FORM 2

THE PATENTS ACT, 1970
(39 of 1970)
AND
THE PATENTS RULES, 2003

COMPLETE SPECIFICATION

(See Section 10; rule 13)

TITLE OF THE INVENTION

"HETEROARYL PYRIDONE AND AZA-PYRIDONE COMPOUNDS AS INHIBITORS OF BTK ACTIVITY"

APPLICANT

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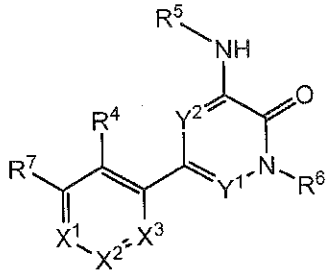
The following specification particularly describes
the invention and the manner in which
it is to be performed

We Claim:

1. A compound selected from Formula I:



I

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

X^1 is CR^1 or N;

X^2 is CR^2 or N;

X^3 is CR^3 or N;

where one or two of X^1, X^2, and X^3 are N;

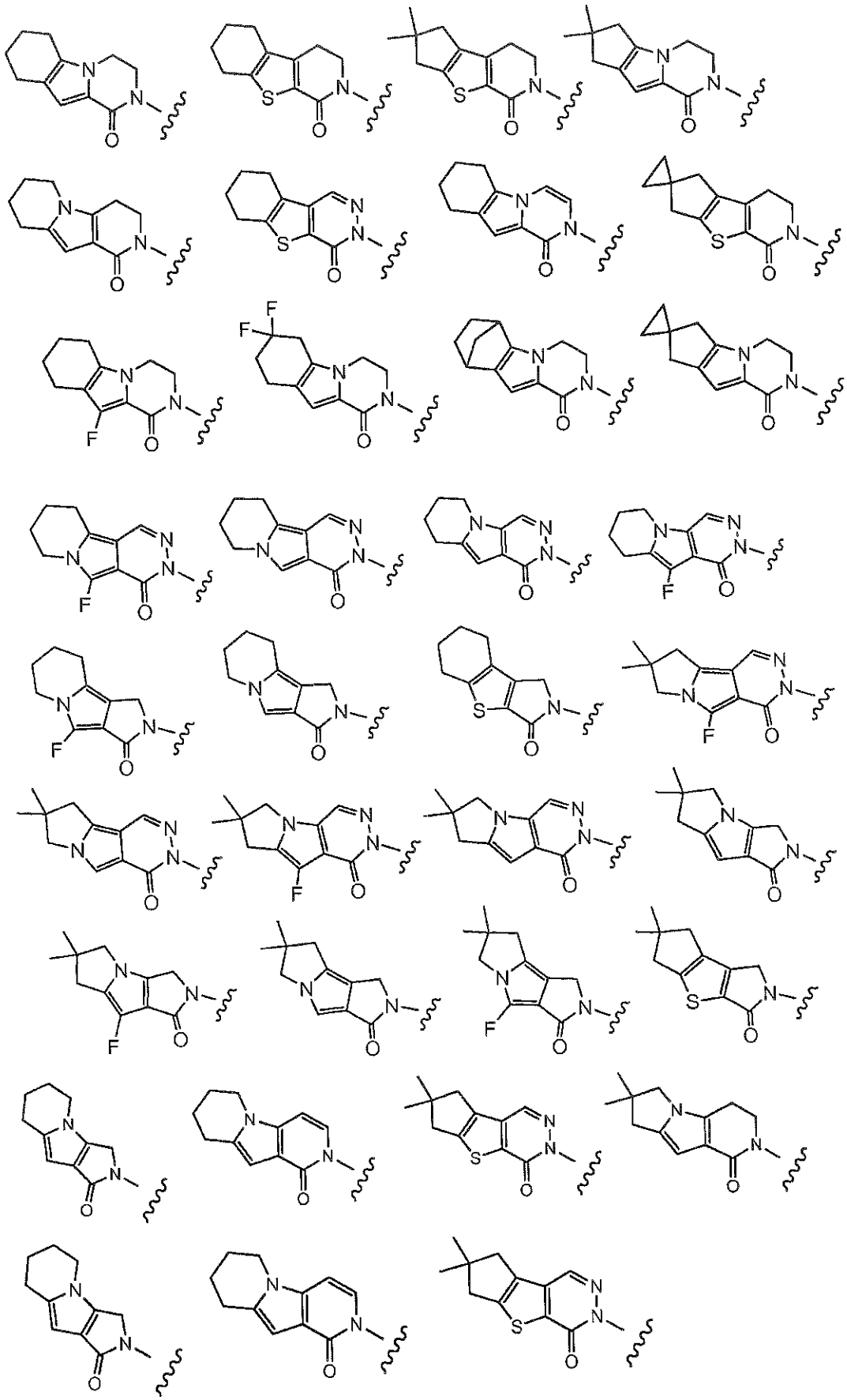
R^1, R^2 and R^3 are independently selected from H, F, Cl, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, and C_1–C_3 alkyl;

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 optionally substituted C_6–C_{20} aryl, C_3–C_{12} carbocyclyl, C_2–C_{20} heterocyclyl, C_1–C_{20} heteroaryl, –(C_6–C_{20} aryl)–(C_2–C_{20} heterocyclyl), –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl), –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl)–(C_2–C_{20} heterocyclyl), –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl)–(C_1–C_6 alkyl), –(C_1–C_{20} heteroaryl)–(C_1–C_6 alkyl), –(C_2–C_{20} heterocyclyl)–(C_1–C_6 alkyl), –(C_2–C_{20} heterocyclyl)–(C_3–C_{12} carbocyclyl), –(C_1–C_{20} heteroaryl)–(C_3–C_{12} carbocyclyl), or –(C_1–C_{20} heteroaryl)–C(=O)–(C_2–C_{20} 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;

where alkyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more groups independently selected from F, Cl, Br, I, –CN, $–CH_3$, $–CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH(CH_3)_2$, $–CH_2OH$, $–CH_2OCH_3$, $–CH_2CH_2OH$, $–C(CH_3)_2OH$, $–CH(OH)CH(CH_3)_2$, $–C(CH_3)_2CH_2OH$, $–CH_2CH_2SO_2CH_3$, $–CH_2OP(O)(OH)_2$, $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$, $–CH_2CHF_2$, $–CH(CH_3)CN$, $–C(CH_3)_2CN$, $–CH_2CN$, $–CO_2H$, $–COCH_3$, $–CO_2CH_3$, $–CO_2C(CH_3)_3$, $–COCH(OH)CH_3$, $–CONH_2$, $–CONHCH_3$, $–CON(CH_3)_2$, $–C(CH_3)_2CONH_2$, $–NH_2$, $–NHCH_3$, $–N(CH_3)_2$, $–NHCOCH_3$, $–N(CH_3)COCH_3$, $–NHS(O)_2CH_3$, $–N(CH_3)C(CH_3)_2CONH_2$, $–N(CH_3)CH_2CH_2S(O)_2CH_3$, $–NO_2$, =O, –OH, $–OCH_3$, $–OCH_2CH_3$, $–OCH_2CH_2OCH_3$, $–OCH_2CH_2OH$, $–OCH_2CH_2N(CH_3)_2$, $–OP(O)(OH)_2$, $–S(O)_2N(CH_3)_2$, $–SCH_3$, $–S(O)_2CH_3$, $–S(O)_3H$, cyclopropyl, oxetanyl, azetidinyl, 1-methylazetidin-3-yl)oxy, N-methyl-N-oxetan-3-ylamino, azetidin-1-ylmethyl, and morpholino.

2. The compound of claim 1 wherein X^1 is N.

3. The compound of claim 1 wherein X^2 is N.

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

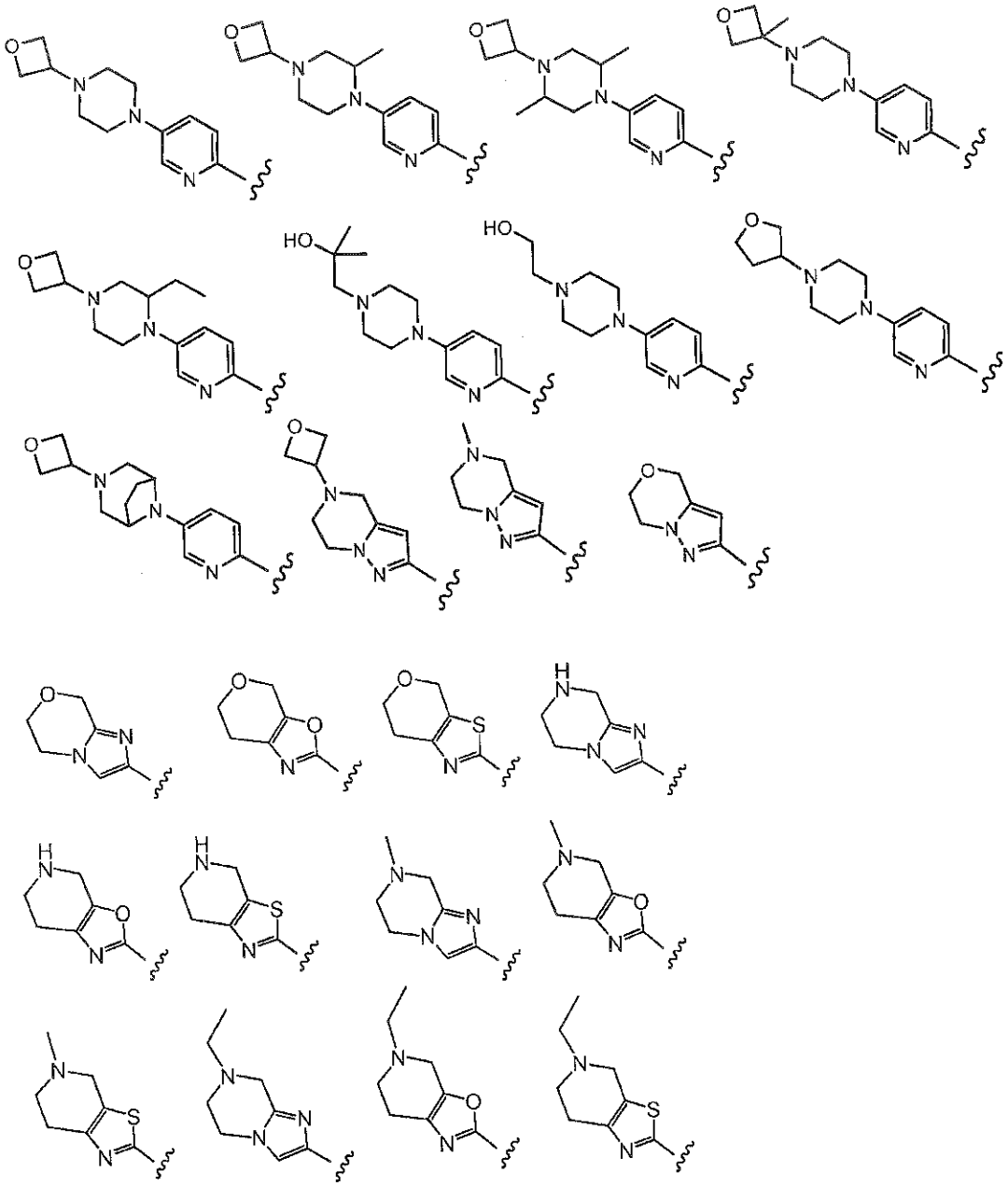
5. The compound of claim 1 wherein X^1 and X^3 are N, X^1 and X^2 are N, or X^2 and X^3 are N.

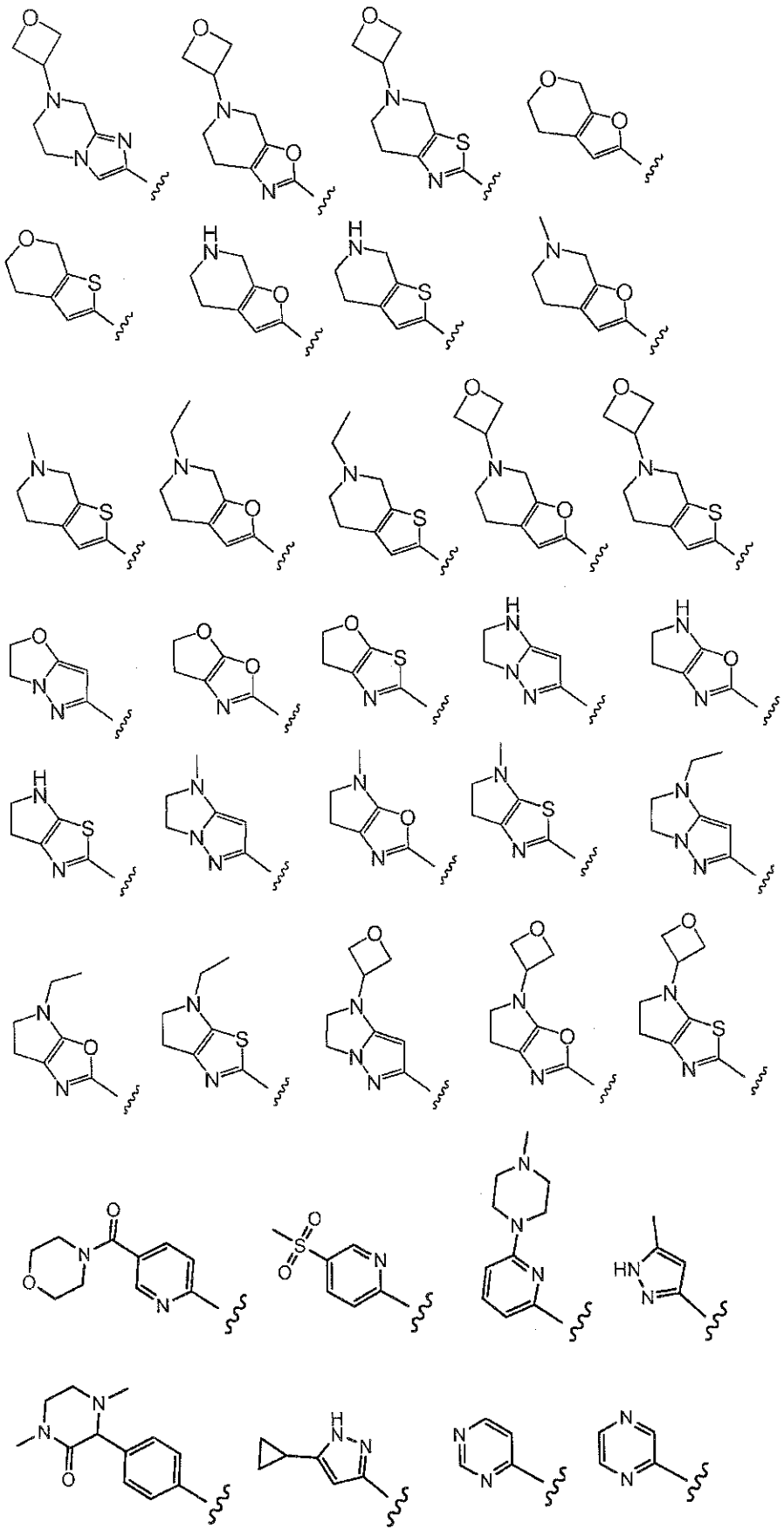
6. The compound of claim 1 wherein R^5 is optionally substituted C_1–C_{20} heteroaryl selected from pyrazolyl, pyridinyl, pyrimidinyl, 5-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 5-acetyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-yl, 6,7-dihydro-4H-pyrazolo[5,1-c][1,4]oxazin-2-yl, and 1-methyl-5-(5-(4-methylpiperazin-1-yl)pyridin-2-yl.

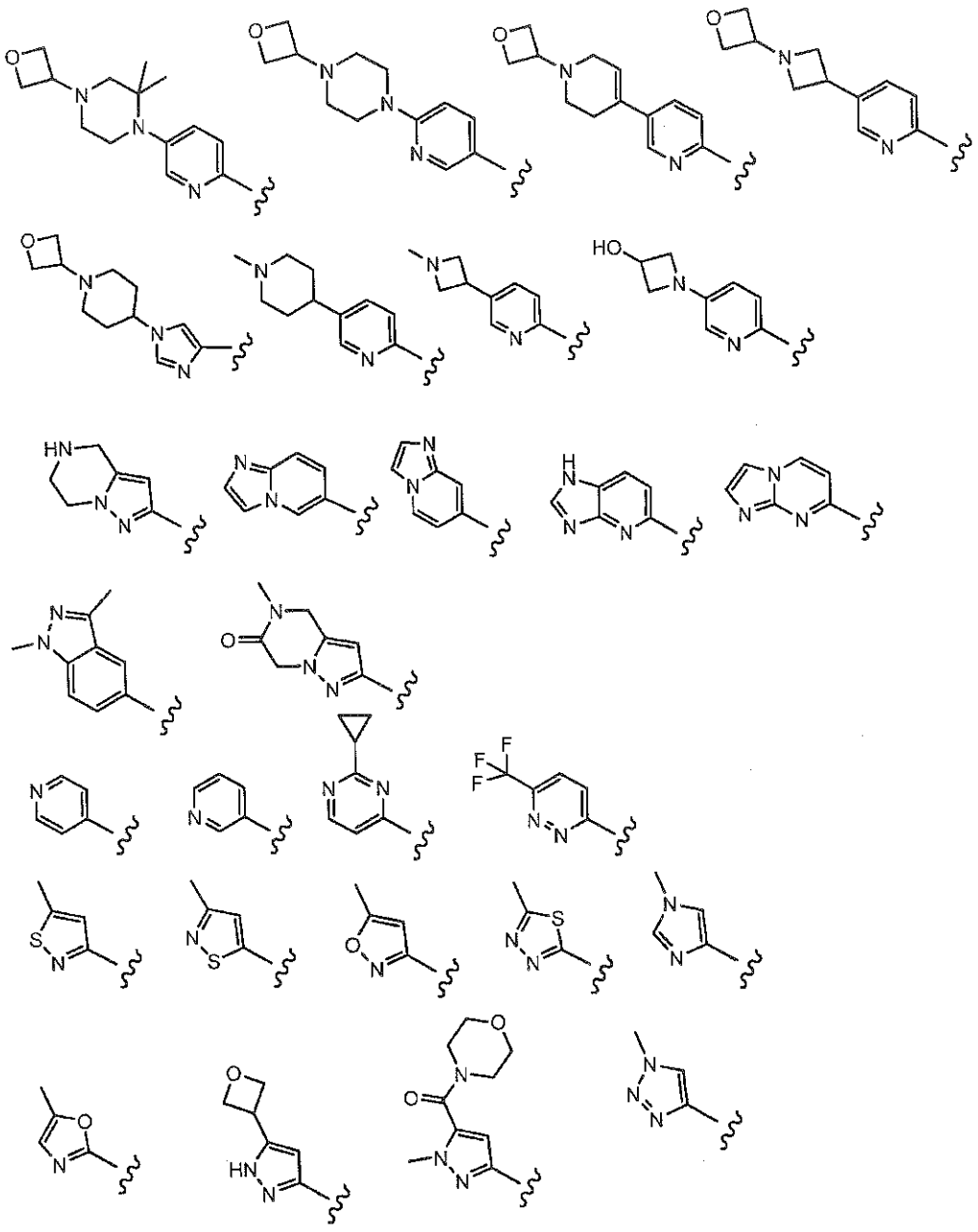
7. The compound of claim 1 wherein R^5 is –(C_1–C_{20} heteroaryl)–(C_2–C_{20} heterocyclyl) where heteroaryl is optionally substituted pyridinyl and heterocyclyl is optionally substituted piperazinyl.

8. The compound of claim 1 wherein R^5 is phenyl, optionally substituted with one or more groups selected from F, Cl, $–CH_3$, $–S(O)_2CH_3$, cyclopropyl, azetidinyl, oxetanyl, and morpholino.

9. The compound of claim 1 wherein R^5 is selected from the structures:

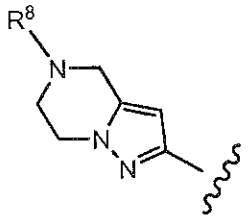






where the wavy line indicates the site of attachment.

10. The compound of claim 1 wherein R^5 is:



where R^8 is selected from H, $-CH_3$, $-CH_2OCH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH_2OH$, $-CH_2CH_2OCH_3$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CF_3$, $-CH_2CHF_2$, $-CH(CH_3)CN$,

$-C(CH_3)_2CN$, $-CH_2CN$, $-C(O)CH_3$, $-C(O)CH_2CH_3$, $-C(O)CH(CH_3)_2$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-OH$, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, cyclopropyl, and oxetanyl.

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

12. The compound of claim 1 wherein Y^1 is CH and Y^2 is N.

13. The compound of claim 1 wherein Y^1 is N and Y^2 is CH.

14. The compound of claim 1 wherein Y^1 and Y^2 are each CH.

15. The compound of claim 1 wherein Y^1 and Y^2 are each CH, and R^6 is CH_3.

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. A method of treating a disease or disorder which comprises administering a therapeutically effective amount of the pharmaceutical composition of claim 18 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 method of claim 21 wherein the disease or disorder is an immune disorder.

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

24. The 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 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 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. 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.

Dated this 30 day of April 2014

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