TETRAHYDROPYRANYL BENZAMIDE DERIVATIVES

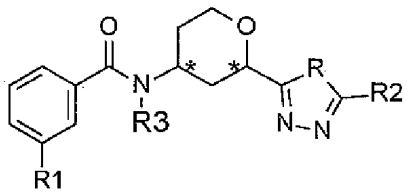
This invention relates to imidazo benzamide compounds, or pharmaceutically acceptable salts thereof, and therapeutic use thereof. Compounds of this invention are agonists of GPR142.

GPR142 is reported to be expressed in pancreatic cells and associated with the stimulation of insulin secretion under conditions of high blood glucose. Compounds that effectuate GPR142 agonism are desired.

Compounds reported to be GPR142 agonists are disclosed in M. Lizarzaburu, et al. "Discovery and Optimization of a novel series of GPR142 agonists for the treatment of type 2 diabetes," Bioorganic and Medicinal Chemistry Letters 22 (2012) 5942-5947. The compounds reported by Lizarzaburu are a series of phenylalanine related structures.

Summary

In one aspect of the present disclosure, there is provided a compound of the Formula 1:

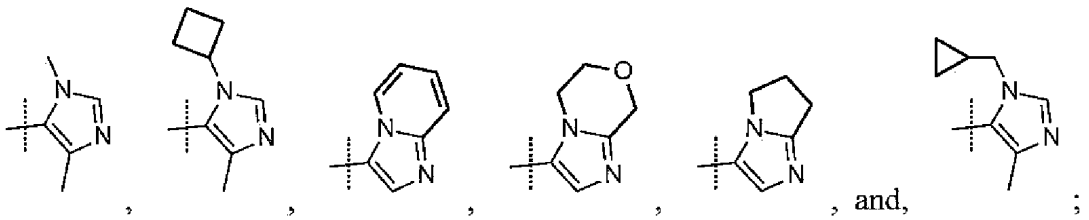


1

wherein R is -NH or O;

R1 is selected from: $-CF_3$, $-OCF_3$, and halogen;

R2 is selected from:

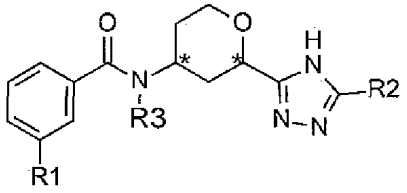

, , , , , and, ;

R3 is C_{1-3}alkyl or  ;

wherein each * designates a chiral center;

or a pharmaceutically acceptable salt thereof.

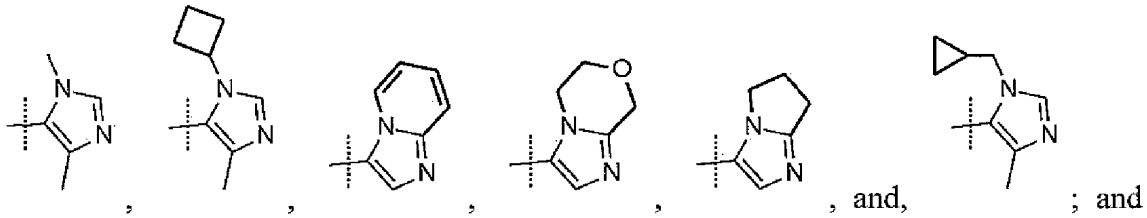
In another aspect of the present disclosure, there is provided a compound of the Formula 2:



2

wherein R1 is selected from: $-CF_3$, $-OCF_3$, halogen;

R2 is selected from:



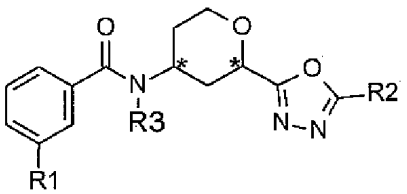
; and

R3 is C_{1-3}alkyl or  ;

wherein each * designates a chiral center;

or a pharmaceutically acceptable salt thereof.

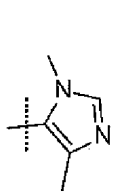
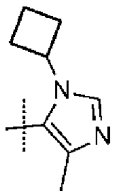
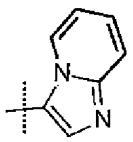
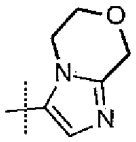
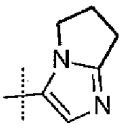
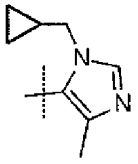
In yet another aspect of the present disclosure, there is provided a compound of the Formula 3:



3

wherein R1 is selected from: $-CF_3$, $-OCF_3$, halogen;

R2 is selected from:

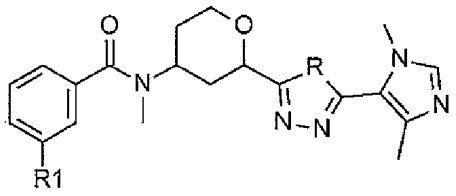
 ,  ,  ,  ,  , and,  ; and

R3 is C_{1-3}alkyl or  ;

wherein each * designates a chiral center;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of the Formula 4



4

wherein R is selected from the group consisting of O and NH;

R^1 is selected from the group consisting of $-CF_3$, $-OCF_3$, and Cl;

or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

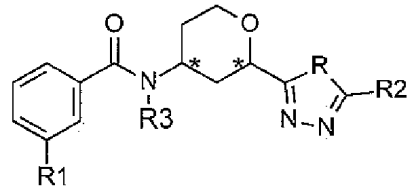
In yet another aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in therapy.

In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in therapy to treat type II diabetes.

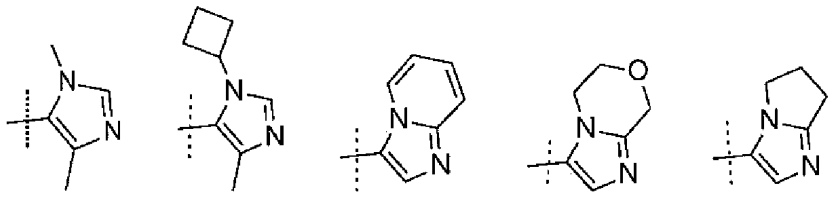
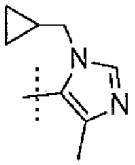
In another aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for treating type II diabetes.

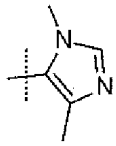
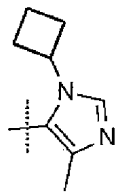
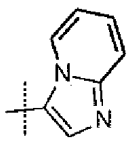
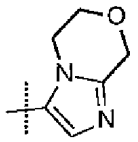
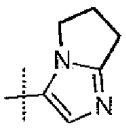
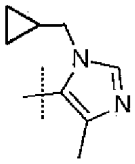
Description

The present invention provides compounds of Formula 1:



1

where R is NH or O; R1 is selected from $-CF_3$, $-OCF_3$, and halogen; R2 is selected from:  , and,  ; and R3 is C_{1-3}alkyl or  ; or a pharmaceutically acceptable salt thereof. The  symbol designates where the R2 or R3 group is attached to the remaining portion of the structure. The * symbol in Formula 1 designates a chiral center. Each individual carbon of the chiral centers at positions 2 and 4 on the

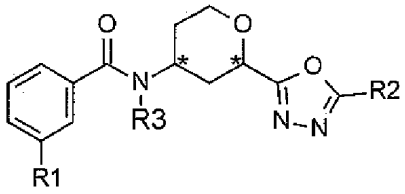
 ,  ,  ,  ,  , and,  ; and

R3 is C_{1-3}alkyl or  ;

wherein each * designates a chiral center;

or a pharmaceutically acceptable salt thereof.

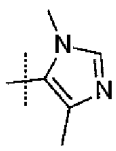
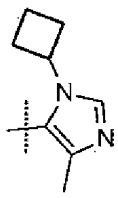
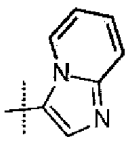
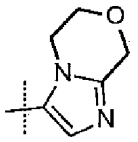
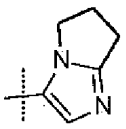
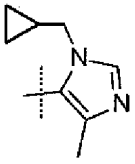
3. A compound of the Formula 3:



3

wherein R1 is selected from: $-CF_3$, $-OCF_3$, halogen;

R2 is selected from:

 ,  ,  ,  ,  , and,  ; and

R3 is C_{1-3}alkyl or  ;

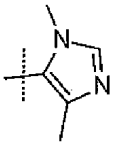
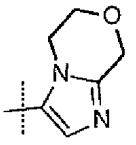
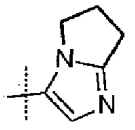
wherein each * designates a chiral center;

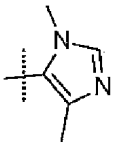
or a pharmaceutically acceptable salt thereof.

4. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 wherein R1 is selected from: $-CF_3$, $-OCF_3$, and Cl.

5. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 4 wherein R1 is $-CF_3$.

6. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5 wherein R2 is selected from:


,

, and

.

7. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 wherein R2 is  .

8. A compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 7 wherein R3 is $-CH_3$.

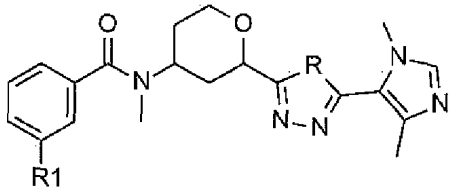
9. A compound, or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is selected from:

Cis-(chiral)-N-[(2-[5-(1,4-Dimethyl-1H-imidazol-5-yl)-4H-1,2,4-triazol-3-yl]tetrahydro-2H-pyran-4-yl]-N-methyl-3-(trifluoromethyl)benzamide isomer 1,

Cis-(chiral)-3-Chloro-N-[2-[5-(1,4-dimethyl-1H-imidazol-5-yl)-4H-1,2,4-triazol-3-yl]tetrahydro-2H-pyran-4-yl]-N-methyl-benzamide isomer 1, and

Cis-(chiral)-N-[2-[5-(1,4-Dimethyl-1H-imidazol-5-yl)-4H-1,2,4-triazol-3-yl]tetrahydro-2H-pyran-4-yl]-N-methyl-3-(trifluoromethoxy)benzamide isomer 1.

10. A compound of the Formula 4



4

wherein R is selected from the group consisting of O and NH;

R^1 is selected from the group consisting of $-CF_3$, $-OCF_3$, and Cl;

or a pharmaceutically acceptable salt thereof.

11. The compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8 wherein the orientation of the functional groups at the 2 and 4 position of the tetrahydropyran are in the cis configuration.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable carrier, diluent, or excipient.

13. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11 for use in therapy.

14. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11 for use in therapy to treat type II diabetes.

15. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 11 in the manufacture of a medicament for treating type II diabetes.