

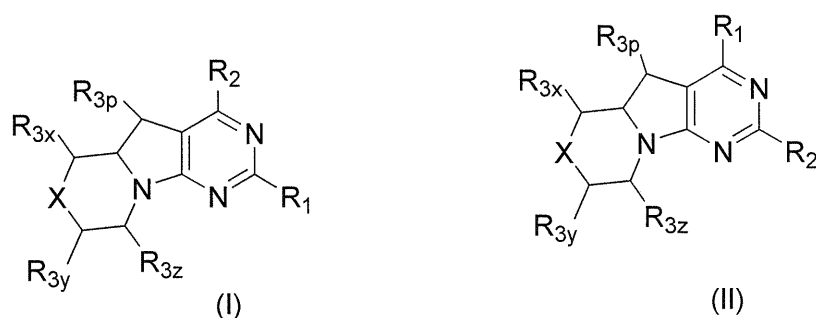
PI3K signaling can have a deleterious effect on cells leading to uncontrolled proliferation, enhanced migration and adhesion-independent growth. These events favor not only the formation of malignant tumors, but also the development of inflammatory and autoimmune disease.

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Summary of the Invention

The invention ~~disclosure~~ relates to conformationally restricted compounds of formula (I) or (II)

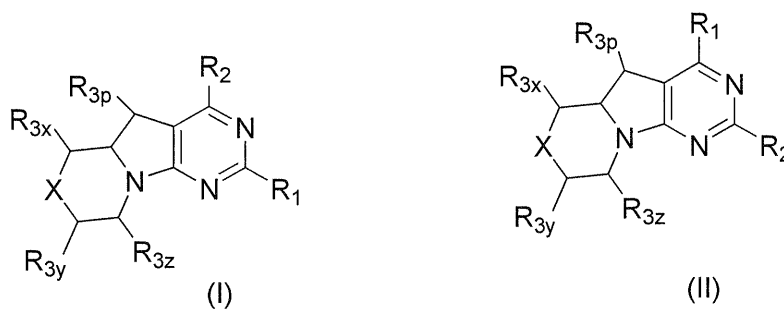
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pharmaceutical compositions comprising these, and their use as therapeutic agents and diagnostic probes.

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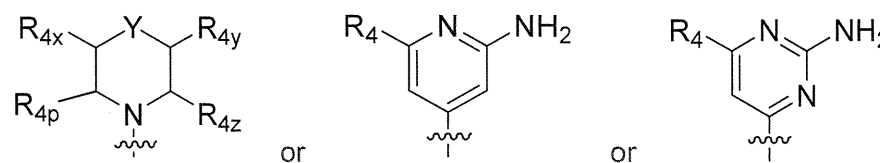
In one aspect, there is provided compounds of formula (I) and (II),



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

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R₁ is



X and Y are independently selected from the group consisting of $C(R_8)_2$, O, S, SO, SO_2 , and NR_7 ;

R_{3x} , R_{3y} , R_{3z} , R_{3p} and R_4 are independently selected from the group consisting of hydrogen, D, F, Cl, Br, I, 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 $-(C_1-C_{12} \text{ alkylene})-(\text{heteroaryl having 5-20 ring atoms})$, $-C(C_1-C_6 \text{ alkyl})_2NR_5R_6$, $-(CR_8R_9)_tNR_5R_6$, $-(CR_8R_9)_nNR_7C(=Z)R_8$, $(CR_8R_9)_nNR_7S(O)_2R_5$, $-CH(OR_5)R_6$, $-(CR_8R_9)_nOR_5$, $-(CR_8R_9)_nS(O)_2R_5$, $-(CR_8R_9)_nS(O)_2NR_5R_6$, $-C(=Z)R_5$, $-C(=Z)OR_5$, $C(=Z)NR_5R_6$, $-C(=Z)NR_7OR_5$, $-C(=O)NR_7S(O)_2R_5$, $-C(=O)NR_7(CR_8R_9)_mNR_5R_6$, $-NO_2$, $-NHR_7$, $-NR_7C(=Z)R_5$, $-NR_7C(=Z)OR_5$, $-NR_7C(=Z)NR_5R_6$, $-NR_7S(O)_2R_5$, $-NR_7SO_2NR_5R_6$, $-S(O)_2R_5$, $-S(O)_2NR_5R_6$, $-SC(=Z)R_5$, $-SC(=Z)OR_5$, C_3 - C_{12} carbocyclyl, C_2 - C_{20} heterocyclyl, C_6 - C_{20} aryl, and C_1 - $C=NR_7$, OR_5 , $-OC(=Z)R_5$, $-OC(=Z)OR_5$, $-OC(=Z)NR_5R_6$, and $-OS(O)_2(OR_5)$;

R_{4x} , R_{4y} , R_{4z} , and R_{4p} are independently selected from the group consisting of hydrogen, D, F, Cl, Br, I, C_1 - C_{12} alkyl, C_2 - C_8 alkenyl, C_2 - C_8 alkynyl, or one or two of R_{4x} , R_{4y} , R_{4z} , and R_{4p} are two geminal substituents methyl and the other ones are hydrogen, or R_{4x} and R_{4y} , or R_{4z} and R_{4p} form together an annulated five- or six-membered carbocyclyl, heterocyclyl, aryl or heteroaryl ring, or R_{4x} and R_{4y} form together bridging ethylene or methylene, R_{4p} and R_{4z} form together bridging ethylene or methylene, or R_{4y} and R_{4p} form together bridging ethylene or methylene;

wherein said alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, CN, CF_3 , NO_2 , oxo, $-C(=Z)R_5$, $-C(=Z)OR_5$, $-C(=Z)NR_5R_6$, $-(CR_8R_9)_nNR_5R_6$, $-(CR_8R_9)_nC(=Z)NR_5R_6$, $-(CR_8R_9)_nC(=Z)OR_5$, $-(CR_8R_9)_nNR_7SO_2R_5$, $-(CR_8R_9)_nOR_5$, $-(CR_8R_9)_nR_5$, $-(CR_8R_9)_nSO_2R_5$, $-NR_5R_6$, $-NR_7C(=Z)R_5$, $-NR_7C(=Z)OR_5$, $-NR_7C(=Z)NR_5R_6$, $-NR_7SO_2R_5$, $-OP(OR_5)(OR_6)$, SR_5 , $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NR_5R_6$, $-S(O)(OR_5)$,

-S(O)₂(OR₅), -SC(=Z)R₅, -SC(=Z)OR₅, -SC(=Z)NR₅R₆, optionally substituted C₁-C₁₂ alkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₁₂ carbocyclyl, optionally substituted C₂-C₂₀ heterocyclyl, optionally substituted C₆-C₂₀ aryl, and optionally substituted C₁-C₂₀ heteroaryl;

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R₅, R₆ and R₇ are independently selected from H, D, C₁-C₁₂ alkyl, C₂-C₈ alkenyl, C₃-C₈ alkynyl, C₃-C₁₂ carbocyclyl, C₂-C₂₀ heterocyclyl, C₆-C₂₀ aryl, and C₁-C₂₀ heteroaryl, or R₅ and R₆ together with the nitrogen to which they are attached form a C₃-C₂₀ heterocyclic ring optionally containing one or more additional ring atoms selected from N, O or S,

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wherein said heterocyclic ring is optionally substituted with one or more groups independently selected from oxo, CF₃, F, Cl, Br, I, C₁-C₁₂ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₁₂ carbocyclyl, C₂-C₂₀ heterocyclyl, C₆-C₂₀ aryl and C₁-C₂₀ heteroaryl;

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R₈ and R₉ are independently selected from H, D, C₁-C₁₂ alkyl, and -(CH₂)_n-aryl, or R₈ and R₉ together with the atoms to which they are attached form a saturated or partially unsaturated C₃-C₁₂ carbocyclic ring;

m is 0, 1, 2, 3, 4, 5 or 6;

n is 1, 2, 3, 4, 5, or 6;

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t is 2, 3, 4, 5 or 6; and

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R₂ is independently selected from the groups consisting of a monocyclic or bicyclic aryl or heteroaryl with 1-6 heteroatoms selected from O, N, S, with 1-4 substituents selected from C₁-C₄ alkyl, D, F, Cl, Br, I, -OR₅, -COOH, COOR₅, -CONR₅R₆, -SO₂NR₅R₆, CN, CF₃, CHF₂, CFH₂, OCF₃, OCOR₅, NR₇COR₅, NR₇SO₂R₅, NR₅R₆, SO₂R₅, SOR₅, and SR₅.

In another aspect, there is provided a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

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The invention disclosure further relates to the use of these compounds as kinase inhibitors and kinase diagnostic probes, in particular as phosphoinositide 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitor compounds with anti-cancer activity.

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The compounds of the invention are potentially useful in the treatment of diseases, conditions and/or disorders modulated by PI3K and mTOR kinases. The compounds

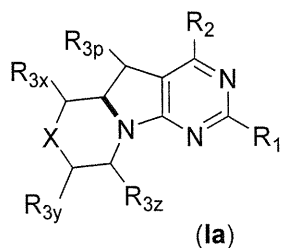
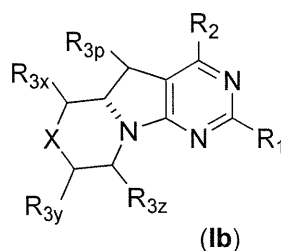
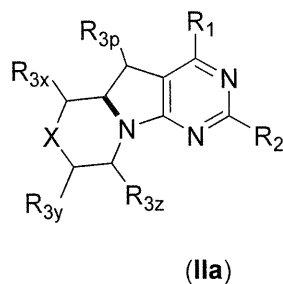
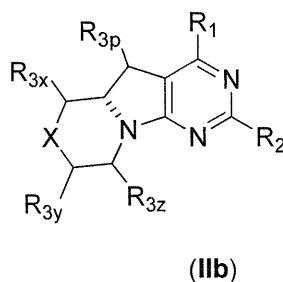
inhibit tumor growth in mammals, show anti-cancer activity, anti-inflammatory activity, immunoregulatory properties, and beneficial properties in associated pathological conditions.

5 | In one aspect, there is provided a compound of the present invention for use in the treatment of cancer.

| The ~~invention~~disclosure also relates to methods of using the compounds for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells and organisms, in particular human cancer patients.

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More specifically, the ~~invention~~disclosure provides enantio-enriched pyrimidine compounds of formula (Ia), (Ib), (IIa) and (IIb)



and stereoisomers, geometric isomers, tautomers, solvates and pharmaceutically acceptable salts thereof.

The substituents R_1 , R_2 and R_3 are described hereinbelow.

In another ~~aspect~~example, the ~~invention~~disclosure provides a pharmaceutical composition comprising compounds of formula (I) or (II), in particular of formula (Ia), (Ib), (IIa) or (IIb), and a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise one or more additional therapeutic agents selected from anti-proliferative agents, anti-inflammatory agents, immunomodulatory agents, neurotropic factors, agents for treating blood disorders, agents for treating diabetes, and agents for treating immunodeficiency disorders.

In another ~~aspect~~example, the ~~invention~~disclosure provides a method of inhibiting PI3 kinase activity, comprising contacting a PI3 kinase with an effective inhibitory amount of a compound of formula (I) or (II), in particular of formula (Ia), (Ib), (IIa) or (IIb), or a stereoisomer, geometric isomer, tautomer, solvate, or pharmaceutically acceptable salt thereof.

In another ~~aspect~~example, the ~~invention~~disclosure provides a method of preventing or treating a disease or disorder modulated by PI3 kinase, comprising administering to a mammal in need of

- such treatment an effective amount of a compound of formula (I) or (II), in particular of formula (Ia), (Ib), (IIa) and (IIb), or a stereoisomer, geometric isomer, tautomer, solvate, or pharmaceutically acceptable salt thereof. Examples of such diseases, conditions and disorders include, but are not limited to, hyperproliferative disorders (e.g., cancer, including melanoma and other cancers of the skin), neurodegeneration, cardiac hypertrophy, pain, migraine, neurotraumatic diseases, stroke, diabetes, hepatomegaly, cardiovascular disease, Alzheimer's disease, cystic fibrosis, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders, inflammation, neurological disorders, hormone-related diseases, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, hyperproliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukaemia (CML), liver disease, pathologic immune conditions involving T cell activation, and CNS disorders.
- 15 | In another aspectexample, the inventiondisclosure provides a method 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) or (II), in particular of formula (Ia), (Ib), (IIa) or (IIb), or a stereoisomer, geometric isomer, tautomer, solvate, or pharmaceutically acceptable salt or thereof, alone or in combination with one or more
- 20 | additional compounds having anti-hyperproliferative properties. In a further aspectexample the present inventiondisclosure provides a method of using a compound of this invention to treat a disease or condition modulated by PI3 kinase and/or mTOR in a mammal.
- 25 | An additional aspectexample of the inventiondisclosure is the use of a compound of this invention in the preparation of a medicament for the treatment or prevention of a disease or condition modulated by PI3 kinase in a mammal.
- 30 | Another aspectexample of the inventiondisclosure includes kits comprising a compound of formula (I) or (II), in particular of formula (Ia), (Ib), (IIa) or (IIb), or a stereoisomer, geometric isomer, tautomer, solvate, or pharmaceutically acceptable salt thereof, a container, and optionally a package insert or label indicating a treatment.
- 35 | Another aspectexample of the inventiondisclosure includes methods of preparing, methods of separating, and methods of purifying compounds of formula (I) or (II), in particular of formula (Ia),