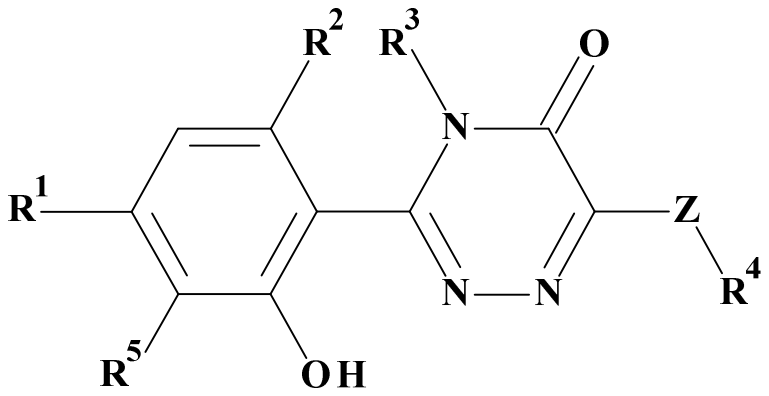
Claims

1. Compounds of formula Ib



Ib

wherein

R^1 is H, acetyl, SF_5, halo, alkyl, haloalkyl, haloalkoxy or nitrile;

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 3-6 membered cycloalkyl ring optionally substituted with 1 to 2 substituents independently selected from halo or alkyl;

R^2 is H, halo, alkyl, haloalkyl, cycloalkyl or cycloalkylalkyl, wherein cycloalkyl or cycloalkylalkyl is optionally substituted with halo;

R^3 is H, alkyl, haloalkyl, cycloalkyl or cycloalkylalkyl, wherein cycloalkyl or cycloalkylalkyl is optionally substituted with halo;

Z is –O-, or –NH-;

R^4 is a heterocycle ring optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, -OH, oxo, -CO_2H, cycloalkylalkyl or cycloalkyl optionally substituted with halo; or

R^4 is a cycloalkyl optionally substituted with 1 to 3 substituents independently selected from alkyl, halo, haloalkyl and –OH; or

R^4 is arylalkyl or heteroarylalkyl wherein arylalkyl or heteroarylalkyl has 1 to 3 substituents independently selected from alkyl, halo, haloalkyl and –OH;

and pharmaceutically acceptable salts.

2. A compound according to claim 1, wherein 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 or R^1 and R^5, and the atoms to which they are bonded, form a 3-6 membered cycloalkyl ring.

3. A compound according to either of claim 1 or 2, wherein R^5 is H or R^1 and R^5, and the atoms to which they are bonded, form a 5 membered heterocycle ring comprising a single O atom.

4. A compound according to any of claims 1 to 3, wherein R^5 is H;

5. A compound according to claims 1 to 4, wherein R^1 is acetyl, SF_5, halo, haloalkyl, haloalkoxy or nitrile.

6. A compound according to claims 1 to 5, wherein R^1 is halo, haloalkyl or haloalkoxy,

7. A compound according to claims 1 to 6, wherein R^1 is haloalkoxy.

8. A compound according to claims 1 to 7, wherein R^2 is H or alkyl.

9. A compound according to claims 1 to 8, wherein R^2 is H.

10. A compound according to claims 1 to 9, wherein R^3 is H, alkyl or cycloalkyl.

11. A compound according to claims 1 to 10, wherein R^3 is alkyl.

12. A compound according to claims 1 to 11, wherein R^4 is a heterocycle ring optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, cycloalkyl, or cycloalkylalkyl; or

R^4 is a cycloalkyl optionally substituted with 2 substituents independently selected from alkyl, and –OH; or

R^4 is arylalkyl substituted with OH;

13. A compound according to claims 1 to 12, wherein R^4 is a piperidyl ring optionally substituted with alkyl

14. A compound according to claims 1 to 13, wherein R^4 is ethylpiperidine.

15. A compound according to claims 1 to 14, wherein Z is –NH-.

16. A compound according to claim 1, wherein

R^1 is acetyl, SF_5, halo, haloalkyl, haloalkoxy or nitrile;

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 or R^1 and R^5, and the atoms to which they are bonded, form a 3-6 membered cycloalkyl ring

R^2 is H or alkyl;

R^3 is H, alkyl or cycloalkyl;

Z is –NH-;

R^4 is a heterocycle ring optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, cycloalkyl, or cycloalkylalkyl; or

R^4 is a cycloalkyl optionally substituted with 2 substituents independently selected from alkyl, and –OH; or

R^4 is arylalkyl substituted with OH;

and pharmaceutically acceptable salts.

17. A compound according to claim 1 or 16, wherein

wherein

R^1 is acetyl, SF_5, halo, haloalkyl, haloalkoxy or nitrile;

R^5 is H;

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

R^2 is H or alkyl;

R^3 is H, alkyl or cycloalkyl;

Z is –NH-;

R^4 is a heterocycle ring optionally substituted with 1 to 3 substituents independently selected from halo, alkyl, cycloalkyl, or cycloalkylalkyl; or

R^4 is a cycloalkyl optionally substituted with 2 substituents independently selected from alkyl, and –OH; or

R^4 is arylalkyl substituted with OH;

and pharmaceutically acceptable salts.

18. A compound according to claim 1, 16 or 17, wherein

R^1 is halo, haloalkyl, or haloalkoxy;

R^5 is H;

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

R^2 is H;

R^3 is alkyl;

Z is –NH-;

R^4 is a piperidyl ring optionally substituted with alkyl;

and pharmaceutically acceptable salts.

19. A compound according to claim 1, 16, 17 or 18, wherein

R^1 is haloalkoxy;

R^5 is H;

R^2 is H;

R^3 is alkyl;

Z is –NH-;

R^4 is a piperidyl ring optionally substituted with alkyl;

and pharmaceutically acceptable salts.

20. A compound according to any one of claims 1 to 19, wherein the compound is selected from

6-((1-Ethylpiperidin-3-yl)amino)-3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-1,2,4-triazin-5(4H)-one;

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

3-[2-Hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-6-[[(3R)-3-piperidyl]amino]-1,2,4-triazin-5-one;

3-[2-Hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-6-[(8-methyl-8-azabicyclo[3.2.1]octan-2-yl)amino]-1,2,4-triazin-5-one;

(R)-6-((1-(Cyclopropylmethyl)piperidin-3-yl)amino)-3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-1,2,4-triazin-5(4H)-one;

(R)-3-(2-Hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-6-((1-methylpiperidin-3-yl)amino)-1,2,4-triazin-5(4H)-one;

6-(1,2,3,5,6,7,8,8a-Octahydroindolizin-8-ylamino)-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

3-[2-Hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-6-[[(3R)-1-propyl-3-piperidyl]amino]-1,2,4-triazin-5-one;

3-[2-Hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-6-[(1,5,5-trimethyl-3-piperidyl)amino]-1,2,4-triazin-5-one;

(R)-6-((1-Cyclopropylpiperidin-3-yl)amino)-3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-1,2,4-triazin-5(4H)-one;

6-(((1S,3S)-3-Hydroxy-3-methylcyclobutyl)amino)-3-(2-hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-1,2,4-triazin-5(4H)-one;

6-[(1-tert-Butyl-3-piperidyl)amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-(2-Azabicyclo[2.2.1]heptan-6-ylamino)-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R,5S)-1-Ethyl-5-methyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R,5R)-1-Ethyl-5-methyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(5S)-5-fluoro-1-methyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R)-6,6-Dimethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[(3-Hydroxyphenyl)methylamino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

4-Cyclopropyl-6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-(4-fluoro-2-hydroxy-phenyl)-4-methyl-1,2,4-triazin-5-one;

4-Ethyl-6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-1,2,4-triazin-5-one;

3-[4-(Difluoromethoxy)-2-hydroxy-phenyl]-6-[[(3R)-1-ethyl-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

3-[4-(1,1-Difluoroethyl)-2-hydroxy-phenyl]-6-[[(3R)-1-ethyl-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

3-(4-Acetyl-2-hydroxy-phenyl)-6-[[(3R)-1-ethyl-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-6-[[(3R)-1-methyl-3-piperidyl]amino]-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

(M or P)-6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

(P or M)-6-[[(3R)-1-ethyl-3-piperidyl]amino]-3-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(pentafluoro-λ6-sulfanyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

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

3-(4-Chloro-2-hydroxy-phenyl)-6-[[(3R)-1-ethyl-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

3-[2-Hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-6-[[(3R)-1-methyl-3-piperidyl]amino]-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4H-1,2,4-triazin-5-one;

6-[[(3R,5S)-1-ethyl-5-fluoro-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4H-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

21. A compound according to any one of claims 1 to 20, wherein the compound is selected from

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

(R)-3-(2-Hydroxy-4-(trifluoromethyl)phenyl)-4-methyl-6-((1-methylpiperidin-3-yl)amino)-1,2,4-triazin-5(4H)-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethyl)phenyl]-4-methyl-1,2,4-triazin-5-one;

3-[4-(Difluoromethoxy)-2-hydroxy-phenyl]-6-[[(3R)-1-ethyl-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one;

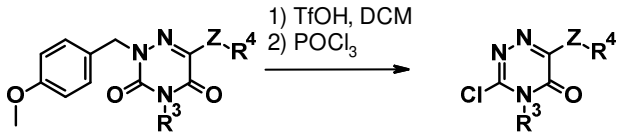
3-(4-Chloro-2-hydroxy-phenyl)-6-[[(3R)-1-ethyl-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

3-[2-Hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-6-[[(3R)-1-methyl-3-piperidyl]amino]-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

22. A compound according to any one of claims 1 to 21, wherein the compound is 6-[[(3R)-1-Ethyl-3-piperidyl]amino]-3-[2-hydroxy-4-(trifluoromethoxy)phenyl]-4-methyl-1,2,4-triazin-5-one, and pharmaceutically acceptable salts thereof.

23. A process to prepare a compound according to any one of claims 1 to 22, comprising the reaction of a compound of formula XI to a compound of formula XII, wherein R^3 and R^4 are as defined above



XI XII

24. A compound according to any one of claims 1 to 22 for use as a therapeutically active substance.

25. A compound according to any one of claims 1 to 22 for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 22 and a therapeutically inert carrier.

27. The use of a compound according to any one of claims 1 to 22 for the treatment or prophylaxis of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

28. A compound according to any one of claims 1 to 22 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

29. The use of a compound according to any one of claims 1 to 22 in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

30. The use of a compound according to any one of claims 1 to 22 for the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

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

32. A method for the treatment or prophylaxis of a disease, disorder or condition, which method comprises administering an effective amount of a compound according to any one of claims 1 to 22, wherein the disease, disorder or condition is selected from Asthma or COPD.

33. A compound according to any one of claims 1 to 22, when manufactured according to the process of claim 23.

~~34. The invention as hereinbefore described.~~