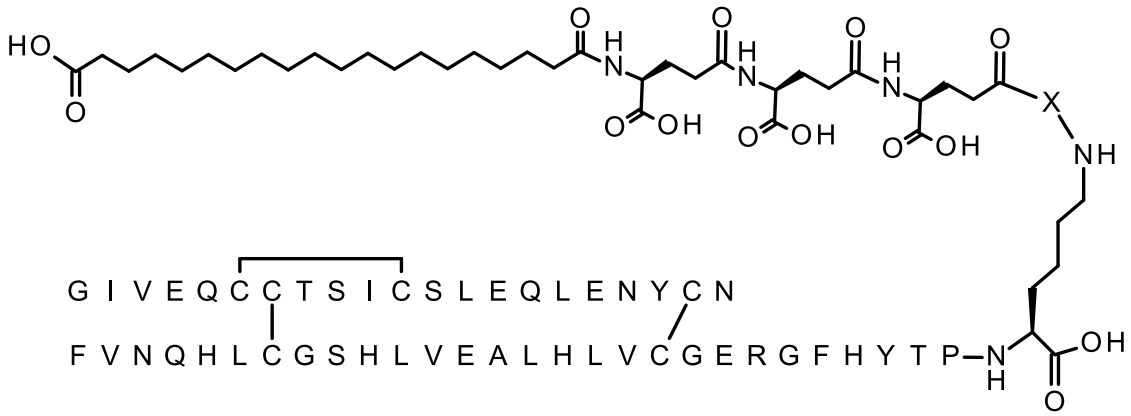
contribute to extended shelf-life stability and/or stability in a concentrated formulation, which would allow for the use in multi-dose devices.

The need exists for alternative treatments for diabetes and/or hyperglycemia in patients. Some acylated insulin compounds are known, see, for example, U.S. Patent No. 7,615,532, U.S. Patent No. 10,400,021, U.S. 9,045,560, U.S. 9,018,161 but there remains a need for additional alternative treatments.

Summary

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



wherein X is selected from the group consisting of -Lys-Gly-, -Lys-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-, and -εLys-Gly-; or a pharmaceutically acceptable salt thereof.

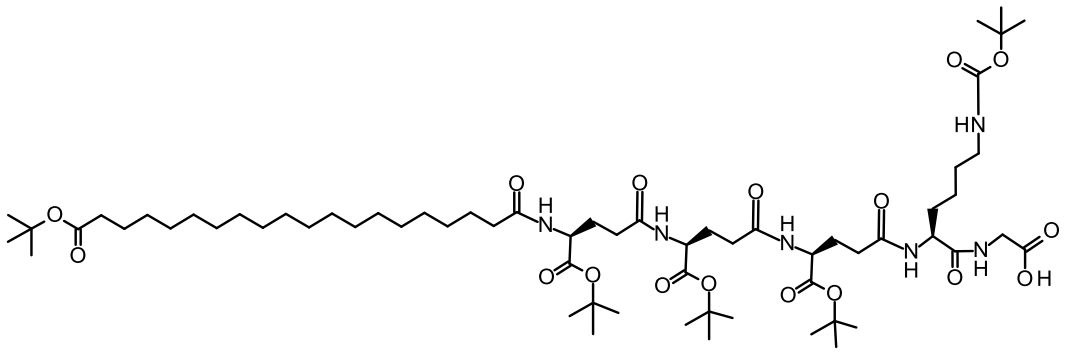
In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

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

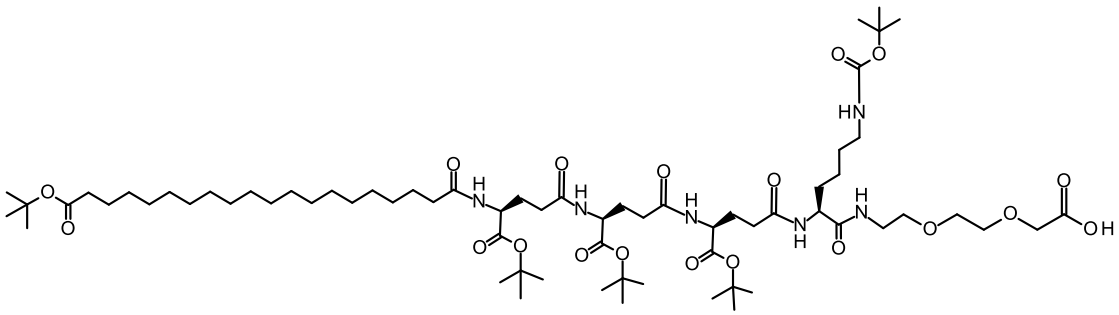
In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in the treatment of Type I and /or Type II diabetes.

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

In another aspect of the present disclosure, there is provided a compound selected from the group consisting of:

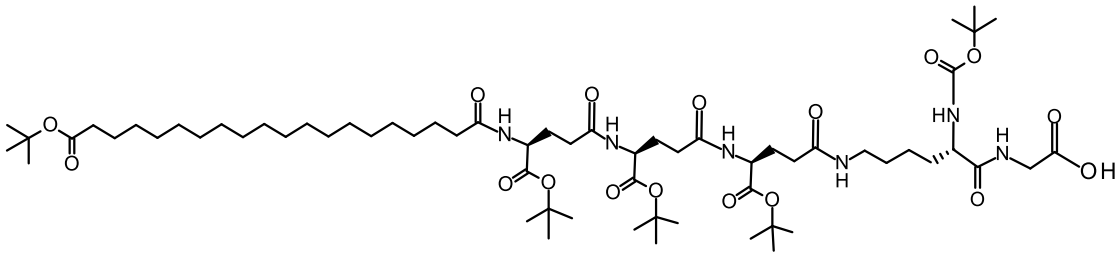


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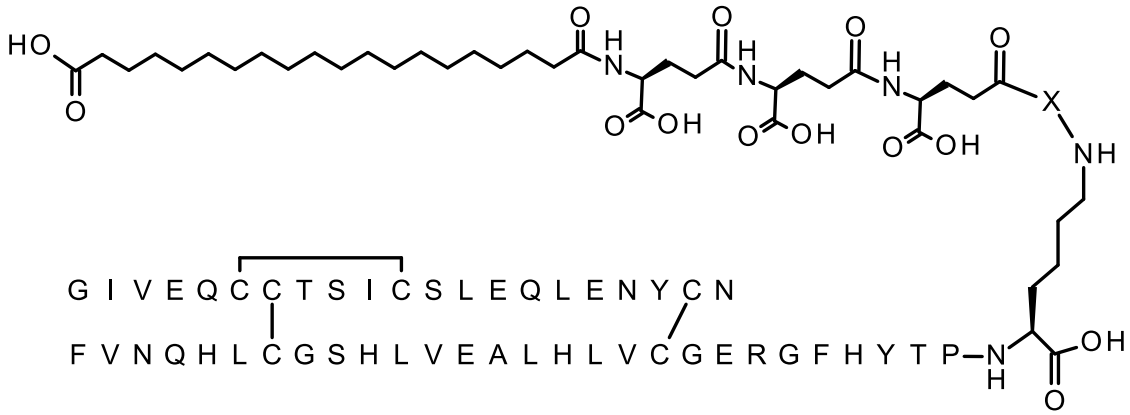
and



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, or a pharmaceutically acceptable salt thereof.

In a further aspect of the present disclosure, there is provided a process for preparing a compound of Formula I,



wherein X is selected from the group consisting of -Lys-Gly-, -Lys-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-, and -εLys-Gly-; or a pharmaceutically acceptable salt thereof, using a compound selected from the group disclosed herein.

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

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

In another aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating Type I and/or Type II diabetes.

In a further aspect of the present disclosure, there is provided a use of the pharmaceutical composition disclosed herein in the manufacture of a medicament for treating hyperglycemia.

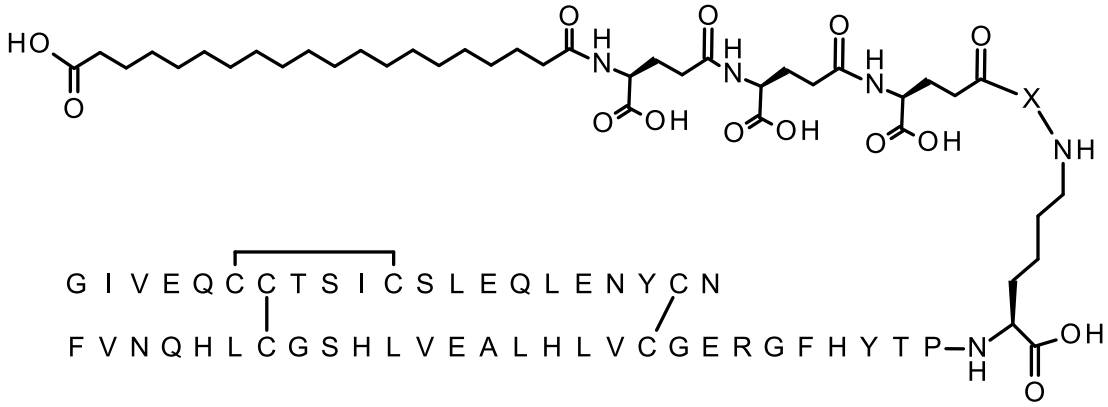
In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein for use in therapy.

Description

The present invention provides extended time action acylated insulin compounds that are useful in treating diabetes, reducing hemoglobin A1c, and/or reducing blood glucose levels in patients in need thereof. Compounds of the present invention have any of the following desirable characteristics: a slower clearance rate than known acylated

insulins (e.g. insulin degludec), enhanced bioavailability, a more stable pharmacokinetic profile in humans over time, and/or an increased duration of action of the compound *in vivo*. In addition, compounds of the present invention exhibit a low chemical degradation rate, which indicates that they have increased chemical stability, and/or could achieve a shelf-life longer than known acylated insulins.

The invention provides a compound of Formula I:

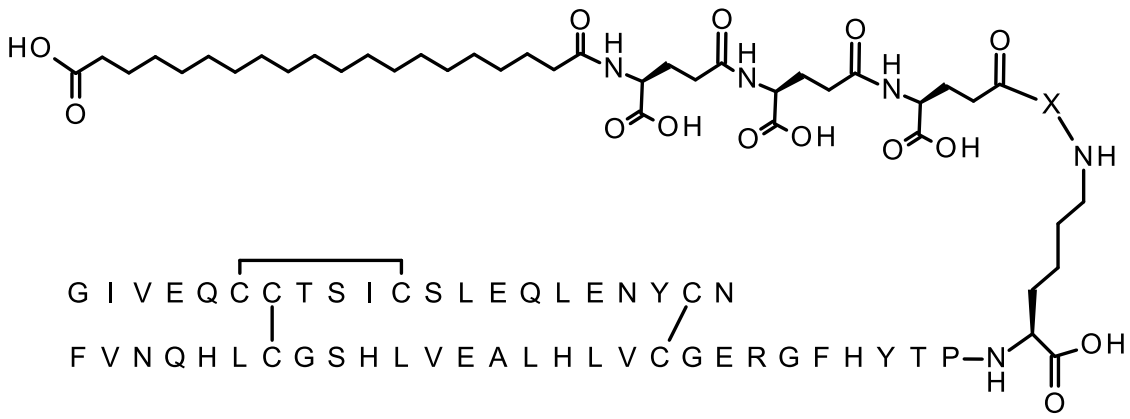


wherein X is selected from the group consisting of -Lys-Gly-, -Lys-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-, and -εLys-Gly-; or a pharmaceutically acceptable salt thereof.

The compound of Formula I is therefore a modified human insulin consisting of: an A chain SEQ ID NO:1, wherein the native tyrosine amino acid residue at position A14 is mutated to a glutamic amino acid residue, and a B chain sequence of SEQ ID NO:2, wherein the native tyrosine amino acid residue at position B16 is mutated to a histidine

WE CLAIM:

1. A compound of Formula I:



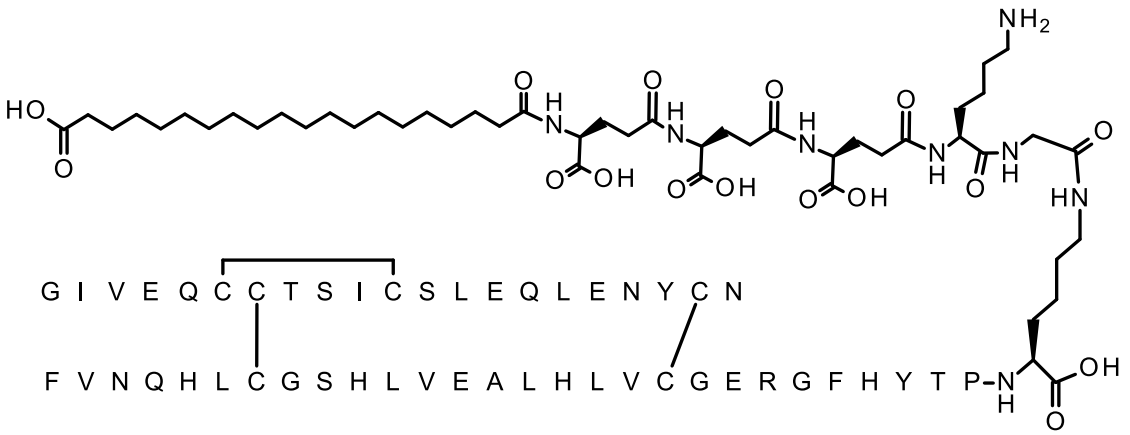
wherein X is selected from the group consisting of -Lys-Gly-, -Lys-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-, and -εLys-Gly-; or a pharmaceutically acceptable salt thereof.

2. The ~~A~~ compound of claim 1 wherein X is -Lys-Gly-, or a pharmaceutically acceptable salt thereof.

3. The ~~A~~ compound of claim 1 wherein X is -Lys-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-, or a pharmaceutically acceptable salt thereof.

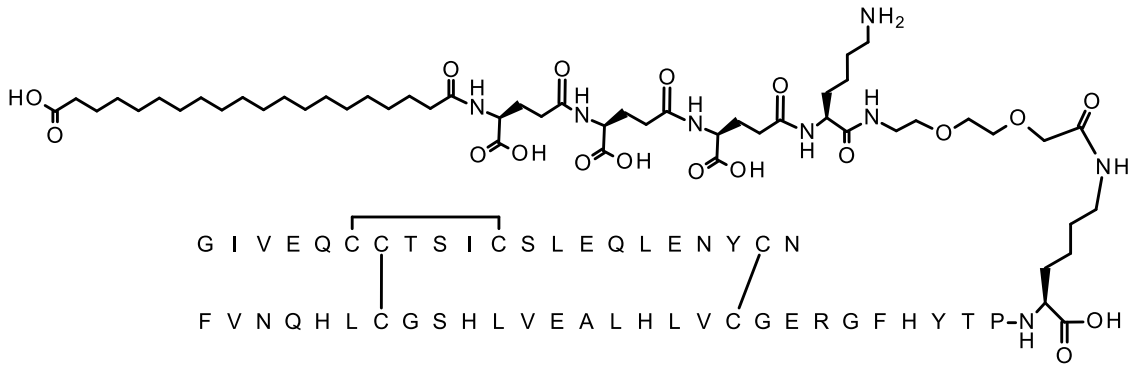
4. The ~~A~~ compound of claim 1 wherein X is -εLys-Gly-, or a pharmaceutically acceptable salt thereof.

5. The ~~A~~ compound of claim 1 that is



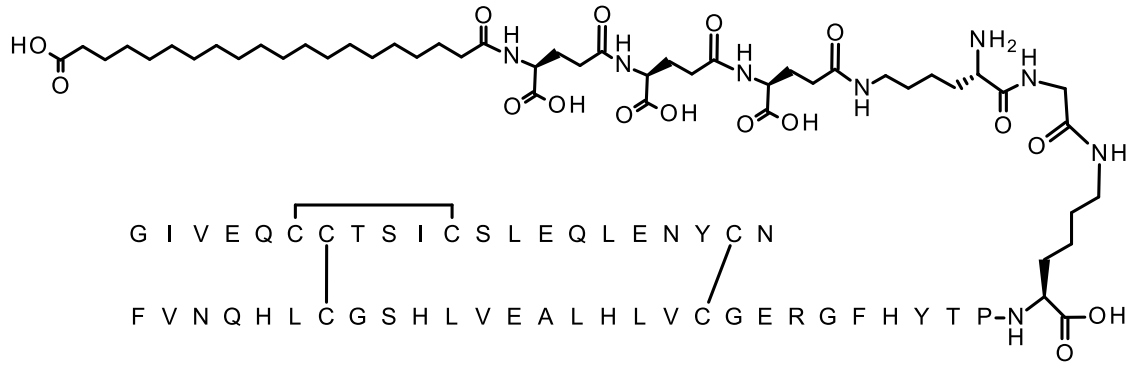
, or a pharmaceutically acceptable salt thereof.

6. The ~~A~~ compound of claim 1 that is



,or a pharmaceutically acceptable salt thereof.

7. The~~A~~ compound of claim 1 that is



, or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising the~~a~~ compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

~~9. A method of treating Type I and /or Type II diabetes in a patient comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 8.~~

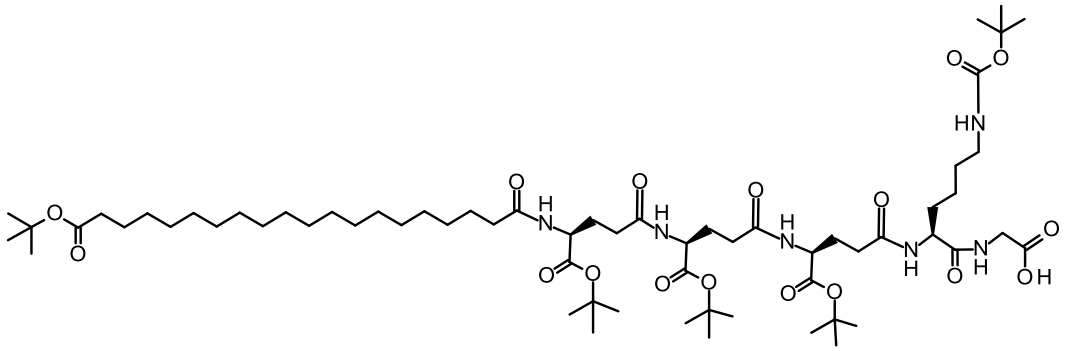
~~10. A method of treating hyperglycemia in a patient comprising administering to a patient in need thereof an effective amount of a compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 8.~~

911. TheA compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use in therapy.

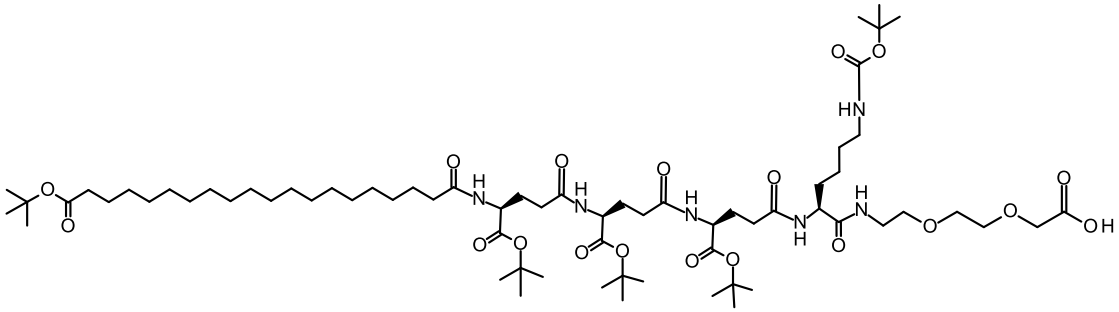
1012. TheA compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the treatment of Type I and /or Type II diabetes.

1113. TheA compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use in the treatment of hyperglycemia.

1214. A compound selected from the group consisting of:

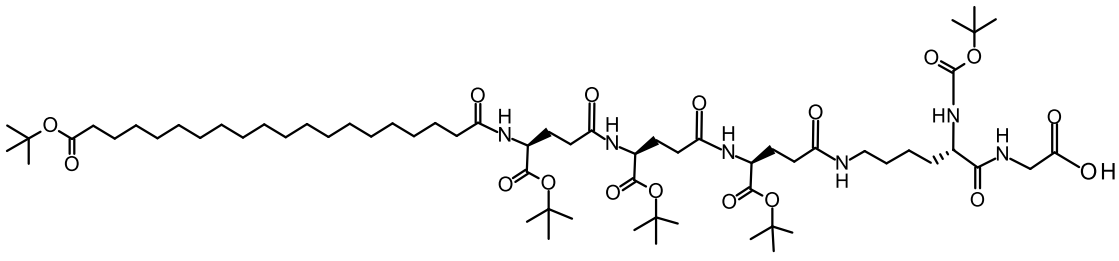


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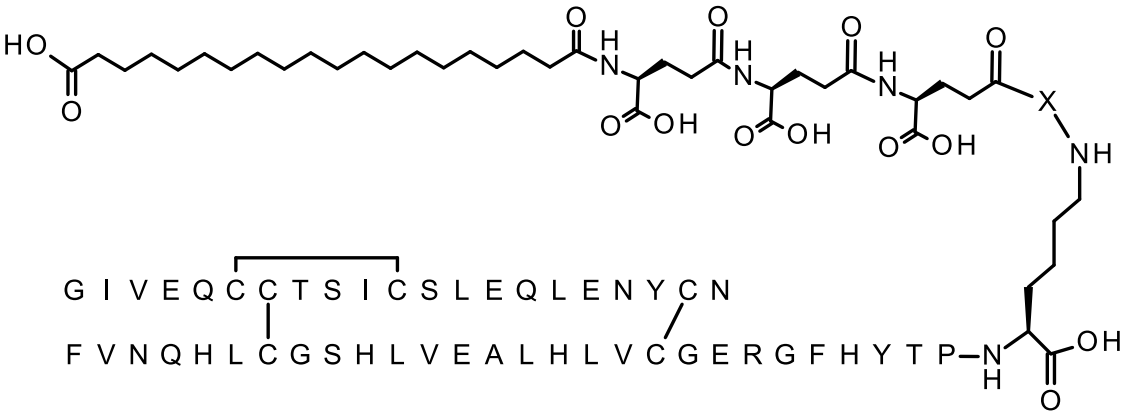
and



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, or a pharmaceutically acceptable salt thereof.

1315. A process for preparing a compound of Formula I,



wherein X is selected from the group consisting of -Lys-Gly-, -Lys-(2-[2-(2-aminoethoxy)ethoxy]acetic acid)-, and -εLys-Gly-; or a pharmaceutically acceptable salt thereof, using a compound selected from the group according to claim 12~~14~~.

14~~16~~. Use~~The use~~ of the~~a~~ compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of diabetes.

15~~17~~. Use~~The use~~ of the~~a~~ compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of hyperglycemia.

16. Use of the pharmaceutical composition of claim 8 in the manufacture of a medicament for treating Type I and/or Type II diabetes.

17. Use of the pharmaceutical composition of claim 8 in the manufacture of a medicament for treating hyperglycemia.

18. The pharmaceutical composition of claim 8 for use in therapy.