

1585-1590; Takeshita, *Int. Immunol.* **1998**, *10*, 435-4444; Whyburn, *J. Immunol.* **2003**, *171*, 1850-1858), BTK inhibitors may offer therapeutic benefit to SLE patients.

Within myeloid cells, BTK signal transduction is necessary for the stimulated release of inflammatory cytokines such as TNF α from stimulated monocytes (Horwood, *J. Exp. Med.* **2003**, *197*, 1603-1611) and for optimal actin cytoskeletal organization and lacunar bone resorption in isolated osteoclasts (Danks, *J. Bone Miner. Res.* **2010**, *26*, 182-192). Bone marrow derived mast cells lacking BTK exhibit impaired activation-induced degranulation and cytokine release. Given the role of BTK in signal transduction processes across multiple cell types implicated in the pathogenesis of autoimmune and allergic disorders, inhibition of BTK activity may provide clinical benefit in diseases such as RA, MS, SLE, lupus nephritis, Sjogren's disease, vasculitis, asthma and allergic disorders.

SUMMARY

Currently, compounds such as A and C (discussed below), and those depicted in, for example, PCT publication number WO2014025976 are known as BTK inhibitors. However, as provided herein below, these compounds cross-react with and inhibit other kinases. Hence, these representatives are not selective for BTK over other targets. The lack of selective BTK inhibition increases the likelihood of adverse effects in a clinical setting.

Beside efficacy and selectivity, a therapeutic compound must have a favorable safety profile such as cardiovascular safety. One parameter for assessing the cardiovascular (CV) safety of a compound is the mean arterial pressure (MAP). A statistically significant change in MAP in a pre-clinical rat CV safety study is indicative of adverse cardiovascular events in human. As provided herein below, comparative compounds A, B, and C show statistically significant increases in MAP in a rat CV study. The data suggests that these compounds may not have a favorable cardiovascular safety profile in human.

In view of the above-mentioned safety concerns with the other known BTK inhibitors, there still remains a need for additional compounds that are highly selective for BTK inhibition and do not have an adverse impact on relevant cardiovascular parameters such as MAP.

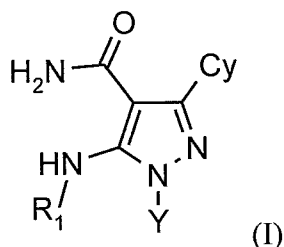
The compounds of the present disclosure maintain the requisite potent inhibitory activity against

BTK to treat the aforementioned BTK-related diseases, and solve the selectivity and cardiovascular safety problems associated with other known BTK inhibitors such as those represented by comparative compounds A, B, and C (discussed below). The BTK selectivity and the favorable cardiovascular safety profile that are demonstrated by the compounds of the instant invention represent unexpected and surprising improvements over other known BTK inhibitors.

In particular, the compounds of the present disclosure solve the efficacy and safety problems associated with other known BTK inhibitors by maintaining a high level of potency and selectivity in inhibiting the BTK activity without having any statistically significant effects on MAP.

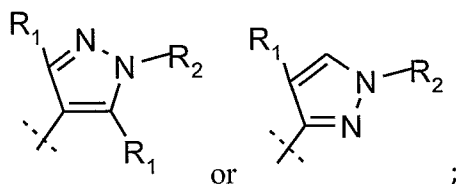
Accordingly, this disclosure comprises a novel class of heteroaromatic compounds and methods for making and using the same. These compounds are useful for the treatment of autoimmune and allergic disorders in that they exhibit excellent inhibitory effect upon BTK.

In a first generic embodiment, there is provided a compound of the formula (I)



in which:

Cy is chosen from



each R₁ is independently chosen from hydrogen or methyl;

R₂ is L-Ar, wherein Ar is phenyl or pyridinyl and each is optionally substituted by one or more of halogen, halo C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CN, halo C₁₋₄ alkoxy, or cycloalkyl;

L is -(CH₂)- or -(CHCH₃)-;

Y is C₆-C₈ spirocycle containing 1 ring nitrogen atom, and is substituted by one R₃;

each R₄ is independently chosen from hydrogen, methyl, or cyclopropyl;
or a pharmaceutically acceptable salt or hydrate thereof.

In a further embodiment, there is provided a compound of the formula (I) according to any of the embodiments herein-above and in which:

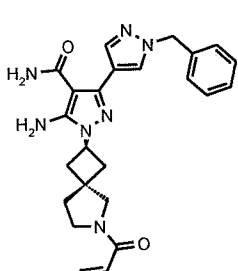
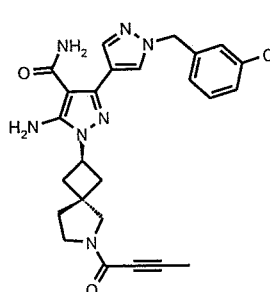
R₂ is L-Ar, wherein Ar is phenyl or pyridinyl and each is optionally substituted by one or more of halogen, halomethyl, methyl, methoxy, -CN, halomethoxy, or cyclopropyl;

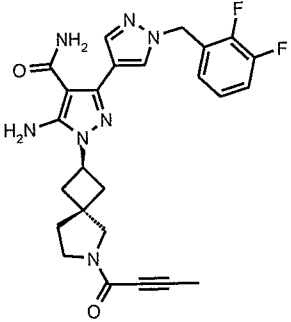
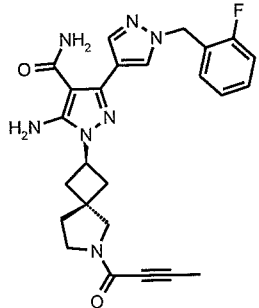
L is -(CH₂)- or -(CHCH₃)-

or a pharmaceutically acceptable salt or hydrate thereof..

In another embodiment, the disclosure provides compounds in Table I which can be made in view of the general schemes, examples and methods described herein and those known in the art.

Table I, Biological and physical properties of representatives of the present invention

Example	Structure	BTK IC ₅₀ (nM)	HPLC Method	RT (min)	<i>m/z</i> [M+H] ⁺
1		36	A	0.65	446.4
2		0.3	B	0.596	491.1

59		0.3	B	0.707	494.2
60		0.5	B	0.688	476.3

In a second generic embodiment, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the first embodiment or any of its related embodiments or a pharmaceutically acceptable salt thereof.

There is provided a method of treating a disease chosen from rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, Sjogren's disease, vasculitis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis, comprising administering to a patient a therapeutically effective amount of a compound according to the first embodiment or any of its related embodiments or a pharmaceutically acceptable salt thereof. In a third generic embodiment, there is provided use of a compound according to the first embodiment or any of its related embodiments or a pharmaceutically acceptable salt or hydrate thereof for the manufacture of a medicament for the treatment of a disease chosen from rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, Sjogren's disease, vasculitis, scleroderma, asthma, allergic rhinitis, allergic eczema, B cell lymphoma, multiple sclerosis, juvenile rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, graft versus host disease, psoriatic arthritis, ankylosing spondylitis and uveitis.

In a forth generic embodiment, there is provided a process for preparation of a compound according to the first embodiment or any of its related embodiments by:

(i) coupling a compound of formula **A**