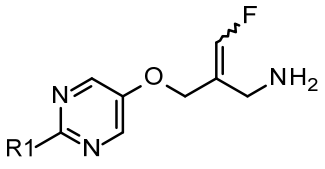
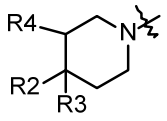
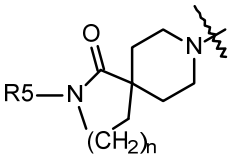
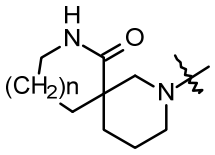
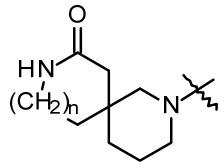
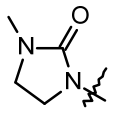
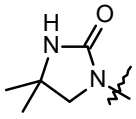
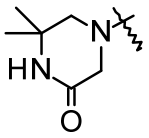
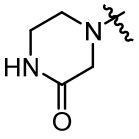
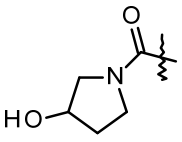
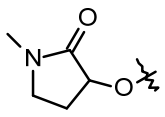
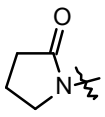
The present invention provides compounds that inhibit the SSAO/VAP-1 enzyme and which may address one or more of these needs.

Summary

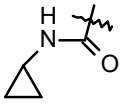
In one aspect of the present disclosure, there is provided a compound of the formula below:



where R1 is selected from:  ,  ,  ,  ,  ,  ,  ,  ;

R2 is selected from: H, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$,  ,  , and  ;

R3 is H or CH_3,

R4 is H or  ;

R5 is selected from: H, $-C_{1\text{-}4}$alkyl, $-C_{3\text{-}4}$ cycloalkyl, $-CH_2\text{-}C_{3\text{-}4}$ cycloalkyl; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

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

In a further aspect of the present disclosure, there is provided a composition disclosed herein, for use in a method of treating non-alcoholic steatohepatitis.

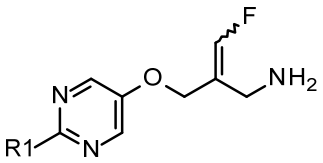
In another aspect of the present disclosure, there is provided a compound disclosed herein for use in therapy.

In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of a non-alcoholic steatohepatitis.

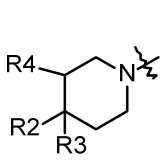
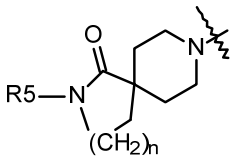
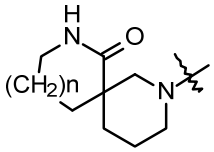
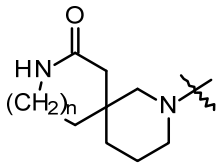
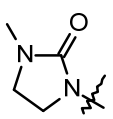
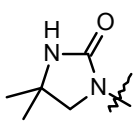
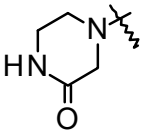
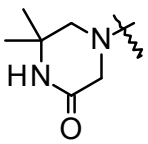
In a further aspect of the present disclosure, there is provided the use of a compound disclosed herein in the manufacture of a medicament to treat a non-alcoholic steatohepatitis.

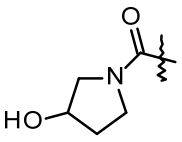
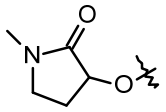
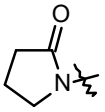
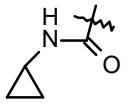
Description

The present invention provides a compound of the Formula 1 below:



1

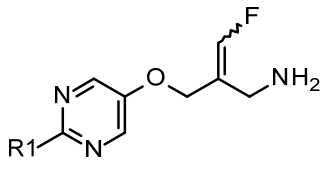
where R1 is selected from:  ,  ,  ,  ,  ,  ,  ,  , and ;

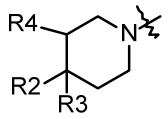
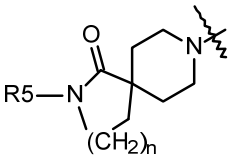
R2 is selected from: H, -C(O)NH_2, -C(O)$NH(CH_3)$, -C(O)$N(CH_3)_2$,  ,  , and  ; R3 is H or CH_3, R4 is H or  ; R5 is selected from: H, -$C_{1\text{-}4}$alkyl, -$C_{3\text{-}4}$ cycloalkyl, -CH_2-$C_{3\text{-}4}$ cycloalkyl; and n is 1 or 2; or a pharmaceutically acceptable salt thereof.

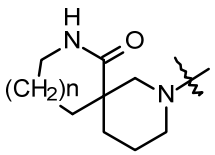
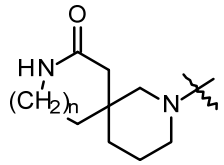
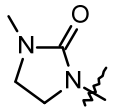
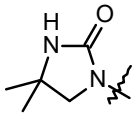
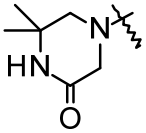
The bond to fluorine illustrated as indicates that the fluorine atom and the methoxypyrimidine group can be either Z (*zusammen*, together) or E (*entgegen,* opposite) relative to each other. (See Brecher, J., *et al.*, "Graphical Representation of Stereochemical Configuration", Pure and Appl. Chem, 2006, 78(10) 1897, at 1959.) The structure illustrated by Formula 1 includes compounds exhibiting the Z stereochemical configuration or the E stereochemical configuration about the double bond; or a mixture of compounds individually exhibiting the Z or E stereochemical configuration. Preferred

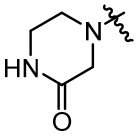
What is claimed is:

1. A compound of the formula below:



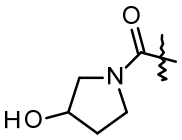
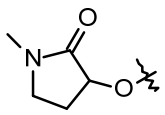
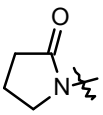
where R1 is selected from:  ,  ,

 ,  ,  ,  ,  ,

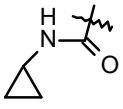


and ;

R2 is selected from: H, -C(O)NH$_2$, -C(O)NH(CH$_3$), -C(O)N(CH$_3$)$_2$,

 ,  , and  ;

R3 is H or CH$_3$,

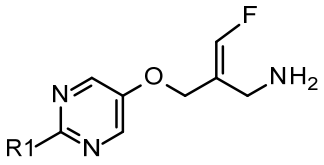
R4 is H or  ;

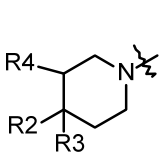
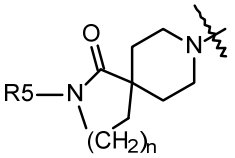
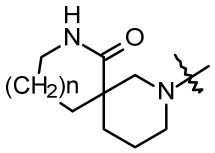
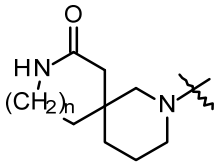
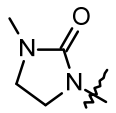
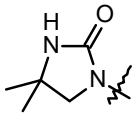
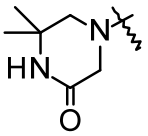
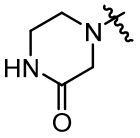
R5 is selected from: H, -C$_{1\text{-}4}$alkyl, -C$_{3\text{-}4}$ cycloalkyl, -CH$_2$-C$_{3\text{-}4}$ cycloalkyl; and

n is 1 or 2;

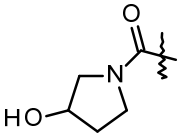
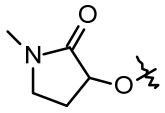
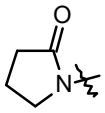
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, which is:

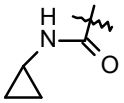


where R1 is selected from:  ,  ,  ,  ,  ,  ,  , 

and ;

R2 is selected from: H, -C(O)NH$_2$, -C(O)NH(CH$_3$), -C(O)N(CH$_3$)$_2$,  ,  , and  ;

R3 is H or CH$_3$;

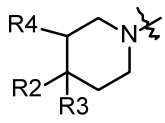
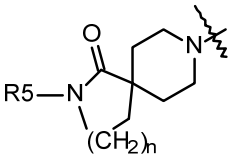
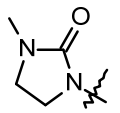
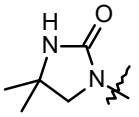
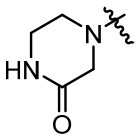
R4 is H or  ;

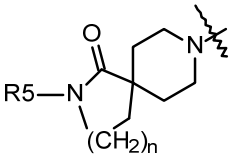
R5 is selected from: H, -C$_{1\text{-}4}$alkyl, -C$_{3\text{-}4}$ cycloalkyl, and -CH$_2$-C$_{3\text{-}4}$ cycloalkyl;

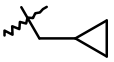
and

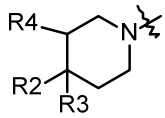
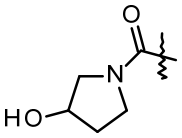
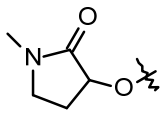
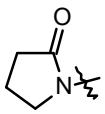
n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

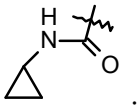
3. A compound according to claim 1 or 2 wherein R1 is selected from:  ,  ,  ,  , and  ; or a pharmaceutically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3 wherein R1 is  ; or a pharmaceutically acceptable salt thereof.

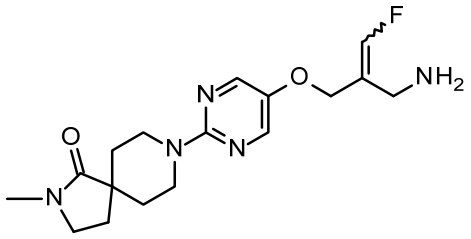
5. A compound according to claim 4 wherein R5 is selected from: H, $-CH_3$,  , and  ; or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1 or 2 wherein R1 is  and R2 is selected from: H, $-C(O)NH_2$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$,  ,  , and  ; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 wherein R3 is H.

8. A compound according to claim 6 wherein R4 is  ; or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 1, which is:



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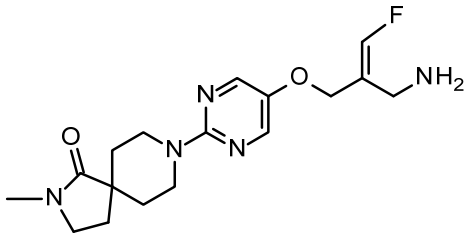
or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 or 2, which is:



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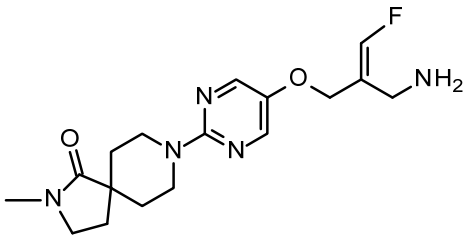
or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10 which is provided as a mono or di hydrochloride addition salt.

12. A compound according to claim 1 which is selected from the group consisting of:



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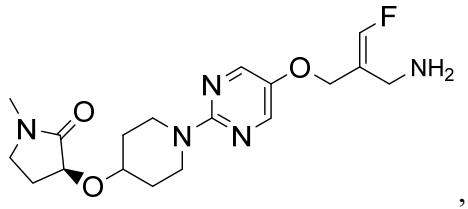

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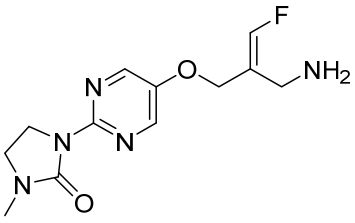

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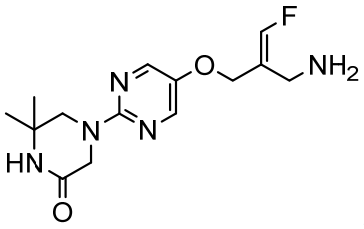

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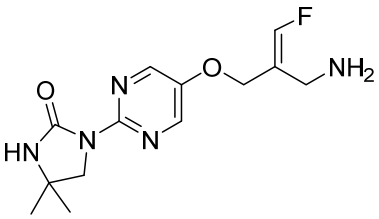
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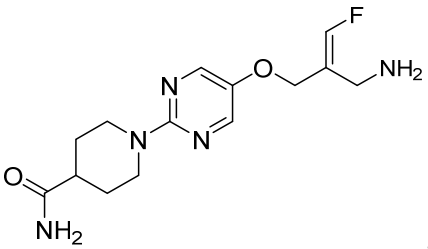
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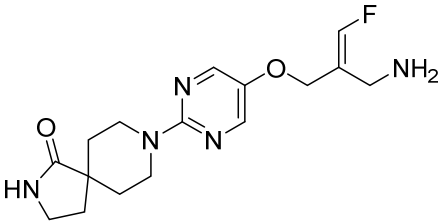
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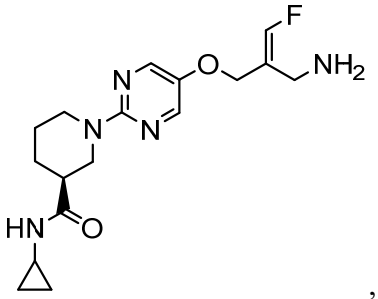
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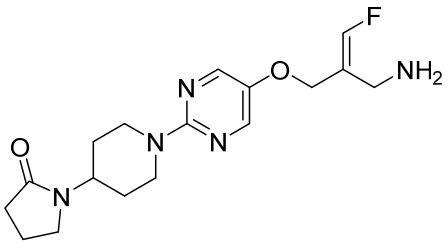
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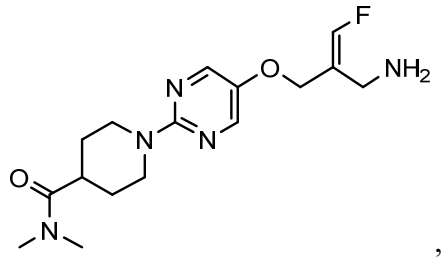
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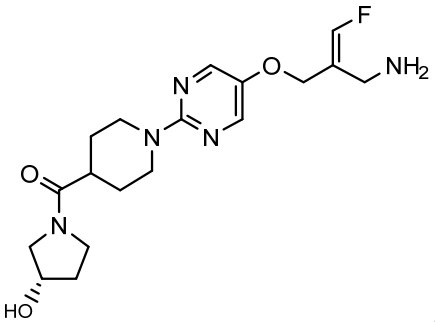
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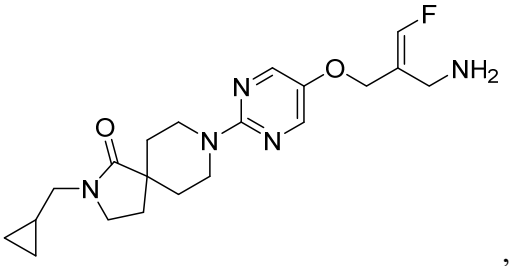
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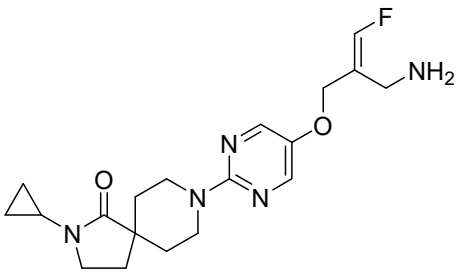
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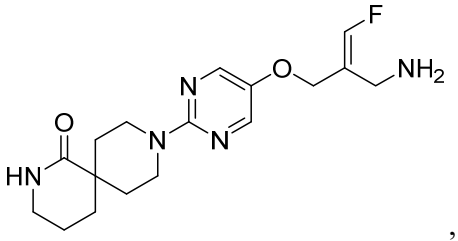
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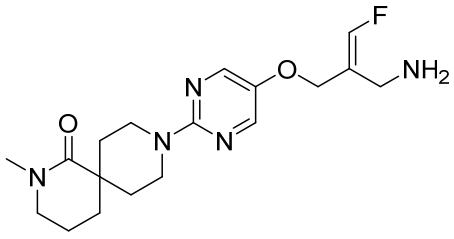
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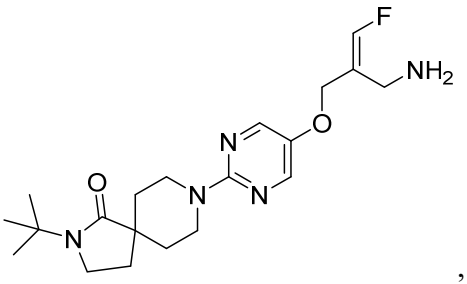
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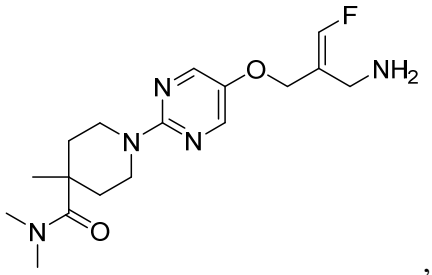
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or a pharmaceutically acceptable salt thereof.

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

14. A composition according to claim 13, for use in a method of treating non-alcoholic steatohepatitis.

15. A compound according to any one of claims 1 to 12 for use in therapy.

16. A compound according to any one of claims 1 to 12 for use in the treatment of a non-alcoholic steatohepatitis.

17. Use of a compound according to any one of claims 1 to 12 in the manufacture of a medicament to treat a non-alcoholic steatohepatitis.