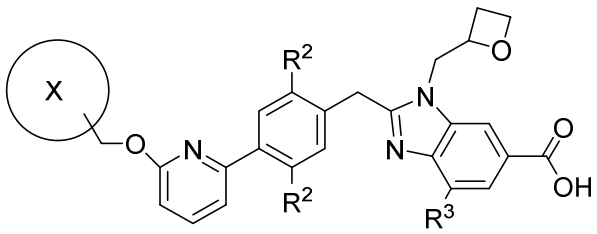
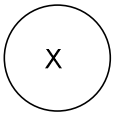
for more potent small molecule GLP-1R agonists. There is especially a need for GLP-1R agonists which are more potent and may be effective at a lower dose.

Summary

In an aspect, there is provided a compound of the formula:



wherein  is phenyl, a 5 or 6-membered heteroaryl or pyridone, which phenyl, heteroaryl or pyridone is optionally substituted with one or two R^1;

R^1 at each occurrence is independently CN, halo, C_1-C_3alkyl, C_1-C_3alkoxy, -C(O)NH_2 or 5-membered heteroaryl;

R^2 at each occurrence is independently halo or methyl;

R^3 is C_1-C_4alkoxy optionally substituted with C_1-C_2alkoxy;

or a pharmaceutically acceptable salt thereof.

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

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

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in the treatment of type II diabetes mellitus.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in lowering blood glucose levels.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in the treatment of hyperglycemia.

In another aspect, there is provided a compound, or a pharmaceutically acceptable salt thereof, as described herein for use in the treatment of obesity.

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

In another aspect, there is provided use of a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament to lower blood glucose levels.

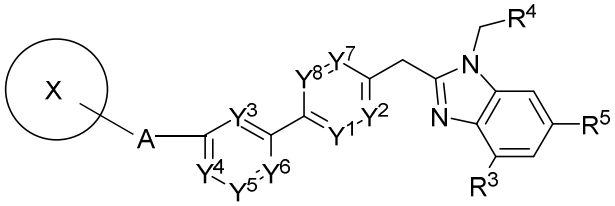
In another aspect, there is provided use of a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for the treatment of hyperglycemia.

In another aspect, there is provided use of a compound, or a pharmaceutically acceptable salt thereof, as described herein in the manufacture of a medicament for the treatment of obesity.

Description

Compounds disclosed herein have GLP-1R agonist activity. Certain compounds of the present invention have comparable *in-vitro* potency at the GLP-1 receptor to native GLP-1(7-36)NH_2.

Accordingly, the present invention provides a compound of the formula:



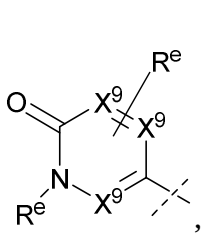
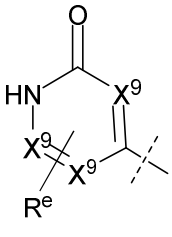
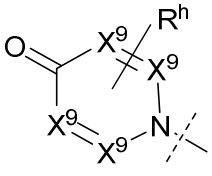
Formula I

wherein



is phenyl, a 5 or 6-membered heteroaryl or pyridone, which phenyl, heteroaryl or pyridone is optionally substituted with one or two R^1;

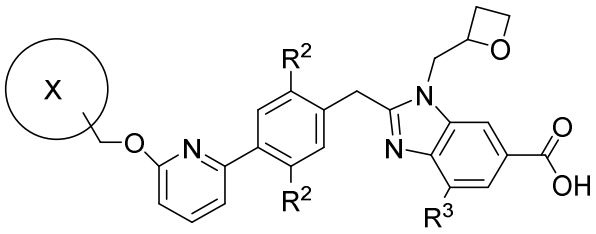
R^1 at each occurrence is independently CN; halo; C_1-C_3alkyl optionally substituted with OH; C_1-C_3haloalkyl; C_1-C_3alkoxy; C_3-C_5cycloalkyl; -SO_2C_1-C_3alkyl; -$C(O)NH_2$;

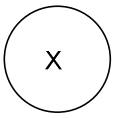
,  or  wherein each X^9 is independently CH or N and no more than one X^9 in the ring is N, each R^e is independently selected from: H, C_1-C_3haloalkyl, halo, C_3-C_5cycloalkyl and C_1-C_3alkyl optionally substituted with OH, R^h is H, C_1-C_3haloalkyl, halo, C_3-C_5cycloalkyl, OH, -NR^cR^d or C_1-C_3alkyl optionally substituted with OH;

5- or 6- membered heteroaryl or phenyl wherein the heteroaryl or phenyl is optionally substituted with one or two substituents independently selected from: C_1-C_3alkoxy, C_3-C_5cycloalkyl, -CH_2-C_3-C_5cycloalkyl, -SO_2C_1-C_3alkyl, C_4-C_5heterocyclyl, -CH_2-C_4-C_5heterocyclyl, halo, C_1-C_3haloalkyl, C_1-C_3haloalkoxy, CN, -$CONR^cR^d$, -NR^cR^d or C_1-C_3alkyl optionally substituted with OH;

Claims

1. A compound of the formula:



wherein 

is phenyl, a 5 or 6-membered heteroaryl or pyridone, which phenyl, heteroaryl or pyridone is optionally substituted with one or two R^1;

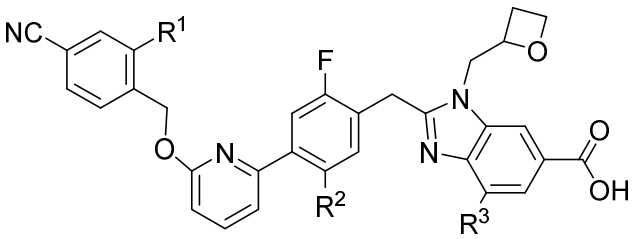
R^1 at each occurrence is independently CN, halo, C_1-C_3alkyl, C_1-C_3alkoxy, -C(O)NH_2 or 5-membered heteroaryl;

R^2 at each occurrence is independently halo or methyl;

R^3 is C_1-C_4alkoxy optionally substituted with C_1-C_2alkoxy;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, which is of the formula:



wherein R^1 is F or OCH_3;

R^2 is F or CH_3; and

R^3 is -OCH_3, or -$OCH_2CH_2OCH_3$,

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1, which is selected from:

2-[[4-[6-[(4-Cyano-2-fluoro-phenyl)methoxy]-2-pyridyl]-2-fluoro-5-methyl-phenyl]methyl]-7-methoxy-3-[[oxetan-2-yl]methyl]benzimidazole-5-carboxylic acid;

2-(4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(4-(6-((5-Cyanopyridin-2-yl)methoxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(4-(6-((6-Cyanopyridin-3-yl)methoxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(4-(6-((4-Cyano-2-fluorobenzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-(2-methoxyethoxy)-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-[[4-[6-[(6-Cyano-2-methyl-3-pyridyl)methoxy]-2-pyridyl]-2,5-difluoro-phenyl]methyl]-7-methoxy-3-[[oxetan-2-yl]methyl]benzimidazole-5-carboxylic acid;
2-[[4-[6-[(6-carbamoyl-2-methyl-3-pyridyl)methoxy]-2-pyridyl]-2,5-difluoro-phenyl]methyl]-7-methoxy-3-[[oxetan-2-yl]methyl]benzimidazole-5-carboxylic acid;
2-[[2,5-Difluoro-4-[6-[(1-methyl-6-oxo-3-pyridyl)methoxy]-2-pyridyl]phenyl]methyl]-7-(2-methoxyethoxy)-3-[[oxetan-2-yl]methyl]benzimidazole-5-carboxylic acid;
2-(4-(6-((5-cyanothiophen-2-yl)methoxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(4-(6-((4-cyano-2-methylbenzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(2,5-difluoro-4-(6-((2-methyl-2H-1,2,3-triazol-4-yl)methoxy)pyridin-2-yl)benzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(4-(6-((4-(1H-1,2,4-triazol-1-yl)benzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(2,5-difluoro-4-(6-(isoxazol-3-ylmethoxy)pyridin-2-yl)benzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(4-(6-((4-cyano-2-methoxybenzyl)oxy)pyridin-2-yl)-2,5-difluorobenzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(2,5-difluoro-4-(6-((1-methyl-1H-pyrazol-3-yl)methoxy)pyridin-2-yl)benzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
2-(2,5-difluoro-4-(6-((2-methyl-2H-tetrazol-5-yl)methoxy)pyridin-2-yl)benzyl)-4-methoxy-1-(oxetan-2-ylmethyl)-1H-benzo[d]imidazole-6-carboxylic acid;
or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 and at least one pharmaceutically acceptable carrier, diluent, or excipient.

5. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in therapy.

6. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in the treatment of type II diabetes mellitus.

7. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in lowering blood glucose levels.

8. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in the treatment of hyperglycemia.

9. A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 for use in the treatment of obesity.

10. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of type II diabetes mellitus.

11. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 in the manufacture of a medicament to lower blood glucose levels.

12. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of hyperglycemia.

13. Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of obesity.