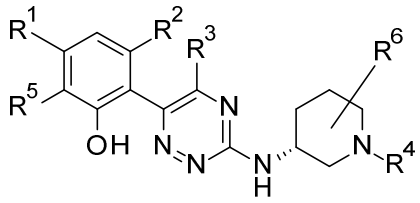
Claims

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 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 treatment or prophylaxis of a cardiovascular disease, disorder or condition.

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

23. A 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.

24. A method for the treatment or prophylaxis of a cardiovascular disease, disorder or condition, which method comprises administering an effective amount of a compound according to any one of claims 1 to 15.