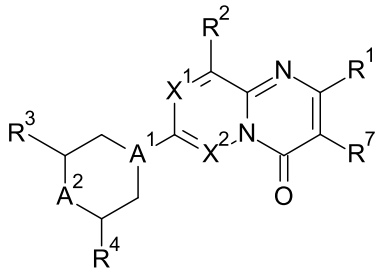
Moreover, genomic-wide association studies (GWAS) showed a strong link between a number of rare loss of function (LoF) variants of TREM2 and an increased risk of late onset Alzheimer's disease (LOAD) (Guerreiro R. et al., N Engl J Med. 2013, 368(2):117–27; Jonsson T. et al., N Engl J Med. 2013, 368(2):107–16). Amongst those, the R47H variant, a LoF mutation associated with structural alterations within the extracellular domain of TREM2 resulting in impaired ability to bind endogenous ligands, was linked to a ca. 3 fold increased risk of LOAD (Sudom, A. et al., J Biol Chem. 2018 10;293(32):12634-12646; doi: 10.1074/jbc.RA118.002352). Studies are ongoing to elucidate the mechanism by which TREM2 LoF mutations contribute to AD. It is likely that patients carrying these mutations have impaired microglia function including reduced clearance of extracellular aggregates (e.g. amyloid and myelin debris) and apoptotic neurons, ultimately reducing their capacity to fight the disease and increasing their susceptibility to neurodegeneration. Indeed decreased microglia activation and failure to cluster around the amyloid plaque were observed in mouse models deficient for TREM2 or DAP12, confirming the central role of TREM2 signalling in microglia function and response to Alzheimer's pathological hallmarks.

In light of all this evidence, pharmacological activation of TREM2 appears to be a viable therapeutic intervention. The small molecules disclosed herein are potent and selective agonists of TREM2.

Summary

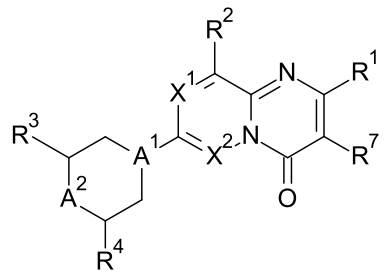
The present disclosure provides compounds of formula (I)



(I)

wherein A^1, A^2, X^1, X^2, R^1, R^2, R^3, R^4, and R^7 are as defined herein.

In one aspect, the present disclosure provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A^1, X^1 and X^2 are each independently selected from N and CH;

A^2 is selected from O and CR^5R^6;

R^1 is selected from C_1-C_6-alkyl and halo-C_1-C_6-alkyl;

R^2 is selected from C_6-C_{10}-aryl, 5- to 6-membered heteroaryl and C_3-C_{10}-cycloalkyl, wherein said C_6-C_{10}-aryl, 5- to 6-membered heteroaryl and C_3-C_{10}-cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C_1-C_6-alkyl and halo-C_1-C_6-alkyl;

R^3 is selected from 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl, wherein said 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl are optionally substituted with 1-3 substituents independently selected from halogen, cyano, amino, hydroxy, oxo, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, halo-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyloxy, 3- to 6-membered heterocyclyl, halo-3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkoxy and 3- to 6-membered heterocyclyloxy;

R^4 is selected from hydrogen and C_1-C_6-alkyl;

R^5 and R^6 are each independently selected from hydrogen and halogen; and

R^7 is selected from hydrogen and C_1-C_6-alkyl.

The disclosure provides compositions including the compounds of formula (I), processes of manufacturing the compounds of formula (I) and methods of using the compounds of formula (I).

In another aspect, the present disclosure provides the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.

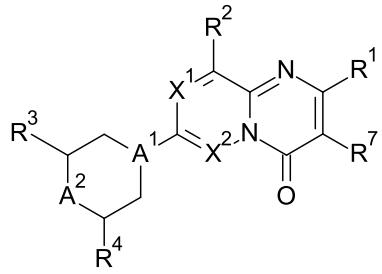
In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

In another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, for use in treating or preventing a condition associated with a loss of function of human TREM2.

In another aspect, the present disclosure provides use of the compound as described herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating or preventing a condition associated with a loss of function of human TREM2.

Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

A^1, X^1 and X^2 are each independently selected from N and CH;

A^2 is selected from O and CR^5R^6;

R^1 is selected from C_1-C_6-alkyl and halo-C_1-C_6-alkyl;

R^2 is selected from C_6-C_{10}-aryl, 5- to 6-membered heteroaryl and C_3-C_{10}-cycloalkyl, wherein said C_6-C_{10}-aryl, 5- to 6-membered heteroaryl and C_3-C_{10}-cycloalkyl are optionally substituted with 1-3 substituents independently selected from halogen, C_1-C_6-alkyl and halo-C_1-C_6-alkyl;

R^3 is selected from 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl, wherein said 5- to 6-membered heteroaryl and 3- to 6-membered heterocyclyl are optionally substituted with 1-3 substituents independently selected from halogen, cyano, amino, hydroxy, oxo, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, halo-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyloxy, 3- to 6-membered heterocyclyl, halo-3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkoxy and 3- to 6-membered heterocyclyloxy;

R^4 is selected from hydrogen and C_1-C_6-alkyl;

R^5 and R^6 are each independently selected from hydrogen and halogen; and

R^7 is selected from hydrogen and C_1-C_6-alkyl.

2. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 and X^2 are both CH; or

(ii) X^1 is CH and X^2 is N; or

(iii) X^1 is N and X^2 is CH.

3. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 is CH and X^2 is N; or

(ii) X^1 is N and X^2 is CH.

4. The compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein A^1 is CH.

5. The compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein A^1 is N.

6. The compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein:

A^2 is selected from O and CR^5R^6;

R^5 and R^6 are both hydrogen or

R^5 and R^6 are both halogen.

7. The compound of formula (I) according to claim 6, or a pharmaceutically acceptable salt thereof, wherein:

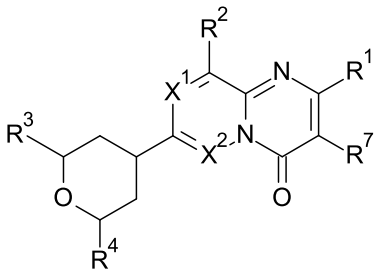
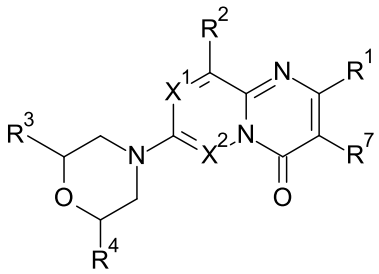
A^2 is selected from O and CR^5R^6;

R^5 and R^6 are both hydrogen or

R^5 and R^6 are both fluoro.

8. The compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein A^2 is O.

9. The compound of formula (I) according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is a compound of formula (II) or (III):


(II)

(III)

wherein the variables are as defined in any one of claims 1 to 3.

10. The compound of formula (I) according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from methyl and CHF_2.

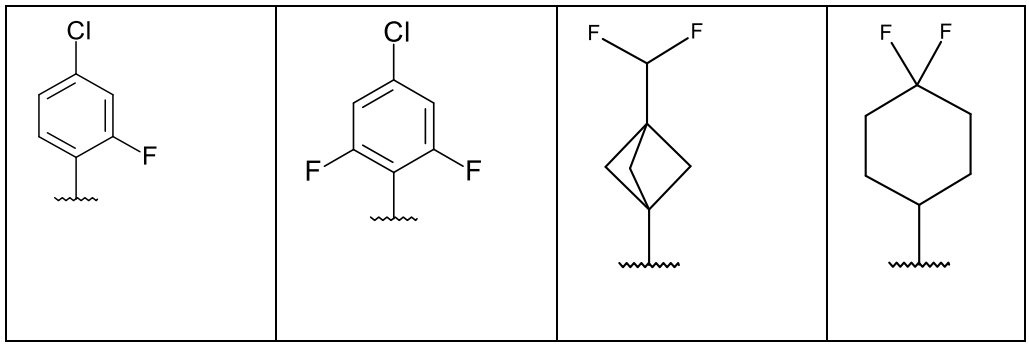
11. The compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from C_6-C_{10}-aryl, C_3-C_{10}-cycloalkyl, and 5- to 6-membered heteroaryl comprising 1-2 heteroatoms independently selected from N, O and S, wherein said C_6-C_{10}-aryl, C_3-C_{10}-cycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with 1-3 substituents independently selected from halogen and halo-C_1-C_6-alkyl.

12. The compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, pyridyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF_2, and CF_3.

13. The compound of formula (I) according to claim 11, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from C_6-C_{10}-aryl and C_3-C_{10}-cycloalkyl, wherein said C_6-C_{10}-aryl and C_3-C_{10}-cycloalkyl are substituted with 1-3 substituents independently selected from halogen and halo-C_1-C_6-alkyl.

14. The compound of formula (I) according to claim 13, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from phenyl, cyclohexyl, and bicyclo[1.1.1]pentane substituted with 1-3 substituents independently selected from fluoro, chloro, and CHF_2.

15. The compound of formula (I) according to claim 14, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:



16. The compound of formula (I) according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is optionally substituted with 1-2 substituents independently selected from C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, halo-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkyl, and 3- to 6-membered heterocyclyl-C_1-C_6-alkoxy, and wherein said 3- to 6-membered heterocyclyl is optionally substituted with 1-2 substituents independently selected from C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, halo-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkoxy, and oxo.

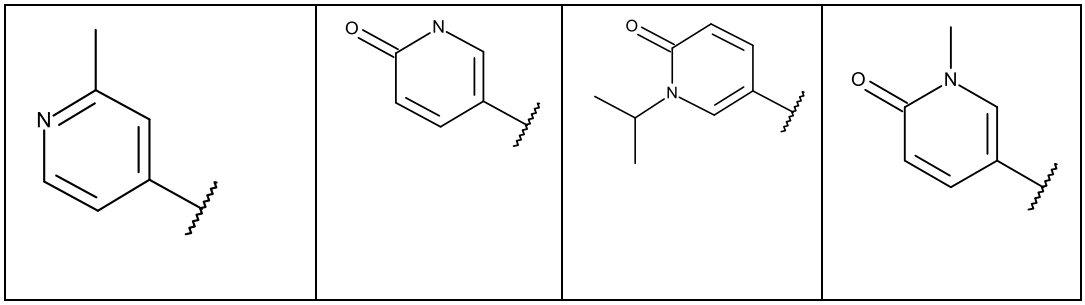
17. The compound of formula (I) according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF_2, CF_3, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-

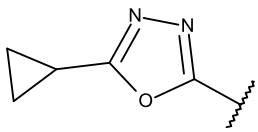
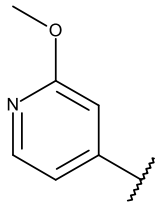
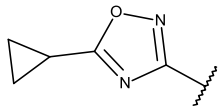
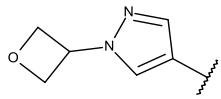
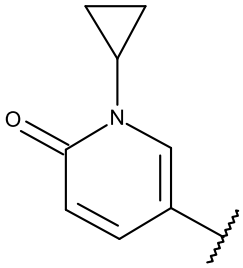
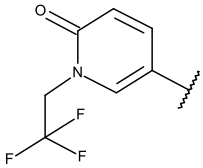
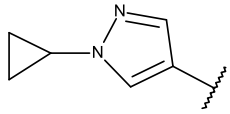
methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, and oxetanylmethoxy, and wherein said 1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF_2, CF_3, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, oxetanylmethoxy, and oxo.

18. The compound of formula (I) according to claim 16, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is substituted with 1 substituent selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, and 3- to 6-membered heterocyclyl, and wherein said 3- to 6-membered heterocyclyl is substituted with oxo and optionally one further substituent selected from C_1-C_6-alkyl, halo-C_1-C_6-alkyl, and C_3-C_{10}-cycloalkyl.

19. The compound of formula (I) according to claim 18, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are substituted with 1 substituent selected from methyl, methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is substituted with oxo and optionally one further substituent selected from methyl, isopropyl, 2,2,2-trifluoroethyl, and cyclopropyl.

20. The compound of formula (I) according to claim 19, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from:



21. The compound of formula (I) according to any one of claims 1 to 20, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from hydrogen and methyl.

22. The compound of formula (I) according to claim 21, or a pharmaceutically acceptable salt thereof, wherein R^4 is hydrogen.

23. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^7 is selected from hydrogen and methyl.

24. The compound of formula (I) according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, wherein R^7 is C_1-C_6-alkyl.

25. The compound of formula (I) according to claim 24, or a pharmaceutically acceptable salt thereof, wherein R^7 is methyl.

26. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 and X^2 are both CH; or

(ii) X^1 is CH and X^2 is N; or

(iii) X^1 is N and X^2 is CH;

A^1 is selected from N and CH;

A^2 is selected from O and CR^5R^6;

R^1 is selected from C_1-C_6-alkyl and halo-C_1-C_6-alkyl;

R^2 is selected from C_6-C_{10}-aryl, C_3-C_{10}-cycloalkyl, and 5- to 6-membered heteroaryl comprising 1-2 heteroatoms independently selected from N, O and S, wherein said C_6-C_{10}-aryl, C_3-C_{10}-cycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with 1-3 substituents independently selected from halogen and halo-C_1-C_6-alkyl;

R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is optionally substituted with 1-2 substituents independently selected from C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, halo-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkyl, and 3- to 6-membered heterocyclyl-C_1-C_6-alkoxy, and wherein said 3- to 6-membered heterocyclyl is optionally substituted with 1-2 substituents independently selected from C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, halo-C_3-C_{10}-cycloalkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl-C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyloxy, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkyl, 3- to 6-membered heterocyclyl-C_1-C_6-alkoxy, and oxo;

R^4 is selected from hydrogen and C_1-C_6-alkyl;

R^5 and R^6 are both hydrogen or

R^5 and R^6 are both halogen; and

R^7 is selected from hydrogen and C_1-C_6-alkyl.

27. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 and X^2 are both CH; or

(ii) X^1 is CH and X^2 is N; or

(iii) X^1 is N and X^2 is CH;

A^1 is selected from N and CH;

A^2 is selected from O and CR^5R^6;

R^1 is selected from methyl and CHF_2;

R^2 is selected from phenyl, pyridyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane, wherein said phenyl, cyclohexyl, bicyclo[3.1.0]hexane and bicyclo[1.1.1]pentane are optionally substituted with 1-3 substituents independently selected from fluoro, chloro, CHF_2, and CF_3;

R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF_2, CF_3, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, and oxetanylmethoxy, and wherein said 1,2-dihydropyridine is optionally substituted with 1-2 substituents independently selected from methyl, ethyl, isopropyl, CHF_2, CF_3, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, methoxy, 2-methoxyethyl, cyclopropyl, cyclobutyl, difluorocyclobutyl, cyclopropylmethyl, cyclobutyloxy, oxetanyl, oxetanylmethyl, oxetanylmethoxy, and oxo;

R^4 is selected from hydrogen and methyl;

R^5 and R^6 are both hydrogen or

R^5 and R^6 are both fluoro; and

R^7 is selected from hydrogen and methyl.

28. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 is CH and X^2 is N; or

(ii) X^1 is N and X^2 is CH;

A^1 is CH;

A^2 is O;

R^1 is selected from C_1-C_6-alkyl and halo-C_1-C_6-alkyl;

R^2 is selected from C_6-C_{10}-aryl and C_3-C_{10}-cycloalkyl, wherein said C_6-C_{10}-aryl and C_3-C_{10}-cycloalkyl are substituted with 1-3 substituents independently selected from halogen and halo-C_1-C_6-alkyl;

R^3 is selected from 5- to 6-membered heteroaryl comprising 1-3 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, and 3- to 6-membered heterocyclyl comprising 1-2 heteroatoms independently selected from N, O, and S, the remaining atoms being carbon, wherein said 5- to 6-membered heteroaryl is substituted with 1 substituent selected from C_1-C_6-alkyl, C_1-C_6-alkoxy, C_3-C_{10}-cycloalkyl, and 3- to 6-membered heterocyclyl, and wherein said 3- to 6-membered heterocyclyl is substituted with oxo and optionally one further substituent selected from C_1-C_6-alkyl, halo-C_1-C_6-alkyl, and C_3-C_{10}-cycloalkyl;

R^4 is hydrogen; and

R^7 is C_1-C_6-alkyl.

29. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

(i) X^1 is CH and X^2 is N; or

(ii) X^1 is N and X^2 is CH;

A^1 is CH;

A^2 is O;

R^1 is selected from methyl and CHF_2;

R^2 is selected from phenyl, cyclohexyl, and bicyclo[1.1.1]pentane substituted with 1-3 substituents independently selected from fluoro, chloro, and CHF_2;

R^3 is selected from pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, and 1,2-dihydropyridine, wherein said pyridyl, pyrazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl are substituted with 1 substituent selected from methyl, methoxy, cyclopropyl, and oxetanyl, and wherein said 1,2-dihydropyridine is substituted with oxo and optionally one further substituent selected from methyl, isopropyl, 2,2,2-trifluoroethyl, and cyclopropyl;

R^4 is hydrogen; and

R^7 is methyl.

30. The compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound of formula (I) is selected from:

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(3S)-3-(1-methylpyrazol-4-yl)-1-piperidyl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(3S)-4,4-difluoro-3-(1-methylpyrazol-4-yl)-1-piperidyl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(2-methylpyridin-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chlorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[2-(trifluoromethyl)-4-pyridyl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one formiate;

9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(2-methoxy-4-pyridyl)morpholin-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(5-methyl-1,3,4-oxadiazol-2-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chlorophenyl)-2,3-dimethyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-7-[(2R)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-7-[(2S)-2-(2-methoxypyridin-4-yl)morpholin-4-yl]-2,3-dimethylpyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-3-methyl-7-[(2S)-2-(1-methylpyrazol-4-yl)morpholino]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluorophenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-[1-(oxetan-3-yl)pyrazol-4-yl]morpholin-4-yl]pyrido[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(1-methyl-6-oxopyridin-3-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(2-methyl-4-pyridyl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluorophenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)oxan-4-yl]-2,3-dimethylpyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluorophenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R,6S)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S,6R)-2-(1-cyclopropylpyrazol-4-yl)-6-methyl-tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2S)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2R)-2-(1-cyclopropylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1H-pyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(trifluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4R)-2-(1-methylpyrazol-4-yl)tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,6S)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,6R)-2-methyl-6-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R)-2-(1H-pyrazol-4-yl)morpholin-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(difluoromethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R)-2-(1-cyclobutylpyrazol-4-yl)morpholin-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2-(difluoromethyl)-3-methyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

2,3-dimethyl-7-[(2R,4S)-2-(1-methylpyrazol-4-yl)oxan-4-yl]-9-[6-(trifluoromethyl)pyridin-3-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2-methoxyethyl)pyrazol-4-yl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

7-[rac-(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[rac-(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(2-fluorophenyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4R)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(oxetan-3-ylmethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-[3-(difluoromethyl)-1-bicyclo[1.1.1]pentanyl]-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-7-[rac-(2R,4R)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

2,3-dimethyl-7-[rac-(2R,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]-9-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1H-pyridin-3-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-ethyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(2-methoxy-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-2-(difluoromethyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-3-methyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-[1-(cyclopropylmethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1,5-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1,3-dimethylpyrazol-4-yl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-(2-methyl-4-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[2-(cyclobutoxy)-4-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[2-[2-(cyclopropylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[2-[2-(oxetan-3-ylmethoxy)-4-pyridyl]tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-(1-cyclopropylpyrazol-4-yl)tetrahydropyran-4-yl]-9-[(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-cyclobutyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[rac-(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(2,2-difluoroethyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[6-keto-1-(2,2,2-trifluoroethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(1-isopropyl-6-keto-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-[1-(3,3-difluorocyclobutyl)-6-keto-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2R,4S)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4,4-difluorocyclohexyl)-7-[(2S,4R)-2-(6-keto-1-methyl-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2R,4S)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2,6-difluoro-phenyl)-2,3-dimethyl-7-[(2S,4R)-2-(1-methyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]pyrimido[1,2-b]pyridazin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2R,4S)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4,4-difluorocyclohexyl)-2,3-dimethyl-7-[(2S,4R)-2-[1-(oxetan-3-yl)pyrazol-4-yl]tetrahydropyran-4-yl]pyrazino[1,2-a]pyrimidin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[rac-(2R,4S)-2-[6-keto-1-(trifluoromethyl)-3-pyridyl]tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2R,4S)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;

9-(4-chloro-2-fluoro-phenyl)-7-[(2S,4R)-2-(2-cyclopropyl-4-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2,6-difluoro-phenyl)-7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
9-(4-chloro-2,6-difluoro-phenyl)-7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-2,3-dimethyl-pyrimido[1,2-b]pyridazin-4-one;
7-[(2R,4S)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one; and
7-[(2S,4R)-2-(1-cyclopropyl-6-oxo-3-pyridyl)tetrahydropyran-4-yl]-9-(4,4-difluorocyclohexyl)-2,3-dimethyl-pyrazino[1,2-a]pyrimidin-4-one.

31. The compound of formula (I) according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.

32. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

33. The compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 32, for use in treating or preventing a condition associated with a loss of function of human TREM2.

34. Use of the compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition according to claim 32, in the manufacture of a medicament for treating or preventing a condition associated with a loss of function of human TREM2.

35. The compound, pharmaceutically acceptable salt thereof or pharmaceutical composition for use according to claim 33, or the use according to claim 34, wherein said condition associated with a loss of function of human TREM2 is selected from Parkinson’s disease, rheumatoid arthritis, Alzheimer’s disease, amyotrophic lateral sclerosis, Nasu-Hakola disease, frontotemporal dementia, multiple sclerosis, prion disease, and stroke.