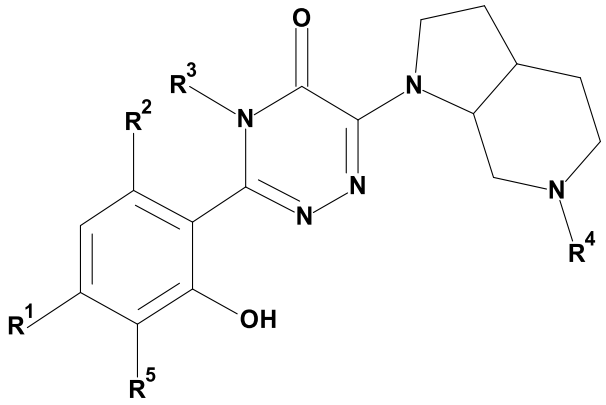
include parthenolide, 3,4-methylenedioxy-β-nitrostyrene and dimethyl sulfoxide (DMSO), although these agents have limited potency and are nonspecific.

Current treatments for NLRP3-related diseases include biologic agents that target IL-1. These are the recombinant IL-1 receptor antagonist anakinra, the neutralizing IL-1β antibody canakinumab and the soluble decoy IL-1 receptor rilonacept. These approaches have proven successful in the treatment of CAPS, and these biologic agents have been used in clinical trials for other IL-1β-associated diseases.

There is a need to provide compounds with improved pharmacological and/or physiological and/or physicochemical properties and/or those that provide a useful alternative to known compounds.

Summary

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



I.

wherein,

R^1 is H, alkyl, alkoxy, -CN, halo, haloalkyl, haloalkoxy, acetyl or SF_6;

R^5 is H;

or R^1 and R^5, and the atoms to which they are bonded, form either an 4-6 membered heterocycle ring comprising a single O heteroatom optionally substituted with one or two substituents independently selected from halo or alkyl, or R^1 and R^5, and the atoms to which they are bonded, form a 4-6 membered cycloalkyl ring optionally substituted with 1 to 2 substituents independently selected from halo or alkyl;

R^2 is H, halo or alkyl and R^3 is H or alkyl, wherein only one of R^2 and R^3 can be H;

R^4 is oxetane, alkyl, or $–(CH_2)_n$-R^6 wherein R^6 is hydroxy or methoxy and n is greater than 1;

and pharmaceutically acceptable salts thereof.

In another aspect, the present disclosure provides a compound as described herein for use as a therapeutically active substance.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described herein and a therapeutically inert carrier.

In another aspect, the present disclosure provides the use of a compound as described herein in the manufacture of a medicament for the treatment or prophylaxis of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prophylaxis of a disease, disorder or condition selected from Parkinson’s Disease or Alzheimer’s Disease.

In another aspect, the present disclosure provides the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

In another aspect, the present disclosure provides the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Parkinson's Disease or Alzheimer's Disease.

In another aspect, the present disclosure provides an *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as described herein to inhibit NLRP3.

The term "alkyl" denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms. In some embodiments, if not otherwise described, alkyl comprises 1 to 6 carbon atoms (C_{1-6}-alkyl), or 1 to 4 carbon atoms (C_{1-4}-alkyl). Examples of C_{1-6}-alkyl include methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl and pentyl. Particular alkyl group is methyl.

The term "alkoxy" denotes a group of the formula -O-R', wherein R' is a C_{1-6}-alkyl group. Examples of C_{1-6}-alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy.

The term "cycloalkyl" denotes monocyclic or polycyclic saturated or partially unsaturated, non-aromatic hydrocarbon. In some embodiments, unless otherwise described, cycloalkyl comprises 3 to 8 carbon atoms, 3 to 6 carbon atoms, or 3 to 5 carbon atoms. In some embodiments, cycloalkyl is a saturated monocyclic or polycyclic hydrocarbon. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and octahydropentalenyl, and the like. Particular example is cyclobutyl. Another particular example is cyclopentyl.

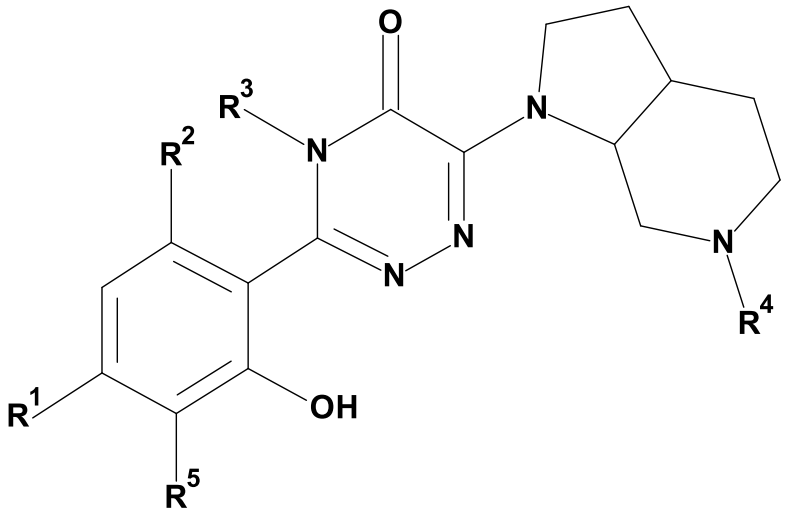
The term “halogen”, “halide” and “halo” are used interchangeably herein and denote fluoro, chloro, bromo or iodo. Particular halogens are fluoro and chloro. Preferred halogen is fluoro.

The term “haloalkyl” denotes a C_{1-6}-alkyl group wherein at least one of the hydrogen atoms of the C_{1-6}-alkyl group has been replaced by the same or different halogen atoms. Example of haloalkyl include fluoromethyl, difluoromethyl and trifluoromethyl. Particular example is trifluoromethyl.

The term “haloalkoxy” denotes a C_{1-6}-alkoxy group wherein at least one of the hydrogen atoms of the C_{1-6}-alkoxy group has been replaced by the same or different halogen atoms. Examples of haloalkoxy are difluoromethoxy, trifluoromethoxy, difluoroethoxy and trifluoroethoxy. Particular examples are difluoromethoxy and trifluromethoxy.

Claims

1. A compound of formula I



I.

wherein,

R^1 is H, alkyl, alkoxy, -CN, halo, haloalkyl, haloalkoxy, acetyl or SF_6;

R^5 is H;

or R^1 and R^5, and the atoms to which they are bonded, form either an 4-6 membered heterocycle ring comprising a single O heteroatom optionally substituted with one or two substituents independently selected from halo or alkyl, or R^1 and R^5, and the atoms to which they are bonded, form a 4-6 membered cycloalkyl ring optionally substituted with 1 to 2 substituents independently selected from halo or alkyl;

R^2 is H, halo or alkyl and R^3 is H or alkyl, wherein only one of R^2 and R^3 can be H;

R^4 is oxetane, alkyl, or $–(CH_2)_n\text{-}R^6$ wherein R^6 is hydroxy or methoxy and n is greater than 1;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R^1 is haloalkyl or haloalkoxy.

3. A compound according to claim 1 or 2, wherein R^2 is H and R^3 is alkyl.

4. A compound according to any of claims 1 to 3, wherein R^4 is alkyl or $–(CH_2)_n\text{-}R^6$ wherein R^6 is hydroxy and n is 2.

5. A compound according to any of claims 1 to 4, wherein R^4 is alkyl.

6. A compound according to claim 1, wherein

R^1 is haloalkyl or haloalkoxy;

R^5 is H;

or R^1 and R^5, with the atoms to which they are attached, form a 4-to-5 membered cycloalkyl or a 5-membered heterocycle comprising a single O heteroatom;

R^2 is H;

R^3 is alkyl;

R^4 is alkyl or or $–(CH_2)_n$-R^6 wherein R^6 is hydroxy and n is 2.

and pharmaceutically acceptable salts thereof.

7. A compound according to claim 1, wherein

R^1 is haloalkyl or haloalkoxy;

R^5 is H;

or R^1 and R^5, with the atoms to which they are attached, form a 4-to-5 membered cycloalkyl or a 5-membered heterocycle comprising a single O heteroatom;

R^2 is H;

R^3 is alkyl;

R^4 is alkyl;

and pharmaceutically acceptable salts thereof.

8. A compound according to any of claims 1 to 7, wherein the compound is selected from

3-[2-Hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-6-(6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl)-1,2,4-triazin-5-one; formic acid;

6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-methyl-1,2,4-triazin-5-one;

3-[4-(Difluoromethoxy)-2-hydroxy-phenyl]-4-methyl-6-(6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl)-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[4-(difluoromethoxy)-2-hydroxy-phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[4-(difluoromethoxy)-2-hydroxy-phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

9. A compound according to any one of claims 1 to 7, wherein the compound is selected from

3-(4-Hydroxyindan-5-yl)-4-methyl-6-(6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl)-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[6-(2-Hydroxyethyl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-(2-Hydroxyethyl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-(2-Hydroxyethyl)-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

10. A compound according to any one of claims 1 to 8, wherein the compound is selected from

6-[(3aR,7aS)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aR,7aS)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[4-(difluoromethoxy)-2-hydroxy-phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

11. A compound according to any of claims 1 to 8, wherein the compound is selected from

6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[4-(difluoromethoxy)-2-hydroxy-phenyl]-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

12. A compound according to any of claims 1 to 7, or claim 9, wherein the compound is 6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one, or a pharmaceutically acceptable salt thereof.

13. A compound according to any of claims 1 to 12, wherein the compound is selected from

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(2-hydroxy-3-bicyclo[4.2.0]octa-1,3,5-trienyl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-[4-(difluoromethoxy)-2-hydroxy-phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3aS,7aR)-6-Methyl-3,3a,4,5,7,7a-hexahydro-2H-pyrrolo[2,3-c]pyridin-1-yl]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

14. A compound according to any one of claims 1 to 13 for use as a therapeutically active substance.

15. A compound according to any one of claims 1 to 13 for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 and a therapeutically inert carrier.

17. The use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment or prophylaxis of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

18. A compound according to any one of claims 1 to 13 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

19. A compound according to any one of claims 1 to 13 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Parkinson’s Disease or Alzheimer’s Disease.

20. The use of a compound according to any one of claims 1 to 13 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

21. The use of a compound according to any one of claims 1 to 13 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Parkinson’s Disease or Alzheimer’s Disease.

22. An *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as claimed in any one of claims 1 to 13 to inhibit NLRP3.