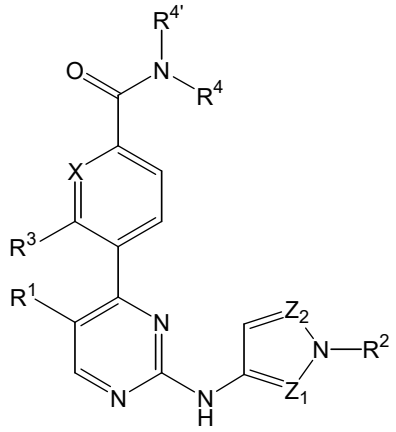
Amended CLAIMS

(Marked)

1. A compound having the structural formula (I):



(I)

wherein

X is N or CR^x, wherein R^x is R', halogen, CN or OR';

each of Z_1 and Z_2 is independently selected from N and CR', *provided* that one of Z_1 and Z_2 is N and the other is CR';

R^1 is Cl;

R^2 is a C_1-C_{16} aliphatic group optionally comprising one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is optionally substituted with one or more of halogen, OR', NRR', CN, CONRR', NRCOR' and C_1-C_6 alkyl, which is in turn optionally substituted with F, OR' or NRR';

R^3 is R', halogen or CN;

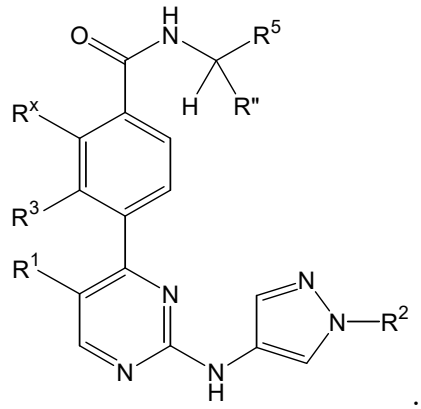
$R^{4'}$ is H or a C_1-C_6 alkyl;

R^4 is -CHR"-R^5, wherein R" is H or a C_1-C_6 alkyl and R^5 is a CN, CF_3, OR' or a C_1-C_{11} aliphatic group with 0 to 4 carbon atoms replaced by one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is optionally substituted with one or more of halogen, OR', NRR', CN, CONRR', NRCOR' and C_1-C_6 alkyl, which is in turn optionally substituted with F, OR' or NRR'; and

each R and R' is independently hydrogen or a C_1-C_{12} unsubstituted or substituted alkyl group,

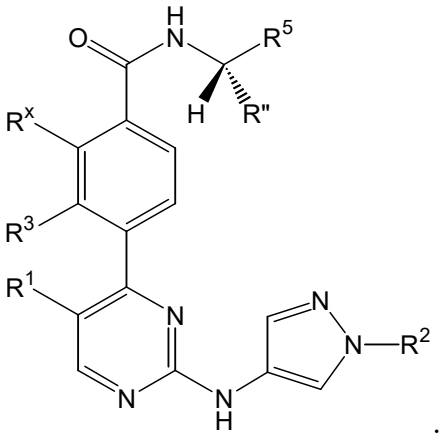
or a pharmaceutically acceptable ~~form or an isotope derivative~~salt thereof.

2. The compound of claim 1, wherein $R^{4'}$ is H, X is CR^x, Z_1 is CH and Z_2 is N, having the structural formula (II):



(II)

3. The compound of claim 1 or 2, wherein R^x is hydrogen, halogen, C_1-C_6 unsubstituted or substituted alkyl or alkoxy.
4. The compound of claim 3, wherein R^x is H.
5. The compound of claim 1, wherein X is N.
6. The compound of any one of claims 1-5, wherein R^3 is H.
7. The compound of any one of claims 1-5, wherein R^3 is F, CH_3 or Cl.
8. The compound of any one of claims 1-5, wherein R^3 is F.
9. The compound of claim 1, wherein X is CR^x, $R^{4'}$ is H, Z_1 is CH and Z_2 is N, having the structural formula (III):



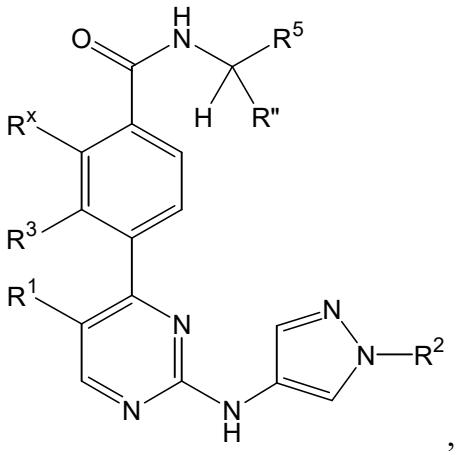
(III)

10. The compound of claim 9, wherein R^x is H, $R^{''}$ is CH_3, R^3 is H and R^5 is CN.

11. The compound of any one of claims 1-10, wherein R^2 is a C_1-C_6 aliphatic group with 0 to 2 carbon atoms replaced by one or more heteroatoms selected from N, O, and S, optionally substituted with a CN or CF_3 group.

12. The compound of any one of claims 1-10, wherein R^2 is a C_7-C_{16} aliphatic group with 0 to 3 carbon atoms replaced by one or more heteroatoms selected from N, O, and S, optionally substituted with a CN or CF_3 group.

13. The compound of claim 1, having the structural formula of (II):



(II)

wherein

R^2 is a C_{3}-C_6 cyclic alkyl;

R^3 is R';

R^5 ~~comprises~~ is a CN;

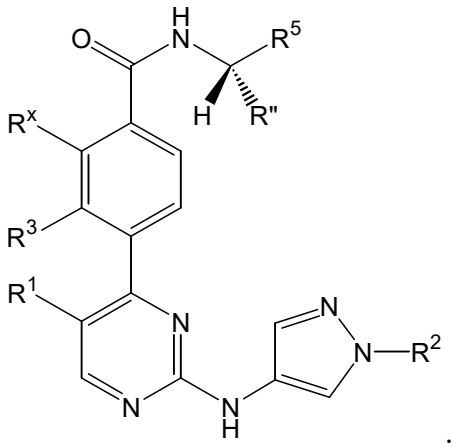
R^x is R', halogen, CN or OR';

R' is ~~hydrogen~~ H or a C_1-C_{12} unsubstituted or substituted alkyl group; and

R" is a ~~H,~~ C_1-C_6 alkyl~~,~~

~~or a pharmaceutically acceptable form or an isotope derivative thereof~~.

14. The compound of claim 13, wherein R" is in the *S*-configuration, having the structural formula (III):



(III)

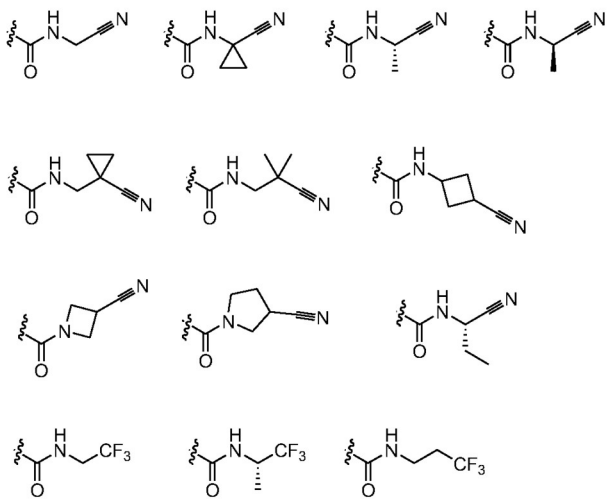
15. The compound of claim 13 or 14, wherein R" is methyl.

16. The compound of any one of claims 13-15, wherein R^x is H~~,~~ and R^3 is H ~~and R^5 is a CN~~.

~~17. The compound of any one of claims 13-16, wherein R^2 comprises a C_3-C_6 cyclic alkyl.~~

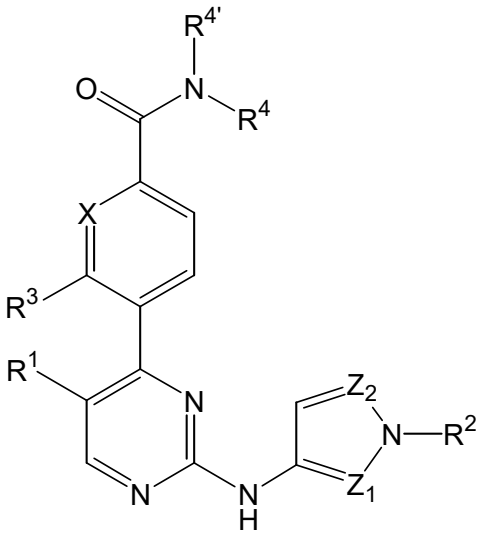
~~18~~17. The compound of claim ~~17~~16, wherein R^2 is cyclopropyl.

18. The compound of claim 1, wherein $C(O)NR^4R^{4'}$ is selected from the below table:



.

19. A compound having the structural formula (I):



(I)

wherein

X is N or CR^x, wherein R^x is R', halogen, CN or OR';

each of Z_1 and Z_2 is independently selected from N and CR', *provided* that one of Z_1 and Z_2 is N and the other is CR';

R^1 is CH_3;

R^2 is a C_1-~~C_{16}~~ C_3 ~~aliphatic~~ alkyl group ~~optionally comprising one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is~~ substituted with

~~one or more of~~ CN~~, CONRR', or NRCOR', which is in turn optionally substituted with F, OR' or NRR'~~;

R^3 is R', halogen or CN;

$R^{4'}$ is H or a C_1-C_6 alkyl;

R^4 is -CHR"-R^5, wherein R" is H or a C_1-C_6 alkyl and R^5 is a CN, CF_3~~,~~ or OR' ~~or a C_1-C_{11} aliphatic group with 0 to 4 carbon atoms replaced by one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is optionally substituted with one or more of halogen, OR', NRR', CN, CONRR', NRCOR' and C_1-C_6 alkyl, which is in turn optionally substituted with F, OR' or NRR'~~; and

each R and R' is independently hydrogen or a C_1-C_{12} unsubstituted or substituted alkyl group,

or a pharmaceutically acceptable ~~form or an isotope derivative~~salt thereof.

~~20. The compound of claim 19, wherein R^2 is a C_1-C_6 aliphatic group substituted with a CN group.~~

~~21. The compound of any one of claims 19 or 20, wherein R^2 is a C_1-C_3 alkyl substituted with a CN group.~~

~~22~~20. The compound of claim ~~21~~19, wherein R^2 is CH_2CN.

~~23~~21. The compound of ~~any one of claims 19-22~~claim 19 or 20, wherein $R^{4'}$ is H.

~~24~~22. The compound of any one of claims 19-~~23~~21, wherein R^4 is -CH_2R^5, wherein R^5 ~~comprises~~ is CN or CF_3.

~~25~~23. The compound of claim ~~24~~22, wherein R^5 is CN.

~~26~~24. The compound of any one of claims 19-~~25~~23, wherein X is CR^x.

~~27~~25. The compound of claim ~~26~~24, wherein R^x is H.

~~28~~26. The compound of any one of claims 19-~~27~~25, wherein X is N.

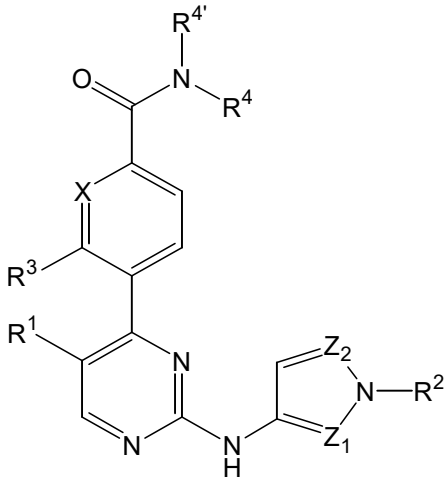
~~29~~27. The compound of any one of claims 19-~~28~~26, wherein R^3 is H.

~~30~~28. The compound of any one of claims 19-~~29~~27, wherein Z_1 is CH and Z_2 is N.

~~31~~29. The compound of claim 19, wherein R^2 is CH_2CN, R^3 is H, $R^{4'}$ is H, X is CR^x, wherein R^x is H, Z_1 is CH and Z_2 is N.

~~32~~30. The compound of claim ~~31~~29, wherein R^4 is -CH_2CN.

~~33~~31. A compound having the structural formula (I):



(I)

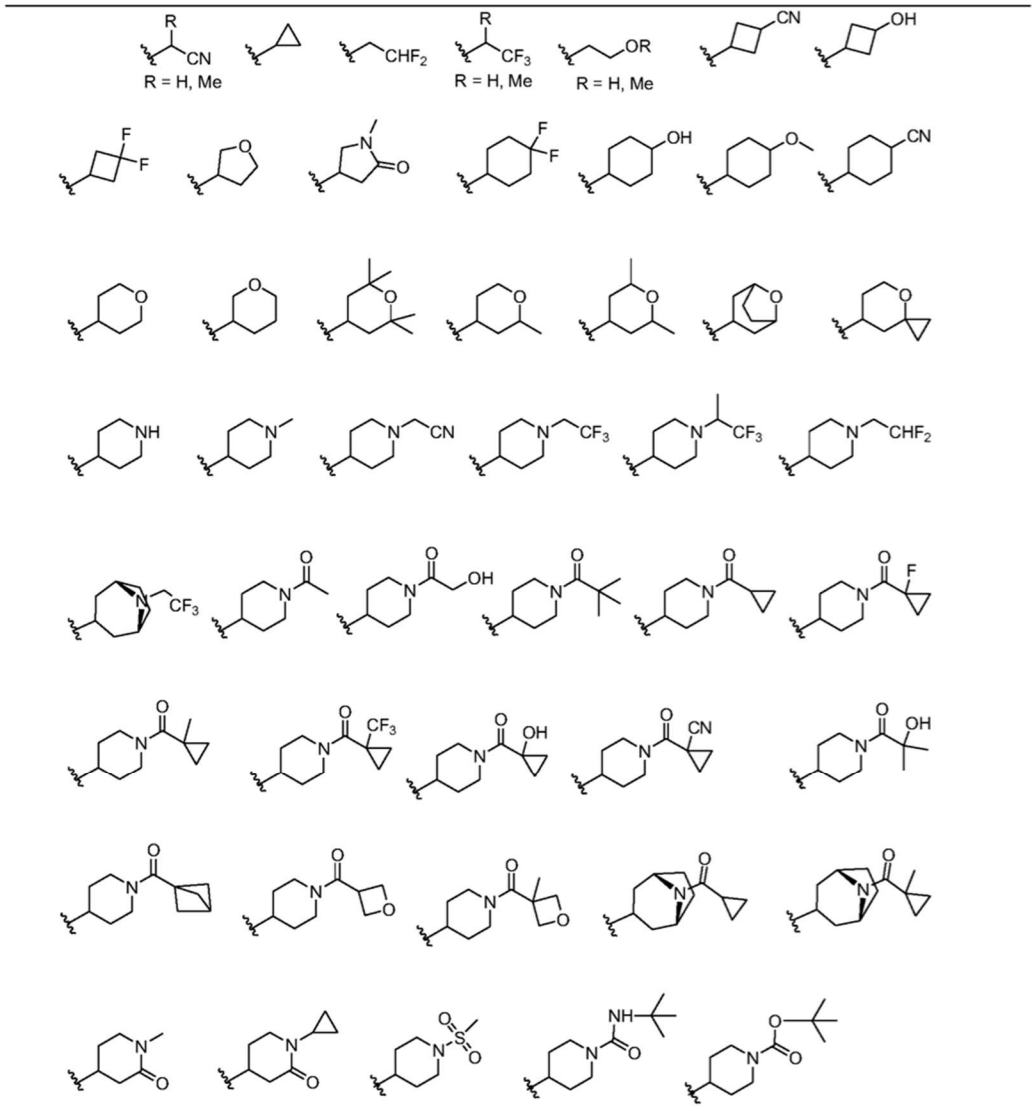
wherein

X is N or CR^x, wherein R^x is R', halogen, CN or OR';

each of Z_1 and Z_2 is independently selected from N and CR', *provided* that one of Z_1 and Z_2 is N and the other is CR';

R^1 is CH_3;

R^2 is ~~a C_3-C_{16} aliphatic group optionally comprising one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is substituted with 0-4 C_1-C_6 alkyl groups~~selected from the below table:



;

R^3 is R', halogen or CN;

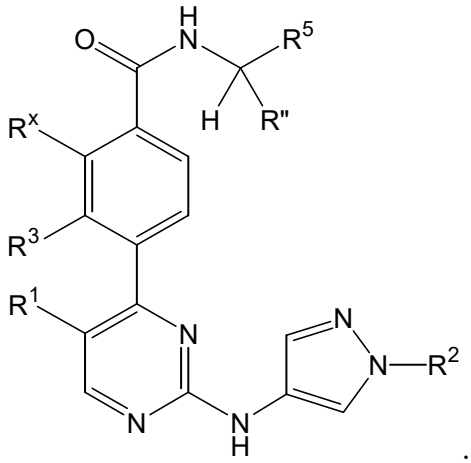
$R^{4'}$ is H or a C_1-C_6 alkyl;

R^4 is -CHR"-R^5, wherein R" is H or a C_1-C_6 alkyl and R^5 is a CN, CF_3 or, OR' ~~or a C_1-C_{11} aliphatic group with 0 to 4 carbon atoms replaced by one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is optionally substituted with one or more of halogen, OR', NRR', CN, CONRR', NRCOR' and C_1-C_6 alkyl, which is in turn optionally substituted with F, OR' or NRR'~~; and

each R and R' is independently hydrogen or a C_1-C_{12} unsubstituted or substituted alkyl group,

or a pharmaceutically acceptable ~~form or an isotope derivative~~salt thereof.

3432. The compound of claim ~~33~~31, wherein $R^{4'}$ is H, X is CR^x, Z_1 is CH, and Z_2 is N, having the structural formula (II):



(II)

3533. The compound of claim ~~33~~31, wherein X is CR^x, wherein R^x is hydrogen, halogen, C_1-C_6 unsubstituted or substituted alkyl or alkoxy.

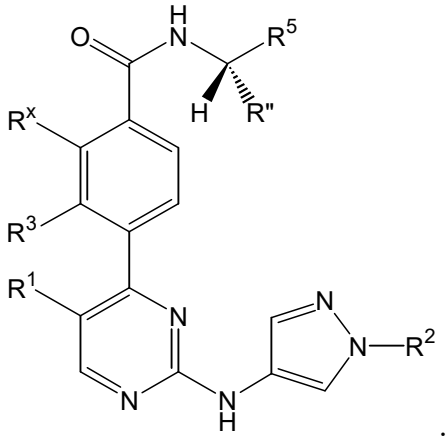
3634. The compound of claim ~~33~~31, wherein X is N.

3735. The compound of any one of claims ~~33~~31-~~28~~34, wherein R^3 is H, F, CH_3 or Cl.

3836. The compound of any one of claims ~~33~~31-~~37~~35, wherein Z_1 is CH and Z_2 is N.

3937. The compound of any one of claims ~~33~~31-~~38~~36, wherein $R^{"}$ is H and R^5 is CN.

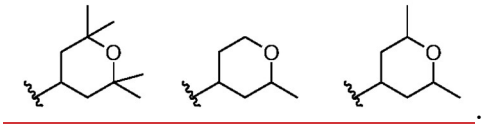
4038. The compound of claim ~~33~~31, wherein X is CR^x, R^3 is H, $R^{4'}$ is H, Z_1 is CH and Z_2 is N, having the structural formula (III):



(III)

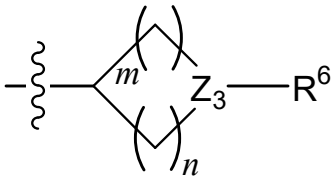
~~41~~39. The compound of claim ~~40~~38, wherein R" is CH_3 and R^5 is CN.

~~42~~40. The compound of any one of claims ~~33~~31-~~41~~39, wherein R^2 is ~~a C_5-C_7 aliphatic group optionally comprising one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is substituted with two or more C_1-C_6 alkyl groups~~selected from:



.

~~43~~41. The compound of claim ~~33~~31, wherein R^2 is:



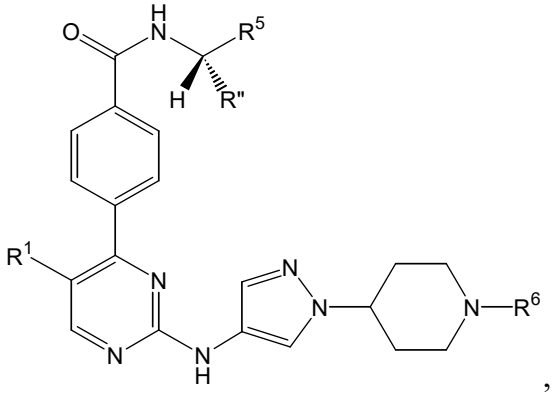
wherein

Z_3 is N, CH or O, wherein when Z_3 is O, R^6 is absent;

each of *m* and *n* is independently 0, 1, 2, 3 or 4; provided that *m* and *n* are not both 0 at the same time, and

R^6 is a C_1-C_6 alkyl, CN, halogen or $C(O)R^7$, wherein R^7 is a C_1-C_6 alkyl; *provided* that when Z_3 is N, R_6 is not CN or halo.

~~44~~42. The compound of claim ~~34~~31, having the structural formula (IV):



,

(IV)

~~Wherein R^x is H, R^3 = H,~~ wherein R" is H or C_1-C_6 alkyl, R^6 is a C_1-C_6 alkyl or $C(O)R^7$, wherein R^7 is a C_1-C_6 alkyl, and R^5 is a CN, CF_3 or, OR' ~~or a C_1-C_{11} aliphatic group with 0 to 4 carbon atoms replaced by one or more heteroatoms selected from N, O, and S, wherein the aliphatic group is optionally substituted with one or more of halogen, OR',~~

~~NRR', CN, CONRR', NRCOR' and C_1-C_6 alkyl, which is in turn optionally substituted with F, OR' or NRR'~~.

~~45~~43. The compound of claim ~~34~~32, wherein R^2 is R^8-CN, wherein R^8 is a $(CH_2)_m$, wherein *m* is 1, 2, 3, 4, 5 or 6.

~~46~~44. The compound of any of claims 1-~~45~~43, selected from the group consisting of:

(S)-4-(5-chloro-2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

4-(5-chloro-2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide

(S)-4-(5-chloro-2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

(S)-4-(5-chloro-2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide-2,3,5,6-d_4

(S)-4-(5-chloro-2-((1-isopropyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

(S)-4-(5-chloro-2-((1-ethyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide 4-methylbenzenesulfonate

(S)-4-(5-chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

(S)-4-(5-chloro-2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanopropyl)benzamide

(S)-4-(5-chloro-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

4-(5-chloro-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide

(S)-4-(5-chloro-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

4-(5-chloro-2-((1-(cyanomethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide

(S)-4-(5-chloro-2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanopropyl)benzamide

(S)-4-(5-chloro-2-((1-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

(S)-4-(5-chloro-2-((1-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanopropyl)benzamide

4-(5-chloro-2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(cyanomethyl)benzamide

(S)-4-(5-chloro-2-((1-(cyanomethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

(S)-4-(5-chloro-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)-N-(1-cyanopropyl)benzamide

(S)-4-(2-((1H-pyrazol-4-yl)amino)-5-chloropyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

(S)-N-(1-cyanobutyl)-4-(2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(2-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(2-((1-(cyanomethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(2-((1-(cyanomethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-4-(2-((1-(cyanomethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)-N-(1-cyanopropyl)benzamide

(S)-N-(1-cyanoethyl)-4-(5-methyl-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(cyano(cyclopropyl)methyl)-4-(5-methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanopropyl)-4-(5-methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanopropyl)-4-(5-methyl-2-((1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(5-methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-((S)-1-cyanoethyl)-4-(2-((1-(trans-2,6-dimethylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

N-((S)-1-cyanoethyl)-4-(2-((1-((2S,4s,6R)-2,6-dimethylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

N-((S)-1-cyanoethyl)-4-(2-((1-((2S,4r,6R)-2,6-dimethylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-N-(cyano(cyclopropyl)methyl)-4-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-N-(1-cyanobutyl)-4-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

(S)-N-(1-cyanopropyl)-4-(2-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(5-methyl-2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(5-methyl-2-((1-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(5-methyl-2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(5-methyl-2-((1-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(cyanomethyl)-2-fluoro-4-(5-methyl-2-((1-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanopropyl)-4-(5-methyl-2-((1-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanopropyl)-4-(5-methyl-2-((1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-((1-cyanocyclopropyl)methyl)-4-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(2-cyano-2-methylpropyl)-4-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(5-methyl-2-((1-methyl-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(5-methyl-2-((1-(1-pivaloylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(5-methyl-2-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-(cyanomethyl)-4-(5-methyl-2-((1-(1-(1-methylcyclopropanecarbonyl)piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(2-((1-(1-(2-hydroxyacetyl)piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)benzamide

4-(2-((1-(trans-4-cyanocyclohexyl)-1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)-N-((S)-1-cyanoethyl)benzamide

N-((S)-1-cyanoethyl)-4-(5-methyl-2-((1-((S*)-1,1,1-trifluoropropan-2-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-((S)-1-cyanoethyl)-4-(5-methyl-2-((1-((R*)-1,1,1-trifluoropropan-2-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-N-(1-cyanoethyl)-4-(5-methyl-2-((1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

(S)-4-(2-((1H-pyrazol-4-yl)amino)-5-methylpyrimidin-4-yl)-N-(1-cyanoethyl)benzamide

N-((S)-1-cyanopropyl)-4-(5-methyl-2-((1-((R*)-1,1,1-trifluoropropan-2-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

N-((S)-1-cyanopropyl)-4-(5-methyl-2-((1-((S*)-1,1,1-trifluoropropan-2-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)benzamide

~~47~~45. A pharmaceutical composition comprising a compound according to any of claims 1-~~46~~44, effective to treat or reduce one or more diseases or disorders, in a mammal, including a human, and a pharmaceutically acceptable excipient, carrier, or diluent.

~~48~~46. The pharmaceutical composition of claim ~~47~~45, being suitable for oral administration, topical administration or GI-restricted administration.

~~49~~47. The pharmaceutical composition of claim ~~47~~ 45 or ~~48~~46, being useful to treat or reduce one or more of inflammatory diseases, immune-mediated diseases and cancers, or a related disease or disorder.

~~50~~48. A unit dosage form comprising a pharmaceutical composition according to any of claims ~~47~~45-~~49~~47.