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.

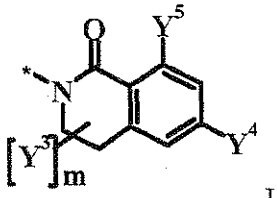
Btk is a member of the Tec family of tyrosine kinases, and has been shown to be a critical regulator of early B-cell development and mature B-cell activation and survival (Khan *et al. Immunity* 1995 3:283; Ellmeier *et al. J. Exp. Med.* 2000 192:1611). Mutation of Btk in humans leads to the condition 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.

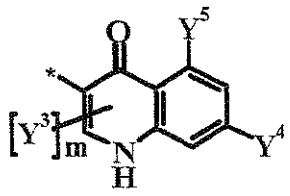
Evidence for a role for Btk in autoimmune and inflammatory diseases has also been provided by Btk-deficient mouse models. In preclinical murine models of systemic lupus erythematosus (SLE), Btk-deficient mice show marked amelioration of disease progression. In addition, Btk-deficient mice are resistant 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).

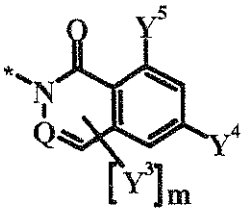
Btk is also expressed by cells other than B-cells that may be involved in disease processes. For example, Btk is expressed by mast cells and Btk-deficient bone marrow derived mast cells demonstrate impaired antigen induced degranulation (Iwaki *et al. J. Biol. Chem.* 2005 280:40261). This shows Btk could 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 the Btk inhibitor compounds of Formula A or Formulae I-III, methods of use thereof, as described herein below:

The application provides, in a first aspect, a compound ~~of~~ of Formula A,


Ia


IIa


IIIa

wherein:

Q is $C(Y^3)$ or N;

each Y^3 is independently H, halogen, or lower alkyl, wherein lower alkyl is 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}; wherein

Y^{4a} is H or halogen;

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

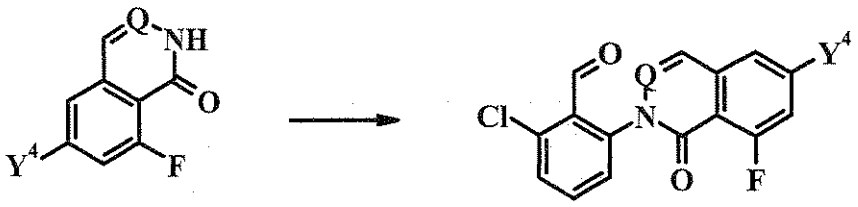
Y^{4c} is lower cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of lower alkyl, lower haloalkyl, halogen, hydroxy, hydroxy lower alkyl, amino, cyano, and lower alkoxy;

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

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

or a pharmaceutically acceptable salt thereof.

In a second aspect, there is provided a process of preparing the compound as defined herein, comprising the step of:



VI VII

treating a compound of formula VI with 2-chloro-6-fluorobenzaldehyde and a metal carbonate to form a compound of formula VII.

In a third aspect, there is provided a process of preparing the compound as defined herein, comprising the steps of:

a) cyclizing a derivative of 2-dimethoxymethyl-6-fluoro-benzoic acid with hydrazine hydrate; and

b) treating the product of step a) with 2-chloro-6-fluorobenzaldehyde and cesium carbonate; or

comprising the steps of:

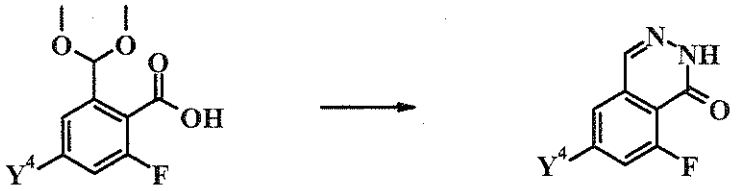


IV V

a) formylation of an aryl bromide using a combination of a Grignard reagent and an alkyl lithium at a non-cryogenic temperature to yield the compound of formula IV;

b) ortholithiation the compound of formula IV, wherein Y^4 is lower alkyl or cycloalkyl; and

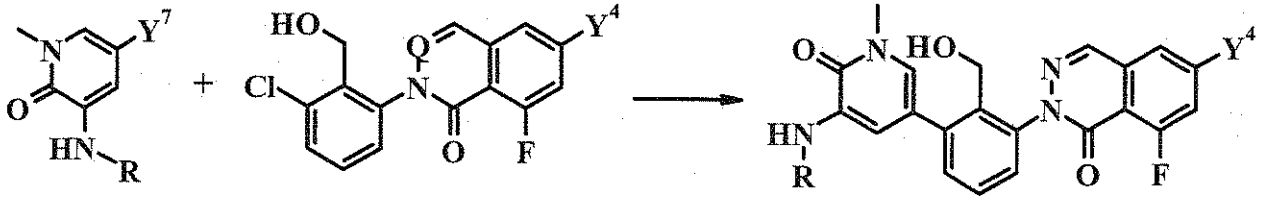
c) carboxylation of the product of step b) to form a compound of formula V, and optionally further comprising the step of:



V VI

d) cyclizing the compound of formula V with hydrazine to form a compound of formula VI, wherein Y^4 is lower alkyl or cycloalkyl.

In a fourth aspect, there is provided a process of preparing the compound as defined herein, comprising the steps of:

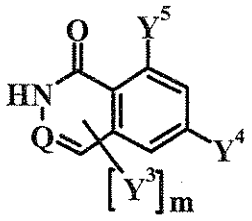


IX VIII X

a) heating a compound of formula IX, wherein Y^7 is boronic acid or pinacol boronate, to about 40 °C to 150 °C, in the presence of a palladium catalyst, base, and a phosphine; and

b) treating the product of step a) with approximately 20% aqueous 1,4-dioxane to form a compound of formula X.

In a fifth aspect, there is provided a compound of formula VI



VI wherein:

Q is CH or N;

each Y^3 is independently H, halogen, or lower alkyl, wherein lower alkyl is optionally substituted with one or more substituents selected from the group consisting of hydroxy, lower alkoxy, amino, and halogen;

m is 0 or 1;

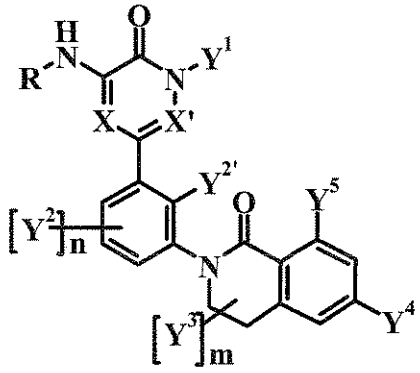
Y^4 is Y^{4a} or Y^{4b};

Y^{4a} is lower alkyl or cycloalkyl, optionally substituted with one or more hydroxy, lower alkoxy, or halogen;

Y^{4b} is amino, lower alkyl amino, or lower dialkyl amino; and

Y^5 is halogen.

The application provides a compound of Formula I,



I