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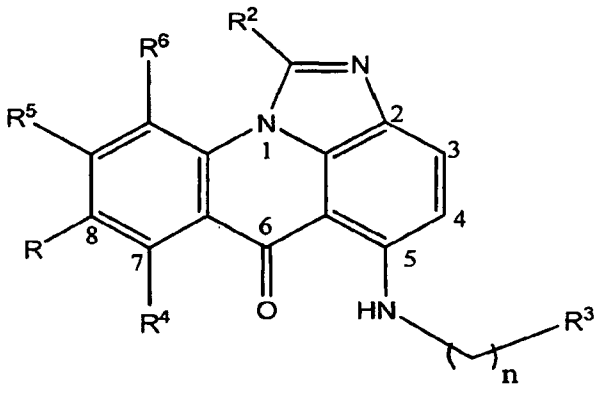
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(54) **Title:** MORPHOLINO COMPOUNDS FOR TREATING INFLAMMATORY AND DEMYELINATING DISEASES AND CANCERS



(I)

(57) **Abstract:** Compounds of formula (I) and a method of treating a patient suffering from certain inflammatory disorders, demyelinating disorders, FLT3-mediated disorders, CSF-I R-mediated disorders, cancers and leukemias, comprising administering to said patient a therapeutically effective amount of a compound of formula (1) or a pharmaceutically acceptable salt thereof. Definitions for the variables are provided therein.

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MORPHOLINO COMPOUNDS FOR TREATING INFLAMMATORY AND DEMYELINATING DISEASES AND CANCERS

RELATED APPLICATIONS

This application claims the benefit of Provisional Application No. 60/835,064, filed August 2, 2006. The entire teachings of the above application is incorporated herein by reference.

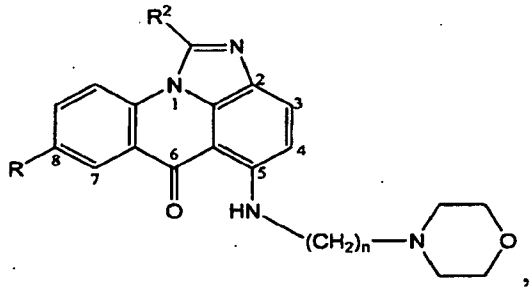
BACKGROUND OF THE INVENTION

There is a need for new pharmaceutically acceptable therapies for an inflammatory disorder, a demyelinating disorder, a FLT3-mediated disorder, a cancer, a leukemia or a CSF-1R-mediated disorder in a patient.

SUMMARY OF THE INVENTION

The present invention is directed to a class of novel compounds that can be used for treatment of an inflammatory disorder, a demyelinating disorder, a FLT3-mediated disorder, a cancer, a leukemia or a CSF-1R-mediated disorder in a patient.

In one embodiment, the present invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof:



wherein R is -F, -OH or $-OCH_3$, R^2 is a -H or a C1-C4 alkyl, and n is 2-5.

In another embodiment, the present invention is a method of treating an inflammatory or a demyelinating disorder in a patient, comprising administering to said

patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In yet another embodiment, the present invention is a method of treating cancers, such as ovarian cancer, melanoma, renal cancer, sarcoma (e.g., liposarcoma and leiomyosarcoma), hepatocellular cancer, thyroid cancer and head and neck cancer comprising administering to a patient suffering from such a cancer a therapeutically effective amount of a compound of formula (I).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows kinase screening phases.

FIG. 2 shows examples of novel FLT3 inhibitors conforming to Formula (I).

FIG. 3 shows FLT3 inhibitor activities of the compound depicted in FIG. 2.

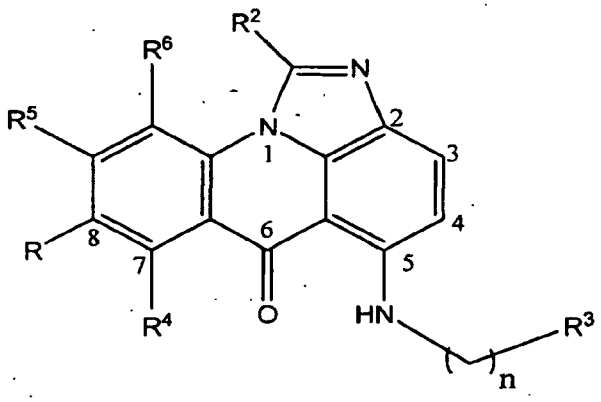
FIGs. 4A is a table that shows a detailed analysis of the FLT3 inhibitor selectivity of a number of known inhibitors in current development or recently approved as therapeutic drugs.

FIG. 4B is a table that illustrates IC50 values of compounds XF-22 (formula (B)) and XF-113 (formual (C)) against a representative selection of kinases.

FIG. 5 shows the plots of cell viability (left panel - RS4 cells; right panel - MV4 cells) as a function of effective concentration of the FLT3 inhibitors shown in FIG. 2.

DETAILED DESCRIPTION OF THE INVENTION

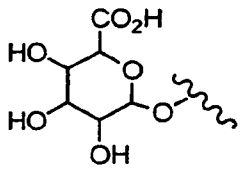
In one embodiment, the present invention is a compound of formula (I) or a pharmaceutically acceptable salt thereof. In another embodiment, the present invention is a method of treating an inflammatory or a demyelinating disease in a patient, comprising administering to said patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.



(I).

Values and preferred values for the variables in Formula (I) are provided in the following paragraphs.

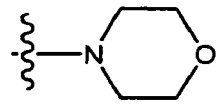
R is -H, an optionally substituted alkyl, hydroxyl, alkoxy group, a halogen, or a group represented by the following structural formula:



More preferably, R is -H, -OH, a C1-C4 alkyl, a halogen or a C1-C4 alkoxy group. Even more preferably, R is -F, -OH or $-OCH_3$.

R^2 is -H an optionally substituted C1-C10 alkyl. Preferably, R^2 is -H, C1-C4 alkyl or C1-C4 haloalkyl. More preferably, R^2 is a -H or a C1-C4 alkyl.

R^3 is a morpholinyl, optionally substituted at one or more substitutable carbon atoms with methyl, hydroxyl, or methoxy. Preferably, R^3 is the compound of formula (I) is represented by the following structural formula:



R^4, R^5 and R^6, are each independently -H, -OH, a halogen or an optionally substituted C1-C6 alkoxy; or R^5 and R^6 taken together with their intervening carbon atoms, form a 5, 6 or 7 member, optionally substituted cycloalkyl or optionally substituted non-aromatic heterocycle. Preferably, R^4, R^5 and R^6 are each independently

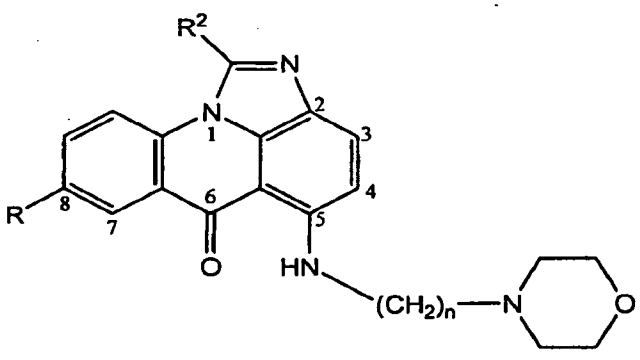
-H, -OH, C1-C4 alkyl or C1-C4 haloalkyl, or R^5 and R^6 taken together are methylenedioxy.

Integer n is from 1 to 5. Preferably, n is 2 or 3. In some embodiments, n is 2 to 5. Alternatively, n is 2. In another embodiment, n is 3; alternatively, n is 4. In yet another embodiment, n is 5.

In one embodiment of the compound of formula (I), R^2 is -H or an optionally substituted C1-C10 alkyl and R^3 is a morpholinyl, optionally substituted at one or more substitutable carbon atoms with methyl, hydroxyl, or methoxy. Values and preferred values for the remainder of the variables are as described for formula (I).

In another embodiment, R^2 is -H, C1-C4 alkyl or C1-C4 haloalkyl, R^3 is a morpholinyl, optionally substituted at one or more substitutable carbon atoms with methyl, hydroxyl, or methoxy, and R^4, R^5 and R^6 are each independently -H, -OH, C1-C4 alkyl or C1-C4 haloalkyl, or R^5 and R^6 taken together are methylenedioxy. Values and preferred values for the remainder of the variables are as described for formula (I).

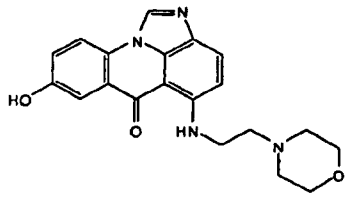
In another embodiment, the compound of formula (I) is of the structural formula (IA):



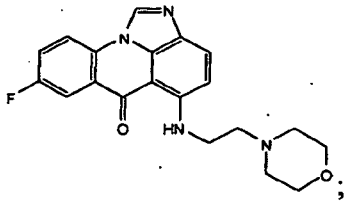
(IA).

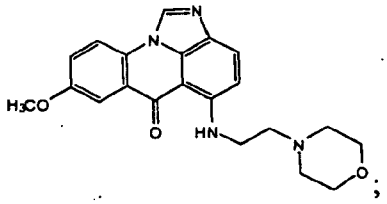
Values and preferred values for the variables of formula (IA) are as described for formula (I). Preferably for formula (IA), R^2 is -H, C1-C4 alkyl or C1-C4 haloalkyl (more preferably R^2 is a -H or a C1-C4 alkyl), and values and preferred values for the remainder of the variables are defined in for formula (I). More preferably for formula (IA), R is -F, -OH or $-OCH_3$, R^2 is -H, C1-C4 alkyl or C1-C4 haloalkyl (more preferably R^2 is a -H or a C1-C4 alkyl) and n is described for formula (I) (preferably, n is 2 or 3).

Specific examples of the preferred embodiment of the compounds of formula (I) are represented by one of the following formulas:

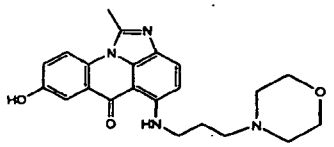


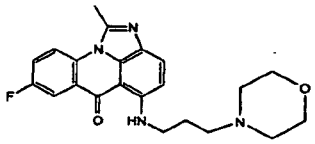
(B) (also referred to as XF-22);

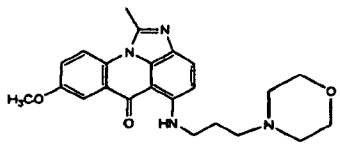


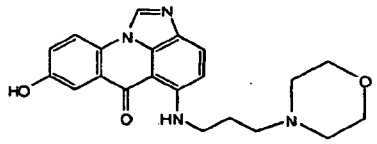


;









(C) (also referred to as XF-113).

The term "alkyl", as used herein, unless otherwise indicated, includes straight or branched saturated monovalent hydrocarbon radicals, typically C1-C10, preferably C1-C6. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and t-butyl. Suitable substituents for a substituted alkyl include -OH, -SH, halogen, cyano, nitro, amino, -COOH, a C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy or C1-C3 alkyl sulfanyl, or $-(CH_2)_p-(CH_2)_q-C(O)OH$, where p and q are independently an integer from 1 to 6.

The term "cycloalkyl", as used herein, is a non-aromatic saturated carbocyclic moieties. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. Suitable substituents for a cycloalkyl are defined above for an alkyl.

The term "haloalkyl", as used herein, includes an alkyl substituted with one or more F, Cl, Br, or I, wherein alkyl is defined above.

The terms "alkoxy", as used herein, means an "alkyl-O-" group, wherein alkyl, is defined above.

The term "haloalkoxy", as used herein, means "haloalkyl-O-", wherein haloalkyl is defined above.

As used herein, an amino group may be a primary ($-NH_2$), secondary ($-NHR_x$), or tertiary ($-NR_xR_y$), wherein R_x and R_y may be any of the optionally substituted alkyls alkyls described above.

The term "aryl", as used herein, refers to a carbocyclic aromatic group. Examples of aryl groups include, but are not limited to phenyl and naphthyl.

The term "heteroaryl", as used herein, refers to aromatic groups containing one or more heteroatoms (O, S, or N). A heteroaryl group can be monocyclic or polycyclic, e.g. a monocyclic heteroaryl ring fused to one or more carbocyclic aromatic groups or other monocyclic heteroaryl groups. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.

The term "non-aromatic heterocycle" refers to non-aromatic carbocyclic ring systems typically having four to eight members, preferably five to six, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Non aromatic heteroccyles can be optionally unsaturated. Examples of non-aromatic heterocyclic rings include 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl,

1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrorolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, and diazolonyl.

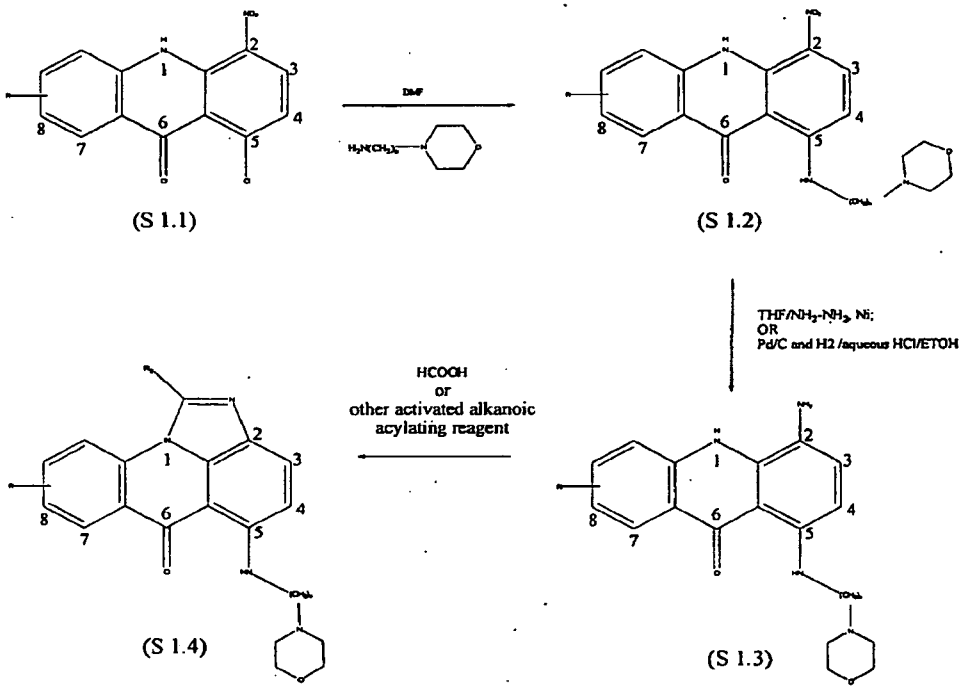
The heteroaryl or non-aromatic heterocyclic groups may be C-attached or N-attached (where such is possible). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

Suitable substituents for an aryl, a heteroaryl, or a non-aromatic heterocyclic group are those that do not substantially interfere with the pharmaceutical activity of the disclosed compound. One or more substituents can be present, which can be identical or different. Examples of suitable substituents for a substitutable carbon atom in aryl, heteroaryl or a non-aromatic heterocyclic group include -OH, halogen (-F, -Cl, -Br, and -I), -R', haloalkyl, -OR', -CH_2R', -CH_2OR', -CH_2CH_2OR', -$CH_2OC(O)R'$, -O-COR', -COR', -SR', -SCH_2R', - CH_2SR', -SOR', -SO_2R', -CN, -NO_2, -COOH, -SO_3H, -NH_2, -NHR', -$N(R')_2$, -COOR', -CH_2COOR', -CH_2CH_2COOR', -CHO, -$CONH_2$, -CONHR', -$CON(R')_2$, -NHCOR', -NR'COR', -$NHCONH_2$, -NHCONR'H, -$NHCON(R')_2$, -$NR'CONH_2$, -NR'CONR'H, -$NR'CON(R')_2$, -C(=NH)-NH_2, -C(=NH)-NHR', -$C(=NH)-N(R')_2$, -C(=NR')-NH_2, -C(=NR')-NHR', -$C(=NR')-N(R')_2$, -NH-C(=NH)-NH_2, -NH-C(=NH)-NHR', -$NH-C(=NH)-N(R')_2$, -NH-C(=NR')-NH_2, -NH-C(=NR')-NHR', -$NH-C(=NR')-N(R')_2$, -$NR'H-C(=NH)-NH_2$, -NR'-C(=NH)-NHR', -$NR'-C(=NH)-N(R')_2$, -NR'-C(=NR')-NH_2, -NR'-C(=NR')-NHR', -$NR'-C(=NR')-N(R')_2$, -SO_2NH_2, -SO_2NHR', -$SO_2NR'_2$, -SH, -SO_kR' (k is 0, 1 or 2) and -NH-C(=NH)-NH_2. Each R' is independently an alkyl group. Oxo (C==O) and thio (C==S) are also suitable substituents for a non-aromatic heterocycle.

Suitable substituents on the nitrogen of a nitrogen-containing non-aromatic heterocyclic group or a heteroaryl group include -R'', -$N(R'')_2$, -C(O)R'', -CO_2 R'', -C(O)C(O)R'', -$C(O)CH_2$ C(O)R'', -SO_2R'', -SO_2 $N(R'')_2$, -$C(=S)N(R'')_2$, -C(=NH)-$N(R'')_2$, and -NR'' SO_2R''. R'' is hydrogen, an alkyl or alkoxy group.

Synthesys of the Compounds of the Invention

Compounds of formula (I) can be synthesized according to a variety of synthetic schemes disclosed in U.S. Pat. Nos. 5,231,100 and 6,229,015, incorporated herein by reference in their entirety. One example of such a scheme is shown below:



(Scheme I).

As used herein, the "activated alkanoic acylating agent" is defined within the references cited. For example: alkyl nitriles are reacted with HCl in methanol or ethanol to give the corresponding acetimidate ester hydrochlorides, R-CN going to R-C(OMe)=NH+.Cl-, where R is an alkyl. This acetimidate reacts with the amine in compound (S I.3) and cyclized to the methyl or ethyl or other alkylimidazole, again per the cited articles.

Disorders Treatable by the Compounds of the Invention

It has now been discovered, that compounds of formula (I) can be used to treat an inflammatory disorder, a demyelinating disorder, a FLT3-mediated disorder, a cancer, a leukemia or a CSF-1R-mediated disorder in a patient. The term "patient" means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs,

and primates such as humans. The terms "treat" or "treating" include any treatment, including, but not limited to, alleviating symptoms, eliminating the causation of the symptoms either on a temporary or permanent basis, or preventing or slowing the appearance of symptoms and progression of the named disorder or condition.

1. Cancers

In one embodiment, the present invention is a method of treating a patient suffering from a cancer. The method comprises administering to a patient a therapeutically effective amount of a compounds of formula (I) or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is a method of treating a subject suffering from a cancer. As used herein, the term "cancer" refers to the uncontrolled growth of abnormal cells that have mutated from normal tissues. A cancerous tumor (malignancy) is of potentially unlimited growth and expands locally by invasion and systemically by metastasis. Examples of cancers that can be treated by the compounds of the present invention include: breast cancer, colorectal cancer, non-small cell lung cancer, ovarian, renal, sarcoma, melanoma, head & neck, hepatocellular, thyroid, multidrug-resistant leukemia, lymphoma, multiple myeloma, esophageal, large bowel, pancreatic, mesothelioma, carcinoma (e.g. adenocarcinoma, including esophageal adenocarcinoma), sarcoma (e.g. spindle cell sarcoma, liposarcoma, leiomyosarcoma, abdominal leiomyosarcoma, sclerosing epithelioid sarcoma) and melanoma (e.g. metastatic malignant melanoma). In one embodiment, the patient can be treated for bone metastases. Treatment of subtypes of the aforementioned cancers is also included. Subtypes are described in the following paragraphs.

"Treating a subject suffering from cancer" includes achieving, partially or substantially, one or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (e.g., reducing size of a tumor or reducing the number of affected sites), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components).

"Treating a bone metastases", as used herein, refers to reducing (partially or completely) the size of the bone metastases, slowing the growth of the metastases relative to the absence of treatment and reducing the extent of further spread of the cancer. "Treating a bone metastases" also includes pain reduction, decreased incidents of fractures, relief of spinal cord compression, control of hypercalcaemia, and/or restoration of normal blood cell counts.

"Breast cancer" includes, but is not limited to, ductal carcinoma, lobular carcinoma, inflammatory carcinoma, medullary carcinoma, colloid or mucinous carcinoma, papillary carcinoma, tubular carinoma, triple negative breast cancer, inflammatory breast cancer, metaplastic carcinoma, Paget's disease, and Phyllodes tumor.

As used herein "ovarian cancer", is cancer of the ovaries or fallopian tubes, including cancers of germ cells, stromal cells, and epithelial cells. Examples of ovarian cancers include but are not limited to:

Epithelial Ovarian Tumors, which include but are not limited to, serous adenomas, mucinous adenomas, and Brenner tumors, tumors of low malignant potential (LMP tumors), borderline epithelial ovarian cancer, epithelial ovarian cancers, carcinomas and undifferentiated epithelial ovarian carcinomas;

Germ Cell tumors which include but are not limited to, teratoma, dysgerminoma, endodermal sinus tumor, and choriocarcinoma; and

Stromal tumors, which include but are not limited to, granulosa cell tumors, granulosa-theca tumors, and Sertoli-Leydig cell tumors.

"Renal cancer" or "kidney cancer", as used herein, includes but is not limited to, transitional cell cancer (TCC) of the renal pelvis, Wilms Tumour and renal cell cancer.

Renal cell cancer is also called renal adenocarcinoma or hypernephroma. In renal cell cancer, the cancerous cells are found in the lining of the tubules (the smallest tubes inside the nephrons that help filter the blood and make urine).

There are several types of renal cell cancer including but not limited to clear cell, chromophilic, chromophobic, oncocytic, collecting duct and sarcomatoid.

Renal cancer also includes cancers containing more than one of the cell types described above.

As used herein, "melanoma" is a type of skin cancer that occurs in the cells that color the skin, called melanocytes. Types of melanoma include but are not limited to: Cutaneous melanoma, superficially spreading melanoma, nodular malignant melanoma, lentiginous malignant melanoma, acral lentiginous melanoma, demoplastic malignant melanomas, giant melanocytic nevus, amelanotic malignant melanoma, acral lentiginous melanoma unusual melanoma variants, including mucosal malignant melanoma and ocular malignant melanoma.

"Sarcomas", as used herein, include but are not limited to, fibrosarcomas from fibrous body tissues, leiomyosarcomas and rhabdomyosarcomas from muscle tissues, liposarcomas from fat, synovial sarcomas, angiosarcomas from blood vessels, MPNST - malignant peripheral nerve sheath tumours (PNSTs), GIST - gastrointestinal stromal sarcoma, osteosarcoma, myosarcoma, chondrosarcoma, bile duct sarcoma, brain sarcoma, breast sarcoma, soft tissue sarcoma, uterine sarcoma, endocardial sarcoma, stromal sarcomas from supporting tissues (endometrial stromal sarcoma), granuloytic, histiolytic, hemangioendothelial, Kupffer-cell, neurogenic, round-cell, reticulum cell, spindle cell, Kaposi's sarcoma of the skin, Ewing's sarcomas and PNETs. In certain embodiments, the sarcoma is leiomyosarcoma or liposarcoma.

"Thyroid cancer", as used herein, includes but is not limited to, papillary and/or mixed papillary/follicular, follicular and/or Hurthle cell, lymphoma, medullary, anaplastic and combinations thereof.

The term "head and neck cancer" as used herein, encompasses tumors that occur in several areas of the head and neck region, including the nasal passages, sinuses, mouth, throat, larynx (voice box), swallowing passages, salivary glands, and skin cancers that develop on the scalp, face, or neck may also be considered head and neck cancers. These cancers include but are not limited to squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, lymphoma, adenocarcinoma, esthesioneuroblastoma, tumors of the nasal cavity and paranasal sinuses, nasopharyngeal cancer, cancers of the oral cavity (including all the various parts of the

mouth: the lips; the lining inside the lips and cheeks (the buccal mucosa); the bottom of the mouth; the front of the tongue; the front part of the top of the mouth (the hard palate); the gums; and the area behind the wisdom teeth (the retromolar trigone)), tumors of the oropharynx, hypopharyngeal tumors, laryngeal cancer and salivary gland cancer (including malignant salivary gland tumor).

As used herein "hepatocellular cancer" or "liver cancer" includes but is not limited to: hepatocellular carcinoma (also sometimes called hepatoma or HCC) "carcinoma", fibrolamellar HCC, cholangiocarcinoma, angiosarcoma (also be called haemangiosarcoma) and hepatoblastoma.

As used herein, "non-small cell lung cancer" includes, squamous cell carcinoma, adenocarcinoma and undifferentiated non-small cell lung cancer (undeveloped cancer cells are known as undifferentiated cells) and large cell carcinoma.

"Colorectal cancer" as used herein, includes any type of colon or rectal cancer, including but not limited to, adenoscarcinoma, sarcoma, melanoma, stromal, carcinoid, and lymphoma.

2. Inflammatory conditions

In one embodiment, the present invention is a method of treating a patient suffering from an inflammatory condition. The method comprises administering to a patient a therapeutically effective amount of a compounds of formula (I) or a pharmaceutically acceptable salt thereof. The condition can be systemic lupus, inflammatory bowl disease, psoriasis, Crohn's disease, rheumatoid arthritis, sarcoid, Alzheimer's disease, insulin dependent diabetes mellitus, atherosclerosis, asthma, spinal cord injury, stroke, a chronic inflammatory demyelinating neuropathy, multiple sclerosis, a congenital metabolic disorder, a neuropathy with abnormal myelination, drug-induced demyelination, radiation induced demyelination, a hereditary demyelinating condition, a prion-induced demyelination, encephalitis-induced demyelination.

Examples of chronic inflammatory demyelinating neuropathies include: Chronic Immune Demyelinating Polyneuropathy (CIDP); multifocal CIDP; multifocal motor neuropathy (MMN); anti-MAG Syndrome (Neuropathy with IgM binding to Myelin-Associated Glycoprotein); GALOP Syndrome (Gait disorder Autoantibody Late-age Onset Polyneuropathy); anti-sulfatide antibody syndrome; anti-GM2 gangliosides antibody syndrome; POEMS syndrome (Polyneuropathy Organomegaly Endocrinopathy or Edema M-protein Skin changes); perineuritis; and IgM anti-GD1b ganglioside antibody syndrome.

3. Demyelinating conditions

In another embodiment, the present invention is a method of treatment of a patient suffering from a demyelinating condition. The method comprises administering to a patient a therapeutically effective amount of a compounds of formula (I) or a pharmaceutically acceptable salt thereof. As used herein, a "demyelinating condition" is a condition that destroys, breaks the integrity of or damages a myelin sheath. As used herein, the term "myelin sheath" refers to an insulating layer surrounding vertebrate peripheral neurons, that increases the speed of conduction and formed by Schwann cells in the peripheral or by oligodendrocytes in the central nervous system. Such condition can be multiple sclerosis, a congenital metabolic disorder, a neuropathy with abnormal myelination, drug-induced demyelination, radiation induced demyelination, a hereditary demyelination condition, a prion-induced demyelination, encephalitis-induced demyelination, a spinal cord injury, Alzheimer's disease as well as chronic inflammatory demyelinating neuropathies, examples of which are given above. In one embodiment, the condition is multiple sclerosis. The method comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention is a method of promoting remyelination of nerve cells in a patient, comprising administering to the patient in need thereof a therapeutically effective amount of a compound of formula (I). The patient can be suffering from any of the demyelinating conditions listed above.

In another embodiment, the present invention is a method of preventing demyelination and promoting remyelination in a patient in need thereof, comprising administering a combination of a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof, and an anti-inflammatory agent as described below.

In another embodiment, the present invention is a method of reversing paralysis in a subject in need thereof with a demyelinating disease, comprising administering to the subject a compound in an amount sufficient to inhibit lymphocyte infiltration of immune cells in the spinal cord to promote remyelination of nerve cells in the spinal cord and thereby treating paralysis in said subject, wherein the compound is of formula formula (I) or a pharmaceutically acceptable salt thereof.

4. FLT3-Mediated Disorders

In one embodiment, the present invention is a method of treating a patient suffering from an acute myeloid leukemia characterized by a FLT3 mutation. The method comprises administering to a patient a therapeutically effective amount of a compounds of formula (I) or a pharmaceutically acceptable salt thereof.

As used herein, the term "FLT3-mediated disorder" is a disorder in which one or more symptoms can be inhibited, alleviated, reduced or whose onset can be delayed by inhibiting completely or partially the FLT3 protein kinase.

The terms "treat" or "treating", when used with reference to a FLT3-mediated condition, include any treatment, including, but not limited to, alleviating symptoms, eliminating the causation of the symptoms associated with a FLT3-mediated condition either on a temporary or permanent basis, or preventing or slowing the appearance of symptoms and progression of the named disorder or condition.

As used herein the term "therapeutically effective amount", when used with reference to a FLT3-mediated condition, is the amount of a compound disclosed herein that will achieve a partial or total inhibition or delay of the progression of a FLT3-mediated disorder in a patient.

FLT3-mediated disorders and conditions include axonal degeneration, acute transverse myelitis, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, organ rejection, bone marrow transplant rejection, non-myeloablative bone marrow transplant rejection, ankylosing spondylitis, aplastic anemia, Behcet's disease, graft-versus-host disease, Graves' disease, autoimmune hemolytic anemia, Wegener's granulomatosis, hyper IgE syndrome, idiopathic thrombocytopenia purpura, and Myasthenia gravis.

FLT3 (Fms-like tyrosine kinase; other names include CD135, FLK2 (Fetal liver kinase 2), STK1 (Stem cell kinase 1)) is a class III receptor tyrosine kinase (RTK) structurally related to the receptors for platelet derived growth factor (PDGF), colony stimulating factor 1 (CSF1), and KIT ligand (KL). These RTKs contain five immunoglobulin-like domains in the extracellular region and an intracelular tyrosine kinase domain split in two by a specific hydrophilic insertion (kinase insert). FLT3, closely related to PDGF receptors and c-Kit is, however, not inhibited by the small molecule inhibitors of PDGF and c-Kit; (G Del Zotto et al., *J. Biol. Regulators Homeostatic Agents* 15: 103-106, 2001).

5. Leukemias

In one embodiment, the compounds of the present invention, for example the compounds of formula (I), can be used to treat certain leukemias, including FLT3-mediated leukemias.

Leukemias are selected from acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL). In one embodiment, the present inevtnion is a method of treating a patient suffering from a hairy cell leukemia (HCL).

As used herein, the term "leukemia" is a cancer of the blood or bone marrow characterized by an abnormal proliferation of blood cells, usually white blood cells (leukocytes). It is part of the broad group of diseases called hematological neoplasms.

Acute lymphocytic leukemia (also known as Acute Lymphoblastic Leukemia, or ALL) is the most common type of leukemia in young children. This disease also affects adults, especially those age 65 and older.

Acute myelogenous leukemia (also known as Acute Myeloid Leukemia, or AML) occurs more commonly in adults than in children. This type of leukemia was previously called acute nonlymphocytic leukemia.

Chronic lymphocytic leukemia (CLL) most often affects adults over the age of 55. It sometimes occurs in younger adults, but it almost never affects children.

Chronic myelogenous leukemia (CML) occurs mainly in adults. A very small number of children also develop this disease.

Hairy Cell Leukemia (HCL) leukemia is an incurable, indolent blood disorder in which mutated, partly matured B cells accumulate in the bone marrow. Its name is derived from the shape of the cells, which look like they are covered with short, fine, hair-shaped projections. Unlike any other leukemia, HCL is characterized by low white blood cell counts.

6. CSF-1R-mediated disorders

In one embodiment, the present invention is a method of treating a CSF-1R-mediated condition in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Colony Stimulating Factor-1 Receptor (CSF-1R) signaling play an important role in the etiology of the disorders and conditions described above is well known and is described, for example in Simoncic *et al.*, Mol.Cel. Biol., Vol. 26, No. 11 (2006), pp. 41-49-4160.; Yang *et al.*; Ann. Rheum. Dis. (2006); 65, pp. 1671-1672; Irving *et al.*, The FASEB J., Vol. 20 (2006): pp.E1315-E1326; Irving *et al.*, The FASEB J., Vol. 20 (2006), pp. 1921-1923; Heinonen *et al.*, PNAS (2006), vol. 103, no. 8, pp. 2776-2781; Conway *et al.*, PNAS (2006), vol. 102, no. 44, pp. 16078-16083; Himes *et al.*, The J. Immunol. (2006), 176: 2219-2228; Pixley *et al.*, Trends in Cell Biol. (2004), Vol. 14, No. 11, pp.628-638; U.S. Pat. App. Pub. No. 2006/0094081; U.S. Pat. App. Pub. No.

2006/0189623; U.S. Pat. App. Pub. No. 2006/0148812; U.S. Pat. App. Pub. No. 2006/0100201; U.S. Pat. 5,714,493; U.S. RE37,650. The relevant portions of all of these publications are incorporated herein by reference.

CSF-1R-mediated disorders include cardiovascular disease (*e.g.* artherial sclerosis), diseases with an inflammatory component including glomerulonephritis, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, asthma, pancreatitis, HIV infection, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain, osteoporosis, Paget's disease, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone, uterine cancer, stomach cancer, hairy cell leukemia, Sjogren's syndrom, or uveitis. The disorders include cancers such as osteolytic sarcoma, myeloma, and tumor metastasis to bone, uterine cancer, stomach cancer, hairy cell leukemia.

Modes of Administration

The term "therapeutically effective amount" means an amount of the compound, which is effective in treating the named disorder or condition. In certain embodiments, therapeutically effective amount means an amount sufficient to effect remyelination of nerve cells in a patient.

In treating a patient afflicted with a conditions described above, all of the disclosed compounds can be administered in any form or mode which makes the compound bioavailable in therapeutically effective amounts. For example, compounds of formula (I) can be administered in a form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salt" means either an acid addition salt or a basic addition salt, whichever is possible to make with the compounds of the present invention. "Pharmaceutically acceptable acid addition salt" is any non-toxic organic or inorganic acid addition salt of the base compounds represented by formula (I). Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium

monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di- and tri-carboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxybenzoic, p-toluenesulfonic acid and sulfonic acids such as methanesulfonic acid and 2-hydroxyethanesulfonic acid. Either the mono- or di-acid salts can be formed, and such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are more soluble in water and various hydrophilic organic solvents and which in comparison to their free base forms, generally demonstrate higher melting points. "Pharmaceutically acceptable basic addition salts" means non-toxic organic or inorganic basic addition salts of the compounds of formula (I). Examples are alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline. The selection of the appropriate salt may be important so that the ester is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art.

Compounds of the present invention can be administered by a number of routes including orally, sublingually, buccally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, topically, and the like. One skilled in the art of preparing formulations can determine the proper form and mode of administration depending upon the particular characteristics of the compound selected for the condition or disease to be treated, the stage of the disease, the condition of the patient and other relevant circumstances. For example, see Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990), incorporated herein by reference.

The disclosed compounds are administered by any suitable route, including, for example, orally in capsules, suspensions or tablets.

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but are not limited to,

tablets (*e.g.*, chewable tablets), caplets, capsules, and liquids (*e.g.*, flavored syrups). Such dosage forms contain predetermined amounts of active ingredients, and may be prepared by methods of pharmacy well known to those skilled in the art. *See generally*, Remington's Pharmaceutical Sciences (1990) 18th ed., Mack Publishing, Easton PA.

Typical oral dosage forms of the invention are prepared by combining the active ingredient(s) in an admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of preparation desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (*e.g.*, powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents.

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials.

The compound of formula (I) of this invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers.

In the embodiments in which the compounds of the invention are used to treat cancer, the dosage range at which the disclosed compounds, for example, compounds of formula (I), including the above-mentioned examples thereof, exhibit their ability to act

therapeutically can vary depending upon the severity of the condition, the patient, the formulation, other underlying disease states that the patient is suffering from, and other medications that may be concurrently administered to the patient. Generally, the compounds described herein will exhibit their therapeutic activities at dosages of between about 0.1 mg/m^2 free base equivalent per square meter of body surface area/single dose to about 1000 mg/m^2 free base equivalent per square meter of body surface area/single dose. These dosages can be administered, for exaple, once per week, once every other week, once every third week or once per week for three out of every four weeks.

Alternatively, when used to treat cancer, the disclosed compounds can be administered daily (typically orally). Daily dose of administration of the compounds of the present invention can be repeated, in one embodiment, for one week. In other embodiments, daily dose can be repeated for one month to six months; for six months to one year; for one year to five years; and for five years to ten years. Representative total daily doses would include those in the range of 10-2000 mg. The total daily dose can be divided into equal doses and administered twice daily, thrice daily, or four times daily. In other embodiments, the length of the treatment by repeated administration is determined by a physician.

When used to treat other indications, the dosage range at which the disclosed compounds of formula (I) exhibit their ability to act therapeutically can vary depending upon the severity of the condition, the patient, the formulation, other underlying disease states that the patient is suffering from, and other medications that may be concurrently administered to the patient. Generally, the inventive compounds of the invention will exhibit their therapeutic activities at dosages of between about 0.001 mg/kg of patient body weight/day to about 100 mg/kg of patient body weight/day. For example, the dosage can be 0.1-100 mg/kg per every other day or per week.

Combination Therapies

The compounds used in the present invention can be administered alone or in combination with one or more other pharmaceutically active agents that are effective against the inflammatory condition and/or the demyelating disorder being treated.

As used herein, the term "combination" with reference to pharmaceutically active agents and the term "co-administering" and "co-administration" refer to administering more than one pharmaceutically active agent to a patient during one treatment cycle and not necessarily simultaneous or in a mixture.

In one embodiment, the compounds of the present invention are administered in combination with an anti-inflammatory agent. The anti-inflammatory agent can be adrenocorticotropic hormone, a corticosteroid, an interferon, glatiramer acetate, or a non-steroidal anti-inflammatory drug (NSAID).

Examples of suitable anti-inflammatory agents include corticosteroid such as prednisone, methylprednisolone, dexamethasone cortisol, cortisone, fludrocortisone, prednisolone, 6α-methylprednisolone, triamcinolone, or betamethasone.

Other examples of suitable anti-inflammatory agents include NSAIDs such as aminoarylcarboxylic acid derivatives (e.g., Enfenamic Acid, Etofenamate, Flufenamic Acid, Isonixin, Meclofenamic Acid, Niflumic Acid, Talniflumate, Terofenamate and Tolfenamic Acid), arylacetic acid derivatives (e.g., Acematicin, Alclofenac, Amfenac, Bufexamac, Caprofen, Cinmetacin, Clopirac, Diclofenac, Diclofenac Sodium, Etodolac, Felbinac, Fenclofenac, Fenclorac, Fenclozic Acid, Fenoprofen, Fentiazac, Flubiprofen, Glucametacin, Ibufenac, Ibuprofen, Indomethacin, Isofezolac, Isoxepac, Ketoprofen, Lonazolac, Metiazinic Acid, Naproxen, Oxametacine, Proglumrtacin, Sulindac, Tenidap, Tiramide, Tolectin, Tolmetin, Zomax and Zomepirac), arylbutyric acid ferivatives (e.g., Bumadizon, Butibufen, Fenbufen and Xenbucin) arylcarboxylic acids (e.g., Clidanac, Ketorolac and Tinoridine), arylproprionic acid derivatives (e.g., Alminoprofen, Benoxaprofen, Bucloxic Acid, Carprofen, Fenoprofen, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, Indoprofen, Ketoprofen, Loxoprofen, Miroprofen, Naproxen, Oxaprozin, Piketoprofen, Piroprofen, Pranoprofen, Protinizinic Acid, Suprofen and Tiaprofenic Acid), pyrazoles (e.g., Difenamizole and Epirizole), pyrazolones (e.g., Apazone, Benzpiperylon, Feprazone, Mofebutazone, Morazone,

Oxyphenbutazone, Phenylbutazone, Pipebuzone, Propyphenazone, Ramifenazone, Suxibuzone and Thiazolinobutazone), salicyclic acid derivatives (e.g., Acetaminosalol, 5-Aminosalicylic Acid, Aspirin, Benorylate, Biphenyl Aspirin, Bromosaligenin, Calcium Acetylsalicylate, Diflunisal, Etersalate, Fendosal, Flufenisal, Gentisic Acid, Glycol Salicylate, Imidazole Salicylate, Lysine Acetylsalicylate, Mesalamine, Morpholine Salicylate, 1-Naphthyl Sallicylate, Olsalazine, Parsalmide, Phenyl Acetylsalicylate, Phenyl Salicylate, 2-Phosphonoxybenzoic Acid, Salacetamide, Salicylamide *O*-Acetic Acid, Salicylic Acid, Salicyloyl Salicylic Acid, Salicylsulfuric Acid, Salsalate and Sulfasalazine), thiazinecarboxamides (e.g., Droxicam, Isoxicam, Piroxicam and Tenoxicam), ε-Acetamidocaproic Acid, *S*-Adenosylmethionine, 3-Amino-4-hydroxybutyric Acid, Amixetrine, Bendazac, Benzydamine, Bucolome, Difenpiramide, Ditazol, Emorfazone, Guaiazulene, Ketorolac, Meclofenamic Acid, Mefenamic Acid, Nabumetone, Nimesulide, Orgotein, Oxaceprol, Paranyline, Perisoxal, Pifoxime, Piroxicam, Proquazone, Tenidap and a COX-2 inhibitor (e.g., Rofecoxib, Valdecoxib and Celecoxib).

Further examples of anti-inflammatory agents include aspirin, a sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, sulfasalazine, olsalazine, a para-aminophenol derivatives, an indole, an indene acetic acid, a heteroaryl acetic acid, an anthranilic acid, an enolic acid, an alkanones, a diaryl-substituted furanone, a diaryl-substituted pyrazoles, an indole acetic acids, or a sulfonanilide.

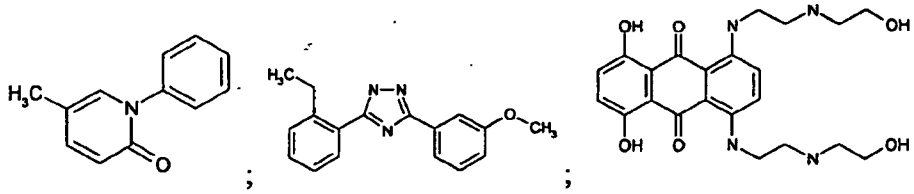
In some embodiments, the compounds of the present invention can be administered in combination with immunotherapeutic agents such as interferons and anti-integrin blocking antibodies like natalizumab.

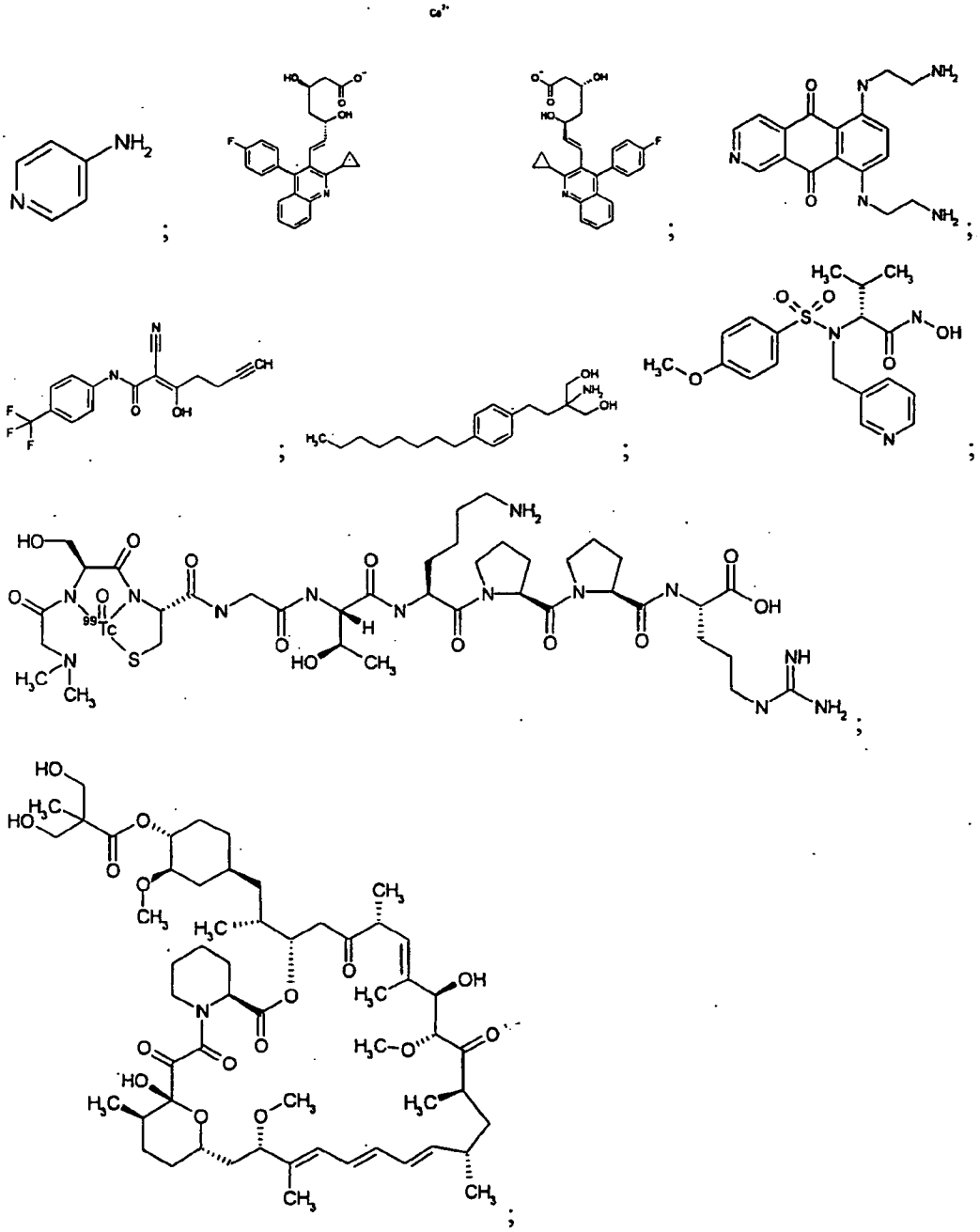
Examples of agents suitable for treating demyelinating disorders include Pirfenidone, Epalrestat, Nefazodone hydrochloride, Memantine hydrochloride, Mitoxantrone hydrochloride, Mitozantrone hydrochloride, Thalidomide, Roquinimex, Venlafaxine hydrochloride, Intaxel, Paclitaxel, recombinant human nerve growth factor; nerve growth factor, ibudilast, Cladribine, Beraprost sodium, Levacecarnine hydrochloride; Acetyl-L-carnitine hydrochloride; Levocarnitine acetyl hydrochloride,

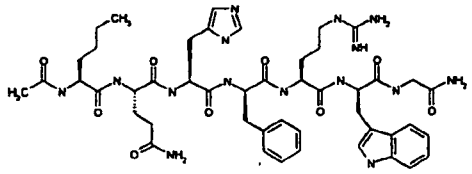
Droxidopa, interferon alfa, natural interferon alpha, human lymphoblastoid interferon, interferon beta-1b, interferon beta-Ser, Alemtuzumab, Mycophenolate mofetil, Zoledronic acid monohydrate, Adapalene, Eliprodil, Donepezil hydrochloride, Dexanabinol, Dexanabinone, Xaliproden hydrochloride, interferon alfa-n3, lipoic acid, thioctic acid, Teriflunomide, Atorvastatin, Pymadin, 4-Aminopyridine, Fampridine, Fidarestat, Priliximab, Pixantrone maleate, Dacliximab, Daclizumab, Glatiramer acetate, Rituximab, Fingolimod hydrochloride, interferon beta-1a, Natalizumab, Abatacept, Temsirolimus, Lenercept, Ruboxistaurin mesilate hydrate, Dextromethorphan/quinidine sulfate, Capsaicin, Dimethylfumarate or Dronabinol/cannabidiol.

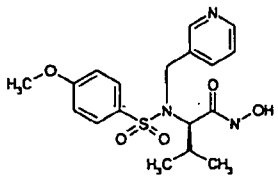
In some embodiments, the compounds of the present invention can be administered in combination with one or more other pharmaceutically active agents that are effective against multiple sclerosis. Examples of such agents include the interferons (interferon beta 1-a, beta 1-b, and alpha), glatiramer acetate or corticosteroids such as methylprednisolone and prednisone as well as chemotherapeutic agents such as mitoxantrone, methotrexate, azathioprine, cladribine cyclophosphamide, cyclosporine and tysabri.

Further examples of pharmaceutically active agents that are effective against multiple sclerosis and are suitable to be administered in combination with compounds of the present invention include compounds of the following structural formulae:

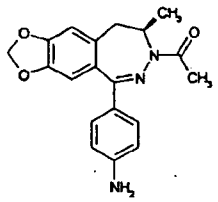




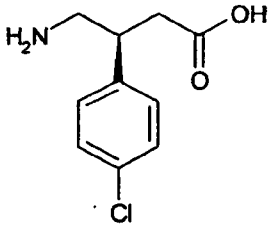




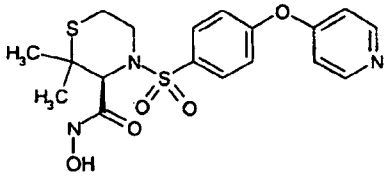
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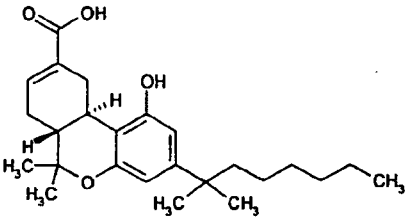


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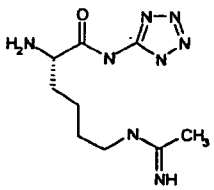


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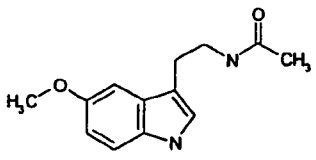




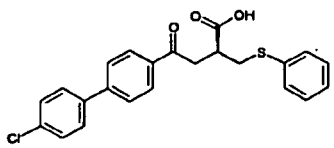
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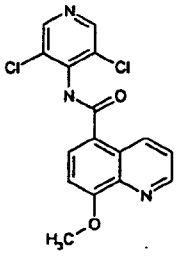
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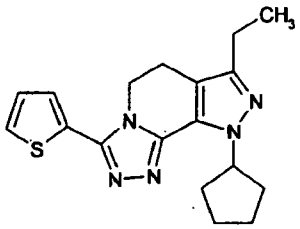
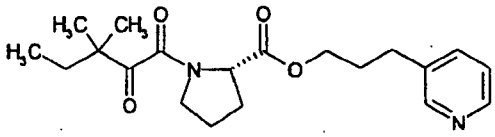
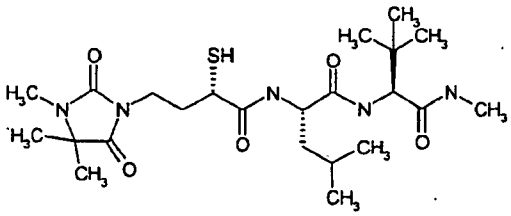
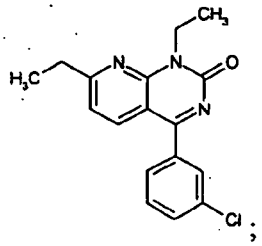
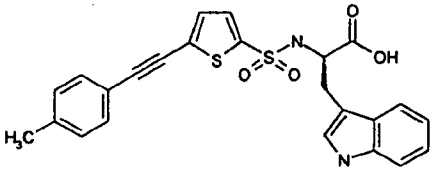
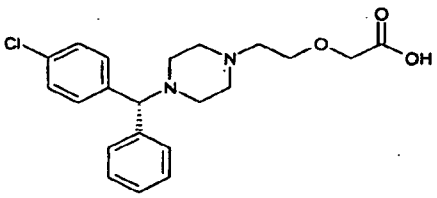
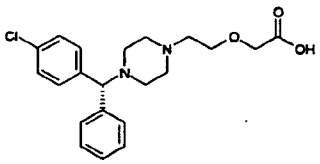
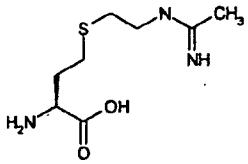
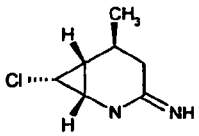
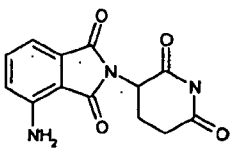
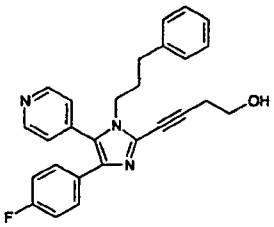
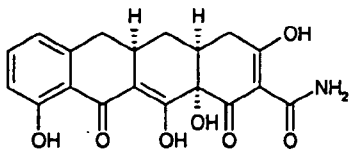
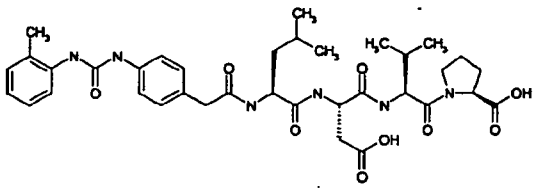
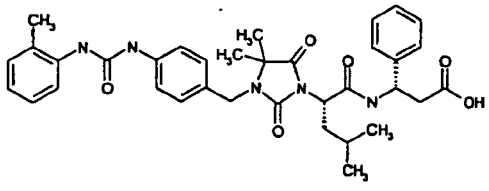
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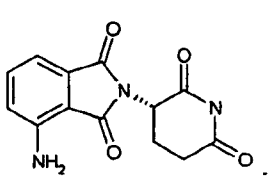
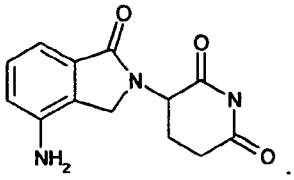
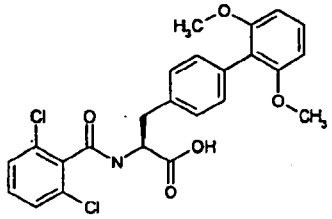
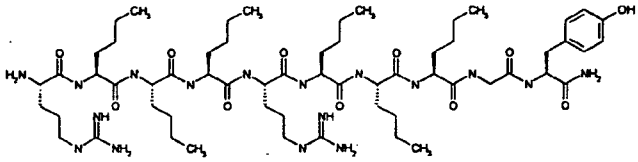
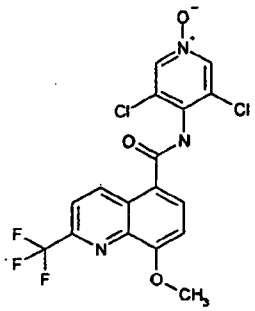
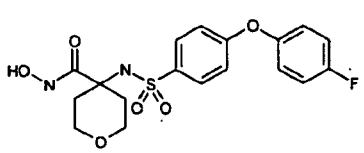
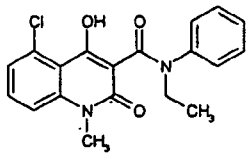
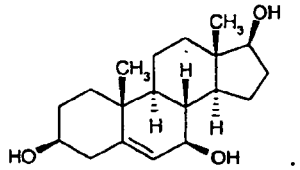


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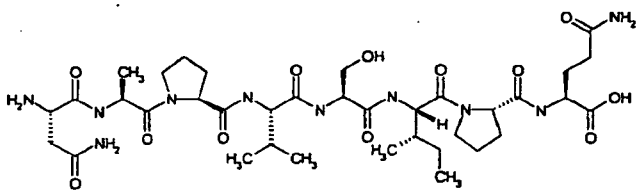
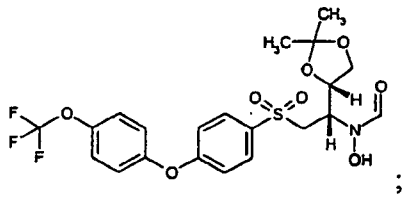
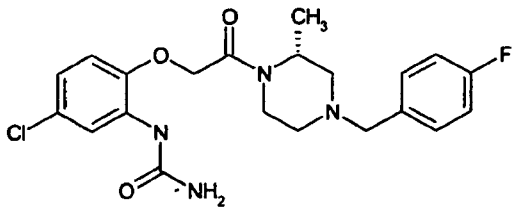
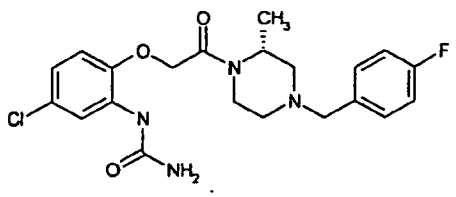


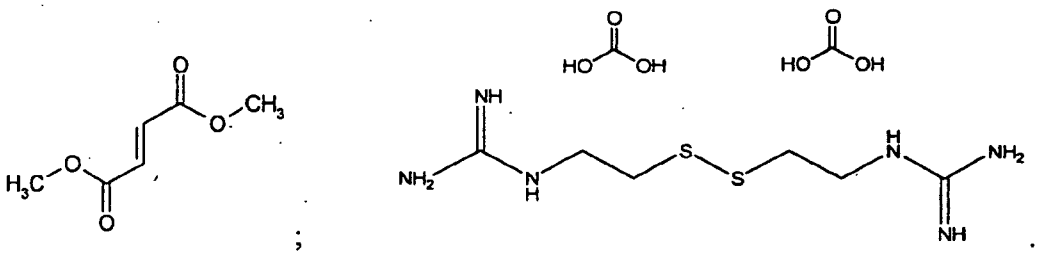
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Further examples of pharmaceutical agents that can be co-administered with the compounds of formula (I) include:

T-cell receptor (TCR) Vβ6 CDR2 peptide vaccine consisting of TCR Vβ6, amino acid sequence 39-58, Leu - Gly - Gln - Gly - Pro - Glu - Phe - Leu - Thr - Tyr - Phe - Gln - Asn - Glu - Ala - Gln - Leu - Glu - Lys - Ser (SEQ ID NO:1);

Myelin basic protein immunogen peptide, aminoacid sequence 75-95, Lys - Ser - His - Gly - Arg - Thr - Gln - Asp - Glu - Asn - Pro - Val - Val - His - Phe - Phe - Lys - Asn - Ile - Val - Thr (SEQ ID NO:2);

Tiplimotide, myelin basic protein immunogen vaccine peptide, aminoacid sequence 83-99, D - Ala - lys - pro - val - val - his - leu - phe - ala - asp - ile - val - thr - pro - arg - thr - pro, (SEQ ID NO:3);

Myelin basic protein immunogen peptide, aminoacid sequence 82-98, Asp - glu - asp - pro - val - val - his - phe - phe - lys - asp - ile - val - thr - pro - arg - thr, (SEQ ID NO:4);

Adrenocorticotropic hormone (ACTH), Ser - Tyr - Ser - met - glu - his - phe - arg - try - gly - lys - pro - val - gly - lys- lys - arg - arg - pro - val - lys - val - tyr- pro - asp - gly - ala - glu - asp - glu - leu - ala - glu - ala - phe - pro - leu - glut - phe, (SEQ ID NO:5).

Further examples of pharmaceutically active agents that are effective against multiple sclerosis and are suitable to be administered in combination with compounds of the present invention include:

3-4 diaminopyridine; ABT-874; Actos® (pioglitazone); ALCAR (acetyl-L-carnitine); Alpha lipoic acid; AndroGel® (testosterone gel); combination of trimethoprim and vitamin C; combination of azithromycin and rifampin; minocycline; donezepil HCL;

Avandia® (rosiglitazone maleate; combination of IFN beta-1a) and acetaminophen, ibuprofen or prednisone; combination of Avonex® (interferon beta-1a) + CellCept® (mycophenolate mofetil); combination of Avonex® (interferon beta-1a) and Copaxone® (glatiramer acetate); combination of Avonex® (interferon beta-1a) and doxycycline; combination of Avonex® (interferon beta-1 a) and EMLA (lidocaine and prilocaine) anesthetic cream; Avonex® (interferon beta-1a) and estrogen and progesterone; combination of Avonex® (interferon beta-1a) + Fludara® (fludarabine phosphate); combination of Avonex® (interferon beta-1a) and methotrexate and leucovorin rescue; combination of Avonex® (interferon beta-1a) and methotrexate and methylprednisolone; combination of Avonex® (interferon beta-1a) and Novantrone® (mitoxantrone); combination of Avonex® (interferon beta-1a) and Prozac® (fluoxetine); combination of Avonex® (interferon beta-1a) and Topamax® (topiramate); combination of Avonex® (interferon beta-1a) and Zocor® (simvastatin); AVP-923 (dextromethorphan/quinidine); combination of Betaseron® (interferon beta-1b) and Imuran® (azathioprine); combination of Betaseron® (interferon beta-1b) and Copaxone® (glatiramer acetate); combination of BHT-3009-01 and Lipitor® (atorvastatin); Bone marrow/peripheral stem cell transplant; CellCept® (mycophenolate mofetil); combination of CellCept® (mycophenolate mofetil) and Avonex® (interferon beta-1a); Oral cladribine; CNTO 1275 (monoclonal antibody); combination of Copaxone® (glatiramer acetate) and Antibiotic therapy (minocycline); combination of Copaxone® (glatiramer acetate) and Novantrone® (mitoxantrone); combination of Copaxone® (glatiramer acetate) and prednisone; combination of Copaxone® (glatiramer acetate) and Proventil® (albuterol); Cyclophosphamide; Daclizumab; Deskar® (pirfenidone); Estriol; Fumaric acid esters; Gabitril® (tiagabine HCL); Ginkgo biloba; IDEC-131 (anti-CD40L or anti-CD 154); the combination of Immunoglobulin and methylprednisolone; Inosine; Interferon tau; Lamictal® (lamotrigine); Lexapro® (escitalopram); Lipitor® (atorvastatin); combination of Lipitor® (atorvastatin) and Rebif® (interferon beta-1a); combination of Lymphocytapheresis (removal of immune cells), Imuran® (azathioprine) and prednisone; MBP8298; Methylprednisolone; combination of Methylprednisolone and Avonex (interferon beta-1a); Modiodal

(modafinil); NBI-5788 (altered peptide ligand); combination of Novantrone® (mitoxantrone for injection concentrate) and Avonex® (Interferon beta-la) or Copaxone® (glatiramer acetate); Omega-3 Fatty Acid Supplementation; Pixantrone (BBR 2778); combination of Provigil® (modafinil) and Avonex® (interferon beta-1a); Rapamune® (sirolimus); RG2077; Rituxan® (rituximab); Rolipram (phosphodiesterase-4 inhibitor); SAIK-MS (laquinimod, ABR-215062); T cell vaccination; Teriflunomide; Tetrahydrocannabinol; Tetrahydrocannabinol (dronabinol); Thalamic stimulation; combination of Tysabri® (natalizumab) and Avonex® (interferon beta-1a); combination of Tysabri® (natalizumab) and Copaxone® (glatiramer acetate); and Viagra® (sildafenil citrate).

Further example of pharmaceutically active agents that are effective against multiple sclerosis and are suitable to be administered in combination with compounds of the present invention is Copaxone (Glatiramer), which can be orally co-administered with the compounds of the present invention.

In other embodiments, pharmaceutically active agents that are effective against multiple sclerosis and are suitable to be administered in combination with compounds of the present invention include compounds include: Mylinax, an oral formulation of cladrlbine used in leukaemia treatment, developed by Serono/Ivex; Teriflunomide, a metabolite of Arava, an oral immunosuppressant, developed by Sanofl-Aventis; FTY 720, an oral immunomodulator (Sphingosine-1-phosphate receptor agonist), developed by Novartis; MBP 8298, a synthetic myelin basis protein designed to reduce the emergence of antibodies directed against the myelin, developed by Bio MS Medical; an orphan drug 4-aminopyridline (4-AP), a potassium channel blocker, developed by Acorda; Gamunex, an intravenous immunoglobulin formulation, developed by Bayer; BG-12 fumarate, a second generation oral futnarate, developed by Biogen Idec/Fumapharm; Temsirolimus, a T-lymphocytes proliferation blocker, developed by Wyeth; E-2007, an AMPA receptor agonist, developed by Eisal; Campath, a humanized antibody directed against CD52, developed by Genzyme; Neuro Vax, a vaccine, developed by Immune Response; Zocor, a statin, developed by Merck; NBI 5788, a myelin-mimicking peptide ligand, developed by Neurocrine; Tauferon, Interferon tau,

developed by Pepgen; Zenapax, a humanized anti-CD25 immunosuppressive antibody, developed by Protein Design; a combination of MS-IET and EMZ 701, a methyl donator, developed by Transition Therapeutics; Laquinlmod, an oral formulation of a derivative of linomide, developed by Active Biotech/Teva; deskar pirfenidone, a TNF-alpha inhibitor, developed by Mamac; ATL-1102, a second generation antisense inhibitor targeting VLA4, developed by Antisense Therapeutics.

In some embodiments, compounds of formula (A) can be administered in combination with antivascular agents, in particular agents inhibiting the growth factor receptors, Epidermal Growth Factor Receptor (EGFR), Vascular Epidermal Growth Factor Receptor (VEGFR), and Fibroblast Growth Factor Receptor (FGFR). Examples of such agents include, Iressa, Tarceva, Erbitux, Pelitinib, AEE-788, CP-547632, CP-547623, Tykerb (GW-2016), INCB-7839, ARRY-334543, BMS-599626, BIBW-2992, Falnidamol, AG1517, E-7080, KRN-951, GFKI-258, BAY-579352, CP-7055, CEP-5214, Sutent, Macugen, Nexavar, Neovastat, Vatalanib succinate, GW-78603413, Lucentis, Teavigo, AG-13958, AMG-706, Axitinib, ABT-869, Evizon, Aplidin, NM-3, PI-88, Coprexa, AZD-2171, XL-189, XL-880, XL-820, XL-647, ZK-CDK, VEGFTrap, OSI-930, Avastin, Revlimid, Endostar, Linomide, Xinlay, SU-668, BIBF-1120, BMS-5826624, BMS-540215.

In some embodiments, compounds of formula (I) can be administered in combination with agents that affect T-cell homing, extravastion and transmigration. Examples of such agents include, FTY-720PKI-166, PTK-787, SU-11248.

In some embodiments, compounds of formula (I) can be administered in combination with agents inhibiting VLA-4. Examples of such agents include, Tysabri, Bio-1211. HMR-1031, SB-683698, RBx-4638,RO-0272441, RBx-7796,SB-683699, DW-908e, AJM-300, and PS-460644.

In certain embodiments, the compound of formula (I) can be administered alone or in combination with an anti-cancer agent.

As used herein, the term "combination" with reference to pharmaceutically active agents and the term "co-administering" and "co-administration" refer to

administering more than one pharmaceutically active agent to a patient during one treatment cycle and not necessarily simultaneous or in a mixture.

Anti-cancer agents that can be employed in combination with the compounds of the invention include Taxol™ (also referred to as "paclitaxel", and compounds that have the basic taxane skeleton), Adriamycin, Dactinomycin, Bleomycin, Vinblastine, Cisplatin, acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; flurocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-n1 ; interferon alfa-n3; interferon beta-I a; interferon gamma-I b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole;

nogalamycin; ormaplatin; oxisuran; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; trestolone acetate; triciribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin and zorubicin hydrochloride.

Other anti-cancer drugs that can be employed in combination with the compounds described herein include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole;

carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexamethasone; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; 9- dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase;

metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding

protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Preferred anti-cancer drugs are 5-fluorouracil and leucovorin.

Other chemotherapeutic agents that can be employed in combination with the compounds of the invention include but are not limited to alkylating agents, antimetabolites, natural products, or hormones.

The invention is illustrated by the following examples, which are not intended to be limiting in any way.

EXEMPLIFICATION

EXAMPLE 1: Synthesis of Compounds

Commercial reagents were purchased from Aldrich Chemical Company (Milwaukee, Wis.). All commercial solvents and reagents were used without further purification. Column chromatography was performed on 70-230 mesh silica gel. Melting points were determined on an Electrothermal capillary melting point apparatus and are uncorrected. .sup.1 H NMR spectra were recorded on a Varian VXR spectrometer operating at 400 MHz, using TMS as an internal standard. Elemental

compositions were verified by elemental analysis (Galbraith Laboratories) or by ion trap and time of flight mass spectrometry with spectral deconvolution of parent and derived ions. Analyses were within +/- 0.4% of theoretical values for C, H, and N.

With reference to the substituted imidazoacridinone in Scheme 1 and more specifically to Structure S1.1 therein, the following is a representative synthesis:

6-Chloro-2-[(4-Fluorophenyl)Amino]-3-nitrobenzoic Acid

A mixture of 2,6-dichloro-3-nitrobenzoic acid (18.88 g, 0.08 mol), 4-fluoroaniline (26.8 g, 0.18 mol) and EtOH (50 ml) was refluxed for 30 hours. The solvent was evaporated, benzene (100 ml) and 2N aqueous NaOH (150 ml) were added to the residue, and the mixture was vigorously stirred for 1 hour. Undissolved material was separated by filtration, the aqueous layer was isolated, and traces of benzene were removed by partial evaporation. The solution was then made acidic by addition of concentrated hydrochloric acid. The resulting yellow precipitate was collected by filtration and washed with water (100 ml). After drying, the crude material was crystallized from toluene to give 15.36 g (62%) of 7: mp 216-220 ^{0}C.

By this method, beginning with the appropriate anilines, the following compounds were prepared: 6-chloro-2-(4-methylphenyl)amino-3-nitro-benzoic acid, 6-chloro-2-(4-methoxyphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(4-benzyloxyphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(3-methylphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(3-methoxyphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(4-cyanophenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(3-cyanophenyl)amino-3-nitrobenzoic acid, 6-chloro-2-[4-(methoxycarbonyloxy)phenyl]amino-3-nitrobenzoic acid, 6-chloro-2-[4-(methanesulfonyl)phenyl]amino-3-nitrobenzoic acid, 6-chloro-2-[4-(trifluoromethoxy)phenyl]amino-3-nitrobenzoic acid, 6-chloro-2-(4-methylphenyl)amino-3-nitro-benzoic acid, 6-chloro-2-(4-methoxyphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(4-benzyloxyphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(3-methylphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(3-methoxyphenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(4-cyanophenyl)amino-3-nitrobenzoic acid, 6-chloro-2-(3-cyanophenyl)amino-3-nitrobenzoic acid, 6-chloro-2-[4-

(methoxycarbonyloxy)phenyl]amino-3-nitrobenzoic acid, 6-chloro-2-[4-(methanesulfonyl)phenyl]amino-3-nitrobenzoic acid, 6-chloro-2-[4-(trifluoromethoxy)phenyl]amino-3-nitrobenzoic acid, 6-chloro-2-[4-(t-butoxycarbonyloxy)trifluoromethoxy)phenyl]amino-3-nitrobenzoic acid and others.

5-Chloro-8-Fluoro-2-nitro-1H-acridin-6-one, (S1.1)

A mixture of 6-chloro-2-[(4-fluorophenyl)amino]-3-nitrobenzoic acid (12.39 g, 0.04 mol), chloroform (100 ml), and $POCl_3$ (60 ml, 0.64 mol) was stirred at reflux for 8 h. Solvents were removed under reduced pressure. To the residue was added 200 ml of a mixture of 1,4-dioxane and water (8:1), and the mixture was acidified with concentrated hydrochloric acid and stirred at reflux for 2 h. Water was added (200 ml) and the precipitate was collected by filtration and crystallized from N,N-dimethylformamide--water to give 10.2 g (87%) of 1b as orange needles: mp 287-291 ^{0}C.

By this method, but starting with the appropriate 6-chloro-2-arylamino-3-nitrobenzoic acids, and separating isomers by recrystalization and/or column chromatography where needed, the following were prepared: 5-chloro-8-methyl-2-nitro-1H-acridin-6-one, 5-chloro-8-methoxy-2-nitro-1H-acridin-6-one, 5-chloro-8-benzyloxy-2-nitro-1H-acridin-6-one, 5-chloro-9-methyl-2-nitro-1H-acridin-6-one, 5-chloro-9-methoxy-2-nitro-1H-acridin-6-one, 5-chloro-8-cyano-2-nitro-1H-acridin-6-one, 5-chloro-9-cyano-2-nitro-1H-acridin-6-one, 5-chloro-8-methoxycarbonyloxy-2-nitro-1H-acridin-6-one, 5-chloro-8-methanesulfonyl-2-nitro-1H-acridin-6-one, 5-chloro-8-trifluoromethoxy-2-nitro-1H-acridin-6-one, 5-chloro-8-t-butoxycarbonyloxy-2-nitro-1H-acridin-6-one, and others.

Each of these synthons was then reacted with appropriate alkylamino-alkylamines to displace the 5-chloro-functionality in structures belonging to the S1.1 cohort, thus affording the corresponding cohort of S1.2 analogs. The nitro group in each of these was reduced to the S1.3 set of structures and these in turn are cyclo-annulated with formic, acetic and other acyl donors to afford the final imidazo acridinones, as per the structure indicated a S1.4 in Scheme 1.

Compounds prepared in this manner afford crystaline salts as the free base or as the hydrochloride salts. Isomeric impurities may first be removed by flash chromatography on silica gel with mixtures of methanol and dimethyl formamide as diluent. Purity is then established by HPLC with the following protocol:

GRADIENT CONDITIONS

Instrument Specifics:

Waters HPLC system
- 2795 separations module equipped with a
- 2474 Variable Fluorescence detector
- 2996 PDA detector.

Column:

Supelco Discovery RP Amide C16, 3.0 x 125mm, 5um or
Alltech Alltima C18, 3.2 x 150mm, 5 µm

Column temperature: 30°C
Sample temperature: 15°C

Detector Conditions:

Fluorescence detector: excitation 420; emission 520 (*Note:Fluorescence detection is not used as this concentration saturates the detector.*)
PDA wavelength: 254

Gradient:

Mobile phase

A: 0.025M Ammonium formate, pH 4
B: Acetonitrile

Gradient

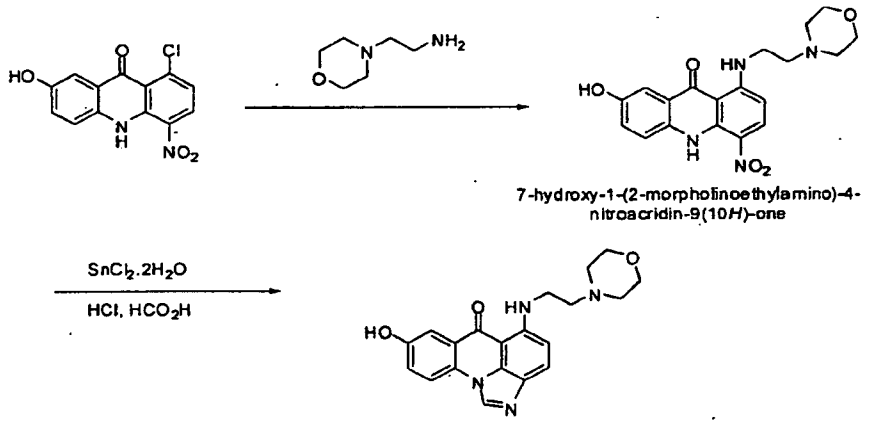
Time	%A	%B	Curve
Initial	90	10	-
30m	30	70	6 (linear)
31m	90	10	6

- Flow rate: 0.7 ml/min
- Run time: 30 min with 5 min equilibration between injections

All of the compounds prepared by the sequence of steps exemplified here proved homogenous by HPLC, with retention times of 7-9 minutes. The precursors from Steps S1.1 through S1.3 and various impurities show retention times less than 6 minutes or greater than 12 minutes. The final purity of these materials was established as greater than 98%, in order to qualify for biological testing. NMR, elemental compositions and mass spectral properties conformed to theory.

Physical Characterization of Representative Compounds Synthesized by the Described Method

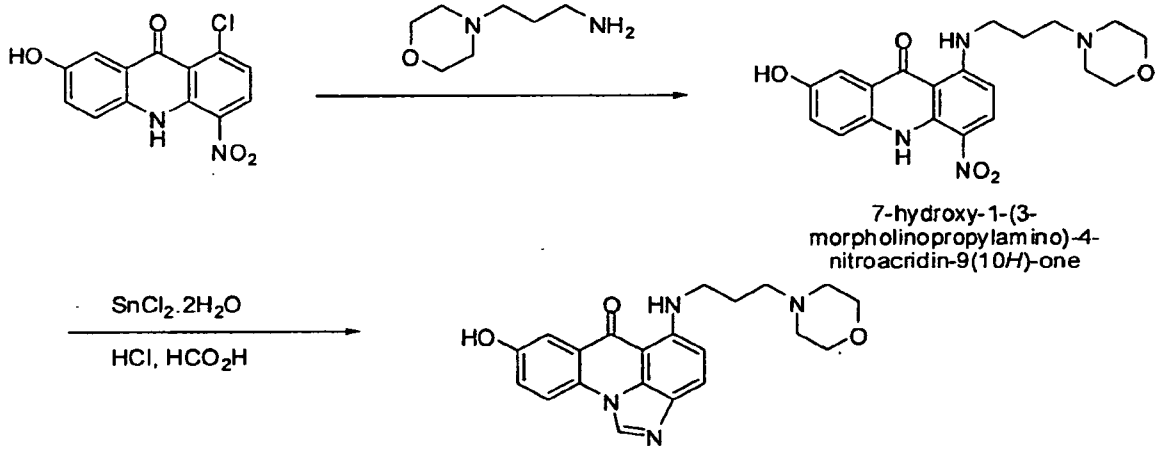
1. Synthesis of 8-hydroxy-5-(2-morpholinoethylamino)-6H-imidazo[4,5,1-de]acridin-6-one



To a stirred slurry of 1-chloro-7-hydroxy-4-nitroacridin-9(10H)-one (17.1 g, 58.8 mmol) in DMF (80 mL) was added 2-morpholinoethylamine (15.5 mL, 118 mmol) at RT. After the addition, the reaction mixture was heated at 55° C for 3.5 hours. Upon cooling to RT, the mixture was treated with water (150 mL), and the resulting precipitate was collected by filtration. The filter cake was washed with water, ethanol, and dried in vacuum to give the title compound (15.03g, 91% yield) as a yellow solid. **^{1}H NMR (400 MHz, DMSO-d6): δ** 12.39 (1H, br, s), 11.92 (1H, br, s), 9.86 (1H, br, s), 8.32 (1H, d, J = 9.5 Hz), 7.78 (1H, d, J = 9.2 Hz), 7.23 (1H, dd, J = 9.2, 2.8 Hz), 6.46 (1H, d, J = 9.5 Hz), 3.62 (4H, m), 3.52 (2H, m), 2.63 (2H, m), 2.47 (4H, m). **HPLC:** t_R = 5.35 minute (95.00%); **LRMS:** m/z = 385 (M+H).

To a stirred solution of 7-hydroxy-1-(2-morpholinoethylamino)-4-nitroacridin-9(10H)-one (6.20 g, 15.6 mmol) in formic acid (99%, 200 mL) was added a solution of tin (II) chloride dehydrate (15.8 g, 70 mmol) in 37% hydrochloric acid (20 mL) at RT. The mixture was heated at 103 °C for 21 hours, and concentrated to dryness. The resulting solid was dissolved in water, basified with an excess of saturated aqueous sodium bicarbonate solution. The resulting precipitate was collected by filtration, washed with water, ethanol, and vacuum-dried to afford the title compound (5.28g, 92% yield) as a yellow solid. **^{1}H NMR (400 MHz, DMSO-d6): δ** 9.09 (1H, s), 9.02 (1H, t, J = 5.1 Hz), 8.24 (1H, d, J = 9.0 Hz), 7.95 (1H, d, J = 8.6 Hz), 7.72 (1H, d, J = 2.7 Hz), 7.32 (1H, dd, J = 8.6, 2.7 Hz), 6.80 (1H, d, J = 8.6 Hz), 3.62 (2H, m), 3.48 (2H, m), 3.41 (2H, m), 3.36-3.31 (4H, m), 2.65 (2H, m). **HPLC:** t_R = 3.41 minute (92.95%); **LRMS:** m/z = 365 (M+H).

2. Synthesis of 8-hydroxy-5-(3-morpholinopropylamino)-6H-imidazo[4,5,1-de]acridin-6-one



To a stirred slurry of 1-chloro-7-hydroxy-4-nitroacridin-9(10H)-one (8.19g, 28.2 mmol) in DMF (110 mL) was added 3-morpholinopropylamine (9.89 mL, 67.7 mmol) at RT. After the addition, the reaction mixture was heated at 55° C for 4.5 hours. Upon cooling to RT, the mixture was treated with water (120 mL), and the resulting precipitate was collected by filtration. The filter cake was washed with water, and dried

in vacuum to give the title compound (10.8g, 95% yield) as a yellow solid. **^{1}H NMR (400 MHz, DMSO-d6): δ** 12.48 (1H, s), 11.96 (1H, s), 8.36 (1H, d, J = 9.4 Hz), 7.86 (1H, d, J = 9.1 Hz), 7.54 (1H, d, J = 2.8 Hz), 7.27 (1H, dd, J = 9.1, 2.8 Hz), 6.58 (1H, d, J = 9.4 Hz), 3.58 (4H, m), 3.52 (2H, m), 2.36 (6H, m), 1.84 (2H, m).

LRMS: m/z = 399.0 (M+H).

To a stirred solution of 7-hydroxy-1-(3-morpholinopropylamino)-4-nitroacridin-9(10H)-one (5.56 g, 13.9 mmol) in formic acid (99%, 100 mL) was added a solution of tin (II) chloride dehydrate (13.99 g, 62 mmol) in 37% hydrochloric acid (18 mL) at RT. The mixture was heated at 103° C for 22 hours, and concentrated to dryness. The resulting solid was dissolved in water, basified with saturated aqueous sodium bicarbonate solution (500 mL). The resulting precipitate was collected by filtration, washed with water, and air-dried. Recrystallization from pyridine gave the title compound (5.11g, 97% yield) as a yellow solid. **^{1}H NMR (400 MHz, DMSO-d6): δ** 10.08 (1H, s), 9.06 (1H, s), 8.89 (1H, s), 8.22 (1H, d, J = 8.6 Hz), 7.91 (1H, d, J = 8.6 Hz), 7.70 (1H, s), 7.31 (1H, d, J = 8.6 Hz), 6.77 (1H, d, J = 8.6 Hz), 3.58 (4H, m), 3.41-3.33 (6H, m), 2.40-2.34 (2H, m), 1.79 (2H, m). **^{13}C NMR (100 MHz, DMSO-d6): δ** 178.13, 155.84, 150.11, 135.71, 132.56, 131.09, 129.60, 128.53, 126.80, 122.74, 118.21, 111.90, 106.86, 102.53, 66.83, 56.51, 54.13, 41.35, 26.15.

HPLC: t_R = 3.63 minute (95.47%); **LRMS:** m/z = 379.0 (M+H)

EXAMPLE 2: Determination of FLT3 and related protein tyrosine kinase activity targeting in vitro

Protein tyrosine kinases are major biological effectors and because of their central role in regulatory signal transduction they have become target for drug development. The structures of many major kinases and their mutants are known, have been cloned and the functional domains, e.g. the juxtamembrane, ATP and catalytic components projecting from the cell membrane into the cytosol have been expressed through recombinant genetic techniques. The recombinant enzymes have been assembled into test panels to exploit the fact that in the presence of ATP they will phosphorylate an appropriate substrate and the phosphorylation rate and extent can then

be measured via an optical reporter system. This testing stratagem and its application in drug development has been discussed in a review by M Vieth et al. (*Drug Disc. Today* 10: 839-846, 2005). The translation of in vitro results and the correlation to in vivo cellular assays is considered to be high and has been validated in cellular models, for example, in the work of J.S. Melnik et al. (*Proc. Nat. Acad. Sci.* 103:3153-3158, 2006).

Testing of the compounds described in this invention was carried out using the SelectScreen™ platform from Invitrogen, Inc. (Carlsbad, CA, USA) and the details of its performance are readily viewed via the web by linking to: http://www.invitrogen.com/downloads/SelectScrn_Brochure.pdf.

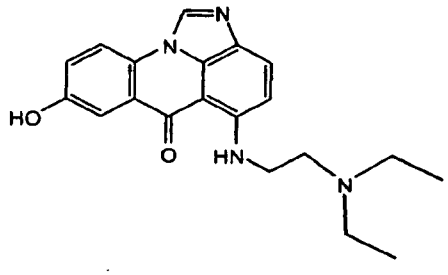
Briefly the approach is based on treating each specific kinase with a unique substrate and optical reporter system in the presence of ATP at 100 micromolar or at the apparent optimal ATP concentration for each kinase. In controls, the substrate is phosphorylated and a baseline optimal response is recorded. Graded amounts of putative inhibitor are then added in separate increments to generate a dose response curve. The latter is obtained by fitting to a sigmoid saturation equation, such as the Hill equation, and the concentration of test article producing 50 per cent inhibition is then noted as the IC_{50}. An effective level of inhibition in the low nanomolar range is considered to qualify the test compound as potential drug or targeting agent against the specific kinase that it has inhibited. The IC_{50} value is, therefore, a measure of potency. Another important feature is specificity. It is considered a desirable property when claiming efficacy to determine how many kinases are inhibited by the same molecule. The fewer number inhibited points toward specificity; the greater to inhibitory promiscuity.

For the compounds of this invention, the in vitro kinase screens revealed not only high activity against FLT3 and its constitutively activate mutant FLT3 D835Y but also a high, and unprecedented specificity, with at least a 2-log unit difference between the EC50 value for FLT3 and the corresponding inhibitory index for other and closely related protein tyrosine kinases, e.g. KDR, cKIT, PDGF, FGF, NTRK and others, in the TK and RTK domains.

The screening was carried out in two phases as shown in FIG. 1. First the compounds of this invention were tested against a subset, the primary kinase screen, to determine initial activity at 1 and 0.1 micromolar concentrations. If greater than 50% inhibition was observed (at 100 mM ATP) against all but INSR, the compounds proceeded to be tested against the broader Secondary Kinase Screen. Thereafter compounds with at least 50% inhibitory activity on any given kinase were re-examined with a 9 point dilution series to obtain the EC_{50} against that kinase. Note should be made that activity against INSR, the insulin receptor, in the primary screen or against INSRR (insulin receptor-related receptor) or IGF1, the insulin like growth factor 1, in the secondary screen would have disqualified the compounds from further development, because inhibition of an essential homeostatic set of receptors is a hallmark of undesirable side effects. None of the compounds of this invention that were tested inhibited these so called "housekeeping" receptors even at 10 micromolar concentration, a high enough concentration generally indicative of drug safety absent.

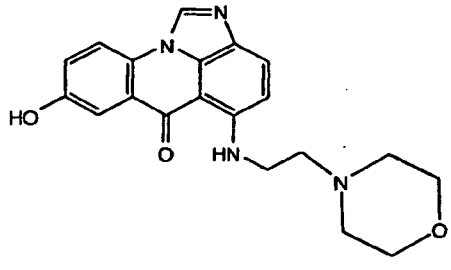
Two examples of FLT3 inhibitors are shown in FIG. 2:

a compound represented by structural formula (A)(also referred to as XF-2):



(A); and

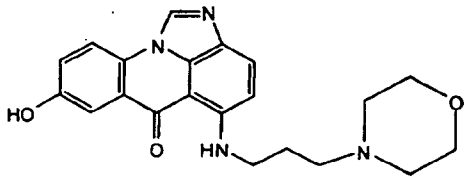
a compound represented by structural formula (B)(also referred to as XF-22):



(B).

FIG. 3 shows their activity as FLT3 inhibitors; a high degree of inhibition is noted, with IC_{50} values of 8 and 12 nM, respectively.

Shown in the tables presented in FIGs. 4A and 4B is a detailed analysis of the specificity of Compounds XF-22 (formula (B)), and XF-113 (formula (C)), compared to a number of known inhibitors in current development or recently approved as therapeutic drugs as well as XF-02 (formula (A)) as positive control:



(C).

Two key novel features emerge from these data. First, XF-22 and XF-113 are active against FLT3 and its mutant form and the activity profile drops off precipitously as one explores additional RTK and TK enzymes. Second, the inhibitory activities of XF-22 and XF-113 are significantly less pronounced when measured against other closely related targets, in particular the KDR, PDGF and TRK members of the RTK family, which are co-inhibited by other more promiscuous inhibitors that have been promulgated as FLT3 inhibitor.

The activity of a representative selection of these latter reference compounds is also shown in FIG. 4A. It is evident that none of them are truly selective against FLT4. The two such references with the closest profile to XF-2 are PKC-412 and CEP-701. The former cross-reacts with KDR, PDGFRb, and PKC. The latter, inhibits FGFR2 and, more significantly, the neurokinin receptor NTRK1.

It should be noted in this context that the activity profile of XF-22 and XF-133 also matched that of XF-2, in contrast to CEP-701 and PKC-412, indicating that high selectivity is a novel and unexpected feature of the imidazoacridinone FLT3 inhibitors.

EXAMPLE 3: Determination of FLT3 and related protein tyrosine kinase activity targeting in cell culture.

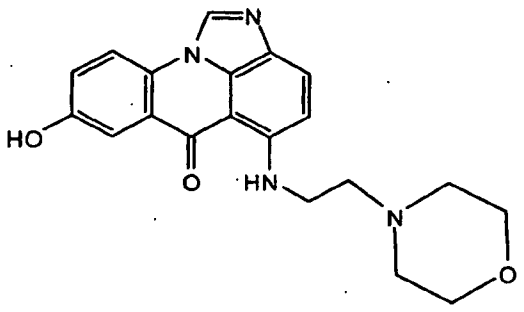
It is now understood that an important subset of human myeloid leukemia cells overexpress FLT3 as constitutively activated mutations. The most prevalent of these is the internal tandem duplication. Two cell lines commonly used to test the potency of FLT3 inhibitors on cell growth and viability are the RS4(11) and MV4(11). The

RS4(11) cell line, also known as RS4;11, was established from a bone marrow patient with acute lymphoblastic leukemia. This female patient was 32 years of age. The cells lack surface and cytoplasmic immunoglobulin, and are negative for CD10. The cells have a characteristic chromosome translocation (4;11)(q21;q23), and an isochromosome for the long arm of chromosome 7. These cells express the wild-type FLT3 receptor and are further characterized by expression of the MHC Class II antigens (HLA DR+); CD9+; CD24+. The MV4(11) cell line, also known as MV-4-11, was established from the blast cells of a 10 year old male with biphenotypic B myelomonocytic leukemia (ATCC). Other sources indicate this cell line is derived from acute monocytic leukemia (AML FAB M5). The cytogenetic analysis reveals that there are 48 chromosomes (+8, +19) and a (4;11)(q21;q23) translocation. These cells express a mutant form of FLT3 containing an internal tandem duplication (ITD), and are further characterized by expression of CD4 (40-96%); CD10 (4-11%); CD15 (96-99%).

When standard protocols for adherent cell culture are followed, according to the instructions supplied by the American Type Culture Collection for the two line, the cell will proliferate with an approximate 30 hour doubling time. However, when exposed to graded amounts of XF-2 or XF-22, the growth and viability of these cell lines is arrested. As shown in FIG. 5, the effective concentration to decrement cell viability by 50% (EC_{50}) for XF-2 in RS4(11) at 72 hrs of continuous exposure is 34 nM, which compares favorably to the positive control, PKC-412, a known FLT3 inhibitor. The EC_{50} for XF-22 fell closer to the micromolar mark, or a third less potent than PKC-412. A similar result was obtained in the more clinically significant MV4(11) line, which bears the internal tandem duplication and requires an active FLT3 signaling cascade for survival. In this case XF-2 and PKC-412 were closely matched, while XF-22 showed less activity. When the drugs were used to arrest growth in a the HL-60 leukemia, which is known to neither express FLT3 nor require the FLT3 signaling cascade for growth or viability, the EC_{50} of both XF-2 and XF-22 rose to values greater than 10 micromolar, as did PKC-412, confirming that their cytotoxicity had been derived in large measure by attack on FLT3.

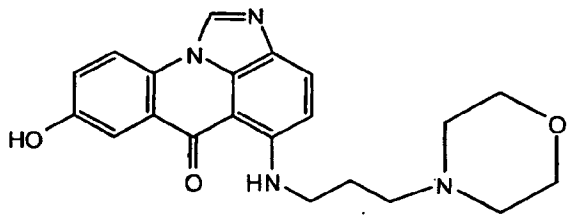
EXAMPLE 4: Efficacy of the Representative Compounds of the Invention

Efficacies of 8-hydroxy-5-(2-morpholinoethylamino)-6H-imidazo[4,5,1-de]acridin-6-one (B) (XF-22)



(B),

and 8-hydroxy-5-(3-morpholinopropylamino)-6H-imidazo[4,5,1-de]acridin-6-one (C) (XF-113)



(C)

have been tested by determining EC50 and E1000 values according to the following protocol.

The terms "IC50" and "EC50" are used interchangeably. As used herein, "EC50" refers to nMolar concentration at median percent inhibition determined by dose respose (DR) assay. As used herein, the term "E1000" refers to percent inhibition at 1000 nMolar determined by assay. EC50 was calculated based on dose response curve was fitted to 4 parameter Hill equation.

Testing of the compounds described in this invention was carried out using the SelectScreen™ platform from Invitrogen, Inc. (Carlsbad, CA, USA) and the details of its performance are readily viewed via the web by linking to: http://www.invitrogen.com/downloads/SelectScrn_Brochure.pdf.

Briefly the approach is based on treating each specific kinase with a unique substrate and optical reporter system in the presence of ATP at 100 micromolar. In controls, the substrate is phosphorylated and a baseline optimal response is recorded.

Compounds were initially tested at 1000 nanomolar concentrations and the % inhibition of enzyme activity determined (E1000). The compounds were then re-tested by adding graded amounts of putative inhibitor which were added in 5 separate increments to generate a dose response curve. The latter is obtained by fitting to a 4 parameter Hill equation, a sigmoid saturation equation. The concentration which causes 50% enzyme inhibition (EC50) was then calculated from the dose response equation.

An effective level of inhibition in the low nanomolar range is considered to qualify the test compound as potential drug or targeting agent against the specific kinase that it has inhibited. The EC_{50} value is, therefore, a measure of potency. Another important feature is specificity. It is considered a desirable property when claiming efficacy to determine how many kinases are inhibited by the same molecule. The fewer number inhibited points toward specificity; the greater to inhibitory promiscuity.

For the compounds of this invention, the experimental condition were as follows. The 2X FLT3/Tyr 02 peptide mixture was prepared in 50 mM HEPES pH 7.5, 0.01 BRIJ-35, 10mM MgCl2, 1mM EGTA. The final 10 uL kinase reaction consists of 0.6-76.0 ng FLT3 and 2 uM Tyr 02 peptide in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM Mg Cl2, 1 mM EGTA. After 1 hour kinase reaction incubation, 5 uL of a 1:64 dilution of development reagent A was added.

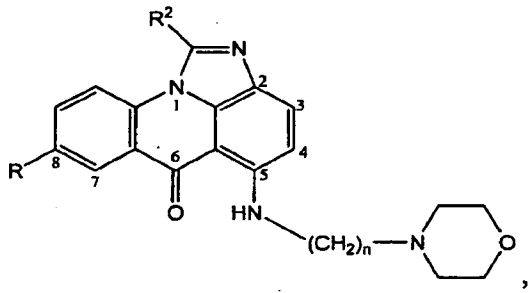
The measurements indicate that compound (II) exhibisted EC50 of 23 nM and E1000 of 94%, while compound (III) exhibited EC50 of 50 nM and E1000 of 91%.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound represented by the following formula, or a pharmaceutically acceptable salt thereof:



wherein:

R is -OH or -OCH_3,

R^2 is a -H or a C1-C4 alkyl, and

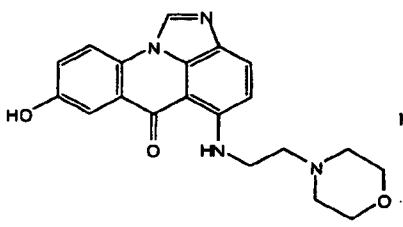
n is 2-5.

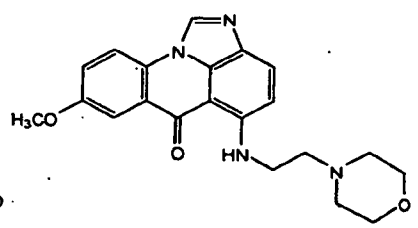
2. The compound of Claim 1, wherein R is –OH.

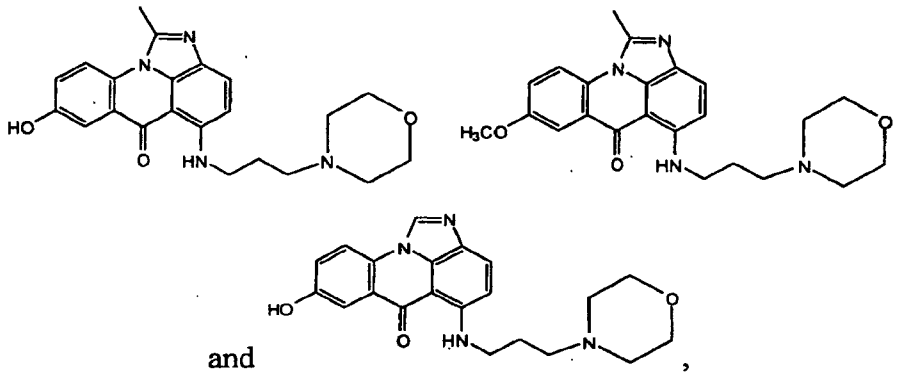
3. The compound of Claim 2, wherein n is 2 or 3.

4. The compound of Claim 3, wherein R^2 is –H.

5. The compound of Claim 1, wherein the compound is represented by one of the following formulas:







and

or a pharmaceutically acceptable salt thereof.

6. A method of treating an inflammatory disorder, a demyelinating disorder, a FLT3-mediated disorder, a cancer, a leukemia or a CSF-1R-mediated disorder in a patient, comprising administering to said patient a therapeutically effective amount of a compound of any one of Claims 1-5.

7. The method of Claim 6, wherein the disorder is a cancer selected from breast cancer, colorectal cancer, non-small cell lung cancer, ovarian, renal, sarcoma, melanoma, head & neck, hepatocellular, thyroid, multidrug-resistant leukemia, lymphoma, multiple myeloma, esophageal, large bowel, pancreatic, mesothelioma, carcinoma, sarcoma and melanoma.

8. The method of Claim 7, wherein the patient is being treated for bone metastases.

9. The method of Claim 6, wherein the disorder is an inflammatory disorder selected from systemic lupus, inflammatory bowl disease, psoriasis, Crohn's disease, rheumatoid arthritis, sarcoid, Alzheimer's disease, insulin dependent diabetes mellitus, atherosclerosis, asthma, spinal cord injury, stroke, a chronic inflammatory demyelinating neuropathy, multiple sclerosis, a congenital metabolic disorder, a neuropathy with abnormal myelination, drug-induced demyelination, radiation induced demyelination, a hereditary demyelinating

condition, a prion-induced demyelination, and encephalitis-induced demyelination.

10. The method of Claim 6, wherein the disorder is a demyelinating condition selected from multiple sclerosis, a congenital metabolic disorder, a neuropathy with abnormal myelination, drug-induced demyelination, radiation induced demyelination, a hereditary demyelination condition, a prion-induced demyelination, encephalitis-induced demyelination, a spinal cord injury, Alzheimer's disease, Chronic Immune Demyelinating Polyneuropathy (CIDP); multifocal CIDP; multifocal motor neuropathy (MMN); anti-MAG Syndrome (Neuropathy with IgM binding to Myelin-Associated Glycoprotein); GALOP Syndrome (Gait disorder Autoantibody Late-age Onset Polyneuropathy); anti-sulfatide antibody syndrome; anti-GM2 gangliosides antibody syndrome; POEMS syndrome (Polyneuropathy Organomegaly Endocrinopathy or Edema M-protein Skin changes); perineuritis; and IgM anti-GD1b ganglioside antibody syndrome.

11. The method of Claim 6, wherein the disorder is a FLT3-mediated disorder selected from axonal degeneration, acute transverse myelitis, amyotrophic lateral sclerosis, infantile spinal muscular atrophy, juvenile spinal muscular atrophy, Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis, organ rejection, bone marrow transplant rejection, non-myeloablative bone marrow transplant rejection, ankylosing spondylitis, aplastic anemia, Behcet's disease, graft-versus-host disease, Graves' disease, autoimmune hemolytic anemia, Wegener's granulomatosis, hyper IgE syndrome, idiopathic thrombocytopenia purpura, and Myasthenia gravis.

12. The method of Claim 6, wherein the disorder is a CSF-1R-mediated disorder selected from a cardiovascular disease, diseases with an inflammatory component including glomerulonephritis, prosthesis failure, sarcoidosis,

congestive obstructive pulmonary disease, asthma, pancreatitis, HIV infection, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, and neurogenic pain, osteoporosis, Paget's disease, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone, uterine cancer, stomach cancer, hairy cell leukemia, Sjogren's syndrom, uveitis, osteolytic sarcoma, uterine cancer, and stomach cancer.

13. The method of Claim 6, wherein one or more additional pharmaceutical agents is co-administered with the compound.

FIG. 1

PRIMARY KINASE SCREEN	SECONDARY KINASE SCREEN		
FLT3	CSF1R (FMS)	MET (cMet)	PTK2 (FAK)
FLT3 D835Y	EGFR (ErbB1)	NTRK1 (TRKA)	SRC
PDGFRA	EPHA1	NTRK2 (TRKB)	PRKCA (PKC alpha)
PDGFRB	EPHA2	NTRK3 (TRKC)	PRKCB1 (PKC beta I)
KDR (VEGFR2)	EPHB2	ROS1	CHEK1 (CHK1)
FGFR1	EPHB4	TEK (Tie2)	CDK1/cyclin B
FGFR2	FLT1 (VEGFR1)	ABL1	CDK2/cyclin A
c-KIT	FLT4 (VEGFR3)	ABL2 (ARG)	ROCK1
BRAF	IGF1R	JAK2	ROCK2
LYN A	INSRR (IRR)	JAK3	
LCK	LYN B		
INSR			

FIG. 2

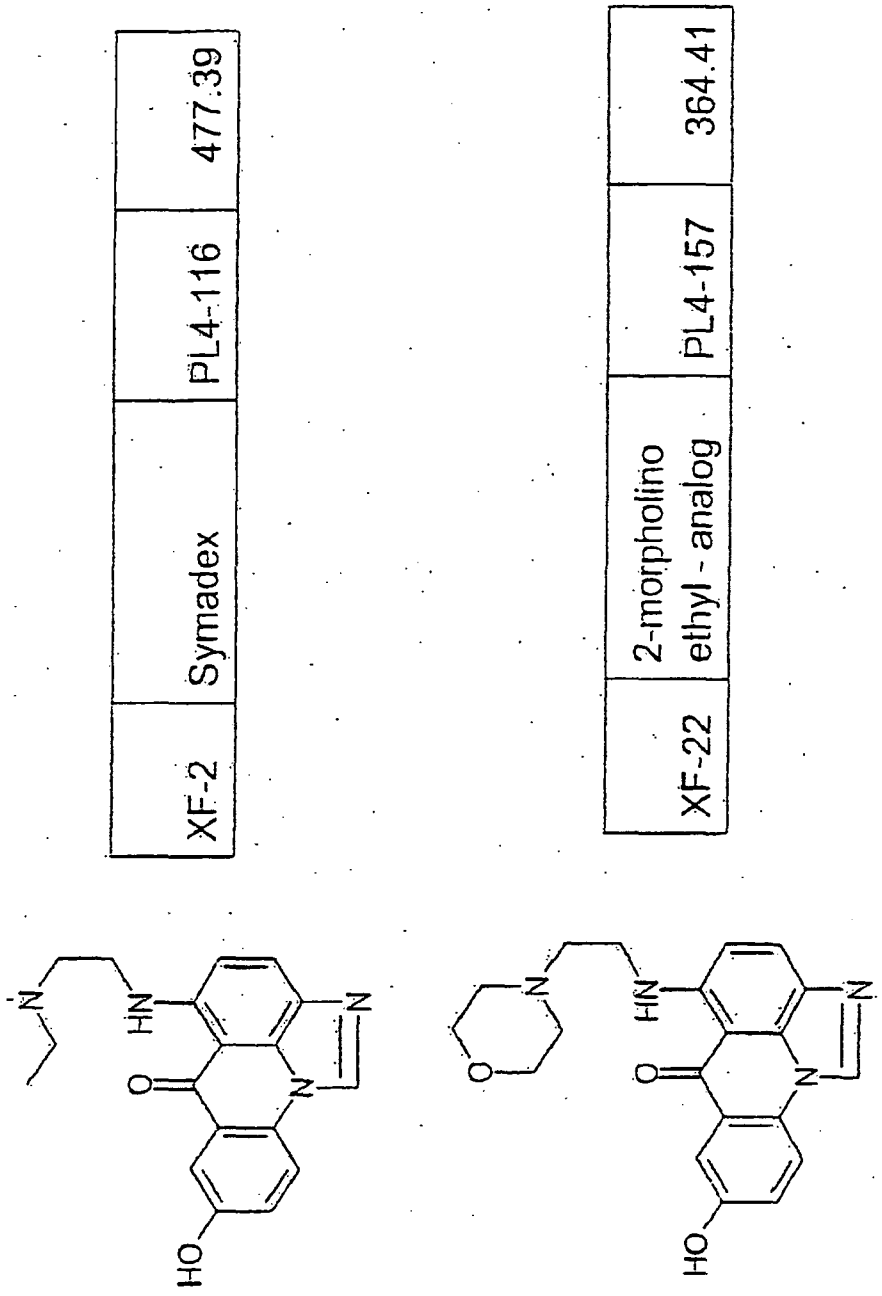

XF-2
Symadex
PL4-116
477.39
XF-22
2-morpholino ethyl - analog
PL4-157
364.41

FIG. 3

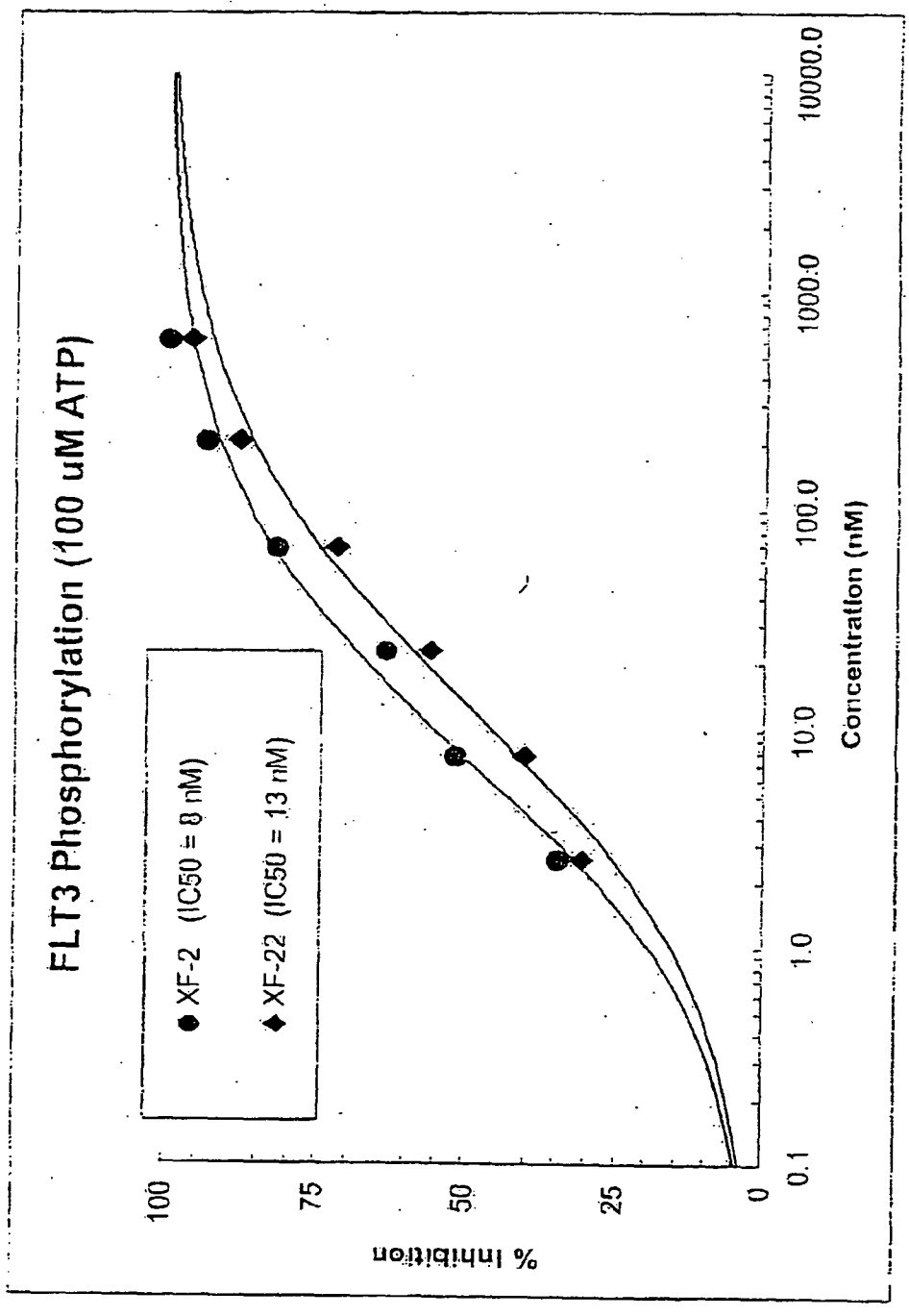

FLT3 Phosphorylation (100 uM ATP)
XF-2 (IC50 = 8 nM)
XF-22 (IC50 = 13 nM)
% Inhibition
100
75
50
25
0
0.1
1.0
10.0
100.0
1000.0
10000.0
Concentration (nM)
*Invitrogen SelectScreenTM at ATP Km[app]

FIG 4A

Kinase* IC_{50} nm	A (nM)	B (nM)	C (nM)	D (nM)	E (nM)	F (nM)
FLT3	8	10	220	10	12	5400
FLT3 (D835Y)	10	6	90	25	8	1
FGFR2	-	3500	>5000	15	150	5
KDR (VEGFR2)	9	86	>5000	10	2500	9
FGFR1	830	1500	-	8	2500	25
NTRK1 (TRKA)	-	-	-	-	10	2
PDGFRA	-	-	-	5000	5000	7
PDGFRB	8	50	200	5000	5000	3
CHK1	-	5000	-	-	-	4
JNK1	-	5000	-	-	-	-
JNK3	-	5000	-	-	-	-
KIT	-	640	170	2	3000	890
JNK2	-	5000	-	-	-	-
PKC	5000	30	5000	-	2400	1
RET	-	-	-	-	-	6

A=sunitinib, B=PKC-412, C=MLN-518, D=CHIR-258, E=CEP-701, F=staurosporine

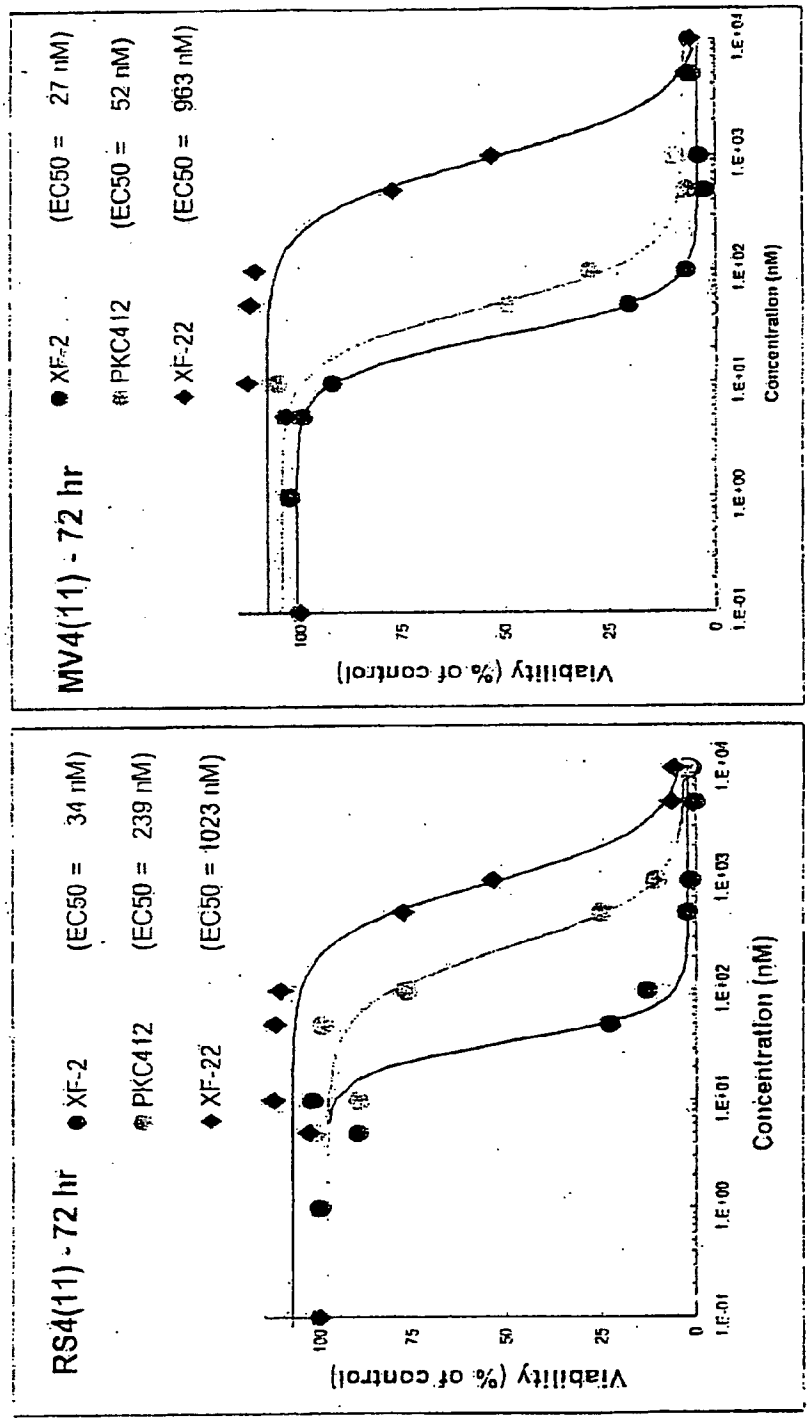
*Invitrogen SelectScreen™ at 100 μM ATP

FIG 4B

Kinase* IC_{50} nm	XF-02 (nM)	XF-22 (nM)	XF-113 (nM)
FLT3	8	23	50
FLT3 (D835Y)	12	15	46
FGFR2	1220	1800	2000
KDR (VEGFR2)	2500	3000	3000
FGFR1	2690	3000	3000
NTRK1 (TRKA)	3000	3000	3000
PDGFRA	3000	3000	4000
PDGFRB	3000	-	-
CHK1	3500	4000	4000
JNK1	4000	4000	4000
JNK3	4000	-	-
KIT	4000	5000	5000
JNK2	4800	-	-
PKC	5000	5000	5000
RET	5000	5000	5000

*Invitrogen SelectScreen™ at 100 μM ATP

FIG. 5


RS4(11) - 72 hr
XF-2 (EC50 = 34 nM)
PKC412 (EC50 = 239 nM)
XF-22 (EC50 = 1023 nM)
Viability (% of control)
Concentration (nM)
MV4(11) - 72 hr
XF-2 (EC50 = 27 nM)
PKC412 (EC50 = 52 nM)
XF-22 (EC50 = 963 nM)
Viability (% of control)
Concentration (nM)