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 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 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 downstream intracellular responses.

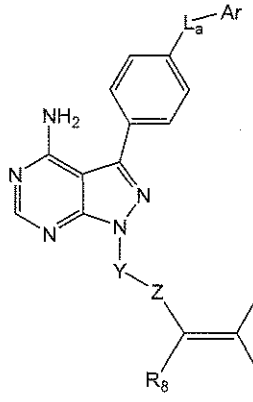
[0004] Btk is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, *Curr Op Imm*, **2000**, 276-281; Schaeffer and Schwartzberg, *Curr Op Imm* **2000**, 282-288). In addition, Btk plays a role in a number of other hematopoetic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor–mediated TNF-α production in macrophages, IgE receptor (FcepsilonRI) signaling in Mast cells, inhibition of Fas/APO-1 apoptotic 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 OF THE ~~INVENTION~~DISCLOSURE

[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 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.

[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 embodiments, 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.

[0006a] In one aspect, there is provided a compound of Formula (D) having the structure:



Formula (D)

wherein:

L_a is CH_2, O, NH or S;

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

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

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

R is H or C_1-C_6alkyl; and

R_7 and R_8 are independently selected from among H, unsubstituted C_1-C_4 alkyl, substituted C_1-C_4alkyl, unsubstituted C_1-C_4heteroalkyl, substituted C_1-C_4heteroalkyl, unsubstituted C_3-C_6cycloalkyl, substituted C_3-C_6cycloalkyl, unsubstituted C_2-C_6heterocycloalkyl, and substituted C_2-C_6heterocycloalkyl; and

R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_4alkyl(C_3-C_8cycloalkyl), or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

wherein R_6, R_7, and R_8 are not all H;

or pharmaceutically acceptable salts thereof.

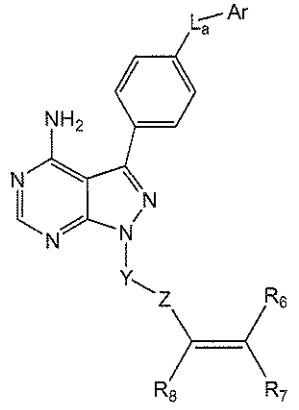
[0007] In one aspect, provided herein is a compound of Formula (D). Formula (D) is as follows:

symptoms of dieases, 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 embodiments, provided herein is a pharmaceutical composition containing: i) a physiologically acceptable carrier, diluent, and/or excipient; and ii) one or more compounds provided herein.

[0018a] In one aspect, there is provided a compound selected from among: (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; (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-methoxybut-2-en-1-one; (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)but-2-en-1-one; (E)-N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide; (E)-N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)-4-methoxybut-2-enamide; (E)-N-((1s,4s)-4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl)but-2-enamide; (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-(dimethylamino)but-2-en-1-one; (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)-4-methoxybut-2-en-1-one; (E)-1-(3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyrrolidin-1-yl)but-2-en-1-one; (E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-(dimethylamino)but-2-en-1-one; (E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)-4-methoxybut-2-en-1-one; (E)-1-(4-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)but-2-en-1-one; (E)-N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(dimethylamino)but-2-enamide; (E)-N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-(dimethylamino)-N-methylbut-2-enamide; (E)-N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-methoxybut-2-enamide; (E)-N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-methoxy-N-methylbut-2-enamide; (E)-N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-4-methoxy-N-methylbut-2-enamide; and (E)-N-(2-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)ethyl)-N-methylbut-2-enamide.

[0018b] In one aspect, there is provided a composition for the treatment of an autoimmune disease, wherein the compound has the following the structure:



Formula (D)

wherein:

L_a is CH_2, O, NH or S;

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

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

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

R is H or C_1-C_6alkyl; and

R_7 and R_8 are independently selected from among H, unsubstituted C_1-C_4 alkyl, substituted C_1-C_4alkyl, unsubstituted C_1-C_4heteroalkyl, substituted C_1-C_4heteroalkyl, unsubstituted C_3-C_6cycloalkyl, substituted C_3-C_6cycloalkyl, unsubstituted C_2-C_6heterocycloalkyl, and substituted C_2-C_6heterocycloalkyl; and

R_6 is H, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_4heteroalkyl, C_1-C_6alkoxyalkyl, C_1-C_8alkylaminoalkyl, substituted or unsubstituted C_3-C_6cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted C_2-C_8heterocycloalkyl, substituted or unsubstituted heteroaryl, C_1-C_4alkyl(aryl), C_1-C_4alkyl(heteroaryl), C_1-C_4alkyl(C_3-C_8cycloalkyl), or C_1-C_4alkyl(C_2-C_8heterocycloalkyl);

wherein R_6, R_7, and R_8 are not all H;

or pharmaceutically acceptable salts thereof.

[0019] In one aspect, provided herein are methods for treating a patient by administering a compound provided herein. In some embodiments, provided herein is a method of inhibiting the activity of tyrsoine 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] In another aspect, 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.

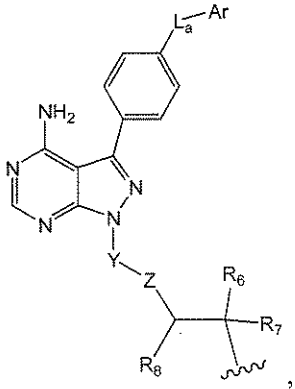
[0021] In some embodiments, compounds provided herein are administered to a human.

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

[0023] In other embodiments, compounds provided herein are used for the formulation of a medicament for the inhibition of tyrosine kinase activity. In some other embodiments, 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] In another aspect 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 embodiment, the inibitor is covalently bound to a cysteine residue on the tyrosine kinase.

[0026] In a further aspect, 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