Amino Pyrimidine SSAO Inhibitors

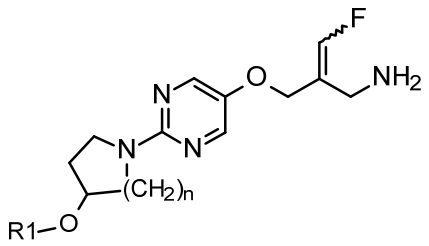
This invention relates to amino pyrimidine compounds, pharmaceutically acceptable salts of the compounds, and therapeutic uses of the compound and salts.

Semicarbazide-sensitive amino oxidase/vascular adhesion protein-1 (SSAO)/VAP-1) is a member of the semicarbazide-sensitive amino oxidase family. SSAO/VAP-1 has been alternatively referred to as VAP-1 or SSAO. SSAO/VAP-1 is an enzyme that exists both as a membrane-bound and a soluble isoform; it is predominantly expressed from endothelial cell surface, vascular smooth muscle and adipose cells. SSAO/VAP-1 participates in many cellular processes including glucose disposition, inflammation responses, and leukocyte recruitment. High activity levels of this enzyme are associated with diabetes, atherosclerosis, strokes, chronic kidney disease, and Alzheimer's disease, among other disorders. Recently SSAO/VAP-1 has been implicated in the pathogenesis of liver diseases such as fatty liver disease. Weston, C.J. *et al.*, J Neural. Transm. 2011, 118, 1055-1064. Fatty liver disease (FLD) encompasses a spectrum of disease states where fat accumulates in the liver in excessive amounts and is accompanied by inflammation. FLD can lead to non-alcoholic fatty liver disease (NAFLD), which is characterized by insulin resistance. Unchecked NAFLD progresses to a persistent inflammatory response or non-alcoholic steatohepatitis (NASH), progressive liver fibrosis, and eventually to cirrhosis. Currently there is a need to provide alternative treatment therapies for liver diseases such as NAFLD and/or NASH.

It is thought that a SSAO/VAP-1 inhibitor will reduce liver inflammation and fibrosis and thereby provide a treatment for liver diseases, in particular, a treatment for NAFLD and/or NASH. The present invention provides compounds that inhibit the SSAO/VAP-1 enzyme and which may address one or more of the needs.

Summary

In one aspect of the present disclosure, there is provided a compound of the formula below:



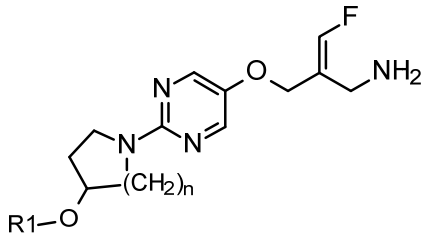
,

wherein n is 1 or 2; and

R1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound of the formula below:



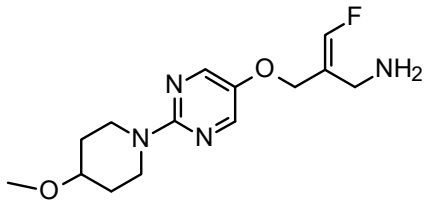
,

wherein n is 1 or 2; and

R1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of the formula below



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or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound, which is (2E)-3-fluoro-2-({[2-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]oxy}methyl)prop-2-en-1-amine 4-methylbenzenesulfonate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å), which comprises peaks at:

a) 18.6, 19.1, 21.0, 21.9, and 22.4 +/- 0.2° in 2 theta, or

b) 17.6, 11.0, 16.8, 18.6, 19.1, 21.0, 21.9, 22.4 and 26.1 +/- 0.2° in 2 theta.

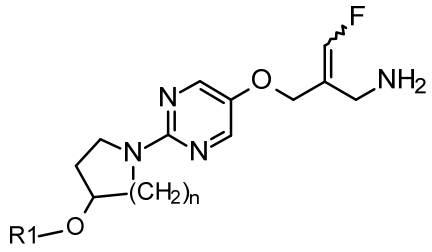
12. The compound according to claim 8, which is (E)-3-fluoro-2-[[2-(4-,methoxy-1-piperidyl)pyrimidin-5-yl]oxymethyl]prop-2-en-1-amine dihydrochloride.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein and a pharmaceutically acceptable carrier, diluent or excipient.

In another aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating a patient in need of treatment for non-alcoholic steatohepatitis.

Description

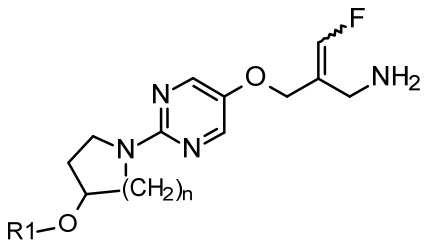
The present invention provides compounds of Formula 1:



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What is claimed is:

1. A compound of the formula below:



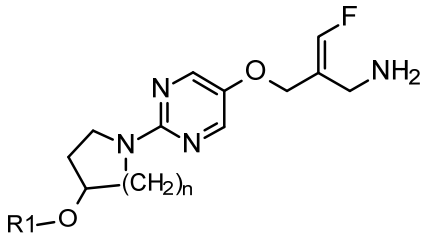
,

wherein n is 1 or 2; and

R1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

2. A compound of the formula below:



,

wherein n is 1 or 2; and

R1 is H or -CH_3,

or a pharmaceutically acceptable salt thereof.

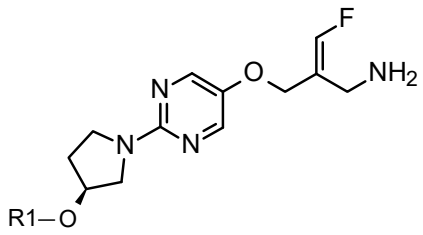
3. The compound according to claim 1 or 2, wherein n is 1, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 or 2, wherein n is 2, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1 or 2, wherein R1 is H, or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1 or 2, wherein R1 is -CH_3, or a pharmaceutically acceptable salt thereof.

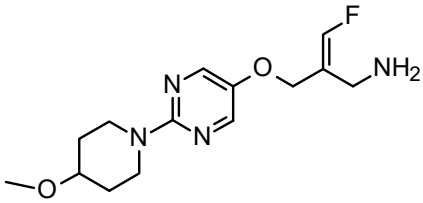
7. The compound according to claim 2, which is



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or a pharmaceutically acceptable salt thereof.

8. A compound of the formula below



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or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 2, which is provided as a mono or di hydrochloride addition salt, methylsulfonic acid addition salt, or a 4-methylbenzenesulfonic acid addition salt.

10. The compound according to claim 8, which is (2E)-3-fluoro-2-({[2-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]oxy}methyl)prop-2-en-1-amine 4-methylbenzenesulfonate.

11. A compound, which is (2E)-3-fluoro-2-({[2-(4-methoxypiperidin-1-yl)pyrimidin-5-yl]oxy}methyl)prop-2-en-1-amine 4-methylbenzenesulfonate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å), which comprises peaks at:

a) 18.6, 19.1, 21.0, 21.9, and 22.4 +/- 0.2° in 2 theta, or

b) 17.6, 11.0, 16.8, 18.6, 19.1, 21.0, 21.9, 22.4 and 26.1 +/- 0.2° in 2 theta.

12. The compound according to claim 8, which is (E)-3-fluoro-2-[[2-(4-,methoxy-1-piperidyl)pyrimidin-5-yl]oxymethyl]prop-2-en-1-amine dihydrochloride.

13. A pharmaceutical composition comprising the compound according to any one of claims 1, 2, or 7 to 12 and a pharmaceutically acceptable carrier, diluent or excipient.

14. Use of the pharmaceutical composition according to claim 13 in the manufacture of a medicament for treating a patient in need of treatment for non-alcoholic steatohepatitis.