# INHIBITORS OF BRUTON'S TYROSINE KINASE

## RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 13/542,440, filed Jul. 5, 2012; which is a continuation of U.S. application Ser. No. 13/479,053, filed May 23, 2012; which is a continuation of U.S. application Ser. No. 13/472,292, filed May 15, 2012; which is a continuation of U.S. application Ser. No. 13/450,158, filed Apr. 18, 2012; which is a continuation of U.S. application Ser. No. 13/361,733, filed Jan. 30, 2012, now U.S. Pat. No. 8,399,470, issued Mar. 19, 2013; which is a continuation of U.S. application Ser. No. 13/340,409, filed Dec. 29, 2011; which is a continuation of U.S. application Ser. No. 13/335,719, filed Dec. 22, 2011; which is a continuation of U.S. application Ser. No. 13/328,718, filed Dec. 16, 2011, now U.S. Pat. No. 8,476,284, issued Jul. 2, 2013; which is a continuation of U.S. application Ser. No. 13/312,606, filed Dec. 6, 2011, now U.S. Pat. No. 8,497,277, issued Jul. 30, 2013; which is a continuation of U.S. application Ser. No. 13/249,066, filed Sep. 29, 2011; which is a continuation of U.S. application Ser. No. 12/356,498, filed Jan. 20, 2009, now U.S. Pat. No. 8,088,781, issued Jan. 3, 2012; which is a divisional of U.S. application Ser. No. 11/617,645, filed Dec. 28, 2006, now U.S. Pat. No. 7,514,444, issued Apr. 7, 2009; which claims benefit of U.S. Provisional Application No. 60/826,720, filed Sep. 22, 2006; and U.S. Provisional Application No. 60/828,590, filed Oct. 6, 2006, all of which are entitled "INHIBITORS OF BRUTON'S TYROSINE KINASE" and herein incorporated by reference.

## SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Apr. 8, 2014, is named 25922-750-320SEQ2.txt and is 3,227 bytes in size.

## 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.



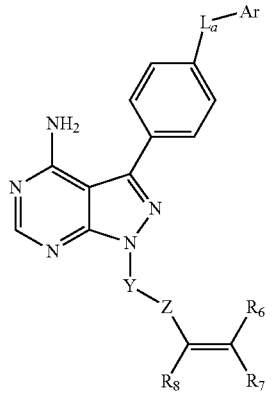
## SUMMARY OF THE INVENTION

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 alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, and heteroarylene;

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 $C_1$-$C_4$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, sub-