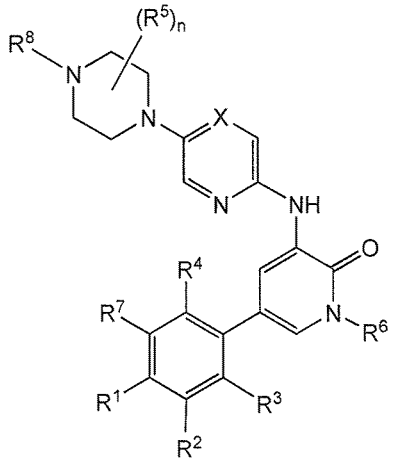
induced arthritis and can be less susceptible to Staphylococcus-induced arthritis. A large body of evidence supports the role of B-cells and the humoral immune system in the pathogenesis of autoimmune and/or inflammatory diseases. Protein-based therapeutics (such as Rituxan) developed to deplete B-cells, 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, alkylated piperazine pyridone compounds with Bruton's Tyrosine Kinase (Btk) modulating activity.

Formula I compounds have the structures:



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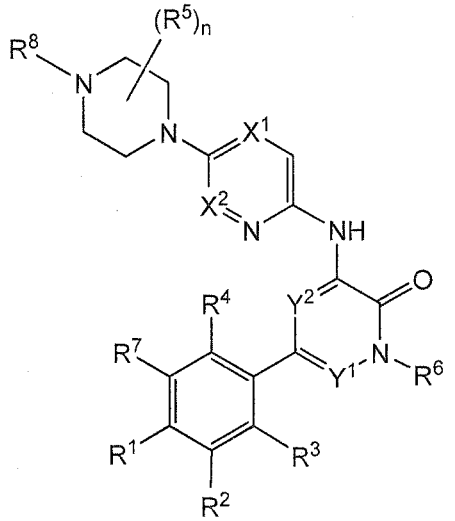
including stereoisomers, tautomers, or pharmaceutically acceptable salts thereof. The various substituents are defined herein below. Hence, one aspect of the disclosure is a compound selected from Formula I:



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

R^1, R^2 and R^3 are independently selected from H, F, Cl, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, and C_1–C_3 alkyl;

R^4 is selected from H, F, Cl, CN, $-CH_2OH$, $-CH(CH_3)OH$, $-C(CH_3)_2OH$, $-CH(CF_3)OH$, $-CH_2F$, $-CHF_2$, $-CH_2CHF_2$, $-CF_3$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(O)CH_3$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, cyclopropyl, cyclopropylmethyl, 1-hydroxycyclopropyl, imidazolyl, pyrazolyl, 3-hydroxy-oxetan-3-yl, oxetan-3-yl, and azetidin-1-yl;

R^5 is selected from $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CN$, and $-CH_2CH_2OH$;

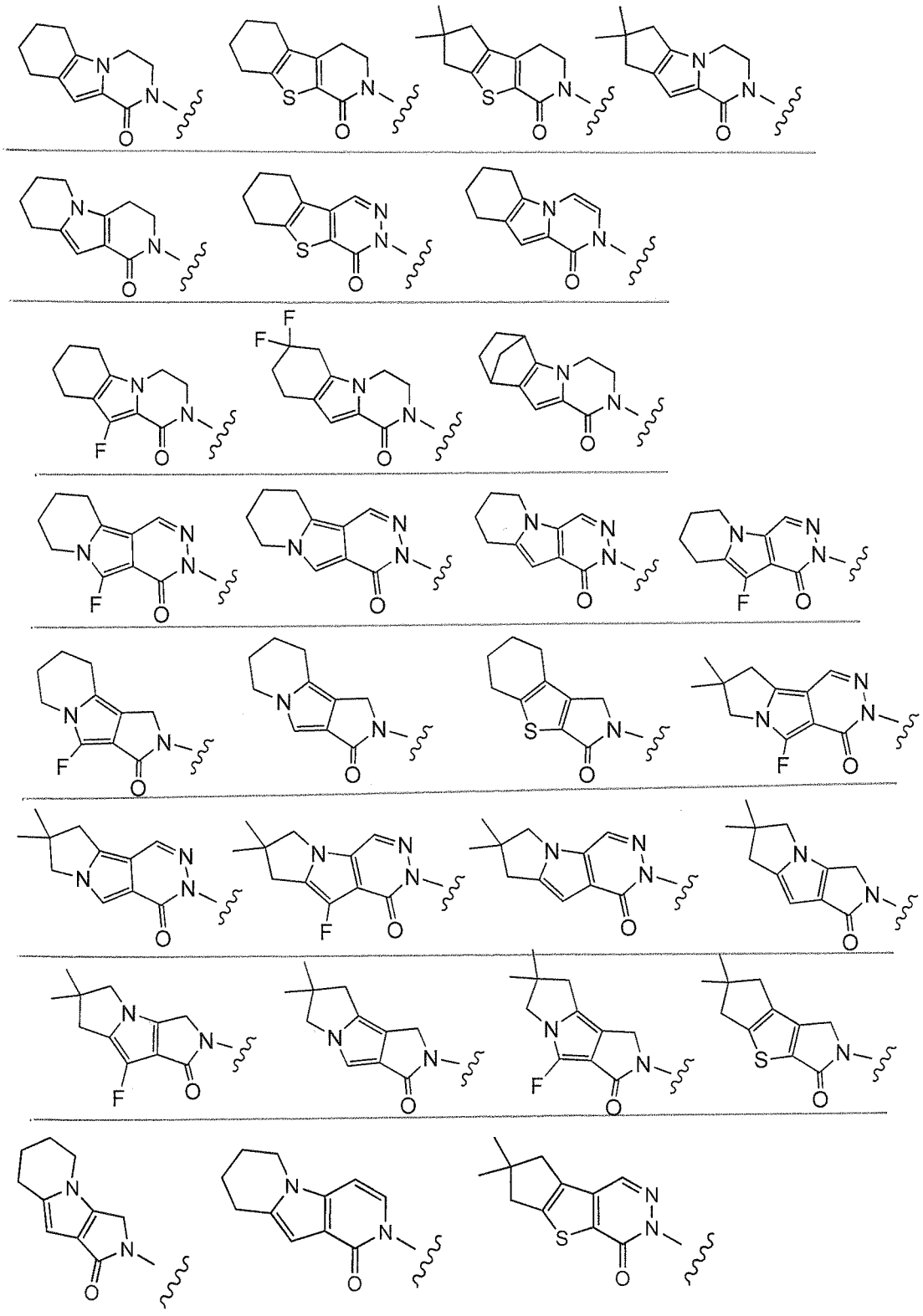
or two R^5 groups form a 3-, 4-, 5-, or 6-membered carbocyclic or heterocyclic ring;

or an R^5 group and an R^8 group form a 3-, 4-, 5-, or 6-membered carbocyclic or heterocyclic ring;

n is 1, 2, 3, or 4;

R^6 is selected from H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-NH_2$, and $-OH$;

R^7 is selected from the structures:



where the wavy line indicates the site of attachment;

R^8 is selected from $-CH_3$, $-S(O)_2CH_3$, cyclopropyl, azetidin-3-yl, oxetan-3-yl, and morpholin-4-yl;

X^1 is CR^9 or N, where R^9 is selected from H, F, Cl, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, and $-OCH_2CH_2OH$;

X^2 is CR^{10} or N, where R^{10} is selected from H, $-CH_3$, $-CH_2CH_3$, and $-CH_2CH_2OH$; and

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

~~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.

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.

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

Another aspect of the ~~The~~ disclosure ~~invention~~ is ~~includes~~ a kit for treating a condition mediated by Bruton's tyrosine kinase, comprising: a) a first pharmaceutical composition 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. Another aspect of the disclosure is the pharmaceutical composition as defined above 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.

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 is use of a pharmaceutical composition as defined above 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.

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

X^2 is CR^{10} or N, where R^{10} is selected from H, $-CH_3$, $-CH_2CH_3$, and $-CH_2CH_2OH$; and Y^1 and Y^2 are independently selected from CH and N, where Y^1 and Y^2 are not each N.

2. The compound of claim 1 wherein X is CR^9, and R^9 is H

3. The compound of claim 1 wherein X is N.

4. The compound of claim 1 wherein R^4 is $-CH_2OH$.

5. The compound of claim 4 wherein R^2 is F.

6. The compound of claim 5 wherein R^1 and R^3 are H.

7. The compound of claim 1 wherein R^6 is CH_3.

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

9. The compound of claim 1 selected from Table 2.

10. A pharmaceutical composition comprised of a compound of any one of claims 1 to 9 and a pharmaceutically acceptable carrier, glidant, diluent, or excipient.

11. The pharmaceutical composition according to claim 10, further comprising a therapeutic agent.

12. A process for making a pharmaceutical composition which comprises combining a compound of any one of claims 1 to 9 with a pharmaceutically acceptable carrier.

13. Use of a ~~A method of treating a disease or disorder which comprises administering a therapeutically effective amount of the~~ pharmaceutical composition of claim 10 in the manufacture of a medicament for 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 wherein the medicament mediate~~sd~~ the ~~by~~ Bruton's tyrosine kinase.

14. The ~~method~~ use of claim 13 wherein the disease or disorder is an immune disorder.

15. The use ~~method~~ of claim 14 wherein the immune disorder is rheumatoid arthritis.

16. The use ~~method~~ of claim 13 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.

17. The use ~~method~~ of claim 13 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.

18. The use ~~method~~ of claim 13 further comprising ~~administering~~ an additional therapeutic agent selected from an anti-inflammatory agent, an immunomodulatory agent, chemotherapeutic agent, 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.

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

a) a pharmaceutical composition of claim 10; and

b) instructions for use.

20. The pharmaceutical composition of claim 10 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.

~~21. Use of a pharmaceutical composition of claim 10 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.~~