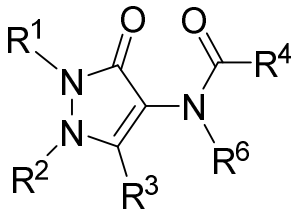
WE CLAIM:

1. A compound of formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonylalkyl, cycloalkyl, (Ar^1)alkyl, or Ar^1;

Ar^1 is cycloalkyl, piperidinyl, phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furanyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, or thiadiazolyl, quinolinyl, isoquinolinyl, or quinoxalinyl and, is substituted with 0-2 R^{5a} and 0-2 R^{5b};

R^2 is alkyl or haloalkyl;

R^3 is phenyl or pyridinyl, and is substituted with 1 R^{3a} and 0-2 R^{3b};

R^{3a} is halo, alkyl, haloalkyl, alkoxy, deuteroalkoxy, haloalkoxy, or cycloalkyl substituent in the para-position with respect to the pyrazol-3-one moiety;

R^{3b} is halo, alkyl, hydroxy, or haloalkyl;

or R^{3a} and the adjacent R^{3b}, together with the two carbon atoms they are attached to, form a 3-6 membered heterocycle comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, or alkoxycarbonyl;

R^4 is phenyl or pyridinyl, and is substituted with 1 R^{4a} and 0-2 R^{4b};

R^{4a} is halo, alkyl, cycloalkyl, haloalkyl, alkoxy, haloalkoxy, or pyrazolyl substituent in the para-position with respect to the amide moiety;

R^{4b} is halo or haloalkyl;

R^{5a} and R^{5b} are independently cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxy, haloalkoxy, hydroxyhaloalkoxy, hydroxyalkoxyalkoxy, alkylsulfonylalkoxy, carboxamide, alkoxycarbonyl, alkylaminoalkyl, alkoxycarbonylalkoxy,

hydroxyalkylcycloalkylalkyl, alkylsulfonyl, aminocarbonylalkyl, -NR^7R^8, cycloalkyl substituted with 0-3 halo, hydroxy, alkyl, or alkoxy, phenyl substituted with 0-3 halo, hydroxy, or alkyl, 4-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, alkyl, hydroxyalkyl, haloalkyl, alkoxycarbonyl, or alkylsulfonyl, heterocyclyloxy, heterocyclylalkyl, or heterocyclylalkoxy, wherein the heterocyclyl moiety of the heterocyclyloxy, heterocyclylalkyl, and heterocyclylalkoxy comprises 4-8 carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, hydroxyalkyl, alkyl, or haloalkyl;

R^6 is hydrogen or lower alkyl;

R^7 and R^8 are independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl, aminocarbonylalkyl, alkylsulfonyl; alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, cycloalkylalkyl, hydroxycycloalkylalkyl, hydroxyalkylcycloalkylalkyl, cycloalkylalkyl, cycloalkyl, wherein each cycloalkyl is substituted with 0-3 halo, hydroxy, or alkyl, or hydroxyalkyl, or 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, or alkoxycarbonyl;

or R^7 and R^8, together with the nitrogen to which they are attached, form a 5-12 membered heterocycle comprising carbon atoms and 0-3 additional heteroatoms selected from N, NH, O, S, and substituted with 0-5 halo, hydroxy, alkyl, alkoxy, oxo, haloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, alkylsulfonylalkyl, aminocarbonyl, or alkoxycarbonyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^1 is Ar^1.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^2 is alkyl or haloalkyl.

4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^3 is phenyl substituted with 1 R^{3a} and 0-2 R^{3b};

R^{3a} is halo, alkyl, haloalkyl, alkoxy, or deuteroalkoxysubstituent in the para-position with respect to the pyrazol-3-one moiety; and

R^{3b} is halo or haloalkyl.

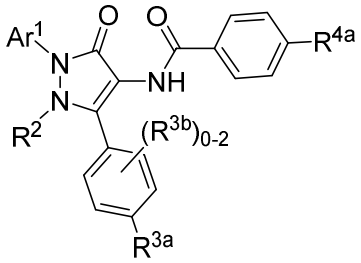
5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

R^4 is phenyl or pyridinyl substituted with 1 R^{4a} in the para-position with respect to the amide moiety and 0-2 R^{4b};

R^{4a} is halo, alkyl, cycloalkyl, haloalkyl, alkoxy, or haloalkoxy; and

R^{4b} is halo or haloalkyl.

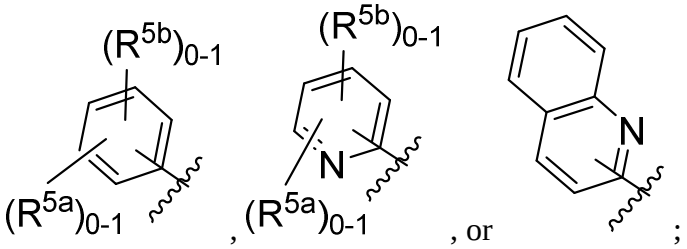
6. The compound of any one of claims 1-5, having formula II



II

or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is



, , or ;

R^2 is alkyl or haloalkyl;

R^{3a} is halo, alkyl, haloalkyl, alkoxy, deuteroalkoxy, haloalkoxy or cycloalkyl;

R^{3b} is halo, alkyl, hydroxy, or haloalkyl;

or R^{3a} and the adjacent R^{3b}, together with the two carbon atoms they are attached to, form a 3-6 membered heterocycle comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, or alkoxycarbonyl;

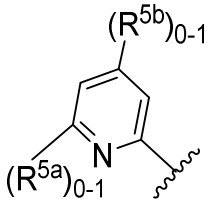
R^{4a} is halo, alkyl, cycloalkyl, haloalkyl, alkoxy, haloalkoxy, or pyrazolyl;

R^{5a} and R^{5b} are independently cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxy, haloalkoxy, hydroxyhaloalkoxy, hydroxyalkoxyalkoxy, alkylsulfonylalkoxy, carboxamide, alkoxycarbonyl, alkylaminoalkyl, alkoxycarbonylalkoxy, hydroxyalkylcycloalkylalkyl, alkylsulfonyl, $-NR^7R^8$, cycloalkyl substituted with 0-3 halo, hydroxy, alkyl, or alkoxy, phenyl substituted with 0-3 halo, hydroxy, or alkyl, 4-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, O, NH, S, and substituted with 0-3 halo, alkyl, hydroxyalkyl, haloalkyl, alkoxycarbonyl, or alkylsulfonyl, heterocyclyloxy, heterocyclylalkyl or heterocyclylalkoxy wherein the heterocyclyl moiety of the heterocyclyloxy and heterocyclylalkoxy comprises 4-8 carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, hydroxyalkyl, alkyl, or haloalkyl; and

R^7 and R^8 are independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl, aminocarbonylalkyl, alkylsulfonyl; alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, cycloalkylalkyl, hydroxycycloalkylalkyl, hydroxyalkylcycloalkylalkyl, cycloalkylalkyl, cycloalkyl, wherein each cycloalkyl is substituted with 0-3 halo, hydroxy, or alkyl, or hydroxyalkyl, or 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, or alkoxycarbonyl;

or R^7 and R^8, together with the nitrogen to which they are attached, form a 5-12 membered heterocycle comprising carbon atoms and 0-3 additional heteroatoms selected from N, NH, O, S and substituted with 0-5 halo, hydroxy, alkyl, alkoxy, oxo, haloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, alkylsulfonylalkyl, aminocarbonyl, or alkoxycarbonyl.

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein

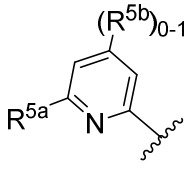
Ar^1 is ;

R^{5a} is cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, alkoxy, haloalkoxy, carboxamide, alkoxycarbonyl, -NR^7R^8, cycloalkyl substituted with 0-1 halo, hydroxy, alkyl, or alkoxy, phenyl substituted with 0-1 halo, hydroxy, or alkyl, or 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-1 halo, hydroxy, or alkyl;

R^{5b} is cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, alkoxy, haloalkoxy, carboxamide, alkoxycarbonyl, or cycloalkyl; and

R^7 and R^8 are independently hydrogen, alkyl, haloalkyl, or hydroxyalkyl; or R^7 and R^8, together with the nitrogen to which they are attached, form a heterocycle with 0-3 additional heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, alkoxy, or oxo.

8. The compound of claim 7 or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is ;

R^{5a} is alkyl, hydroxyalkyl, -NR^7R^8, cyclobutyl substituted with 0-1 halo, hydroxy, alkyl, alkoxy, or phenyl;

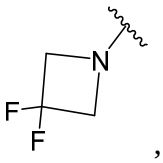
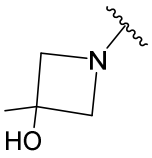
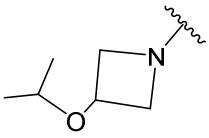
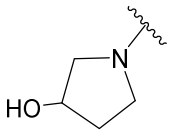
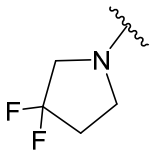
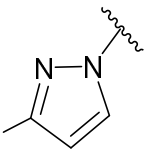
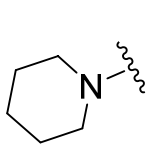
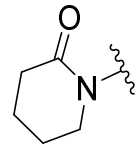
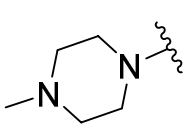
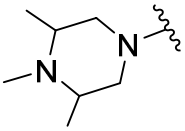
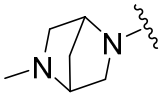
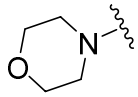
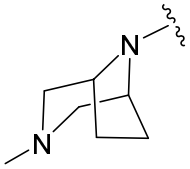
R^{5b} is alkoxy; and

R^7 and R^8 are independently alkyl or hydroxyalkyl; or R^7 and R^8, together with the nitrogen to which they are attached, form a heterocycle with 0-2 additional nitrogen atoms and substituted with 0-3 halo, hydroxy, alkyl, alkoxy, or oxo.

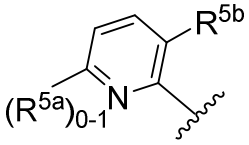
9. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein

R^{5a} is $-NR^7R^8$; and

R^7 and R^8 are independently alkyl or hydroalkyl; or R^7 and R^8, together with the nitrogen to which they are attached form

, , , , , , , , , , , , or .

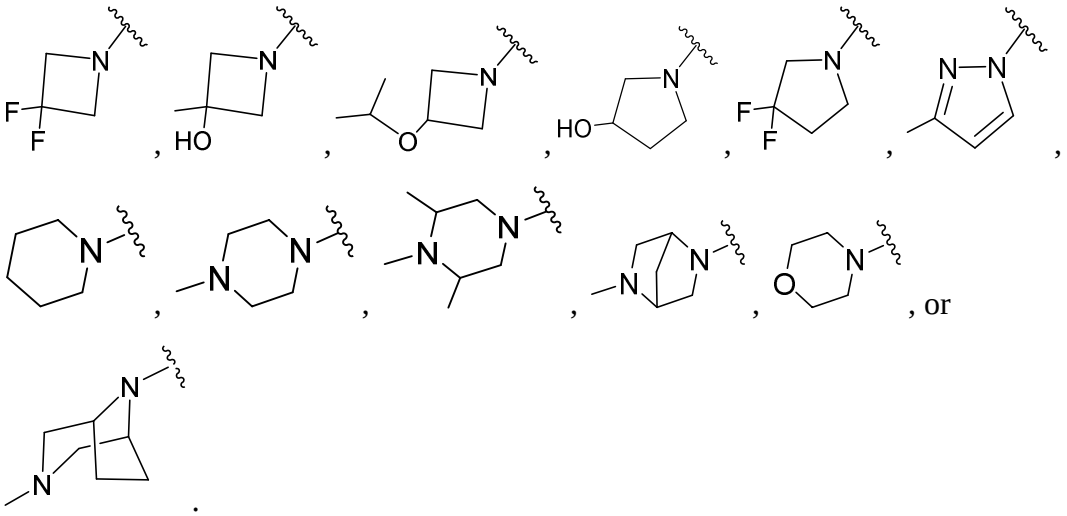
10. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein

Ar^1 is ;

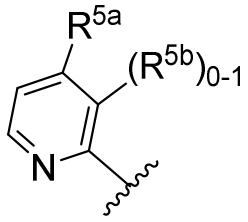
R^{5a} is cyano, halo, alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, $-NR^7R^8$, or cycloalkyl substituted with 0-1 alkoxy;

R^{5b} is cyano, halo, alkyl, or haloalkyl; and

R^7 and R^8 are independently alkyl or hydroxyalkyl; or R^7 and R^8, together with the nitrogen to which they are attached, form



11. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein

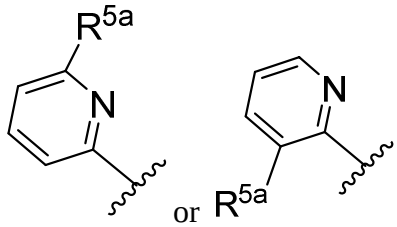


Ar^1 is ;

R^{5a} is cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, alkoxy, or haloalkoxy; and

R^{5b} is cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, alkoxy, or haloalkoxy.

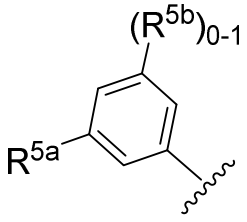
12. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein



Ar^1 is or ; and

R^{5a} is alkyl, haloalkyl, hydroxyalkyl, alkoxy, haloalkoxy, or cycloalkyl.

13. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein

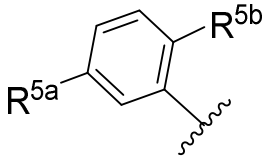
Ar^1 is 

;

R^{5a} is halo, alkoxy, haloalkoxy, carboxamide, alkoxycarbonyl, or cycloalkyl substituted with 0-1 hydroxy; and

R^{5b} is cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, alkoxy, haloalkoxy, carboxamide, alkoxycarbonyl, or cycloalkyl.

14. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein

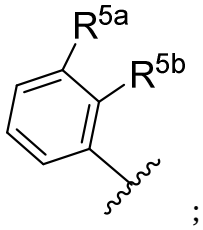
Ar^1 is 

;

R^{5a} is cyano, halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, or alkoxy; and

R^{5b} is cyano, halo, alkyl, or haloalkyl.

15. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein

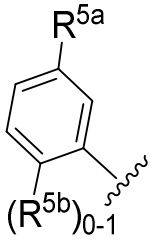
Ar^1 is 

;

R^{5a} is halo; and

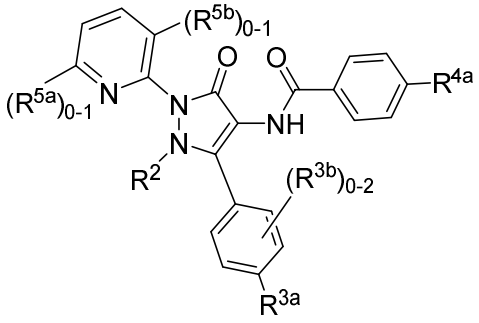
R^{5b} is halo.

16. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein



Ar^1 is ; R^{5a} is halo, alkyl, alkoxy, or haloalkoxy; and R^{5b} is halo, alkyl, haloalkyl, alkoxyalkyl, hydroxyalkyl, alkoxy, or haloalkoxy.

17. The compound of claim 6, having formula III



III

or a pharmaceutically acceptable salt thereof, wherein

R^2 is alkyl or haloalkyl;

R^{3a} is halo, alkyl, haloalkyl, alkoxy, deuteroalkoxy, haloalkoxy or cycloalkyl;

R^{3b} is halo, alkyl, hydroxy, or haloalkyl; or R^{3a} and the adjacent R^{3b}, together with the two carbon atoms they are attached to, form a 3-6 membered heterocycle comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, or alkoxycarbonyl;

R^{4a} is halo, alkyl, cycloalkyl, haloalkyl, alkoxy, haloalkoxy, or pyrazolyl;

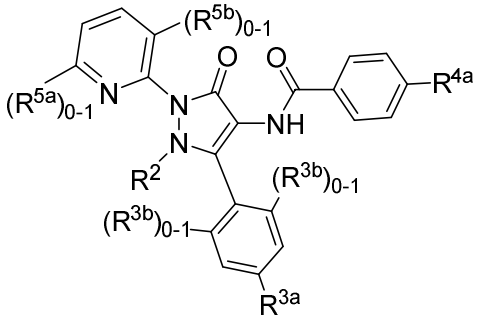
R^{5a} is halo, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxy, alkylaminoalkyl, alkoxycarbonylalkoxy, hydroxyalkylcycloalkylalkyl, alkylsulfonyl, aminocarbonylalkyl, hydroxyalkylcycloalkylalkyl, $-NR^7R^8$, 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, alkoxycarbonyl, or alkylsulfonyl, or heterocyclylalkyl wherein the heterocyclyl comprises 5-8 carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, or haloalkyl;

R^{5b} is cyano, halo, allyl, alkoxy, or haloalkyl; and

R^7 and R^8 are independently hydrogen, alkyl, haloalkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl, aminocarbonylalkyl, alkylsulfonyl; alkylaminocarbonylalkyl, cycloalkylaminocarbonylalkyl, cycloalkylalkyl, hydroxycycloalkylalkyl, hydroxyalkylcycloalkylalkyl, cycloalkylalkyl, cycloalkyl, wherein each cycloalkyl is substituted with 0-3 halo, hydroxy, or alkyl, or hydroxyalkyl, or 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, alkyl, haloalkyl, or alkoxycarbonyl;

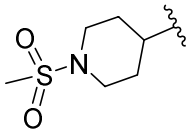
or R^7 and R^8, together with the nitrogen to which they are attached, form a 5-12 membered heterocycle comprising carbon atoms and 0-3 additional heteroatoms selected from N, NH, O, S and substituted with 0-5 halo, hydroxy, alkyl, alkoxy, oxo, haloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, alkylsulfonylalkyl, aminocarbonyl, or alkoxycarbonyl.

18. The compound of claim 17, having formula IV



IV

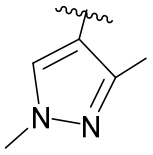
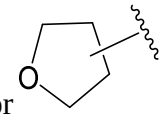
or a pharmaceutically acceptable salt thereof, wherein

R^{5a} is halo, hydroxyalkyl, alkoxy, alkoxyalkoxy, hydroxyalkoxy, hydroxyalkylcycloalkylalkyl, aminocarbonylalkyl, $-NR^7R^8$, or 

;

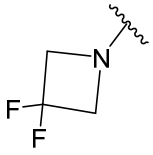
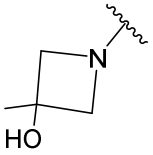
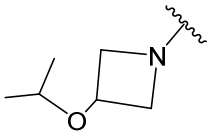
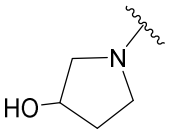
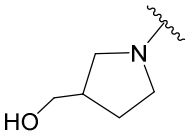
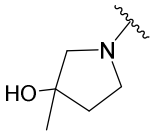
R^{5b} is halo or haloalkyl; and

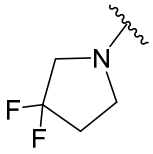
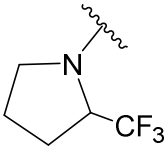
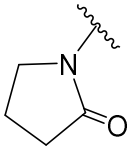
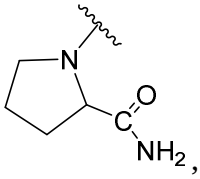
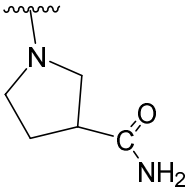
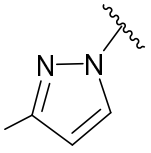
R^7 and R^8 are independently hydrogen, alkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl, aminocarbonylalkyl, hydroxycycloalkylalkyl,

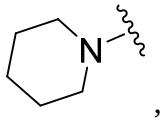
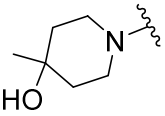
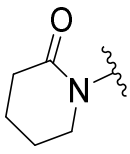
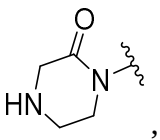
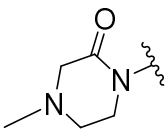
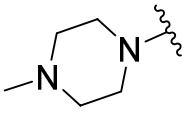
hydroxyalkylcycloalkylalkyl, cycloalkylalkyl, cycloalkyl,  , or 

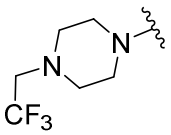
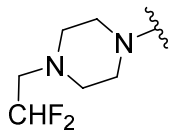
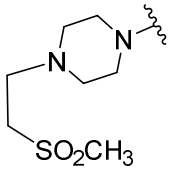
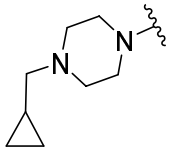
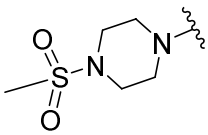
;

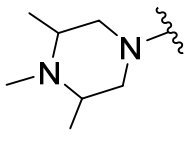
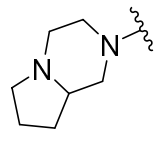
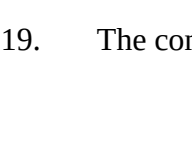
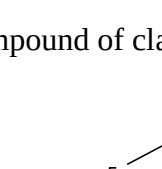
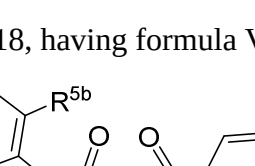
or R^7 and R^8, together with the nitrogen to which they are attached form

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,  ,

 ,  ,  ,  ,  ,

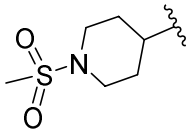
 ,  , ,  ,  , or  .

10 19. The compound of claim 18, having formula V

V

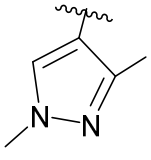
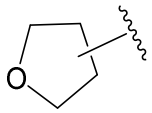
or a pharmaceutically acceptable salt thereof, wherein

R^{5a} is halo, hydroxyalkyl, alkoxyalkoxy, hydroxyalkoxy, -NR^7R^8, or

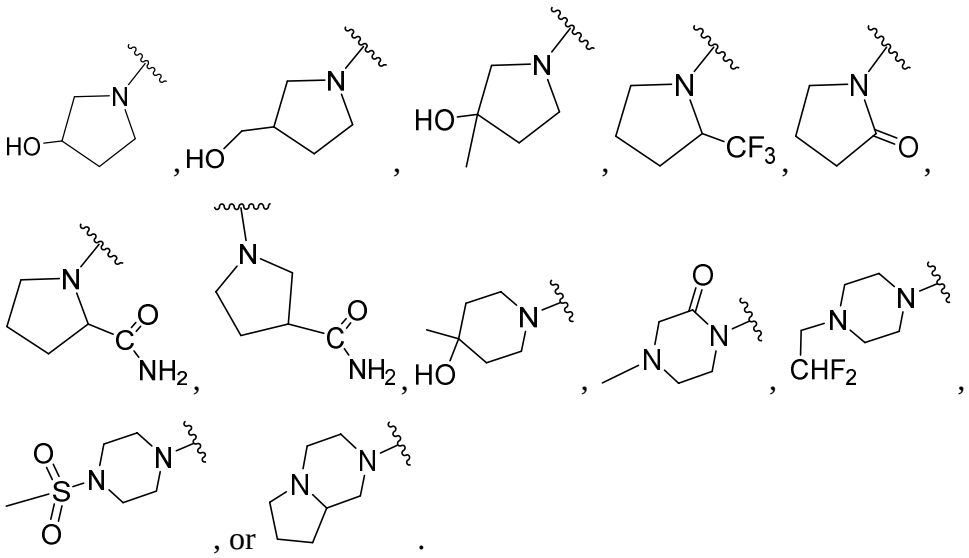

;

R^{5b} is Cl or CF_3;

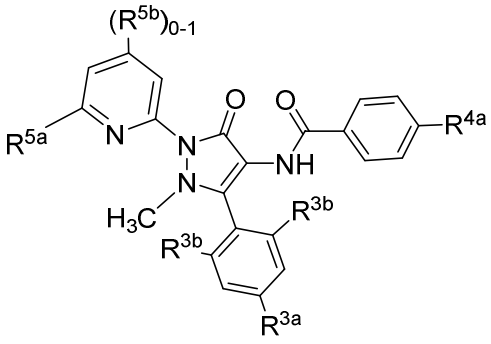
R^7 is hydrogen; and

R^8 is alkyl, hydroxyalkyl, halohydroxyalkyl, alkoxyalkyl, aminocarbonylalkyl, hydroxycycloalkylalkyl, hydroxyalkylcycloalkylalkyl, cycloalkylalkyl, cycloalkyl, , or ;

or R^7 and R^8, together with the nitrogen to which they are attached form



20. The compound of claim 6, having formula VI



or a pharmaceutically acceptable salt thereof, wherein

R^{3a} is halo, alkyl, haloalkyl, alkoxy, haloalkoxy, or deuteroalkoxy;

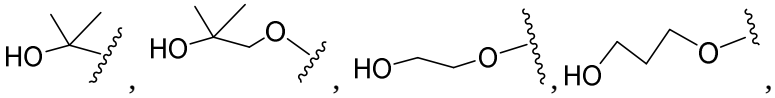
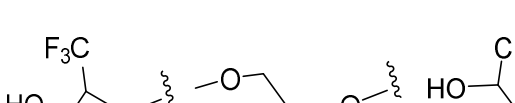
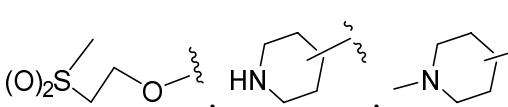
R^{3b} is halo;

R^{4a} is haloalkoxy;

R^{5a} is cyano, halo, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkoxy, hydroxyalkoxy, hydroxyhaloalkoxy, hydroxyalkoxyalkoxy, alkylsylfonylalkoxy, 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, alkyl, hydroxyalkyl, haloalkyl, or alkylsulfonyl, or heterocyclylalkoxy wherein the heterocyclyl comprises 5-8 carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, hydroxy, hydroxyalkyl, alkyl, or haloalkyl; and

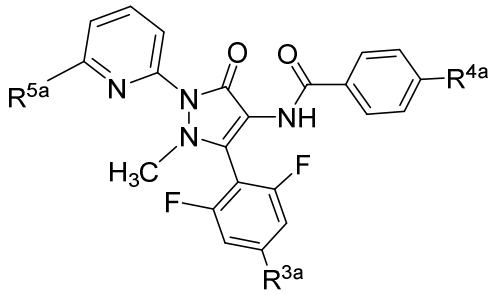
R^{5b} is cano, alkyl, hydroxyalkyl, alkoxy, hydroxyalkoxy, 5-8 membered heterocyclyl comprising carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with 0-3 halo, alkyl, or heterocyclyloxy wherein the heterocyclyl moiety comprises 5-8 carbon atoms and 1-3 heteroatoms selected from N, NH, O, S, and substituted with alkyl, heterocyclyl substituted with 0-1 alkyl.

21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein

R^{5a} is , , ,

R^{5b} is -OCH_3 or CH_3.

22. The compound of claim 20, having formula VII

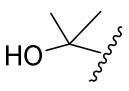
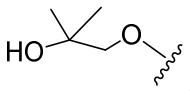
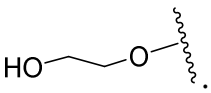


VII

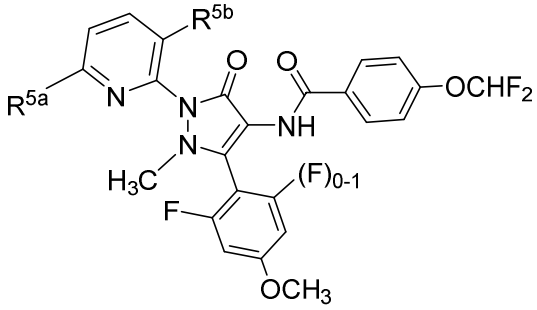
or a pharmaceutically acceptable salt thereof, wherein

R^{3a} is Cl, CF_3, CH_3, CH_3CH_2, CD_3, OCH_3, OCF_3, OCF_2, or OCD_3;

R^{4a} is OCF_3 or OCF_2; and

R^{5a} is , , or .

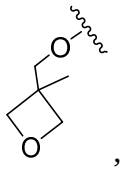
23. The compound of claim 6, having formula VIII

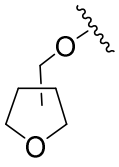


VIII

or a pharmaceutically acceptable salt thereof, wherein

R^{5a} is cyano, alkyl, or haloalkyl;

R^{5b} is cyano, alkyl, hydroxyalkyl, alkoxy, hydroxyalkoxy, $-NR^7R^8$,  ,

or  ;

R^7 is hydrogen or alkyl; and

R^8 is alkyl or .

24. A pharmaceutical composition comprising a compound of any one of claims 1-23, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

25. Use ~~A method for treating a heart disease comprising administering a therapeutically effective amount~~ of a compound of any one of claims 1-23 or a pharmaceutical composition of claim 24 in the manufacture of a medicament for treating a heart disease~~to a patient in need thereof~~.

26. The use ~~method~~ of claim 25 wherein the heart disease is selected from the group consisting of angina pectoris, unstable angina, myocardial infarction, heart failure, acute coronary disease, acute heart failure, chronic heart failure, and cardiac iatrogenic damage.

27. The use ~~method~~ of claim 26 wherein the heart failure is selected from the group consisting of congestive heart failure, systolic heart failure, diastolic heart failure, heart failure with reduced ejection fraction (HF_REF), heart failure with preserved ejection fraction (HF_PEF), acute heart failure, chronic heart failure of ischemic and non-ischemic origin.

28. A compound of any one of claims 1-23 or pharmaceutical composition of claim 24 for use in therapy.

29. A compound of claim 1, having FPR2 EC_{50} values ≤ 0.005 μM.

5