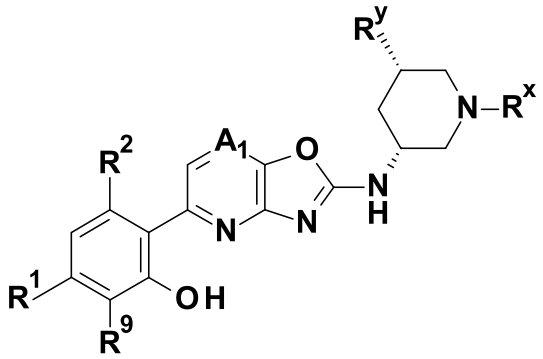
composing the blood–brain barrier and blood–testis barrier, where it pumps xenobiotics back into the capillaries and limiting brain exposure. The compounds of formula I achieve peripheral preference by showing an increased efflux in a transcellular assay expressing active P-gp transporters and/or reduced passive permeability without compromising systemic distribution. By slightly increasing the polar surface area the compounds of formula I surprising yield the desired profile and demonstrate lower permeability. In addition there was a need for compounds showing a reduced phospholipidosis risk for chronic indications with compounds that display a combination of increased polarity and fine-tuned pKa.

Summary

The present disclosure provides novel compounds of formula I



I

wherein,

R^1 is cyano, halo, or haloalkyl, and R^9 is H, or

R^1 and R^9 and the atoms to which they are attached form a 5-membered cycloalkyl or a 5-membered heterocycle comprising 1 O heteroatom;

R^2 is alkyl, hydroxyalkyl, alkoxyalkyl or cyano, wherein if R^1 is cyano then R^2 is not cyano;

A_1 is $–CR^{10}$- or –N-;

R^{10} is H, fluoro or alkoxy;

R^x is H, alkyl, heteroarylalkyl, hydroxyalkyl or COOH-alkyl, wherein the heteroaryl of the heteroarylalkyl is oxazolyl, tetrazolyl or oxadiazolyl;

R^y is H or -OH;

wherein, if R^1 is haloalkyl, then R^x is hydroxyalkyl or COOH-alkyl and R^y is -OH;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;2,2,2-trifluoroacetic acid

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

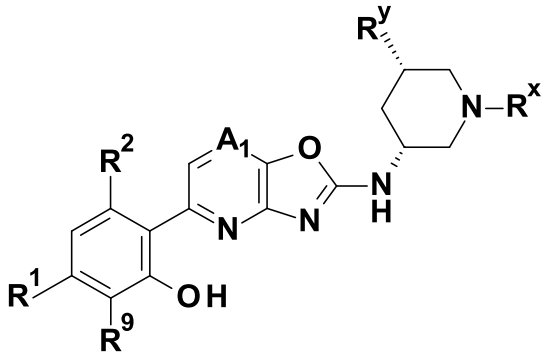
5-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

5-Chloro-3-methyl-2-[2-[[(3R)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;dihydrochloride;

5-Chloro-3-methyl-2-[2-[[(3R)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

and pharmaceutically acceptable salts thereof.

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



I

wherein,

R^1 is cyano, halo, or haloalkyl, and R^9 is H, or

R^1 and R^9 and the atoms to which they are attached form a 5-membered cycloalkyl or a 5-membered heterocycle comprising 1 O heteroatom;

R^2 is alkyl, hydroxyalkyl, alkoxyalkyl or cyano, wherein if R^1 is cyano then R^2 is not cyano;

A_1 is $–CR^{10}$- or –N-;

R^{10} is H, fluoro or alkoxy;

R^x is H, alkyl, heteroarylalkyl, hydroxyalkyl or COOH-alkyl, wherein the heteroaryl of the heteroarylalkyl is oxazolyl, tetrazolyl or oxadiazolyl;

R^y is H or -OH;

wherein, if R^1 is haloalkyl, then R^x is hydroxyalkyl or COOH-alkyl and R^y is -OH;

and pharmaceutically acceptable salts thereof, provided that the compound is not a compound selected from:

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-benzonitrile;

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-(methoxymethyl)phenol;2,2,2-trifluoroacetic acid;

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-(methoxymethyl)phenol;

5-Chloro-3-methyl-2-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

5-Chloro-3-methyl-2-[2-[[(3R)-1-propyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

(3S,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-methyl-piperidin-3-ol;

(3R,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-ethyl-piperidin-3-ol;formic acid;

(3R,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-ethyl-piperidin-3-ol;

5-Chloro-2-[2-[[(3R)-1-(3,3-difluoropropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-2-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-3-(hydroxymethyl)-2-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

5-Chloro-2-[2-[[(3R)-1-(3-hydroxypropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-3-methyl-2-[2-[[(3R)-1-(2-hydroxypropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

(3S,5R)-5-[[5-[4-Chloro-2-hydroxy-6-(methoxymethyl)phenyl]oxazolo[4,5-b]pyridin-2-yl]amino]-1-methyl-piperidin-3-ol;

5-Chloro-2-[2-[[(3R)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-methyl-phenol;2,2,2-trifluoroacetic acid;

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

(3S,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-ethyl-piperidin-3-ol;

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

5-Fluoro-3-methyl-2-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-5-methyl-4-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]benzonitrile;

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;formic acid;

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R,5S)-5-hydroxy-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

4-[2-[[(3R,5R)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;2,2,2-trifluoroacetic acid

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

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

5-Chloro-3-methyl-2-[2-[[(3R)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;dihydrochloride;

5-Chloro-3-methyl-2-[2-[[(3R)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

and pharmaceutically acceptable salts thereof.

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 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 cardiovascular disease, disorder or condition.

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

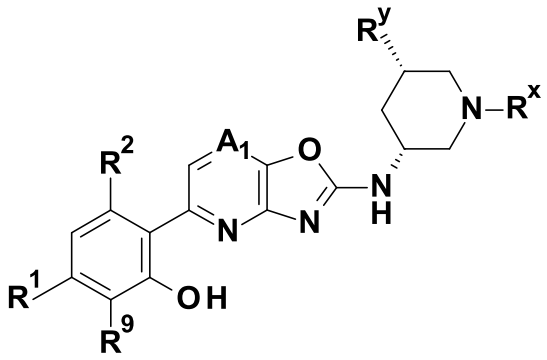
In another aspect, the present disclosure provides an *in vitro* method of inhibiting NLRP3, which method comprises administering an effective amount of a compound as described herein to inhibit NLRP3.

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 are methyl and ethyl.

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 is cyano, halo, or haloalkyl, and R^9 is H, or

R^1 and R^9 and the atoms to which they are attached form a 5-membered cycloalkyl or a 5-membered heterocycle comprising 1 O heteroatom;

R^2 is alkyl, hydroxyalkyl, alkoxyalkyl or cyano, wherein if R^1 is cyano then R^2 is not cyano;

A_1 is $–CR^{10}$- or –N-;

R^{10} is H, fluoro or alkoxy;

R^x is H, alkyl, heteroarylalkyl, hydroxyalkyl or COOH-alkyl, wherein the heteroaryl of the heteroarylalkyl is oxazolyl, tetrazolyl or oxadiazolyl;

R^y is H or -OH;

wherein, if R^1 is haloalkyl, then R^x is hydroxyalkyl or COOH-alkyl and R^y is -OH;

and pharmaceutically acceptable salts thereof, provided that the compound is not a compound selected from:

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-benzonitrile;

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-(methoxymethyl)phenol;2,2,2-trifluoroacetic acid;

5-Chloro-2-[2-[[(3*R*)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-(methoxymethyl)phenol;

5-Chloro-3-methyl-2-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

5-Chloro-3-methyl-2-[2-[[(3R)-1-propyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

(3S,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-methyl-piperidin-3-ol;

(3R,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-ethyl-piperidin-3-ol;formic acid;

(3R,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-ethyl-piperidin-3-ol;

5-Chloro-2-[2-[[(3R)-1-(3,3-difluoropropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-2-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-3-(hydroxymethyl)-2-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

5-Chloro-2-[2-[[(3R)-1-(3-hydroxypropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-methyl-phenol;

5-Chloro-3-methyl-2-[2-[[(3R)-1-(2-hydroxypropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

(3S,5R)-5-[[5-[4-Chloro-2-hydroxy-6-(methoxymethyl)phenyl]oxazolo[4,5-b]pyridin-2-yl]amino]-1-methyl-piperidin-3-ol;

5-Chloro-2-[2-[[(3R)-1-ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-methyl-phenol;2,2,2-trifluoroacetic acid;

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

(3S,5R)-5-[[5-(4-Chloro-2-hydroxy-6-methyl-phenyl)oxazolo[4,5-b]pyridin-2-yl]amino]-1-ethyl-piperidin-3-ol;

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

5-Fluoro-3-methyl-2-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-5-methyl-4-[2-[[(3R)-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]benzonitrile;

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;formic acid;

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R,5S)-5-hydroxy-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

4-[2-[[(3R,5R)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;2,2,2-trifluoroacetic acid

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R)-1-Ethyl-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

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

5-Chloro-3-methyl-2-[2-[[(3R)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;dihydrochloride;

5-Chloro-3-methyl-2-[2-[[(3R)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]phenol;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R^1 is cyano or haloalkyl, and R^9 is H, or R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom.

3. A compound according to any of claims 1 to 2, wherein R^1 is cyano and R^9 is H, or R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom.

4. A compound according to any of claims 1 to 3, wherein R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom.

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

6. A compound according to any of claims 1 to 5, wherein R^{10} is H or alkoxy.

7. A compound according to any of claims claim 1 to 6, wherein R^{10} is H.

8. A compound according to any of claims 1 to 7, wherein R^x is H, alkyl, heteroarylalkyl, hydroxyalkyl or COOH-alkyl, wherein the heteroaryl of heteroarylalkyl is oxazolyl.

9. A compound according to any of claims 1 to 8, wherein R^x is H, alkyl, heteroarylalkyl or hydroxyalkyl, wherein the heteroaryl of heteroarylalkyl is oxyzolyl.

10. A compound according to any of claims 1 to 9, wherein R^x is alkyl, heteroarylalkyl or hydroxyalkyl, wherein the heteroaryl of heteroarylalkyl is oxyzolyl.

11. A compound according to any of claims 1 to 10, wherein R^x is alkyl or hydroxyalkyl.

12. A compound according to any of claims 1 to 11, wherein R^x is hydroxyalkyl.

13. A compound according to any of claims 1 to 12, wherein R^y is H.

14. A compound according to claim 1, wherein,

R^1 is cyano or haloalkyl, and R^9 is H, or
R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom;
R^2 is alkyl or alkoxyalkyl;
A_1 is $–CR^{10}-$ or –N-;
R^{10} is H or alkoxy;
R^x is H, alkyl, heteroarylalkyl, hydroxyalkyl or COOH-alkyl, wherein the heteroaryl of the heteroarylalkyl is oxazolyl;
R^y is H or -OH;
wherein, if R^1 is haloalkyl, then R^x is hydroxyalkyl or COOH-alkyl and R^y is –OH:
and pharmaceutically acceptable salts thereof.

15. A compound according to claim 1, wherein,

R^1 is cyano and R^9 is H, or
R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom;
R^2 is alkyl or alkoxyalkyl;
A_1 is $–CR^{10}-$ or –N-;
R^{10} is H or alkoxy;
R^x is alkyl or hydroxyalkyl;

R^y is H or -OH;

and pharmaceutically acceptable salts thereof.

16. A compound according to claim 1, wherein

R^1 is cyano and R^9 is H, or

R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom;

R^2 is alkyl or alkoxyalkyl;

A_1 is $–CR^{10}$- or –N-;

R^{10} is H;

R^x is hydroxyalkyl;

R^y is H;

and pharmaceutically acceptable salts thereof.

17. A compound according to claim 1, wherein

R^1 and R^9 and the atoms to which they are attached form a 5-membered heterocycle comprising 1 O heteroatom;

R^2 is alkyl or alkoxyalkyl;

A_1 is–N-;

R^x is hydroxyalkyl;

R^y is H;

and pharmaceutically acceptable salts thereof.

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

3-Hydroxy-5-methyl-4-[2-[[(3R)-1-(2-oxazol-2-ylethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-5-(methoxymethyl)benzonitrile;

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

and pharmaceutically acceptable salts thereof.

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

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;

and pharmaceutically acceptable salts thereof.

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

4-[(3S,5R)-3-Hydroxy-5-[[5-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]oxazolo[4,5-b]pyridin-2-yl]amino]-1-piperidyl]butanoic acid;

(3S,5R)-1-(2-Hydroxyethyl)-5-[[5-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]oxazolo[4,5-b]pyridin-2-yl]amino]piperidin-3-ol;

3-Hydroxy-4-[2-[[(3R,5S)-5-hydroxy-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

3-Hydroxy-4-[2-[[(3R,5S)-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;

and pharmaceutically acceptable salts thereof.

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

(3S,5R)-1-(2-Hydroxyethyl)-5-[[5-[2-hydroxy-6-methyl-4-(trifluoromethyl)phenyl]oxazolo[4,5-b]pyridin-2-yl]amino]piperidin-3-ol;

3-Hydroxy-4-[2-[[(3R,5S)-5-hydroxy-1-methyl-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

and pharmaceutically acceptable salts thereof.

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

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

and pharmaceutically acceptable salts thereof.

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

3-hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-(methoxymethyl)benzonitrile;2,2,2-trifluoroacetic acid;

3-hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-(methoxymethyl)benzonitrile;

3-hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-5-methyl-benzonitrile;

4-[2-[[(3R,5S)-1-ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

5-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-methyl-indan-4-ol;

5-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-6-methyl-indan-4-ol;

3-hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-5-(methoxymethyl)benzonitrile;

5-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

4-[2-[[(3R,5S)-1-ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R,5S)-1-ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-(methoxymethyl)benzonitrile;

(3S,5R)-1-(2-hydroxyethyl)-5-[[5-(4-hydroxy-6-methyl-2,3-dihydrobenzofuran-5-yl)oxazolo[4,5-b]pyrazin-2-yl]amino]piperidin-3-ol;

(3S,5R)-1-ethyl-5-[[5-(4-hydroxy-6-methyl-2,3-dihydrobenzofuran-5-yl)oxazolo[4,5-b]pyrazin-2-yl]amino]piperidin-3-ol;

3-hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-(methoxymethyl)benzonitrile;

4-[2-[[(3R,5S)-1-ethyl-5-hydroxy-3-piperidyl]amino]-7-fluoro-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-hydroxy-5-methyl-4-[2-[[(3R)-1-(3-oxazol-2-ylpropyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]benzonitrile;

4-[7-fluoro-2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

4-[2-[[(3R,5S)-1-ethyl-5-hydroxy-3-piperidyl]amino]-7-methoxy-oxazolo[4,5-b]pyridin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

(3S,5R)-1-ethyl-5-[[5-(4-hydroxy-6-methyl-2,3-dihydrobenzofuran-5-yl)oxazolo[4,5-b]pyridin-2-yl]amino]piperidin-3-ol;

and pharmaceutically acceptable salts thereof.

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

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

4-[2-[[(3R,5S)-1-Ethyl-5-hydroxy-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-3-hydroxy-5-methyl-benzonitrile;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

and pharmaceutically acceptable salts thereof.

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

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;2,2,2-trifluoroacetic acid;

3-Hydroxy-4-[2-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-5-methyl-benzonitrile;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

and pharmaceutically acceptable salts thereof.

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

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-(methoxymethyl)-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyrazin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

5-[2-[[(3R)-1-(2-Hydroxyethyl)-3-piperidyl]amino]oxazolo[4,5-b]pyridin-5-yl]-6-methyl-2,3-dihydrobenzofuran-4-ol;

and pharmaceutically acceptable salts thereof.

27. A compound according to any one of claims 1 to 26 for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

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

29. The use of a compound according to any one of claims 1 to 26 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.

30. A compound according to any one of claims 1 to 26 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

31. A compound according to any one of claims 1 to 26 for use in the treatment or prophylaxis of a cardiovascular disease, disorder or condition.

32. A compound according to any one of claims 1 to 26 for use in the treatment or prophylaxis of a cardiometabolic disease, disorder or condition.

33. The use of a compound according to any one of claims 1 to 26 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

34. The use of a compound according to any one of claims 1 to 26 in the preparation of a medicament for the treatment or prophylaxis of a cardiovascular disease, disorder or condition.

35. The use of a compound according to any one of claims 1 to 26 in the preparation of a medicament for the treatment or prophylaxis of a cardiometabolic disease, disorder or condition.

36. 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 26 to inhibit NLRP3.