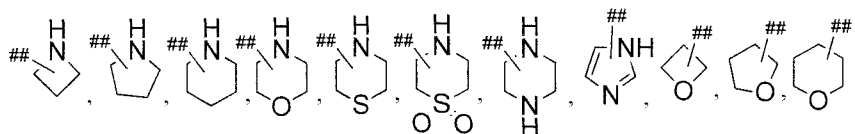


alkyl, C3-C8 cycloalkyl, $-(CH_2)_m-OR_8$, $-(CH_2)_m-NR_8(R_9)$, $-(CH_2)_m-R_7$, or cyano, wherein each alkylene is optionally substituted with C1-C4 alkyl;

each R5 is individually and independently hydrogen, C1-C6 alkyl, deuterio-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, $-(CH_2)_m-C(O)NR_8(R_9)$, $-(CH_2)_m-C(O)R_7$, $-(CH_2)_m-OR_8$, $-(CH_2)_m-NR_8(R_9)$, or $-(CH_2)_m-R_7$, wherein each alkylene is optionally substituted with C1-C4 alkyl;

each R6 is individually and independently hydrogen, C1-C6 alkyl, branched C3-C8 alkyl, C3-C8 cycloalkyl, $-(CH_2)_m-CN$, $-(CH_2)_m-OR_8$, $-(CH_2)_m-NR_8(R_9)$, or $-(CH_2)_m-R_7$, wherein each alkylene is optionally substituted with C1-C4 alkyl;

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



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

each R7 is optionally substituted with $-(R_{10})_p$;

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

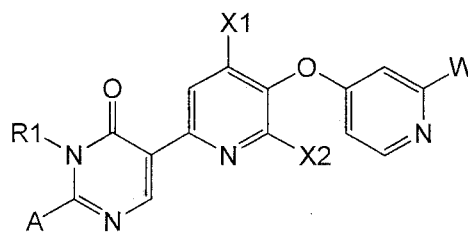
each R10 is individually and independently C1-C6 alkyl, $-(CH_2)_m-CN$, $-(CH_2)_m-OR_3$, $-(CH_2)_m-NR_8(R_9)$, or $-(CH_2)_m-C(O)-R_6$, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

wherein each alkylene is optionally substituted with C1-C4 alkyl

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

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

[0011a] A compound of Formula I.

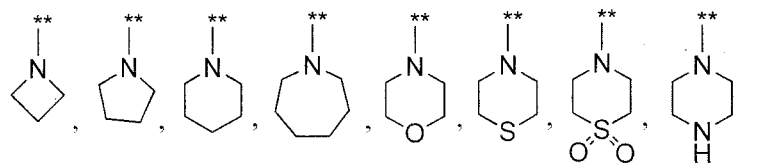


Formula I

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

A is taken from the group consisting of $-N(R_2)R_3$ and G;

G is selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the pyrimidine ring;

each G moiety may be further substituted with one, two, or three R_4 moieties;

W is C5-C6heteroaryl, phenyl, $-NHC(O)R_6$, $-NHC(O)R_7$, $-NHC(O)N(R_8)R_9$ or $-C(O)N(R_8)R_9$, and wherein each C5-C6heteroaryl or phenyl is optionally substituted by one, two, or three R_5 moieties;

X_1 and X_2 are individually and independently hydrogen or C1-C6 alkyl;

R_1 is hydrogen, C1-C6 alkyl, deuterio-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, or branched C3-C8 alkyl;

R_2 is hydrogen, C1-C6 alkyl, deuterio-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, C3-C8 cycloalkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated, $-(CH_2)_m-OR_8$, or a 3-8 membered heterocycle, wherein each alkylene is optionally substituted with C1-C4 alkyl;

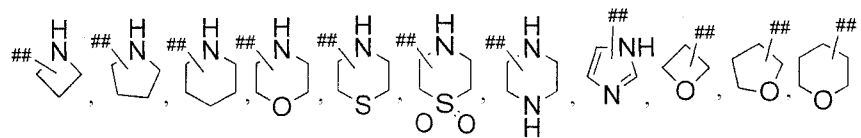
R_3 is hydrogen, C1-C6 alkyl, deuterio-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, C3-C8 cycloalkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated or a 3-8 membered heterocycle;

each R_4 is individually and independently hydrogen, halogen, C1-C6 alkyl, fluoro-C1-C6 alkyl wherein the alkyl chain is partially or completely fluorinated, branched C3-C8 alkyl, C3-C8 cycloalkyl, $-(CH_2)_m-OR_8$, $-(CH_2)_m-NR_8(R_9)$, $-(CH_2)_m-R_7$, or cyano, wherein each alkylene is optionally substituted with C1-C4 alkyl;

each R_5 is individually and independently hydrogen, C1-C6 alkyl, deuterio-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, $-(CH_2)_m-C(O)NR_8(R_9)$, $-(CH_2)_m-C(O)R_7$, $-(CH_2)_m-OR_8$, $-(CH_2)_m-NR_8(R_9)$, or $-(CH_2)_m-R_7$, wherein each alkylene is optionally substituted with C1-C4 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 alkylene is optionally substituted with C1-C4 alkyl;

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



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

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

each R8 and R9 is individually and independently hydrogen, 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;

wherein each alkylene is optionally substituted with C1-C4 alkyl

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

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

[0012] In one embodiment of Formula I, A is $-N(R2)R3$.

[0013] In one embodiment of Formula I, A is G.

[0014] In one embodiment of Formula I, W is C5-C6heteroaryl optionally substituted by one, two, or three R5.

[0015] In one embodiment of Formula I, W is $-NHC(O)R6$, $-NHC(O)R7$, or $-NHC(O)N(R8)R9$.

[0016] In one embodiment of Formula I, W is $-NHC(O)R6$.

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.

[0130] 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 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.

[0130a] In one aspect, the present disclosure provides a use of a compound as disclosed herein 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, or osteoporosis, mastocytosis, or mast cell leukemia.~~ cancer, 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, or osteoporosis, mastocytosis, or mast cell leukemia.

[0131] In some embodiments, the 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.

[0131a] In one aspect, the present disclosure provides a use of a compound as disclosed herein 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.

[0132] In certain embodiments, the 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.

[0132a] In one aspect, the present disclosure provides a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use 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, or osteoporosis, mastocytosis, or mast cell leukemia.~~

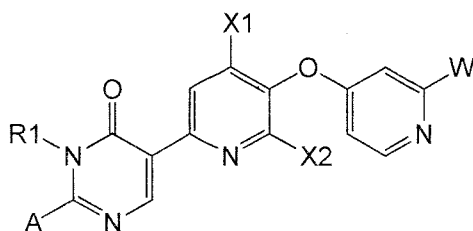
[0132b] In another aspect, the present disclosure provides a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of glioblastomas, breast cancers, pancreatic cancers, ~~metastasis of primary tumor sites~~, or cancers that are metastatic to bone.

[0133] 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

CLAIMS

What is claimed is:

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

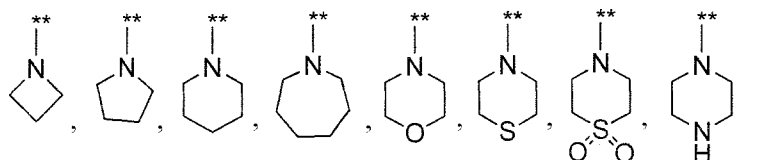


Formula I

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

A is taken from the group consisting of $-N(R_2)R_3$ and G;

G is selected from the group consisting of



and wherein the symbol (**) is the point of attachment to the pyrimidine ring;

each G moiety may be further substituted with one, two, or three R_4 moieties;

W is C5-C6heteroaryl, phenyl, $-NHC(O)R_6$, $-NHC(O)R_7$, $-NHC(O)N(R_8)R_9$ or $-C(O)N(R_8)R_9$, and wherein each C5-C6heteroaryl or phenyl is optionally substituted by one, two, or three R_5 moieties;

X_1 and X_2 are individually and independently hydrogen or C1-C6 alkyl;

R_1 is hydrogen, C1-C6 alkyl, deuterio-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, or branched C3-C8 alkyl;

R_2 is hydrogen, C1-C6 alkyl, deuterio-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, C3-C8 cycloalkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated, $-(CH_2)_m-OR_8$, or a 3-8 membered heterocycleheterocyclic ring, wherein each alkylene is optionally substituted with C1-C4 alkyl;

R_3 is hydrogen, C1-C6 alkyl, deuterio-C1-C6 alkyl wherein the alkyl chain is partially or completely deuterated, branched C3-C8 alkyl, C3-C8 cycloalkyl, fluoroC1-C6alkyl wherein the alkyl is fully or partially fluorinated or a 3-8 membered heterocycleheterocyclic ring;

17. The composition of claim 16 further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.
18. The compound 2-(isopropylamino)-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one.
19. A pharmaceutical composition, comprising the compound of claim 18 and a pharmaceutically acceptable carrier.
20. The composition of claim 19 further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.
21. The compound 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one.
22. A pharmaceutical composition, comprising the compound of claim 21 and a pharmaceutically acceptable carrier.
23. The composition of claim 22 further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.
24. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.
25. The composition of claim 24 further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.
26. Use of of a compound of claim 1 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, or osteoporosis; ~~mastocytosis, or mast cell leukemia.~~

27. Use of a compound of claim 1 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.
28. The use of any one of claims 26 or 27, wherein the compound is to be administered orally, parenterally, by inhalation, or subcutaneously.
29. A compound of claim 1, or a pharmaceutically acceptable salt thereof, for use 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, or
osteoporosis, ~~mastocytosis, or mast cell leukemia.~~

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