-R^{11}$, where R^{11} is (C_{1-6} alkyl)heterocycloalkyl.

"Hydroxy" refers to –OH.

"Hydroxy(C_{1-6} alkyl)" refers to a C_{1-6} alkyl group substituted with hydroxy.

"Hydroxy(C_{1-6} alkylaminocarbonyl)" refers to a C_{1-6} alkylaminocarbonyl group substituted with hydroxy.

"Sulfonyl" refers herein to the group $-SO_2-$.

"Sulfanyl" refers herein to the group -S-. "Alkylsulfonyl" refers to a substituted sulfonyl of the structure $-SO_2R^{12}$ in which R^{12} is alkyl. "Alkylsulfanyl" refers to a substituted sulfanyl of the structure $-SR^{12}$ in which R^{12} is alkyl. Alkylsulfonyl and alkylsulfanyl groups employed in compounds of the present invention include (C_{1-6} alkyl)sulfonyl and (C_{1-6} alkyl)sulfanyl. Thus, typical groups include, e.g., methylsulfonyl and methylsulfanyl (i.e., where R^{12} is methyl), ethylsulfonyl, and ethylsulfanyl (i.e., where R^{12} is ethyl), propylsulfonyl, and propylsulfanyl (i.e., where R^{12} is propyl) and the like.

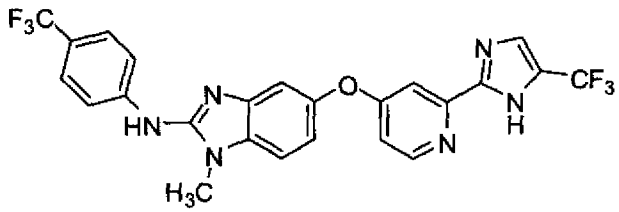
"Hydroxy protecting group" refers to protecting groups for an OH group. The term, as used herein, also refers to protection of the OH group of an acid COOH. Suitable hydroxy protecting groups, as well as suitable conditions for protecting and deprotecting particular functional groups are well-known in the art. For example, numerous such protecting groups are described in T. W. Greene and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York (1999). Such hydroxy protecting groups include C_{1-6} alkyl ethers, benzyl ethers, *p*-methoxybenzyl ethers, silyl ethers and the like.

"Optionally substituted" or "substituted" refers to the replacement of one or more hydrogen atoms with a monovalent or divalent radical.

When the substituted substituent includes a straight chain group, the substitution can occur either within the chain, e.g., 2-hydroxypropyl, 2-aminobutyl and the like; or at the chain terminus, e.g., 2-hydroxyethyl, 3-cyanopropyl and the like. Substituted substitutents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

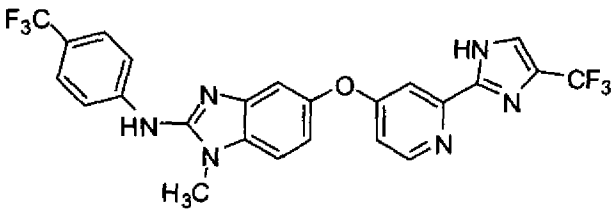
It is understood that the above definitions are not intended to include impermissible substitution patterns, e.g., methyl substituted with five fluoro groups or a halogen atom substituted with another halogen atom. Such impermissible substitution patterns are well-known to the skilled artisan.

Compounds within the scope of formula (I) and the process for their manufacture are disclosed in U.S. Patent No. 7,071,216, U.S. Patent Application No. 11/513,959 and U.S. Patent Application No. 11/513,745 which are hereby incorporated into the present application by reference. A preferred compound is 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethylphenyl)-amine and pharmacutially acceptable salts thereof of formula (II):



(II)

or a tautomer of the compound of formula (II) or a pharmaceutically acceptable salt of the tautomer having the formula (III):



(III).

In each case where citations of patent applications or scientific publications are given in particular for the BENZIMIDAZOLE DERIVATIVE compounds, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications. The corresponding content thereof is hereby incorporated by reference.

It has now surprisingly been found that BENZIMIDAZOLE DERIVATIVES possess therapeutic properties, which render them useful to treat non-cancerous, benign brain tumors, especially neurofibromastosis.

The present invention thus concerns the use of BENZIMIDAZOLE DERIVATIVES for the preparation of a drug for the treatment of non-cancerous, benign brain tumors, especially neurofibromastosis.

The present invention more particularly concerns the use of BENZIMIDAZOLE DERIVATIVES for the preparation of a drug for the treatment of non-cancerous, benign brain tumors, especially neurofibromastosis.

In another embodiment, the instant invention provides a method for treating non-cancerous, benign brain tumors, especially NF comprising administering to a mammal in need of such treatment a therapeutically effective amount of BENZIMIDAZOLE DERIVATIVES, or pharmaceutically acceptable salts or prodrugs thereof.

Preferably the instant invention provides a method for treating mammals, especially humans, suffering from non-cancerous, benign brain tumors, especially NF comprising administering to a mammal in need of such treatment an inhibiting amount of 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoro-methylphenyl)-amine (Compound (II)) or a pharmaceutically acceptable salt thereof.

Preferably, this method is used for treating NF1 or NF2.

In another embodiment, the instant invention relates to the use of BENZIMIDAZOLE DERIVATIVES for the preparation of a pharmaceutical composition for use in treating non-cancerous, benign brain tumors, especially NF.

In the present description, the term "treatment" includes both prophylactic or preventative treatment, as well as curative or disease suppressive treatment, including treatment of patients at risk of contracting the disease or suspected to have contracted the disease, as

well as ill patients. This term further includes the treatment for the delay of progression of the disease.

The term "curative", as used herein, means efficacy in treating ongoing episodes involving non-cancerous, benign brain tumors, especially NF.

The term "prophylactic" means the prevention of the onset or recurrence of diseases involving non-cancerous, benign brain tumors, especially NF.

The term "delay of progression", as used herein, means administration of the active compound to patients being in a pre-stage or in an early phase of the disease to be treated, in which patients, e.g., a pre-form of the corresponding disease is diagnosed or which patients are in a condition, e.g., during a medical treatment or a condition resulting from an accident, under which it is likely that a corresponding disease will develop.

This unforeseeable range of properties means that the use of BENZIMIDAZOLE DERIVATIVES are of particular interest for the manufacture of a medicament for the treatment of non-cancerous, benign brain tumors, especially NF.

To demonstrate that BENZIMIDAZOLE DERIVATIVES are particularly suitable for the treatment of non-cancerous, benign brain tumors, especially NF with good therapeutic margin and other advantages, clinical trials can be carried out in a manner known to the skilled person.

The precise dosage of BENZIMIDAZOLE DERIVATIVES to be employed for inhibiting non-cancerous, benign brain tumors, especially NF depends upon several factors including the host, the nature and the severity of the condition being treated, the mode of administration. The compound of formula (I) can be administered by any route including orally, parenterally, e.g., intraperitoneally, intravenously, intramuscularly, subcutaneously, intratumorally, or rectally, or enterally. Preferably, the compound of formula (I) is administered orally, preferably at a daily dosage of 1-300 mg/kg body weight or, for most larger primates, a daily dosage of 50-5000 mg, preferably 500-3000 mg.

Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

Compounds of formula (I) may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g., orally, in the form of tablets, capsules, caplets, etc. or parenterally, e.g., intraperitoneally or intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The BENZIMIDAZOLE DERIVATIVES can be used alone or combined with at least one other pharmaceutically active compound for use in these pathologies. Combination partners include antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (TEMODAL®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array PioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

The term "aromatase inhibitor", as used herein, relates to a compound which inhibits the estrogen production, i.e., the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to, steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g., under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g., under the trademark LENTARON.

Fadrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g., under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g., under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g., breast tumors.

The term "antiestrogen", as used herein, relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to, tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g., under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g., under the trademark EVISTA. Fulvestrant can be formulated as disclosed in U.S. Patent No. 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g., under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g., breast tumors.

The term "anti-androgen", as used herein, relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g., as disclosed in U.S. Patent No. 4,636,505.

The term "gonadorelin agonist", as used herein, includes, but is not limited to, abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Patent No. 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZOLADEX. Abarelix can be formulated, e.g., as disclosed in U.S. Patent No. 5,843,901.

The term "topoisomerase I inhibitor", as used herein, includes, but is not limited to, topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g., under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor", as used herein, includes, but is not limited to, the anthracyclines, such as doxorubicin (including liposomal formulation, e.g., CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g., in the form as it is marketed, e.g., under the trademark ETOPOPHOS. Teniposide can be administered, e.g., in the form as it is marketed, e.g., under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark FARMORUBICIN. Idarubicin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g., in the form as it is marketed, e.g., under the trademark NOVANTRON.

The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to, taxanes, e.g., paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, e.g., epothilone B or D or derivatives thereof. Paclitaxel may be administered, e.g., in the form as it is marketed, e.g., TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g., under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g., under the trademark VINBLASTIN R.P. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g., under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in U.S. Patent No. 5,010,099. Also included are epothilone derivatives which are disclosed in WO 98/10121, U.S. Patent No. 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are epothilone A and/or B.

The term "alkylating agent", as used herein, includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g., under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists, such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g., under the trademark GEMZAR.

The term "platin compound", as used herein, includes, but is not limited to, carboplatin, cisplatin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g., under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g., under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds", as used herein, includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g., a N-phenyl-2-pyrimidine-amine derivative, e.g., imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, e.g., imatinib;

h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g., imatinib;

i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g., BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g., a N-phenyl-2-pyrimidine-amine derivative, e.g., imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825);

j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in U.S. Patent No. 5,093,330, e.g., midostaurin; examples of further compounds include, e.g., UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds, such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor);

k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline

class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g., EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g., the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347, e.g., compound known as CP 358774, WO 96/33980, e.g., compound ZD 1839 and WO 95/03283, e.g., compound ZM105180; e.g. trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g., unrelated to protein or lipid kinase inhibition, e.g., thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are, e.g., inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g., okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are, e.g., retinoic acid, α-, γ- or δ-tocopherol or α-, γ- or δ-tocotrienol.

The term "cyclooxygenase inhibitor", as used herein, includes, but is not limited to, e.g., Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g., 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates", as used herein, includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark SKELID. "Pamidronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g., in the form as it is marketed, e.g., under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity, such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor", as used herein, refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

The term "biological response modifier", as used herein, refers to a lymphokine or interferons, e.g., interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g., H-Ras, K-Ras or N-Ras, as used herein, refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor", e.g., L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g., telomestatin.

The term "methionine aminopeptidase inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are, e.g., bengamide or a derivative thereof.

The term "proteasome inhibitor", as used herein, refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, e.g., Bortezomid (Velcade™) and MLN 341.

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor), as used herein, includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g., hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "compounds used in the treatment of hematologic malignancies", as used herein, includes, but is not limited to, FMS-like tyrosine kinase inhibitors, e.g., compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, e.g., compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g., PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors", as used herein, includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of

HSP90, e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

The term "antiproliferative antibodies", as used herein, includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1,erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 antibody. By antibodies is meant, e.g., intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

The term "antileukemic compounds" includes, e.g., Ara-C, a pyrimidine analog, which is the 2′-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate.

Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors, such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in U.S. Patent No. 6,552,065, in particular, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

Somatostatin receptor antagonists as used herein refers to compounds which target, treat or inhibit the somatostatin receptor, such as octreotide, and SOM230.

Tumor cell damaging approaches refer to approaches, such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays, such as X-rays and gamma rays; or particles, such as alpha and beta particles. Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in *Principles and Practice of Oncology*, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

The term EDG binders as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

The term ribonucleotide reductase inhibitors refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., *Acta Oncologica*, Vol. 33, No. 8, pp. 953-961 (1994).

The term "S-adenosylmethionine decarboxylase inhibitors", as used herein, includes, but is not limited to, the compounds disclosed in U.S. Patent No. 5,461,076.

Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF disclosed in WO 98/35958, e.g., 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g., the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al, *Cancer Res*, Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci U S A*, Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res*, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., *Toxicol Pathol*, Vol. 27, No. 1, pp. 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell*, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., *Cell*, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

"Photodynamic therapy", as used herein, refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy includes treatment with compounds, such as, e.g., VISUDYNE and porfimer sodium.

"Angiostatic steroids", as used herein, refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

Implants containing corticosteroids refers to compounds, such as, e.g., fluocinolone, dexamethasone.

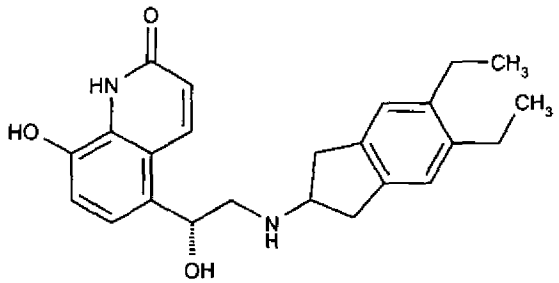
Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

The compounds of the invention are also useful as co-therapeutic compounds for use in combination with other drug substances, such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, e.g., as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

Suitable anti-inflammatory drugs include steroids, in particular, glucocorticosteroids, such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445, WO 03/072592, non-steroidal glucocorticoid receptor agonists such as those described in WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195, WO 04/005229;

LTB4 antagonists, such as LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 and those described in U.S. Patent No. 5,451,700; LTD4 antagonists, such as montelukast and zafirlukast; PDE4 inhibitors, such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544,

WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; A2a agonists such as those disclosed in EP 409 595 A2, EP 1 052 264, EP 1 241 176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO 04/039766, WO 04/045618 and WO 04/046083; A2b antagonists, such as those described in WO 02/42298; and beta-2 adrenoceptor agonists, such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula (I) of WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula (I) of WO 04/16601, and also compounds of WO 04/033412.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424 021, U.S. Patent No. 5,171,744, U.S. Patent No. 3,714,357, WO 03/33495 and WO 04/018422.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine, as well as those disclosed in WO 03/099807, WO 04/026841 and JP 2004107299.

Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g., CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists, such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists, such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770), and CCR-5 antagonists described in U.S. Patent No. 6,166,037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

The structure of the active compounds identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g., Patents International, e.g., IMS World Publications.

The above-mentioned compounds, which can be used in combination with a compound of the formula (I), can be prepared and administered as described in the art, such as in the documents cited above.

A compound of the formula (I) may also be used to advantage in combination with known therapeutic processes, e.g., the administration of hormones or especially radiation.

A compound of formula (I) may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the formula (I) and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic effect.

The treatment of non-cancerous, benign brain tumors, especially NF with the above combination may be a so-called first line treatment, i.e., the treatment of a freshly-diagnosed disease without any preceeding chemotherapy or the like, or it may also be a so-called second line treatment, i.e., the treatment of the disease after a preceeding treatment with imatrinib or a BENZIMIDAZOLE DERIVATIVES, depending on the severity or stage of the disease, as well as the over all condition of the patient, etc.

Results:

The compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine exhibited potent inhibition (IC_{50} <0.1 μM) of B-Raf, c-Raf and mutant B-Raf (V600E) activity as shown below in Table 1.

Table 1 ***In Vitro*** **Potency of the Compound 1-Methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine Against Raf Activity**

Target	Compound of Example 1 Biochemical IC_{50}
B-Raf (V600E)	0.0053 μM
B-Raf	0.068 μM
c-Raf	0.004 μM

As shown above in Table 1, the compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine displays potent inhibitory activity against wild-type isoform B-Raf, wild-type isoform c-Raf, and mutant B-Raf (V600E) Raf kinase. The Raf kinases are activated by Ras and phosphorylate and activate Mek1 and Mek2, which in turn activate Mitogen Activated Kinases 1 and 2 (MAPK), in the MAPK pathway. Raf kinases are known to influence and regulate cellular proliferation, differentiation, survival, oncogenic transformation and apoptosis. The B-Raf isoform has been shown to be the most active form of Raf involved in signaling and key in propagating Ras signaling.

As shown below in Table 2, the compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine is a potent inhibitor of VEGFR-2, c-Kit, PDGFR-β and CSF-1R.

Table 2 Inhibition of Tyrosine Kinases with the Compound 1-Methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine

Target	Compound of Example 1 Biochemical IC_{50}	Compound of Example 1 Cell-based EC50
VEGFR-2	0.07 μM	0.14 μM
c-Kit	0.02 μM	1.1 μM
PDGFR-β	0.0032 μM	0.7 μM
CSF-1R	0.20 μM	ND

Cell-based assays were also used to measure the activity of the compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine against the target molecules shown in Table 2 as follows.

Target modulation in HEK-KDR-93 cells after treatment with the compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine showed inhibition of VEGF mediated VEGFR-2 phosphorylation with an EC_{50} of 0.19 μM, as measured by a decrease in phospho-VEGFR by ELISA (not shown).

Analysis of inhibition of c-Kit in Mo7e cells after treatment with compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine showed inhibition of c-Kit phosphorylation with an EC_{50} of 1.1 μM as measured by a decrease in phospho-c-Kit by ELISA.

Analysis of inhibition of PDGFR-β in MG63 cells after treatment with compound 1-methyl-5-[2-(5-trifluoromethyl-1H-imidazol-2-yl)-pyridin-4-yloxy]-1H-benzoimidazol-2-yl}-(4-trifluoromethyl-phenyl)-amine showed inhibition of phospho-PDGFR-β with an EC_{50} of 0.7 μM as measured by a decrease in phospho-PDGFR-β by ELISA.

The ST88 cell line ($NF1^{+/-}$) contains elevated levels of Ras-GTP and is often used as a pre-clinical model for NF1. Internal Novartis data indicate that treatment of ST88 cells with RAF265 results in decreased levels of phospho-MEK and phospho-ERK and subsequent inhibition of proliferation.

Pathway inhibition and anti-proliferative activity of RAF265 in ST88 cells.

Assay	EC_{50} (μM)
phospho-MEK ELISA	0.15
phospho-ERK ELISA	0.185
proliferation	0.207

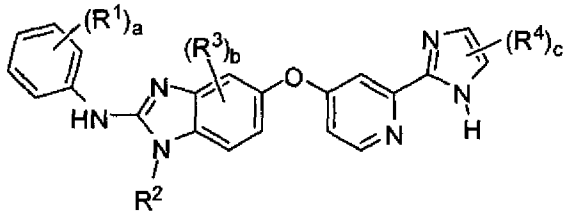
These data indicate that RAF265 has similar potency against an NF1 deficient tumor cell line as cell lines expressing mutant B-Raf (B-RafV600E) or N-Ras (N-RasQ61R). While this is a limited dataset, there is precedence in the literature for treating NF1 deficient neurofibromas by inhibiting targets downstream of Ras. For example, treatment of ST88 and NF90 cells (both NF1+/-) with MEK inhibitors CI-1040 decreased levels of phospho-ERK and inhibited proliferation (Mattingly et al. 2005).

Due to the inhibition of VEGFR-2, RAF265 also has anti-angiogenic activity which may also provide a therapeutic benefit in treating neurofibromas. To confirm that RAF265 inhibits the growth of new blood vessels (i.e., angiogenesis) *in vivo*, mice were implanted with Matrigel® containing Chinese hamster ovary cells (CHO) overexpressing VEGF and then treated mice with a dose range of RAF265 or a vehicle control (days 1 and 4). In this model, VEGF expressed from the CHO cells induces angiogenesis within the Matrigel® plug. Plugs are excised on day 5 and assayed for hemoglobin using Drabkin's reagent, as a measure of the degree of angiogenesis.

As shown in Figure XX, VEGF-CHO cells clearly induced angiogenesis, since Matrigel implanted with cells had a much higher level of hemoglobin compared to Matrigel implanted without VEGF-CHO cells. RAF265 caused a dose-dependent decrease in hemoglobin content, with a maximal suppresssion at 50 mg/kg. These data indicate that RAF265 has anti-angiogenic activity *in vivo* and may provide additional anti-tumor activity in NF1 tumors.

We Claim:

1. A method of treating or preventing a condition caused by neurofibromatosis, comprising administering a benzimidazole derivative of formula (I):



(I)

wherein,

each R^1 is independently selected from hydroxy, halo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)sulfanyl, (C_{1-6} alkyl)sulfonyl, cycloalkyl, heterocycloalkyl, phenyl, and heteroaryl;

R^2 is C_{1-6} alkyl or halo(C_{1-6} alkyl);

each R^3 is independently selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy;

each R^4 is independently selected from hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, carboxyl, (C_{1-6} alkoxy)carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, carbonitrile, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, phenyl and heteroaryl;

wherein R^1, R^2, R^3 and R^4 may be optionally substituted with one or more substituents independently selected from hydroxy, halo, C_{1-6} alkyl, halo(C_{1-6} alkyl), C_{1-6} alkoxy and halo(C_{1-6} alkoxy);

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

b is 0, 1, 2, or 3; and

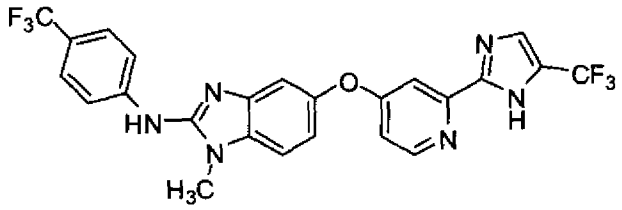
c is 1 or 2;

or a tautomer or stereoisomer, thereof or a pharmaceutically acceptable salt of the compound, tautomer or stereoisomer.

2. A method according to Claim 1, where the condition caused by neurofibromatosis is selected from non-cancerous, benign brain tumors, meningiomas, schwannomas, craniopharyngiomas, dermoids, epidermoids, hemangioblastomas, choroid plexus papillomas and pineal region tumors.

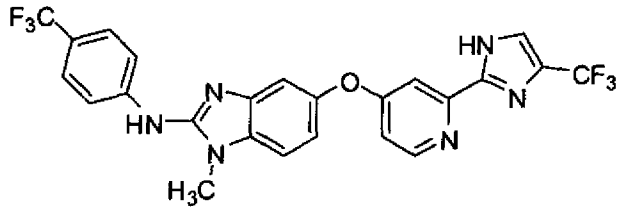
3. A method according to Claim 1, where the neurofibromatosis is selected from neurofibromatosis type 1 or type 2.

4. A method according to Claim 1, where the compound of formula (I) is 4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-N-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide of formula (II):



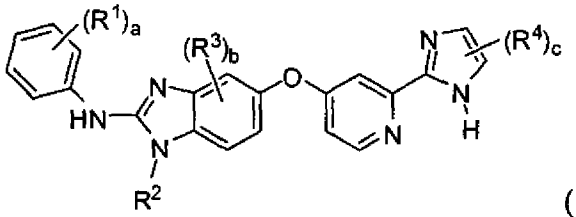
(II)

or a tautomer of the compound of formula (II) or a pharmaceutically acceptable salt of the tautomer having the formula (III):



(III).

5. Use of a compound of formula (I)



(I)

wherein,

each R^1 is independently selected from hydroxy, halo, C_{1-6} alkyl, C_{1-6} alkoxy, (C_{1-6} alkyl)sulfanyl, (C_{1-6} alkyl)sulfonyl, cycloalkyl, heterocycloalkyl, phenyl and heteroaryl;

R^2 is C_{1-6} alkyl or halo(C_{1-6} alkyl);

each R^3 is independently selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy;

each R^4 is independently selected from hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo, carboxyl, (C_{1-6} alkoxy)carbonyl, aminocarbonyl, C_{1-6} alkylaminocarbonyl, carbonitrile, cycloalkyl, heterocycloalkyl, heterocycloalkylcarbonyl, phenyl and heteroaryl;

wherein R^1, R^2, R^3, and R^4 may be optionally substituted with one or more substituents independently selected from hydroxy, halo, C_{1-6} alkyl, halo(C_{1-6} alkyl), C_{1-6} alkoxy and halo(C_{1-6} alkoxy);

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

b is 0, 1, 2, or 3; and

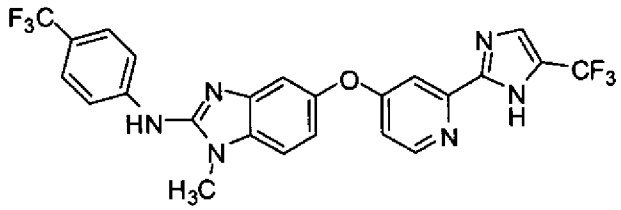
c is 1 or 2;

or a tautomer or stereoisomer, thereof or a pharmaceutically acceptable salt of the compound, tautomer, or stereoisomer for the preparation of a pharmaceutical composition for the treatment conditions caused by neurofibromatosis.

6. Use according to Claim 4, where said condition caused by neurofibromatosis is selected from non-cancerous, benign brain tumors, meningiomas, schwannomas, craniopharyngiomas, dermoids, epidermoids, hemangioblastomas, choroid plexus papillomas and pineal region tumors.

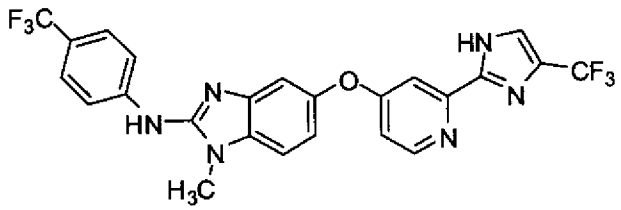
7. Use according to Claim 4, where said neurofibromatosis is selected from neurofibromatosis type 1 or type 2.

8. The use of a compound of formula (II):



(II)

or a tautomer of the compound of formula (II) or a pharmaceutically acceptable salt of the tautomer having the formula (III):



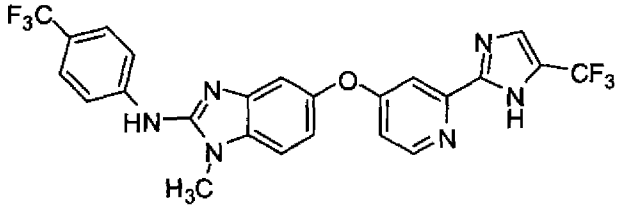
(III)

or pharmaceutically acceptable salts thereof for the preparation of a pharmaceutical composition for the treatment of conditions caused by neurofibromatosis.

9. Use according to Claim 7, where said condition caused by neurofibromatosis is selected from non-cancerous, benign brain tumors, meningiomas, schwannomas, craniopharyngiomas, dermoids, epidermoids, hemangioblastomas, choroid plexus papillomas and pineal region tumors.

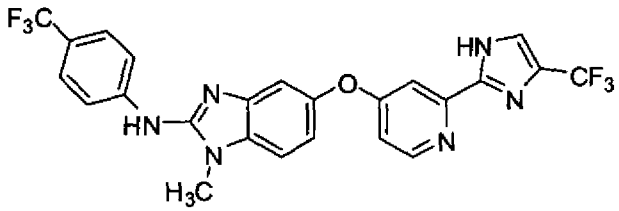
10. Use according to Claim 7, where said neurofibromatosis is selected from neurofibromatosis type 1 or type 2.

11. A method for treating mammals, including humans, suffering from non-cancerous, benign brain tumors comprising administering to a mammal in need of such treatment an effective amount of a compound of formula (II):



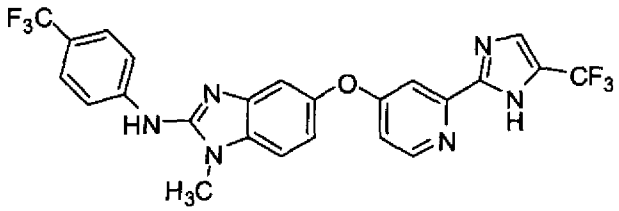
(II)

or a tautomer of the compound of formula (II) or a pharmaceutically acceptable salt of the tautomer having the formula (III):



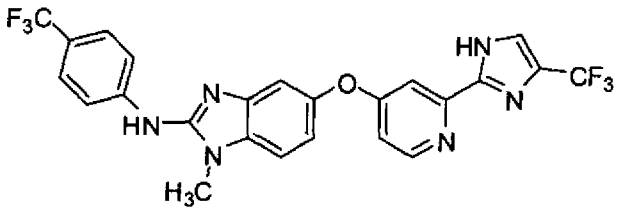
(III).

12. A pharmaceutical preparation for the treatment of non-cancerous, benign brain tumors, comprising a compound of formula (II):



(II)

or a tautomer of the compound of formula (II) or a pharmaceutically acceptable salt of the tautomer having the formula (III):



(III).

Inhibition of angiogenesis by RAF265 in Matrigel plugs containing VEGF-CHO cells.

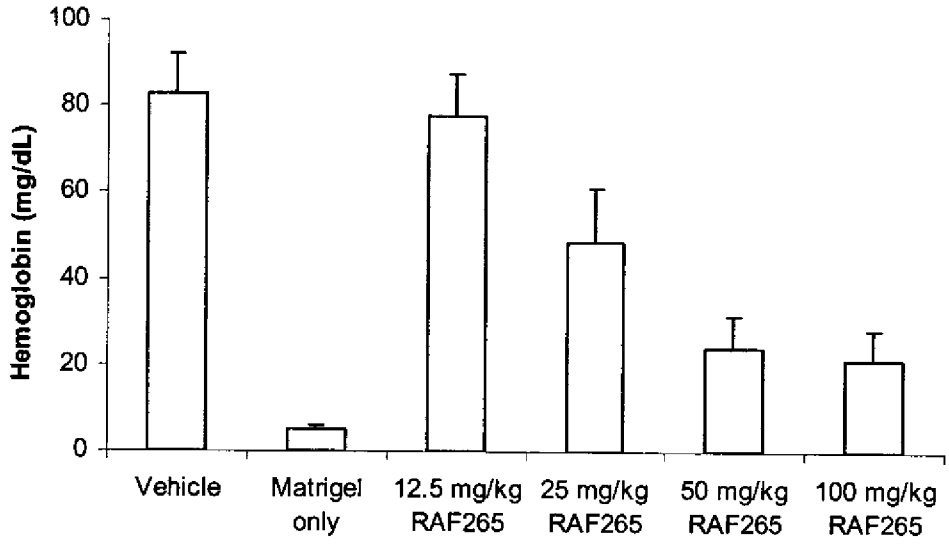


FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/046971

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4439

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)
A61K

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, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/027523 A (NOVARTIS AG [CH]; GULLAPALLI RAMPURNA [US]; HASHASH AHMAD [US]; KARPIN) 6 March 2008 (2008-03-06) claims 1,40,41 page 7, last line - page 8, line 1 page 24, paragraph 2 -----	1,3-5,7, 8,10
X	WO 2007/131689 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; LANE HEIDI [CH] NOVARTIS) 22 November 2007 (2007-11-22) claim 1 page 25, line 23 - page 26, line 12 page 32, lines 15-19 page 33, line 16 - page 34, line 11 ----- -/--	1-12

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
25 August 2009	07/09/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/046971

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2008/070616 A (UNIV UTAH RES FOUND [US]; HUANG L ERIC [US]) 12 June 2008 (2008-06-12) claims 38,41 page 73, paragraph 229 page 77, paragraph 239 page 85, paragraph 265	1-12
P,X	WO 2009/018238 A (ARDEA BIOSCIENCES INC [US]; MINER JEFFREY N [US]; CHAPMAN MARK S [US];) 5 February 2009 (2009-02-05) claims 1,98,101,104 page 93, last paragraph - page 94, paragraph 1 page 95, paragraph 1	1-12
A	REED NEVADA ET AL: "Tumorigenesis in neurofibromatosis: New insights and potential therapies" TRENDS IN MOLECULAR MEDICINE, vol. 7, no. 4, April 2002 (2002-04), pages 157-162, XP002542746 ISSN: 1471-4914 page 157, left-hand column, paragraph 2 - right-hand column, paragraph 1 page 159, right-hand column, paragraph 2 page 161, right-hand column, paragraph 3 - page 162	1-10
A	DILWORTH JOSHUA T ET AL: "Molecular targets for emerging anti-tumor therapies for neurofibromatosis type 1" BIOCHEMICAL PHARMACOLOGY, vol. 72, no. 11, November 2006 (2006-11), pages 1485-1492, XP025053217 ISSN: 0006-2952 page 1487 - page 1488, right-hand column, paragraph 2	1-10

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/046971

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AMBROSINI GRAZIA ET AL: "Sorafenib inhibits growth and mitogen-activated protein kinase signaling in malignant peripheral nerve sheath cells" MOLECULAR CANCER THERAPEUTICS, vol. 7, no. 4, April 2008 (2008-04), pages 890-896, XP002542747 ISSN: 1535-7163 page 890, right-hand column, paragraph 3 - page 891, left-hand column, paragraph 3 page 894, right-hand column, paragraph 3 - page 896	1-10
A	STUART DARRIN D ET AL: "RAF265 is a potent Raf kinase inhibitor with selective anti-proliferative activity in vitro and in vivo" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW YORK, NY, US, vol. 49, 12 April 2008 (2008-04-12), pages 1161-200804, XP001537184 ISSN: 0197-016X abstract	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/046971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		CA 2660376 A1	06-03-2008
		CL 25332007 A1	08-02-2008
		EP 2059518 A2	20-05-2009
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		EP 2023956 A2	18-02-2009
		KR 20090010112 A	28-01-2009
		US 2009105285 A1	23-04-2009
US 2007049622 A1	01-03-2007	US 2008287682 A1	20-11-2008
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