

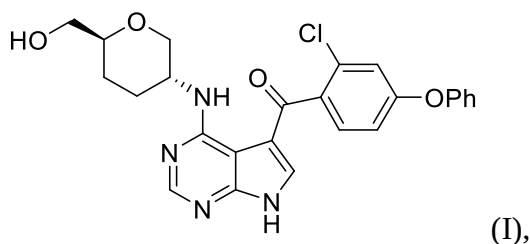
asthma (DiPaolo et. al., *Nature Chem. Biol.* **2011**, 7(1):41-50; Liu et. al., *Jour. Pharmacol. and Exp. Ther.* **2011**, 338(1):154-163).

[0004] Moreover, BTK's role in apoptosis demonstrates the utility of inhibition of BTK activity for the treatment of cancers, B-cell lymphoma, leukemia, and other hematological malignancies. In addition, given the role of BTK in osteoclast function, inhibition of BTK activity can be useful for the treatment of bone disorders such as osteoporosis.

[0005] Inhibition of BTK with small molecule inhibitors therefore has the potential to be a treatment for immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders, and neurological disorders. Thus, there remains a considerable need for potent small molecule inhibitors of BTK.

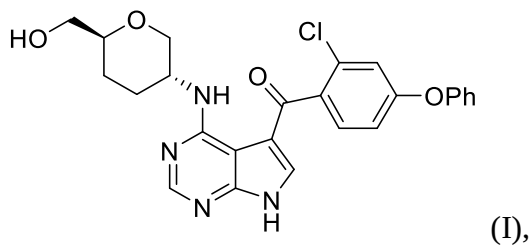
Summary

[0006] The application relates to a compound of Formula (I):



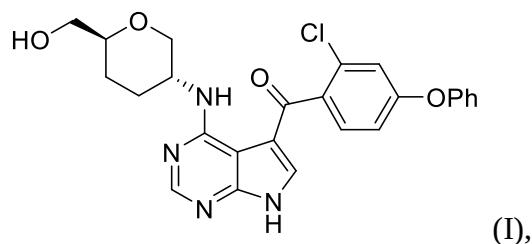
or pharmaceutically acceptable salts thereof, tautomers, prodrugs, solvates, metabolites, polymorphs, analogs or derivatives thereof. As used herein, the expressions “compound of Formula (I)” and “Compound (I),” refer to the same compound and can be used interchangeably.

[0006a] A first aspect of the application relates to a compound of Formula (I):



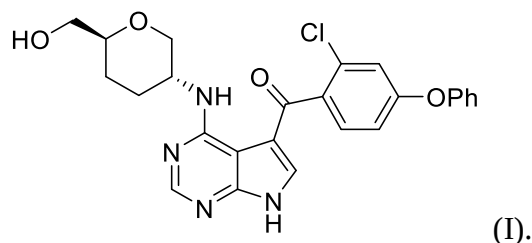
or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

[0006b] Another aspect of the application relates to a compound of Formula (I):



or a pharmaceutically acceptable salt thereof.

[0006c] Another aspect of the application relates to a compound of Formula (I):



[0007] The application also relates to a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier. Another aspect of the application relates to a pharmaceutical composition comprising a compound as defined herein or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein and a pharmaceutically acceptable diluent, excipient or carrier.

[0008] The application also relates to a method of treating a BTK-mediated disorder. The method comprises administering to a patient in need of a treatment for diseases or disorders associated with modulation of BTK kinase a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof.

[0009] The application also relates to a method of treating a BTK-mediated disorder. The method comprises administering to a patient in need of a treatment for diseases or disorders associated with modulation of BTK kinase a therapeutically effective amount of a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

[0010] The application also relates to a method of treating a cell proliferative disorder. The method comprises administering to a patient in need thereof a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof.

[0011] The application also relates to a method of treating a cell proliferative disorder. The method comprises administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

[0012] The application also relates to a method of treating cancer. The method comprises administering to a patient in need thereof a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof.

[0013] The application also relates to a method of treating cancer. The method comprises administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

[0014] The application also relates to a method of modulating (*e.g.*, inhibiting) BTK. The method comprises administering to a patient in need thereof a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof.

[0015] The application also relates to a method of modulating (*e.g.*, inhibiting) BTK. The method comprises administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising the compound of Formula (I)

or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier.

[0016] The application also relates to the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, for use in a method of treating a BTK-mediated disorder, a cell proliferative disorder, or cancer, or of modulating (*e.g.*, inhibiting) BTK. The compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof is administered in a therapeutically effective amount to a patient in need thereof.

[0017] The application also relates to a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier for use in a method of treating a BTK-mediated disorder, a cell proliferative disorder, or cancer, or of modulating (*e.g.*, inhibiting) BTK. The composition is administered in a therapeutically effective amount to a patient in need thereof. Another aspect of the application relates to a pharmaceutical composition for treating a BTK-mediated disorder in a patient, or for modulating BTK in a patient, the composition comprising a therapeutically effective amount of a compound as defined herein or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein.

[0018] The application also relates to the use of the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, in the manufacture of a medicament for treating a BTK-mediated disorder, a cell proliferative disorder, or cancer, or for modulating (*e.g.*, inhibiting) BTK. The compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof is administered in a therapeutically effective amount to a patient in need thereof.

[0019] The application also relates to the use of a pharmaceutical composition comprising the compound of Formula (I) or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof, and a pharmaceutically acceptable diluent, excipient or carrier in the manufacture of a medicament for

treating a BTK-mediated disorder, a cell proliferative disorder, or cancer, or for modulating (*e.g.*, inhibiting) BTK. The composition is administered in a therapeutically effective amount to a patient in need thereof

[0020] The present application further provides methods of treating a disease or disorder associated with modulation of BTK kinase including, but not limited to, immune disorders,

cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders, and neurological disorders comprising, administering to a patient suffering from at least one of said diseases or disorders the compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof.

[0021] The present application provides inhibitors of BTK that are therapeutic agents in the treatment of diseases such as immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders, neurological disorders and other disease associated with the modulation of BTK kinase.

[0021a] Another aspect of the application relates to use of a compound as defined herein or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein, or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating a BTK-mediated disorder selected from immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders.

[0022] The present application further provides compounds and compositions with an improved efficacy and safety profile relative to known BTK inhibitors. The present application also provides agents with novel mechanisms of action toward BTK kinase in the treatment of various types of diseases including immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders, and neurological disorders. Ultimately the present application provides the medical community with a novel pharmacological strategy for the treatment of diseases and disorders associated with BTK kinase.

[0022a] Another aspect of the application relates to use of a compound as defined herein or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein, or a pharmaceutical composition as defined herein in the manufacture of a medicament for treating a BTK-mediated disorder selected from rheumatoid arthritis, systemic and local inflammation, arthritis, inflammation related to immune suppression, organ transplant rejection, allergies, ulcerative colitis, Crohn's disease, dermatitis, asthma, systemic lupus erythematosus, Sjogren's Syndrome, multiple sclerosis, scleroderma/systemic sclerosis, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, chronic obstructive pulmonary disease (COPD), or psoriasis.

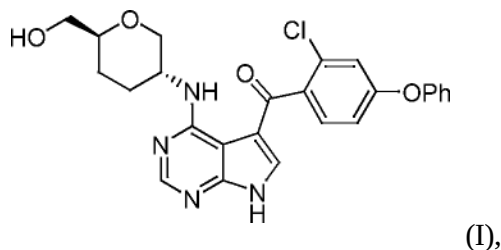
Detailed Description

[0023] The present application relates to a compound and compositions that are capable of modulating the activity Bruton's Tyrosine Kinase (BTK). The application features methods of treating, preventing or ameliorating a disease or disorder in which BTK plays a role by administering to a patient in need thereof a therapeutically effective amount of the compound of Formula (I), or a pharmaceutically acceptable salt, tautomer, prodrug, solvate, metabolite, polymorph, analog or derivative thereof. The methods of the present application can be used in the treatment of a variety of BTK-mediated diseases and disorders by inhibiting the activity of BTK kinase. Inhibition of BTK provides treatment, prevention, or amelioration of diseases including, but not limited to, immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders.

[0024] In a first aspect of the application, the compound of Formula (I) is described:

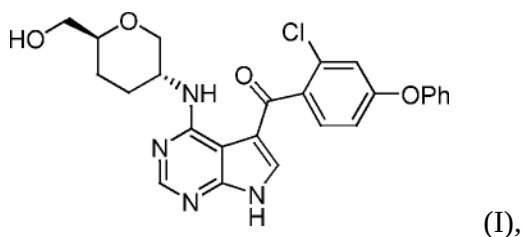
CLAIMS

1. A compound of Formula (I):



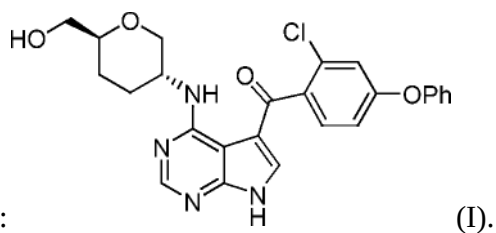
or a pharmaceutically acceptable salt, tautomer, or solvate thereof.

2. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof.

3. A compound of Formula (I):



4. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound of claim 2 or a pharmaceutically acceptable salt thereof, or a compound of claim 3, and a pharmaceutically acceptable diluent, excipient or carrier.
5. A pharmaceutical composition for treating a BTK-mediated disorder in a patient, or for modulating BTK in a patient, the composition comprising a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound of claim 2 or a pharmaceutically acceptable salt thereof, or a compound of claim 3.

6. The pharmaceutical composition of claim 5, wherein the BTK-mediated disorder is selected from immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders.
7. The pharmaceutical composition of claim 6, wherein the cancer is selected from a cancer of the breast, ovary, cervix, prostate, testis, esophagus, larynx, stomach, skin, lung, bone, pancreas, colon, thyroid, biliary passage, hairy cells, buccal cavity, naso-pharyngeal, lip, tongue, mouth, large intestine, small intestine, colon-rectum, rectum, brain and central nervous system, bronchus, liver, intrahepatic bile duct, urinary bladder, uterine corpus, kidney, renal pelvis, oral cavity, pharynx, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma, kidney carcinoma, myeloid disorders, lymphoma, Hodgkin's leukemia, hepatocellular cancer, glioma, endometrial cancer, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, chronic lymphoid leukemia (CLL), myeloid leukemia, non-Hodgkin lymphoma, and villous colon adenoma.
8. The pharmaceutical composition of claim 6, wherein the cancer is chronic lymphoid leukemia.
9. The pharmaceutical composition of claim 6, wherein the cancer is lymphoma.
10. The pharmaceutical composition of claim 9, wherein the lymphoma is non-Hodgkin lymphoma.
11. The pharmaceutical composition of claim 9, wherein the lymphoma is B-cell lymphoma.
12. The pharmaceutical composition of claim 11, wherein the B-cell lymphoma is B-cell non-Hodgkin lymphoma.
13. The pharmaceutical composition of claim 9, wherein the lymphoma is anaplastic large cell lymphoma.
14. The pharmaceutical composition of claim 9, wherein the lymphoma is central nervous system (CNS) lymphoma.

15. The pharmaceutical composition of claim 14, wherein the CNS lymphoma is primary CNS lymphoma.
16. The pharmaceutical composition of claim 9, wherein the lymphoma is Waldenstrom macroglobulinemia.
17. The pharmaceutical composition of claim 6, wherein the cancer is myeloid disorders.
18. The pharmaceutical composition of claim 6, wherein the cancer is myeloid leukemia.
19. The pharmaceutical composition of claim 6, wherein the cancer is acute myelogenous leukemia.
20. The pharmaceutical composition of claim 6, wherein the cancer is multiple myeloma.
21. The pharmaceutical composition of claim 6, wherein the cancer is lymphocytic leukemia.
22. The pharmaceutical composition of claim 6, wherein the cancer is sarcoma.
23. The pharmaceutical composition of claim 6, wherein the cancer is brain tumor.
24. The pharmaceutical composition of claim 5, wherein the BTK-mediated disorder is rheumatoid arthritis, systemic and local inflammation, arthritis, inflammation related to immune suppression, organ transplant rejection, allergies, ulcerative colitis, Crohn's disease, dermatitis, asthma, systemic lupus erythematosus, Sjogren's Syndrome, multiple sclerosis, scleroderma/systemic sclerosis, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, chronic obstructive pulmonary disease (COPD), or psoriasis.

25. Use of a compound of claim 1 or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound of claim 2 or a pharmaceutically acceptable salt thereof, or a compound of claim 3, or a pharmaceutical composition of claim 4 in the manufacture of a medicament for treating a BTK-mediated disorder selected from immune disorders, cancer, cardiovascular diseases, viral infections, inflammation, metabolism/endocrine function disorders and neurological disorders.

26. The use of claim 25, wherein the cancer is selected from a cancer of the breast, ovary, cervix, prostate, testis, esophagus, larynx, stomach, skin, lung, bone, pancreas, colon, thyroid, biliary passage, hairy cells, buccal cavity, naso-pharyngeal, lip, tongue, mouth, large intestine, small intestine, colon-rectum, rectum, brain and central nervous system, bronchus, liver, intrahepatic bile duct, urinary bladder, uterine corpus, kidney, renal pelvis, oral cavity, pharynx, glioblastoma, neuroblastoma, keratoacanthoma, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung adenocarcinoma, adenoma, adenocarcinoma, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma, kidney carcinoma, myeloid disorders, lymphoma, Hodgkin's leukemia, hepatocellular cancer, glioma, endometrial cancer, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, chronic lymphoid leukemia (CLL), myeloid leukemia, non-Hodgkin lymphoma, and villous colon adenoma.

27. The use of claim 25, wherein the cancer is chronic lymphoid leukemia.

28. The use of claim 25, wherein the cancer is lymphoma.

29. The use of claim 28, wherein the lymphoma is non-Hodgkin lymphoma.

30. The use of claim 28, wherein the lymphoma is B-cell lymphoma.

31. The use of claim 30, wherein the B-cell lymphoma is B-cell non-Hodgkin lymphoma.

32. The use of claim 28, wherein the lymphoma is anaplastic large cell lymphoma.

33. The use of claim 28, wherein the lymphoma is central nervous system (CNS) lymphoma.

34. The use of claim 33, wherein the CNS lymphoma is primary CNS lymphoma.

35. The use of claim 28, wherein the lymphoma is Waldenstrom macroglobulinemia.

- 36. The use of claim 25, wherein the cancer is myeloid disorders.
- 37. The use of claim 25, wherein the cancer is myeloid leukemia.
- 38. The use of claim 25, wherein the cancer is acute myelogenous leukemia.
- 39. The use of claim 25, wherein the cancer is multiple myeloma.
- 40. The use of claim 25, wherein the cancer is lymphocytic leukemia.
- 41. The use of claim 25, wherein the cancer is sarcoma.
- 42. The use of claim 25, wherein the cancer is brain tumor.
- 43. Use of a compound of claim 1 or a pharmaceutically acceptable salt, tautomer, or solvate thereof, or a compound of claim 2 or a pharmaceutically acceptable salt thereof, or a compound of claim 3, or a pharmaceutical composition of claim 4 in the manufacture of a medicament for treating a BTK-mediated disorder selected from rheumatoid arthritis, systemic and local inflammation, arthritis, inflammation related to immune suppression, organ transplant rejection, allergies, ulcerative colitis, Crohn's disease, dermatitis, asthma, systemic lupus erythematosus, Sjogren's Syndrome, multiple sclerosis, scleroderma/systemic sclerosis, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, chronic obstructive pulmonary disease (COPD), or psoriasis.