

INHIBITORS OF BRUTON'S TYROSINE KINASE

RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Application No. 60/826,720 entitled "INHIBITORS OF BRUTON'S TYROSINE KINASE" filed September 22, 2006; and U.S. Provisional Application No. 60/828,590
5 entitled "INHIBITORS OF BRUTON'S TYROSINE KINASE" filed October 6, 2006, both of which are herein incorporated by reference.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments containing such compounds, and methods of using such compounds and compositions to inhibit
10 the activity of tyrosine kinases.

BACKGROUND OF THE INVENTION

[0003] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to
15 downstream intracellular responses.

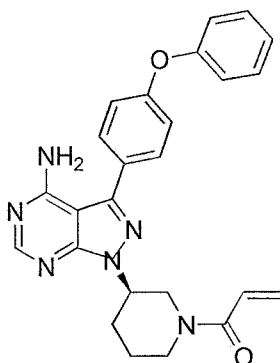
[0004] Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, *Curr Op Imm*, 2000, 276-281; Schaeffer and Schwartzberg, *Curr Op Imm* 2000, 282-288). In addition, Btk plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF- α production in macrophages, IgE receptor (Fc ϵ silonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic
20 signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. See, e.g., C. A. Jeffries, et al., (2003), *Journal of Biological Chemistry* 278:26258-26264; N. J. Horwood, et al., (2003), *The Journal of Experimental Medicine* 197:1603-1611; Iwaki et al. (2005), *Journal of Biological Chemistry* 280(48):40261-40270; Vassilev et al. (1999), *Journal of Biological Chemistry* 274(3):1646-1656, and Quek et al. (1998), *Current Biology* 8(20):1137-1140.

SUMMARY

[0005] Described herein are inhibitors of Bruton's tyrosine kinase (Btk). Also described herein are irreversible inhibitors of Btk. Further described are irreversible inhibitors of Btk that form a covalent bond with a cysteine residue on Btk. Further described herein are irreversible inhibitors of other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a
30 covalent bond with the irreversible inhibitor (such tyrosine kinases, are referred herein as "Btk tyrosine kinase cysteine homologs"). Also described herein are methods for synthesizing such irreversible inhibitors, methods for using such irreversible inhibitors in the treatment of diseases (including diseases wherein irreversible inhibition of Btk provides therapeutic benefit to a patient having the disease). Further described are pharmaceutical formulations that include an irreversible inhibitor of Btk.

[0005a]

In one aspect, provided herein is a compound having the structure:



or a pharmaceutically acceptable salt thereof.

[0005b]

In another aspect, provided herein is a pharmaceutical composition comprising a therapeutically effective amount of the compound as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0005c]

In another aspect, provided herein is use of the compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament of a B-cell proliferative disorder.

[0005d]

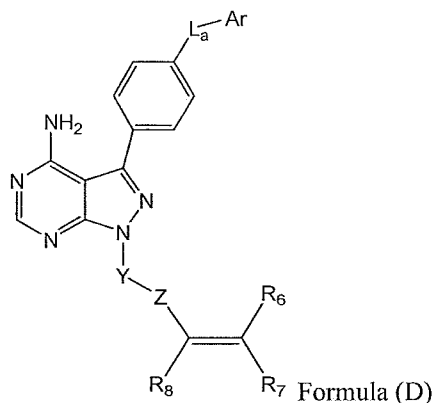
In another aspect, provided herein is a compound as described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein for use in the treatment of a B-cell proliferative disorder.

[0006]

Compounds described herein include those that have a structure of any of Formula (A), Formula (B), Formula (C), or Formula (D), and pharmaceutically acceptable salts, solvates, esters, acids and prodrugs thereof. In certain examples, isomers and chemically protected forms of compounds having a structure represented by any of Formula (A), Formula (B), Formula (C), or Formula (D), are also provided.

[0007]

Provided herein is a compound of Formula (D). Formula (D) is as follows:



wherein:

L_a is CH_2 , O, NH or S;

Ar is a substituted or unsubstituted aryl, or a substituted or unsubstituted heteroaryl;

5 Y is an optionally substituted group selected from among alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl;

Z is $C(=O)$, $OC(=O)$, $NHC(=O)$, $C(=S)$, $S(=O)_x$, $OS(=O)_x$, $NHS(=O)_x$, where x is 1 or 2;

10 R_7 and R_8 are independently selected from among H, unsubstituted C_1 - C_4 alkyl, substituted C_1 - C_4 alkyl, unsubstituted C_1 - C_4 heteroalkyl, substituted C_1 - C_4 heteroalkyl, unsubstituted C_3 - C_6 cycloalkyl, substituted C_3 - C_6 cycloalkyl, unsubstituted C_2 - C_6 heterocycloalkyl, and substituted C_2 - C_6 heterocycloalkyl; or

R_7 and R_8 taken together form a bond;

15 R_6 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, C_1 - C_6 alkoxyalkyl, C_1 - C_8 alkylaminoalkyl, substituted or unsubstituted C_3 - C_6 cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2 - C_8 heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1 - C_4 alkyl(aryl), C_1 - C_4 alkyl(heteroaryl), C_1 - C_4 alkyl(C_3 - C_8 cycloalkyl), or C_1 - C_4 alkyl(C_2 - C_8 heterocycloalkyl); and

pharmaceutically active metabolites, or pharmaceutically acceptable solvates, pharmaceutically acceptable salts, or pharmaceutically acceptable prodrugs thereof.

20 **[0008]** For any and all of the examples, substituents can be selected from among from a subset of the listed alternatives. For example, in some examples, L_a is CH_2 , O, or NH. In other examples, L_a is O or NH. In yet other examples, L_a is O.

[0009] In some examples, Ar is a substituted or unsubstituted aryl. In yet other examples, Ar is a 6-membered aryl. In some other examples, Ar is phenyl.

25 **[0010]** In some examples, x is 2. In yet other examples, Z is $C(=O)$, $OC(=O)$, $NHC(=O)$, $S(=O)_x$, $OS(=O)_x$, or $NHS(=O)_x$. In some other examples, Z is $C(=O)$, $NHC(=O)$, or $S(=O)_2$.

[0011] In some examples, R_7 and R_8 are independently selected from among H, unsubstituted C_1 - C_4 alkyl, substituted C_1 - C_4 alkyl, unsubstituted C_1 - C_4 heteroalkyl, and substituted C_1 - C_4 heteroalkyl; or R_7 and R_8 taken together form a bond. In yet other examples, each of R_7 and R_8 is H; or R_7 and R_8 taken together form a bond.

30 **[0012]** In some examples, R_6 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or unsubstituted C_1 - C_4 heteroalkyl, C_1 - C_6 alkoxyalkyl, C_1 - C_8 alkylaminoalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, C_1 - C_4 alkyl(aryl), C_1 - C_4 alkyl(heteroaryl), C_1 - C_4 alkyl(C_3 - C_8 cycloalkyl), or C_1 - C_4 alkyl(C_2 - C_8 heterocycloalkyl). In some other examples, R_6 is H, substituted or unsubstituted C_1 - C_4 alkyl, substituted or

unsubstituted C₁-C₄heteroalkyl, C₁-C₆alkoxyalkyl, C₁-C₂alkyl-N(C₁-C₃alkyl)₂, C₁-C₄alkyl(aryl), C₁-C₄alkyl(heteroaryl), C₁-C₄alkyl(C₃-C₈cycloalkyl), or C₁-C₄alkyl(C₂-C₈heterocycloalkyl). In yet other examples, R₆ is H, substituted or unsubstituted C₁-C₄alkyl, -CH₂-O-(C₁-C₃alkyl), -CH₂-N(C₁-C₃alkyl)₂, C₁-C₄alkyl(phenyl), or C₁-C₄alkyl(5- or 6-membered heteroaryl). In yet other examples, R₆ is H, substituted or unsubstituted C₁-C₄alkyl, -CH₂-O-(C₁-C₃alkyl), -CH₂-N(C₁-C₃alkyl)₂, C₁-C₄alkyl(phenyl), or C₁-C₄alkyl(5- or 6-membered heteroaryl containing 1 or 2 N atoms), or C₁-C₄alkyl(5- or 6-membered heterocycloalkyl containing 1 or 2 N atoms).

[0013] In some examples, Y is an optionally substituted group selected from among alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl. In other examples, Y is an optionally substituted group selected from among C₁-C₆alkyl, C₁-C₆heteroalkyl, 4-, 5-, 6-, or 7-membered cycloalkyl, and 4-, 5-, 6-, or 7-membered heterocycloalkyl. In yet other examples, Y is an optionally substituted group selected from among C₁-C₆alkyl, C₁-C₆heteroalkyl, 5- or 6-membered cycloalkyl, and 5- or 6-membered heterocycloalkyl containing 1 or 2 N atoms. In some other examples, Y is a 5- or 6-membered cycloalkyl, or a 5- or 6-membered heterocycloalkyl containing 1 or 2 N atoms. In some examples, Y is a 4-, 5-, 6-, or 7-membered cycloalkyl ring; or Y is a 4-, 5-, 6-, or 7-membered heterocycloalkyl ring.

[0014] Any combination of the groups described above for the various variables is contemplated herein. It is understood that substituents and substitution patterns on the compounds provided herein can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be synthesized by techniques known in the art, as well as those set forth herein.

[0015] Provided herein is a compound selected from among:

1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound 4); (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)but-2-en-1-one (Compound 5); 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)sulfonylethene (Compound 6); 1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-yn-1-one (Compound 8); 1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound 9); N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)acrylamide (Compound 10); 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound 11); 1-((S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)prop-2-en-1-one (Compound 12); 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound 13); 1-((S)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound 14); and (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one (Compound 15).

[0016] Provided herein are pharmaceutical compositions, which include a therapeutically effective amount of at least one of any of the compounds herein, or a pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate. In certain examples, compositions provided herein further include a pharmaceutically acceptable diluent, excipient and/or binder.

[0017] Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically effective derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more

symptoms of diseases, disorders or conditions that are modulated or otherwise affected by tyrosine kinase activity, or in which tyrosine kinase activity is implicated, are provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases, disorders or conditions disclosed herein.

[0018] In certain examples, provided herein is a pharmaceutical composition containing: i) a physiologically acceptable carrier, diluent, and/or excipient; and ii) one or more compounds provided herein.

[0019] Provided herein are methods for treating a patient by administering a compound provided herein. In some examples, provided herein is a method of inhibiting the activity of tyrosine kinase(s), such as Btk, or of treating a disease, disorder, or condition, which would benefit from inhibition of tyrosine kinase(s), such as Btk, in a patient, which includes administering to the patient a therapeutically effective amount of at least one of any of the compounds herein, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate.

[0020] Provided herein is the use of a compound disclosed herein for inhibiting Bruton's tyrosine kinase (Btk) activity or for the treatment of a disease, disorder, or condition, which would benefit from inhibition of Bruton's tyrosine kinase (Btk) activity.

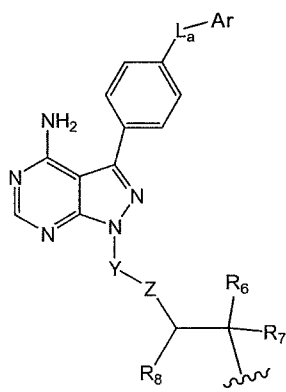
[0021] In some examples, compounds provided herein are administered to a human.

[0022] In some examples, compounds provided herein are orally administered.

[0023] In other examples, compounds provided herein are used for the formulation of a medicament for the inhibition of tyrosine kinase activity. In some other examples, compounds provided herein are used for the formulation of a medicament for the inhibition of Bruton's tyrosine kinase (Btk) activity.

[0024] Articles of manufacture including packaging material, a compound or composition or pharmaceutically acceptable derivative thereof provided herein, which is effective for inhibiting the activity of tyrosine kinase(s), such as Btk, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable salt, pharmaceutically active metabolite, pharmaceutically acceptable prodrug, or pharmaceutically acceptable solvate thereof, is used for inhibiting the activity of tyrosine kinase(s), such as Btk, are provided.

[0025] Provided herein are inhibited tyrosine kinases comprising a Bruton's tyrosine kinase, a Bruton's tyrosine kinase homolog, or a Btk tyrosine kinase cysteine homolog thereof covalently bound to an inhibitor having the structure:



, wherein  indicates the point of attachment between the inhibitor and the tyrosine kinase. In a further example, the inhibitor is covalently bound to a cysteine residue on the tyrosine kinase.

[0026] Provided herein is a method for inhibiting Bruton's tyrosine kinase in a subject in need thereof by administering to the subject thereof a composition containing a therapeutically effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). In some

examples, the subject in need is suffering from an autoimmune disease, e.g., inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome,

5 ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, or vulvodynia.

10 **[0027]** In other examples, the subject in need is suffering from a heteroimmune condition or disease, e.g., graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, or atopic dermatitis.

[0028] In certain examples, the subject in need is suffering from an inflammatory disease, e.g., asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis,

15 cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis,

20 or vulvitis.

[0029] In further examples, the subject in need is suffering from a cancer. In one example, the cancer is a B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström

25 macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In some examples, where the subject is suffering from a cancer, an anti-cancer agent is administered to the subject in addition to one of the above-mentioned compounds. In one example, the anti-cancer agent is an inhibitor of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901,

30 ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002.

[0030] In further examples, the subject in need is suffering from a thromboembolic disorder, e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, or deep venous thrombosis.

35 **[0031]** Provided herein is a method for treating an autoimmune disease by administering to a subject in need thereof a composition containing a therapeutically effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). In one example, the autoimmune disease is arthritis. In another example, the autoimmune disease is lupus. In some examples, the autoimmune disease is inflammatory bowel disease (including Crohn's disease and ulcerative colitis), rheumatoid arthritis, psoriatic arthritis,

40 osteoarthritis, Still's disease, juvenile arthritis, lupus, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease Sjögren's syndrome, multiple sclerosis, Guillain-Barré

syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylitis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, coeliac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, or vulvodynia.

[0032] Provided herein is a method for treating a heteroimmune condition or disease by administering to a subject in need thereof a composition containing a therapeutically effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). In some examples, the heteroimmune condition or disease is graft versus host disease, transplantation, transfusion, anaphylaxis, allergy, type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, or atopic dermatitis.

[0033] Provided herein is a method for treating an inflammatory disease by administering to a subject in need thereof a composition containing a therapeutically effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). In some examples, the inflammatory disease is asthma, inflammatory bowel disease (including Crohn's disease and ulcerative colitis), appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis.

[0034] Provided herein is a method for treating a cancer by administering to a subject in need thereof a composition containing a therapeutically effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). In one example, the cancer is a B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In some examples, where the subject is suffering from a cancer, an anti-cancer agent is administered to the subject in addition to one of the above-mentioned compounds. In one example, the anti-cancer agent is an inhibitor of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002.

[0035] Provided herein is a method for treating a thromboembolic disorder by administering to a subject in need thereof a composition containing a therapeutically effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). In some examples, the thromboembolic disorder is myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, or deep venous thrombosis.

[0036] Provided herein is a method for treating an autoimmune disease by administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with Bruton's tyrosine kinase. In one example, the compound forms a covalent bound with the activated form of Bruton's tyrosine kinase. In further or alternative examples, the compound irreversibly inhibits the Bruton's tyrosine kinase to which it is covalently bound. In a further or alternative example, the compound forms a covalent bond with a cysteine residue on Bruton's tyrosine kinase.

[0037] Provided herein is a method for treating a heteroimmune condition or disease by administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with Bruton's tyrosine kinase. In one example, the compound forms a covalent bound with the activated form of Bruton's tyrosine kinase. In further or alternative examples, the compound irreversibly inhibits the Bruton's tyrosine kinase to which it is covalently bound. In a further or alternative example, the compound forms a covalent bond with a cysteine residue on Bruton's tyrosine kinase.

[0038] Provided herein is a method for treating an inflammatory disease by administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with Bruton's tyrosine kinase. In one example, the compound forms a covalent bound with the activated form of Bruton's tyrosine kinase. In further or alternative examples, the compound irreversibly inhibits the Bruton's tyrosine kinase to which it is covalently bound. In a further or alternative example, the compound forms a covalent bond with a cysteine residue on Bruton's tyrosine kinase. Provided herein is a method for treating a cancer by administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with Bruton's tyrosine kinase. In one example, the compound forms a covalent bound with the activated form of Bruton's tyrosine kinase. In further or alternative examples, the compound irreversibly inhibits the Bruton's tyrosine kinase to which it is covalently bound. In a further or alternative example, the compound forms a covalent bond with a cysteine residue on Bruton's tyrosine kinase. Provided herein is a method for treating a thromboembolic disorder by administering to a subject in need thereof a composition containing a therapeutically effective amount of a compound that forms a covalent bond with Bruton's tyrosine kinase. In one example, the compound forms a covalent bound with the activated form of Bruton's tyrosine kinase. In further or alternative examples, the compound irreversibly inhibits the Bruton's tyrosine kinase to which it is covalently bound. In a further or alternative example, the compound forms a covalent bond with a cysteine residue on Bruton's tyrosine kinase.

[0039] Provided herein are methods for modulating, including irreversibly inhibiting the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with at least one irreversible inhibitor described herein, in a mammal comprising administering to the mammal at least once an effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). Provided herein are methods for modulating, including including irreversibly inhibiting, the activity of Btk in a mammal comprising administering to the mammal at least once an effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D). Provided herein are methods for treating Btk-dependent or Btk mediated conditions or diseases, comprising administering to the mammal at least once an effective amount of at least one compound having the structure of any of Formula (A), Formula (B), Formula (C), or Formula (D).

[0040] Provided herein are methods for treating inflammation comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (A), (B), (C), or (D).

[0041] Provided herein are methods for the treatment of cancer comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (A), (B), (C), or (D). The type of cancer may include, but is not limited to, pancreatic cancer and other solid or hematological tumors.

[0042] Provided herein are methods for treating respiratory diseases comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (A), (B), (C), or (D). In a further example, the respiratory disease is asthma. In a further example, the respiratory disease includes, but is not limited to, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma,

[0043] Provided herein are methods for preventing rheumatoid arthritis and osteoarthritis comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (A), (B), (C), or (D).

[0044] Provided herein are methods for treating inflammatory responses of the skin comprising administering to the mammal at least once an effective amount of at least one compound having the structure of Formula (A), (B), (C), or (D). Such inflammatory responses of the skin include, by way of example, dermatitis, contact dermatitis, eczema, urticaria, rosacea, and scarring. Provided herein are methods for reducing psoriatic lesions in the skin, joints, or other tissues or organs, comprising administering to the mammal an effective amount of a first compound having the structure of Formula (A), (B), (C), or (D).

[0045] Provided herein is the use of a compound of Formula (A), (B), (C), or (D) in the manufacture of a medicament for treating an inflammatory disease or condition in an animal in which the activity of Btk or other tyrosine kinases, wherein the other tyrosine kinases share homology with Btk by having a cysteine residue (including a Cys 481 residue) that can form a covalent bond with at least one irreversible inhibitor described herein, contributes to the pathology and/or symptoms of the disease or condition. In one example, the tyrosine kinase protein is Btk. In another or further example, the inflammatory disease or conditions are respiratory, cardiovascular, or proliferative diseases.

[0046] Provided herein are further examples in which administration is enteral, parenteral, or both, and wherein (a) the effective amount of the compound is systemically administered to the mammal; (b) the effective amount of the compound is administered orally to the mammal; (c) the effective amount of the compound is intravenously administered to the mammal; (d) the effective amount of the compound administered by inhalation; (e) the effective amount of the compound is administered by nasal administration; or (f) the effective amount of the compound is administered by injection to the mammal; (g) the effective amount of the compound is administered topically (dermal) to the mammal; (h) the effective amount of the compound is administered by ophthalmic administration; or (i) the effective amount of the compound is administered rectally to the mammal.

[0047] Provided herein are further examples comprising single administrations of the effective amount of the compound, including further examples in which (i) the compound is administered once; (ii) the compound is administered to the mammal multiple times over the span of one day; (iii) continually; or (iv) continuously.

[0048] Provided herein are further examples comprising multiple administrations of the effective amount of the compound, including further examples in which (i) the compound is administered in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered

to the mammal every 8 hours. In further or alternative examples, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. The length of the drug holiday can vary from 2 days to 1 year.

5 [0049] Provided herein involving the treatment of proliferative disorders, including cancer, are further examples comprising administering at least one additional agent selected from the group consisting of alemtuzumab, arsenic trioxide, asparaginase (pegylated or non-), bevacizumab, cetuximab, platinum-based compounds such as cisplatin, cladribine, daunorubicin/doxorubicin/idarubicin, irinotecan, fludarabine, 5-fluorouracil, gemtuzumab, methotrexate, Paclitaxel™, taxol, temozolomide, thioguanine, or classes of drugs including hormones (an
10 antiestrogen, an antiandrogen, or gonadotropin releasing hormone analogues, interferons such as alpha interferon, nitrogen mustards such as busulfan or melphalan or mechlorethamine, retinoids such as tretinoin, topoisomerase inhibitors such as irinotecan or topotecan, tyrosine kinase inhibitors such as gefinitinib or imatinib, or agents to treat signs or symptoms induced by such therapy including allopurinol, filgrastim, granisetron/ondansetron/palonosetron, dronabinol.

15 [0050] Provided herein involving the prevention or treatment of Btk-dependent or tyrosine kinase mediated diseases or conditions are further examples comprising identifying patients by screening for a tyrosine kinase gene haplotype. In further or alternative examples the tyrosine kinase gene haplotype is a tyrosine kinase pathway gene, while in still further or alternative examples, the tyrosine kinase gene haplotype is a Btk haplotype.

[0051] In a further or alternative example, the compound of formula (A), (B), (C) or (D) are irreversible
20 inhibitors of Bruton's tyrosine kinase (Btk), while in still further or alternative examples, such irreversible inhibitors are selective for Btk. In even further or alternative examples, such inhibitors have an IC₅₀ below 10 microM in enzyme assay. In one example, a Btk irreversible inhibitor has an IC₅₀ of less than 1 microM, and in another example, less than 0.25 microM.

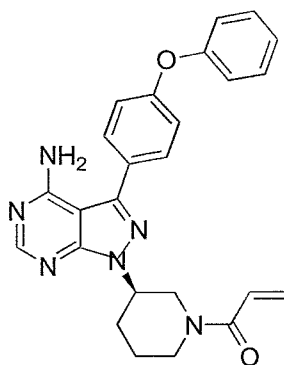
[0052] In further or alternative example, the compound of formula ((A), (B), (C) or (D) are selective
25 irreversible inhibitors for Btk over Itk. In further or alternative example, the compound of formula (A), (B), (C) or (D) are selective irreversible inhibitors for Btk over Lck. In further or alternative example, the compound of formula (A), (B), (C) or (D) are selective irreversible inhibitors for Btk over ABL. In further or alternative example, the compound of formula (A), (B), (C) or (D) are selective irreversible inhibitors for Btk over CMET. In further or alternative example, the compound of formula (A), (B), (C) or (D) are selective irreversible inhibitors for Btk over
30 EGFR. In further or alternative example, the compound of formula (A), (B), (C) or (D) are selective irreversible inhibitors for Btk over Lyn.

[0053] In further or alternative examples, the irreversible Btk inhibitors are also inhibitors of EGFR.

[0054] Other objects, features and advantages of the methods and compositions described herein will
35 become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the present disclosure will become apparent to those skilled in the art from this detailed description. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books,
40 manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

WHAT IS CLAIMED IS:

1. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

- 5 2. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1,
or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
3. Use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a
medicament of a B-cell proliferative disorder.
4. The use of claim 3, wherein the B-cell proliferative disorder is selected from lymphoma, myeloma, or
10 leukemia.
5. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutical
composition of claim 2 for use in the treatment of a B-cell proliferative disorder.
6. The compound or pharmaceutical composition for use of claim 5, wherein the B-cell proliferative disorder
is selected from lymphoma, myeloma or leukemia.