

AMINOPYRIMIDINES AS ALK INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

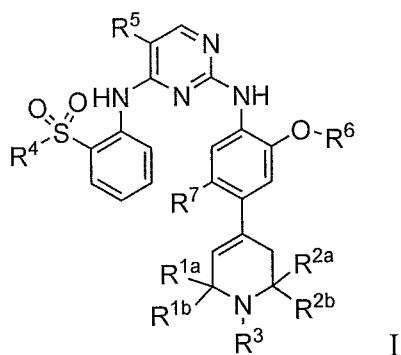
- [0001] The present disclosure provides anaplastic lymphoma kinase inhibitors and therapeutic methods of treating conditions and diseases wherein inhibition of anaplastic lymphoma kinase provides a benefit.

Background

- [0002] Anaplastic lymphoma kinase (ALK), a member of the insulin receptor superfamily of receptor tyrosine kinases, has been implicated in oncogenesis in hematopoietic and non-hematopoietic tumors. The aberrant expression of full-length ALK receptor proteins has been reported in neuroblastomas and glioblastomas; and ALK fusion proteins have occurred in anaplastic large cell lymphoma. The study of ALK fusion proteins has also raised the possibility of new therapeutic treatments for patients with ALK-positive malignancies. Pulford *et al.*, *Cell. Mol. Life. Sci.* 61:2939-2953 (2004).
- [0003] Small molecule ALK inhibitors have therapeutic potential for the treatment of diseases and conditions in which ALK has a role, including cancer. Roskoski, *Pharmacological Research* 68:68– 94 (2013). ALK inhibitors are disclosed in U.S. 8,039,479 and WO 2015/130014.
- [0004] There is an ongoing need for new agents, e.g., small molecules, for treating and/or preventing cancer and other diseases responsive to ALK inhibition.

BRIEF SUMMARY OF THE INVENTION

- [0004a] In one aspect, the present invention refers to a compound having Formula I:



or a pharmaceutically acceptable salt or solvate thereof, wherein: R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and C₃₋₈ cycloalkyl; R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and C₃₋₈ cycloalkyl; R³ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₄₋₈ heterocyclo, R⁴ is selected from the group consisting of C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; R⁵ is halo; R⁶ is selected from the group consisting of C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; and R⁷ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl, with proviso that when R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each hydrogen, then R³ is selected from the group consisting of C₃₋₆ cycloalkyl and C₄₋₈ heterocyclo. In another aspect, the present invention refers to a pharmaceutical composition comprising the compound of the present invention, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier. In yet another aspect, the present invention also refers to the compound of the present invention or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of the present invention for use in therapy. In another aspect, the present invention also provides use of the compound of the present invention, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of the present invention, for the manufacture of a medicament for the treatment of cancer.

[0005] In one example, the present disclosure provides compounds represented by any one of Formulae I-VI, below, and the pharmaceutically acceptable salts and solvates thereof, collectively referred to as "Compounds of the Disclosure." Compounds of the Disclosure are ALK inhibitors and are thus useful in treating or preventing diseases or conditions wherein ALK inhibition provides a benefit.

[0006] In another example, the present disclosure provides methods of treating or preventing a condition or disease by administering a therapeutically effective amount of a Compound of the Disclosure to an individual, e.g., a human, in need thereof. The disease or condition of interest is treatable or preventable by inhibition of ALK, for example,

a cancer, a chronic autoimmune disorder, an inflammatory condition, a proliferative disorder, sepsis, or a viral infection. Also provided are methods of preventing the proliferation of unwanted proliferating cells, such as in cancer, in a subject comprising administering a therapeutically effective amount of a Compound of the Disclosure to a subject at risk of developing a condition characterized by unwanted proliferating cells. In some examples, the Compounds of the Disclosure may reduce the proliferation of unwanted cells by inducing apoptosis in those cells.

[0007] In another example, the present disclosure provides a method of inhibiting ALK in an individual, comprising administering to the individual an effective amount of at least one Compound of the Disclosure.

[0008] In another example, the present disclosure provides a pharmaceutical composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier.

[0009] In another example, the present disclosure provides a composition comprising a Compound of the Disclosure and an excipient and/or pharmaceutically acceptable carrier for use treating or preventing diseases or conditions wherein inhibition of ALK provides a benefit, e.g., cancer.

[0010] In another example, the present disclosure provides a composition comprising: (a) a Compound of the Disclosure; (b) a second therapeutically active agent; and (c) optionally an excipient and/or pharmaceutically acceptable carrier.

[0011] In another example, the present disclosure provides a Compound of the Disclosure for use in treatment or prevention of a disease or condition of interest, e.g., cancer.

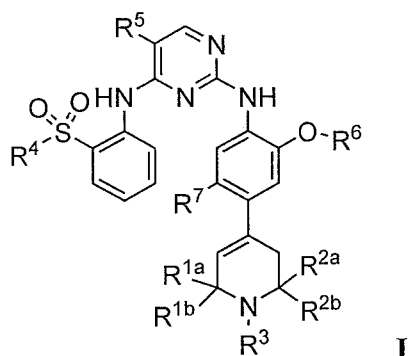
[0012] In another example, the present disclosure provides a use of a Compound of the Disclosure for the manufacture of a medicament for treating a disease or condition of interest, e.g., cancer.

[0013] In another example, the present disclosure provides a kit comprising a Compound of the Disclosure, and, optionally, a packaged composition comprising a second therapeutic agent useful in the treatment of a disease or condition of interest, and a package insert containing directions for use in the treatment of a disease or condition, e.g., cancer.

[0014] In another example, the present disclosure provides methods of preparing Compounds of the Disclosure.

What is claimed is:

1. A compound having Formula I:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and C₃₋₈ cycloalkyl;

R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, and C₃₋₈ cycloalkyl;

R³ is selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₄₋₈ heterocyclo,

R⁴ is selected from the group consisting of C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

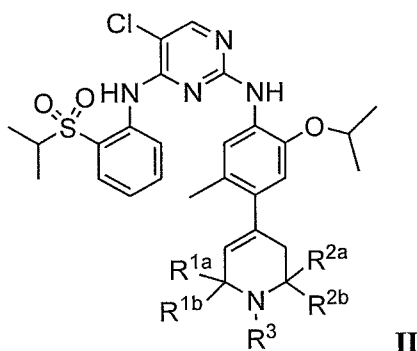
R⁵ is halo;

R⁶ is selected from the group consisting of C₁₋₄ alkyl, and C₃₋₆ cycloalkyl; and

R⁷ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl,

with proviso that when R^{1a}, R^{1b}, R^{2a}, and R^{2b} are each hydrogen, then R³ is selected from the group consisting of C₃₋₆ cycloalkyl and C₄₋₈ heterocyclo.

2. The compound of claim 1 having Formula II:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{1a} and R^{1b} are independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

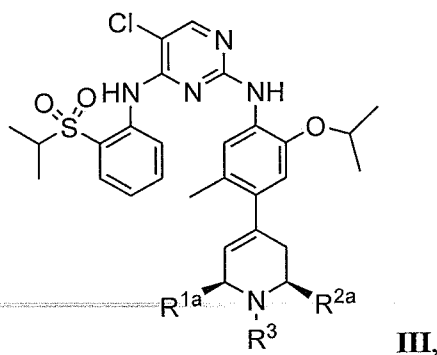
R^{2a} and R^{2b} are independently selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{3-6} cycloalkyl; and

R^3 is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, and C_{4-8} heterocyclo.

3. The compound of claims 1 or 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{1b} and R^{2b} are each hydrogen.

4. The compound of claim 3, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{1a} and R^{2a} are each hydrogen.

5. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, having Formula III:

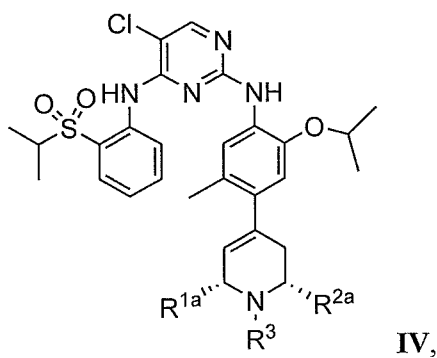


wherein:

R^{1a} and R^{2a} are each independently selected from the group consisting of C_{1-4} alkyl, and C_{3-6} cycloalkyl; and

the compound has an enantiomeric excess of 90% or more.

6. The compound of claim 3, or a pharmaceutically acceptable salt or solvate thereof, having Formula IV:



wherein:

the compound has an enantiomeric excess of 90% or more.

V.

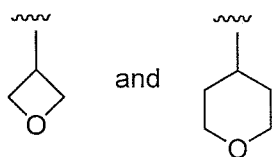
the compound has an enantiomeric excess of 90% or more.

VI

the compound has an enantiomeric excess of 90% or more.

79

10. The compound of claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from the group consisting of:



11. The compound of claim 1, or a pharmaceutically acceptable salt or hydrate thereof, selected from the group consisting of:

- 5-chloro-*N*²-(2-isopropoxy-5-methyl-4-(1,2,2,6,6-pentamethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(2-isopropoxy-5-methyl-4-(2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((cis)-2,6-diethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((cis)-2,6-diethyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(2-isopropoxy-5-methyl-4-(1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(2-isopropoxy-5-methyl-4-(1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((cis)-2,6-dicyclobutyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((cis)-2,6-dicyclobutyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((cis)-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(2-isopropoxy-5-methyl-4-((cis)-1,2,6-trimethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((trans)-2,6-diethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((trans)-2,6-diethyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
- 5-chloro-*N*²-(4-((trans)-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(2-isopropoxy-5-methyl-4-((trans)-1,2,6-trimethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((cis)-2,6-dicyclopropyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((cis)-2,6-dicyclopropyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclobutyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclobutyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclopropyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclopropyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((cis)-2,6-dimethyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((cis)-2,6-dimethyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-diethyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2S,6S)-2,6-diethyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dimethyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dimethyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((cis)-2,6-dicyclopropyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((cis)-2,6-dicyclopropyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclobutyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclobutyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclopentyl-1-(tetrahydro-2H-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((trans)-2,6-dicyclopentyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2S,6R)-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(2-isopropoxy-5-methyl-4-((2S,6R)-1,2,6-trimethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2R,6R)-2,6-dicyclopentyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2R,6R)-2,6-dicyclopentyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2R,6S)-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(2-isopropoxy-5-methyl-4-((2R,6S)-1,2,6-trimethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2S,6S)-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(2-isopropoxy-5-methyl-4-((2S,6S)-1,2,6-trimethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2R,6R)-2,6-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(2-isopropoxy-5-methyl-4-((2R,6R)-1,2,6-trimethyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2S,6S)-2,6-dicyclopentyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2S,6S)-2,6-dicyclopentyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro- N^2 -(4-((2R,6S)-2,6-dicyclopentyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)- N^4 -(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;

5-chloro-*N*²-(4-((2*R*,6*S*)-2,6-dicyclopropyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*R*)-2,6-dicyclopropyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*R*)-2,6-dicyclopropyl-1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*R*,6*S*)-2,6-dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*R*,6*S*)-2,6-dimethyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*S*)-2,6-dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*S*)-2,6-dimethyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*R*,6*R*)-2,6-dimethyl-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*R*,6*R*)-2,6-dimethyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*S*)-2,6-dicyclopropyl-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*S*)-2,6-dicyclopropyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*R*,6*S*)-2,6-dicyclopropyl-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*R*,6*S*)-2,6-dicyclopropyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine;
5-chloro-*N*²-(4-((2*S*,6*R*)-2,6-dicyclopropyl-1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine; and

5-chloro-*N*²-(4-((2*S*,6*R*)-2,6-dicyclopropyl-1-(oxetan-3-yl)-1,2,3,6-tetrahydropyridin-4-yl)-2-isopropoxy-5-methylphenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine.

12. The compound of claim 11, or a pharmaceutically acceptable salt or hydrate thereof, which is 5-chloro-*N*²-(2-isopropoxy-5-methyl-4-(1-(tetrahydro-2*H*-pyran-4-yl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-*N*⁴-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine.

13. A pharmaceutical composition comprising the compound of any one of claims 1-12, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

14. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of claim 13 for use in therapy.

15. Use of the compound of any one of claims 1-12, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, or the pharmaceutical composition of claim 13, for the manufacture of a medicament for the treatment of cancer.

16. The use of claim 15, wherein the cancer is selected from the group consisting of anaplastic large-cell lymphoma, non-small cell lung cancer, diffuse large B-cell lymphoma, inflammatory myofibroblastic tumors, neuroblastoma, anaplastic thyroid cancer, rhabdomyosarcoma, breast cancer, colorectal cancer, esophageal squamous cell cancer, and renal cell carcinoma.