

US 2017/0183328 A1 discloses substituted 3-azabicyclo[3.1.0]hexanes as KHK inhibitors. Recently published data shows that ketohexokinase inhibitor PF-06835919 administered for 6 weeks reduces whole liver fat as measured by magnetic resonance imaging-proton density fat fraction in subjects with non-alcoholic fatty liver disease (*J.*

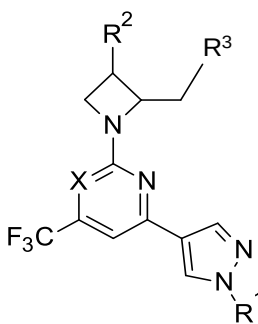
5 *Hepatology*. EASL International Liver Congress Abstracts, Supplement N°1S Vol. 70, April 2019).

Compounds containing carboxylic functional groups carry a risk associated with the formation of acyl glucuronide metabolites (Vleet Van *et al.*, *Toxicology Letters*, 272 (2017) 1-7). Acyl glucuronide metabolites are often unstable and may be chemically reactive leading to covalent bonding with macromolecules and toxicity.

There is a need for alternate treatments for metabolic syndrome and associated indications including T2DM, heart failure, diabetic kidney disease and NASH. In particular, there is a need for compounds which are potent inhibitors of KHK. There is a need for KHK inhibitor compounds having advantageous properties, for example, good oral bioavailability to support once daily dosing. Furthermore, there is a need for KHK inhibitor compounds which do not have a carboxylic acid moiety and lack the ability to form acyl glucuronides.

Summary

In a first aspect, the present disclosure refers to a compound of the formula:

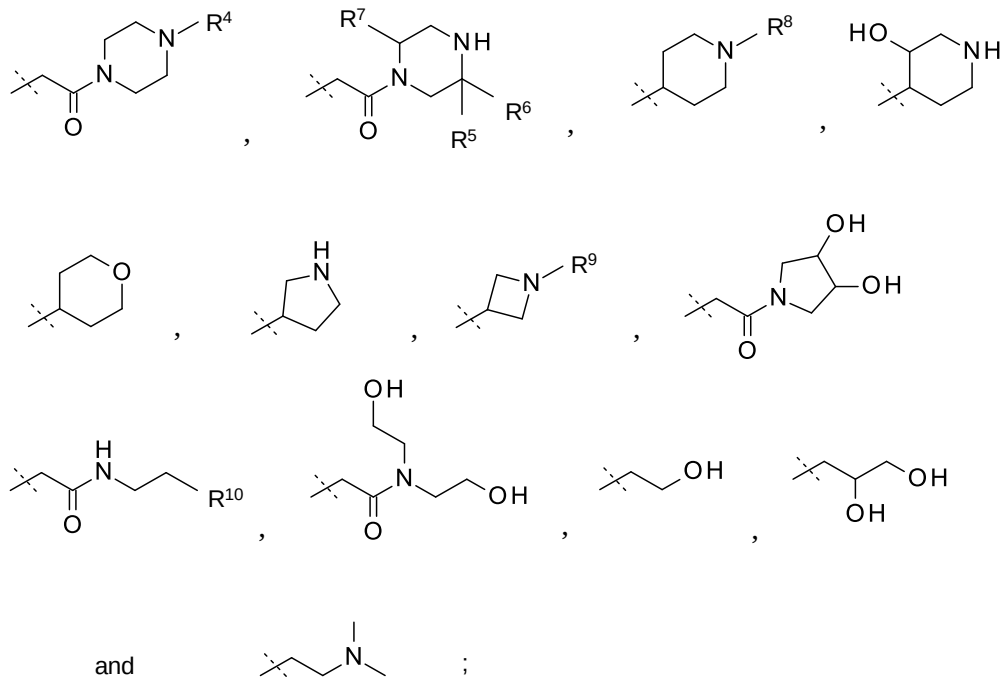


20 wherein

X is N, or C substituted with CN;

R¹ is selected from: H,

-2a-



R^2 and R^3 are both H, or one is H and the other is OH;

R^4 , R^5 , R^6 , R^7 and R^9 are independently H or CH_3 ;

R^8 is H, CH_3 , CH_2CH_2OH , $C(=O)CH_2NH_2$, or $C(=O)CH_3$; and

R^{10} is OH or NH_2 ;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes mellitus.

In yet another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating heart failure.

In a further aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating diabetic kidney disease.

In another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-alcoholic steatohepatitis.

5 In yet another aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating chronic kidney disease.

In a further aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use in therapy.

10 In another aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use in treating type 2 diabetes mellitus.

In yet another aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use in treating heart failure.

In a further aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use in treating diabetic kidney disease.

15 In another aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use in treating non-alcoholic steatohepatitis.

In yet another aspect, the present disclosure refers to a compound, or a pharmaceutically acceptable salt thereof disclosed herein, for use in treating chronic kidney disease.

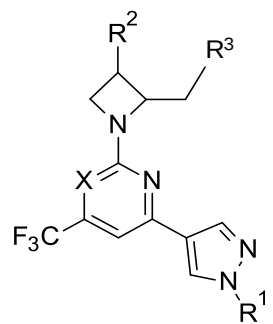
20 In a further aspect, the present disclosure refers to a pharmaceutical composition, comprising a compound, or a pharmaceutically acceptable salt thereof disclosed herein, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

In another aspect, the present disclosure refers to a process for preparing a pharmaceutical composition, comprising admixing a compound, or a pharmaceutically acceptable salt thereof disclosed herein, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Description

Accordingly, in one embodiment, the present invention provides a compound of the Formula I:

-2c-



Formula I

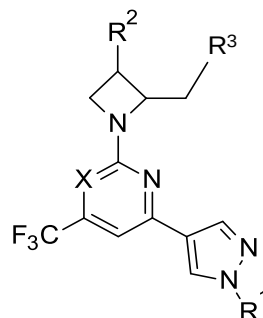
wherein

X is N, or C substituted with CN;

5 R¹ is selected from: H,

CLAIMS

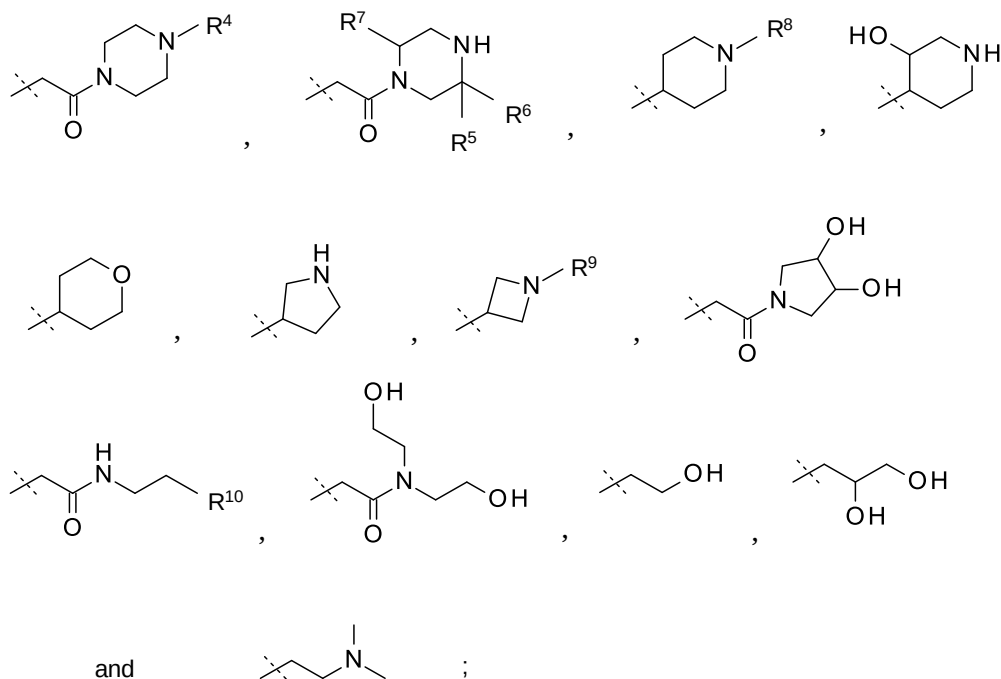
1. A compound of the formula:



wherein

- 5 X is N, or C substituted with CN;

R¹ is selected from: H,



R² and R³ are both H, or one is H and the other is OH;

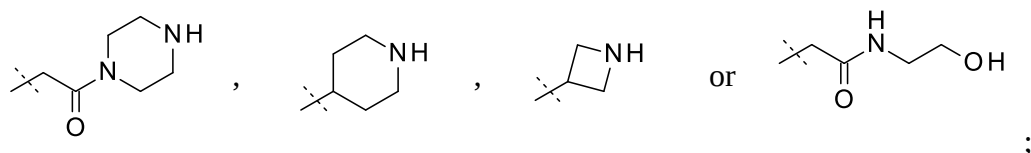
R⁴, R⁵, R⁶, R⁷ and R⁹ are independently H or CH₃;

- 10 R⁸ is H, CH₃, CH₂CH₂OH, C(=O)CH₂NH₂, or C(=O)CH₃; and

R¹⁰ is OH or NH₂;

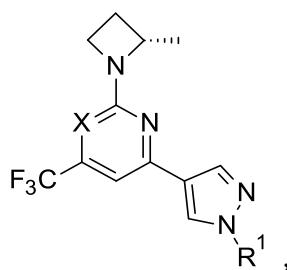
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R¹ is selected from:



or a pharmaceutically acceptable salt thereof.

- 5 3. The compound according to claim 1 or claim 2, wherein the compound is:

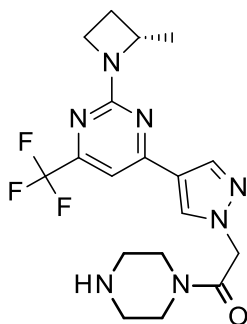


or a pharmaceutically acceptable salt thereof.

- 10 4. The compound according to any one of the claims 1 to 3, wherein X is N, or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 3, wherein X is C substituted with CN, or a pharmaceutically acceptable salt thereof.

- 15 6. The compound according to any one of claims 1 to 4, wherein the compound



is:

or a pharmaceutically acceptable salt thereof.

7. The compound, or pharmaceutically acceptable salt thereof, according to claim 6, which is a succinate salt.
- 5 8. Use of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating type 2 diabetes mellitus.
- 10 9. Use of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating heart failure.
- 15 10. Use of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating diabetic kidney disease.
- 20 11. Use of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating non-alcoholic steatohepatitis.
- 25 12. Use of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating chronic kidney disease.
13. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 for use in therapy.
14. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 for use in treating type 2 diabetes mellitus.

15. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 for use in treating heart failure.
- 5 16. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 for use in treating diabetic kidney disease.
17. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 for use in treating non-alcoholic steatohepatitis.
- 10 18. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 for use in treating chronic kidney disease.
- 15 19. A pharmaceutical composition, comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 with one or more pharmaceutically acceptable carriers, diluents, or excipients.
- 20 20. A process for preparing a pharmaceutical composition, comprising admixing a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 with one or more pharmaceutically acceptable carriers, diluents, or excipients.