INHIBITORS OF BRUTON'S TYROSINE KINASE

The present invention relates to the use of novel derivatives which inhibit Bruton's Tyrosine Kinase (Btk) and are useful for the treatment of autoimmune and inflammatory diseases caused by aberrant B-cell activation. The novel 5-phenyl-1H-pyridin-2-one, 6-phenyl-2H-pyridazin-3-one, and 5-phenyl-1H-pyrazin-2-one derivatives described herein are useful for the treatment of arthritis.

Protein kinases constitute one of the largest families of human enzymes and regulate many different signaling processes by adding phosphate groups to proteins (T. Hunter, *Cell* 1987 50:823-829). Specifically, tyrosine kinases phosphorylate proteins on the phenolic moiety of tyrosine residues. The tyrosine kinase family includes members that control cell growth, migration, and differentiation. Abnormal kinase activity has been implicated in a variety of human diseases including cancers, autoimmune and inflammatory diseases. Since protein kinases are among the key regulators of cell signaling they provide a target to modulate cellular function with small molecular kinase inhibitors and thus make good drug design targets. In addition to treatment of kinase-mediated disease processes, selective and efficacious inhibitors of kinase activity are also useful for investigation of cell signaling processes and identification of other cellular targets of therapeutic interest.

There is good evidence that B-cells play a key role in the pathogenesis of autoimmune and/or inflammatory disease. Protein-based therapeutics that deplete B cells such as Rituxan are effective against autoantibody-driven inflammatory diseases such as rheumatoid arthritis (Rastetter *et al. Annu Rev Med* 2004 55:477). Therefore inhibitors of the protein kinases that play a role in B-cell activation should be useful therapeutics for B-cell mediated disease pathology such as autoantibody production.

Signaling through the B-cell receptor (BCR) controls a range of B-cell responses including proliferation and differentiation into mature antibody producing cells. The BCR is a key regulatory point for B-cell activity and aberrant signaling can cause deregulated B-cell proliferation and formation of pathogenic autoantibodies that lead to multiple autoimmune and/or inflammatory diseases. Bruton's Tyrosine Kinase (Btk) is a non-BCR associated kinase

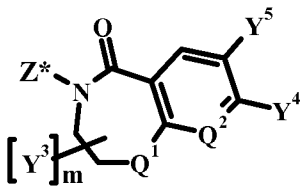
that is membrane proximal and immediately downstream from BCR. Lack of Btk has been shown to block BCR signaling and therefore inhibition of Btk could be a useful therapeutic approach to block B-cell mediated disease processes.

Btk is a member of the Tec family of tyrosine kinases, and has been shown to be a critical regulator of early B-cell development and mature B-cell activation and survival (Khan *et al. Immunity* 1995 3:283; Ellmeier *et al. J. Exp. Med.* 2000 192:1611). Mutation of Btk in humans leads to the condition X-linked agammaglobulinemia (XLA) (reviewed in Rosen *et al. New Eng. J. Med.* 1995 333:431 and Lindvall *et al. Immunol. Rev.* 2005 203:200). These patients are immunocompromised and show impaired maturation of B-cells, decreased immunoglobulin and peripheral B-cell levels, diminished T-cell independent immune responses as well as attenuated calcium mobilization following BCR stimulation.

Evidence for a role for Btk in autoimmune and inflammatory diseases has also been provided by Btk-deficient mouse models. In preclinical murine models of systemic lupus erythematosus (SLE), Btk-deficient mice show marked amelioration of disease progression. In addition, Btk-deficient mice are resistant to collagen-induced arthritis (Jansson and Holmdahl *Clin. Exp. Immunol.* 1993 94:459). A selective Btk inhibitor has been demonstrated dose-dependent efficacy in a mouse arthritis model (Z. Pan *et al.*, *Chem. Med Chem.* 2007 2:58-61).

Btk is also expressed by cells other than B-cells that may be involved in disease processes. For example, Btk is expressed by mast cells and Btk-deficient bone marrow derived mast cells demonstrate impaired antigen induced degranulation (Iwaki *et al. J. Biol. Chem.* 2005 280:40261). This shows Btk could be useful to treat pathological mast cells responses such as allergy and asthma. Also monocytes from XLA patients, in which Btk activity is absent, show decreased TNF alpha production following stimulation (Horwood et al. J Exp Med 197:1603, 2003). Therefore TNF alpha mediated inflammation could be modulated by small molecular Btk inhibitors. Also, Btk has been reported to play a role in apoptosis (Islam and Smith *Immunol. Rev.* 2000 178:49) and thus Btk inhibitors would be useful for the treatment of certain B-cell lymphomas and leukemias (Feldhahn *et al. J. Exp. Med.* 2005 201:1837).

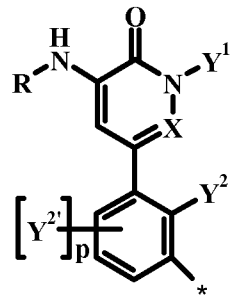
The present application provides a compound of Formula A,



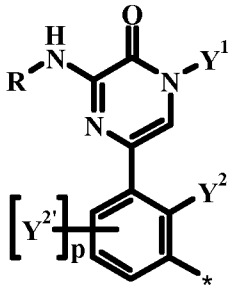
(A)

wherein:

Z* is selected from the group consisting of:



;



;

and wherein:

Q^1 is NH or O;

Q^2 is N or $C(Y^6)$;

R is H, $-R^1$, $-R^1-R^2-R^3$, $-R^1-R^3$, or $-R^2-R^3$;

R^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with one or more lower alkyl, hydroxy, hydroxy lower alkyl, lower alkoxy, halo, nitro, amino, amido, cyano, oxo, or halo-lower alkyl;

R^2 is $-C(=O)$, $-C(=O)O$, $-C(=O)NR^{2'}$, $-NHC(=O)O$, $-C(=NH)NR^{2'}$, or $-S(=O)_2$;

$R^{2'}$ is H or lower alkyl;

R^3 is H or R^4;

R^4 is lower alkyl, amino, aryl, arylalkyl, alkylaryl, heteroaryl, alkyl heteroaryl, heteroaryl alkyl, cycloalkyl, alkyl cycloalkyl, cycloalkyl alkyl, heterocycloalkyl, alkyl heterocycloalkyl, or heterocycloalkyl alkyl, and is optionally substituted with one or more lower alkyl, hydroxy, lower alkoxy, hydroxy lower alkyl, hydroxy lower alkoxy, lower alkyl sulfonyl, lower alkyl sulfonamido, carbamate, carboxy, ester, amido, acyl, halo, nitro, amino, cyano, oxo, or halo-lower alkyl;

X is CH or N;

Y^1 is H, lower alkyl, or lower haloalkyl;

Y^2 is Y^{2a} or Y^{2b};

Y^{2a} is H or halogen;

Y^{2b} is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2b'}$;

$Y^{2b'}$ is hydroxy or halogen;

each $Y^{2'}$ is independently $Y^{2'a}$ or $Y^{2'b}$;

$Y^{2'a}$ is halogen or hydroxy;

$Y^{2'b}$ is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2'b'}$;

$Y^{2'b'}$ is hydroxy or halogen;

p is 0, 1, or 2;

Y^3 is Y^{3a} or Y^{3b};

Y^{3a} is halogen or hydroxy;

Y^{3b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

Y^4 is Y^{4a}, Y^{4b}, Y^{4c}, or Y^{4d};

Y^{4a} is hydroxy or halogen;

Y^{4b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

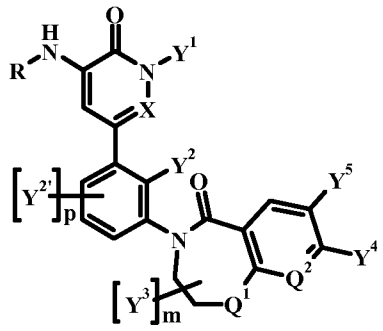
Y^{4d} is amino, optionally substituted with one or more lower alkyl, alkoxy lower alkyl, or hydroxy lower alkyl;

Y^5 is halogen, hydroxy, lower alkyl, lower alkoxy, lower haloalkoxy, lower hydroxyalkyl, or lower haloalkyl; and

Y^6 is H, hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower thioalkyl, amino, or lower hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

The present application provides a compound of Formula I,



I

wherein:

Q^1 is NH or O;

Q^2 is N or $C(Y^6)$;

R is H, $-R^1$, $-R^1-R^2-R^3$, $-R^1-R^3$, or $-R^2-R^3$;

R^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with one or more lower alkyl, hydroxy, hydroxy lower alkyl, lower alkoxy, halo, nitro, amino, amido, cyano, oxo, or halo-lower alkyl;

R^2 is $-C(=O)$, $-C(=O)O$, $-C(=O)NR^{2'}$, $-NHC(=O)O$, $-C(=NH)NR^{2'}$, or $-S(=O)_2$;

$R^{2'}$ is H or lower alkyl;

R^3 is H or R^4;

R^4 is lower alkyl, amino, aryl, arylalkyl, alkylaryl, heteroaryl, alkyl heteroaryl, heteroaryl alkyl, cycloalkyl, alkyl cycloalkyl, cycloalkyl alkyl, heterocycloalkyl, alkyl heterocycloalkyl, or heterocycloalkyl alkyl, and is optionally substituted with one or more lower alkyl, hydroxy, lower alkoxy, hydroxy lower alkyl, hydroxy lower alkoxy, lower alkyl sulfonyl, lower alkyl sulfonamido, carbamate, carboxy, ester, amido, acyl, halo, nitro, amino, cyano, oxo, or halo-lower alkyl;

X is CH or N;

Y^1 is H, lower alkyl, or lower haloalkyl;

Y^2 is Y^{2a} or Y^{2b};

Y^{2a} is H or halogen;

Y^{2b} is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2b'}$;

$Y^{2b'}$ is hydroxy or halogen;

each $Y^{2'}$ is independently $Y^{2'a}$ or $Y^{2'b}$;

$Y^{2'a}$ is halogen or hydroxy;

$Y^{2'b}$ is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2'b'}$;

$Y^{2'b'}$ is hydroxy or halogen;

p is 0, 1, or 2;

Y^3 is Y^{3a} or Y^{3b};

Y^{3a} is halogen or hydroxy;

Y^{3b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

Y^4 is Y^{4a}, Y^{4b}, Y^{4c}, or Y^{4d};

Y^{4a} is hydroxy or halogen;

Y^{4b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4d} is amino, optionally substituted with one or more lower alkyl, alkoxy lower alkyl, or hydroxy lower alkyl;

Y^5 is halogen, hydroxy, lower alkyl, lower alkoxy, lower haloalkoxy, lower hydroxyalkyl, or lower haloalkyl; and

Y^6 is H, hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower thioalkyl, amino, or lower hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

In one variation of the compound of formula I, Y^1 is methyl.

In one variation of the compound of formula I, m is 0.

In one variation of the compound of formula I, Y^1 is methyl and m is 0.

In one variation of the compound of formula I, p is 0.

In one variation of the compound of formula I, Y^1 is methyl and p is 0.

In one variation of the compound of formula I, m is 0 and p is 0.

In one variation of the compound of formula I, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Y^2 is hydroxymethyl.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula I, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula I, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula I, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl and X is CH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is CH and Q^1 is NH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or

pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is CH and Q^1 is O.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl and X is N.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is N and Q^1 is NH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is N and Q^1 is O.

In one variation of the compound of formula I, Y^5 is fluorine.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

In one variation of the compound of formula I, X is CH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, and Y^5 is fluorine.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine and X is CH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine, X is CH and Q^1 is NH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine, X is CH and Q^1 is O.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, and X is CH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is CH and Q^1 is NH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is CH and Q^1 is O.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine and X is N.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine, X is N and Q^1 is NH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine, X is N and Q^1 is O.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or

pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, and X is N.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is N and Q^1 is NH.

In one variation of the compound of formula I, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, p is 0, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, X is N and Q^1 is O.

In one variation of the compound of formula I, X is CH, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, X is CH, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

In one variation of the compound of formula I, Q^1 is NH.

In one variation of the compound of formula I, Q^1 is NH, X is CH, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Q^1 is NH, X is CH, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

In one variation of the compound of formula I, Q^1 is O.

In one variation of the compound of formula I, Q^1 is O, X is CH, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Q^1 is O, X is CH, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

In one variation of the compound of formula I, X is N.

In one variation of the compound of formula I, X is N, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, X is N, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

In one variation of the compound of formula I, Q^1 is NH.

In one variation of the compound of formula I, Q^1 is NH, X is N, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Q^1 is NH, X is N, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

In one variation of the compound of formula I, Q^1 is O.

In one variation of the compound of formula I, Q^1 is O, Q^2 is CH, X is N, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0.

In one variation of the compound of formula I, Q^1 is O, Q^2 is CH, X is N, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, Y^1 is methyl, m is 0, and p is 0, and Y^5 is fluorine.

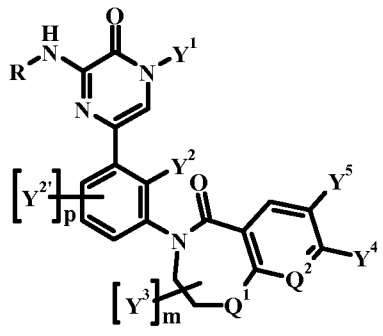
In one variation of the compound of formula I, R^3 is R^4 and R^4 is piperazine.

In one variation of the compound of formula I, R^3 is R^4 and R^4 is piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula I, R is $-R^1-R^3$, R^1 is pyridyl, R^3 is R^4 and R^4 is piperazine.

In one variation of the compound of formula I, R is $-R^1-R^3$, R^1 is pyridyl, R^3 is R^4 and R^4 is piperazine, optionally substituted with one or more lower alkyl.

The present application provides a compound of Formula II,



II

wherein:

Q^1 is NH or O;

Q^2 is N or $C(Y^6)$;

R is H, $-R^1$, $-R^1-R^2-R^3$, $-R^1-R^3$, or $-R^2-R^3$;

R^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with one or more lower alkyl, hydroxy, hydroxy lower alkyl, lower alkoxy, halo, nitro, amino, amido, cyano, oxo, or halo-lower alkyl;

R^2 is –C(=O), –C(=O)O, –C(=O)$NR^{2'}$, –NHC(=O)O, –C(=NH)$NR^{2'}$, or –$S(=O)_2$;

$R^{2'}$ is H or lower alkyl;

R^3 is H or R^4;

R^4 is lower alkyl, amino, aryl, arylalkyl, alkylaryl, heteroaryl, alkyl heteroaryl, heteroaryl alkyl, cycloalkyl, alkyl cycloalkyl, cycloalkyl alkyl, heterocycloalkyl, alkyl heterocycloalkyl, or heterocycloalkyl alkyl, and is optionally substituted with one or more lower alkyl, hydroxy, lower alkoxy, hydroxy lower alkyl, hydroxy lower alkoxy, lower alkyl sulfonyl, lower alkyl sulfonamido, carbamate, carboxy, ester, amido, acyl, halo, nitro, amino, cyano, oxo, or halo-lower alkyl;

Y^1 is H, lower alkyl, or lower haloalkyl;

Y^2 is Y^{2a} or Y^{2b};

Y^{2a} is H or halogen;

Y^{2b} is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2b'}$;

$Y^{2b'}$ is hydroxy or halogen;

each $Y^{2'}$ is independently $Y^{2'a}$ or $Y^{2'b}$;

$Y^{2'a}$ is halogen or hydroxy;

$Y^{2'b}$ is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2'b'}$;

$Y^{2'b'}$ is hydroxy or halogen;

p is 0, 1, or 2;

Y^3 is Y^{3a} or Y^{3b};

Y^{3a} is halogen or hydroxy;

Y^{3b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

Y^4 is Y^{4a}, Y^{4b}, Y^{4c}, or Y^{4d};

Y^{4a} is hydroxy or halogen;

Y^{4b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4d} is amino, optionally substituted with one or more lower alkyl, alkoxy lower alkyl, or hydroxy lower alkyl;

Y^5 is halogen, hydroxy, lower alkyl, lower alkoxy, lower haloalkoxy, lower hydroxyalkyl, or lower haloalkyl; and

Y^6 is H, hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower thioalkyl, amino, or lower hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

In one variation of the compound of formula II, Y^1 is methyl.

In one variation of the compound of formula II, m is 0.

In one variation of the compound of formula II, Y^1 is methyl and m is 0.

In one variation of the compound of formula II, p is 0.

In one variation of the compound of formula II, Y^1 is methyl and p is 0.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0.

In one variation of the compound of formula II, Y^2 is hydroxymethyl.

In one variation of the compound of formula II, Y^2 is hydroxymethyl, m is 0, Y^1 is methyl and p is 0.

In one variation of the compound of formula II, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, R is $-R^1-R^2-R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, R is $-R^1-R^2-R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, R is $-R^1-R^2-R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, and Y^5 is fluorine.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, R is $-R^1-R^2-R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, and Q^1 is NH.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, R is $-R^1-R^2-R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, and Q^1 is O.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, Y^5 is fluorine.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, Q^1 is NH.

In one variation of the compound of formula II, Q^1 is NH, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, Q^1 is NH, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, Q^1 is O.

In one variation of the compound of formula II, Q^1 is O, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, Q^1 is O, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, n is 0, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, Q^1 is NH, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, Q^1 is NH, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, Q^1 is O, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

In one variation of the compound of formula II, Q^1 is O, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl, Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, and Y^5 is fluorine.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine and Q^1 is NH.

In one variation of the compound of formula II, m is 0, Y^1 is methyl and p is 0, Y^2 is hydroxymethyl and Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl, R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl, Y^5 is fluorine and Q^1 is O.

In one variation of the compound of formula II, R^3 is R^4 and R^4 is piperazine.

In one variation of the compound of formula II, R^3 is R^4 and R^4 is piperazine, optionally substituted with one or more lower alkyl.

In one variation of the compound of formula II, R is $–R^1-R^3$, R^1 is pyridyl, R^3 is R^4 and R^4 is piperazine.

In one variation of the compound of formula II, R is $–R^1-R^3$, R^1 is pyridyl, R^3 is R^4 and R^4 is piperazine, optionally substituted with one or more lower alkyl.

The present application provides a compound selected from the group consisting of:

8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one;
8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one;
8-*tert*-Butyl-4-(3-{5-[5-(4-ethyl-piperazin-1-yl)-pyridin-2-ylamino]-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl}-2-hydroxymethyl-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one;
8-*tert*-Butyl-7-chloro-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one;
8-*tert*-Butyl-7-chloro-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one;
8-*tert*-Butyl-7-fluoro-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one;

8-Cyclopropyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one;
8-Cyclopropyl-4-{2-hydroxymethyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one;
8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one; and
8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one.

The application provides a method for treating an inflammatory and/or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of the above Formulae or variations thereof.

The application provides a method for treating an arthritis comprising administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of the above Formulae or variations thereof. The application further provides a method for treating arthritis, wherein the arthritis is rheumatoid arthritis.

The application provides a method of inhibiting B-cell proliferation comprising administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of the above Formulae or variations thereof.

The application provides a method for inhibiting Btk activity comprising administering the Btk inhibitor compound of any one of the above Formulae or variations thereof, wherein the Btk inhibitor compound exhibits an IC_{50} of 50 micromolar or less in an *in vitro* biochemical assay of Btk activity.

In one variation of the above method, the Btk inhibitor compound exhibits an IC_{50} of 100 nanomolar or less in an *in vitro* biochemical assay of Btk activity.

In one variation of the above method, the compound exhibits an IC_{50} of 10 nanomolar or less in an *in vitro* biochemical assay of Btk activity.

The application provides a method for treating an inflammatory condition comprising co-administering to a patient in need thereof a therapeutically effective amount of an anti-

inflammatory compound in combination with the Btk inhibitor compound of any one of the above Formulae or variations thereof.

The application provides a method for treating arthritis comprising co-administering to a patient in need thereof a therapeutically effective amount of an anti-inflammatory compound in combination with the Btk inhibitor compound of any one of the above Formulae or variations thereof. The application further provides a method for treating arthritis, wherein the arthritis is rheumatoid arthritis.

The application provides a method for treating a lymphoma or a BCR-ABL1$^+$ leukemia cells by administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of the above Formulae or variations thereof.

The application provides a pharmaceutical composition comprising the Btk inhibitor compound of any one of the above Formulae or variations thereof, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

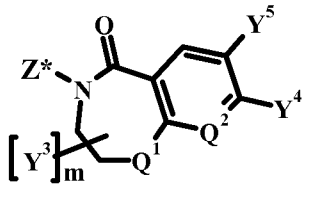
The application provides a method for treating an asthma comprising administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of the above Formulae.

The application provides a method for treating an lupus comprising administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of the above Formulae.

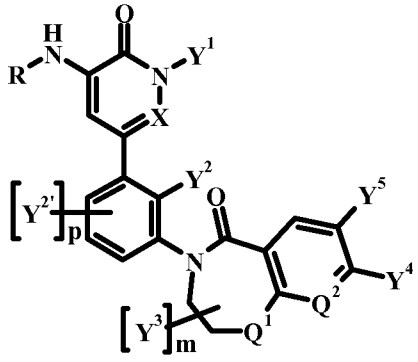
The present application provides compounds of generic Formula A or generic Formulae I-II, wherein variables Z* or Q^1, Q^2, R, X, Y^1, Y^2, $Y^{2'}$, Y^3, Y^4, Y^5, m, and p are as defined herein above.

In one embodiment of the present invention, there is provided a compound according to generic Formula I which comprises the exemplified Btk inhibitor compounds of Formulae I-1 to I-10.

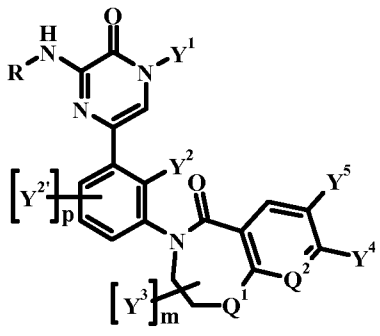
The present application discloses 5-phenyl-1H-pyridin-2-one, 6-phenyl-2H-pyridazin-3-one, and 5-phenyl-1H-pyrazin-2-one derivatives according to generic Formula A or generic Formulae I-II:



A;



I



II

wherein, variables Z* or Q^1, Q^2, R, X, Y^1, Y^2, $Y^{2'}$, Y^3, Y^4, Y^5, m, and p are defined as described herein, which inhibit Btk.

The phrase "as defined herein above" refers to the broadest definition for each group as provided in the description or the broadest claim. In all other aspects, variations and embodiments provided, substituents which can be present in each embodiment and which are not explicitly defined retain the broadest definition provided in the description.

The compounds of generic Formula A or generic Formulae I-II inhibit Bruton's tyrosine kinase (Btk). Activation of Btk by upstream kinases results in activation of phospholipase-Cγ which, in turn, stimulates release of pro-inflammatory mediators. The compounds of generic Formula A or generic Formulae I-II, incorporating side chains, or derivatives thereof, of 1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one, 3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one, 1,2,3,4-tetrahydro-pyrido[2,3-e][1,4]diazepin-5-one, or 7,8-dihydro-6H-9-oxa-1,6-diaza-benzocyclohepten-5-one on the 5-phenyl-1H-pyridin-2-one, 6-phenyl-2H-pyridazin-3-one, and 5-phenyl-1H-pyrazin-2-one ring systems, exhibit unexpectedly enhanced inhibitory activity compared to analogues with other side chains. Compounds of Formula A or Formulae I-II are useful in the treatment of arthritis and other anti-inflammatory and autoimmune diseases. Compounds according to Formula A or Formulae I-II are, accordingly, useful for the treatment of arthritis. Compounds of Formula A or Formulae I-II are useful for inhibiting Btk in cells and for modulating B-cell development. The present invention further comprises pharmaceutical compositions containing compounds of Formula A or Formulae I-II admixed with pharmaceutically acceptable carrier, excipients or diluents.

The phrase “a” or “an” entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms “a” (or “an”), “one or more”, and “at least one” can be used interchangeably herein.

The phrase "as defined herein above" refers to the broadest definition for each group as provided in the description or the broadest claim. In all other embodiments provided below, substituents which can be present in each embodiment and which are not explicitly defined retain the broadest definition provided in the description.

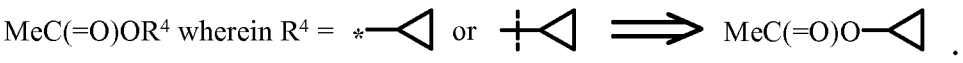
As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or composition includes at least the recited features or components, but may also include additional features or components.

As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or".

The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R" appears twice and is defined as "independently carbon or nitrogen", both R"s can be carbon, both R"s can be nitrogen, or one R" can be carbon and the other nitrogen.

When any variable occurs more than one time in any moiety or formula depicting and describing compounds employed or claimed in the present invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such compounds result in stable compounds.

The symbols "*" at the end of a bond or " ------ " drawn through a bond each refer to the point of attachment of a functional group or other chemical moiety to the rest of the molecule of which it is a part. Thus, for example:

MeC(=O)OR^4 wherein R^4 =  .

A bond drawn into ring system (as opposed to connected at a distinct vertex) indicates that the bond may be attached to any of the suitable ring atoms.

The term “optional” or “optionally” as used herein means that a subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted” means that the optionally substituted moiety may incorporate a hydrogen or a substituent.

The phrase “optional bond” means that the bond may or may not be present, and that the description includes single, double, or triple bonds. If a substituent is designated to be a "bond" or "absent", the atoms linked to the substituents are then directly connected.

The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

Certain compounds of Formula A or formulae I-II may exhibit tautomerism. Tautomeric compounds can exist as two or more interconvertable species. Prototropic tautomers result from the migration of a covalently bonded hydrogen atom between two atoms. Tautomers generally exist in equilibrium and attempts to isolate an individual tautomers usually produce a mixture whose chemical and physical properties are consistent with a mixture of compounds. The position of the equilibrium is dependent on chemical features within the molecule. For example, in many aliphatic aldehydes and ketones, such as acetaldehyde, the keto form predominates while; in phenols, the enol form predominates. Common prototropic tautomers include keto/enol (-C(=O)-CH- ⇆ -C(-OH)=CH-), amide/imidic acid (-C(=O)-NH- ⇆ -C(-OH)=N-) and amidine (-C(=NR)-NH- ⇆ -C(-NHR)=N-) tautomers. The latter two are particularly common in heteroaryl and heterocyclic rings and the present invention encompasses all tautomeric forms of the compounds.

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Ed., McGraw Hill Companies Inc., New York (2001). Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described.

Materials, reagents and the like to which reference are made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

The definitions described herein may be appended to form chemically-relevant combinations, such as “heteroalkylaryl”, “haloalkylheteroaryl”, “arylalkylheterocyclyl”, “alkylcarbonyl”, “alkoxyalkyl”, and the like. When the term “alkyl” is used as a suffix following another term, as in “phenylalkyl”, or “hydroxyalkyl”, this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents selected from the other specifically-named group. Thus, for example, “phenylalkyl” refers to an alkyl group having one to two phenyl substituents, and thus includes benzyl, phenylethyl, and biphenyl. An “alkylaminoalkyl” is an alkyl group having one to two alkylamino substituents. “Hydroxyalkyl" includes 2-hydroxyethyl, 2-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 2,3-dihydroxybutyl, 2-(hydroxymethyl), 3-hydroxypropyl, and so forth. Accordingly, as used herein, the term “hydroxyalkyl” is used to define a subset of heteroalkyl groups defined below. The term -(ar)alkyl refers to either an unsubstituted alkyl or an aralkyl group. The term (hetero)aryl or (het)aryl refers to either an aryl or a heteroaryl group.

The term “acyl” as used herein denotes a group of formula -C(=O)R wherein R is hydrogen or lower alkyl as defined herein. The term or "alkylcarbonyl" as used herein denotes a group of formula -C(=O)R wherein R is alkyl as defined herein. The term C_{1-6} acyl refers to a group -C(=O)R with R containing 1-6 carbon atoms. The term "arylcarbonyl" as used herein means a group of formula -C(=O)R wherein R is an aryl group; the term "benzoyl" as used herein is an "arylcarbonyl" group wherein R is phenyl.

The term “alkyl” as used herein denotes an unbranched or branched chain, saturated, monovalent hydrocarbon residue containing 1 to 10 carbon atoms. The term “lower alkyl” denotes a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms. "C_{1-10} alkyl" as used herein refers to an alkyl composed of 1 to 10 carbon atoms. Examples of alkyl groups or lower alkyl groups include, but are not limited to, methyl, ethyl, propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl or pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl.

When the term “alkyl” is used as a suffix following another term, as in “phenylalkyl”, or “hydroxyalkyl”, this is intended to refer to an alkyl group, as defined above, being substituted with one to two substituents selected from the other specifically-named group. Thus, for example, “phenylalkyl” denotes the radical R'R"-, wherein R' is a phenyl radical, and R" is an alkylene radical as defined herein with the understanding that the attachment point of the

phenylalkyl moiety will be on the alkylene radical. Examples of arylalkyl radicals include, but are not limited to, benzyl, phenylethyl, 3-phenylpropyl. The terms “arylalkyl” or "aralkyl" are interpreted similarly except R' is an aryl radical. The terms "(het)arylalkyl" or "(het)aralkyl" are interpreted similarly except R' is optionally an aryl or a heteroaryl radical.

The terms “haloalkyl” or “halo-lower alkyl” or “lower haloalkyl” refers to a straight or branched chain hydrocarbon residue containing 1 to 6 carbon atoms wherein one or more carbon atoms are substituted with one or more halogen atoms.

The term "alkylene" or "alkylenyl" as used herein denotes a divalent saturated linear hydrocarbon radical of 1 to 10 carbon atoms (*e.g.*, $(CH_2)_n$) or a branched saturated divalent hydrocarbon radical of 2 to 10 carbon atoms (*e.g.*, -CHMe- or $-CH_2CH(i\text{-Pr})CH_2-$), unless otherwise indicated. Except in the case of methylene, the open valences of an alkylene group are not attached to the same atom. Examples of alkylene radicals include, but are not limited to, methylene, ethylene, propylene, 2-methyl-propylene, 1,1-dimethyl-ethylene, butylene, 2-ethylbutylene.

The term "alkoxy" as used herein means an -O-alkyl group, wherein alkyl is as defined above. "Lower alkoxy" as used herein denotes an alkoxy group with a "lower alkyl" group as previously defined. "C_{1-10} alkoxy" as used herein refers to an-O-alkyl wherein alkyl is C_{1-10}. Examples of alkoxy groups or lower alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *t*-butyloxy, pentyloxy, hexyloxy, including their isomers.

The term "hydroxyalkyl" as used herein denotes an alkyl radical as herein defined wherein one to three hydrogen atoms on different carbon atoms is/are replaced by hydroxyl groups.

The terms "alkylsulfonyl" and "arylsulfonyl" as used herein refers to a group of formula $-S(=O)_2R$ wherein R is alkyl or aryl respectively and alkyl and aryl are as defined herein. The term “heteroalkylsulfonyl” as used herein refers herein denotes a group of formula $-S(=O)_2R$ wherein R is “heteroalkyl” as defined herein.

The terms "alkylsulfonylamino" and "arylsulfonylamino"as used herein refers to a group of formula $-NR'S(=O)_2R$ wherein R is alkyl or aryl respectively, R' is hydrogen or C_{1-3} alkyl, and alkyl and aryl are as defined herein.

The term “cycloalkyl” as used herein refers to a saturated carbocyclic ring containing 3 to 8 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl.

"C_{3-7} cycloalkyl" as used herein refers to an cycloalkyl composed of 3 to 7 carbon atoms in the carbocyclic ring.

The term carboxy-alkyl as used herein refers to an alkyl moiety wherein one, hydrogen atom has been replaced with a carboxyl with the understanding that the point of attachment of the alkyl radical is through a carbon atom. The term “carboxy” or “carboxyl” refers to a $–CO_2H$ moiety.

The term "heteroaryl” or "heteroaromatic" as used herein means a monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing four to eight atoms per ring, incorporating one or more N, O, or S heteroatoms, the remaining ring atoms being carbon, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. As well known to those skilled in the art, heteroaryl rings have less aromatic character than their all-carbon counter parts. Thus, for the purposes of the invention, a heteroaryl group need only have some degree of aromatic character. Examples of heteroaryl moieties include monocyclic aromatic heterocycles having 5 to 6 ring atoms and 1 to 3 heteroatoms include, but is not limited to, pyridinyl, pyrimidinyl, pyrazinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazol, isoxazole, thiazole, isothiazole, triazoline, thiadiazole and oxadiaxoline which can optionally be substituted with one or more, preferably one or two substituents selected from hydroxy, cyano, alkyl, alkoxy, thio, lower haloalkoxy, alkylthio, halo, lower haloalkyl, alkylsulfinyl, alkylsulfonyl, halogen, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, and dialkylaminoalkyl, nitro, alkoxycarbonyl and carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, alkylcarbonylamino and arylcarbonylamino. Examples of bicyclic moieties include, but are not limited to, quinolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, benzoxazole, benzisoxazole, benzothiazole and benzisothiazole. Bicyclic moieties can be optionally substituted on either ring; however the point of attachment is on a ring containing a heteroatom.

The term "heterocyclyl", “heterocycloalkyl” or "heterocycle" as used herein denotes a monovalent saturated cyclic radical, consisting of one or more rings, preferably one to two rings, including spirocyclic ring systems, of three to eight atoms per ring, incorporating one or more ring heteroatoms (chosen from N,O or $S(O)_{0-2}$), and which can optionally be independently substituted with one or more, preferably one or two substituents selected from hydroxy, oxo, cyano, lower alkyl, lower alkoxy, lower haloalkoxy, alkylthio, halo, lower haloalkyl, hydroxyalkyl, nitro, alkoxycarbonyl, amino, alkylamino, alkylsulfonyl, arylsulfonyl, alkylaminosulfonyl, arylaminosulfonyl, alkylsulfonylamino, arylsulfonylamino, alkylaminocarbonyl, arylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, unless otherwise indicated. Examples of heterocyclic radicals include, but are not limited to, azetidinyl,

pyrrolidinyl, hexahydroazepinyl, oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, oxazolidinyl, thiazolidinyl, isoxazolidinyl, morpholinyl, piperazinyl, piperidinyl, tetrahydropyranyl, thiomorpholinyl, quinuclidinyl and imidazolinyl.

Commonly used abbreviations include: acetyl (Ac), azo-*bis*-isobutyrylnitrile (AIBN), atmospheres (Atm), 9-borabicyclo[3.3.1]nonane (9-BBN or BBN), *tert*-butoxycarbonyl (Boc), di-*tert*-butyl pyrocarbonate or boc anhydride (BOC_2O), benzyl (Bn), butyl (Bu), Chemical Abstracts Registration Number (CASRN), benzyloxycarbonyl (CBZ or Z), carbonyl diimidazole (CDI), 1,4-diazabicyclo[2.2.2]octane (DABCO), diethylaminosulfur trifluoride (DAST), dibenzylideneacetone (dba), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), N,N'-dicyclohexylcarbodiimide (DCC), 1,2-dichloroethane (DCE), dichloromethane (DCM), diethyl azodicarboxylate (DEAD), di-*iso*-propylazodicarboxylate (DIAD), di-*iso*-butylaluminumhydride (DIBAL or DIBAL-H), di-iso-propylethylamine (DIPEA), N,N-dimethyl acetamide (DMA), 4-N,N-dimethylaminopyridine (DMAP), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), 1,1'-*bis*-(diphenylphosphino)ethane (dppe), 1,1'-*bis*-(diphenylphosphino)ferrocene (dppf), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), ethyl (Et), ethyl acetate (EtOAc), ethanol (EtOH), 2-ethoxy-2*H*-quinoline-1-carboxylic acid ethyl ester (EEDQ), diethyl ether (Et_2O), O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate acetic acid (HATU), acetic acid (HOAc), 1-N-hydroxybenzotriazole (HOBt), high pressure liquid chromatography (HPLC), *iso*-propanol (IPA), lithium hexamethyl disilazane (LiHMDS), methanol (MeOH), melting point (mp), $MeSO_2$- (mesyl or Ms), methyl (Me), acetonitrile (MeCN), *m*-chloroperbenzoic acid (MCPBA), mass spectrum (ms), methyl *t*-butyl ether (MTBE), N-bromosuccinimide (NBS), N-carboxyanhydride (NCA), N-chlorosuccinimide (NCS), N-methylmorpholine (NMM), N-methylpyrrolidone (NMP), pyridinium chlorochromate (PCC), pyridinium dichromate (PDC), phenyl (Ph), propyl (Pr), *iso*-propyl (*i*-Pr), pounds per square inch (psi), pyridine (pyr), room temperature (rt or RT), *tert*-butyldimethylsilyl or *t*-$BuMe_2Si$ (TBDMS), triethylamine (TEA or Et_3N), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), triflate or CF_3SO_2- (Tf), trifluoroacetic acid (TFA), 1,1'-*bis*-2,2,6,6-tetramethylheptane-2,6-dione (TMHD), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), thin layer chromatography (TLC), tetrahydrofuran (THF), trimethylsilyl or Me_3Si (TMS), *p*-toluenesulfonic acid monohydrate (TsOH or pTsOH), 4-Me-$C_6H_4SO_2$- or tosyl (Ts), N-urethane-N-carboxyanhydride (UNCA). Conventional nomenclature including the prefixes *normal* (*n*), *iso* (*i*-), *secondary* (*sec*-), *tertiary* (*tert*-) and *neo* have their

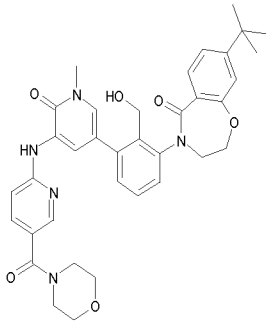
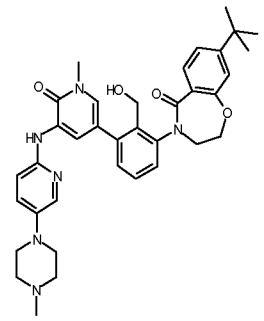
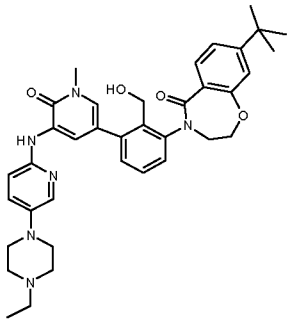
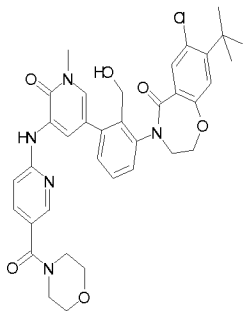
customary meaning when used with an alkyl moiety. (J. Rigaudy and D. P. Klesney, *Nomenclature in Organic Chemistry,* IUPAC 1979 Pergamon Press, Oxford.).

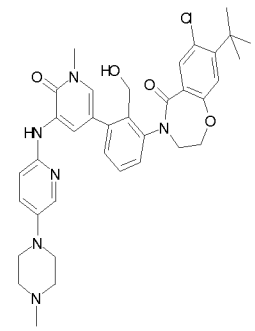
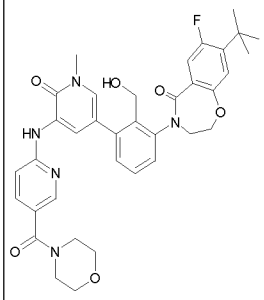
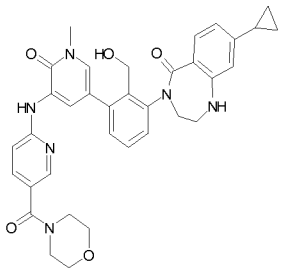
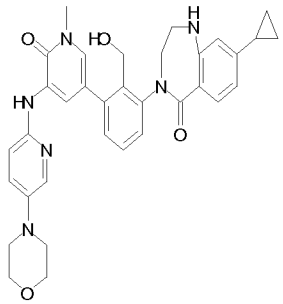
Examples of representative compounds encompassed by the present invention and within the scope of the invention are provided in the following Table. These examples and preparations which follow are provided to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

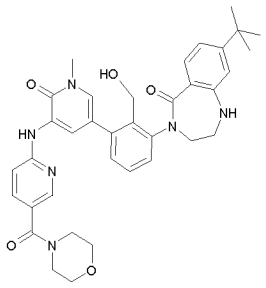
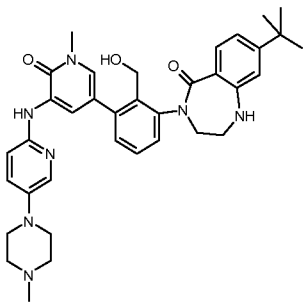
In general, the nomenclature used in this Application is based on AUTONOMTM v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. If there is a discrepancy between a depicted structure and a name given that structure, the depicted structure is to be accorded more weight. In addition, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it.

TABLE I depicts examples of compounds according to generic Formula A or generic Formulae I-II:

TABLE I.

Compound	Structure	Nomenclature	Ic50:human whole blood
I-1		8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one	0.016
I-2		8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one	0.004
I-3		8-*tert*-Butyl-4-(3-{5-[5-(4-ethyl-piperazin-1-yl)-pyridin-2-ylamino]-1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl}-2-hydroxymethyl-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one	0.008
I-4		8-*tert*-Butyl-7-chloro-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one	0.946

I-5		8-*tert*-Butyl-7-chloro-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one	
I-6		8-*tert*-Butyl-7-fluoro-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2*H*-benzo[*f*][1,4]oxazepin-5-one	0.04
I-7		8-Cyclopropyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one	0.111
I-8		8-Cyclopropyl-4-{2-hydroxymethyl-3-[1-methyl-5-(5-morpholin-4-yl-pyridin-2-ylamino)-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl}-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one	0.096

I-9		8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one	0.018
I-10		8-*tert*-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(4-methyl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[*e*][1,4]diazepin-5-one	0.038

The pyridinone and pyridazinone derivatives described herein are kinase inhibitors, in particular Btk inhibitors. These inhibitors can be useful for treating one or more diseases responsive to kinase inhibition, including diseases responsive to Btk inhibition and/or inhibition of B-cell proliferation, in mammals. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of the invention with Btk results in the inhibition of Btk activity and thus in the pharmaceutical utility of these compounds. Accordingly, the invention includes a method of treating a mammal, for instance a human, having a disease responsive to inhibition of Btk activity, and/or inhibiting B-cell proliferation, comprising administrating to the mammal having such a disease, an effective amount of at least one chemical entity provided herein. An effective concentration may be ascertained experimentally, for example by assaying blood concentration of the compound, or theoretically, by calculating bioavailability. Other kinases that may be affected in addition to Btk include, but are not limited to, other tyrosine kinases and serine/threonine kinases.

Kinases play notable roles in signaling pathways controlling fundamental cellular processes such as proliferation, differentiation, and death (apoptosis). Abnormal kinase activity has been implicated in a wide range of diseases, including multiple cancers, autoimmune and/or inflammatory diseases, and acute inflammatory reactions. The multifaceted role of kinases in key

cell signaling pathways provides a significant opportunity to identify novel drugs targeting kinases and signaling pathways.

An embodiment includes a method of treating a patient having an autoimmune and/or inflammatory disease, or an acute inflammatory reaction responsive to inhibition of Btk activity and/or B-cell proliferation.

Autoimmune and/or inflammatory diseases that can be affected using compounds and compositions according to the invention include, but are not limited to: psoriasis, allergy, Crohn's disease, irritable bowel syndrome, Sjogren's disease, tissue graft rejection, and hyperacute rejection of transplanted organs, asthma, systemic lupus erythematosus (and associated glomerulonephritis), dermatomyositis, multiple sclerosis, scleroderma, vasculitis (ANCA-associated and other vasculitides), autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), atherosclerosis, rheumatoid arthritis, chronic Idiopathic thrombocytopenic purpura (ITP), Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, and myasthenia gravis.

Included herein are methods of treatment in which at least one chemical entity provided herein is administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxgenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immuno-suppressants and methotrexate.

Examples of NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors such as celecoxib, valdecoxib, lumiracoxib and/or etoricoxib.

In some embodiments, the anti-inflammatory agent is a salicylate. Salicylates include by are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, or prednisone.

In additional embodiments the anti-inflammatory agent is a gold compound such as gold sodium thiomalate or auranofin.

The invention also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

Other embodiments of the invention pertain to combinations in which at least one anti-inflammatory compound is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

Still other embodiments of the invention pertain to combinations in which at least one active agent is an immunosuppressant compound such as an immunosuppressant compound chosen from methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil.

B-cells and B-cell precursors expressing BTK have been implicated in the pathology of B-cell malignancies, including, but not limited to, B-cell lymphoma, lymphoma (including Hodgkin's and non-Hodgkin's lymphoma), hairy cell lymphoma, multiple myeloma, chronic and acute myelogenous leukemia and chronic and acute lymphocytic leukemia.

BTK has been shown to be an inhibitor of the Fas/APO-1 (CD-95) death inducing signaling complex (DISC) in B-lineage lymphoid cells. The fate of leukemia/lymphoma cells may reside in the balance between the opposing proapoptotic effects of caspases activated by DISC and an upstream anti-apoptotic regulatory mechanism involving BTK and/or its substrates (Vassilev *et al.*, J. *Biol. Chem.* 1998, 274, 1646-1656).

It has also been discovered that BTK inhibitors are useful as chemosensitizing agents, and, thus, are useful in combination with other chemotherapeutic drugs, in particular, drugs that induce apoptosis. Examples of other chemotherapeutic drugs that can be used in combination with chemosensitizing BTK inhibitors include topoisomerase I inhibitors (camptothecin or topotecan),

topoisomerase II inhibitors (e.g. daunomycin and etoposide), alkylating agents (e.g. cyclophosphamide, melphalan and BCNU), tubulin directed agents (e.g. taxol and vinblastine), and biological agents (e.g. antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines).

Btk activity has also be associated with some leukemias expressing the *bcr-abl* fusion gene resulting from translocation of parts of chromosome 9 and 22. This abnormality is commonly observed in chronic myelogenous leukemia. Btk is constitutively phosphorylated by the *bcr-abl* kinase which initiates downstream survival signals which circumvents apoptosis in *bcr-abl* cells. (N. Feldhahn *et al. J. Exp. Med.* 2005 201(11):1837-1852).

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms and carriers. Oral administration can be in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions, syrups, or suspensions. Compounds of the present invention are efficacious when administered by other routes of administration including continuous (intravenous drip) topical parenteral, intramuscular, intravenous, subcutaneous, transdermal (which may include a penetration enhancement agent), buccal, nasal, inhalation and suppository administration, among other routes of administration. The preferred manner of administration is generally oral using a convenient daily dosing regimen which can be adjusted according to the degree of affliction and the patient's response to the active ingredient.

A compound or compounds of the present invention, as well as their pharmaceutically useable salts, together with one or more conventional excipients, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. A typical preparation will contain from about 5% to about 95% active compound or compounds (w/w). The term "preparation" or "dosage form" is intended to include both solid and liquid formulations of the active compound and one skilled

in the art will appreciate that an active ingredient can exist in different preparations depending on the target organ or tissue and on the desired dose and pharmacokinetic parameters.

The term "excipient" as used herein refers to a compound that is useful in preparing a pharmaceutical composition, generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipients that are acceptable for veterinary use as well as human pharmaceutical use. The compounds of this invention can be administered alone but will generally be administered in admixture with one or more suitable pharmaceutical excipients, diluents or carriers selected with regard to the intended route of administration and standard pharmaceutical practice.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

A "pharmaceutically acceptable salt" form of an active ingredient may also initially confer a desirable pharmacokinetic property on the active ingredient which were absent in the non-salt form, and may even positively affect the pharmacodynamics of the active ingredient with respect to its therapeutic activity in the body. The phrase "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Solid form preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

Liquid formulations also are suitable for oral administration include liquid formulation including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions. These include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

The compounds of the present invention may be formulated for parenteral administration (*e.g.*, by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (*e.g.*, olive oil), and injectable organic esters (*e.g.*, ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in

powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, *e.g.*, sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The

active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of *e.g.*, gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylaza-cycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into to the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polyactic acid.

Suitable formulations along with pharmaceutical carriers, diluents and expcipients are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. A skilled formulation scientist may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration without rendering the compositions of the present invention unstable or compromising their therapeutic activity.

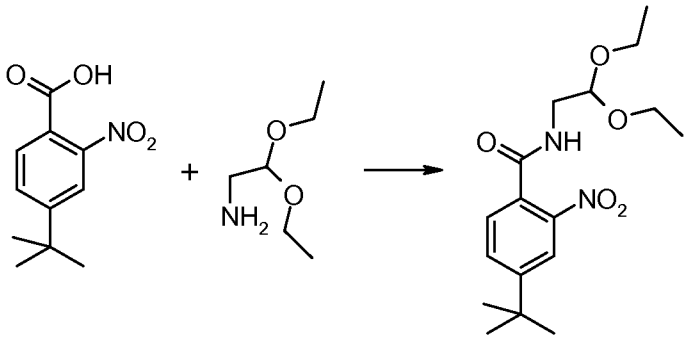
The modification of the present compounds to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications (salt formulation, esterification, etc.), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in patients.

The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of the disease in an individual. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the disease to be treated, the age and general health condition of the patient, other medicaments with which the patient is being treated, the route and form of administration and the preferences and experience of the medical practitioner involved. For oral administration, a daily dosage of between about 0.01 and about 1000 mg/kg body weight per day should be appropriate in monotherapy and/or in combination therapy. A preferred daily dosage is between about 0.1 and about 500 mg/kg body weight, more preferred 0.1 and about 100 mg/kg body weight and most preferred 1.0 and about 10 mg/kg body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 7 mg to 0.7 g per day. The daily dosage can be administered as a single dosage or in divided dosages, typically between 1 and 5 dosages per day. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect for the individual patient is reached. One of ordinary skill in treating diseases described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and the disclosures of this application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease and patient.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

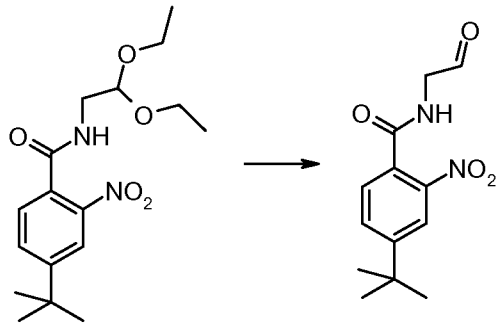
EXAMPLES

Example 1. Preparation of 2-Nitro-4-tert-butyl-N-(2,2-diethoxy-ethyl)-benzamide:



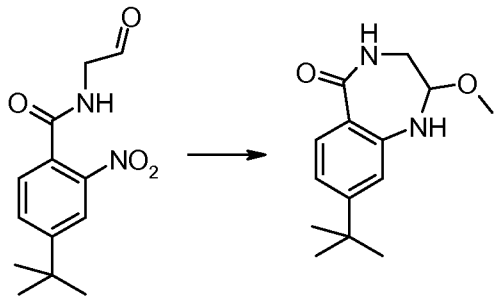
2-nitro-4-tert-butylbenzoic acid (1.5 g, 7 mmol, prepared according to *J. Am. Chem. Soc*, **1955**, *77*, 5441) was stirred in THF at room temperature, 1.7 ml diisopropylethyl amine (13 mmol, 2 eq) was added, followed by 984 mg (7.7 mmol, 1.1 eq) 2-amino acetaldehyde diethylacetal. (3-Dimethylamino-propyl)-ethyl-carbodiimide (1.55g, 8 mmol, 1.2 eq) was added, followed by a catalytic amount (ca. 50 mgs) hydroxybenzotriazole hydrate. The mixture was stirred at room temperature for 16 hours, diluted with water, extracted with diethyl ether 3x, the ether layers were washed with water, brine, and dried over $MgSO_4$. Removal of solvent under vaccum, followed by chromatography on silica gel, eluting with 25% ethyl acetate in hexanes, gave the title compound 0.950 g, $(M+H)^+ = 224$.

Example 2. Preparation of 2-nitro-4-tert-butyl-N-(2-oxo-ethyl)-benzamide:



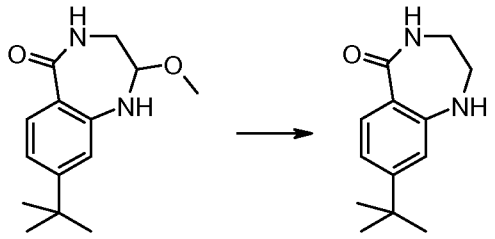
Added 2 ml 1 N aqueous HCl to 950 mg (3 mmol) 2-Amino-4-tert-butyl-N-(2,2-diethoxy-ethyl)-benzamide stirring in 20 ml acetone at room temperature. Stirred 12 hours at which time 2 ml 1 N aqueous HCl was added and stirring continued for an additional 6 hours. The reaction was diluted with water, extracted with ethyl acetate 3x, washed brine, dried $MgSO_4$. Removal of solvent under vaccum gave an oil, 717 mg of the title compound which was used in the next step without purification.

Example 3. Preparation of 8-tert-Butyl-2-methoxy-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one:



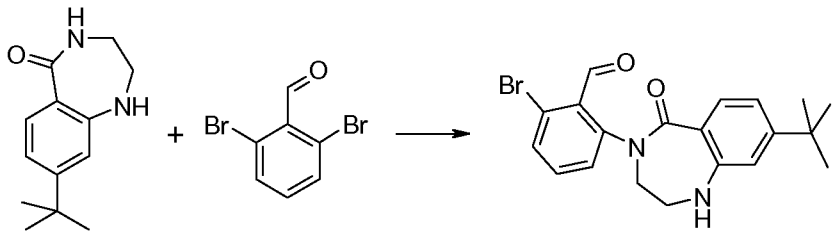
70 mg 10 wt % Pd on carbon was wetted with a small amount of methanol under argon. To this was added 717 mg (3 mmol) 2-nitro-4-tert-butyl-N-(2-oxo-ethyl)-benzamide dissolved in 20 ml methanol. The flask was evacuated and the atmosphere replaced with hydrogen gas using a balloon as ballast, and the mixture was hydrogenated for 3 hours. The reaction was filtered through celite under argon, the celite washed with ethyl acetate. Solvent was removed under vacuum to give a solid. NMR and LC/MS shows this to be a mixture of the title compound and 8-tert-Butyl-3,4-dihydro-benzo[e][1,4]diazepin-5-one as a one to one mixture, which was used without purification.

Example 4. Preparation of 8-tert-Butyl-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one:



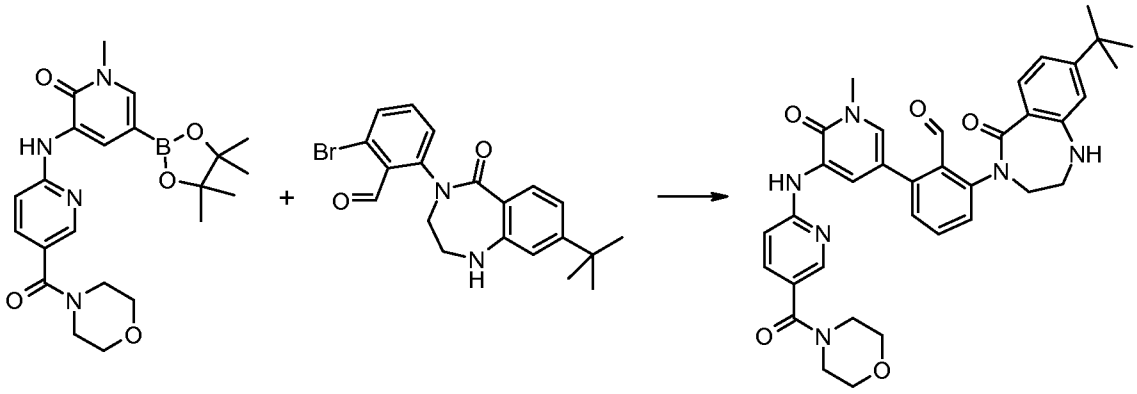
275 mg 8-tert-Butyl-3,4-dihydro-benzo[e][1,4]diazepin-5-one was dissolved in 5 ml methanol. Sodium cyanoborohydride (139 mg, 2 mmol, 2 eq) was added and the reaction was stirred for 16 hours. The reaction was quenched with water, extracted ethyl acetate 3x, washed saturated sodium bicarbonate, brine, and dried over $MgSO_4$. Solvent was removed under vacuum and the residue chromatographed over silica gel eluting with 80 % to 100% ethyl acetate in hexanes to give the title compound, 98 mg, $(M+H)^+ = 219$.

Example 5. Preparation of 2-Bromo-6-(8-tert-butyl-5-oxo-1,2,3,5-tetrahydrobenzo[e][1,4]diazepin-4-yl)-benzaldehyde:



8-tert-Butyl-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one (420 mg, 2 mmol), 2,6-Dibromo-benzaldehyde (2.03 g, 8 mmol, 3eq), Xanthphos (22 mg, 0.02eq), and cesium carbonate (1.23 g, 4 mmol, 2 eq) were taken up in dioxane (5.0mL) and a stream of argon gas was bubbled through the mixture for 1 minute. The catalyst $Pd(dba)_2$ (33 mg, 0.03 eq) was added and argon was bubbled through for an additional minute. The resulting mixture was sealed under argon and stirred at 100 °C for 18 hours. The reaction was cooled and filtered. The collected solid was triturated with water and filtered to give a solid. The dioxane filtrate was combined with this solid, the solvent removed under vaccum, and the residue chromatographed, eluting with 50% ethyl acetate in hexanes gave a solid, 81 mg. $(M+H)^+ = 402$.

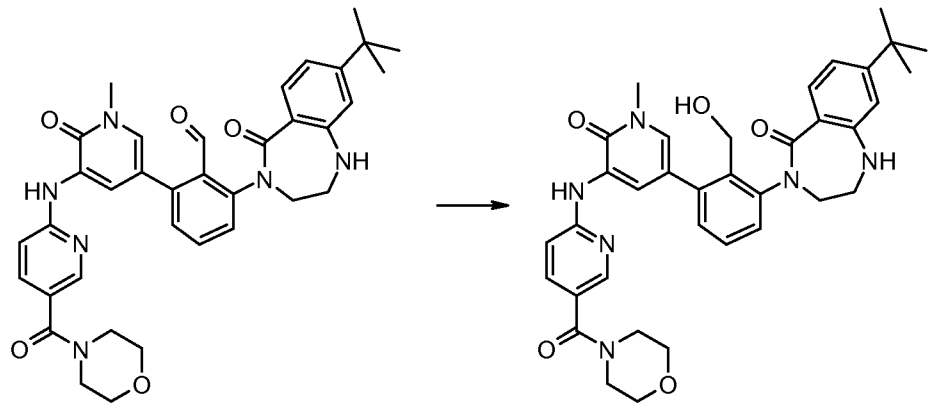
Example 6. Preparation of 2-(8-tert-Butyl-5-oxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-6-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-benzaldehyde:



2-Bromo-6-(8-tert-butyl-5-oxo-1,2,3,5-tetrahydrobenzo[e][1,4]diazepin-4-yl)-benzaldehyde (0.100 g, 0.23 mmol),1-Methyl-3-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one (0.091 g, 1.0 eq), xantphos (12 mg, 0.09 eq), and potassium phosphate (0.096 g, 2 eq) were taken up in n-butanol (3 mL) and water (0.5 mL) and a stream of argon was bubbled through the mixture for 1 minute. $Pd(dba)_2$ (0.008 g, 0.06 eq) was added and argon was bubbled through for an additional minute. The reaction was heated under argon and stirred at 100 °C for 3 hours. The reaction was cooled, solvent was removed under vacuum, and placed directly on a silica gel column, eluted with 100% ethyl

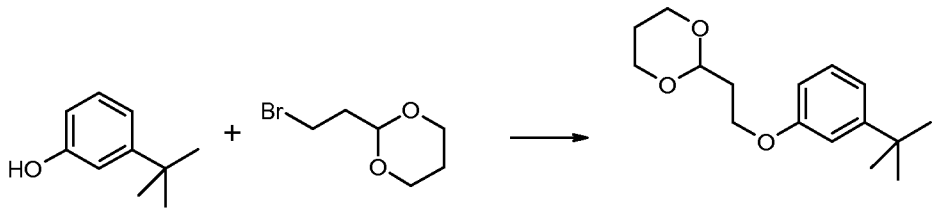
acetate, then 4% MeOH in CH_2Cl_2 to give the title compound as a brown solid, 76 mg as a 60:40 mixture (the title compound as the major component) with an impurity and used without further purification.

Example 7. Preparation of 8-tert-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-1,2,3,4-tetrahydro-benzo[e][1,4]diazepin-5-one:



The 60:40 mixture from the previous step, with the major component being 2-(8-tert-Butyl-5-oxo-1,2,3,5-tetrahydro-benzo[e][1,4]diazepin-4-yl)-6-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-benzaldehyde, 76 mg, was dissolved in 3 ml THF, and 3 ml absolute ethanol was added. Sodium borohydride (5 mg, 1 eq), was added, and the reaction stirred for 20 minutes, during which time the reaction changed from purple color to colorless. The reaction was quenched with water, and then 1 drop glacial acetic acid was added. The mixture was extracted with ethyl acetate 3x, the organic layers combined and washed with aqueous saturated sodium bicarbonate solution and brine, dried over $MgSO_4$, filtered, and the organic solvent removed under vacuum. The residue was chromatographed over silica gel, eluting first with methylene chloride, and then 3% methanol in methylene chloride, to give the title compound as a white solid, 33 mg, $(M+H)^+ = 637$.

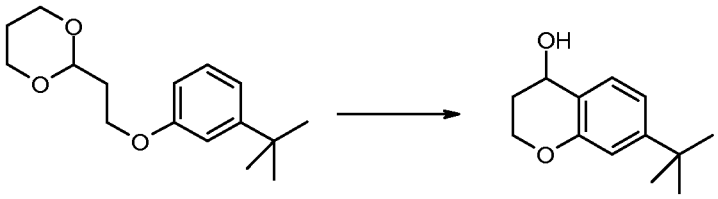
Example 8. Preparation of 2-[2-(3-tert-Butyl-phenoxy)-ethyl]-[1,3]dioxane:



Sodium hydroxide (3.46g, 1.3 eq) was taken up in water (20mL) and stirred for about 30 minutes. Then 3-tert-butyl phenol (10.0 g, 66.6 mmol) was added and the resulting mixture was

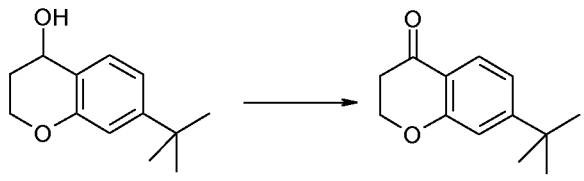
stirred at room temperature for 30 minutes. Next, 2-(2-bromoethyl)-[1,3] dioxane (9.9 mL, 1.1 eq) was added ant the resulting mixture was heated at reflux for 40 hours. The reaction mixture was cooled to room temperature and then added ethyl acetate (150 mL) and with stirring acetic acid was added to pH = 4, followed by dilution with water (100 mL) and ethyl acetate (150 mL). After partitioning, the layers were separated and then washed the organic layer with water (3X 100mL) and the ethyl acetate layers were dried over magnesium sulfate, filtered and concentrated to give the title compound as a colorless oil (16.91g).

Example 9. Preparation of 7-tert-Butyl-chroman-4-ol:



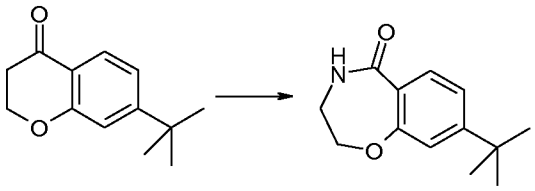
Concentrated hydrochloric acid (70 mL) was cooled in an ice bath and then about 40 mL of THF was added and stirred. At 0 °C with stirring was added 2-[2-(3-tert-Butyl-phenoxy)-ethyl]-[1,3]dioxane (8.48 g, 32.1 mmol) slowly in THF (30mL). After the addition was complete the ice bath was removed and the resulting mixture was stirred vigorously at room temperature for 3 hours. Then ether was added (300mL) and the layers were separated, and the organic layer was extracted with water (3x100 mL) and finally dried over magnesium sulfate, filtered and concentrated to give the title compound as a light yellow oil and used for the next step without further purification.

Example 10. Preparation of 7-tert-Butyl-chroman-4-one:



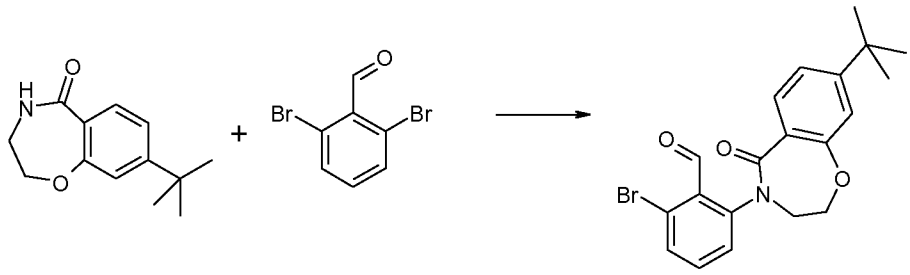
7-tert-Butyl-chroman-4-ol (assumed 32.1 mmol) was taken up in dichloromethane (250 mL) and with stirring was added PCC (14.36g, 2eq) portion-wise. After the addition was complete, the resulting mixture was stirred for about 3 hours by which time the reaction was complete by TLC analysis. About 250 mL of hexanes were added to the mixture and it was then filtered through a pad of celite and the filtrate was concentrated. Purification by column chromatography on silica gel eluting with a gradient of 2% ethyl acetate in hexanes to 10% ethyl acetate in hexanes afforded the title compound as an off-white solid (3.838g) $(M+H)^+$=205.

Example 11. Preparation of 8-tert-Butyl-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one:



7-tert-Butyl-chroman-4-one (1.3 g, 6.36 mmol) was taken up in dichloromethane (11.25 mL) and methane sulfonic acid (7.5mL) and cooled to 0 °C. With stirring at 0 °C was added sodium azide (827 mg, 2 eq) portion-wise. The resulting mixture was stirred at 0 °C for 3 hours and by TLC analysis there was no more starting material remaining, so the reaction mixture was poured into a 20% solution of $NaOH_{(aq)}$ (25 mL) at 0 °C. This solution was stirred for 10 minutes and then it was extracted with dichloromethane (3X50 mL) and the combined dichloromethane layers were washed with brine (1X50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. Purification by column chromatorgraphy on silica gel eluting with a gradient of 5% ethyl acetate in hexanes to 100% ethyl acetate afforded the title compound as a white solid (1.304g) $(M+H)^+$=220.

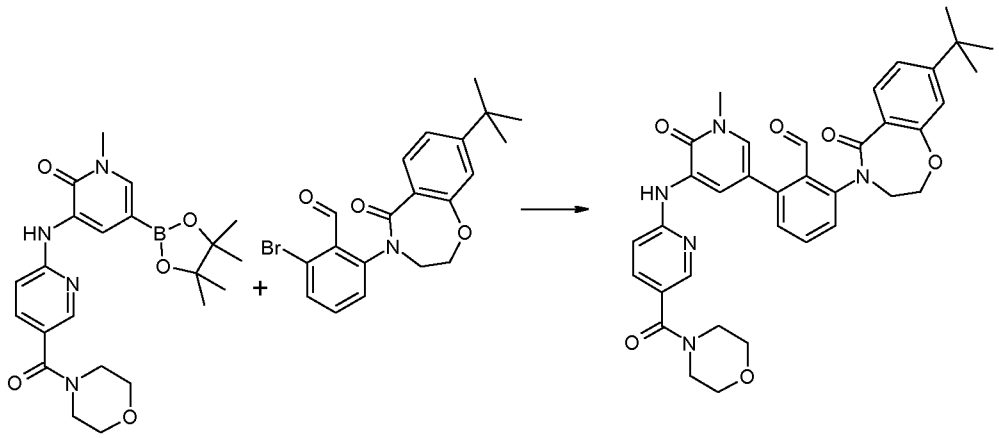
Example 12. Preparation of 2-Bromo-6-(8-tert-butyl-5-oxo-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)-benzaldehyde:



8-tert-Butyl-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one (600 mg, 2.74 mmol, 2,6-Dibromo-benzaldehyde (3.62g, 5eq), Xanthphos (71 mg, 0.045eq), and cesium carbonate (1.25g, 1.4 eq) were taken up in dioxane (5.3 mL) and a stream of Argon gas was bubbled through the mixture for 10 minutes. The catalyst $Pd(dba)_2$ (47 mg, 0.03 eq) was added and the resulting mixture was placed under argon and stirred at 100 °C for three hours. By TLC, the reaction was complete and after cooling the mixture to room temperature, ethyl acetate (150 mL) and water (50 mL) were added and the layers were partitioned and separated. The organic layer was further washed with water (3X50 mL) and finally washed with brine (1X50 mL) before it was dried over magnesium sulfate, filtered and concentrated. Purification by column chromatography on silica

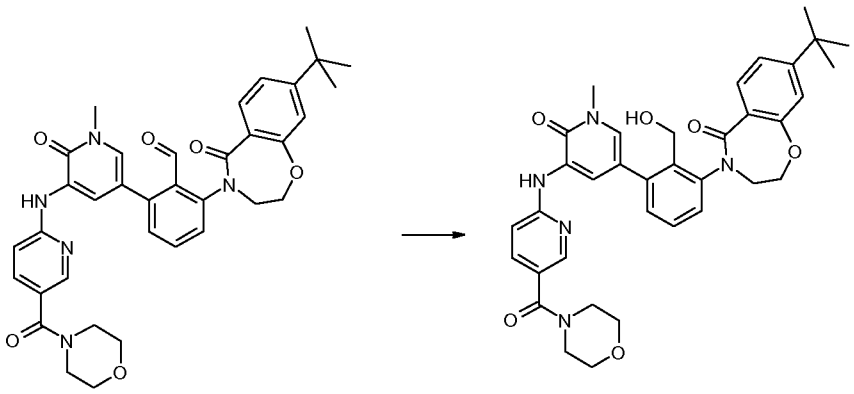
gel eluting with a gradient of 5% ethyl acetate to 30% ethyl acetate afforded the title compound as an off-white powder (793 mg) $(M+H)^+$=404.

Example 13. Preparation of 2-(8-tert-Butyl-5-oxo-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)-6-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-benzaldehyde:



2-Bromo-6-(8-tert-butyl-5-oxo-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)benzaldehyde (109 mg, 0.27 mmol), 1-Methyl-3-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyridin-2-one (179 mg, 1.5 eq), XPHOS (8 mg, 0.06 eq), and potassium phosphate (115 mg, 2 eq) were taken up in n-butanol (2 mL) and water (0.5 mL) and a stream of argon was bubbled through the mixture for 10 minutes. Then the catalyst $Pd(dba)_2$ (5 mg, 0.03 eq) was added and the reaction was placed under argon and stirred at 100 °C for 40 minutes. By TLC analysis the reaction was complete, so it was cooled to room temperature and diluted with ethyl acetate (150 mL) and water (50 mL). The layers were partitioned and then separated and the organic layer was further washed with water (3X50 mL) and then finally washed with brine (1X50 mL). The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated. Purification by Preparative Thin Layer Chromatography on silica gel eluting with 7% methanol in dichloromethane gave the title compound as an off-white powder (168 mg) $(M+H)^+$=636.

Example 14. Preparation of 8-tert-Butyl-4-(2-hydroxymethyl-3-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-phenyl)-3,4-dihydro-2H-benzo[f][1,4]oxazepin-5-one:



To 2-(8-tert-Butyl-5-oxo-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl)-6-{1-methyl-5-[5-(morpholine-4-carbonyl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl}-benzaldehyde (0.27 mmol) in isopropanol (5mL) and THF (10 mL) at 0 °C with stirring was added sodium borohydride (21 mg, 2 eq) and then the ice bath was removed and the resulting mixture was stirred at room temperature for 45 minutes. TLC analysis indicated that the reaction was complete so the mixture was diluted with ethyl acetate (150 mL) and water (50 mL). The layers were partitioned, then separated and the organic layer was further washed with water (3X50 mL) and then finally washed with brine ((1X50 mL). The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated. Purification by Thin Layer Chromatography on silica gel eluting with 10% methanol in dichloromethane afforded the title compound as a light grey powder (94 mg), $(M+H)^+$=638.

Assay Data

Bruton's tyrosine kinase (Btk) inhibition Assay

The assay is a capture of radioactive ^{33}P phosphorylated product through filtration. The interactions of Btk, biotinylated SH_2 peptide substrate (Src homology), and ATP lead to phosphorylation of the peptide substrate. Biotinylated product is bound streptavidin sepharose beads. All bound, radiolabeled products are detected by scintillation counter.

Plates assayed are 96-well polypropylene (Greiner) and 96-well 1.2 μm hydrophilic PVDF filter plates (Millipore). Concentrations reported here are final assay concentrations: 10- 100 μM compounds in DMSO (Burdick and Jackson), 5–10 nM Btk enzyme (His-tagged, full-length), 30 μM peptide substrate (Biotin-Aca-AAAEEIYGEI-NH_2), 100 μM ATP (Sigma), 8 mM imidazole (Sigma, pH 7.2), 8 mM glycerol-2-phosphate (Sigma), 200 μM EGTA (Roche Diagnostics), 1 mM $MnCl_2$ (Sigma), 20 mM $MgCl_2$ (Sigma), 0.1 mg/ ml BSA (Sigma), 2 mM DTT (Sigma), 1 μCi ^{33}P ATP (Amersham), 20% streptavidin sepharose beads (Amersham), 50 mM EDTA

(Gibco), 2 M NaCl (Gibco), 2 M NaCl w/ 1% phosphoric acid (Gibco), microscint-20 (Perkin Elmer).

IC_{50} determinations are calculated from 10 data points per compound utilizing data produced from a standard 96-well plate assay template. One control compound and seven unknown inhibitors were tested on each plate and each plate was run twice. Typically, compounds were diluted in half-log starting at 100 μM and ending at 3 nM.The control compound was staurosporine. Background was counted in the absence of peptide substrate. Total activity was determined in the presence of peptide substrate. The following protocol was used to determine Btk inhibition.

1) Sample preparation: The test compounds were diluted at half-log increments in assay buffer (imidazole, glycerol-2-phosphate, EGTA, $MnCl_2$, $MgCl_2$, BSA).

2) Bead preparation

a.) rinse beads by centrifuging at 500 g

b.) reconstitute the beads with PBS and EDTA to produce a 20% bead slurry

3) Pre-incubate reaction mix without substrate (assay buffer, DTT, ATP, ^{33}P ATP) and mix with substrate (assay buffer, DTT, ATP, ^{33}P ATP, peptide substrate) 30°C for 15 min.

4) To start assay, pre-incubate 10 μL Btk in enzyme buffer (imidazole, glycerol-2-phosphate, BSA) and 10μL of test compounds for 10 min at RT.

5) Add 30 μL reaction mixture without or with substrate to Btk and compounds.

6) Incubate 50 μL total assay mix for 30 min at 30°C.

7) Transfer 40 μL of assay to 150 μL bead slurry in filter plate to stop reaction.

8) Wash filter plate after 30 min, with following steps

a.) 3 x 250 μL NaCl

b.) 3 x 250 μL NaCl containing 1% phosphoric acid

c.) 1 x 250 μL H_2O

9) Dry plate for 1 h at 65°C or overnight at RT

10) Add 50 μL microscint-20 and count ^{33}P cpm on scintillation counter.

Calculate percent activity from raw data in cpm

percent activity = (sample – bkg) / (total activity – bkg) x 100

Calculate IC_{50} from percent activity, using one-site dose response sigmoidal model

$y = A + ((B - A) / (1 + ((x / C)^D))))$

x = cmpd conc, y = % activity, A = min, B = max, C = IC_{50}, D = 1 (hill slope)

Inhibition of B cell activation in whole blood measured by CD69 expression

A procedure to test the ability of Btk inhibitors to suppress B cell receptor-mediated activation of B cells in human blood is as follows:

Human whole blood (HWB) is obtained from healthy volunteers, with the following restrictions: 24 hr drug-free, non-smokers. Blood is collected by venipuncture into Vacutainer tubes anticoagulated with sodium heparin. Test compounds are diluted to ten times the desired starting drug concentration in PBS (20x), followed by three-fold serial dilutions in 10% DMSO in PBS to produce a nine point dose-response curve. 5.5µl of each compound dilution is added in duplicate to a 2ml 96-well V bottom plate (Analytical Sales and Services, #59623-23); 5.5µl of 10% DMSO in PBS is added to control and no-stimulus wells. HWB (100µl) is added to each well, and after mixing the plates are incubated at 37C, 5% CO_2, 100% humidity for 30 minutes. Goat F(ab')2 anti-human IgM (Southern Biotech, #2022-14) (10µl of a 500µg/ml solution, 50µg/ml final concentration) is added to each well (except the no-stimulus wells) with mixing and the plates are incubated for an additional 20 hours. At the end of the 20 hour incubation, samples are incubated with florescent-probe-labeled anti-bodies (15 µl PE Mouse anti-Human CD20, BD Pharmingen, #555623, and/or 20 µl APC Mouse anti-Human CD69, BD Pharmingen #555533) for 30 minutes, at 37C, 5% CO_2, 100% humidity. Included are induced control, unstained and single stains for compensation adjustments and initial voltage settings. Samples are then lysed with 1ml of 1X Pharmingen Lyse Buffer (BD Pharmingen # 555899), and plates are centrifuged at 1800 rpm for 5 minutes. Supernatants are removed via suction and the remaining pellets are lysed again with another 1ml of 1X Pharmingen Lyse Buffer, and plates are spun down as before. Supernatants are aspirated and remaining pellets are washed in FACs buffer (PBS + 1% FBS). After a final spin, the supernantants are removed and pellets are resuspended in 180ul of FACs buffer. Samples are transferred to a 96 well plate suitable to be run on the HTS 96 well system on the BD LSR II flow cytometer. Using appropriate excitation and emission wavelengths for the fluorophores used, data are acquired and percent positive cell values are obtained using Cell Quest Software. Results are initially analyzed by FACS analysis software (Flow Jo). The IC50 for test compounds is defined as the concentration which decreases by 50% the percentage of CD69-positive cells that are also CD20-positive after stimulation by anti-IgM (average of 8 control wells, after subtraction of the average of 8 wells

for the no-stimulus background). The IC50 values are calculated using XLfit software version 3, equation 201.

Representative compound data for this assay are listed below in Table II.

TABLE II.

Compound	Human Whole Blood (μM)
I-1	0.016
I-3	0.008
I-7	0.111
I-8	0.096

Inhibition of B-cell Activation - B cell FLIPR assay in Ramos cells

Inhibition of B-cell activation by compounds of the present invention is demonstrated by determining the effect of the test compounds on anti-IgM stimulated B cell responses.

The B cell FLIPR assay is a cell based functional method of determining the effect of potential inhibitors of the intracellular calcium increase from stimulation by an anti-IgM antibody. Ramos cells (human Burkitt's lymphoma cell line. ATCC-No. CRL-1596) were cultivated in Growth Media (described below). One day prior to assay, Ramos cells were resuspended in fresh growth media (same as above) and set at a concentration of 0.5 x 10^6/mL in tissue culture flasks. On day of assay, cells are counted and set at a concentration of 1 x 10^6/mL in growth media supplemented with 1μM FLUO-3AM (TefLabs Cat-No. 0116, prepared in anhydrous DMSO and 10% Pluronic acid) in a tissue culture flask, and incubated at 37° C (4% CO_2) for one h. To remove extracellular dye, cells were collected by centrifugation (5min, 1000 rpm), resuspended in FLIPR buffer (described below) at 1 x 10^6 cells/mL and then dispensed into 96-well poly-D-lysine coated black/clear plates (BD Cat-No. 356692) at 1 x 10^5 cells per well. Test compounds were added at various concentrations ranging from 100 μM to 0.03 μM (7 concentrations, details below), and allowed to incubate with cells for 30 min at RT. Ramos cell Ca^{2+} signaling was stimulated by the addition of 10 μg/mL anti-IgM (Southern Biotech, Cat-No. 2020-01) and

measured on a FLIPR (Molecular Devices, captures images of 96 well plates using a CCD camera with an argon laser at 480nM excitation).

Media/Buffers:

Growth Medium: RPMI 1640 medium with L-glutamine (Invitrogen, Cat-No. 61870-010), 10% Fetal Bovine Serum (FBS, Summit Biotechnology Cat-No. FP-100-05); 1mM Sodium Pyruvate (Invitrogen Cat. No. 11360-070).

FLIPR buffer: HBSS (Invitrogen, Cat-No. 141175-079), 2mM $CaCl_2$ (Sigma Cat-No. C-4901), HEPES (Invitrogen, Cat-No. 15630-080), 2.5mM Probenecid (Sigma, Cat-No. P-8761), 0.1% BSA (Sigma, Cat-No.A-7906), 11mM Glucose (Sigma, Cat-No.G-7528).

Compound dilution details:

In order to achieve the highest final assay concentration of 100 μM, 24 μL of 10 mM compound stock solution (made in DMSO) is added directly to 576 μL of FLIPR buffer. The test compounds are diluted in FLIPR Buffer (using Biomek 2000 robotic pipettor) resulting in the following dilution scheme: vehicle, 1.00×10^{-4} M, 1.00×10^{-5}, 3.16×10^{-6}, 1.00×10^{-6}, 3.16×10^{-7}, 1.00×10^{-7}, 3.16×10^{-8}.

Assay and Analysis:

Intracellular increases in calcium were reported using a max – min statistic (subtracting the resting baseline from the peak caused by addition of the stimulatory antibody using a Molecular Devices FLIPR control and statistic exporting software. The IC_{50} was determined using a non-linear curve fit (GraphPad Prism software).

Pharmaceutical compositions of the subject Compounds for administration via several routes were prepared as described in this Example.

Composition for Oral Administration (A)

Ingredient	% wt./wt.
Active ingredient	20.0%
Lactose	79.5%

Magnesium stearate	0.5%

The ingredients are mixed and dispensed into capsules containing about 100 mg each; one capsule would approximate a total daily dosage.

Composition for Oral Administration (B)

Ingredient	% wt./wt.
Active ingredient	20.0%
Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidine)	1.0%

The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

Composition for Oral Administration (C)

Ingredient	% wt./wt.
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g

Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

The ingredients are mixed to form a suspension for oral administration.

Parenteral Formulation (D)

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection to	100 ml

The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

Suppository Formulation (E)

Ingredient	% wt./wt.
Active ingredient	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

Topical Formulation (F)

Ingredients	grams
Active compound	0.2-2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. 100

Mouse Collagen-induced arthritis (mCIA)

On day 0 mice are injected at the base of the tail or several spots on the back with an emulsion of Type II Collagen (i.d.) in Complete Freund's adjuvant (CFA). Following collagen immunization, animals will develop arthritis at around 21 to 35 days. The onset of arthritis is synchronized (boosted) by systemic administration of collagen in Incomplete Freund's adjuvant (IFA; i.d.) at day 21. Animals are examined daily after day 20 for any onset of mild arthritis (score of 1 or 2; see score description below) which is the signal to boost. Following boost, mice are scored and dosed with candidate therapeutic agents for the prescribed time (typically 2—3 weeks) and dosing frequency, daily (QD) or twice-daily (BID).

Rat Collagen-induced arthritis (rCIA)

On day 0, rats are injected with an emulsion of Bovine Type II Collagen in Incomplete Freund's adjuvant (IFA) is injected intradermally (i.d.) on several locations on the back. A booster injection of collagen emulsion is given around day 7, (i.d.) at the base of the tail or alternative sites on the back. Arthritis is generally observed 12-14 days after the initial collagen injection. Animals may be evaluated for the development of arthritis as described below (Evaluation of arthritis) from day 14 onwards. Animals are dosed with candidate therapeutic agents in a preventive fashion starting at the time of secondary challenge and for the prescribed time (typically 2—3 weeks) and dosing frequency, daily (QD) or twice-daily (BID).

Evaluation of Arthritis:

In both models, developing inflammation of the paws and limb joints is quantified using a scoring system that involves the assessment of the 4 paws following the criteria described below:

Scoring: 1= swelling and/or redness of paw or one digit.

2= swelling in two or more joints.

3= gross swelling of the paw with more than two joints involved.

4= severe arthritis of the entire paw and digits.

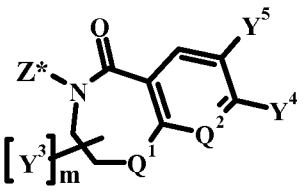
Evaluations are made on day 0 for baseline measurement and starting again at the first signs or swelling for up to three times per week until the end of the experiment. The arthritic index for each mouse is obtained by adding the four scores of the individual paws, giving a maximum score of 16 per animal.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

Claims

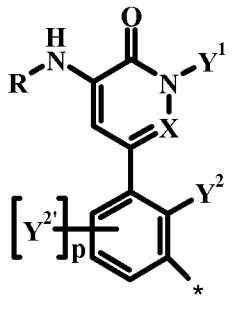
1. A compound of Formula A,



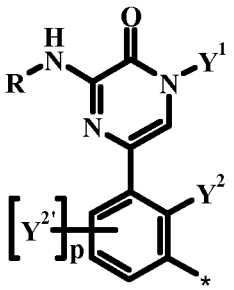
(A)

wherein:

Z* is selected from the group consisting of:



;



;

and wherein:

Q^1 is NH or O;

Q^2 is N or $C(Y^6)$;

R is H, $-R^1$, $-R^1-R^2-R^3$, $-R^1-R^3$, or $-R^2-R^3$;

R^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with one or more lower alkyl, hydroxy, hydroxy lower alkyl, lower alkoxy, halo, nitro, amino, amido, cyano, oxo, or halo-lower alkyl;

R^2 is $-C(=O)$, $-C(=O)O$, $-C(=O)NR^{2'}$, $-NHC(=O)O$, $-C(=NH)NR^{2'}$, or $-S(=O)_2$;

$R^{2'}$ is H or lower alkyl;

R^3 is H or R^4;

R^4 is lower alkyl, amino, aryl, arylalkyl, alkylaryl, heteroaryl, alkyl heteroaryl, heteroaryl alkyl, cycloalkyl, alkyl cycloalkyl, cycloalkyl alkyl, heterocycloalkyl, alkyl heterocycloalkyl, or heterocycloalkyl alkyl, and is optionally substituted with one or more lower alkyl, hydroxy, lower alkoxy, hydroxy lower alkyl, hydroxy lower alkoxy, lower alkyl sulfonyl, lower alkyl sulfonamido, carbamate, carboxy, ester, amido, acyl, halo, nitro, amino, cyano, oxo, or halo-lower alkyl;

X is CH or N;

Y^1 is H, lower alkyl, or lower haloalkyl;

Y^2 is Y^{2a} or Y^{2b};

Y^{2a} is H or halogen;

Y^{2b} is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2b'}$;

$Y^{2b'}$ is hydroxy or halogen;

each $Y^{2'}$ is independently $Y^{2'a}$ or $Y^{2'b}$;

$Y^{2'a}$ is halogen or hydroxy;

$Y^{2'b}$ is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2'b'}$;

$Y^{2'b'}$ is hydroxy or halogen;

p is 0, 1, or 2;

Y^3 is Y^{3a} or Y^{3b};

Y^{3a} is halogen or hydroxy;

Y^{3b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

Y^4 is Y^{4a}, Y^{4b}, Y^{4c}, or Y^{4d};

Y^{4a} is hydroxy or halogen;

Y^{4b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

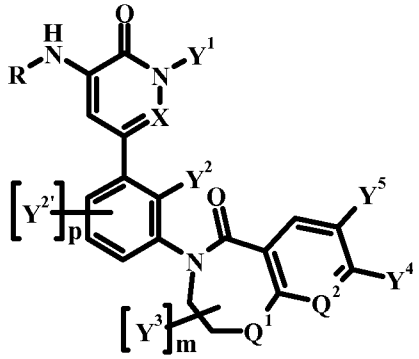
Y^{4d} is amino, optionally substituted with one or more lower alkyl, alkoxy lower alkyl, or hydroxy lower alkyl;

Y^5 is halogen, hydroxy, lower alkyl, lower alkoxy, lower haloalkoxy, lower hydroxyalkyl, or lower haloalkyl; and

Y^6 is H, hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower thioalkyl, amino, or lower hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula I according to claim 1,



I

wherein:

Q^1 is NH or O;

Q^2 is N or $C(Y^6)$;

R is H, $-R^1$, $-R^1-R^2-R^3$, $-R^1-R^3$, or $-R^2-R^3$;

R^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with one or more lower alkyl, hydroxy, hydroxy lower alkyl, lower alkoxy, halo, nitro, amino, amido, cyano, oxo, or halo-lower alkyl;

R^2 is $-C(=O)$, $-C(=O)O$, $-C(=O)NR^{2'}$, $-NHC(=O)O$, $-C(=NH)NR^{2'}$, or $-S(=O)_2$;

$R^{2'}$ is H or lower alkyl;

R^3 is H or R^4;

R^4 is lower alkyl, amino, aryl, arylalkyl, alkylaryl, heteroaryl, alkyl heteroaryl, heteroaryl alkyl, cycloalkyl, alkyl cycloalkyl, cycloalkyl alkyl, heterocycloalkyl, alkyl heterocycloalkyl, or heterocycloalkyl alkyl, and is optionally substituted with one or more lower alkyl, hydroxy, lower alkoxy, hydroxy lower alkyl, hydroxy lower alkoxy, lower alkyl sulfonyl, lower alkyl sulfonamido, carbamate, carboxy, ester, amido, acyl, halo, nitro, amino, cyano, oxo, or halo-lower alkyl;

X is CH or N;

Y^1 is H, lower alkyl, or lower haloalkyl;

Y^2 is Y^{2a} or Y^{2b};

Y^{2a} is H or halogen;

Y^{2b} is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2b'}$;

$Y^{2b'}$ is hydroxy or halogen;

each $Y^{2'}$ is independently $Y^{2'a}$ or $Y^{2'b}$;

$Y^{2'a}$ is halogen or hydroxy;

$Y^{2'b}$ is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2'b'}$;

$Y^{2'b'}$ is hydroxy or halogen;

p is 0, 1, or 2;

Y^3 is Y^{3a} or Y^{3b};

Y^{3a} is halogen or hydroxy;

Y^{3b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

Y^4 is Y^{4a}, Y^{4b}, Y^{4c}, or Y^{4d};

Y^{4a} is hydroxy or halogen;

Y^{4b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4d} is amino, optionally substituted with one or more lower alkyl, alkoxy lower alkyl, or hydroxy lower alkyl;

Y^5 is halogen, hydroxy, lower alkyl, lower alkoxy, lower haloalkoxy, lower hydroxyalkyl, or lower haloalkyl; and

Y^6 is H, hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower thioalkyl, amino, or lower hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2, wherein Y^1 is methyl.

4. The compound of claim 3, wherein m is 0.

5. The compound of claim 4, wherein p is 0.

6. The compound of claim 5, wherein Y^2 is hydroxymethyl.

7. The compound of claim 6, wherein Y^4 is *tert*-butyl, dimethylamine, or cyclopropyl.

8. The compound of claim 7, wherein R is $–R^1–R^2–R^3$; R^1 is phenyl or pyridyl; R^2 is –C(=O); R^3 is R^4; and R^4 is morpholine or piperazine, optionally substituted with one or more lower alkyl.

9. The compound of claim 8, wherein Y^5 is fluorine.

10. The compound of claim 7 wherein X is CH.

11. The compound of claim 10, wherein Q^1 is NH

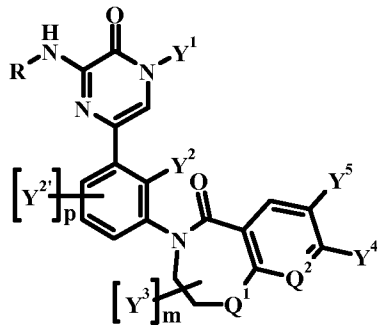
12. The compound of claim 10, wherein Q^1 is O.

13. The compound of claim 7, wherein X is N.

14. The compound of claim 13, wherein Q^1 is NH

15. The compound of claim 13, wherein Q^1 is O.

16. A compound of Formula II according to claim 1,



II

wherein:

Q^1 is NH or O;

Q^2 is N or $C(Y^6)$;

R is H, $-R^1$, $-R^1-R^2-R^3$, $-R^1-R^3$, or $-R^2-R^3$;

R^1 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, and is optionally substituted with one or more lower alkyl, hydroxy, hydroxy lower alkyl, lower alkoxy, halo, nitro, amino, amido, cyano, oxo, or halo-lower alkyl;

R^2 is $-C(=O)$, $-C(=O)O$, $-C(=O)NR^{2'}$, $-NHC(=O)O$, $-C(=NH)NR^{2'}$, or $-S(=O)_2$;

$R^{2'}$ is H or lower alkyl;

R^3 is H or R^4;

R^4 is lower alkyl, amino, aryl, arylalkyl, alkylaryl, heteroaryl, alkyl heteroaryl, heteroaryl alkyl, cycloalkyl, alkyl cycloalkyl, cycloalkyl alkyl, heterocycloalkyl,

alkyl heterocycloalkyl, or heterocycloalkyl alkyl, and is optionally substituted with one or more lower alkyl, hydroxy, lower alkoxy, hydroxy lower alkyl, hydroxy lower alkoxy, lower alkyl sulfonyl, lower alkyl sulfonamido, carbamate, carboxy, ester, amido, acyl, halo, nitro, amino, cyano, oxo, or halo-lower alkyl;

Y^1 is H, lower alkyl, or lower haloalkyl;

Y^2 is Y^{2a} or Y^{2b};

Y^{2a} is H or halogen;

Y^{2b} is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2b'}$;

$Y^{2b'}$ is hydroxy or halogen;

each $Y^{2'}$ is independently $Y^{2'a}$ or $Y^{2'b}$;

$Y^{2'a}$ is halogen or hydroxy;

$Y^{2'b}$ is lower alkoxy or lower alkyl, optionally substituted with one or more $Y^{2'b'}$;

$Y^{2'b'}$ is hydroxy or halogen;

p is 0, 1, or 2;

Y^3 is Y^{3a} or Y^{3b};

Y^{3a} is halogen or hydroxy;

Y^{3b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

Y^4 is Y^{4a}, Y^{4b}, Y^{4c}, or Y^{4d};

Y^{4a} is hydroxy or halogen;

Y^{4b} is lower alkoxy or lower alkyl, optionally substituted with one or more substituents selected from the group consisting of lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, amino, cyano, and lower alkoxy;

Y^{4d} is amino, optionally substituted with one or more lower alkyl, alkoxy lower alkyl, or hydroxy lower alkyl;

Y^5 is halogen, hydroxy, lower alkyl, lower alkoxy, lower haloalkoxy, lower hydroxyalkyl, or lower haloalkyl; and

Y^6 is H, hydroxy, halogen, lower alkyl, lower haloalkyl, lower alkoxy, lower thioalkyl, amino, or lower hydroxyalkyl;

or a pharmaceutically acceptable salt thereof.

17. A method for treating an inflammatory and/or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of the Btk inhibitor compound of any one of claims 1-16.

18. A pharmaceutical composition comprising the Btk inhibitor compound of any one of claims 1-16, admixed with at least one pharmaceutically acceptable carrier, excipient or diluent.

19. A compound of any one of claims 1-16 for use in treating an inflammatory and/or autoimmune condition.

20. The invention as hereinbefore described.