

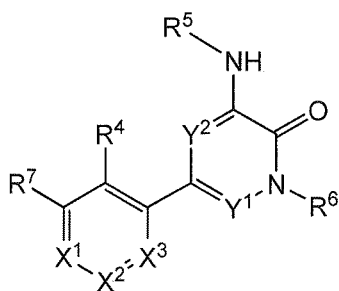
induced arthritis and can be less susceptible to Staphylococcus-induced arthritis. A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, represent an approach to the treatment of a number of autoimmune and/or inflammatory diseases. Because of Btk's role in B-cell activation, inhibitors of Btk can be useful as inhibitors of B-cell mediated pathogenic activity (such as autoantibody production). Btk is also expressed in osteoclasts, mast cells and monocytes and has been shown to be important for the function of these cells. For example, Btk deficiency in mice is associated with impaired IgE-mediated mast cell activation (marked diminution of TNF-alpha and other inflammatory cytokine release), and Btk deficiency in humans is associated with greatly reduced TNF-alpha production by activated monocytes.

Thus, inhibition of Btk activity can be useful for the treatment of allergic disorders and/or autoimmune and/or inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, and asthma (Di Paolo et al (2011) Nature Chem. Biol. 7(1):41-50; Liu et al (2011) Jour. of Pharm. and Exper. Ther. 338(1):154-163). In addition, Btk has been reported to play a role in apoptosis; thus, inhibition of Btk activity can be useful for cancer, as well as the treatment of B-cell lymphoma, leukemia, and other hematological malignancies. Moreover, given the role of Btk in osteoclast function, the inhibition of Btk activity can be useful for the treatment of bone disorders such as osteoporosis. Specific Btk inhibitors have been reported (Liu (2011) Drug Metab. and Disposition 39(10):1840-1849; US 7884108, WO 2010/056875; US 7405295; US 7393848; WO 2006/053121; US 7947835; US 2008/0139557; US 7838523; US 2008/0125417; US 2011/0118233; PCT/US2011/050034 "PYRIDINONES/PYRAZINONES, METHOD OF MAKING, AND METHOD OF USE THEREOF", filed 31 Aug 2011; PCT/US2011/050013 "PYRIDAZINONES, METHOD OF MAKING, AND METHOD OF USE THEREOF", filed 31 Aug 2011; US Ser. No. 13/102720 "PYRIDONE AND AZA-PYRIDONE COMPOUNDS AND METHODS OF USE", filed 6 May 2011).

~~SUMMARY OF THE INVENTION~~

The ~~invention~~ disclosure relates generally to Formula I, heteroaryl pyridone and aza-pyridone compounds with Bruton's Tyrosine Kinase (Btk) modulating activity.

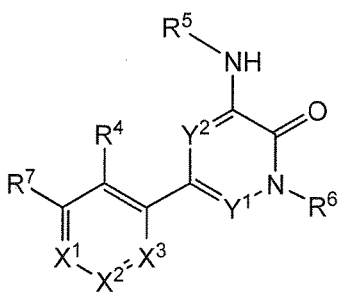
Formula I compounds have the structures:



I

including stereoisomers, tautomers, or pharmaceutically acceptable salts thereof. The various substituents are defined herein below.

One aspect of the disclosure is a compound selected from Formula I:



I

or stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, wherein:

X¹ is CR¹ or N;

X² is CR² or N;

X³ is CR³ or N;

where one or two of X¹, X², and X³ are N;

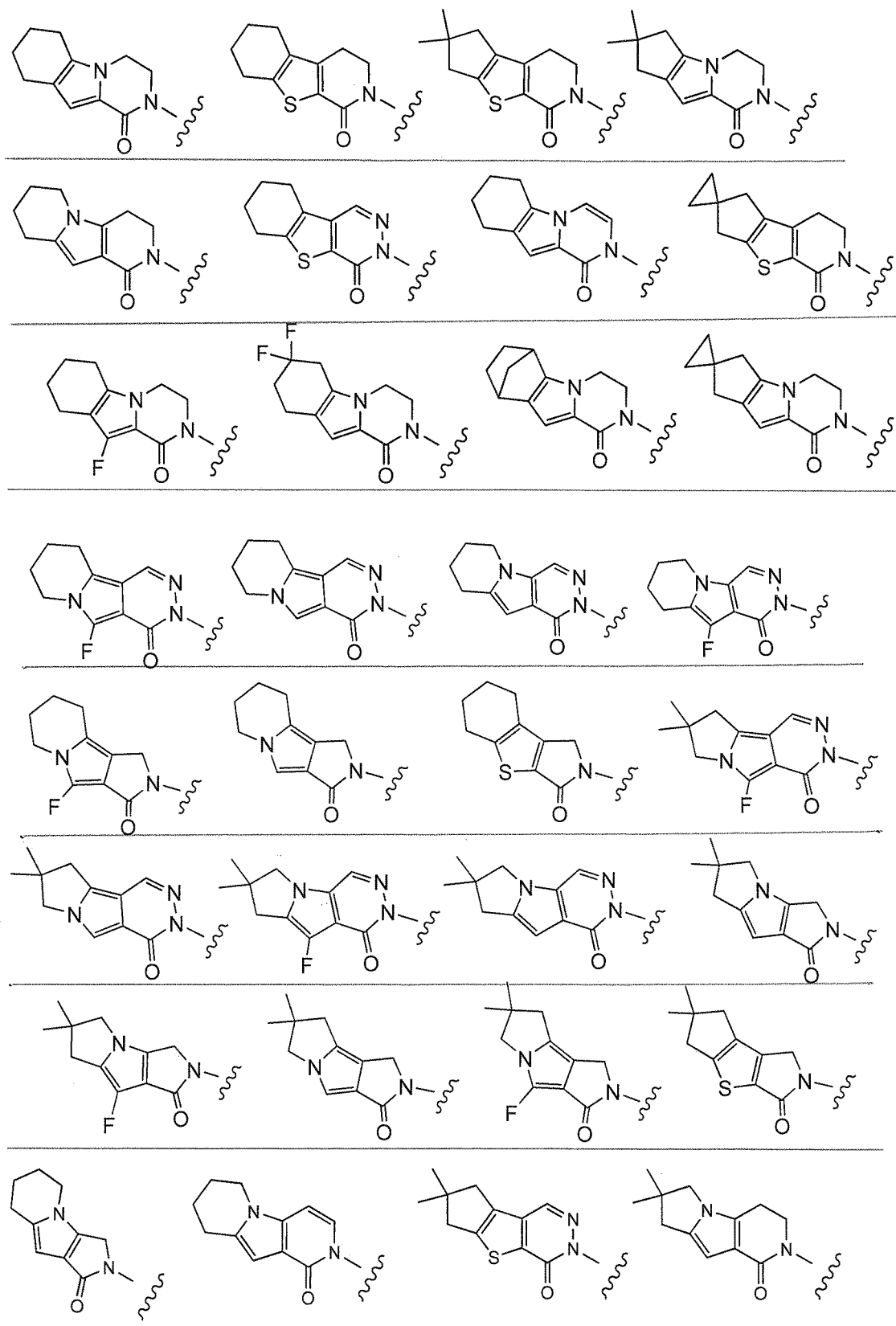
R¹, R² and R³ are independently selected from H, F, Cl, -NH₂, -NHCH₃, -N(CH₃)₂, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂OH, and C₁-C₃ alkyl;

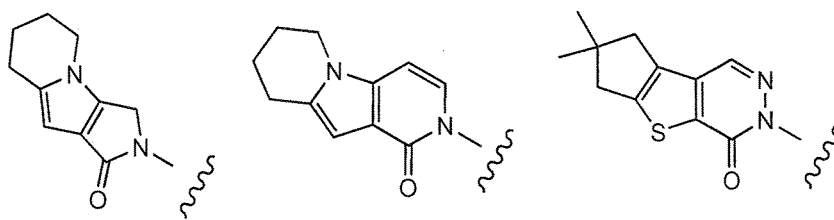
R⁴ is selected from H, F, Cl, CN, -CH₂OH, -CH(CH₃)OH, -C(CH₃)₂OH, -CH(CF₃)OH, -CH₂F, -CHF₂, -CH₂CHF₂, -CF₃, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -NHC(O)CH₃, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂OH, cyclopropyl, cyclopropylmethyl, 1-hydroxycyclopropyl, imidazolyl, pyrazolyl, 3-hydroxy-oxetan-3-yl, oxetan-3-yl, and azetidin-1-yl;

R⁵ is optionally substituted C₆-C₂₀ aryl, C₃-C₁₂ carbocyclyl, C₂-C₂₀ heterocyclyl, C₁-C₂₀ heteroaryl, -(C₆-C₂₀ aryl)-(C₂-C₂₀ heterocyclyl), -(C₁-C₂₀ heteroaryl)-(C₂-C₂₀ heterocyclyl), -(C₁-C₂₀ heteroaryl)-(C₂-C₂₀ heterocyclyl)-(C₂-C₂₀ heterocyclyl), -(C₁-C₂₀ heteroaryl)-(C₂-C₂₀ heterocyclyl)-(C₁-C₆ alkyl), -(C₁-C₂₀ heteroaryl)-(C₁-C₆ alkyl), -(C₂-C₂₀ heterocyclyl)-(C₁-C₆ alkyl), -(C₂-C₂₀ heterocyclyl)-(C₃-C₁₂ carbocyclyl), -(C₁-C₂₀ heteroaryl)-(C₃-C₁₂ carbocyclyl), or -(C₁-C₂₀ heteroaryl)-C(=O)-(C₂-C₂₀ heterocyclyl);

R^6 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-CHF_2$, $-NH_2$, or $-OH$;

R^7 is selected from the structures:





where the wavy line indicates the site of attachment; and

Y^1 and Y^2 are independently selected from CH and N, where Y^1 and Y^2 are not each

N;

- 5 where alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, $-\text{CN}$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{OH})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$, $-\text{CH}_2\text{OP}(\text{O})(\text{OH})_2$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}(\text{CH}_3)\text{CN}$, $-\text{C}(\text{CH}_3)_2\text{CN}$, $-\text{CH}_2\text{CN}$, $-\text{CO}_2\text{H}$, $-\text{COCH}_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{C}(\text{CH}_3)_3$, $-\text{COCH}(\text{OH})\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $-\text{CON}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{NH}_2$, $-\text{NHCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NHCOCH}_3$, $-\text{N}(\text{CH}_3)\text{COCH}_3$, $-\text{NHS}(\text{O})_2\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CONH}_2$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{NO}_2$, $=\text{O}$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OP}(\text{O})(\text{OH})_2$, $-\text{S}(\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{SCH}_3$, $-\text{S}(\text{O})_2\text{CH}_3$, $-\text{S}(\text{O})_3\text{H}$, cyclopropyl, oxetanyl, azetidiny, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, and morpholino
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One ~~Another~~ aspect of the ~~disclosure invention~~ is a pharmaceutical composition comprised of a Formula I compound and a pharmaceutically acceptable carrier, glidant, diluent, or excipient. The pharmaceutical composition may further comprise a second therapeutic agent.

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Another aspect of the ~~disclosure invention~~ is a process for making a pharmaceutical composition which comprises combining a Formula I compound with a pharmaceutically acceptable carrier.

Another aspect of the disclosure is a pharmaceutical composition as defined above for use in the treatment of a disease or disorder selected from immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Bruton's tyrosine kinase.

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The ~~disclosure invention~~ includes a method of treating a disease or disorder which method comprises administering a therapeutically effective amount of a Formula I compound to a patient with a disease or disorder selected from immune disorders, cancer, cardiovascular

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disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Bruton's tyrosine kinase.

Another aspect of the disclosure ~~The invention~~ includes a kit for treating a condition mediated by Bruton's tyrosine kinase, comprising: a) a first pharmaceutical composition
5 comprising a Formula I compound; and b) instructions for use.

The ~~disclosure invention~~ includes a Formula I compound for use as a medicament, and for use in treating a disease or disorder selected from immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Bruton's tyrosine kinase.

10 The ~~disclosure invention~~ includes use of a Formula I compound in the manufacture of a medicament for the treatment of immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and where the medicament mediates Bruton's tyrosine kinase. Another aspect of the disclosure includes use of a pharmaceutical composition as defined above in the manufacture
15 of a medicament for the treatment of immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders; and wherein the medicament mediates the Bruton's tyrosine kinase.

The ~~disclosure invention~~ includes methods of making a Formula I compound.

BRIEF DESCRIPTION OF THE DRAWINGS

–C(CH₃)₂CN, –CH₂CN, –C(O)CH₃, –C(O)CH₂CH₃, –C(O)CH(CH₃)₂, –NH₂, –NHCH₃, –N(CH₃)₂, –OH, –OCH₃, –OCH₂CH₃, –OCH₂CH₂OH, cyclopropyl, and oxetanyl.

11. The compound of claim 1 wherein R⁶ is CH₃.

12. The compound of claim 1 wherein Y¹ is CH and Y² is N.

13. The compound of claim 1 wherein Y¹ is N and Y² is CH.

14. The compound of claim 1 wherein Y¹ and Y² are each CH.

15. The compound of claim 1 wherein Y¹ and Y² are each CH, and R⁶ is CH₃.

16. The compound of claim 1 selected from Table 1.

17. The compound of claim 1 selected from Table 2

18. A pharmaceutical composition comprised of a compound of any one of claims 1 to 17 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

19. The pharmaceutical composition according to claim 18, further comprising a therapeutic agent.

20. A process for making a pharmaceutical composition which comprises combining a compound of any one of claims 1 to 17 with a pharmaceutically acceptable carrier.

~~21. The A method of treating a disease or disorder which comprises administering a therapeutically effective amount of the pharmaceutical composition of claim 18 for use in the treatment of to a patient with a disease or disorder selected from immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Bruton's tyrosine kinase.~~

~~22. The pharmaceutical composition method of claim 21 wherein the disease or disorder is an immune disorder.~~

~~23. The pharmaceutical composition method of claim 22 wherein the immune disorder is rheumatoid arthritis.~~

~~24. The pharmaceutical composition method of claim 21 wherein the disease or disorder is systemic and local inflammation, arthritis, inflammation related to immune suppression, organ transplant rejection, allergies, ulcerative colitis, Crohn's disease, dermatitis, asthma, systemic lupus erythematosus, Sjögren's Syndrome, multiple sclerosis, scleroderma/systemic sclerosis, idiopathic thrombocytopenic purpura (ITP), anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, chronic obstructive pulmonary disease (COPD), psoriasis.~~

~~25. The pharmaceutical composition method of claim 21 wherein the disease or disorder is cancer selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach, skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, non-small cell lung carcinoma (NSCLC), small cell carcinoma, lung~~

adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, pancreatic, myeloid disorders, lymphoma, hairy cells, buccal cavity, naso-pharyngeal, pharynx, lip, tongue, mouth, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, Hodgkin's, leukemia, bronchus, thyroid, liver and intrahepatic bile duct, hepatocellular, gastric, glioma/glioblastoma, endometrial, melanoma, kidney and renal pelvis, urinary bladder, uterine corpus, uterine cervix, multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, lymphocytic leukemia, chronic lymphoid leukemia (CLL), myeloid leukemia, oral cavity and pharynx, non-Hodgkin lymphoma, melanoma, and villous colon adenoma.

26. The ~~pharmaceutical composition method~~ of claim 21 further comprising ~~administering~~ an additional therapeutic agent selected from an anti-inflammatory agent, an immunomodulatory agent, chemotherapeutic agent, an apoptosis-enhancer, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, and an agent for treating immunodeficiency disorders.

27. A kit for treating a condition mediated by Bruton's tyrosine kinase, comprising:

- a) a pharmaceutical composition of claim 18; and
- b) instructions for use.

~~28. The pharmaceutical composition of claim 18 for use as a medicament in treating a disease or disorder selected from immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders, and mediated by Bruton's tyrosine kinase.~~

~~29~~28. Use of a pharmaceutical composition of claim 18 in the manufacture of a medicament for the treatment of immune disorders, cancer, cardiovascular disease, viral infection, inflammation, metabolism/endocrine function disorders and neurological disorders; and wherein the medicament mediates the Bruton's tyrosine kinase.