defined using *Nlrp3*$^{-/-}$ mice, but there have also been insights into the specific activation of NLRP3 in these diseases. In type 2 diabetes mellitus (T2D), the deposition of islet amyloid polypeptide in the pancreas activates NLRP3 and IL-1β signalling, resulting in cell death and inflammation.

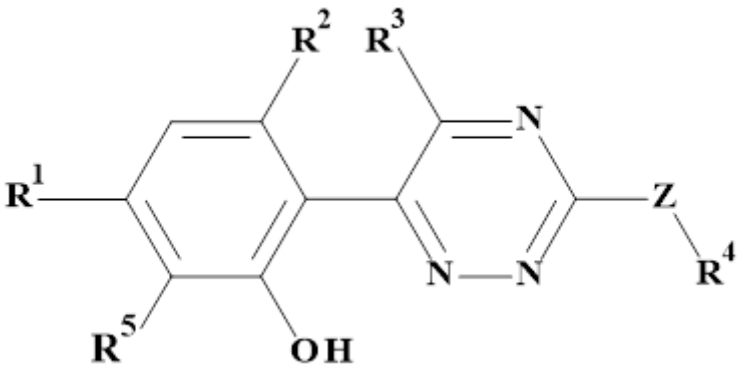
Several small molecules have been shown to inhibit the NLRP3 inflammasome. Glyburide inhibits IL-1β production at micromolar concentrations in response to the activation of NLRP3 but not NLRC4 or NLRP1. Other previously characterised weak NLRP3 inhibitors include parthenolide, 3,4-methylenedioxy-β-nitrostyrene 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.

Summary

In one aspect, the present disclosure provides compounds of formula Ib



Ib

wherein

R^1 is H, 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 a 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 one or two 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 or haloalkoxy;

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

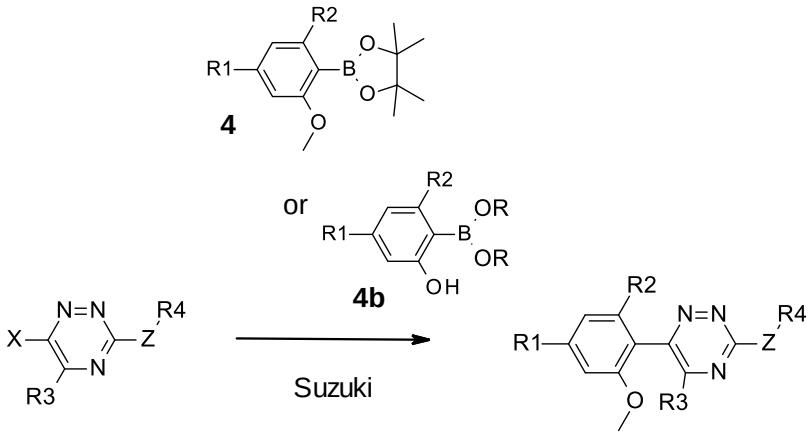
Z is –O-, –NH-, or -$NHCH_2$-;

R^4 is a heterocycle ring optionally substituted with 1 to 2 substituents independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, -OH, oxo, -CO_2H, 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;

and pharmaceutically acceptable salts thereof.

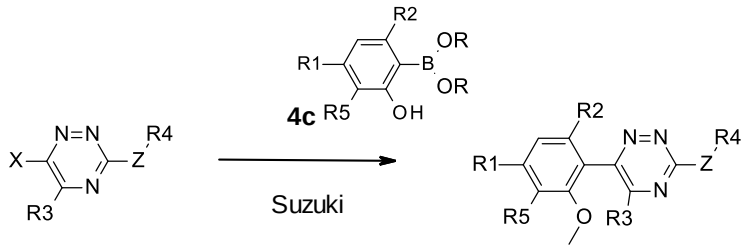
In another aspect, the present disclosure provides a process to prepare a compound as described herein comprising the reaction of a compound of IV to a compound of V in the presence of a palladium catalyst and a boronic acid or boronic pinacol ester, wherein R^1, R^2, R^3, R^4, and Z are as defined above



IV **V**

.

In another aspect, the present disclosure provides a process to prepare a compound as described herein comprising the reaction of a compound of IV to a compound of Va in the presence of a palladium catalyst and a boronic acid or boronic pinacol ester, wherein R^1, R^2, R^3, R^4, R^5 and Z are as defined above



IV **Va**

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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 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 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.

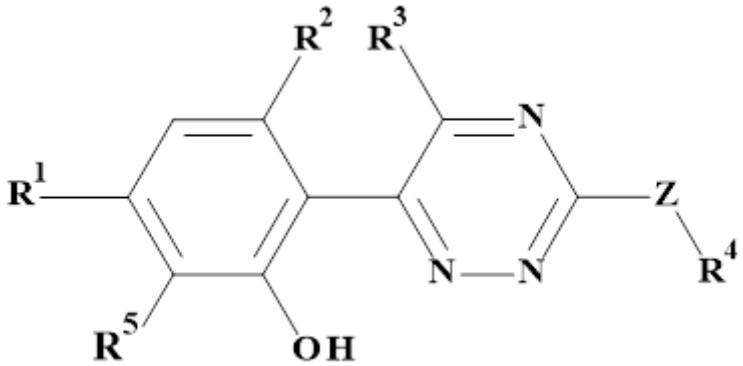
In another aspect, the present disclosure provides an *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as described herein to inhibit NLRP3.

In another aspect, the present disclosure provides a compound as described herein, when manufactured according to a process as described herein.

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. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons may be encompassed.

Claims

1. Compounds of formula Ib



Ib

wherein

R^1 is H, 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 a 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 one or two 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 or haloalkoxy;

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

Z is –O-, –NH-, or -$NHCH_2$-;

R^4 is a heterocycle ring optionally substituted with 1 to 2 substituents independently selected from halo, alkyl, haloalkyl, hydroxyalkyl, -OH, oxo, -CO_2H, 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;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

R^1 is 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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4-5 membered cycloalkyl ring.

3. A compound according to claim 1 or claim 2, wherein

R^1 is haloalkyl or haloalkoxy;

R^5 is H;

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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4-5 membered cycloalkyl ring.

4. A compound according to any one of claims 1 to 3, wherein

R^1 is haloalkyl;

R^5 is H;

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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4 membered cycloalkyl ring.

5. A compound according to any one of claims 1 to 4, wherein R^2 is H, halo, or alkyl.

6. A compound according to any one of claims 1 to 5, wherein R^2 is H.

7. A compound according to any one of claims 1 to 6, wherein R^3 is H, alkyl or haloalkyl.

8. A compound according to any one of claims 1 to 7, wherein R^3 is alkyl.

9. A compound according to any one of claims 1 to 8, wherein R^4 is

a 6-to-9-membered heterocycle ring comprising a 1 or 2 N heteroatom; or

a 6-membered heterocycle ring comprising 1 N heteroatom, substituted with 1 to 2 substituents independently selected from alkyl and -OH; or

a 4-to-6 membered cycloalkyl substituted with 1 to 2 substituents independently selected from alkyl and –OH-.

10. A compound according to any one of claims 1 to 9, wherein R^4 is

a 9-membered heterocycle ring comprising a single N heteroatom; or

a 6-membered heterocycle ring comprising 1 N heteroatom, substituted with 1 alkyl substituent.

11. A compound according to any one of claims 1 to 10, wherein R^4 is methylpiperidyl or ethylpiperidyl.

12. A compound according to any one of claims 1 to 11, wherein R^4 is ethylpiperidyl.

13. A compound according to any one of claims 1 to 12, wherein Z is –NH-.

14. A compound according to claim 1, wherein

R^1 is 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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4-5 membered cycloalkyl ring;

R^2 is H, halo, or alkyl;

R^3 is H, alkyl or haloalkyl;

Z is –NH-;

R^4 is

a 6-to-9-membered heterocycle ring comprising a 1 or 2 N heteroatom; or

a 6-membered heterocycle ring comprising 1 N heteroatom, substituted with 1 to 2 substituents independently selected from alkyl and -OH; or

a 4-to-6 membered cycloalkyl substituted with 1 to 2 substituents independently selected from alkyl and –OH-;

and pharmaceutically acceptable salts thereof.

15. A compound according to claim 1, wherein

R^1 is 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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4-5 membered cycloalkyl ring;

R^2 is H;

R^3 is alkyl;

Z is –NH-;

R^4 is

a 9-membered heterocycle ring comprising a single N heteroatom; or

a 6-membered heterocycle ring comprising 1 N heteroatom, substituted with 1 alkyl substituent;

and pharmaceutically acceptable salts thereof.

16. A compound according to claim 1, wherein

R^1 is haloalkyl or haloalkoxy;

R^5 is H;

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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4-5 membered cycloalkyl ring;

R^2 is H;

R^3 is alkyl;

Z is –NH-;

R^4 is methylpiperidyl or ethylpiperidyl;

and pharmaceutically acceptable salts thereof.

17. A compound according to claim 1, wherein

R^1 is haloalkyl;

R^5 is H;

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

a 5 membered heterocycle ring comprising a single O heteroatom, or

R^1 and R^5, and the atoms to which they are bonded, form a 4 membered cycloalkyl ring.

R^2 is H;

R^3 is alkyl;

Z is –NH-;

R^4 is ethylpiperidyl;

and pharmaceutically acceptable salts thereof.

18. A compound according to any one of claims 1 to 17, selected from

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

5-Chloro-2-[3-[(1-ethyl-3-piperidyl)amino]-5-methyl-1,2,4-triazin-6-yl]phenol;

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

2-[3-[(3-Hydroxy-3-methyl-cyclobutyl)amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

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

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

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

and pharmaceutically acceptable salts thereof.

19. A compound according to any one of claims 1 to 17, selected from

3-[3-[[(3R)-1-Ethyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;

2-[3-[[(3R)-1-ethyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-3-fluoro-5-(trifluoromethyl)phenol;

2-[3-[[(3R or 3S)-1-tert-Butyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[3-[[(3S or 3R)-1-tert-Butyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

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

2-[3-[[(3R,5S)-5-Fluoro-1-methyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[5-Methyl-3-(5,6,7,8-tetrahydroimidazo[1,2-a]pyridin-8-ylamino)-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

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

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

2-[5-Methyl-3-[[(3R)-3-piperidyl]amino]-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

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

2-[3-[[(1R,2R)-2-Hydroxycyclohexyl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

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

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

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

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

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

2-[5-Methyl-3-[[*rac*-(8*S*,8a*R*)-1,2,3,5,6,7,8,8a-octahydroindolizin-8-yl]amino]-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[5-Methyl-3-[[rac-(8S,8aS)-1,2,3,5,6,7,8,8a-octahydroindolizin-8-yl]amino]-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[3-[[(8R,8aS or 8S,8aR)-1,2,3,5,6,7,8,8a-Octahydroindolizin-8-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-3-methyl-5-(trifluoromethyl)phenol;

2-[3-[[(8S,8aR or 8R,8aS)-1,2,3,5,6,7,8,8a-Octahydroindolizin-8-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-3-methyl-5-(trifluoromethyl)phenol;

2-[3-[[(3R)-1-Ethyl-3-piperidyl]amino]-5-(trifluoromethyl)-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;2,2,2-trifluoroacetic acid;

2-[3-[[(6S or 6R,8aS or 8aR)-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[3-[[(6R or 6S,8aS or 8aR)-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[3-[[(6S or 6R,8aR or 8aS)-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

2-[3-[[(6R or 6S, 8aR or 8aS)-1,2,3,5,6,7,8,8a-octahydroindolizin-6-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

and pharmaceutically acceptable salts thereof.

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

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

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

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

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

3-[3-[[(3R)-1-Ethyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;

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

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

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

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

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

2-[3-[[(8R,8aS)-1,2,3,5,6,7,8,8a-octahydroindolizin-8-yl]amino]-5-methyl-1,2,4-triazin-6-yl]-3-methyl-5-(trifluoromethyl)phenol;

and pharmaceutically acceptable salts thereof.

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

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

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

3-[3-[[(3R)-1-Ethyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;

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

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

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

and pharmaceutically acceptable salts thereof.

22. A compound according to any one of claims 1 to 21, selected from

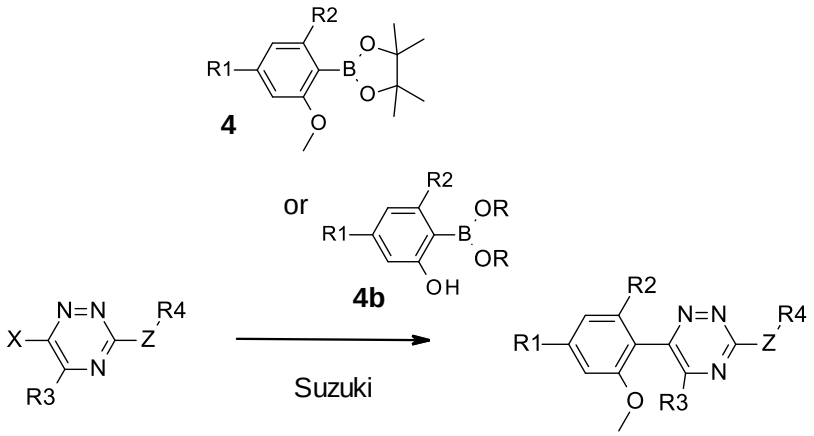
2-[3-[[(3R)-1-Ethyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]-5-(trifluoromethyl)phenol;

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

3-[3-[[(3R)-1-Ethyl-3-piperidyl]amino]-5-methyl-1,2,4-triazin-6-yl]bicyclo[4.2.0]octa-1(6),2,4-trien-2-ol;

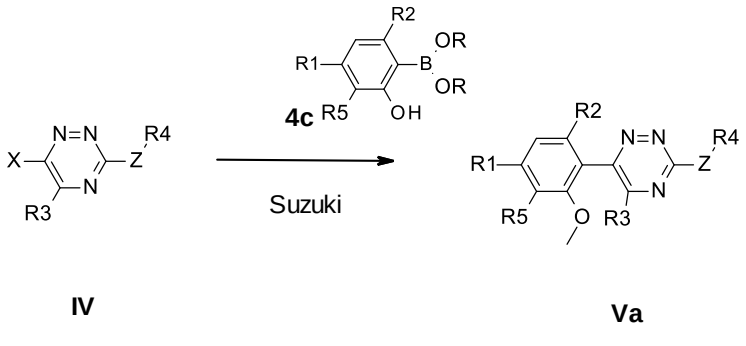
and pharmaceutically acceptable salts thereof.

23. A process to prepare a compound according to any one of claims 1 to 22 comprising the reaction of a compound of IV to a compound of V in the presence of a palladium catalyst and a boronic acid or boronic pinacol ester, wherein R^1, R^2, R^3, R^4, and Z are as defined above



IV **V**

24. A process to prepare a compound according to any one of claims 1 to 22 comprising the reaction of a compound of IV to a compound of Va in the presence of a palladium catalyst and a boronic acid or boronic pinacol ester, wherein R^1, R^2, R^3, R^4, R^5 and Z are as defined above



IV **Va**

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

26. 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.

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

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 preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

30. 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 22 to inhibit NLRP3.

31. A compound according to any one of claims 1 to 17, when manufactured according to a process of claim 22.