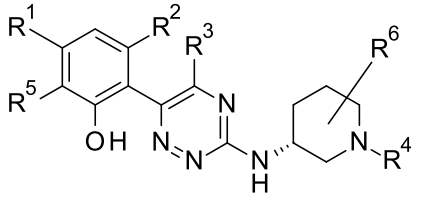
Several small molecules have been shown to inhibit the NLRP3 inflammasome. Glyburide inhibits IL-1β production at micromolar concentrations in response to the activation of NLRP3 but not NLRC4 or NLRP1. Other previously characterised weak NLRP3 inhibitors include parthenolide, 3,4-methylenedioxy-β-nitrostyrene 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. Further, in developing a NLRP3 inhibitor for treating peripheral indications, it is advantageous to minimize the exposure of an NLRP3 inhibiting compound in the brain relative to systemic exposure to minimize the risk of potential side effects in the central nervous system (CNS). The compounds of formula I achieve this by showing an increased efflux in a transcellular assay expressing active P-gp protein and/or reduced permeability. P-gp (P-glycoprotein) is an important transporter that is expressed in the capillary endothelial cells composing the blood–brain barrier and blood–testis barrier, where it pumps xenobiotics back into the capillaries and limiting brain exposure.

Summary

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



I

wherein

R^1 and R^5, and the atoms to which they are bonded, form either

i. a 4-6 membered heterocycle ring comprising a single O heteroatom, or

ii. a 4-5 membered cycloalkyl ring;

R^2 and R^3 are selected from H and alkyl, wherein only one of R^2 or R^3 can be H or alkyl;

R^4 is selected from

i. alkyl,

ii. hydroxyalkyl,

iii. alkoxyalkyl,

iv. cycloalkyl substituted with hydroxy or alkoxy,

v. cycloalkylalkyl substituted with hydroxyl, alkoxy, or –COOH,

vi. a 4-6 membered heterocycle comprising a single O heteroatom,

vii. $(CH_2)_nC(O)OH$, $(CH_2)_nC(O)OCH_3$, or $(CH_2)_nC(O)NHCH_3$, wherein n is 2 or 3,

viii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is a tetrazole, oxadiazole or an oxazole heteroaryl,

ix. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is a pyrazole;

x. $-(CH_2)_nS(O)_2CH_3$ or $(CH_2)_nCN$ wherein n is 3,

xi. $-(CH_2)_nC(O)NR'R''$, wherein n is 3 and R' and R'' are both CH_3, R' is CH_3 and R'' is a hydroxylalkyl, or R' and R'' together with the N to which they are connected form either

a. a 5 member heterocycle ring, wherein the heterocycle ring is optionally substituted with OH, or

b. a 6 member heterocycle ring additionally comprising 1 O heteroatom;

R^6 is H or –OH,

wherein R^4 can only be alkyl when R^6 is –OH;

and pharmaceutically acceptable salts.

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 preparation 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 cardiovascular disease, disorder or condition.

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 cardiovascular disease, disorder or condition.

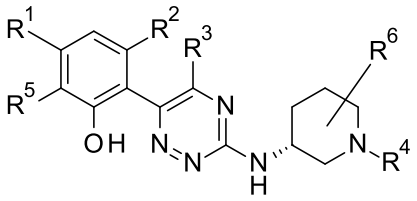
In another aspect, the present disclosure provides an *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as described herein to inhibit NLRP3.

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 groups include methyl and ethyl. Other particular alkyl group is propyl.

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.

Claims

1. A compound of formula I



I

wherein

R^1 and R^5, and the atoms to which they are bonded, form either

i. a 4-6 membered heterocycle ring comprising a single O heteroatom, or

ii. a 4-5 membered cycloalkyl ring;

R^2 and R^3 are selected from H and alkyl, wherein only one of R^2 or R^3 can be H or alkyl;

R^4 is selected from

i. alkyl,

ii. hydroxyalkyl,

iii. alkoxyalkyl,

iv. cycloalkyl substituted with hydroxy or alkoxy,

v. cycloalkylalkyl substituted with hydroxyl, alkoxy, or –COOH,

vi. a 4-6 membered heterocycle comprising a single O heteroatom,

vii. $(CH_2)_nC(O)OH$, $(CH_2)_nC(O)OCH_3$, or $(CH_2)_nC(O)NHCH_3$, wherein n is 2 or 3,

viii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is a tetrazole, oxadiazole or an oxazole heteroaryl,

ix. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is a pyrazole;

x. $-(CH_2)_nS(O)_2CH_3$ or $(CH_2)_nCN$ wherein n is 3,

xi. $-(CH_2)_nC(O)NR'R''$, wherein n is 3 and R' and R" are both CH_3, R' is CH_3 and R" is a hydroxylalkyl, or R' and R" together with the N to which they are connected form either

a. a 5 member heterocycle ring, wherein the heterocycle ring is optionally substituted with OH, or

b. a 6 member heterocycle ring additionally comprising 1 O heteroatom;

R^6 is H or –OH,

wherein R^4 can only be alkyl when R^6 is –OH;

and pharmaceutically acceptable salts.

2. A compound according to claim 1, wherein R^1 and R^5, and the atoms to which they are bonded, form a 5-membered heterocycle ring comprising a single O heteroatom.

3. A compound according to claim 1 or claim 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 selected from
   i. alkyl,
   ii. hydroxyalkyl,
   iii. alkoxyalkyl,
   iv. cycloalkylalkyl substituted with hydroxy,
   v. a 4-membered heterocycle comprising a single O heteroatom,
   vi. $(CH_2)_nC(O)OH$, $(CH_2)_nC(O)OCH_3$, or $(CH_2)_nC(O)NHCH_3$, wherein n is 3,
   vii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is an oxazole heteroaryl,
   viii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is a pyrazole;
   ix. $-(CH_2)_nS(O)_2CH_3$ or $(CH_2)_nCN$ wherein n is 3,
   x. $-(CH_2)_nC(O)NR'R''$, wherein n is 3 and R' and R'' are both CH_3, R' is CH_3 and R'' is a hydroxylalkyl, or R' and R'' together with the N to which they are connected form either
      a. a 5 member heterocycle ring, wherein the heterocycle ring is optionally substituted with OH, or
      b. a 6 member heterocycle ring additionally comprising 1 O heteroatom;

   wherein R^4 can only be alkyl when R^6 is –OH.

5. A compound according to any of claims 1 to 3, wherein R^4 is selected from
   i. alkyl,
   ii. hydroxyalkyl,
   iii. alkoxyalkyl,
   iv. cycloalkylalkyl substituted with hydroxy,

v. a 4-membered heterocycle comprising a single O heteroatom,
vi. $(CH_2)_nC(O)OH$, $(CH_2)_nC(O)OCH_3$, or $(CH_2)_nC(O)NHCH_3$, wherein n is 3,
vii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is an oxazole heteroaryl;

wherein R^4 can only be alkyl when R^6 is –OH.

6. A compound according to any of claims 1 to 3, wherein R^4 is selected from
   i. cycloalkyl substituted with hydroxy or alkoxy,
   ii. cycloalkylalkyl substituted with hydroxy or alkoxy, and
   iii. a 4-6 membered heterocycle comprising a single O heteroatom.

7. A compound according to any of claims 1 to 3, wherein R^4 is selected from
   i. cycloalkyl substituted with hydroxy or alkoxy, and
   ii. cycloalkylalkyl substituted with hydroxy or alkoxy.

8. A compound according to any of claims 1 to 7, wherein R^6 is H.

9. A compound according to claim 1, wherein
   R^1 and R^5, and the atoms to which they are bonded, form a 5-membered heterocycle ring comprising a single O heteroatom;
   R^2 is H and R^3 is methyl;
   R^4 is selected from
      i. alkyl,
      ii. hydroxyalkyl,
      iii. alkoxyalkyl,
      iv. cycloalkylalkyl substituted with hydroxy,
      v. a 4-membered heterocycle comprising a single O heteroatom,
      vi. $(CH_2)_nC(O)OH$, $(CH_2)_nC(O)OCH_3$, or $(CH_2)_nC(O)NHCH_3$, wherein n is 3,
      vii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is an oxazole heteroaryl,
      viii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is a pyrazole,
      ix. $-(CH_2)_nS(O)_2CH_3$ or $(CH_2)_nCN$ wherein n is 3,

x. $-(CH_2)_nC(O)NR'R''$, wherein n is 3 and R' and R" are both CH_3, R' is CH_3 and R" is a hydroxylalkyl, or R' and R" together with the N to which they are connected form either
   a. a 5 member heterocycle ring, wherein the heterocycle ring is optionally substituted with OH, or
   b. a 6 member heterocycle ring additionally comprising 1 O heteroatom;

R^6 is H or –OH,

wherein R^4 can only be alkyl when R^6 is –OH;

and pharmaceutically acceptable salts.

10. A compound according to claim 1, wherein

R^1 and R^5, and the atoms to which they are bonded, form a 5-membered heterocycle ring comprising a single O heteroatom;

R^2 is H and R^3 is methyl;

R^4 is selected from

i. alkyl,
ii. hydroxyalkyl,
iii. alkoxyalkyl,
iv. cycloalkylalkyl substituted with hydroxy,
v. a 4-membered heterocycle comprising a single O heteroatom,
vi. $(CH_2)_nC(O)OH$, $(CH_2)_nC(O)OCH_3$, or $(CH_2)_nC(O)NHCH_3$, wherein n is 3,
vii. heteroarylalkyl, wherein the heteroaryl in heteroarylalkyl is an oxazole heteroaryl;

R^6 is H or –OH,

wherein R^4 can only be alkyl when R^6 is –OH;

and pharmaceutically acceptable salts.

11. A compound according to claim 1, wherein the compound is 5-[3-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol or pharmaceutically acceptable salts thereof.

12. A compound according to claim 1, wherein the compound is selected from

5-[5-Methyl-3-[[rac-(3R)-1-(2-hydroxypropyl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

5-[3-[[(3R)-1-(3-Hydroxypropyl)-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

5-[3-[[(3R)-1-[(1-Hydroxycyclopropyl)methyl]-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

5-[3-[[(3R)-1-(2-Methoxyethyl)-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol; formic acid salt;

5-[3-[[(3R)-1-(2-Methoxyethyl)-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

(3S,5R)-1-Ethyl-5-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]piperidin-3-ol;

5-[5-Methyl-3-[[rac-(3R)-1-(2-methoxypropyl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

5-[5-Methyl-3-[[(3R)-1-(oxetan-3-yl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]butanoic acid;

4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl];

Methyl 4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]butanoate;

4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-N-methyl-butanamide;

5-[5-methyl-3-[[(3R)-1-(2-oxazol-2-ylethyl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;

and pharmaceutically acceptable salts thereof.

13. A compound according to claim 1, wherein the compound is selected from

4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-N,N-dimethyl-butanamide;

4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-1-pyrrolidin-1-yl-butan-1-one;
4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-N-(2-hydroxyethyl)-N-methyl-butanamide;
1-(3-hydroxypyrrolidin-1-yl)-4-[rac-(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]butan-1-one; formic acid;
1-(3-hydroxypyrrolidin-1-yl)-4-[rac-(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]butan-1-one;
4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-1-morpholino-butan-1-one;
5-[5-methyl-3-[[(3R)-1-(2-pyrazol-1-ylethyl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;
5-[5-methyl-3-[[(3R)-1-[3-(1H-tetrazol-5-yl)propyl]-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol; formic acid;
5-[5-methyl-3-[[(3R)-1-[3-(1H-tetrazol-5-yl)propyl]-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;
4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]butanenitrile;
5-[5-methyl-3-[[(3R)-1-(3-oxazol-2-ylpropyl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;
4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-N,N-dimethyl-butanamide; formic acid"
4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-N,N-dimethyl-butanamide; formic acid;
5-[5-methyl-3-[[(3R)-1-[2-(1H-tetrazol-5-yl)ethyl]-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;
5-[5-methyl-3-[[(3R)-1-(3-methylsulfonylpropyl)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;
and pharmaceutically acceptable salts thereof.

14. A compound according to claim 1, wherein the compound is 4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]butanoic acid, or pharmaceutically acceptable salts thereof.

15. A compound according to claim 1, wherein the compound is selected from
    5-[5-methyl-3-[[(3R)-1-[3-(1H-tetrazol-5-yl)propyl]-3-piperidyl]amino]-1,2,4-triazin-6-yl]-2,3-dihydrobenzofuran-4-ol;
    4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-N,N-dimethyl-butanamide;
    4-[(3R)-3-[[6-(4-hydroxy-2,3-dihydrobenzofuran-5-yl)-5-methyl-1,2,4-triazin-3-yl]amino]-1-piperidyl]-1-pyrrolidin-1-yl-butan-1-one;
    and pharmaceutically acceptable salts thereof.

16. A compound according to any one of claims 1 to 15 for use as a therapeutically active substance.

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

18. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 and a therapeutically inert carrier.

19. The use of a compound according to any one of claims 1 to 15 in the preparation 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.

20. A compound according to any one of claims 1 to 15 for use in the treatment or prophylaxis of a cardiovascular disease, disorder or condition.

21. The use of a compound according to any one of claims 1 to 15 in the preparation of a medicament for the treatment or prophylaxis of a cardiovascular disease, disorder or condition.
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 15 to inhibit NLRP3.