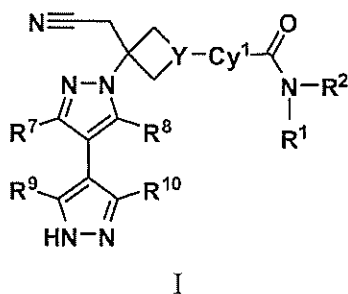


WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof; wherein:

Cy¹ is phenyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl, each of which is optionally substituted by 1, 2, 3, or 4 groups independently selected from R³, R⁴, R⁵, and R⁶;

Y is N or CH;

R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, 4-7 membered heterocycloalkyl, 4-7 membered heterocycloalkyl-C₁₋₃ alkyl, phenyl, phenyl-C₁₋₃ alkyl, 5-6 membered heteroaryl or 5-6 membered heteroaryl-C₁₋₃ alkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, chloro, C₁₋₃ alkyl, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -C(=O)N(C₁₋₃ alkyl)₂, -C(=O)NH(C₁₋₃ alkyl), -C(=O)NH₂, -C(=O)O(C₁₋₃ alkyl), -S(=O)₂(C₁₋₃ alkyl), -S(=O)₂(C₃₋₆ cycloalkyl), -C(=O)(C₃₋₆ cycloalkyl), and -C(=O)(C₁₋₃ alkyl);

R² is H or C₁₋₃ alkyl; wherein said C₁₋₃ alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, chloro, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(C₁₋₃ alkyl), and -N(C₁₋₃ alkyl)₂; or

R¹ and R², together with the nitrogen atom to which they are attached, form a 4-, 5- or 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from F, Cl, -OH, -O(C₁₋₃ alkyl), -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -CH₂CN, and -CH₂OH;

R³ is H, F, Cl, -CN, C₁₋₃ alkyl, C₁₋₃ fluoroalkyl, -O(C₁₋₃ alkyl), or -O(C₁₋₃ fluoroalkyl);

R^4 is H, F, Cl, -CN, C_{1-3} alkyl, C_{1-3} fluoroalkyl, -O(C_{1-3} alkyl), or -OC(C_{1-3} fluoroalkyl);

R^5 is H, F, Cl, -CN, C_{1-3} alkyl, C_{1-3} fluoroalkyl, -O(C_{1-3} alkyl), or -OC(C_{1-3} fluoroalkyl);

R^6 is H, F, Cl, -CN, C_{1-3} alkyl, C_{1-3} fluoroalkyl, -O(C_{1-3} alkyl), or -OC(C_{1-3} fluoroalkyl);

R^7 is H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, -NR¹⁷R^{17a}, -NHC(=O)R^{17b}, -C(=O)NR^{17a}R^{17b}, -NHS(=O)₂R^{17b}, or -S(=O)₂NR^{17a}R^{17b}, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, Cl, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(CH₃), -N(CH₃)₂, OH, -OCH₃, -OCF₃, -OCHF₂, and -OCH₂F;

R^8 is H, F, Cl, C_{1-3} alkyl, or C_{1-3} haloalkyl;

R^9 is H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, cyclopropyl, -CN, -NH₂, -NH(C_{1-3} alkyl), or -N(C_{1-3} alkyl)₂, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

R^{10} is H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, cyclopropyl, -CN, -NH₂, -NH(C_{1-3} alkyl), or -N(C_{1-3} alkyl)₂, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

R^{17} is C_{1-6} alkyl, phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with 1, 2, 3 or 4 independently selected R^{27} substituents;

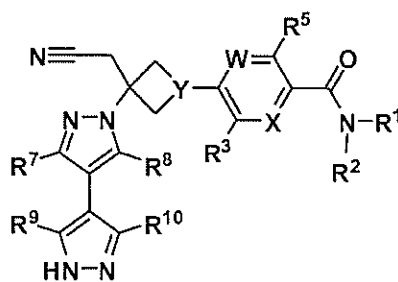
R^{17a} is H or C_{1-3} alkyl;

R^{17b} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(CH₃), -N(CH₃)₂, OH, -OCH₃, and -OCF₃, -OCHF₂, and -OCH₂F; and

each R^{27} is independently selected from halo, -OH, NO₂, -CN, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} haloalkyl, cyano- C_{1-3} alkyl, HO- C_{1-3} alkyl, CF₃- C_{1-3} hydroxyalkyl, C_{1-3} alkoxy- C_{1-3} alkyl, C_{3-7} cycloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, H₂N-, (C_{1-3} alkyl)NH-, (C_{1-3} alkyl)₂N-, HS-, C_{1-3} alkyl-S-, C_{1-3} alkyl-S(=O)-, C_{1-3} alkyl-S(=O)₂-, carbamyl, C_{1-3} alkylcarbamyl, di(C_{1-3} alkyl)carbamyl, carboxy, C_{1-3} alkyl-C(=O)-, C_{1-4} alkoxy-C(=O)-, C_{1-3} alkyl-C(=O)O-, C_{1-3} alkyl-C(=O)NH-, C_{1-3} alkyl-S(=O)₂NH-, H₂N-SO₂-, C_{1-3} alkyl-NH-S(=O)₂-, (C_{1-3} alkyl)₂N-S(=O)₂-, H₂N-S(=O)₂NH-, C_{1-3} alkyl-

NHS(=O)₂NH-, (C₁₋₃ alkyl)₂N-S(=O)₂NH-, H₂N-C(=O)NH-, C₁₋₃ alkyl-NHC(=O)NH-, and (C₁₋₃ alkyl)₂N-C(=O)NH-.

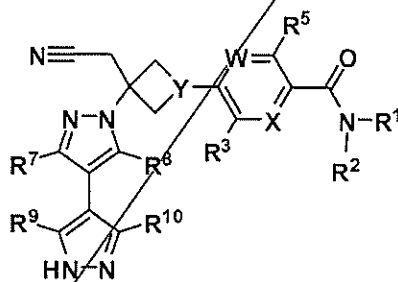
2. The compound of claim 1, having Formula Ia:



Ia

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, having Formula Ia:



Ia

or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR⁴;

W is N or CR⁶;

Y is N or CH;

R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C₁₋₃ alkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, chloro, C₁₋₃ alkyl, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -C(=O)N(C₁₋₃ alkyl)₂, -C(=O)NH(C₁₋₃ alkyl), -C(=O)NH₂, -C(=O)O(C₁₋₃

alkyl), $-S(=O)_2(C_{1-3} \text{ alkyl})$, $-S(=O)_2(C_{3-6} \text{ cycloalkyl})$, $-C(=O)(C_{3-6} \text{ cycloalkyl})$, and $-C(=O)(C_{1-3} \text{ alkyl})$;

R^2 is H or C_{1-3} alkyl; wherein said C_{1-3} alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, chloro, $-OH$, $-O(C_{1-3} \text{ alkyl})$, $-CN$, $-CF_3$, $-CHF_2$, $-CH_2F$, NH_2 , $-NH(C_{1-3} \text{ alkyl})$, and $-N(C_{1-3} \text{ alkyl})_2$; or

R^1 and R^2 , together with the nitrogen atom to which they are attached, form a 4-, 5- or 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, $-OH$, $-O(C_{1-3} \text{ alkyl})$, $-CN$, C_{1-3} alkyl, C_{1-3} haloalkyl, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, $-N(C_{1-3} \text{ alkyl})_2$, and $-CH_2CN$;

R^3 is H, F, Cl, $-CN$, C_{1-3} alkyl, $-OCF_3$, $-CF_3$, or $-O(C_{1-3} \text{ alkyl})$;

R^4 is H, F, Cl, $-CN$, C_{1-3} alkyl, or $-O(C_{1-3} \text{ alkyl})$;

R^5 is H, F, Cl, $-CN$, C_{1-3} alkyl, or $-O(C_{1-3} \text{ alkyl})$;

R^6 is H, F, Cl, $-CN$, or C_{1-3} alkyl;

R^7 is H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, $-NR^{17}R^{17a}$, $-NHC(=O)R^{17b}$, $-C(=O)NR^{17a}R^{17b}$, $-NHS(=O)_2R^{17b}$, or $-S(=O)_2NR^{17a}R^{17b}$, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, Cl, $-CN$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, and OH ;

R^8 is H, F, Cl, C_{1-3} alkyl, or C_{1-3} haloalkyl;

R^9 is H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, cyclopropyl, $-CN$, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, or $-N(C_{1-3} \text{ alkyl})_2$, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, $-CN$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, and OH ;

R^{10} is H, F, Cl, C_{1-3} alkyl, C_{1-3} haloalkyl, cyclopropyl, $-CN$, $-NH_2$, $-NH(C_{1-3} \text{ alkyl})$, or $-N(C_{1-3} \text{ alkyl})_2$, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, $-CN$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, and OH ;

R^{17} is C_{1-6} alkyl, phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with 1, 2, 3 or 4 substituents independently selected from R^{27} ;

R^{17a} is H or C_{1-3} alkyl;

R^{17b} is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents selected from F, chloro, $-CN$, $-CF_3$, $-CHF_2$, $-CH_2F$, $-NH_2$, and OH and

each R²⁷ is independently selected from halo, -OH, NO₂, -CN, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, CF₃-C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₃₋₇ cycloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, H₂N-, (C₁₋₃ alkyl)NH-, (C₁₋₃ alkyl)₂N-, HS-, C₁₋₃ alkyl-S-, C₁₋₃ alkyl-S(=O)-, C₁₋₃ alkyl-S(=O)₂-, carbamyl, C₁₋₃ alkylcarbamyl, di(C₁₋₃ alkyl)carbamyl, carboxy, C₁₋₃ alkyl-C(=O)-, C₁₋₄ alkoxy-C(=O)-, C₁₋₃ alkyl-C(=O)O-, C₁₋₃ alkyl-C(=O)NH-, C₁₋₃ alkyl-S(=O)₂NH-, H₂N-SO₂-, C₁₋₃ alkyl-NH-S(=O)₂-, (C₁₋₃ alkyl)₂N-S(=O)₂-, H₂N-S(=O)₂NH-, C₁₋₃ alkyl-NHS(=O)₂NH-, (C₁₋₃ alkyl)₂N-S(=O)₂NH-, H₂N-C(=O)NH-, C₁₋₃ alkyl-NHC(=O)NH-, and (C₁₋₃ alkyl)₂N-C(=O)NH-.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein: R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or C₃₋₆ cycloalkyl-C₁₋₃ alkyl, wherein said C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkyl-C₁₋₃ alkyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -CF₃, and methyl;

R² is H or methyl;

R³ is H, F, or Cl;

R⁴ is H or F;

R⁵ is H or F;

R⁶ is H or F;

R⁷ is H, methyl, ethyl or HO-CH₂-;

R⁸ is H or methyl;

R⁹ is H, methyl or ethyl; and

R¹⁰ is H, methyl, ethyl or HO-CH₂-.

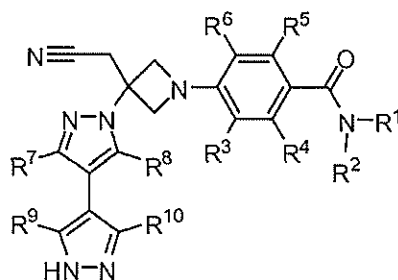
5. The compound of any one of claims 2 to 4, or a pharmaceutically acceptable salt thereof, wherein Y is N.

6. The compound of any one of claims 2 to 4, or a pharmaceutically acceptable salt thereof, wherein Y is CH.

7. The compound of any one of claims 2 to 6, or a pharmaceutically acceptable salt thereof, wherein X is N.
8. The compound of any one of claims 2 to 6, or a pharmaceutically acceptable salt thereof, wherein X is CR⁴.
9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H or F.
10. The compound of any one of claims 2 to 9, or a pharmaceutically acceptable salt thereof, wherein W is N.
11. The compound of any one of claims 2 to 9, or a pharmaceutically acceptable salt thereof, wherein W is CR⁶.
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R⁶ is H, F, or Cl.
13. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R⁶ is H or F.
14. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein R⁶ is H.
15. The compound of any one of claims 2 to 14, or a pharmaceutically acceptable salt thereof, wherein R³ is H or F.
16. The compound of any one of claims 2 to 15, or a pharmaceutically acceptable salt thereof, wherein R⁵ is H or F.

17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or methyl.
18. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^2 is H.
19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, or C_{3-6} cycloalkyl- C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{3-6} cycloalkyl- C_{1-3} alkyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, - CF_3 , and methyl.
20. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl, ethyl, 1-methylpropyl, 2,2,2-trifluoro-1-methylethyl, 1-cyclopropylethyl, cyclopropyl, 1-trifluoromethylcyclopropyl, 1-cyclopropyl-2,2,2-trifluoroethyl, 2,2,2-trifluoroethyl, or 2,2-difluoroethyl.
21. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl, ethyl, 1-methylpropyl, or 2,2,2-trifluoro-1-methylethyl.
22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R^7 is H, methyl, ethyl, or $HO-CH_2-$.
23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^8 is H or methyl.
24. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^8 is H.

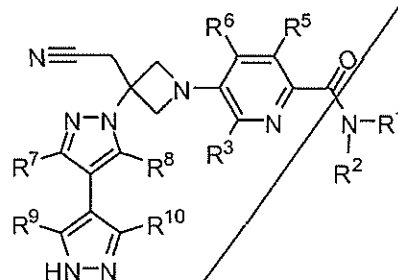
25. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R⁹ is H, methyl or ethyl.
26. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R⁹ is H.
27. The compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, wherein R⁹ is methyl.
28. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is H, methyl, ethyl, or HO-CH₂-.
29. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is H.
30. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is methyl.
31. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is ethyl.
32. The compound of any one of claims 1 to 27, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is HO-CH₂-.
33. The compound of any one of claims 1-4, 8-9, and 11-32, or a pharmaceutically acceptable salt thereof, wherein having Formula II:



II

or a pharmaceutically acceptable salt thereof.

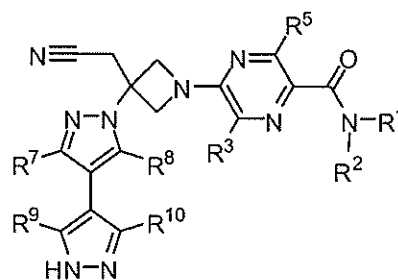
34. The compound of any one of claims 1-4, 8-10, and 15-32, or a pharmaceutically acceptable salt thereof, wherein having Formula III:



III

or a pharmaceutically acceptable salt thereof.

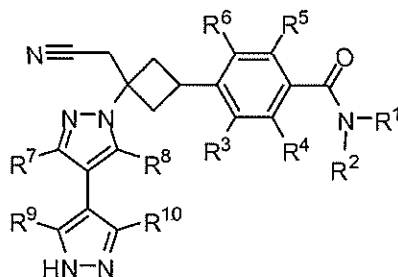
35. The compound of any one of claims 1-4, 7, 10, and 15-32, or a pharmaceutically acceptable salt thereof, wherein, having Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

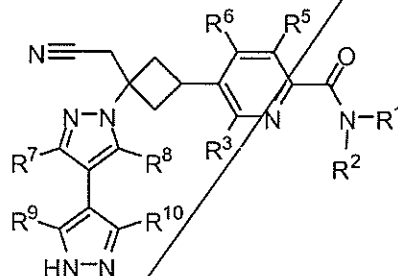
36. The compound of any one of claims 1-4, 8-9, and 11-32, or a pharmaceutically acceptable salt thereof, wherein, having Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

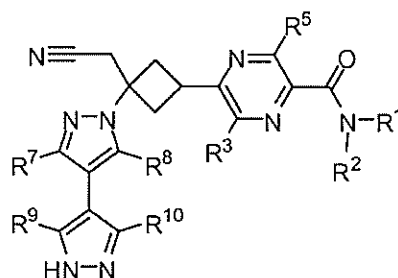
37. The compound of any one of claims 1-4, 8-10, and 15-32, or a pharmaceutically acceptable salt thereof, wherein, having Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

38. The compound of any one of claims 1-4, 7, 10, and 15-32, or a pharmaceutically acceptable salt thereof, wherein, having Formula IVa:



IVa

or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1 selected from:

5-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

4-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylbenzamide;

4-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-[3-(1H,1'H-4,4'-Bipyrazol-1-yl)-3-(cyanomethyl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-[3-(cyanomethyl)-3-(3,3'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3'-ethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

4-{3-(cyanomethyl)-3-[3'-(hydroxymethyl)-1H,1'H-4,4'-bipyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-{3-(cyanomethyl)-3-[3-(hydroxymethyl)-3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

or a pharmaceutically acceptable salt thereof.

40. A compound according to claim 1, which is 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide, or a pharmaceutically acceptable salt thereof.

41. A salt selected from:

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt;

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide hydrochloric acid salt;

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide hydrobromic acid salt; and

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide sulfuric acid salt.

42. A composition comprising a compound or salt according to any one of claims 1 to 41 and a pharmaceutically acceptable carrier.

43. A method of inhibiting an activity of JAK1 comprising contacting JAK1 with a compound or salt according to any one of claims 1 to 41.

44. A method according to claim 43, wherein said compound or salt is selective for JAK1 over JAK2.

45. A method of treating an autoimmune disease, a cancer, a myeloproliferative disorder, an inflammatory disease, a bone resorption disease, or organ transplant rejection in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt according to any one of claims 1 to 41.

46. A method according to claim 45, wherein said autoimmune disease is a skin disorder, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, type I diabetes, lupus, inflammatory bowel disease, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, or autoimmune thyroid disorder.
47. A method according to claim 45, wherein said autoimmune disease is rheumatoid arthritis.
48. A method according to claim 45, wherein said autoimmune disease is a skin disorder.
49. A method according to claim 48, wherein said skin disorder is atopic dermatitis, psoriasis, skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.
50. A method according to claim 45, wherein said cancer is a solid tumor.
51. A method according to claim 45, wherein said cancer is prostate cancer, renal cancer, hepatic cancer, breast cancer, lung cancer, thyroid cancer, Kaposi's sarcoma, Castleman's disease or pancreatic cancer.
52. A method according to claim 45, wherein said cancer is lymphoma, leukemia, or multiple myeloma.
53. A method according to claim 45, wherein said myeloproliferative disorder is polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), idiopathic myelofibrosis (IMF), or systemic mast cell disease (SMCD).

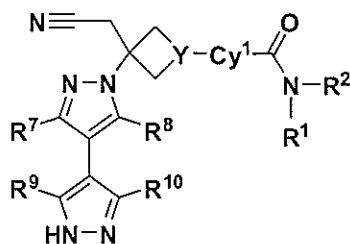
54. A method according to claim 45, wherein said myeloproliferative disorder is myelofibrosis.
55. A method according to claim 45, wherein said myeloproliferative disorder is primary myelofibrosis (PMF).
56. A method according to claim 45, wherein said myeloproliferative disorder is post polycythemia vera myelofibrosis (Post-PV MF).
57. A method according to claim 45, wherein said myeloproliferative disorder is post-essential thrombocythemia myelofibrosis (Post-ET MF).
58. A method of treating a myelodysplastic syndrome (MDS) in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound or salt according to any one of claims 1 to 41.
59. The method according to claim 58, wherein said myelodysplastic syndrome is selected from refractory cytopenia with unilineage dysplasia (RCUD), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts-1 (RAEB-1), refractory anemia with excess blasts-2 (RAEB-2), myelodysplastic syndrome, unclassified (MDS-U), and myelodysplastic syndrome associated with isolated del(5q).
60. A process of preparing 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt, comprising:
- (a) dissolving the 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt in methanol at a temperature from about 40 °C to about 70 °C to form a first mixture;

(b) adding n-heptane to the first mixture at a temperature from about 40 °C to about 70 °C to form a second mixture; and

(c) cooling the second mixture to provide 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt.

The Claims defining the invention are as follows:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein:

Cy¹ is phenyl, pyridyl, pyrimidinyl, pyrazinyl, or pyridazinyl, each of which is optionally substituted by 1, 2, 3, or 4 groups independently selected from R³, R⁴, R⁵, and R⁶;

Y is N or CH;

R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl-C₁₋₃ alkyl, 4-7 membered heterocycloalkyl, 4-7 membered heterocycloalkyl-C₁₋₃ alkyl, phenyl, phenyl-C₁₋₃ alkyl, 5-6 membered heteroaryl or 5-6 membered heteroaryl-C₁₋₃ alkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, chloro, C₁₋₃ alkyl, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -C(=O)N(C₁₋₃ alkyl)₂, -C(=O)NH(C₁₋₃ alkyl), -C(=O)NH₂, -C(=O)O(C₁₋₃ alkyl), -S(=O)₂(C₁₋₃ alkyl), -S(=O)₂(C₃₋₆ cycloalkyl), -C(=O)(C₃₋₆ cycloalkyl), and -C(=O)(C₁₋₃ alkyl);

R² is H or C₁₋₃ alkyl; wherein said C₁₋₃ alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, chloro, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, NH₂, -NH(C₁₋₃ alkyl), and -N(C₁₋₃ alkyl)₂; or

R¹ and R², together with the nitrogen atom to which they are attached, form a 4-, 5- or 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from F, Cl, -OH, -O(C₁₋₃ alkyl), -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -CH₂CN, and -CH₂OH;

R³ is H, F, Cl, -CN, C₁₋₃ alkyl, C₁₋₃ fluoroalkyl, -O(C₁₋₃ alkyl), or -O(C₁₋₃ fluoroalkyl);

R⁴ is H, F, Cl, -CN, C₁₋₃ alkyl, C₁₋₃ fluoroalkyl, -O(C₁₋₃ alkyl), or -OC(C₁₋₃ fluoroalkyl);

R⁵ is H, F, Cl, -CN, C₁₋₃ alkyl, C₁₋₃ fluoroalkyl, -O(C₁₋₃ alkyl), or -OC(C₁₋₃ fluoroalkyl);

5 R⁶ is H, F, Cl, -CN, C₁₋₃ alkyl, C₁₋₃ fluoroalkyl, -O(C₁₋₃ alkyl), or -OC(C₁₋₃ fluoroalkyl);

R⁷ is H, F, Cl, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -NR^{17a}R^{17b}, -NHC(=O)R^{17b}, -C(=O)NR^{17a}R^{17b}, -NHS(=O)₂R^{17b}, or -S(=O)₂NR^{17a}R^{17b}, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents selected
10 from F, Cl, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(CH₃), -N(CH₃)₂, OH, -OCH₃, -OCF₃, -OCHF₂, and -OCH₂F;

R⁸ is H, F, Cl, C₁₋₃ alkyl, or C₁₋₃ haloalkyl;

R⁹ is H, F, Cl, C₁₋₃ alkyl, C₁₋₃ haloalkyl, cyclopropyl, -CN, -NH₂, -NH(C₁₋₃ alkyl), or -N(C₁₋₃ alkyl)₂, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or
15 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

R¹⁰ is H, F, Cl, C₁₋₃ alkyl, C₁₋₃ haloalkyl, cyclopropyl, -CN, -NH₂, -NH(C₁₋₃ alkyl), or -N(C₁₋₃ alkyl)₂, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

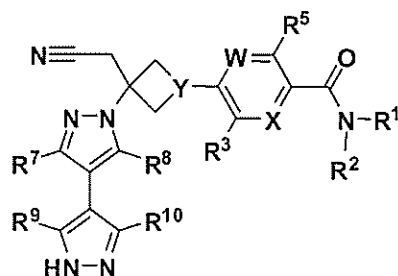
R¹⁷ is C₁₋₆ alkyl, phenyl or 5-6 membered heteroaryl, each of which is
20 optionally substituted with 1, 2, 3 or 4 independently selected R²⁷ substituents;

R^{17a} is H or C₁₋₃ alkyl;

R^{17b} is C₁₋₃ alkyl optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(CH₃), -N(CH₃)₂, OH, -OCH₃, and -OCF₃, -OCHF₂, and -OCH₂F; and

25 each R²⁷ is independently selected from halo, -OH, NO₂, -CN, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, CF₃-C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₃₋₇ cycloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, H₂N-, (C₁₋₃ alkyl)NH-, (C₁₋₃ alkyl)₂N-, HS-, C₁₋₃ alkyl-S-, C₁₋₃ alkyl-S(=O)-, C₁₋₃ alkyl-S(=O)₂-, carbamyl, C₁₋₃ alkylcarbamyl, di(C₁₋₃ alkyl)carbamyl, carboxy, C₁₋₃ alkyl-C(=O)-, C₁₋₄ alkoxy-C(=O)-, C₁₋₃ alkyl-C(=O)O-, C₁₋₃ alkyl-C(=O)NH-, C₁₋₃ alkyl-S(=O)₂NH-, H₂N-SO₂-, C₁₋₃ alkyl-NH-S(=O)₂-, (C₁₋₃ alkyl)₂N-S(=O)₂-, H₂N-S(=O)₂NH-, C₁₋₃ alkyl-NHS(=O)₂NH-, (C₁₋₃ alkyl)₂N-S(=O)₂NH-, H₂N-C(=O)NH-, C₁₋₃ alkyl-NHC(=O)NH-, and (C₁₋₃ alkyl)₂N-C(=O)NH-.

2. The compound of claim 1, having Formula Ia:



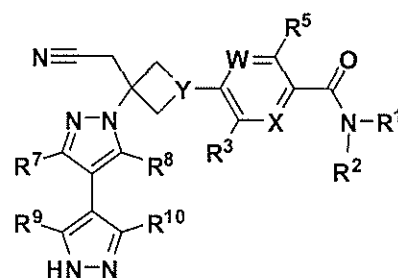
Ia

5 or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR⁴; and

W is N or CR⁶.

3. The compound of claim 1, having Formula Ia:



Ia

or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR⁴;

W is N or CR⁶;

15 Y is N or CH;

R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkyl-C₁₋₃ alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C₁₋₃ alkyl, each of which is optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, chloro, C₁₋₃ alkyl, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, -C(=O)N(C₁₋₃ alkyl)₂, -C(=O)NH(C₁₋₃ alkyl), -C(=O)NH₂, -C(=O)O(C₁₋₃ alkyl), -S(=O)₂(C₁₋₃ alkyl), -S(=O)₂(C₃₋₆ cycloalkyl), -C(=O)(C₃₋₆ cycloalkyl), and -C(=O)(C₁₋₃ alkyl);

R² is H or C₁₋₃ alkyl; wherein said C₁₋₃ alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, chloro, -OH, -O(C₁₋₃ alkyl), -CN, -CF₃, -CHF₂, -CH₂F, NH₂, -NH(C₁₋₃ alkyl), and -N(C₁₋₃ alkyl)₂; or

R¹ and R², together with the nitrogen atom to which they are attached, form a 4-, 5- or 6-membered heterocycloalkyl ring, which is optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C₁₋₃ alkyl), -CN, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -NH₂, -NH(C₁₋₃ alkyl), -N(C₁₋₃ alkyl)₂, and -CH₂CN;

R³ is H, F, Cl, -CN, C₁₋₃ alkyl, -OCF₃, -CF₃, or -O(C₁₋₃ alkyl);

R⁴ is H, F, Cl, -CN, C₁₋₃ alkyl, or -O(C₁₋₃ alkyl);

R⁵ is H, F, Cl, -CN, C₁₋₃ alkyl, or -O(C₁₋₃ alkyl);

R⁶ is H, F, Cl, -CN, or C₁₋₃ alkyl;

R⁷ is H, F, Cl, C₁₋₃ alkyl, C₁₋₃ haloalkyl, -NR^{17a}R^{17b}, -NHC(=O)R^{17b}, -C(=O)NR^{17a}R^{17b}, -NHS(=O)₂R^{17b}, or -S(=O)₂NR^{17a}R^{17b}, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, Cl, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

R⁸ is H, F, Cl, C₁₋₃ alkyl, or C₁₋₃ haloalkyl;

R⁹ is H, F, Cl, C₁₋₃ alkyl, C₁₋₃ haloalkyl, cyclopropyl, -CN, -NH₂, -NH(C₁₋₃ alkyl), or -N(C₁₋₃ alkyl)₂, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

R¹⁰ is H, F, Cl, C₁₋₃ alkyl, C₁₋₃ haloalkyl, cyclopropyl, -CN, -NH₂, -NH(C₁₋₃ alkyl), or -N(C₁₋₃ alkyl)₂, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH;

R¹⁷ is C₁₋₆ alkyl, phenyl or 5-6 membered heteroaryl, each of which is optionally substituted with 1, 2, 3 or 4 substituents independently selected from R²⁷;

R^{17a} is H or C₁₋₃ alkyl;

R^{17b} is C₁₋₃ alkyl optionally substituted with 1, 2, or 3 substituents selected from F, chloro, -CN, -CF₃, -CHF₂, -CH₂F, -NH₂, and OH and

each R²⁷ is independently selected from halo, -OH, NO₂, -CN, C₁₋₃ alkyl, C₂₋₃ alkenyl, C₂₋₃ alkynyl, C₁₋₃ haloalkyl, cyano-C₁₋₃ alkyl, HO-C₁₋₃ alkyl, CF₃-C₁₋₃ hydroxyalkyl, C₁₋₃ alkoxy-C₁₋₃ alkyl, C₃₋₇ cycloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, H₂N-, (C₁₋₃ alkyl)NH-, (C₁₋₃ alkyl)₂N-, HS-, C₁₋₃ alkyl-S-, C₁₋₃ alkyl-S(=O)-, C₁₋₃ alkyl-S(=O)₂-, carbamyl, C₁₋₃ alkylcarbamyl, di(C₁₋₃ alkyl)carbamyl, carboxy, C₁₋₃ alkyl-C(=O)-, C₁₋₄ alkoxy-C(=O)-, C₁₋₃ alkyl-C(=O)O-, C₁₋₃ alkyl-C(=O)NH-, C₁₋₃ alkyl-

S(=O)₂NH-, H₂N-SO₂-, C₁₋₃ alkyl-NH-S(=O)₂-, (C₁₋₃ alkyl)₂N-S(=O)₂-, H₂N-S(=O)₂NH-, C₁₋₃ alkyl-NHS(=O)₂NH-, (C₁₋₃ alkyl)₂N-S(=O)₂NH-, H₂N-C(=O)NH-, C₁₋₃ alkyl-NHC(=O)NH-, and (C₁₋₃ alkyl)₂N-C(=O)NH-.

- 5 4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein:

R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or C₃₋₆ cycloalkyl-C₁₋₃ alkyl, wherein said C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkyl-C₁₋₃ alkyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -
10 CF₃, and methyl;

R² is H or methyl;

R³ is H, F, or Cl;

R⁴ is H or F;

R⁵ is H or F;

15 R⁶ is H or F;

R⁷ is H, methyl, ethyl or HO-CH₂-;

R⁸ is H or methyl;

R⁹ is H, methyl or ethyl; and

R¹⁰ is H, methyl, ethyl or HO-CH₂-.

20

5. The compound of any one of claims 2 to 4, or a pharmaceutically acceptable salt thereof, wherein:-

a) Y is N; or

b) Y is CH.

25

6. The compound of any one of claims 2 to 5, or a pharmaceutically acceptable salt thereof, wherein:-

a) X is N; or

b) X is CR⁴; or

30

c) X is CR⁴ and R⁴ is H or F.

7. The compound of any one of claims 2 to 6, or a pharmaceutically acceptable salt thereof, wherein:-

- a) W is N; or
- b) W is CR⁶; or
- c) W is CR⁶ and R⁶ is H, F, or Cl; or
- d) W is CR⁶ and R⁶ is H or F; or
- e) W is CR⁶ and R⁶ is H.

8. The compound of any one of claims 2 to 7, or a pharmaceutically acceptable salt thereof, wherein R³ is H or F.

9. The compound of any one of claims 2 to 8, or a pharmaceutically acceptable salt thereof, wherein R⁵ is H or F.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein:-

- a) R² is H or methyl; or
- b) R² is H.

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein:-

a) R¹ is C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₃₋₆ cycloalkyl, or C₃₋₆ cycloalkyl-C₁₋₃ alkyl, wherein said C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₃₋₆ cycloalkyl-C₁₋₃ alkyl, are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -CF₃, and methyl; or

b) R¹ is isopropyl, ethyl, 1-methylpropyl, 2,2,2-trifluoro-1-methylethyl, 1-cyclopropylethyl, cyclopropyl, 1-trifluoromethylcyclopropyl, 1-cyclopropyl-2,2,2-trifluoroethyl, 2,2,2-trifluoroethyl, or 2,2-difluoroethyl; or

c) R¹ is isopropyl, ethyl, 1-methylpropyl, or 2,2,2-trifluoro-1-methylethyl.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R⁷ is H, methyl, ethyl, or HO-CH₂-.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein:-

a) R⁸ is H or methyl; or

b) R⁸ is H.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein:-

a) R⁹ is H, methyl or ethyl; or

b) R⁹ is H; or

c) R⁹ is methyl.

15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, wherein:-

a) R¹⁰ is H, methyl, ethyl, or HO-CH₂-; or

b) R¹⁰ is H; or

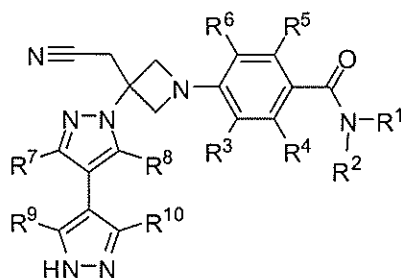
c) R¹⁰ is methyl; or

d) R¹⁰ is ethyl; or

e) R¹⁰ is HO-CH₂-.

16. The compound of any one of claims 1-4 and 6-15, or a pharmaceutically acceptable salt thereof, wherein:-

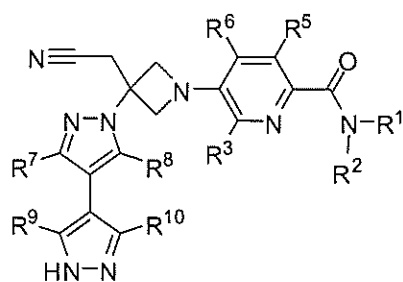
a) having Formula II:



II

or a pharmaceutically acceptable salt thereof; or

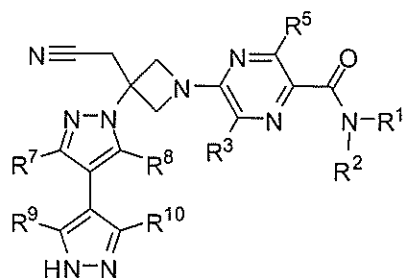
b) having Formula III:



III

or a pharmaceutically acceptable salt thereof; or

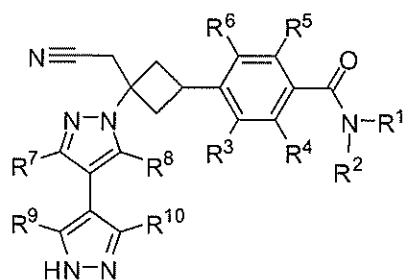
c) having Formula IV:



IV

or a pharmaceutically acceptable salt thereof; or

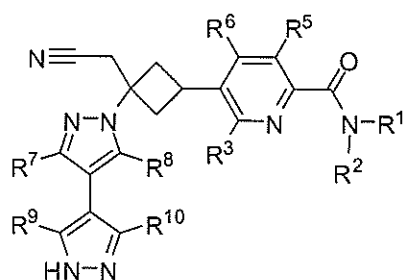
d) having Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof; or

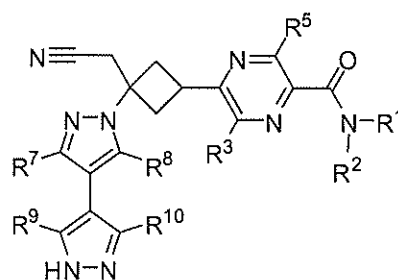
e) having Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof; or

f) having Formula IVa:



IVa

or a pharmaceutically acceptable salt thereof.

5

17. The compound of claim 1 selected from:

5-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

10

4-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylbenzamide;

4-[3-(cyanomethyl)-3-(3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

15

4-[3-(1H,1'H-4,4'-Bipyrazol-1-yl)-3-(cyanomethyl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-[3-(cyanomethyl)-3-(3,3'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

20

5-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

25

5-[3-(cyanomethyl)-3-(3-methyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-isopropylpyrazine-2-carboxamide;

5-[3-(cyanomethyl)-3-(3'-ethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

4-{3-(cyanomethyl)-3-[3'-(hydroxymethyl)-1H,1'H-4,4'-bipyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-{3-(cyanomethyl)-3-[3-(hydroxymethyl)-3'-methyl-1H,1'H-4,4'-bipyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

5 or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 1, which is 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide, or a pharmaceutically acceptable salt thereof.

10

19. A salt according to claim 1, which is selected from:

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt;

15

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide hydrochloric acid salt;

4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide hydrobromic acid salt; and

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4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide sulfuric acid salt.

20. A composition comprising a compound or salt according to any one of claims 1 to 19 and a pharmaceutically acceptable carrier.

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21. A method of inhibiting an activity of JAK1 comprising:-

a) contacting JAK1 *in vitro* with a compound or salt according to any one of claims 1 to 19; or

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b) contacting JAK1 *in vitro* with a compound or salt according to any one of claims 1 to 19, wherein said compound or salt is selective for JAK1 over JAK2.

22. A compound or salt according to any one of claims 1 to 19 for use in a method of treating an autoimmune disease, a cancer, a myeloproliferative disorder, an inflammatory disease, a bone resorption disease, or organ transplant rejection.

5 23. A compound or salt for use according to claim 22, wherein:-

a) said autoimmune disease is a skin disorder, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, type I diabetes, lupus, inflammatory bowel disease, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, or autoimmune thyroid disorder; or

10 b) said autoimmune disease is rheumatoid arthritis; or

c) said autoimmune disease is a skin disorder; or

d) said autoimmune disease is a skin disorder, wherein said skin disorder is atopic dermatitis, psoriasis, skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.

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24. A compound or salt for use according to claim 22, wherein:-

a) said cancer is a solid tumor; or

b) said cancer is prostate cancer, renal cancer, hepatic cancer, breast cancer, lung cancer, thyroid cancer, Kaposi's sarcoma, Castleman's disease or pancreatic cancer; or

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c) said cancer is lymphoma, leukemia, or multiple myeloma.

25. A compound or salt for use according to claim 22, wherein:-

25 a) said myeloproliferative disorder is polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), idiopathic myelofibrosis (IMF), or systemic mast cell disease (SMCD); or

b) said myeloproliferative disorder is myelofibrosis; or

c) said myeloproliferative disorder is primary myelofibrosis (PMF); or

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d) said myeloproliferative disorder is post polycythemia vera myelofibrosis (Post-PV MF); or

e) said myeloproliferative disorder is post-essential thrombocythemia myelofibrosis (Post-ET MF).

26. A compound or salt according to any one of claims 1 to 19 for use in a method of treating:-

a) a myelodysplastic syndrome (MDS); or

5 b) a myelodysplastic syndrome (MDS), wherein said myelodysplastic syndrome is selected from refractory cytopenia with unilineage dysplasia (RCUD), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts-1 (RAEB-1), refractory anemia with excess blasts-2 (RAEB-2), myelodysplastic syndrome, unclassified
10 (MDS-U), and myelodysplastic syndrome associated with isolated del(5q).

27. A process of preparing 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt, comprising:

15 (a) dissolving the 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt in methanol at a temperature from 40 °C to 70 °C to form a first mixture;

(b) adding n-heptane to the first mixture at a temperature from 40 °C to 70
20 °C to form a second mixture; and

(c) cooling the second mixture to provide 4-[3-(cyanomethyl)-3-(3',5'-dimethyl-1H,1'H-4,4'-bipyrazol-1-yl)azetidin-1-yl]-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide phosphoric acid salt.