Other diseases:

- Inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis

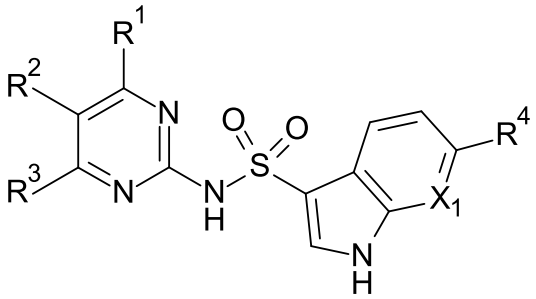
The compounds of formula I bind to and modulates GPR17 activity.

The compounds of formula I are therefore particularly useful in the treatment of diseases related to GPR17 antagonism.

The compounds of formula I are particularly useful in the treatment or prophylaxis of multiple sclerosis (MS), conditions related to direct damage to myelin sheaths such as carbon monoxide poisoning or virus induced demyelination, primary demyelinating disorders such as acute and multiphasic disseminated encephalomyelitis, and other CNS disorders associated with myelin loss such as Alzheimer's disease, schizophrenia, Parkinson's disease and Huntington's disease.

Summary

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



I

wherein

R^1 is H, alkoxy, or haloalkoxy;

R^2 is 1,1,2,2-tetradeuterio-2-fluoro-ethoxy, 1,1-dideuterio-2-fluoro-ethoxy, or 1,1-dideuterio-2,2-difluoro-ethyl;

R^3 is alkoxy or haloalkoxy;

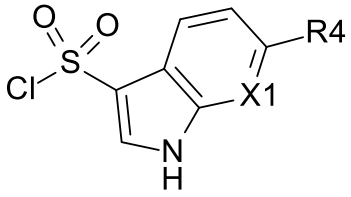
X_1 is CR^5 or N;

R^4 is H, halo, alkyl, or haloalkyl;

R^5 is H or halo;

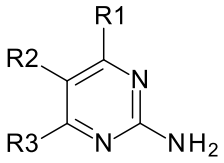
and pharmaceutically acceptable salts.

In another aspect, the present disclosure provides a process to prepare a compound as described herein comprising reacting a compound of formula II



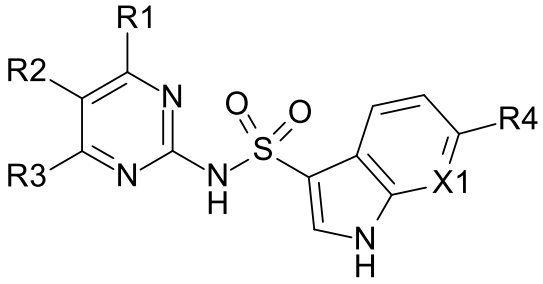
II

with a compound of formula III



III

in the presence of a base selected from N,N-diisopropylethylamine, pyridine, potassium phosphate or sodium hydride to provide a compound of formula I



I

wherein the substituents R^1, R^2, R^3, R^4 and X_1 are as defined above.

In another aspect, the present disclosure provides a compound as described herein for use as therapeutically active substance.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment of a disease modulated by GPR17.

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 multiple sclerosis.

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 conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

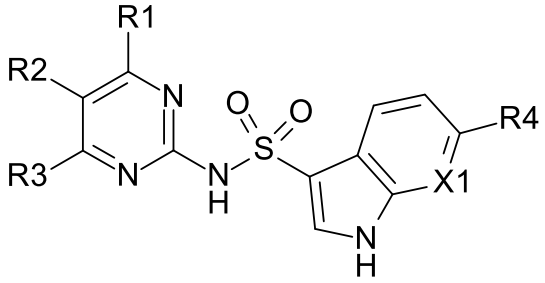
In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

In another aspect, the present disclosure provides a compound as described herein for use in the treatment or prophylaxis of multiple sclerosis.

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

Claims

1. Compounds of formula I



I

wherein

R^1 is H, alkoxy, or haloalkoxy;

R^2 is 1,1,2,2-tetradeuterio-2-fluoro-ethoxy, 1,1-dideuterio-2-fluoro-ethoxy, or 1,1-dideuterio-2,2-difluoro-ethyl;

R^3 is alkoxy or haloalkoxy;

X_1 is CR^5 or N;

R^4 is H, halo, alkyl, or haloalkyl;

R^5 is H or halo;

and pharmaceutically acceptable salts.

2. A compound according to claim 1, wherein R^1 is H or alkoxy.

3. A compound according to either claim 1 or claim 2, wherein R^2 is 1,1,2,2-tetradeuterio-2-fluoro-ethoxy, or 1,1-dideuterio-2,2-difluoro-ethyl.

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

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

6. A compound according to any of claims 1 to 5, wherein R^4 is halo.

7. A compound according to any of claims 1 to 6, wherein R^5 is halo.

8. A compound according to claim 1 wherein

R^1 is H or alkoxy;

R^2 is 1,1,2,2-tetradeuterio-2-fluoro-ethoxy, 1,1-dideuterio-2-fluoro-ethoxy, or 1,1-dideuterio-2,2-difluoro-ethyl;

R^3 is alkoxy;

X_1 is CR^5 or N;

R^4 is halo or alkyl;

R^5 is H or halo;

and pharmaceutically acceptable salts.

9. A compound according to claim 1 wherein

R^1 is H or alkoxy;

R^2 is 1,1,2,2-tetradeuterio-2-fluoro-ethoxy, or 1,1-dideuterio-2,2-difluoro-ethyl;

R^3 is alkoxy;

X_1 is CR^5 or N;

R^4 is halo;

R^5 is H or halo;

and pharmaceutically acceptable salts.

10. A compound according to any of claims 1 to 9, selected from

6-chloro-7-fluoro-N-[4-methoxy-5-(1,1,2,2-tetradeuterio-2-fluoro-ethoxy)pyrimidin-2-yl]-1H-indole-3-sulfonamide;

6-bromo-N-[4,6-dimethoxy-5-(1,1,2,2-tetradeuterio-2-fluoro-ethoxy)pyrimidin-2-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide;

6-chloro-N-[4,6-dimethoxy-5-(1,1,2,2-tetradeuterio-2-fluoro-ethoxy)pyrimidin-2-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide;

N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4-methoxy-pyrimidin-2-yl]-6-fluoro-1H-indole-3-sulfonamide;

and pharmaceutically acceptable salts thereof.

11. A compound according to any of claims 1 to 9 selected from

6-chloro-N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4-methoxy-pyrimidin-2-yl]-7-fluoro 1H-indole-3-sulfonamide;

6-chloro-N-[5-(1,1-dideuterio-2-fluoro-ethoxy)-4-methoxy-pyrimidin-2-yl]-7-fluoro-1H-indole-3-sulfonamide;

6-chloro-N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4-methoxy-pyrimidin-2-yl]-1H-indole-3-sulfonamide;

6-bromo-N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4-methoxy-pyrimidin-2-yl]-7-fluoro-1H-indole-3-sulfonamide;

6-bromo-N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide;

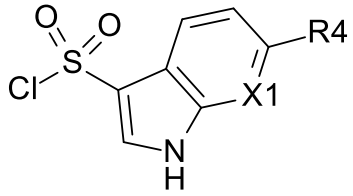
6-bromo-N-[5-(1,1-dideuterio-2,2-difluoro-ethoxy)-4,6-dimethoxy-pyrimidin-2-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide;

6-chloro-N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4,6-dimethoxy-pyrimidin-2-yl]-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide;

N-[5-(1,1-dideuterio-2,2-difluoro-ethyl)-4,6-dimethoxy-pyrimidin-2-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-3-sulfonamide;

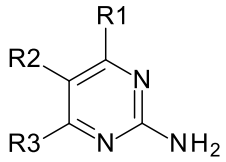
and pharmaceutically acceptable salts thereof.

12. A process to prepare a compound according to any one of claims 1 to 11 comprising reacting a compound of formula II



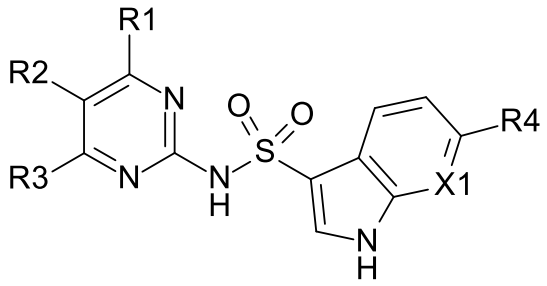
II

with a compound of formula III



III

in the presence of a base selected from N,N-diisopropylethylamine, pyridine, potassium phosphate or sodium hydride to provide a compound of formula I



I

wherein the substituents R^1, R^2, R^3, R^4 and X_1 are as defined above.

13. A compound according to any one of claims 1 to 11 for use as therapeutically active substance.

14. A compound according to any one of claims 1 to 11 for use in the treatment of a disease modulated by GPR17.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11 and a therapeutically inert carrier.

16. The use of a compound according to any one of claims 1 to 11 in the preparation of a medicament for the treatment or prophylaxis of multiple sclerosis.

17. The use of a compound according to any one of claims 1 to 11 in the preparation of a medicament for the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

18. A compound according to any one of claims 1 to 11 for use in the treatment or prophylaxis of conditions resulting from direct damage to myelin sheaths (including but

not limited central pontine and extra-pontine myelinolysis, carbon monoxide poisoning, nutritional deficiency, and virus-induced demyelination), demyelinating disorders (including but not limited to multiple sclerosis, acute and multiphasic disseminated encephalomyelitis, neuromyelitis optica spectrum disorders, and leukodystrophies), CNS disorders associated with myelin loss (including but not limited to Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis, and Ischemia due to stroke), and inflammation in the CNS for instance following encephalitis, primary angiitis, meningitis and obesity.

19. A compound according to any one of claims 1 to 11 for use in the treatment or prophylaxis of multiple sclerosis.

20. A compound according to any one of claims 1 to 11, when manufactured according to a process of claim 12.

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