

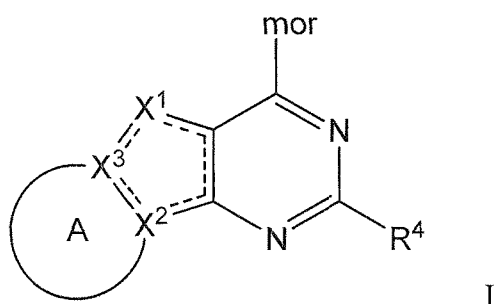
SUMMARY OF THE INVENTION

The ~~invention~~-disclosure relates generally to tricyclic PI3K inhibitor compounds of Formula I with anti-cancer activity, anti-inflammatory activity, or immunoregulatory properties, and more specifically with PI3 kinase modulating or inhibitory activity. Certain

5 hyperproliferative disorders are characterized by the modulation of PI3 kinase function, for example by mutations or overexpression of the proteins. Accordingly, the compounds of the ~~disclosure invention~~ may be useful in the treatment of hyperproliferative disorders such as cancer. The compounds may inhibit tumor growth in mammals and may be useful for treating human cancer patients.

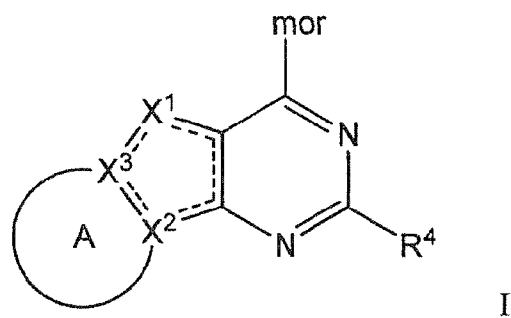
10 The ~~disclosure invention~~ also relates to methods of using the tricyclic PI3K inhibitor compounds of Formula I for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells, organisms, or associated pathological conditions.

Formula I compounds include:



15 and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof. The dashed lines indicate an optional double bond, and at least one dashed line is a double bond. The substituents are as described herein.

One aspect of the present disclosure provides a compound selected from Formula I:



and stereoisomers, geometric isomers, tautomers, and pharmaceutically acceptable salts thereof, wherein:

the dashed lines indicate an optional double bond, and at least one dashed line is a double bond;

X^1 is N, CR^1 , or $-C(R^1)_2O-$;

X^2 is N;

X^3 is C or CR^3 ;

A is a 5, 6, or 7-membered carbocyclyl or heterocyclyl ring fused to X^2 and X^3 , optionally substituted with one or more R^5 groups;

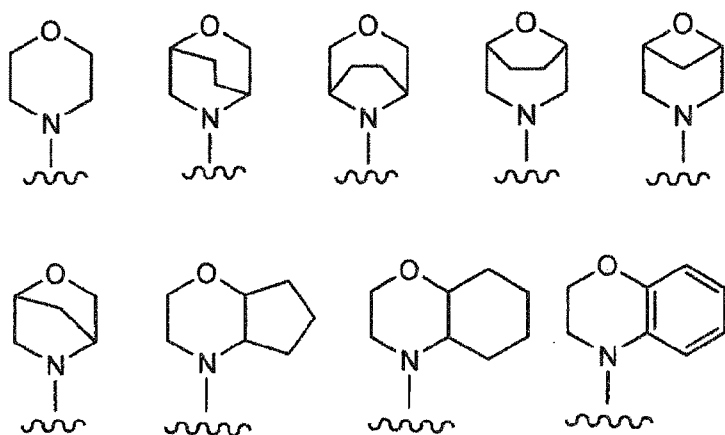
R^1 and R^3 are independently selected from H, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2OCH_3$, $-CN$, $-CF_3$, $-CO_2H$, $-COCH_3$, $-COC(CH_3)_3$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $-CON(CH_3)_2$, $-C(CH_3)_2CONH_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHCOCH_3$, $-NHS(O)_2CH_3$, $-N(CH_3)C(CH_3)_2CONH_2$, $-N(CH_3)CH_2CH_2S(O)_2CH_3$, $=O$, $-OH$, $-OCH_3$, $-S(O)_2N(CH_3)_2$, $-SCH_3$, $-S(O)_2CH_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, and 1,1-dioxo-thiopyran-4-yl;

R^4 is selected from C_6-C_{20} aryl, heterocyclyl having 3-20 ring atoms and heteroaryl having 5-20 ring atoms, each of which are optionally substituted with one or more groups R^6 groups independently selected from F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_3$, $-CH_2CN$, $-CN$, $-CF_3$, $-CH_2OH$, $-CO_2H$, $-CONH_2$, $-CONH(CH_3)$, $-CON(CH_3)_2$, $-NO_2$, $-NH_2$, $-NHCH_3$, $-NHCOCH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH(CH_3)_2$, $-SH$, $-NHC(=O)NHCH_3$, $-NHC(=O)NHCH_2CH_3$, $-NHC(=O)NHCH(CH_3)_2$, $-NHS(O)_2CH_3$, $-N(CH_3)C(=O)OC(CH_3)_3$, $-S(O)_2CH_3$, benzyl, benzyloxy, morpholinyl, morpholinomethyl, and 4-methylpiperazin-1-yl; and

R^5 is independently selected from C_1-C_{12} alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, $-(C_1-C_{12} \text{ alkylene})-(C_3-C_{12} \text{ carbocyclyl})$, $-(C_1-C_{12} \text{ alkylene})-(\text{heterocyclyl having 3-20 ring atoms})$, $-(C_1-C_{12} \text{ alkylene})-C(=O)-(\text{heterocyclyl having 3-20 ring atoms})$, $-(C_1-C_{12} \text{ alkylene})-(C_6-C_{20} \text{ aryl})$, and $-(C_1-C_{12} \text{ alkylene})-(\text{heteroaryl having 5-20 ring atoms})$; or two geminal R^5 groups form a 3, 4, 5, or 6-membered carbocyclyl or

heterocyclyl ring, where alkyl, alkenyl, alkynyl, alkylene, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CN}$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CO}_2\text{H}$, $-\text{COCH}_3$, $-\text{COC}(\text{CH}_3)_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CON}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{NHS}(\text{O})_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, cyclopropyl, cyclobutyl, oxetanyl, morpholino, and 1,1-dioxo-thiopyran-4-yl;

mor is selected from:



optionally substituted with one or more R^7 groups independently selected from F, Cl, Br, I, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CHF}_2$, $-\text{CN}$, $-\text{CF}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{CH}_3)\text{OH}$, $-\text{CH}(\text{CH}_2\text{CH}_3)\text{OH}$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OCH}_3$, $-\text{CH}(\text{CH}_3)\text{F}$, $-\text{C}(\text{CH}_3)\text{F}_2$, $-\text{CH}(\text{CH}_2\text{CH}_3)\text{F}$, $-\text{C}(\text{CH}_2\text{CH}_3)_2\text{F}$, $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{CON}(\text{CH}_2\text{CH}_3)_2$, $-\text{COCH}_3$, $-\text{CON}(\text{CH}_3)_2$, $-\text{NO}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCH}_2\text{CH}_3$, $-\text{NHCH}(\text{CH}_3)_2$, $-\text{NHCH}_2\text{CH}_2\text{OH}$, $-\text{NHCH}_2\text{CH}_2\text{OCH}_3$, $-\text{NHCOCH}_3$, $-\text{NHCOCH}_2\text{CH}_3$, $-\text{NHCOCH}_2\text{OH}$, $-\text{NHS}(\text{O})_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{S}(\text{O})_2\text{CH}_3$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{SH}$, $-\text{NHC}(=\text{O})\text{NHCH}_3$, $-\text{NHC}(=\text{O})\text{NHCH}_2\text{CH}_3$, $-\text{S}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_2\text{NH}_2$, $-\text{S}(\text{O})_2\text{NHCH}_3$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$.

~~Another aspect of the disclosure invention~~ provides a pharmaceutical composition comprising a tricyclic PI3K inhibitor compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise one or more additional therapeutic agent. Another aspect of the disclosure provides a pharmaceutical composition comprised of a compound of this disclosure and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

~~Another aspect of the disclosure invention~~ provides methods of inhibiting PI3 kinase activity, comprising contacting a PI3 kinase with an effective inhibitory amount of a compound of Formula I.

~~Another aspect of the disclosure invention~~ provides methods of preventing or treating a hyperproliferative disease or disorder modulated by PI3 kinases, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I. Examples of such hyperproliferative disease or disorder include, but are not limited to, cancer.

~~Another aspect of the disclosure invention~~ provides methods of preventing or treating a hyperproliferative disorder, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I, alone or in combination with one or more additional compounds having anti-hyperproliferative properties.

5 ~~In a further aspect of the present disclosure invention~~ provides a method of using a compound of this ~~disclosure invention~~ to treat a hyperproliferative disease or condition modulated by PI3 kinase in a mammal.

~~An additional aspect of the disclosure invention provides~~ is the use of a compound of this ~~disclosure invention~~ for treating cancer modulated by PI3 kinase in a mammal.

10 ~~An additional~~ Another aspect of the disclosure invention is a compound of this disclosure invention for use as therapeutically active substance.

~~An additional aspect of the disclosure invention provides~~ is the use of a compound of this ~~disclosure invention~~ for treating cancer modulated by PI3 kinase in a mammal.

15 ~~An additional aspect of the disclosure invention provides~~ is the use of a compound of this ~~disclosure invention~~ for the preparation of a medicament for treating cancer modulated by PI3 kinase in a mammal. Another aspect of the disclosure provides the use of a compound of this disclosure for the preparation of a medicament for treating cancer.

20 ~~An additional aspect of the disclosure invention provides~~ is a compound of this ~~disclosure invention~~ for use for treating cancer modulated by PI3 kinase in a mammal. Another aspect of the disclosure provides a compound of this disclosure for use in treating cancer.

~~Another aspect of the disclosure invention~~ includes kits comprising a compound of Formula I, a container, and optionally a package insert or label indicating a treatment.

~~Another aspect of the disclosure invention~~ includes methods of preparing, methods of separating, and methods of purifying compounds of Formula I.

25 ~~Another aspect of the disclosure invention~~ includes novel intermediates useful for preparing Formula I compounds.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they

3-(4-morpholino-6-(trifluoromethyl)-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)phenol,

5-(4-((2S,6R)-2,6-dimethylmorpholino)-6,6-dimethyl-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine,

5-(4-(2,2-dimethylmorpholino)-6,6-dimethyl-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine,

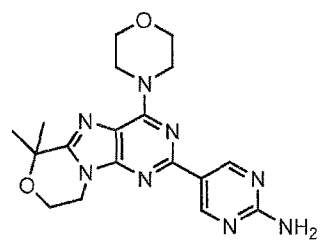
N-(5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-yl)acetamide,

5-(4-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)-6,6-dimethyl-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine,

10 2-(2-aminopyrimidin-5-yl)-6-methyl-4-morpholino-6,7-dihydropyrazino[2,1-e]purin-8(9H)-one,
5-(6,7-dimethyl-4-morpholino-6,7,8,9-tetrahydropyrazino[2,1-e]purin-2-yl)pyrimidin-2-amine;
and

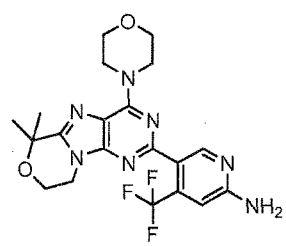
(5-(8,8-Dimethyl-1-morpholin-4-yl-5,6-dihydro-8H-7-oxa-2,4,4b-triaza-fluoren-3-yl)-pyrimidin-2-yl)amine.

15 19. A compound of claim 1 which is



5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6h-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine.

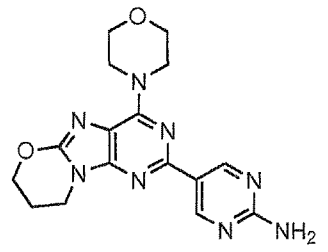
20. A compound of claim 1 which is



20 5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6h-[1,4]oxazino[3,4-e]purin-2-yl)-4-

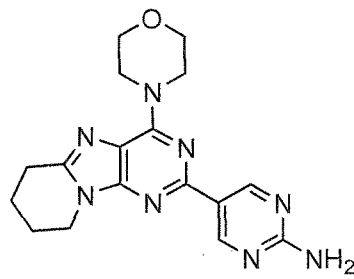
(trifluoromethyl)pyridyl-2-amine.

21. A compound of claim 1 which is



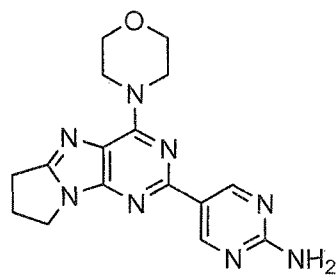
5-(4-morpholino-8,9-dihydro-7h-[1,3]oxazino[2,3-e]purin-2-yl)pyrimidin-2-amine.

22. A compound of claim 1 which is



5-(4-morpholino-6,7,8,9-tetrahydropyrido[2,1-e]purin-2-yl)pyrimidin-2-amine.

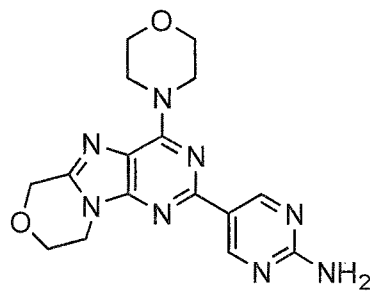
23. A compound of claim 1 which is



5-(4-morpholino-7,8-dihydro-6h-pyrrolo[2,1-e]purin-2-yl)pyrimidin-2-amine.

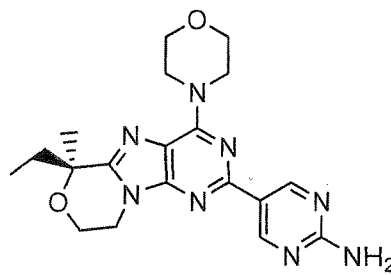
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24. A compound of claim 1 which is



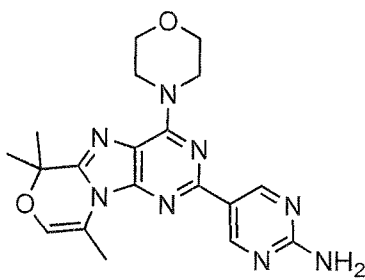
5-(4-morpholino-8,9-dihydro-6h-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine.

25. A compound of claim 1 which is



(S)-5-(6-ethyl-6-methyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine.

26. A compound of claim 1 which is



5-(6,6,9-trimethyl-4-morpholino-6h-[1,4]oxazino[3,4-e]purin-2-yl)pyrimidin-2-amine.

1927. A pharmaceutical composition comprised of a compound of any one of claims 1-18-26 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

2028. The pharmaceutical composition according to claim 1927, further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an
5 agent for treating diabetes, and an agent for treating immunodeficiency disorders.

2129. A compound of any one of claims ~~1-18~~26 for use as therapeutically active substance.

2230. The use of a compound of any one of claims ~~1-18~~26 for the preparation of a medicament for treating cancer.

5 2331. The use of claim 2230, wherein the cancer is selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary
10 carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, renal, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's or leukemia.

2432. The use of claim 2331, wherein the cancer is a brain cancer.

2533. The use of any one of claims ~~22~~30 to ~~24~~32, further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-angiogenesis therapeutic agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent
5 for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

2634. The use of claim 2533, wherein the additional therapeutic agent is bevacizumab.

2735. A compound of any one of claims 1-~~18~~26 for use in treating cancer.