

PROCESS FOR PREPARING A GIP/GLP1 DUAL AGONIST

The present invention provides processes and intermediates for making a GIP/GLP1 dual agonist peptide, tirzepatide, or a pharmaceutically acceptable salt thereof.

Diabetes mellitus is a chronic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. In type 2 diabetes mellitus (“T2D”), the combined effects of impaired insulin secretion and insulin resistance are associated with elevated blood glucose levels. The GIP/GLP1 dual agonist, tirzepatide is described and claimed in United States patent 9474780 (“780 Patent”). Tirzepatide can be useful in the treatment of T2D.

US9474780 generally describes peptides and a method for making a GIP/GLP1 dual agonist.

There is a need for processes and intermediates to enable improved technology for production of tirzepatide having a combination of advantages including commercially desired purity. Similarly, there is a need for efficient and environmentally “green” processes, including stable intermediates to provide tirzepatide with fewer purification steps. Improved technology is also needed to provide tirzepatide manufacturing processes producing minimal waste streams for both environmental and operator enhanced safety. The preparation of large-scale, pharmaceutically-elegant tirzepatide presents a number of technical challenges that may affect the overall yield and purity. There is a need for processes to avoid the use of transition metals and/or harsh reaction conditions that are incompatible with peptide synthesis.

Summary

In an aspect of the present disclosure, there is provided a compound of SEQ ID NO:17, or a pharmaceutically acceptable salt thereof.

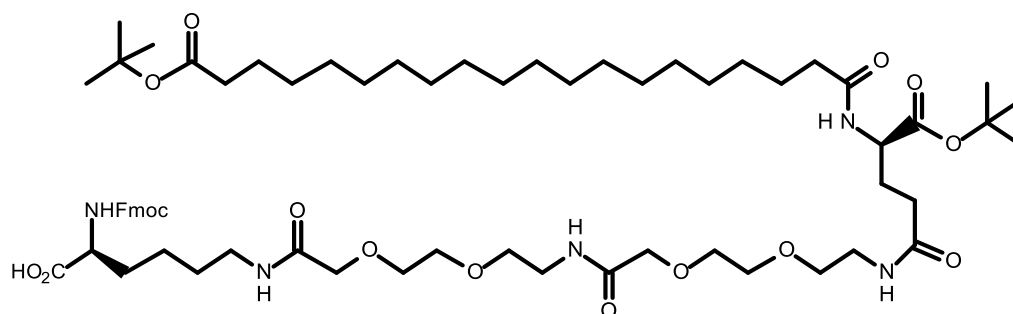
In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:11, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of SEQ ID NO:22, or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:21, or a pharmaceutically acceptable salt thereof.

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

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



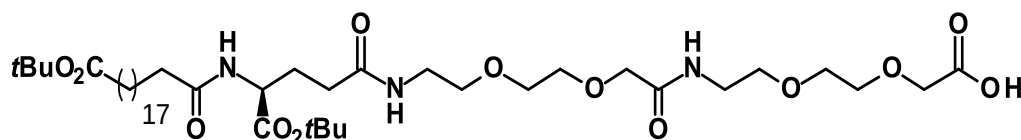
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or a pharmaceutically acceptable salt thereof.

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

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

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or a pharmaceutically acceptable salt thereof.

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

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In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:7, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of SEQ ID NO:14, or a pharmaceutically acceptable salt thereof.

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In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:17, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of SEQ ID NO:33, or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:32, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of SEQ ID NO:34, or a pharmaceutically acceptable salt thereof.

5 In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:35, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of SEQ ID NO:36, or a pharmaceutically acceptable salt thereof.

10 In another aspect of the present disclosure, there is provided a compound of SEQ ID NO:38, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a compound of SEQ ID NO:39, or a pharmaceutically acceptable salt thereof.

15 In another aspect of the present disclosure, there is provided a process to prepare tirzepatide or a pharmaceutically acceptable salt thereof, comprising nanofiltration of an intermediate tirzepatide.

In a further aspect of the present disclosure, there is provided a process to prepare tirzepatide or a pharmaceutically acceptable salt thereof, comprising deprotecting a compound of SEQ ID NO:22, or a pharmaceutically acceptable salt thereof.

20 In another aspect of the present disclosure, there is provided a process to selectively acylate a lysine amino acid in a peptide comprising coupling a resin bound peptide-Lysine-NH₂ with t-butyl-eicosanedioyl- Glu-(O-tert-butyl)- (8-amino-3,6-dioxaoctanoic acid) –(8-amino-3,6-dioxaoctanoic acid)-OH.

In a further aspect of the present disclosure, there is provided a process to convert a depsi peptide isomer to the desired peptide comprising:

- 25 a. adjusting the depsi peptide isomer to a pH between about pH 7 to about pH 10; and
- b. incubating the depsi peptide isomer at pH 7 to pH 10 for at least one hour.

30 In another aspect of the present disclosure, there is provided a process to desulfurize an incretin, or pharmaceutically acceptable salt thereof, comprising contacting the incretin with a radical initiator.

Description

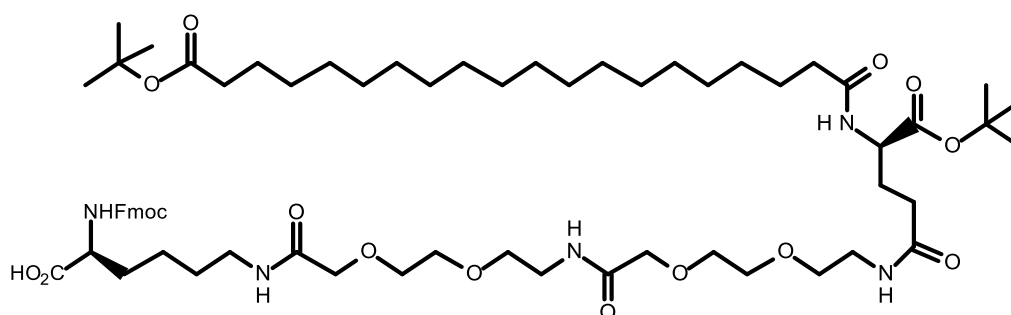
The present invention seeks to meet these needs by providing novel intermediates and processes useful in the manufacture of tirzepatide (SEQ ID NO:1), or a pharmaceutically acceptable salt thereof. The improved tirzepatide manufacturing processes of the present invention provide intermediates and process reactions embodying a combination of advances, including an efficient route having fewer steps, while at the same time maintaining high quality and purity. Importantly, the improved processes and intermediates decrease resource intensity and minimize waste streams.

5 The improved processes described herein provide various embodiments of intermediates useful for production of tirzepatide.

10 The present invention provides a compound of SEQ ID NO:17, or a pharmaceutically acceptable salt thereof. The present invention provides a compound of

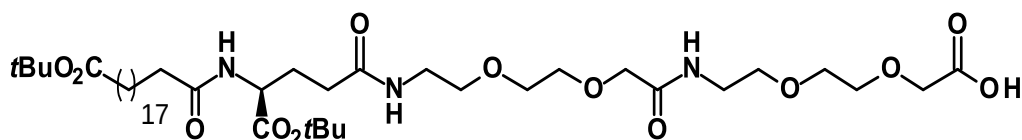
WE CLAIM:

1. A compound of SEQ ID NO:17, or a pharmaceutically acceptable salt thereof.
2. A compound of SEQ ID NO:11, or a pharmaceutically acceptable salt thereof.
- 5 3. A compound of SEQ ID NO:22, or a pharmaceutically acceptable salt thereof.
4. A compound of SEQ ID NO:21, or a pharmaceutically acceptable salt thereof.
5. A compound of SEQ ID NO:20, or a pharmaceutically acceptable salt thereof.
6. A compound of the formula:



- 10 or a pharmaceutically acceptable salt thereof.

7. A compound of SEQ ID NO:2, or a pharmaceutically acceptable salt thereof.
8. A compound of the formula:



- or a pharmaceutically acceptable salt thereof.

- 15 9. A compound of SEQ ID NO:4, or a pharmaceutically acceptable salt thereof
10. A compound of SEQ ID NO:7 or a pharmaceutically acceptable salt thereof.
11. A compound of SEQ ID NO:14, or a pharmaceutically acceptable salt thereof.
12. A compound of SEQ ID NO:17, or a pharmaceutically acceptable salt thereof.
13. A compound of SEQ ID NO:33, or a pharmaceutically acceptable salt thereof.
- 20 14. A compound of SEQ ID NO:32, or a pharmaceutically acceptable salt thereof.
15. A compound of SEQ ID NO:34, or a pharmaceutically acceptable salt thereof.
16. A compound of SEQ ID NO:35, or a pharmaceutically acceptable salt thereof.
17. A compound of SEQ ID NO:36, or a pharmaceutically acceptable salt thereof.
18. A compound of SEQ ID NO:38, or a pharmaceutically acceptable salt thereof.
- 25 19. A compound of SEQ ID NO:39, or a pharmaceutically acceptable salt thereof.

20. A process to prepare tirzepatide or a pharmaceutically acceptable salt thereof, comprising nanofiltration of an intermediate tirzepatide.
- 5 21. A process as claimed by Claim 20 wherein the intermediate tirzepatide is SEQ ID NO:27.
22. A process as claimed by Claim 20 wherein the intermediate tirzepatide is SEQ ID NO:29.
23. A process as claimed by Claim 20 wherein the nanofiltration process comprises diafiltration.
- 10 24. A process as claimed by Claim 20 wherein the process comprises a DMF diafiltration.
25. A process to prepare tirzepatide or a pharmaceutically acceptable salt thereof, comprising deprotecting a compound of SEQ ID NO:22, or a pharmaceutically acceptable salt thereof.
- 15 26. A process as claimed by Claim 25 wherein the deprotection solution comprises dithiothreitol, triisopropylsilane, and trifluoroacetic acid.
27. A process to selectively acylate a lysine amino acid in a peptide comprising coupling a resin bound peptide-Lysine-NH₂ with t-butyl-eicosanedioyl- Glu-(O-tert-butyl)- (8-amino-3,6-aioxaoctanoic acid) –(8-amino-3,6-dioxaoctanoic acid)-OH.
- 20 28. A process as claimed by Claim 27 wherein the peptide is an incretin.
29. A process as claimed by any one of Claims 27 or 28 wherein the resin bound peptide-Lysine-NH₂ is SEQ ID NO:24, or a pharmaceutically acceptable salt thereof.
- 25 30. A process to convert a depsi peptide isomer to the desired peptide comprising:
- a. adjusting the depsi peptide isomer to a pH between about pH 7 to about pH 10; and
 - b. incubating the depsi peptide isomer at pH 7 to pH 10 for at least one hour.
- 30 31. A process as claimed by Claim 30 wherein the depsi peptide isomer is adjusted to about pH 8.5 to about pH 9.5.
32. A process as claimed by Claim 30 wherein the peptide is an incretin.

33. A process as claimed by Claim 30 wherein the depsipeptide isomer is recovered from a process waste stream.
34. A process as claimed by Claim 30 wherein the depsipeptide isomer is SEQ ID NO:40, or a pharmaceutically acceptable salt thereof.
- 5 35. A process to desulfurize an incretin, or pharmaceutically acceptable salt thereof, comprising contacting the incretin with a radical initiator.
36. A process as claimed by Claim 35, wherein the radical initiation is a water soluble radical initiator.
- 10 37. A process as claimed by Claim 35 wherein the radical initiator is an azo initiator.
38. A process as claimed by Claim 35 wherein the radical initiator is selected from the group consisting of 2,2'-azobis[2-(2-imidazolin-2-yl)propane] Dihydrochloride and 2,2'-Azobis(2-methylpropionamidine)dihydrochloride.
- 15 39. A process as claimed by Claim 35 wherein the incretin is SEQ ID NO:35, or a pharmaceutically acceptable salt thereof.
40. A process as claimed by Claim 35 wherein the desulfurization process provides a peptide of SEQ ID NO:1.