INHIBITORS OF BRUTON'S TYROSINE KINASE

RELATED APPLICATIONS

This application is a continuation application of U.S. application Ser. No. 13/249,066 entitled "INHIBITORS OF BRUTONS TYROSINE KINASE" filed Sep. 29, 2011; which is a continuation of U.S. application Ser. No. 12/356,498 entitled "INHIBITORS OF BRUTONS TYROSINE KINASE" filed Jan. 20, 2009; now U.S. Pat. No. 8,088,781 which is a divisional application of U.S. application Ser. No. 11/617,645, now U.S. Pat. No. 7,514,444 entitled "INHIBITORS OF BRUTONS TYROSINE KINASE" filed Dec. 28, 2006; which claims benefit of U.S. Provisional Application No. 60/826,720 entitled "INHIBITORS OF BRUTON'S TYROSINE KINASE" filed Sep. 22, 2006; and U.S. Provisional Application No. 60/828,590 entitled "INHIBITORS OF BRUTON'S TYROSINE KINASE" filed Oct. 6, 2006, all of which are herein incorporated by reference.

FIELD OF THE INVENTION

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

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.

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.

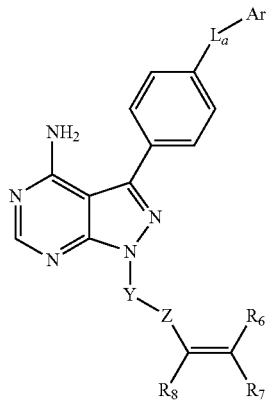
SUMMARY OF THE INVENTION

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.

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.

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

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

R_7 and R_8 are independently selected from among H, unsubstituted C_1-C_4alkyl, 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; or

R_7 and R_8 taken together form a bond;

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); and

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

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