

AMINOPYRIMIDINES AS ALK INHIBITORS

BACKGROUND OF THE INVENTION

Field of the Invention

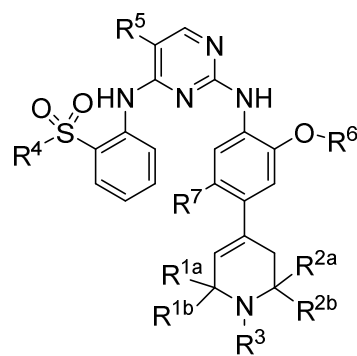
- [0001]** The present disclosure provides anaplastic lymphoma kinase inhibitors and therapeutic methods of treating conditions and diseases wherein inhibition of anaplastic lymphoma kinase provides a benefit.

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

- [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. In one aspect, the present



disclosure refers to a compound having Formula **I**:

pharmaceutically acceptable salt or solvate thereof, wherein: R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each C_{1-3} alkyl; R^3 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{4-8} heterocyclo, R^4 is selected from the group consisting of C_{1-4} alkyl, and C_{3-6} cycloalkyl; R^5 is halo; R^6 is selected from the group consisting of C_{1-4} alkyl, and C_{3-6} cycloalkyl; and R^7 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{3-6} cycloalkyl, with proviso that when R^{1a} , R^{1b} , R^{2a} , and R^{2b} are each hydrogen, then R^3 is selected from the group consisting of C_{3-6} cycloalkyl and C_{4-8} heterocyclo.

[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. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt or hydrate thereof, and a 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. In yet another aspect, the present disclosure refers to use of a therapeutically effective amount of the compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof in the manufacture of a medicament for treating a patient having cancer, a chronic autoimmune disorder, an

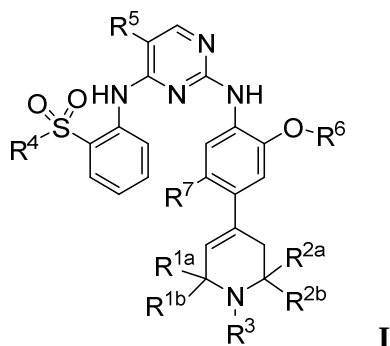
inflammatory condition, or a proliferative disorder. In yet another aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein for use in therapy. In yet another aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder. In yet another aspect, the present disclosure refers to the compound as disclosed herein for use in treating 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. In yet another aspect, the present disclosure refers to a kit comprising the compound as disclosed herein, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and instructions for administration of the compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, to a patient having cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder.

[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}, R^{1b}, R^{2a}, and R^{2b} are each C₁₋₃ alkyl;

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;

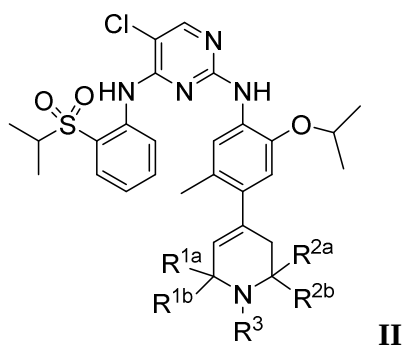
R⁵ is halo;

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}, R^{1b}, R^{2a}, and R^{2b} are each C₁₋₃ alkyl; and

R³ is selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, and C₄₋₈ heterocyclo.

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

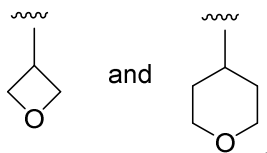
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is hydrogen.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is C₁₋₃ alkyl.

6. The compound of claim 5, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is methyl.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is C₃₋₆ heterocyclo.

8. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from the group consisting of:



9. A pharmaceutical composition comprising the compound of any one of claims 1-8, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier.

10. Use of a therapeutically effective amount of the compound of any one of claims 1-8, or a pharmaceutically acceptable salt, hydrate, or solvate thereof in the manufacture of a medicament for treating a patient having cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder.
11. The use of claim 10, wherein the patient has cancer.
12. The use of claim 11, 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.
13. The pharmaceutical composition of claim 9 for use in therapy.
14. The pharmaceutical composition of claim 13 for use in treating cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder.
15. The pharmaceutical composition of claim 14, 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.
16. A compound of any one of claims 1-8, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, for use in treatment of cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder.
17. The compound of claim 16 for use in treating cancer.

18. The compound of claim 17, 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.

19. A kit comprising the compound of any one of claims 1-8, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, and instructions for administration of the compound, or a pharmaceutically acceptable salt, hydrate, or solvate thereof, to a patient having cancer, a chronic autoimmune disorder, an inflammatory condition, or a proliferative disorder.

20. The kit of claim 19, wherein the patient has cancer; optionally 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.