

Glucagon-like Peptide 1 Receptor Agonists

This invention relates to glucagon-like peptide-1 receptor agonists and therapeutic uses of the compounds to treat type II diabetes mellitus.

5 Glucagon-like peptide-1 (GLP-1) is a member of the incretin family of peptide hormones secreted by intestinal enteroendocrine L-cells. GLP-1 induces the release of insulin from beta cells in a glucose dependent manner. However, GLP-1 is rapidly metabolized so that only a small percentage of the GLP-1 can be utilized to induce insulin secretion. To offset this, GLP-1 receptor (GLP-1R) agonists have been developed to enhance insulin secretion as a treatment for
10 type II diabetes mellitus.

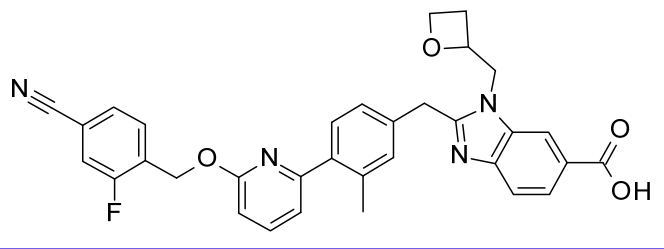
The majority of GLP-1R agonists that have been approved to treat type II diabetes mellitus are injectable agents. Patients often prefer orally administered drugs because of the drawbacks associated with injection such as inconvenience, pain, and the potential for injection site irritation.

15 WO2018/109607 discloses certain benzimidazole derivatives, which are described as GLP-1R agonists.

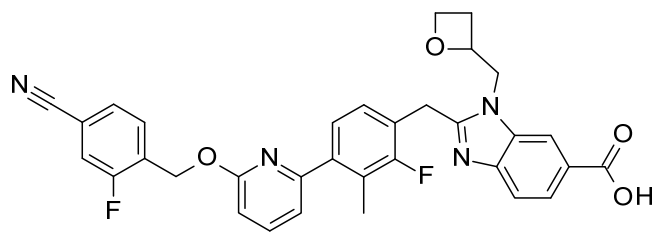
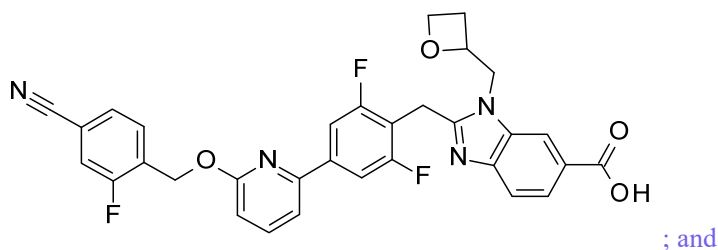
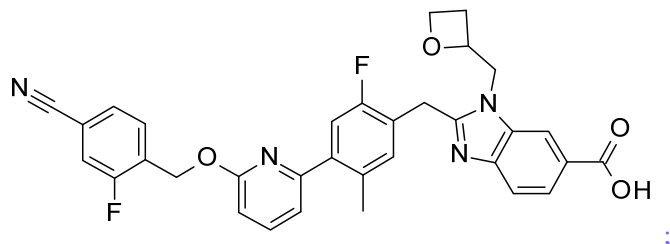
However, there is a need for alternative GLP-1R agonists. In particular, there is a need for GLP-1R agonists which can be administered orally. There is especially a need for GLP-1R agonists having improved potency, a favourable toxicology profile and/or a pharmacokinetic
20 profile which supports once daily dosing.

Summary

In one aspect of the present disclosure, there is provided a compound selected from:



-1a-



5

or a pharmaceutically acceptable salt thereof.

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

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In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, disclosed herein for use in therapy.

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

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In a further aspect of the present disclosure, there is provided a compound, or a pharmaceutically acceptable salt thereof, disclosed herein for use in lowering blood glucose levels.

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

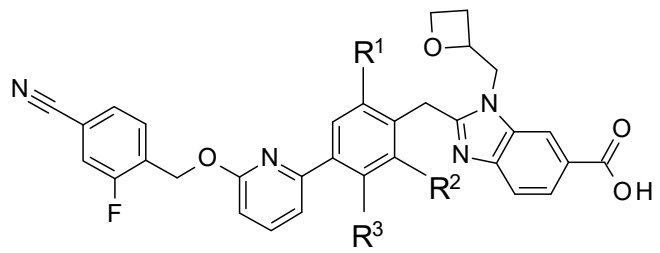
5 In a further aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein in the manufacture of a medicament for the treatment of type II diabetes mellitus.

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

10 In a further aspect of the present disclosure, there is provided a use of a compound, or a pharmaceutically acceptable salt thereof, disclosed herein in the manufacture of a medicament for the treatment of hyperglycemia.

Description

15 ~~Accordingly,~~ The present invention provides a compound of the formula:



Formula I

wherein

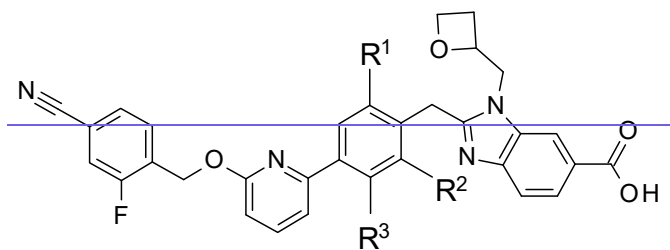
R¹ is H or F;

20 R² is H or F; and

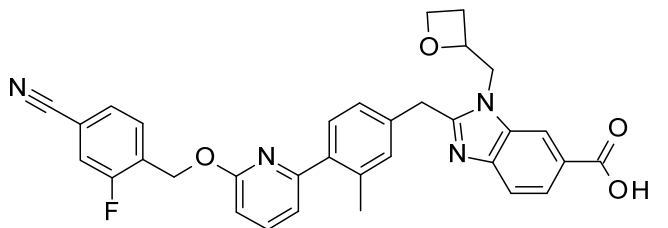
R³ is H or CH₃;

Claims

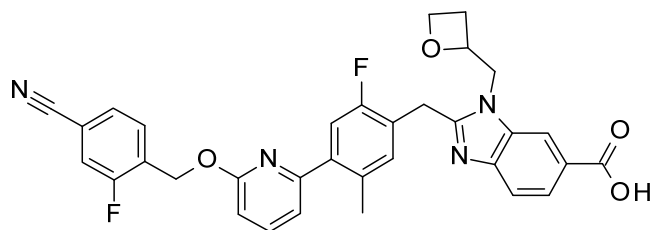
1. A compound selected from the formula:



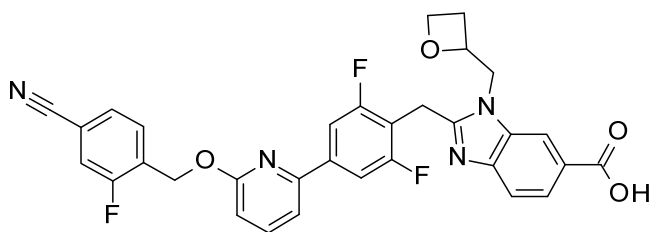
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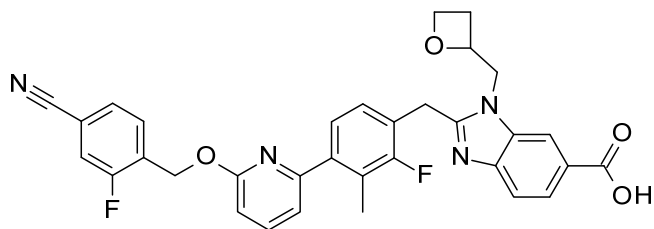
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;



; and



10

wherein

R^1 is H or F;

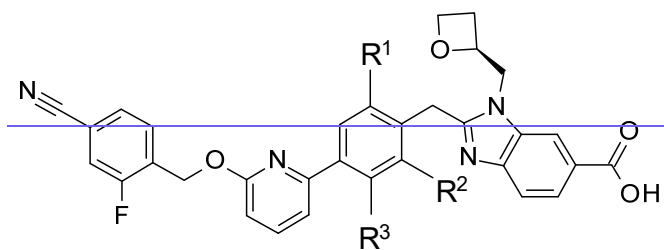
R^2 is H or F; and

5 R^3 is H or CH_3 ;

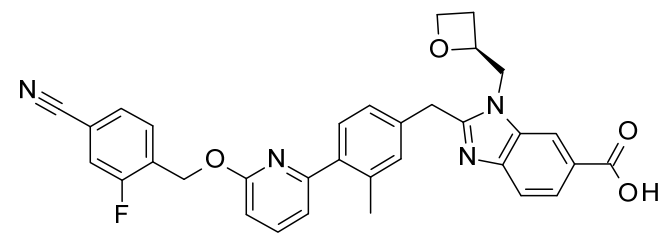
or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 selected from, wherein the compound is of
the formula:

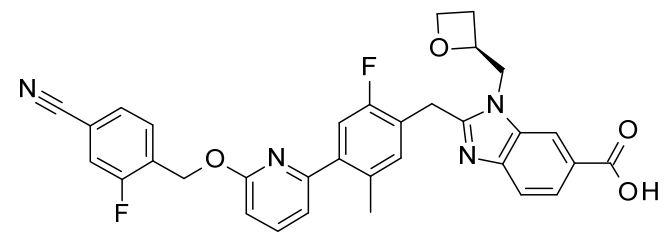
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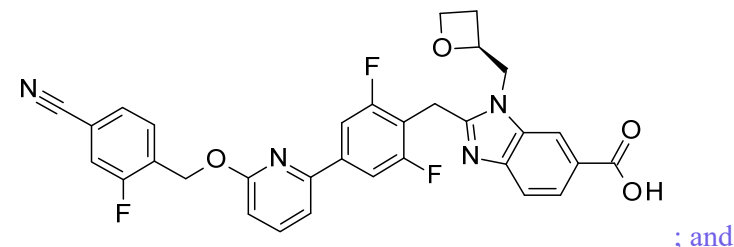
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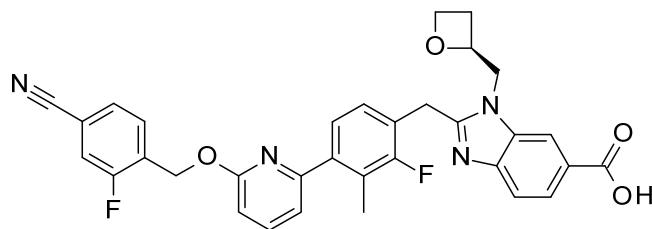
;



;



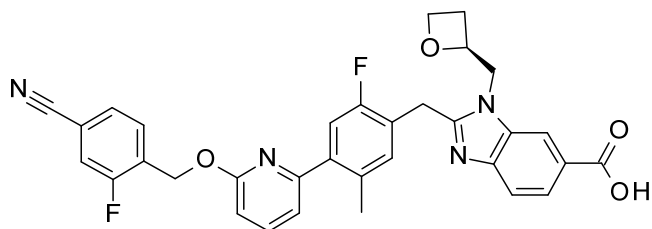
; and



or a pharmaceutically acceptable salt thereof.

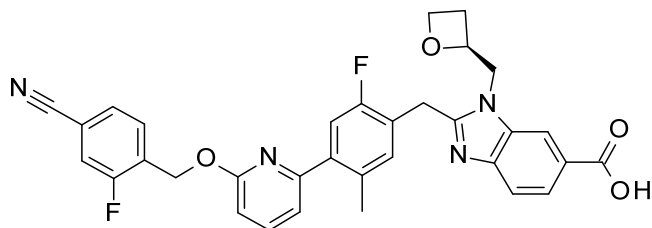
- 5 ~~3.~~ The compound according to claim 1 or claim 2, wherein R^2 is H and R^3 is CH_3 , or a pharmaceutically acceptable salt thereof.

~~4.3.~~ The compound according to claim ~~3~~12, wherein the compound is:



- 10 or a pharmaceutically acceptable salt thereof.

~~5.4.~~ The compound according to claim ~~43~~43, which is the *tert*-butylamine salt of:



- 15 ~~6.~~ The compound according to claim 1 or claim 2, wherein R^1 is F and R^3 is H, or a pharmaceutically acceptable salt thereof.

~~7.5.~~ A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~46~~ and at least one pharmaceutically acceptable carrier, diluent, or excipient.

5 ~~8. — A method of treating type II diabetes mellitus in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.~~

10 ~~9. — A method of lowering blood glucose levels in a mammal comprising administering an effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.~~

15 ~~10. — A method of treating hyperglycemia in a mammal comprising administering to the mammal an effective amount of a compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof.~~

~~11. — The method according to any one of claims 8 to 10 wherein the compound is administered orally.~~

20 ~~12.6.~~ A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~46~~ for use in therapy.

~~13.7.~~ A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~64~~ for use in the treatment of type II diabetes mellitus.

25 ~~14.8.~~ A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~46~~ for use in lowering blood glucose levels.

30 ~~15.9.~~ A compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~46~~ for use in the treatment of hyperglycemia.

~~16.10.~~ A compound, or a pharmaceutically acceptable salt thereof, for use according to any one of claims ~~6 to 9~~^{6 to 12 to 15}, wherein the compound is to be administered orally.

5 ~~17.11.~~ Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~46~~ in the manufacture of a medicament for the treatment of type II diabetes mellitus.

10 ~~18.12.~~ Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~64~~ in the manufacture of a medicament to lower blood glucose levels.

15 ~~19.13.~~ Use of a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to ~~64~~ in the manufacture of a medicament for the treatment of hyperglycemia.