

improved pharmacokinetic (PK) or pharmacodynamic (PD) properties compared to pramlintide, they may still show poor physical stability under certain conditions. In addition, the polypeptides generally do not show selectivity for the amylin receptor over the calcitonin receptor. US2014/0087995 relates to polypeptides comprising amylin agonist peptides with selectivity for the amylin receptor over the calcitonin receptor. However, there remains a need for amylin agonist peptide drug candidates with higher potency, lower developability risk, lower immunogenicity risk, improved chemical stability, and compatibility with formulation at a neutral pH.

There is a need for compounds (e.g., peptides) that show selectivity for agonism of the amylin receptor over the calcitonin receptor. In addition, the need exists for amylin receptor agonists with extended time of action and preserved potency. Therapeutically desirable compounds would agonize the amylin receptor and provide one or more advantageous properties such as lowering any of the following: food intake, body weight, blood glucose levels, HbA1c, triglycerides, and/or insulin levels. In addition, therapeutically desirable compounds may have one or more additional advantageous properties such as extended time of action with preserved or improved potency in agonizing the amylin receptor, a low risk of immunogenic response, and/or a low risk of fibrillation.

Further, combination of an amylin receptor agonist of the present disclosure, optionally combined with an incretin or incretin analog, is desired to provide treatment for diabetes, obesity, NASH, and/or dyslipidemia. Such combination will also preferably be more effective than either molecule alone. For example, such treatment with such combination may allow for use of lower doses of either or both molecules as compared to each molecule alone, potentially leading to lower side effects (or a shorter duration of one or the other therapy) while maintaining efficacy. It is believed that the novel combination(s) provided herein will be effective treatments for diabetes, obesity, NASH, and/or dyslipidemia.

SUMMARY

In an aspect of the present disclosure, there is provided a compound comprising:

Xaa₁-C-Xaa₃-TATCAT- Xaa₁₀- Xaa₁₁-Xaa₁₂-AE-Xaa₁₅-LVRSS-Xaa₂₁-Xaa₂₂-FGP-Xaa₂₆-LPPTVEGSNTY (SEQ ID NO:14), wherein
Xaa₁ is K or γE;

Xaa₃ is E, N, or G;

Xaa₁₀ is G or Q;

Xaa₁₁ is Orn or K;

Xaa₁₂ is L or α MeL;

5 Xaa₁₅ is α MeF or F;

Xaa₂₁ is N or H;

Xaa₂₂ is NMeD, NMeN, or N; and

Xaa₂₆ is I or K,

or a pharmaceutically acceptable salt thereof.

10 In another aspect of the present disclosure, there is provided a compound consisting of SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound consisting of SEQ ID NO:4 or a pharmaceutically acceptable salt thereof.

15 In another aspect of the present disclosure, there is provided a compound consisting of SEQ ID NO:6, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound consisting of SEQ ID NO:8 or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.

20 In a further aspect of the present disclosure, there is provided a compound comprising SEQ ID NO:4 or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound comprising SEQ ID NO:6, or a pharmaceutically acceptable salt thereof.

25 In a further aspect of the present disclosure, there is provided a compound comprising SEQ ID NO:8 or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

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

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

5 In a further aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein for use in the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

10 In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

15 In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

DESCRIPTION

20 Accordingly, the present disclosure provides a method of treating diabetes, obesity, NASH, and/or dyslipidemia, comprising administering to a patient in need of such treatment an effective amount of an amylin receptor agonist of the present invention and an effective amount of an additional agent.

Claims

1. A compound comprising:

Xaa₁-C-Xaa₃-TATCAT- Xaa₁₀- Xaa₁₁-Xaa₁₂-AE-Xaa₁₅-LVRSS-Xaa₂₁-Xaa₂₂-
FGP-Xaa₂₆-LPPTTEVGSNTY (SEQ ID NO:14), wherein

5 Xaa₁ is K or γ E;

Xaa₃ is E, N, or G;

Xaa₁₀ is G or Q;

Xaa₁₁ is Orn or K;

Xaa₁₂ is L or α MeL;

10 Xaa₁₅ is α MeF or F;

Xaa₂₁ is N or H;

Xaa₂₂ is NMeD, NMeN, or N; and

Xaa₂₆ is I or K,

or a pharmaceutically acceptable salt thereof.

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2. The compound of Claim 1, wherein

Xaa₁ is γ E;

Xaa₃ is N;

Xaa₁₀ is G;

20 Xaa₁₁ is Orn;

Xaa₁₂ is L;

Xaa₁₅ is α MeF;

Xaa₂₁ is N;

Xaa₂₂ is NMeN; and

25 Xaa₂₆ is K (SEQ ID NO:22),

or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1, wherein

Xaa₁ is γ E;

30 Xaa₃ is N;

Xaa₁₀ is G;

Xaa₁₁ is Orn;

Xaa₁₂ is L;

Xaa₁₅ is αMeF;

Xaa₂₁ is N;

Xaa₂₂ is NMeD; and

5 Xaa₂₆ is K (SEQ ID NO:23),
or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 2 or 3, wherein the lysine at Xaa₂₆ is attached to a fatty acid linker moiety according to the formula: (γE)₂-CO-(CH₂)₁₈-CO₂H.

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5. The compound of Claim 1, wherein

Xaa₁ is K;

Xaa₃ is E;

Xaa₁₀ is G;

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Xaa₁₁ is Orn;

Xaa₁₂ is L;

Xaa₁₅ is αMeF;

Xaa₂₁ is N;

Xaa₂₂ is NMeD; and

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Xaa₂₆ is I (SEQ ID NO:24),
or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 1, wherein

Xaa₁ is K;

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Xaa₃ is E;

Xaa₁₀ is G;

Xaa₁₁ is Orn;

Xaa₁₂ is αMeL;

Xaa₁₅ is F;

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Xaa₂₁ is H;

Xaa₂₂ is N; and

Xaa₂₆ is I (SEQ ID NO:25),

or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 5 or 6, wherein the lysine at Xaa₁ is attached to a fatty acid linker moiety according to the formula: (γE)₂-CO-(CH₂)₁₈-CO₂H.

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8. The compound of any of the preceding claims, wherein there is a thioacetal bridge between the cysteines at position 2 and 7.

9. The compound of Claim 1, wherein the compound is selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, and SEQ ID NO:13, or a pharmaceutical salt thereof.

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10. A compound consisting of SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.

11. A compound consisting of SEQ ID NO:4 or a pharmaceutically acceptable salt thereof.

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12. A compound consisting of SEQ ID NO:6, or a pharmaceutically acceptable salt thereof.

13. A compound consisting of SEQ ID NO:8, or a pharmaceutically acceptable salt thereof.

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- ~~14. A method of treating Type 2 diabetes in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~

15. ~~A method of treating obesity in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
- 5 16. ~~A method of treating dyslipidemia in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
17. ~~A method of treating NASH in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
- 10 18. ~~A method of lowering food intake in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
- 15 19. ~~A method of lowering body weight in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
20. ~~A method of lowering blood glucose in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
21. ~~A method of lowering triglycerides in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any of Claims 1-13, or a pharmaceutically acceptable salt thereof.~~
- 20 22. ~~The method of any one of Claims 13-21, wherein the compound is administered once weekly.~~
- 25 14. A compound comprising SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.
15. A compound comprising SEQ ID NO:4, or a pharmaceutically acceptable salt thereof.
- 30 16. A compound comprising SEQ ID NO:6, or a pharmaceutically acceptable salt thereof.

17. A compound comprising SEQ ID NO:8, or a pharmaceutically acceptable salt thereof.

5 23.18. A pharmaceutical composition comprising a compound according to any one of Claims 1-~~17~~13, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

10 ~~24. A method of treating a condition in a patient in need thereof, selected from the group consisting of: clinical or pre-clinical diabetes, obesity, NASH, and dyslipidemia, comprising administering to the patient an effective amount of the compound of Claim 1 in combination with an effective amount of an incretin or incretin analog.~~

15 ~~25. The method of treatment according to Claim 24 wherein the compound is selected from a group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, and SEQ ID NO:8, or a pharmaceutical salt thereof, and wherein the incretin or incretin analog is SEQ ID NO:21.~~

26.19. The A compound of any one of Claims 1-~~17~~13, or a pharmaceutically acceptable salt thereof, for use in therapy.

20 27.20. The A pharmaceutical composition of Claim 23-18 for use in therapy.

28.21. The A compound of any one of Claims 1-~~17~~13, or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

25 29.22. The A pharmaceutical composition of Claim 23-18 for use in the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

30 30.23. Use of ~~the a~~ compound of any one of Claims 1-~~17~~13 in the manufacture of a medicament for the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.

24. Use of a pharmaceutical composition of claim 18 in the manufacture of a medicament for the treatment of a condition selected from the group consisting of Type 2 diabetes, obesity, dyslipidemia, and NASH.