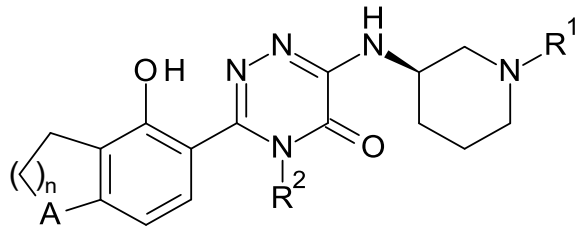
Further, in developing a NLRP3 inhibitor for treating peripheral indications, it is advantageous to minimize the exposure of an NLRP3 inhibiting compound in the brain relative to systemic exposure as central exposure does not add to therapeutic benefit. Further, this approach minimizes the risk of potential side effects in the central nervous system (CNS) and hence offers the opportunity to provide higher dose administration if necessary. The compounds of formula I achieve this by showing an increased efflux in a transcellular assay expressing active P-gp transporters and/or reduced passive permeability without compromising systemic distribution. 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

The present disclosure provides novel compounds of formula I



I

wherein,

A is –O– or CH_2;

R^1 is hydroxyalkyl or acetyl;

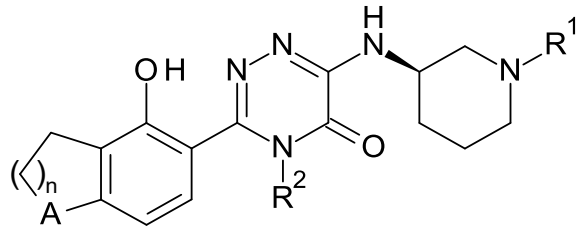
R^2 is alkyl;

n is 0 or 1;

wherein if n is 0 then A is CH_2.

and pharmaceutically acceptable salts thereof.

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



I

wherein,

A is –O– or CH_2;

R^1 is hydroxyalkyl;

R^2 is alkyl;

n is 0 or 1;

wherein if n is 0 then A is CH_2.

and pharmaceutically acceptable salts thereof.

In another aspect, the present disclosure provides the compound 3-(4-Hydroxy-2,3-dihydrobenzofuran-5-yl)-6-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides the compound 3-(4-Hydroxy-2,3-dihydrobenzofuran-5-yl)-6-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one.

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 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 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, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

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.

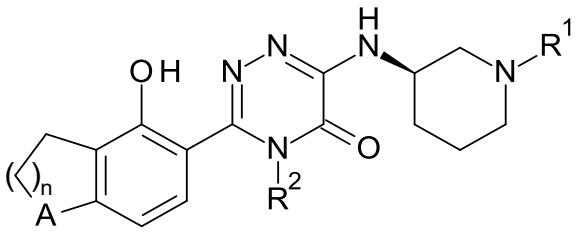
In another aspect, the present disclosure provides a method of *in vitro* inhibiting NLRP3, which method comprises administering an effective amount of a compound as described herein to inhibit NLRP3.

The term “acetyl” denotes a group of the formula –C(=O)-R’, wherein R’ is an alkyl group. Examples of acetyl include –C(=O)CH_3.

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

Claims

1. A compound of formula I



I

wherein,

A is –O– or CH_2;

R^1 is hydroxyalkyl;

R^2 is alkyl;

n is 0 or 1;

wherein if n is 0 then A is CH_2.

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R^2 is methyl.

3. A compound according to any one of claims 1 to 2, selected from

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

6-[[(3*R*)-1-(2-Hydroxyethyl)-3-piperidyl]amino]-3-(4-hydroxyindan-5-yl)-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

4. A compound according to any one of claims 1 to 2, selected from

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

3-(2-hydroxy-3-bicyclo[4.2.0]octa-1(6),2,4-trienyl)-6-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one;

and pharmaceutically acceptable salts thereof.

5. The compound 3-(4-Hydroxy-2,3-dihydrobenzofuran-5-yl)-6-[[(3R)-1-(2-hydroxyethyl)-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one, or a pharmaceutically acceptable salt thereof.

6. The compound 3-(4-Hydroxy-2,3-dihydrobenzofuran-5-yl)-6-[[(3*R*)-1-(2-hydroxyethyl)-3-piperidyl]amino]-4-methyl-1,2,4-triazin-5-one.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a therapeutically inert carrier.

8. A compound according to any one of claims 1 to 6 for use as a therapeutically active substance.

9. A compound according to any one of claims 1 to 6 for use in the treatment or prevention of a disease, disorder or condition, wherein the disease, disorder or condition is responsive to NLRP3 inhibition.

10. A compound according to any one of claims 1 to 6 for use in the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

11. The use of a compound according to any one of claims 1 to 6 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.

12. The use of a compound according to any one of claims 1 to 6 in the preparation of a medicament for the treatment or prophylaxis of a disease, disorder or condition selected from Asthma or COPD.

13. A method of *in vitro* inhibiting NLRP3, which method comprises administering an effective amount of a compound as claimed in any one of claims 1 to 6 to inhibit NLRP3.