(2010) 115: 1461). Irradiation of glioblastoma tumors in mice was shown to cause a temporary decrease in tumor size only to be followed by a rebound tumor vasculogenesis mediated by the recruitment of bone marrow derived monocytes expressing CD11b and F4/80 surface antigens (M. Kioi et al, Journal of Clinical Investigation (2010) 120: 694). CD11b+ and F4/80+ monocytes are also known to express functional c-FMS receptors. Hence, blockade of tumor infiltrating c-FMS+ bone marrow derived monocytes by the use of c-FMS kinase inhibitors offers the potential to prevent tumor rebound vasculogenesis and glioblastoma tumor progression. CSF-1R blockade has also been shown to reverse immunotolerance mechanisms in an immunocompetent murine breast cancer model and promote the appearance of anti-tumor immune programs by upregulating CD8+ T-cell-mediated tumor suppression. Restoration of an anti-tumor immune program was mechanistically linked to c-FMS inhibitor blockade of TAM-mediated Programmed Death Ligand-1 (PDL-1) immunotolerance (D. G. DeNardo, et al. Cancer Discovery (2011) 1: OF52).

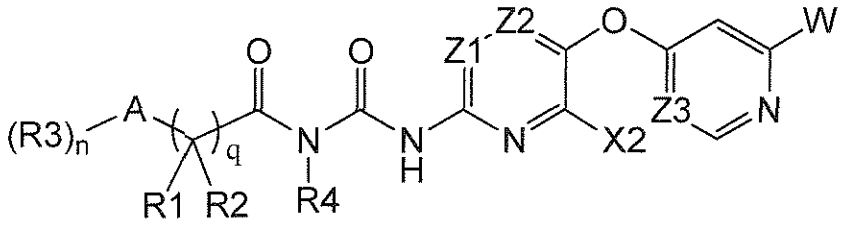
[0009] Hence, small molecule inhibitors of c-FMS kinase, c-KIT kinase, or PDGFR kinases provide a rational approach to new therapies for the treatment of autoimmune diseases, and to particularly block the chronic tissue destruction mediated by the innate immune system. Inhibition of c-FMS kinase also provides a rational approach to new therapies for the treatment of cancers, especially for the treatment of cancer invasiveness, cancer angiogenesis or vasculogenesis, cancer metastasis, cancer immunotolerance, and for the treatment of cancers prone to bone metastases.

[0010] There is a need to provide kinase inhibitors which selectively inhibit kinases causative of the chronic tissue destruction in autoimmune disease (c-FMS, c-KIT, PDGFR), without inhibiting other kinases targeted by marketed cancer therapeutics (ABL, BCR-ABL, KDR, SRC, LCK, LYN, FGFR and other kinases). The present invention discloses novel inhibitors that inhibit c-FMS, c-KIT, and/or PDGFR kinases for the treatment of autoimmune diseases which also exhibit selectivity by not potently inhibiting other kinases including ABL, BCR-ABL, KDR, SRC, LCK, LYN, FGFR, MET and other kinases. The inhibitors of the present invention also find utility in the treatment of other mammalian diseases, including human diseases, mediated by c-FMS, c-KIT, or PDGFR kinases.

[0011] Such diseases include, without limitation, cancers, autoimmune diseases, and bone resorptive diseases.

Summary ~~of the Invention~~

[0012] In one aspect, the present disclosure provides compounds of ~~the~~ Formula I: ~~are described:~~



Formula I

or pharmaceutically acceptable salts, enantiomers, stereoisomers, or tautomers thereof,

wherein

A is taken from the group consisting of C1-C6 alkyl, deutero-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8alkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated, C3-C8carbocyclyl, C6-C12 spirobicycloalkyl, adamantyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octyl, or a 4-8 membered heterocyclic ring, and wherein each A moiety may be further substituted with one, two, or three R3 moieties;

W is a C5-C6heteroaryl or phenyl, and wherein each W is optionally substituted by one, two, or three R5;

each X1 and X2 and X3 are individually and independently hydrogen, C1-C6 alkyl, or fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated;

Z1 is CX3 or N;

Z2 is CX1 or N;

Z3 is CH or N;

each R1 and R2 is individually and independently H, C1-C6 alkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated, hydroxyl, C1-C6 alkoxy, fluoroC1-C6alkoxy wherein the alkyl group is fully or partially fluorinated, or cyano;

each R3 is individually and independently H, halogen, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, branched C3-C8 alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, fluoro-C1-C6 alkoxy wherein the alkyl chain is partially or completely fluorinated, branched C3-C6 alkoxy, hydroxyl, or cyano;

each R4 is individually and independently hydrogen, C1-C6 alkyl, or branched C3-C8 alkyl;

[0182] In one embodiment of Formula Id, W pyrazolyl.

[0183] In one embodiment of Formula Id, W is imidazolyl.

[0184] In one embodiment of Formula Id, W is isoxazolyl.

[0185] In one embodiment of Formula Id, W is oxazolyl.

[0186] In one embodiment of Formula Id, W is thiazolyl.

[0187] In one embodiment of Formula Id, W is triazolyl.

[0188] In one embodiment of Formula Id, W is pyridinyl.

[0189] In one embodiment of Formula Id, W is phenyl.

[0190] In one embodiment of Formula Id, X1 and X2 are individually and independently hydrogen, C1-C6 alkyl, or fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated.

[0191] In one embodiment of Formula Id, X1 and X2 are individually and independently hydrogen or C1-C6 alkyl.

[0192] In one embodiment of Formula Id, X1 and X2 are hydrogen.

[0193] In one embodiment of Formula Id, one of X1 and X2 is hydrogen and the other is C1-C6alkyl.

[0194] In one embodiment of Formula Id, X1 is hydrogen and X2 is C1-C6alkyl.

[0195] In one embodiment of Formula Id, X1 is hydrogen and X2 is methyl.

[0196] In one embodiment of Formula Id, X1 is C1-C6alkyl and X2 is hydrogen.

[0197] In one embodiment of Formula Id, X1 is methyl and X2 is hydrogen.

[0198] In some embodiments, the ~~invention~~ present disclosure comprises a compound selected from the group consisting of trans-3-fluoro-3-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)cyclobutanecarboxamide, 3,3-dimethyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)cyclobutanecarboxamide, N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-3-(1-(trifluoromethyl)cyclopropyl)propanamide, N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide, 3,3-dimethyl-N-((5-((6-(1-methyl-1H-pyrazol-4-yl)pyrimidin-4-yl)oxy)pyridin-2-yl)carbamoyl)cyclobutanecarboxamide, N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide, N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propionamide, N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-2-(tetrahydro-2H-pyran-4-yl)acetamide, trans-4-methyl-N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-

yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 1-methoxy-N-((4-methyl-5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)cyclopentanecarboxamide, 4-methyl-N-((5-((2-(2-methyloxazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)tetrahydro-2H-pyran-4-carboxamide, 2-methoxy-2-methyl-N-((4-methyl-5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, N-((4,6-dimethyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-4-methyltetrahydro-2H-pyran-4-carboxamide, 1-methoxy-N-((6-methyl-5-((2-(3-methylisoxazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)cyclopentanecarboxamide, N-((6-ethyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-4-methyltetrahydro-2H-pyran-4-carboxamide, 1-methoxy-N-((5-((2'-methyl-[2,4'-bipyridin]-4-yl)oxy)pyridin-2-yl)carbamoyl)cyclopentanecarboxamide, N-((5-((2-(2-isopropyl-1H-imidazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide, N-((5-((2-(1-ethyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-2-methoxy-2-methylpropanamide, N-((5-((2-(1H-1,2,3-triazol-4-yl)pyridin-4-yl)oxy)-6-methylpyridin-2-yl)carbamoyl)pivalamide, N-((5-((2-(1-allyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-2-methoxy-2-methylpropanamide, N-((5-((2-(2-isopropyl-1H-imidazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)-2-methoxy-2-methylpropanamide, N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyrimidin-2-yl)carbamoyl)pivalamide, 4-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)tetrahydro-2H-pyran-4-carboxamide, N-((5-((2-(1-ethyl-2-isopropyl-1H-imidazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide, and N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyrazin-2-yl)carbamoyl)pivalamide, or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof.

[0198a] In another aspect of the present disclosure, there is provided a compound selected from N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide, N-((5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide, N-((5-((2-(1-methyl-1H-imidazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide, and N-((5-((2-(2-methyloxazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide.

[0198b] In a further aspect of the present disclosure, there is provided a compound selected from 2-methoxy-2-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 2-ethoxy-2-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 2-methoxy-2-methyl-N-

((5-((2-(1-methyl-1H-imidazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 2-methoxy-2-methyl-N-((5-((2-(2-methyloxazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 2-methoxy-2-methyl-N-((5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 2-methoxy-2-methyl-N-((6-methyl-5-((2'-methyl-[2,4'-bipyridin]-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide, 2-methoxy-2-methyl-N-((5-((2'-methyl-[2,4'-bipyridin]-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide or 2-methoxy-2-methyl-N-((4-methyl-5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198c] In another aspect of the present disclosure, there is provided a compound selected from N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)tetrahydro-2H-pyran-4-carboxamide, 4-methyl-N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)tetrahydro-2H-pyran-4-carboxamide, N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)tetrahydrofuran-3-carboxamide, or 3-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)oxetane-3-carboxamide.

[0198d] In yet another aspect of the present disclosure, there is provided a compound N-((5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide.

[0198e] In a further aspect of the present disclosure, there is provided a compound 2-methoxy-2-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198f] In another aspect of the present disclosure, there is provided a compound 2-ethoxy-2-methyl-N-((5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198g] In yet another aspect of the present disclosure, there is provided a compound 2-methoxy-2-methyl-N-((5-((2-(1-methyl-1H-imidazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198h] In a further aspect of the present disclosure, there is provided a compound 2-methoxy-2-methyl-N-((5-((2-(4-methyl-1H-imidazol-1-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198i] In another aspect of the present disclosure, there is provided a compound N-((5-((2-(2-methyloxazol-5-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)pivalamide.

[0198j] In yet another aspect of the present disclosure, there is provided a compound 2-methoxy-2-methyl-N-((6-methyl-5-((2'-methyl-[2,4'-bipyridin]-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198k] In a further aspect of the present disclosure, there is provided a compound 2-methoxy-2-methyl-N-((5-((2'-methyl-[2,4'-bipyridin]-4-yl)oxy)pyridin-2-yl)carbamoyl)propanamide.

[0198l] In another aspect of the present disclosure, there is provided a compound 4-methyl-N-((6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)carbamoyl)tetrahydro-2H-pyran-4-carboxamide.

[0199] In certain embodiments, the ~~invention~~ present disclosure comprises a method of treating mammalian disease wherein the disease etiology or progression is at least partially mediated by the kinase activity of c-FMS, PDGFR-β, or c-KIT kinases, wherein the kinase is a wildtype form, a mutant oncogenic form, an aberrant fusion protein form or a polymorph therof, the method comprising administering to a mammal in need thereof an effective amount of a compound of formula I.

[0199a] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising the compound as disclosed herein and a pharmaceutically acceptable carrier.

[0200] In other embodiments, the present ~~invention~~ present disclosure comprises a pharmaceutical composition, comprising a compound of formula I and a pharmaceutically acceptable carrier.

[0201] In certain embodiments, the composition comprises an additive selected from adjuvants, excipients, diluents, or stabilizers.

[0202] In some embodiments, the ~~invention~~ present disclosure includes a method of treating cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

[0203] In some embodiments, the ~~invention~~ present disclosure includes a method of treating glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

[0204] In certain embodiments of the present methods, the compound is administered orally, parenterally, by inhalation, or subcutaneously.

[0204a] In yet another aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in treating cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia.

[0204b] In a further aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in treating glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone.

[0205] In some embodiments, the ~~invention~~ present disclosure provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the treatment of cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer,

pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

[0206] In some embodiments, the ~~invention~~ present disclosure provides the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, in the treatment of glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

[0206a] In a further aspect of the present disclosure, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia.

[0206b] In another aspect of the present disclosure, there is provided a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone.

[0207] In some embodiments, the ~~invention~~ present disclosure provides for the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia.

[0208] In certain embodiments, the ~~invention~~ present disclosure provides for the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone.

[0209] The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0210] Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications and this disclosure.

[0211] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. The initial definition provided for a group or term

46. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

47. The composition of claim 46, further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.

48. ~~A method of treating~~Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia~~, the method comprising administering to a patient in need thereof an effective amount of a compound of claim 1~~.

49. ~~A method of treating~~ Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone~~, the method comprising administering to a patient in need thereof an effective amount of a compound of claim 1~~.

50. The ~~method~~ use of any one of claims 48 or 49, wherein the compound is to be administered orally, parenterally, by inhalation, or subcutaneously.

~~51. The method of claim 49, wherein the compound is administered orally, parenterally, by inhalation, or subcutaneously.~~

~~52. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the treatment of cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid~~

~~arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia.~~

~~53. Use of a compound of claim 1, or a pharmaceutically acceptable salt thereof, in the treatment of glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone.~~

~~54~~51. ~~Use of a~~A compound of Claim 1, or a pharmaceutically acceptable salt thereof, ~~for the manufacture of a medicament for the treatment of~~ for use in treating cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, metastasis of primary tumor sites, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, colonic cancers, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia.

~~55~~52. ~~Use of a~~ A compound of Claim 1, or a pharmaceutically acceptable salt thereof, ~~for the manufacture of a medicament for the treatment of~~ for use in treating glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone.