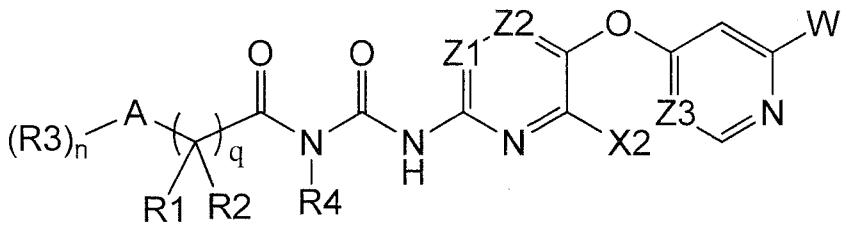
[0012] ~~In one aspect, t~~The present disclosure provides compounds of Formula I:



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;

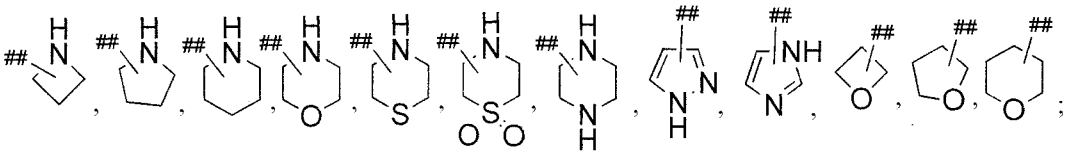
each R3 is individually and independently H, halogen, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, branched C3-C8 alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, fluoro-C1-C6 alkoxy wherein the alkyl chain is partially or completely fluorinated, branched C3-C6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

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

each R5 is individually and independently hydrogen, C1-C6 alkyl, deutero-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, halogen, cyano, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, $-(CH_2)_m$-C(O)NR8(R9), $-(CH_2)_m$-C(O)-R6, $-(CH_2)_m$-C(O)R7, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR8, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-R7, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

Each R6 is individually and independently hydrogen, C1-C6 alkyl, branched C3-C8 alkyl, C3-C8 cycloalkyl, $-(CH_2)_m$-CN ,$-(CH_2)_m$-OR8, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-R7, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each R7 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R5 or R6 moieties containing a R7 moiety;

each R7 is optionally substituted with $-(R10)_p$;

each R8 and R9 is individually and independently H, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, or branched C3-C8 alkyl;

each R10 is individually and independently C1-C6 alkyl, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR3, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-C(O)-R6, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each m is individually and independently 0, 1, 2, or 3;

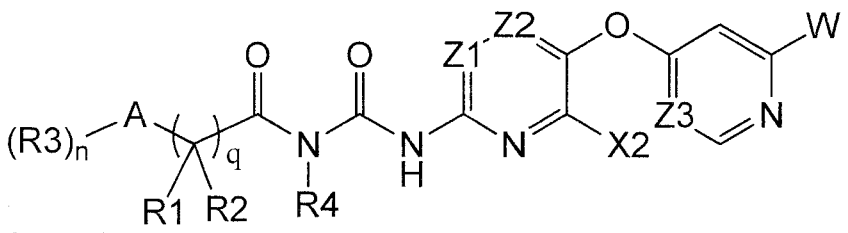
each n is individually and independently 0, 1, 2, or 3;

each p is 0, 1, 2, or 3;

each q is 0, 1, 2, or 3;

and with the proviso that only one of Z1 and Z2 is N.

[0012a] In one aspect of the present disclosure, there is provided a compound of Formula I,



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer 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 non-aromatic 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;

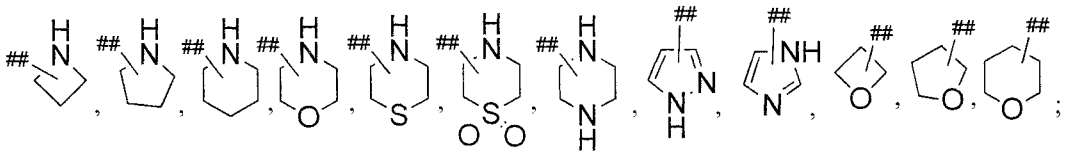
each R3 is individually and independently H, halogen, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, branched C3-C8 alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, fluoro-C1-C6 alkoxy wherein the alkyl chain is partially or completely fluorinated, branched C3-C6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

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

each R5 is individually and independently hydrogen, C1-C6 alkyl, deutero-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, halogen, cyano, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, $-(CH_2)_m$-C(O)NR8(R9), $-(CH_2)_m$-C(O)-R6, $-(CH_2)_m$-C(O)R7, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR8, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-R7, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

Each R6 is individually and independently hydrogen, C1-C6 alkyl, branched C3-C8 alkyl, C3-C8 cycloalkyl, $-(CH_2)_m$-CN ,$-(CH_2)_m$-OR8, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-R7, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each R7 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R5 or R6 moieties containing a R7 moiety;

each R7 is optionally substituted with $-(R10)_p$;

each R8 and R9 is individually and independently H, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, or branched C3-C8 alkyl;

each R10 is individually and independently C1-C6 alkyl, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR3, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-C(O)-R6, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each m is individually and independently 0, 1, 2, or 3;

each n is individually and independently 0, 1, 2, or 3;

each p is 0, 1, 2, or 3;

each q is 0, 1, 2, or 3;

and with the proviso that when Z1 is N, Z2 is CX1 and when Z2 is N, Z1 is CX3.

[0013] In one embodiment of Formula I, A is C1-C6alkyl.

[0014] In one embodiment of Formula I, A is branched C3-C8alkyl.

[0015] In one embodiment of Formula I, A is fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated.

[0016] In one embodiment of Formula I, A is C3-C8carbocyclyl.

[0017] In one embodiment of Formula I, A is a 4-8 membered heterocyclic ring.

[0202] In some embodiments, the 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 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,~~or colonic cancers~~, rheumatoid arthritis, osteoarthritis, multiple sclerosis, autoimmune nephritis, lupus, Crohn's disease, asthma, chronic obstructive pulmonary disease, osteoporosis, mastocytosis, or mast cell leukemia~~.

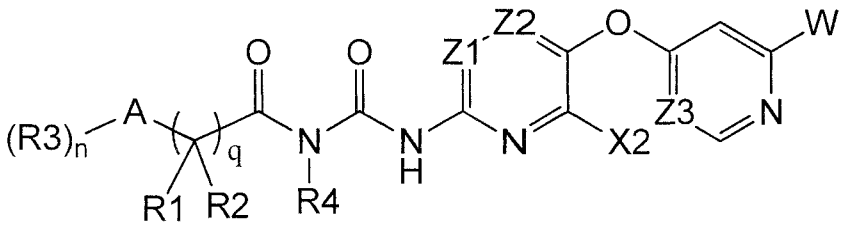
[0204b] In a further aspect of the present disclosure, there is provided a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in treating glioblastomas, breast cancers, pancreatic cancers, metastasis of primary tumor sites, or cancers that are metastatic to bone.

[0205] In some embodiments, the 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,

CLAIMS

What is claimed is:

1. A compound of **Formula I**,



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer 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 non-aromatic 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;

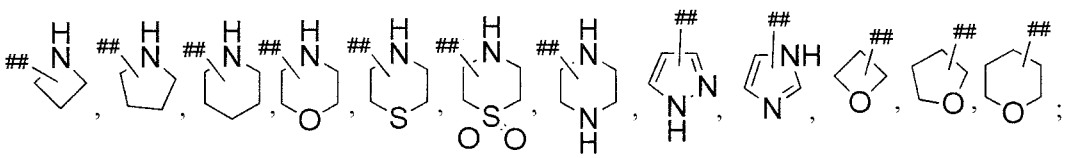
each R3 is individually and independently H, halogen, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, branched C3-C8 alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, fluoro-C1-C6 alkoxy wherein the alkyl chain is partially or completely fluorinated, branched C3-C6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

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

each R5 is individually and independently hydrogen, C1-C6 alkyl, deutero-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, halogen, cyano, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, $-(CH_2)_m$-C(O)NR8(R9), $-(CH_2)_m$-C(O)-R6, $-(CH_2)_m$-C(O)R7, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR8, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-R7, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

Each R6 is individually and independently hydrogen, C1-C6 alkyl, branched C3-C8 alkyl, C3-C8 cycloalkyl, $-(CH_2)_m$-CN ,$-(CH_2)_m$-OR8, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-R7, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each R7 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment to respective R5 or R6 moieties containing a R7 moiety;

each R7 is optionally substituted with $-(R10)_p$;

each R8 and R9 is individually and independently H, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, or branched C3-C8 alkyl;

each R10 is individually and independently C1-C6 alkyl, $-(CH_2)_m$-CN, $-(CH_2)_m$-OR3, $-(CH_2)_m$-NR8(R9), or $-(CH_2)_m$-C(O)-R6, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each m is individually and independently 0, 1, 2, or 3;

each n is individually and independently 0, 1, 2, or 3;

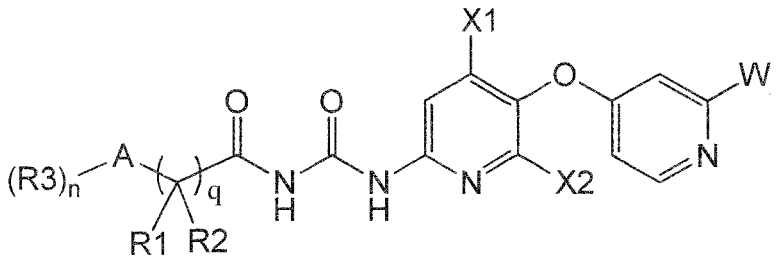
each p is 0, 1, 2, or 3;

each q is 0, 1, 2, or 3;

and with the proviso that ~~only one of Z1 and Z2 is N~~when Z1 is N, Z2 is CX1 and when Z2 is N, Z1 is CX3.

2. The compound of claim 1, wherein W is selected from the group consisting of pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, thiazolyl, triazolyl, pyridinyl, and phenyl.

3. The compound of claim 2, wherein the compound is a compound of **Formula Ia**,



Formula Ia

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein the A moiety is selected from C1-C6 alkyl, branched C3-C8alkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated, C3-C8carbocyclyl, or a 4-8 membered non-aromatic heterocyclic ring.

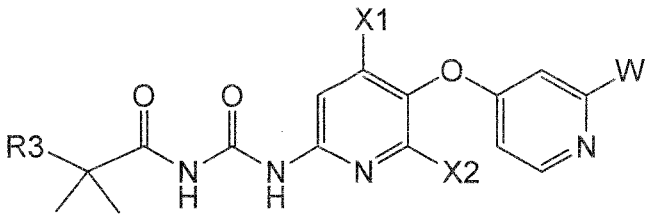
4. The compound of claim 3, wherein W is pyrazolyl, imidazolyl, pyridinyl, phenyl, or oxazolyl, wherein each W is optionally substituted with $-(R5)_p$.

5. The compound of claim 4, wherein X1 is H and X2 is C1-C6 alkyl.

6. The compound of claim 4 wherein X1 is C1-C6 alkyl and X2 is H.

7. The compound of claim 4 wherein X1 and X2 are H.

8. The compound of claim 4, wherein the compound is a compound of **Formula Ib,**



Formula Ib

wherein R3 is C1-C6alkyl, hydrogen or C1-C6alkoxy,

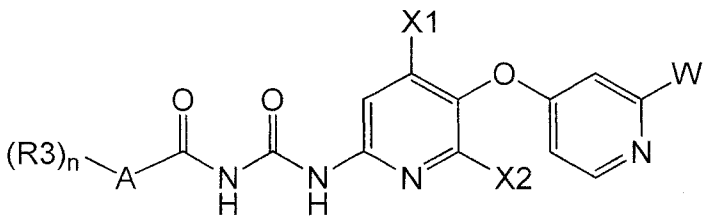
or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof.

9. The compound of claim 8, wherein X1 is H and X2 is C1-C6 alkyl.

10. The compound of claim 8 wherein X1 is C1-C6 alkyl and X2 is H.

11. The compound of claim 8 wherein X1 and X2 are H.

12. The compound of claim 4, wherein the compound is a compound of **Formula Ic,**



Formula Ic

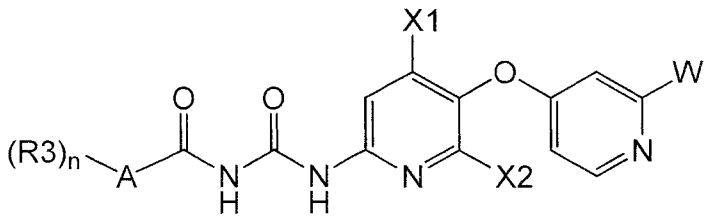
or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein A is C3-C8 carbocyclyl and R3 is C1-C6alkyl, hydrogen or C1-C6alkoxy.

13. The compound of claim 12, wherein X1 is H and X2 is C1-C6 alkyl.

14. The compound of claim 12 wherein X1 is C1-C6 alkyl and X2 is H.

15. The compound of claim 12 wherein X1 and X2 are H.

16. The compound of claim 4, wherein the compound is a compound of **Formula Id,**



Formula Id

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein A is a 4-8 membered non-aromatic heterocyclic ring and R3 is hydrogen or C1-C6alkyl.

17. The compound of claim 16, wherein X1 is H and X2 is C1-C6 alkyl.

18. The compound of claim 16 wherein X1 is C1-C6 alkyl and X2 is H.

19. The compound of claim 16 wherein X1 and X2 are H.

20. The compound of claim 1 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-

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

49. 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.

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