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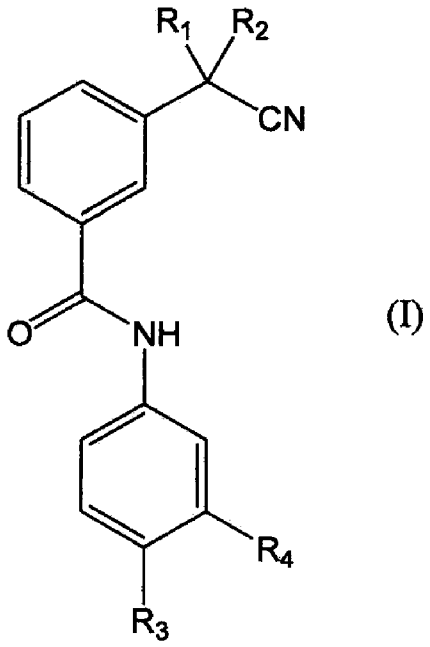
(54) Title: HETEROCYCLIC COMPOUNDS AS B-RAF INHIBITORS FOR TREATMENT OF CANCER

(57) Abstract: This invention relates to novel heterocyclic compounds that are useful for treating cancer and other cellular proliferative diseases and/or disorders associated with B-Raf activity. The compounds of the invention may be illustrated by the Formula (I). (Formula (I))



(I)

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TITLE OF THE INVENTION

HETEROCYCLIC COMPOUNDS AS B-RAF INHIBITORS FOR TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the benefit of U.S. Provisional Application No. 61/479,179, filed April 26, 2011, hereby incorporated by reference herein.

BACKGROUND OF THE INVENTION

Cellular growth is regulated by signal transduction cascades which include receptor protein kinases. For example, the Ras/Raf/MEK/ERK signal transduction pathway plays a central role in a large variety of processes including apoptosis, cell cycle progression, differentiation, and proliferation (as reviewed in, *e.g.*, Wellbrock et al, 2004, *Nat. Rev. Mol. Cell. Biol.* 5:875-885). Upon activation of Ras, Raf is recruited to the plasma membrane where it is phosphorylated and activated. Activated Raf then phosphorylates and activates MEK which, in turn, phosphorylates and activates ERK. Phosphorylated ERK translocates to the nucleus where it activates several downstream transcription factors. Thus, the Raf kinases work at the entry point of the signaling module, connecting cell-surface receptors and Ras proteins to nuclear transcription factors.

In cancer cells, activation of signal transduction cascades results in tumor formation and growth, progression of the disease and metastasis. Activation of the Ras/Raf/MEK/ERK pathway has been shown to contribute to the tumorigenic phenotype by inducing immortalization, growth factor-independent growth, insensitivity to growth-inhibitory signals, angiogenesis and apoptosis inhibition. Activating mutations and/or hyperactivity of many members of this pathway are commonly found in human cancers (see, *e.g.*, Davies, H. et al., 2002, *Nature* 417:949-954; Allen, L.F. et al., 2003, *Semin. Oncol.* 30:105-116).

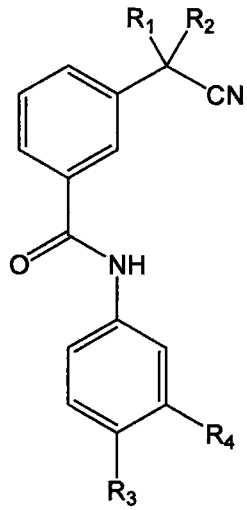
Three Raf serine/threonine protein kinase isoforms have been reported, A-Raf, B-Raf and C-Raf. These Raf kinases are highly homologous but have distinct biochemical functions, including differences in activation of the kinase pathways and tissue distribution. B-Raf, in particular, is mutated at a high frequency in human cancers (see Wellbrock et al., *supra*). Thus, B-Raf inhibitors may be of therapeutic use in the treatment of cancers. To this end, a need exists for compounds that inhibit B-Raf and intervene with the activated Ras/Raf/MEK/ERK pathway for the potential treatment of human cancers driven by the activation of this pathway.

SUMMARY OF THE INVENTION

The instant invention provides for heterocyclic compounds that inhibit B-Raf activity. The invention also provides for compositions comprising such inhibitory compounds and methods of inhibiting B-Raf activity by administering the compound to a patient in need of treatment of cancer and/or other cellular proliferative diseases.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel heterocyclic compounds that may be useful for treating cancer and other cellular proliferative diseases, treating disorders associated with B-Raf activity, and/or inhibiting the B-Raf kinase. The compounds of the invention are illustrated by the compound of Formula I:



(I)

wherein:

R_1 and R_2 are independently H, OH, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein R_1 and R_2 can be combined to form a C_3-C_6 cycloalkyl;

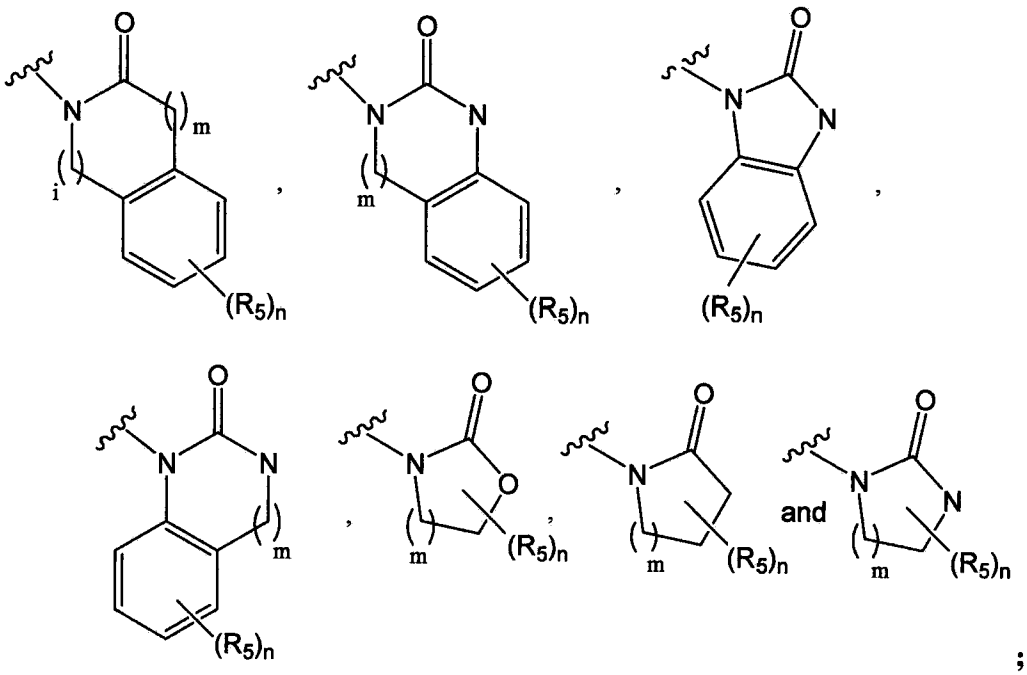
R_3 is H, OH, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

R_4 is a heteroaryl or heterocyclyl optionally substituted with one or more substituents selected from R_5;

R_5 is independently selected from OH, oxo, C_1-C_6 alkyl, OC_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or phenyl; or

a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In a second embodiment of formula I, R_4 is selected from:



wherein:

n is 0, 1, 2, or 3;

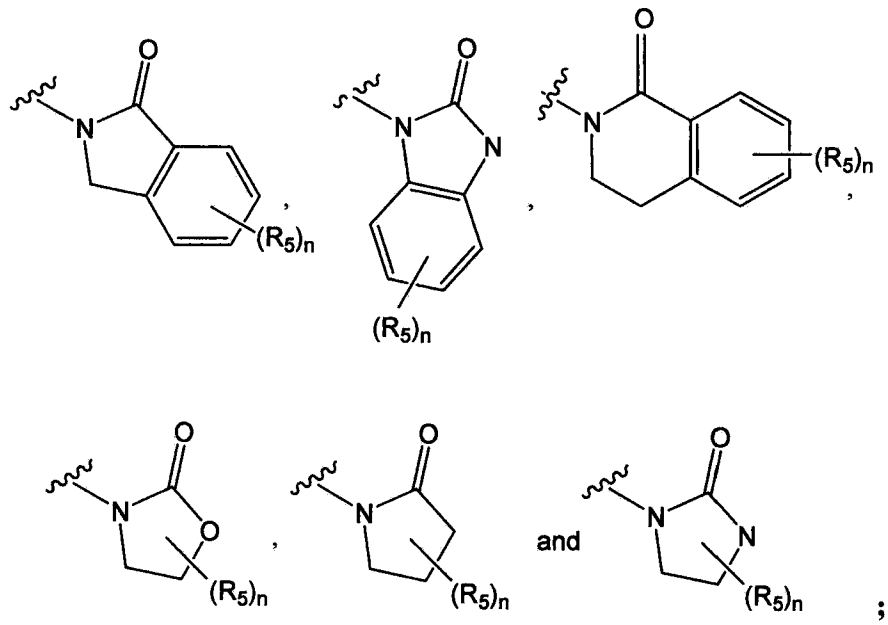
m is 0, 1, 2, or 3;

i is 0, 1, or 2; and,

all other variables and substituents are as defined above; or

a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

In a third embodiment of formula I, R_1, R_2 and R_3 are methyl, and R_4 is selected from:



wherein:

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

all other variables and substituents are as defined above; or

a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

Specific examples of the compounds of the instant invention include, but are not limited to:

3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)benzamide;

3-(Cyano-dimethyl-methyl)-N-[3-(6-methoxy-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-4-phenyl-pyrrolidin-1-yl)-phenyl]-benzamide;

3-(2-cyanopropan-2-yl)-*N*-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-5-phenyl-oxazolidin-3-yl)-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-3-phenyl-imidazolidin-1-yl)-phenyl]-benzamide; or,

3-(Cyano-dimethyl-methyl)-N-[3-(6-methoxy-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-4-methyl-phenyl]-benzamide;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, *Stereochemistry of Carbon Compounds*, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers and mixtures thereof, including optical isomers, all such stereoisomers being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted.

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (1H) and deuterium (2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

When any variable (*e.g.*, R_5) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds. Lines drawn into the ring systems from substituents represent that the indicated bond may be attached to any of the substitutable ring atoms. If the ring system is bicyclic, it is intended that the bond be attached to any of the suitable atoms in the bicyclic system.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results. The phrase "optionally substituted with one or more substituents" or "substituted with one or more substituents" should be taken to be equivalent to the phrase "optionally substituted with at least one substituent" or "substituted with at least one substituent," respectively, and in such cases another embodiment will have from zero to three substituents.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In an embodiment of the invention the term "cycloalkyl" includes the groups described immediately above and further includes monocyclic unsaturated aliphatic hydrocarbon groups. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, cyclopentenyl, cyclobutenyl and so on.

The term "haloalkyl" means an alkyl radical as defined above, unless otherwise specified, that is substituted with one to five, preferably one to three halogen atoms. Representative examples include, but are not limited to, trifluoromethyl, dichloroethyl, and the like.

"Alkoxy" represents either a cyclic or non-cyclic alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Alkoxy" therefore encompasses the definitions of alkyl and cycloalkyl above.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing from 2 to 10 carbon atoms and at least 1 carbon to carbon double bond. Preferably 1 carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an

alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing from 2 to 10 carbon atoms, unless otherwise specified, containing at least 1 carbon to carbon triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, CH(CH_3)CH_2CH(CH_3)Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "heteroaryl," as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, benzimidazolonyl, benzoxazolonyl, quinolinyl, isoquinolinyl, dihydroisoindolonyl, imidazopyridinyl, isoindolonyl, indazolyl, oxazolyl, oxadiazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

The term "heterocycle" or "heterocyclyl," as used herein, is intended to mean a 3- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected

from the group consisting of O, N and S, and includes bicyclic groups. For the purposes of this invention, the term "heterocyclic" is also considered to be synonymous with the terms "heterocycle" and "heterocyclyl" and is understood as also having the definitions set forth herein. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: azetidinyl, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxooxazolidinyl, oxazolyl, oxazoline, oxopiperazinyl, oxopyrrolidinyl, oxomorpholinyl, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, dioxidothiomorpholinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

The alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise. For example, a (C_1-C_6)alkyl may be substituted with one, two or three substituents selected from OH, oxo, halogen, alkoxy, dialkylamino, or heterocyclyl, such as morpholinyl, piperidinyl, and so on. In this case, if one substituent is oxo and the other is OH, the following are included in the definition: -C=O)CH_2CH(OH)CH_3, -(C=O)OH, -CH_2(OH)CH_2CH(O), and so on.

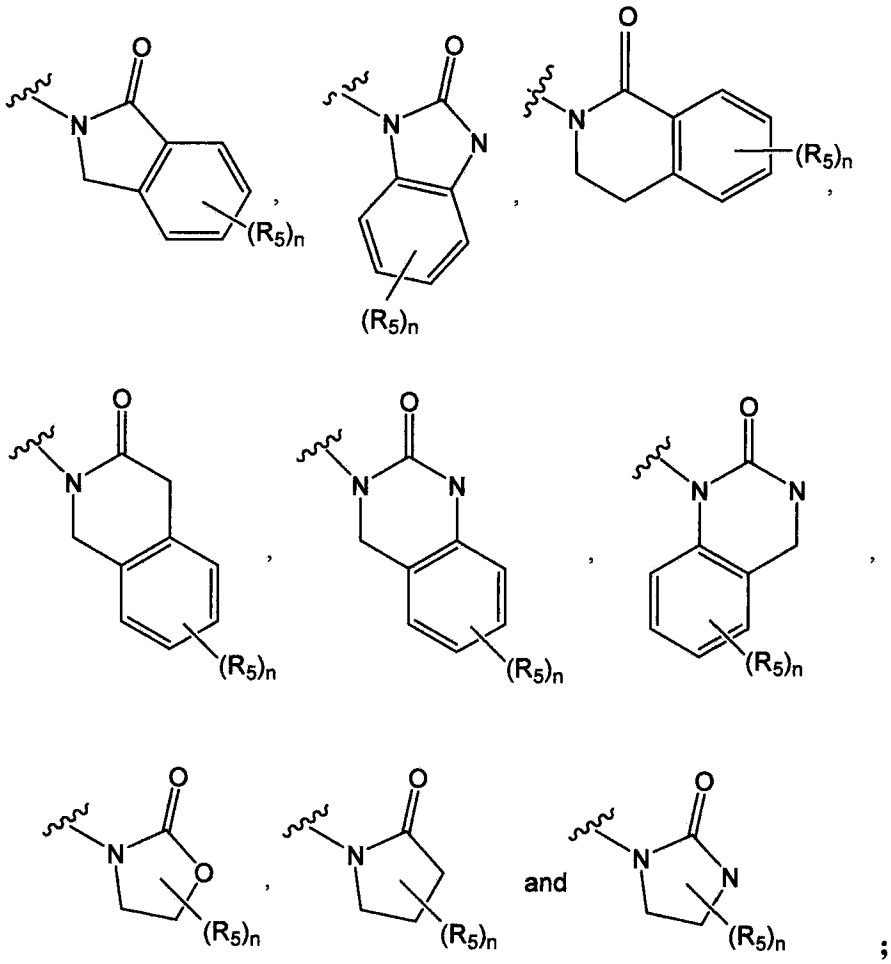
As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

In an embodiment, R_1 is H, OH, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl, or C_2-C_4 alkynyl. In a further embodiment, R_1 is methyl.

In an embodiment, R_2 is H, OH, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl, or C_2-C_4 alkynyl. In a further embodiment, R_2 is methyl.

In an embodiment, R_3 is H, OH, halo, C_1-C_4 alkyl, C_2-C_4 alkenyl, or C_2-C_4 alkynyl. In a further embodiment, R_3 is methyl.

In an embodiment, R_4 is selected from:

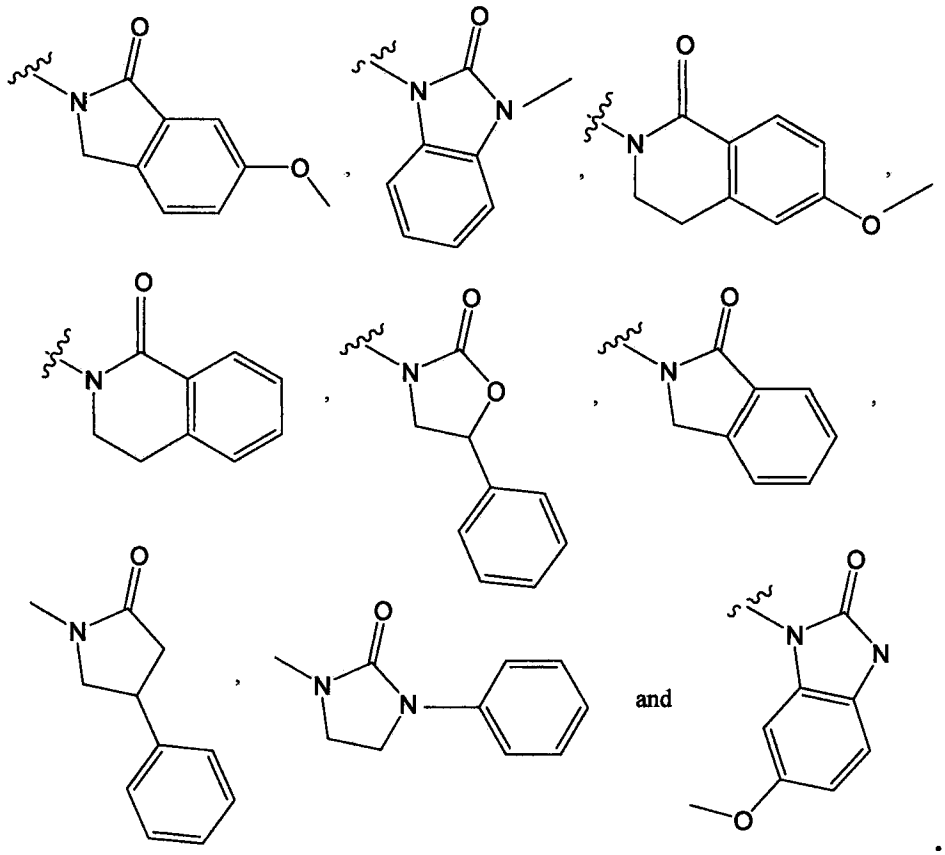


wherein:

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

R_5 is independently selected from OH, C_1-C_6 alkyl, OC_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or phenyl.

In a further embodiment, R_4 is selected from:



In an embodiment, R_5 is independently selected from OH, oxo, C_1-C_6 alkyl, OC_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or phenyl. In a further embodiment, R_5 is independently selected from OH, oxo, C_1-C_4 alkyl, OC_1-C_4 alkyl, C_2-C_4 alkenyl, or C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, or phenyl. In a further embodiment, R_5 is independently selected from C_1-C_4 alkyl, OC_1-C_4 alkyl, or phenyl. In a further embodiment, R_5 is independently selected from CH_3, or OCH_3.

In an embodiment, m is 1, 2 or 3. In a further embodiment, m is 1 or 2.

In an emdodiment, n is 0, 1 or 2. In a further embodiument, n is 1 or 2.

Included in the instant invention is the free form of compounds of the instant invention, as well as the pharmaceutically acceptable salts and stereoisomers thereof. The term "free form" refers to the amine compounds in non-salt form. The encompassed pharmaceutically acceptable salts not only include the salts exemplified for the specific compounds described herein, but also all the typical pharmaceutically acceptable salts of the free form of compounds of the instant invention. The free form of the specific salt compounds described may be isolated using techniques known in the art. For example, the free form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous NaOH, potassium carbonate,

ammonia and sodium bicarbonate. The free forms may differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise pharmaceutically equivalent to their respective free forms for purposes of the invention.

The pharmaceutically acceptable salts of the instant compounds can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Thus, pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed by reacting a basic instant compound with an inorganic or organic acid. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and

the like. When the compound of the present invention is acidic, the term "free form" refers to the compound in its non-salt form, such that the acidic functionality is still protonated.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

It will also be noted that the compounds of the present invention may potentially be internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom. An isolated compound having internally balance charges, and thus not associated with a intermolecular counterion, may also be considered the "free form" of a compound.

Utilities

The compounds of the invention find use in a variety of applications. As will be appreciated by those skilled in the art, the kinase activity of B-Raf may be modulated in a variety of ways; that is, one can affect the phosphorylation/activation of B-Raf either by modulating the initial phosphorylation of the protein or by modulating the autophosphorylation of the other active sites of the protein. Alternatively, the kinase activity of B-Raf may be modulated by affecting the binding of a substrate of B-Raf phosphorylation.

The compounds of the invention may be useful to treat or prevent cellular proliferation diseases. Disease states which may be treated by the methods and compositions provided herein include, but are not limited to, cancer (further discussed below), autoimmune disease, viral disease, fungal disease, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia, cardiovascular disease, graft rejection, inflammatory bowel disease, proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. It is appreciated that in some cases the cells may not be in a hyper- or hypoproliferation state (abnormal state) and still require treatment. Thus, in one embodiment, the present invention includes application of a compound disclosed herein to cells or individuals which are afflicted or may eventually become afflicted with any one of these disorders or states.

The compounds, compositions and methods provided herein may be useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas,

testicular carcinomas, etc. In an embodiment, the instant compounds are useful for treating cancer. In particular, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia,), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord (neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia,

chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and, Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions. In an embodiment of the invention, cancers that may be treated by the compounds, compositions and methods of the invention include, in addition to the cancers listed above: Lung: bronchogenic carcinoma (non-small cell lung); Gastrointestinal: rectal, colorectal and colon; Genitourinary tract: kidney (papillary renal cell carcinoma); and, Skin: head and neck squamous cell carcinoma.

In another embodiment, the compounds of the instant invention may be useful for treating cancer selected from: head and neck squamous cell carcinomas, histiocytic lymphoma, lung adenocarcinoma, small cell lung cancer, non-small cell lung cancer, pancreatic cancer, papillary renal cell carcinoma, liver cancer, gastric cancer, colon cancer, multiple myeloma, glioblastomas and breast carcinoma. In yet another embodiment, the compounds of the instant invention may be useful for treating cancer selected from: histiocytic lymphoma, lung adenocarcinoma, small cell lung cancer, pancreatic cancer, liver cancer, gastric cancer, colon cancer, multiple myeloma, glioblastomas and breast carcinoma. In still another embodiment, the compounds of the instant invention may be useful for treating cancer selected from: histiocytic lymphoma, lung adenocarcinoma, small cell lung cancers, pancreatic cancer, liver cancer, gastric cancer, colon cancer, multiple myeloma, glioblastomas and breast carcinoma.

In another embodiment, the compounds of the instant invention may be useful for the modulation of the metastases of cancer cells and cancer. In particular, the compounds of the instant invention may be useful to modulate the metastases of ovarian cancer, childhood hepatocellular carcinoma, metastatic head and neck squamous cell carcinomas, gastric cancers, breast cancer, colorectal cancer, cervical cancer, lung cancer, nasopharyngeal cancer, pancreatic cancer, glioblastoma and sarcomas.

In a further embodiment, the compounds of the present invention, and pharmaceutical compositions thereof, are useful to inhibit the B-Raf kinase as part of a treatment regimen for individuals displaying one or more cellular proliferative disorders.

The compounds of this invention may be administered to mammals, preferably humans, either alone or in combination with pharmaceutically acceptable carriers, excipients or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The

compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration. The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropylcellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a

hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active

ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulation.

The injectable solutions or microemulsions may be introduced into a patient's blood stream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter,

glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the instant invention can be selected in accordance with a variety of factors including type, species, age, weight, sex and the type of cancer being treated; the severity (i.e., stage) of the cancer to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

In a further example, compounds of the instant invention can be administered in a total daily dose of up to 1000 mg. Compounds of the instant invention can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). Compounds of the instant invention can be administered at a total daily dosage of up to 1000 mg, e.g., 200 mg, 300 mg, 400 mg, 600 mg, 800 mg or 1000 mg, which can be administered in one daily dose or can be divided into multiple daily doses as described above.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms "intermittent" or "intermittently," as used herein, means stopping and starting at either regular or irregular intervals. For example, intermittent administration of a compound of the instant invention may be administration one to six days per week or it may mean administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days.

In addition, the compounds of the instant invention may be administered according to any of the schedules described above, consecutively for a few weeks, followed by a rest period. For example, the compounds of the instant invention may be administered according to any one of the schedules described above from two to eight weeks, followed by a rest period of one week, or twice daily at a dose of 100 - 500 mg for three to five days a week. In another particular embodiment, the compounds of the instant invention may be administered three times daily for two consecutive weeks, followed by one week of rest.

The instant compounds also may be useful in combination with known therapeutic agents. For example, instant compounds may be useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents and agents that interfere with cell cycle checkpoints. The instant compounds may be particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds may be useful in combination with known anti-cancer agents including the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-

difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see PCT International patent application published as WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and bortezomib.

Examples of microtubule inhibitors/microtubule-stabilising agents include paclitaxel, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in patent application publications WO 01/30768, WO 01/98278, WO 03/050,064, WO 03/050,122, WO 03/049,527, WO 03/049,679, WO 03/049,678, WO04/039774, WO03/079973, WO03/099211, WO03/105855, WO03/106417, WO04/037171, WO04/058148, WO04/058700, WO04/126699, WO05/018638, WO05/019206, WO05/019205, WO05/018547, WO05/017190, US2005/0176776. In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98, valproic acid and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al., 2003, *J. Med. Chem.* 46(24):5097-5116.

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK) (in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996), and in US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin, Orthop.* Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids,

mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in PCT Publication WO 03/013526.

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs as described by Bume-Jensen and Hunter, *Nature*, 411:355-365, 2001.

"Inhibitors of cell proliferation and survival signaling pathway" refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (e.g., gefitinib and erlotinib), inhibitors of ERB-2 (e.g., trastuzumab), inhibitors of IGFR, inhibitors of cytokine receptors, inhibitors of MET, PI3K kinase family inhibitors (e.g., LY294002) including inhibitos of PI3K-a, PI3K-b, PI3K-g and PI3K-d, serine/threonine kinases (including, but not limited to, inhibitors of Akt such as described in WO 02/083064, WO 02/083139, WO 02/083140, US 2004-0116432, WO 02/083138, US 2004-0102360, WO 03/086404, WO 03/086279, WO 03/086394, WO 03/084473, WO 03/086403, WO 2004/041162, WO 2004/096131, WO 2004/096129, WO 2004/096135, WO 2004/096130, WO 2005/100356, WO 2005/100344),

inhibitors of Raf kinase (e.g., BAY-43-9006), MAP kinase pathway inhibitors, mTOR inhibitors (e.g., ridaforolimus, also known as AP 23573, MK-8669 and deforolimus (described in U.S. Patent No. 7,091,213 to Ariad Gene Therapeutics, Inc,), temsirolimus, everolimus, other rapamycin-analogs), inhibitors of MEK (e.g., CI-1040 and PD-098059), ERK inhibitors and inhibitors of B-Raf. Such agents include small molecule inhibitor compounds and antibody antagonists.

Specific anti-IGF-1R antibodies include, but are not limited to, dalotuzumab, figitumumab, cixutumumab, SHC 717454, Roche R1507, EM164 or Amgen AMG479.

Temsirolimus, also known as Torisel®, is currently marketed for the treatment of renal cell carcinoma. A description and preparation of temsirolimus is described in U.S. Patent No. 5,362,718 to American Home Products Corporation, which is hereby incorporated by reference in its entirety.

Everolimus, also known as Certican® or RAD001, marketed by Novartis, has greater stability and enhanced solubility in organic solvents, as well as more favorable pharmokinetics with fewer side effects than rapamycin (sirolimus). Everolimus has been used in conjunction with microemulsion cyclosporin (Neoral®, Novartis) to increase the efficacy of the immunosuppressive regime.

"Apoptosis inducing agents" include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAIDs which are selective COX-2 inhibitors. For purposes of this specification NSAIDs which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat. 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265, U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that may be particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)-phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)-phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, imatinib (STI571), CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the

treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am J Hum Genet* 61:785-789, 1997) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998;5(8):1105-13), and interferon gamma (*J Immunol* 2000;164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be

used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such

compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

A compound of the instant invention may also be useful for treating cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

A compound of the instant invention may also be useful for treating breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating cancer in combination with siRNA therapeutics.

The compounds of the instant invention may also be administered in combination with γ-secretase inhibitors and/or inhibitors of NOTCH signaling. Such inhibitors include compounds described in WO 01/90084, WO 02/30912, WO 01/70677, WO 03/013506, WO 02/36555, WO 03/093252, WO 03/093264, WO 03/093251, WO 03/093253, WO 2004/039800, WO 2004/039370, WO 2005/030731, WO 2005/014553, USSN 10/957,251, WO 2004/089911, WO 02/081435, WO 02/081433, WO 03/018543, WO 2004/031137, WO 2004/031139, WO 2004/031138, WO 2004/101538, WO 2004/101539 and WO 02/47671 (including LY-450139).

A compound of the instant invention may also be useful for treating cancer in combination with PARP inhibitors.

A compound of the instant invention may also be useful for treating cancer in combination with the following therapeutic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin (Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bendamustine hydrochloride (Treanda®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); brefeldin A; busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); dalteparin sodium injection (Fragmin®); Darbepoetin alfa (Aranesp®); dasatinib (Sprycel®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®);

degarelix (Firmagon®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); dexrazoxane hydrochloride (Totect®); didemnin B; 17-DMAG; docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (Dromostanolone ®); dromostanolone propionate (Masterone Injection®); eculizumab injection (Soliris®); Elliott's B Solution (Elliott's B Solution®); eltrombopag (Promacta®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); ethinyl estradiol; etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); everolimus tablets (Afinitor®); exemestane (Aromasin®); ferumoxytol (Feraheme Injection®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); geldanamycin; gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); iobenguane I 123 injection (AdreView®); irinotecan (Camptosar®); ixabepilone (Ixempra®); lapatinib tablets (Tykerb®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen (Uvadex®); 8-methoxypsoralen; mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); mitramycin; nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); nilotinib (Tasigna®); Nofetumomab (Verluma®); ofatumumab (Arzerra®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); panitumumab (Vectibix®); pazopanib tablets (Votrienttm®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plerixafor (Mozobil®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); pralatrexate injection (Folotyn®); procarbazine (Matulane®); quinacrine

(Atabrine®); rapamycin; Rasburicase (Elitek®); raloxifene hydrochloride (Evista®); Rituximab (Rituxan®); romidepsin (Istodax®); romiplostim (Nplate®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); temsirolimus (Torisel®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiopurine; thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); trans-retinoic acid; Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); triethylenemelamine; Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); vorinostat (Zolinza®); wortmannin; and zoledronate (Zometa®).

Thus, the scope of the instant invention encompasses the use of the instantly claimed compounds in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an apoptosis inducing agent, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs), an agent that interferes with a cell cycle checkpoint and any of the therapeutic agents listed above.

Any one or more of the specific dosages and dosage schedules of the compounds of the instant invention, may also be applicable to any one or more of the therapeutic agents to be used in the combination treatment (hereinafter refered to as the "second therapeutic agent").

Moreover, the specific dosage and dosage schedule of this second therapeutic agent can further vary, and the optimal dose, dosing schedule and route of administration will be determined based upon the specific second therapeutic agent that is being used.

Of course, the route of administration of the compounds of the instant invention is independent of the route of administration of the second therapeutic agent. In an embodiment, the administration for a compound of the instant invention is oral administration. In another

embodiment, the administration for a compound of the instant invention is intravenous administration. Thus, in accordance with these embodiments, a compound of the instant invention is administered orally or intravenously, and the second therapeutic agent can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form.

In addition, a compound of the instant invention and second therapeutic agent may be administered by the same mode of administration, i.e. both agents administered e.g. orally, by IV. However, it is also within the scope of the present invention to administer a compound of the instant invention by one mode of administration, e.g. oral, and to administer the second therapeutic agent by another mode of administration, e.g. IV or any other ones of the administration modes described hereinabove.

The first treatment procedure, administration of a compound of the instant invention, can take place prior to the second treatment procedure, i.e., the second therapeutic agent, after the treatment with the second therapeutic agent, at the same time as the treatment with the second therapeutic agent, or a combination thereof. For example, a total treatment period can be decided for a compound of the instant invention. The second therapeutic agent can be administered prior to onset of treatment with a compound of the instant invention or following treatment with a compound of the instant invention. In addition, anti-cancer treatment can be administered during the period of administration of a compound of the instant invention but does not need to occur over the entire treatment period of a compound of the instant invention.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue,

system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to an effect that results in the inhibition of growth and/or metastasis of the cancer.

In an embodiment, the angiogenesis inhibitor to be used as the second compound is selected from a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived growth factor, an MMP (matrix metalloprotease) inhibitor, an integrin blocker, interferon-α, interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, or an antibody to VEGF. In an embodiment, the estrogen receptor modulator is tamoxifen or raloxifene.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a compound selected from: an estrogen receptor modulator, an androgen receptor modulator, retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, an apoptosis inducing agent, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic and an agent that interferes with a cell cycle checkpoint.

And yet another embodiment of the invention is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab.

The invention further encompasses a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with a COX-2 inhibitor.

The instant invention also includes a pharmaceutical composition useful for treating cancer that comprises a therapeutically effective amount of a compound of Formula I and a compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist; an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic and an agent that interferes with a cell cycle checkpoint.

Further included within the scope of the invention is a method of treating or preventing a disease in which angiogenesis is implicated, which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the present invention. Other inhibitors of MET may also be administered for this method of treatment. Ocular neovascular diseases, which may result in certain forms of blindness, are examples of conditions where much of the resulting tissue damage can be attributed to aberrant infiltration of blood vessels in the eye. The undesirable infiltration can be triggered by ischemic retinopathy, such as that resulting from diabetic retinopathy, retinopathy of prematurity, retinal vein occlusions, etc., or by degenerative diseases, such as the choroidal neovascularization observed in age-related macular degeneration. Inhibiting the growth of blood vessels by administration of the present compounds may therefore reduce the infiltration of blood vessels and treat diseases where angiogenesis is implicated, such as ocular diseases like retinal vascularization, diabetic retinopathy, age-related macular degeneration, and the like.

Routes of systemic administration of the compounds of the present invention described above may be utilized in the treatment of such ocular neovascular diseases. Other routes of ocular administration may also be employed, such as topical, periocular, intravitreal and the like. Intravitreal implants coated with a drug:polymer matrix may also be employed.

Ophthalmic pharmaceutical compositions that are adapted for topical administration to the eye may be in the form of solutions, suspensions, ointments, creams or as a solid insert. Ophthalmic formulations of this compound may contain from 0.01 ppm to 1% and especially 0.1 ppm to 1% of medicament. For a single dose, from between 0.01 to 5000 ng, preferably 0.1 to 500 ng, and especially 1 to 100 ng of the compound can be applied to the human eye. Formulations useful for intravitreal administration are similar to saline solutions described previously for intravenous administration.

These and other aspects of the invention will be apparent from the teachings contained herein.

Schemes and Examples

The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard manipulations that are known in the literature or exemplified in the experimental procedures. The illustrative schemes below, therefore, are not limited by the compounds listed or by any particular substituents employed for illustrative purposes. Substituent numbering as shown in the schemes does not necessarily correlate to that used in the claims and often, for clarity, a single substituent is shown attached to the compound where multiple substituents are allowed under the definitions of the instant invention hereinabove.

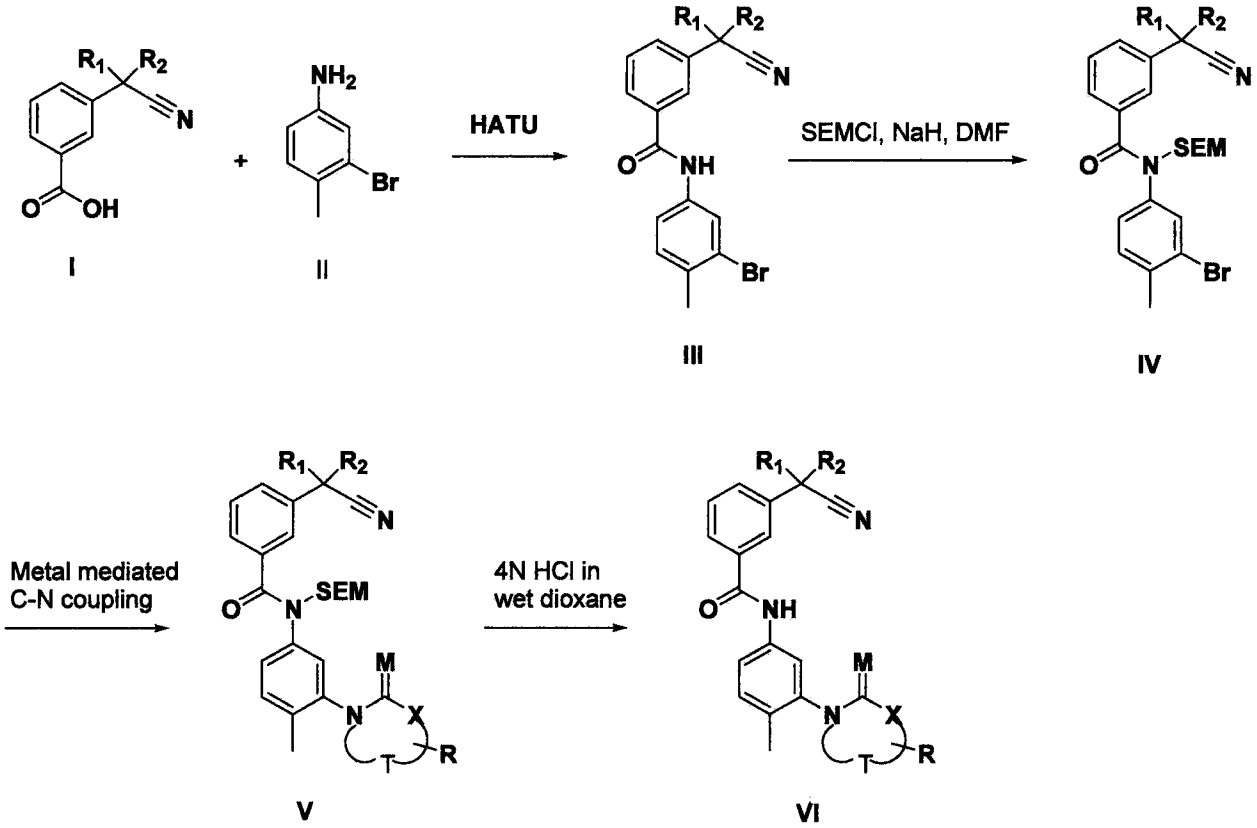
Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be illustrative of the invention and not limiting of the reasonable scope thereof.

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

CuI =	Copper(I) iodide
Da =	Dalton
DCM or CH_2Cl_2 =	dichloromethane
DMF =	N,N-dimethylformamide
HATU =	2-(1H-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium
HCl =	hydrochloric acid
K_3PO_4 =	potassium phosphate
K_2CO_3 =	potassium cabonate
NaH =	sodium hydride
$NaHCO_3$ =	sodium bicarbonate
Na_2SO_4 =	sodium sulfate
NH_4Cl =	ammonium chloride
$Pd_2(aba)_3$ =	Tris(dibenzylideneacetone)dipalladium

$^{i}Pr_2NEt$ =	*N,N*-diisopropylethylamine
SEM =	2-(trimethylsilyl)ethoxymethoxy
SiO_2 =	silicon dioxide
XantPhos =	4,5-Bis(diphenylphosphino)-9,0-dimethylxanthene

General Scheme



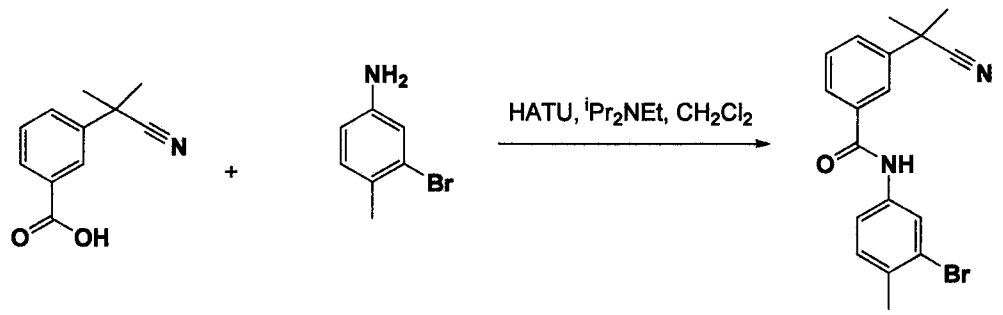
Substituted benzonic acid **I** is coupled with 3-bromo-4-methylaniline II in the presence of HATU at room temperature in an appropriate solvent or solvent mixture such as DCM, DCM-CH_3CN and DMF to provide the corresponding amide intermediate **III** (General Scheme 1). Amide intermediate **III** is treated with NaH followed by SEMCl in an appropriate solvent or solvent mixture such as DMF at room temperature to afford the corresponding SEM protected amide interemediate **IV**. SEM protected amide intermediate **IV** is treated with an appropriate heterocycle, such as lactam or cyclic urea, in the presence of metal catalyst in an appropriate

solvent or solvent mixture such as dixane at 100 °C to afford the corresponding heterocycle **V**. Heterocycle **V** is treated with an appropriate acid such as HCl in dioxane to afford the corresponding heterocycle **VI**.

EXAMPLES

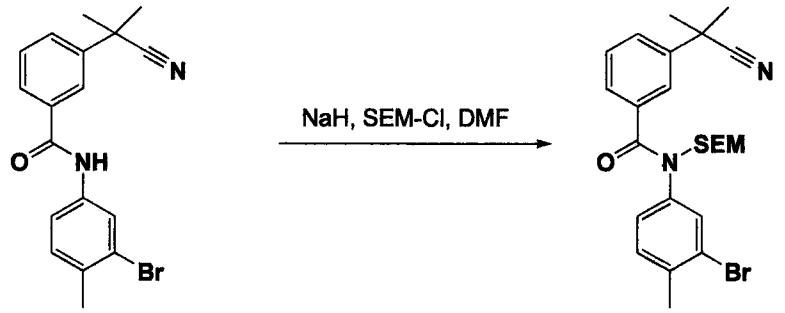
Example 1 - Preparation of 3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)benzamide

Step 1: Preparation of *N*-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)benzamide.



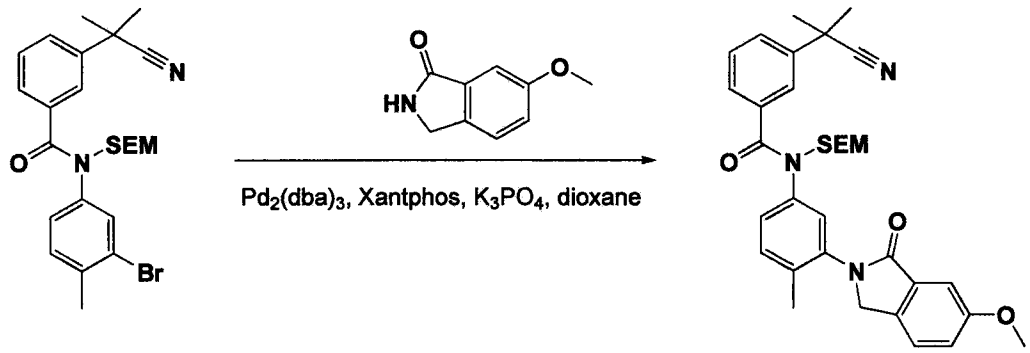
3-(2-cyanopropan-2-yl)benzoic acid (2.12 g, 11.22 mmol) was dissolved in CH_2Cl_2 (100 mL) at room temperature and treated with 3-bromo-4-methylaniline (2.5 g, 13.46 mmol), HATU (5.11 g, 13.46 mmol) followed by *N,N*-diisopropylethylamine (7.11 ml, 40.38 mmol). The reaction mixture was stirred at room temperature overnight, and quenched by addition of saturated aqueous NH_4Cl (100 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (1 × 250 mL), brine (1 × 250 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to provide crude material which was purified by column chromatography (SiO_2, 0-50% ethyl acetate-hexane) to afford pure *N*-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)benzamide.

Step 2: Preparation of *N*-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)benzamide.



Compound *N*-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)benzamide (500 mg, 1.44 mmol) was dissolved in DMF (14 mL) under argon and cooled to 0°C. It was then treated with NaH (86.4 mg, 60% dispersion in oil, 2.16 mmol). After 2 mins, SEM-Cl (0.31 mL, 1.75 mmol) was added dropwise and the mixture was stirred at 0°C for 15 min followed by 45 min at room temperature. The reaction mixture was quenched by addition of ice-water. Ethyl acetate was added and two layers were separated. The organic layer was collected and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layer was washed with brine (1 × 200 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to provide crude *N*-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)benzamide which was purified by column chromatography (SiO_2, 0-10% Ethyl acetate-Hexane).

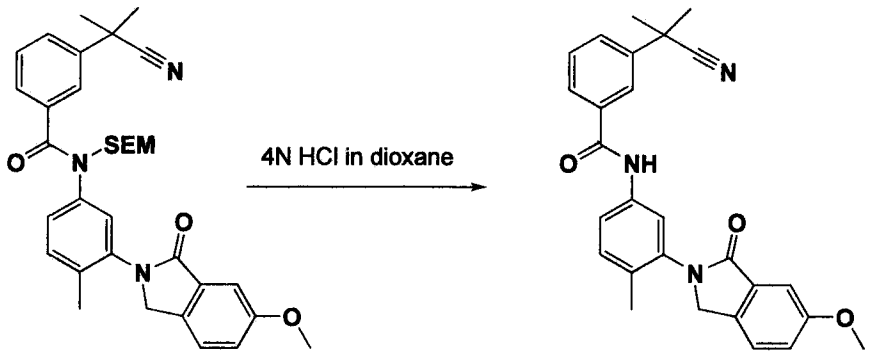
Step 3: Preparation of 3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)benzamide.



N-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy) methyl)benzamide (52 mg, 0.104 mmol) was mixed with 6-methoxyisoindolin-1-one (25.12 mg, 0.154 mmol), $pd_2(dba)_3$ (9.52 mg, 0.01 mmol), Xantphos (12.03 mg, 0.021 mmol) and K_3PO_4 (66.14 mg, 0.312 mmol) under argon and then dioxane (2 mL) was introduced. The mixture was heated at 100°C for 12 h. It was cooled to room temperature and the ethyl acetate (5 mL),

followed by water (5 mL), was added. Two layers were separated and the organic layer was collected. The aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was washed with brine (15 ml), dried (Na_2SO_4), filtered and evaporated under reduced pressure to provide crude 3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)benzamide which was purified by column chromatography (SiO_2, 0-20% ethyl acetate-hexane).

Step 4: Preparation of 3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)benzamide



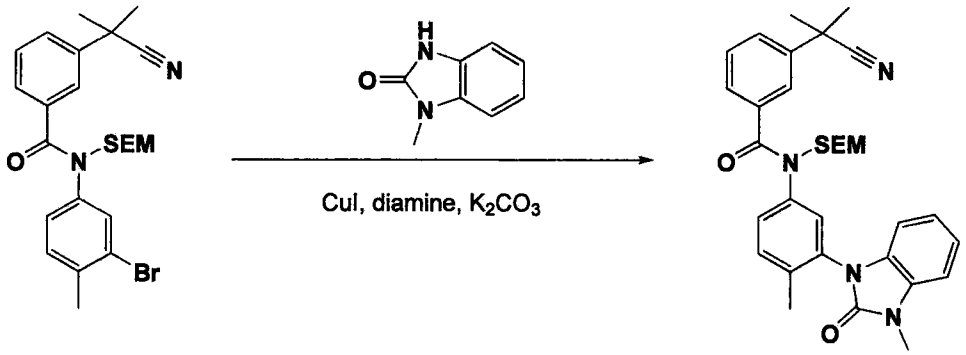
3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)benzamide (32 mg) was dissolved in CH_2Cl_2 (6 mL) and treated with trifluoroacetic acid (1 mL) at room temperature. It was then treated with HCl (2 ml, 4N in dioxane) and heated to 65°C for 30 min. It was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to provide crude 3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)benzamide which was purified by preparative HPLC.

Compounds 1-1 to 1-5 were synthesized according to the process described in this Example 1, shown in Table 1 below.

Example 2 - Preparation of 3-(2-cyanopropan-2-yl)-*N*-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)benzamide

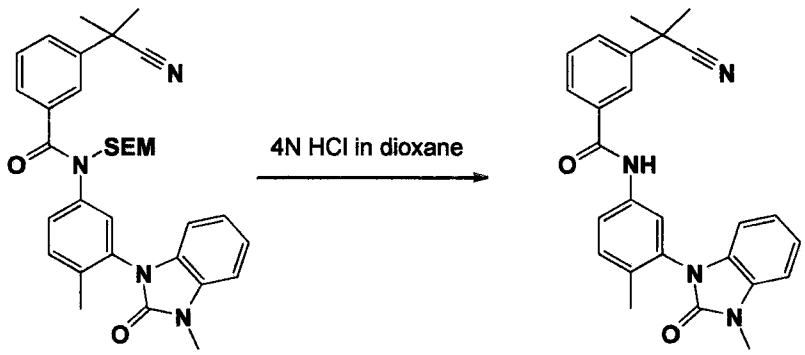
Step 1: Preparation of 3-(2-cyanopropan-2-yl)-N-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)-N-((2-(trimethylsilyl)ethoxy)methyl)benzamide.

N-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)benzamide was first prepared using the reactions outlined in Steps 1 and 2 of Example 1.



N-(3-bromo-4-methylphenyl)-3-(2-cyanopropan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy) methyl)benzamide (29.8 mg, 0.06 mmol) was mixed with 1-methyl-1H-benzo[d] imidazol-2(3H)-one (13.52 mg, 0.09 mmol), CuI (11.61 mg, 0.06 mmol) and trans-*N*,*N*-dimethyl-1,2-cyclohexanediamine (14.5 mg, 0.102 mmol) and K_2CO_3 (25.24 mg, 0.18 mmol) under argon. The mixture was heated neat at 150°C for 12 h. The reaction mixture was cooled to room temperature and ethyl acetate, followed by water, was added. Two layers were separated and the organic layer was collected. The organic layer was washed with brine (1 × 10 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to provide crude 3-(2-cyanopropan-2-yl)-N-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)-N-((2-(trimethylsilyl)ethoxy)methyl)benzamide which was purified by preparative HPLC.

Step 2: Preparation of 3-(2-cyanopropan-2-yl)-*N*-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)benzamide.



3-(2-cyanopropan-2-yl)-N-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d] imidazol-1-yl)phenyl)-N-((2-(trimethylsilyl)ethoxy)methyl)benzamide (10 mg) was treated with HCl (4 ml, 4N in dioxane) and heated to 80°C for 10 min. It was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by preparative HPLC to provide pure 3-(2-cyanopropan-2-yl)-*N*-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)benzamide.

Compounds 1-6 to 1-9 were synthesized according to the process described in this Example 2, shown in Table 1 below.

Example 3 - B-Raf Kinase Activity

The compounds of the instant invention described in the Examples were tested by the B-Raf kinase assay described below and were found to have B-Raf inhibitory activity. Other assays are known in the literature and could be readily performed by those of skill in the art.

Abbreviations: "ATP" = Adenosine 5'-triphosphate; "DMSO" = Dimethyl Sulfoxide; "DTT" = DL-Dithiothreitol; "FP" = Fluorescence polarisation; "mP" = milli P; and, "cwl" = central wave length.

Materials and Reagents:

1) Black 384-F Optiplates (#6007279, Packard),
2) Dimethyl Sulfoxide (DMSO), >99.0% (for example #41650, Fluka)
3) Adenosine 5'-triphosphate (ATP), 100% (absorbance), (for example #10 519987 001, Roche)
4) DL-Dithiothreitol (DTT), >99% (for example #D9163, Sigma)
5) Tris(hydroxymethyl)-aminomethane, >99.8% (for example #1.08382, Merck)
6) Magnesium chloride ($MgCl_2$), >99% (for example #1.05833, Merck)
7) Polyoxyethylenesorbitan monolaurate (Tween-20), (for example #1379, Sigma)
8) Sodium azide (NaN_3), >99.5%, (for example #S2002, Sigma)
9) B-raf, active enzyme (for example #14-530, Upstate)
10) MEK1, inactive enzyme (for example #14-420, Upstate)
11) MAP Kinase 2/ERK2, inactive enzyme (for example #14-536, Upstate)
12) IMAP™ Buffer Kit with Progressive Binding System (for example #R8127, Molecular Devices)

13) Fluorescein labeled substrate peptide ("ERK-tide"; IPTTPITTTYFFFK-5FAM-COOH), (for example #R7292/#R7293, Molecular Devices)

Thaw enzymes on ice and keep the enzyme stocks on ice during the assay. Quickly freeze the enzymes in dry ice/ethanol and store at -80°C after use.

Reaction Mixtures: Stock solutions which can be used are:

1) 20 mM ATP in water

2) 1 M DTT in water

3) Reaction buffer: 10 mM Tris-HCl, 10 mM $MgCl_2$, 0.01% Tween-20, 0.05% NaN_3 pH 7.2

4) 20 μM Fl-ERK-tide substrate in Kinase Reaction buffer (KR-buffer)

Prepare fresh Kinase Reaction buffer (KR-buffer) just before use: 50 mL Reaction buffer + 50 μl 1 M DTT (1 mM final concentration). Serial dilutions of test compounds are made in 100% DMSO. For example a 10 points half log serial dilution from 1 mM to 31.6 nM leading to a final compound concentration range in the assay from 10 μM to 0.316 nM can be used.

Equipment:

1) Automated liquid handling system (Biomek FX, Beckman Coulter or comparable equipment)

2) Reader suitable for reading FP signal (suggested settings include: Dichroic mirror D505FP/D535, excitation filter: 480 nm cwl. Parallel and perpendicular filters 535 nm cwl). Envision 2102 Multi-label Plate Reader or comparable equipment.

Assay Procedure:

1) Add 2.5 μL/well test compound in KR-buffer (this solution contains 8% DMSO) or (in minimum, maximum and background wells) 2.5 μL/well KR-buffer containing 8% DMSO. (Final DMSO concentration in the assay is 1%).

2) Add 5 μL/well 0.8 U/mL B-raf enzyme diluted in KR-buffer (final B-raf enzyme concentration in the assay is 0.2 U/mL) to all wells.

3) Pre-incubate 60 minutes at room temperature in the dark.

4) Add 5 μL/well 256 ng/mL MEK1 enzyme diluted in KR-buffer (final MEK1 enzyme concentration in the assay is 64 ng/mL) to all wells.

5) Add 5 μL/well 2.4 μg/mL Erk2 enzyme with 200 nM Fl-peptide substrate diluted in KR-buffer (final concentration in the assay of Erk2 enzyme is 600 ng/mL and of Fl-peptide substrate is 50 nM) to all wells except the background wells. Add here 5 μL/well 2.4 μg/mL Erk2 enzyme without 200 nM Fl-peptide substrate.

6) Add 2.5 μL/well 400 μM ATP to minimum and compound wells (50x dilution of the 20 mM stock in KR-buffer, final ATP concentration in the assay is 50 μM) or (in maximum wells) 2.5 μl/well KR-buffer.

7) Incubate 60 minutes at 30°C in the dark.

8) Add 20 μL/well IMAP Progressive Binding Solution (IMAP Progressive Binding Solution: 75% 1x buffer A and 25% 1x buffer B with 1:900 dilution of Progressive Binding Reagent, all kit contents) to all wells.

9) Incubate 60 minutes at room temperature in the dark.

10) Read the FP signal on Envision multi-label reader.

On every 384-well assay plate, 16-18 wells are used as minimum wells (wells without inhibitor, 0% effect), 16-18 wells are used as maximum wells (wells without ATP, 100% effect). 16 wells are used for measuring the background signal (everything but not substrate). For all assay plates duplicates are prepared.

The difference between the maximum and minimum wells should be more than 50 mP at least (=window).

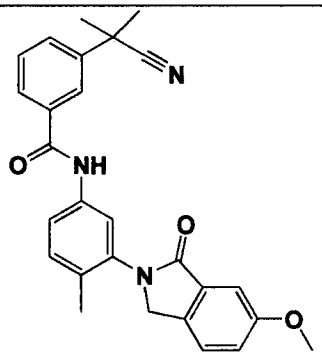
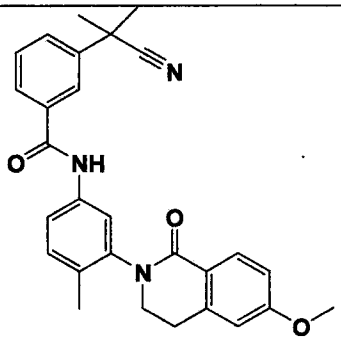
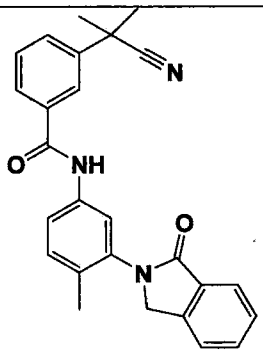
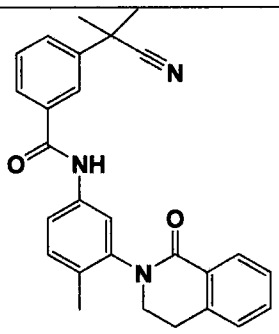
Specific activity (U/mg) can vary from enzyme batch to enzyme batch. An enzyme titration curve has to be made to determine the optimal enzyme concentration for each batch.

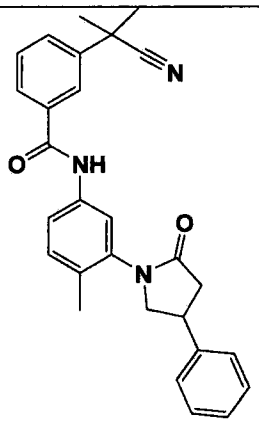
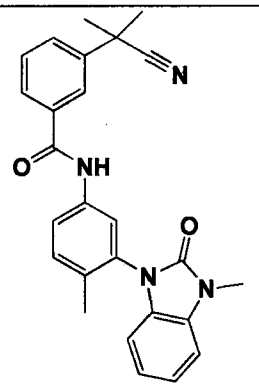
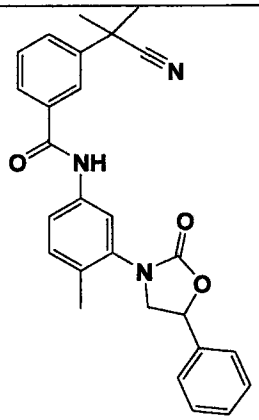
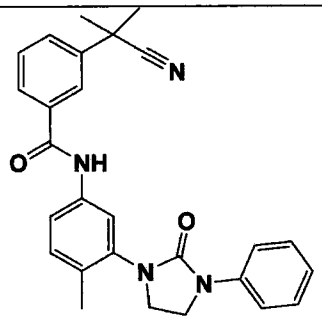
Run as two independent experiments (N=2) on duplicate plates (n=2).

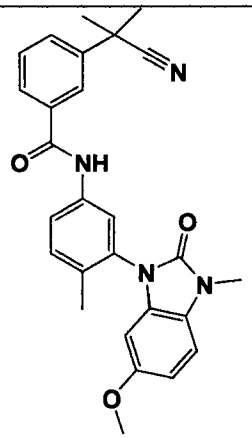
IC50 Determinations: mP values of compound test wells are converted to percent effect based on 0% effect and 100% effect controls. Dose-response curves were generated from percent effect data plotted against test compound concentration, each in duplicate, from 10 point serial dilutions of inhibitory compounds. To generate IC50 values, the dose-response curves were fitted to a standard sigmoidal curve and IC50 values were derived by nonlinear regression analysis.

Results:

Table 1:

Cmp	Structure	Name	Method	MW (Da)	LCMS MH^+ m/z	HPLC MS t_R	IC50 (nM)
1-1		3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)benzamide	Example 1	439.5	440.6	4.37	++
1-2		3-(Cyano-dimethyl-methyl)-N-[3-(6-methoxy-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-phenyl]-benzamide	Example 1	453.5	454.1	4.80	+
1-3		3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-phenyl]-benzamide	Example 1	409.1	409.9	5.11	+
1-4		3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-benzamide	Example 1	423.2	424.1	5.21	+

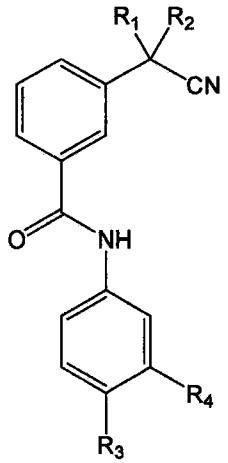
1-5		3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-4-phenyl-pyrrolidin-1-yl)-phenyl]-benzamide	Example 1	437.2	438.2	5.33	++
1-6		3-(2-cyanopropan-2-yl)-*N*-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)benzamide	Example 2	424.1	425.6	4.56	++
1-7		3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-5-phenyl-oxazolidin-3-yl)-phenyl]-benzamide	Example 2	439.2	440.3	4.85	++
1-8		3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-3-phenyl-imidazolidin-1-yl)-phenyl]-benzamide	Example 2	438.2	439.2	4.93	+++

1-9		3-(Cyano-dimethyl-methyl)-N-[3-(6-methoxy-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-4-methyl-phenyl]-benzamide	Example 2	454.2	455.4	4.31	+++

+++ IC50 > 100 nM
++ IC50 > 50 - 100 nM
+ IC50 = 10 – 50 nM

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof,

wherein:

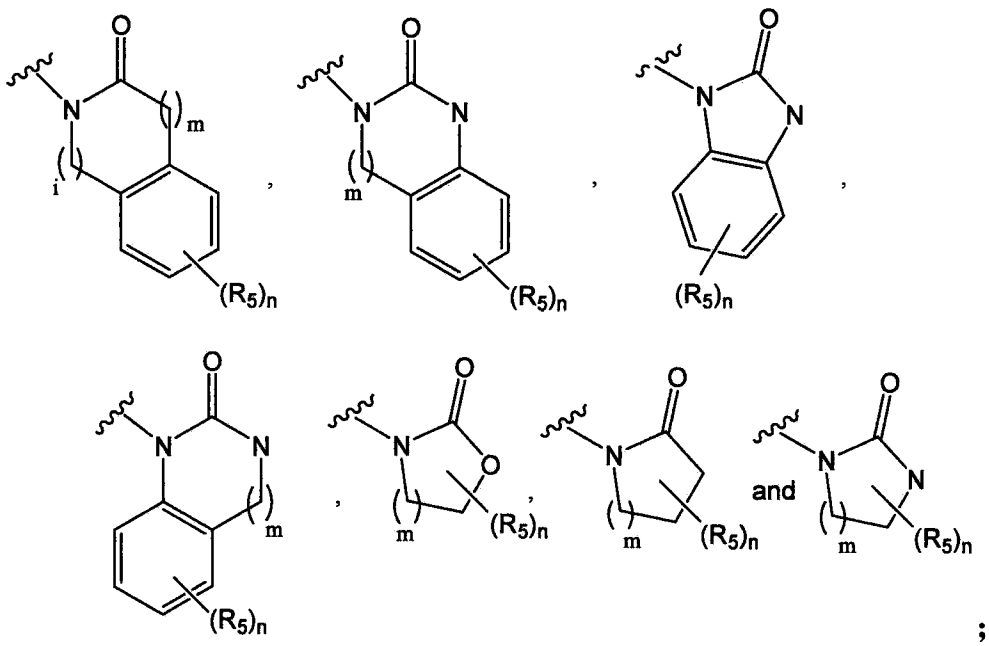
R_1 and R_2 are independently H, OH, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein R_1 and R_2 can be combined to form a C_3-C_6 cycloalkyl;

R_3 is H, OH, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

R_4 is a heteroaryl or heterocyclyl optionally substituted with one or more substituents selected from R_5; and,

R_5 is independently selected from OH, oxo, C_1-C_6 alkyl, OC_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or phenyl.

2. The compound of claim 1, wherein R_4 is selected from:



;

wherein:

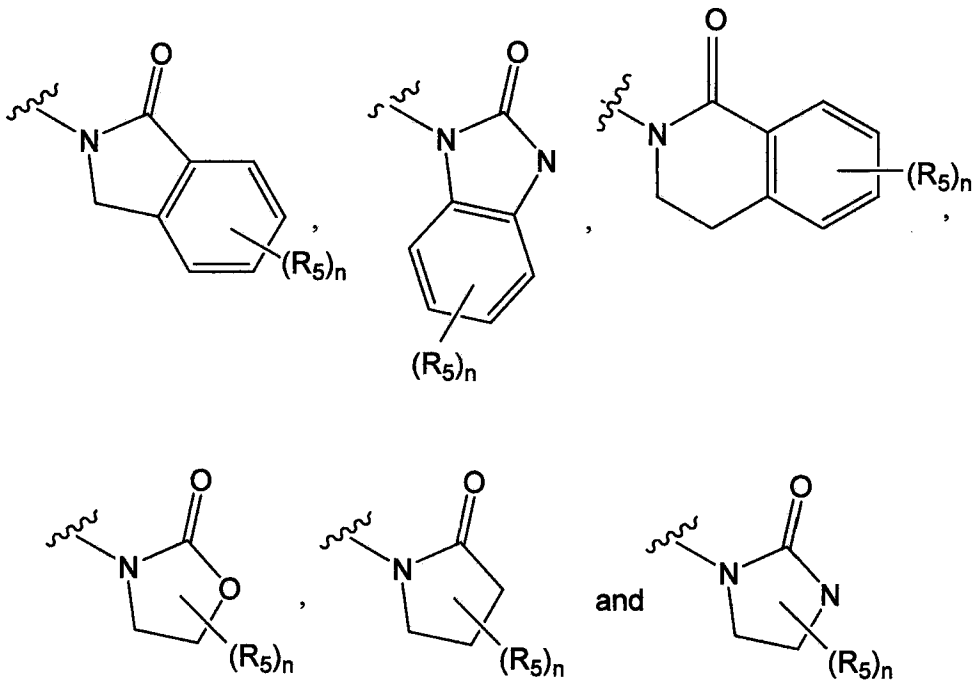
n is 0, 1, 2, or 3;

m is 0, 1, 2, or 3;

i is 0, 1, or 2; and,

R_5 is independently selected from OH, C_1-C_6 alkyl, OC_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, or phenyl.

3. The compound of claim 1 or claim 2, wherein R_1, R_2 and R_3 are methyl, and R_4 is selected from:



wherein n is 0, 1, 2, or 3.

4. A compound selected from:

3-(2-cyanopropan-2-yl)-*N*-(3-(6-methoxy-1-oxoisoindolin-2-yl)-4-methylphenyl)benzamide;

3-(Cyano-dimethyl-methyl)-N-[3-(6-methoxy-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-4-methyl-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(1-oxo-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-4-phenyl-pyrrolidin-1-yl)-phenyl]-benzamide;

3-(2-cyanopropan-2-yl)-*N*-(4-methyl-3-(3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)phenyl)benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-5-phenyl-oxazolidin-3-yl)-phenyl]-benzamide;

3-(Cyano-dimethyl-methyl)-N-[4-methyl-3-(2-oxo-3-phenyl-imidazolidin-1-yl)-phenyl]-benzamide; or,

3-(Cyano-dimethyl-methyl)-N-[3-(6-methoxy-3-methyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-4-methyl-phenyl]-benzamide;

or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof.

5. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any of claims 1 to 4, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, and a pharmaceutically acceptable carrier.

6. The pharmaceutical composition according to claim 5, further comprising a second therapeutic agent useful in treating cancer.

7. A compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt, stereoisomer or tautomer thereof, for use in the treatment of cancer.

8. The use of the compound according to any of claims 1 to 4 in preparation of a medicament for treating cancer.

9. A method of treating cancer, which method comprises administering a therapeutically effective amount of (i) the compound of any of claims 1 to 4, or (ii) the composition of claim 5 or claim 6.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/34341

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/12, 37/44; A61K 31/195 (2012.01)
USPC - 514/563, 613
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/563, 613

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/555 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar, WIPO, SureChem (structure search)
benzamide, benzanilide, 3-(cyano-dimethyl-methyl), 2-oxo-1-pyrrolidin$, 1-pyrrolidon$, kinase, inhibit$, modulat$, raf, B-raf, BRaf

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0249119 A1 (HIROSE et al.) 30 September 2010 (30.09.2010) para [0001], [0035]-[0044], [0055], [0098], [0121]-[0125], [0327], [0392]-[0393], [0397], [1986]	1-4
Y	WO 2006/015859 A1 (CARAVATTI et al.) 16 February 2006 (16.02.2006) pg 1, para 1; pg 2, para 3- pg 3, para 1	1-4
Y	US 2010/0113458 A1 (FINK et al.) 06 May 2010 (06.05.2010) para [0651], Table 9	2-4
Y	WAN et al. Mechanism of Activation of the RAF-ERK Signaling Pathway by Oncogenic Mutations of B-RAF. Cell, 2004, Vol116, pp 855-867; pg 858, col 2, para 2 - pg 861, col 1, para 1; pg 861, Fig 4 Downloaded from: http://www.unc.edu/courses/2005spring/envr/230/001/Cell%202004%20v-Raf%20V599E.pdf	4
A	US 2008/0146570 A1 (AQUILA et al.) 19 June 2008 (19.06.2008) para [0001], [0006]-[0144]	1-4

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 July 2012 (08.07.2012)	03 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/34341

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.