Although stabilized analogues of native glucagon in liquid solution are desirable, no stable liquid formulation of any such glucagon analogue is commercially available.

On that basis, it is clear that there is a strong need for glucagon analogues that, in addition to having satisfactorily high activity at the glucagon receptor, are sufficiently soluble (especially at physiological pH, where native glucagon is not) and stable (both physically and chemically) in aqueous liquid medium. These analogues (i) may advantageously be provided in the form of a ready-to-use liquid pharmaceutical formulation adapted for immediate injection, and (ii) may be able to be stored (including carried by the subject or patient in question under ambient conditions) for a satisfactorily long period of time prior to use.

SUMMARY ~~OF THE INVENTION~~

In some examples~~embodiments~~, the present disclosure~~invention~~ provides a compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2; and
Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;
X3 is selected from His, Pro, Dab(Ac), Dap(Ac) and Gln(Me);
X4 is DAla;
X9 is Glu;

X10 is selected from Val, Leu, N-Me-Tyr and N-Me-DTyr;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;
X17 is selected from Ala and Ser;
X20 is selected from Glu and Lys;
X21 is selected from Glu, Lys and Ser;
X24 is selected from Lys, Ser, Glu and Ala;
X28 is selected from Ser, Glu, and Lys, or is absent;
X29 is selected from Ser and Ala, or is absent;
with the proviso that Z is not selected from:
HSQGTFTSDYSKYLDSARAEDFVKWLEST; and
HSQGTFTSDYSKYLESRRAKEFVEWLEST.

In one aspect, the present invention provides a compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2; and

Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at sequence positions selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;
X3 is selected from His, Pro, Dab(Ac), Dap(Ac) and Gln(Me);
X4 is DAla;
X9 is Glu;
X10 is selected from Val, Leu, N-Me-Tyr and N-Me-DTyr;
X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;

X17 is selected from Ala and Ser;

X20 is selected from Glu and Lys;

X21 is selected from Glu, Lys and Ser;

X24 is selected from Lys, Ser, Glu and Ala;

X28 is selected from Ser and Lys, and Glu, or is absent;

X29 is selected from Ser and Ala, or is absent;with the proviso that Z is not selected from:

HSQGTFTSDYSKYLDSARAEDFVKWLEST; and

HSQGTFTSDYSKYLESRRAKEFVEWLEST;

wherein the compound has glucagon agonist activity and improved solubility and/or stability as compared to native human glucagon.

In some examples~~embodiments~~, the present disclosure~~invention~~ provides a compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2; and

Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at amino acid sequence positions selected from 2, 3, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;

X3 is selected from His and Pro,;

X9 is Glu;

X10 is selected from N-Me-Tyr and N-Me-DTyr;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;
X17 is selected from Ala and Ser;
X20 is selected from Glu and Lys;
X21 is selected from Glu, Lys and Ser;
X24 is selected from Lys, Ser, Glu and Ala;
X28 is selected from Ser and Lys, or is absent;
X29 is selected from Ser and Ala, or is absent;
with the proviso that Z is not selected from:
HSQGTFTSDYSKYLDSARAEDFVKWLEST; and
HSQGTFTSDYSKYLESRRAKEFVEWLEST.

In one aspect, the present invention provides a compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2; and

Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at sequence positions (designated as X) selected from 2, 3, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;
X3 is selected from His and Pro;
X9 is Glu;
X10 is selected from N-Me-Tyr and N-Me-DTyr;
X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;

X17 is selected from Ala and Ser;

X20 is selected from Glu and Lys;

X21 is selected from Glu, Lys and Ser;

X24 is selected from Lys, Ser, Glu and Ala;

X28 is selected from Ser and Lys, or is absent;

X29 is selected from Ser and Ala, or is absent;

with the proviso that Z is not selected from:

HSQGTFTSDYSKYLDSARAEDFVKWLEST; and

HSQGTFTSDYSKYLESRRAKEFVEWLEST;

wherein the compound has glucagon agonist activity and improved solubility and/or stability as compared to native human glucagon.

In some ~~embodiments~~examples, the at least four amino acid substitutions or deletions at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I are as follows:

X2 is selected from Aib and Ala;

X3 is selected from His and Pro, Dab(Ac) , Dap(Ac) and Gln(Me);

X4 is DAla;

X9 is Glu;

X10 is selected from Val, Leu, N-Me-Tyr and N-Me-DTyr;

X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, Val, Phe, His and Arg;

X17 is selected from Ala and Ser;

X20 is selected from Glu and Lys;

X21 is selected from Glu, Lys and Ser;

X24 is selected from Lys, Ser, Glu and Ala;

X28 is selected from Ser, Glu, and Lys, or is absent;

X29 is selected from Ser and Ala, or is absent.

In some ~~embodiments~~examples, the at least four amino acid substitutions or deletions are at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 10, 15, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I, and are as follows:

X2 is Ala;
X3 is Dab(Ac), Dap(Ac) and Gln(Me);
X4 is DAla;
X10 is selected from Leu and Val;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, and Val;
X17 is Ala;
X20 is selected from Glu and Lys;
X21 is selected from Glu and Ser;
X24 is selected from Lys, Ser and Glu;
X28 is selected from Ser, Glu and Lys;
X29 is Ala, or is absent.

In some ~~embodiments~~examples, the at least four amino acid substitutions or deletions are at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I, and are as follows:

X2 is Ala;
X3 is Dab(Ac), Dap(Ac), Gln(Me) or His;
X4 is DAla;
X16 is selected from Aib, Lys, Glu;
X17 is Ala;
X20 is selected from Glu and Lys;
X21 is selected from Glu and Ser;
X24 is selected from Lys, Ser and Glu;
X28 is selected from Ser, Glu and Lys;

X29 is Ala, or is absent.

It will be understood that any individual molecule comprises at least 4 differences from the sequence of formula Ia, which may be any combination of at least 4 substitutions and deletions permitted within the definitions provided.

The peptide sequence Z may have a maximum of 4 substitutions and deletions (taken in combination), a maximum of 5 substitutions and deletions, a maximum of 6 substitutions and deletions, a maximum of 7 substitutions and deletions, a maximum of 8 substitutions and deletions, a maximum of 9 substitutions and deletions, a maximum of 10 substitutions and deletions, a maximum of 11 substitutions and deletions, a maximum of 12 substitutions and deletions, or a maximum of 13 substitutions and deletions compared to the amino acid sequence of Formula Ia.

For example, the compounds may have between 4 and 11 substitutions and deletions, between 6 and 11 substitutions and deletions, between 4 and 9 substitutions and deletions, or between 6 and 9 substitutions and deletions.

The compounds of the disclosure~~invention~~ have glucagon agonist activity.

The compounds of the disclosure~~invention~~ have improved solubility and/or stability as compared to native human glucagon.

Improved solubility may comprise or constitute improved solubility compared to native glucagon at pH 4 (e.g. in 100mM acetate buffer at pH 4), pH 5 (e.g. in 100mM acetate buffer at pH 5), pH 6 (e.g. in 100mM phosphate buffer at pH 6), pH 7 (e.g. in 100mM phosphate buffer at pH 7), and/or pH 7.5 (e.g. in 100mM phosphate buffer at pH 7.5). The determination may be performed under the conditions set out in Example 4. A solubility of $\geq$ 1 mg/ml may be desirable.

Improved stability may comprise or constitute improved physical stability and/or improved chemical stability as compared to native human glucagon.

Improved physical stability may comprise or constitute reduced tendency to aggregate, e.g. to form either soluble or insoluble aggregates, e.g. fibrils. Aggregation (e.g. fibril formation) may

be determined, for example, at a starting concentration of 1 mg/ml dissolved peptide at pH 7.5 and 40°C. Any appropriate time period may be used, e.g. 24 hours, 48 hours or 96 hours. Aggregation may be determined under the conditions set out in Example 5, with or without agitation.

Improved chemical stability may comprise or constitute a reduced tendency to peptide cleavage or degradation in aqueous buffer, typically in the absence of contaminating protease or peptidase activity. Stability may be determined, for example, at a starting concentration of 1 mg/ml dissolved peptide at pH 4.0 or 7.5 and 40°C. The assessment may comprise determining intact peptide remaining after incubation for a suitable time period. This may involve determining intact peptide purity as defined in Example 6. Incubation may be performed for any suitable time period, e.g. 1 day, 7 days or 14 days. Stability may be determined under the conditions set out in Example 6.

In one aspect, there is provided a nucleic acid construct encoding a peptide Z according to the present invention wherein said peptide is composed entirely of naturally occurring amino acids. In another aspect, there is provided an expression vector comprising a nucleic acid construct according to the present invention. In another aspect, there is provided a host cell comprising a nucleic acid construct according to the present invention or an expression vector according to the present invention. In a further aspect, there is provided a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt or solvate thereof, according to the present invention and a pharmaceutically acceptable carrier. In yet a further aspect, there is provided a compound or pharmaceutically acceptable salt or solvate thereof according to the present invention for use in a method of medical treatment. In another aspect, there is provided a compound or pharmaceutically acceptable salt or solvate thereof according to the present invention for use in the treatment of hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease. In yet another aspect, there is provided use of a compound or pharmaceutically acceptable salt or solvate thereof according to the present invention in the preparation of a medicament for the treatment of hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease.

Further ~~embodiments~~examples ~~of the present invention~~ include, but are not limited to:

a compound, or a pharmaceutically acceptable salt or solvate thereof, of the ~~invention~~disclosure for use in therapy (e.g. in the treatment of acute or chronic hypoglycaemia);

a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt or solvate thereof, of the ~~invention~~disclosure and a pharmaceutically acceptable carrier;

a method of treating a disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt or solvate thereof, of the ~~invention~~disclosure, or a pharmaceutical composition ~~of the invention~~as disclosed herein to the subject;

use of a compound, or a salt or solvate thereof, of the ~~invention~~disclosure, or a pharmaceutical composition of the ~~invention~~disclosure, in the manufacture of a medicament for use in therapy (e.g. *in treatment of acute or chronic hypoglycaemia*);

a nucleic acid construct (e.g., a DNA or RNA construct) encoding a compound (peptide) or a peptide Z of the ~~invention~~disclosure;

an expression vector comprising such a nucleic acid construct of the ~~invention~~disclosure; and

a host cell comprising such a nucleic acid construct or expression vector of the ~~invention~~disclosure.

In some ~~embodiments~~examples, a disease or condition to be treated with a compound or method of the ~~invention~~disclosure is selected from the group consisting of: hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease. In particular ~~embodiments~~examples, the disease or condition is hypoglycaemia. In certain examples~~embodiments~~, the hypoglycaemia is selected from the group consisting of: diabetic hypoglycaemia, acute insulin-induced hypoglycaemia, non-diabetic hypoglycaemia, reactive hypoglycaemia, fasting hypoglycaemia, drug-induced hypoglycaemia, alcohol-induced hypoglycaemia, gastric bypass-induced hypoglycaemia, and hypoglycaemia occurring during pregnancy.

In some ~~embodiments~~examples, the ~~invention~~disclosure includes a compound or pharmaceutically acceptable salt or solvate thereof for the treatment of hypoglycaemia.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing the effect of a single subcutaneous administration of vehicle (PBS, pH 7.4), human glucagon (20 nmol/kg body weight) or Compound 14 of the invention (20 and 60 nmol/kg body weight), respectively, on blood glucose levels for 120 minutes in anaesthetized, 5-hour-fasted euglycemic male Sprague-Dawley rats. Data are mean values with SEM (n= 6/group).

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

CLAIMS

1. A compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2; and

Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at sequence positions selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;

X3 is selected from His, Pro, Dab(Ac), Dap(Ac) and Gln(Me);

X4 is DAla;

X9 is Glu;

X10 is selected from Val, Leu, N-Me-Tyr and N-Me-DTyr;

X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;

X17 is selected from Ala and Ser;

X20 is selected from Glu and Lys;

X21 is selected from Glu, Lys and Ser;

X24 is selected from Lys, Ser, Glu and Ala;

X28 is selected from Ser and Lys, and Glu, or is absent;

X29 is selected from Ser and Ala, or is absent;with the proviso that Z is not selected from: HSQGTFTSDYSKYLDSARAEDFVKWLEST; and

HSQGTFTSDYSKYLESRRAKEFVEWLEST;

wherein the compound has glucagon agonist activity and improved solubility and/or stability as compared to native human glucagon.

2. A compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;
wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2; and
Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at sequence positions (designated as X) selected from 2, 3, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;
X3 is selected from His and Pro;
X9 is Glu;
X10 is selected from N-Me-Tyr and N-Me-DTyr;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;
X17 is selected from Ala and Ser;
X20 is selected from Glu and Lys;
X21 is selected from Glu, Lys and Ser;
X24 is selected from Lys, Ser, Glu and Ala;
X28 is selected from Ser and Lys, or is absent;

X29 is selected from Ser and Ala, or is absent;

with the proviso that Z is not selected from:
HSQGTFTSDYSKYLDSARAEDFVKWLEST; and
HSQGTFTSDYSKYLESRRAKEFVEWLEST;

wherein the compound has glucagon agonist activity and improved solubility and/or stability as compared to native human glucagon.

3. The compound or pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein said at least four amino acid substitutions or deletions at amino acid sequence positions (designated as X) selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I are as follows:

X2 is selected from Aib and Ala;
X3 is selected from His and Pro;
X4 is DAla;
X9 is Glu;
X10 is selected from N-Me-Tyr and N-Me-DTyr;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, Val, Phe, His and Arg;
X17 is selected from Ala and Ser;
X20 is selected from Glu and Lys;
X21 is selected from Glu, Lys and Ser;
X24 is selected from Lys, Ser, Glu and Ala;
X28 is selected from Ser, Glu, and Lys, or is absent;
X29 is selected from Ser and Ala, or is absent.

4. The compound or pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein the at least four amino acid substitutions or deletions are at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 10, 15, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I, and are as follows:

X2 is Ala;

X3 is Dab(Ac), Dap(Ac) and Gln(Me);

X4 is DAla;

X10 is selected from Leu and Val;

X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, and Val;

X17 is Ala;

X20 is selected from Glu and Lys;

X21 is selected from Glu and Ser;

X24 is selected from Lys, Ser and Glu;

X28 is selected from Ser, Glu and Lys;

X29 is Ala, or is absent.

5. The compound or pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein the at least four amino acid substitutions or deletions are at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I, and are as follows:

X2 is Ala;

X3 is Dab(Ac), Dap(Ac), Gln(Me) or His;

X4 is DAla;

X16 is selected from Aib, Lys, Glu;

X17 is Ala;

X20 is selected from Glu and Lys;

X21 is selected from Glu and Ser;

X24 is selected from Lys, Ser and Glu;

X28 is selected from Ser, Glu and Lys;

X29 is Ala, or is absent.6. The compound according to any one of claims 1 to 5, wherein X17 is Ala.

7. The compound according to any one of claims 1 to 5, wherein Z is selected from the group consisting of:

HSQGTFTSDYSKYLDSARAESFVKWLEST	(SEQ ID NO: 2)
HSQGTFTSDYSKYLDSARAEDFVKWLEET	(SEQ ID NO: 3)
HSQGTFTSDYSKYLDKARAEDFVKWLEST	(SEQ ID NO: 4)
HSQGTFTSDYSKYLDSARAEDFVAWLEST	(SEQ ID NO: 5)
HSQGTFTSDYSKYLDEARAKDFVEWLEKT	(SEQ ID NO: 6)
HSQGTFTSDYSKYLDSARAEDFVEWLEST	(SEQ ID NO: 7)
HSQGTFTSDYSKYLESARAEDFVKWLEST	(SEQ ID NO: 9)
HSQGTFTSDYSKYLDSARAEEFVKWLEST	(SEQ ID NO: 10)
HSQGTFTSDYSKYLDSARAEDFVSWLEST	(SEQ ID NO: 11)
HSQGTFTSDLSKYLDSARAEDFVKWLEST	(SEQ ID NO: 12)
HSQGTFTSDYSKYLD-Aib-ARAEDFVKWLEST	(SEQ ID NO: 13)
HSQGTFTSDYSKYLDSARAEDFVKWLES	(SEQ ID NO: 14)
HSQGTFTSDYSKYLDEARAEDFVKWLEST	(SEQ ID NO: 15)
HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 16)
HSQGTFTSDYSKYLESARAESFVKWLEST	(SEQ ID NO: 17)
HSQGTFTSDYSKYLDLARAEDFVKWLEST	(SEQ ID NO: 18)
HSQGTFTSDYSKYLDKRRAEDFVSWLEST	(SEQ ID NO: 19)
HSQGTFTSDYSKYLDVARAESFVKWLEST	(SEQ ID NO: 20)
HAQGTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 21)
HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEST	(SEQ ID NO: 22)
HSQ-DAla-TFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 23)
HSQGTFTSDVSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 24)
HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 25)
HSQGTFTSDYSKYLD-Aib-RRAESFVKWLEST	(SEQ ID NO: 26)
HS-[Gln(Me)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 27)
HSQGTFTSDYSKYLDEARAKSFVEWLEKT	(SEQ ID NO: 28)
HSQGTFTSDYSKYLDEARAKSFVEWLEST	(SEQ ID NO: 29)
HSQGTFTSDYSKYLD-Aib-ARAKSFVEWLEKT	(SEQ ID NO: 30)
HSQGTFTSDYSKYLD-Aib-ARAESFVKWLESA	(SEQ ID NO: 31)

HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST (SEQ ID NO: 32)

HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST (SEQ ID NO: 33)

HSQGTFTSDYSKYLD-Aib-ARAEEFVSWLEKT (SEQ ID NO: 34)

HSQGTFTSDYSKYLD-Aib-ARAEKFVEWLEST (SEQ ID NO: 35)

HSQGTFTSDYSKYLD-Aib-ARAEEFVAWLEST (SEQ ID NO: 36)

HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEET (SEQ ID NO: 37)

HSQGTFTSDYSKYLE-Aib-ARAEEFVKWLEST (SEQ ID NO: 38)

HSHGTFTSDYSKYLD-Aib-ARAEEFVKWLEST (SEQ ID NO: 39)

HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST (SEQ ID NO: 40)

and

HS-[Dap(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST (SEQ ID NO: 41).

8. The compound according to any one of claims 1 to 5, selected from the group consisting of:

Hy-HSQGTFTSDYSKYLDSARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVKWLEET-OH

Hy-HSQGTFTSDYSKYLDKARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVAWLEST-OH

Hy-HSQGTFTSDYSKYLDEARAKDFVEWLEKT-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVEWLEST-OH

Hy-HSQGTFTSDYSKYLESARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEEFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVSWLEST-OH

Hy-HSQGTFTSDLSKYLDSARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVKWLES-OH

Hy-HSQGTFTSDYSKYLDEARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLESARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDLARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDKRRAEDFVSWLEST-OH
Hy-HSQGTFTSDYSKYLDVARAESFVKWLEST-OH
Hy-HAQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-OH
Hy-HSQ-DAla-TFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
Hy-HSQGTFTSDVSKYLD-Aib-ARAESFVKWLEST-OH
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2
Hy-HSQGTFTSDYSKYLD-Aib-RRAESFVKWLEST-OH
Hy-HS-[Gln(Me)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
Hy-HSQGTFTSDYSKYLDEARAKSFVEWLEKT-OH
Hy-HSQGTFTSDYSKYLDEARAKSFVEWLEST-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAKSFVEWLEKT-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLESA-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVSWLEKT-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAEKFVEWLEST-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVAWLEST-OH
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEET-OH
Hy-HSQGTFTSDYSKYLE-Aib-ARAEEFVKWLEST-OH
Hy-HSHGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST-OH
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2
Hy-HS-[Dap(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2

and pharmaceutically acceptable salts and solvates thereof.

9. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

10. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAEDFVKWLEET-OH

or a pharmaceutically acceptable salt or solvate thereof.

11. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDKARAEDFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

12. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAEDFVAWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

13. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDEARAKDFVEWLEKT-OH
or a pharmaceutically acceptable salt or solvate thereof.

14. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAEDFVEWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

15. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLESARAEDFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

16. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAEEFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

17. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAEDFVSWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

18. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDLSKYLDSARAEDFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

19. The compound according to any one of claims 1, 3, 4 or 8 which is:

Hy-HSQGTFTSDYSKYLD-Aib-ARAEDFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

20. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDSARAEDFVKWLES-OH
or a pharmaceutically acceptable salt or solvate thereof.

21. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDEARAEDFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

22. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

23. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLESARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

24. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDLARAEDFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

25. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDKRRAEDFVSWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

26. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDVARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

27. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HAQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

28. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

29. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQ-DAla-TFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

30. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDVSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

31. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

32. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-RRAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

33. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HS-[Gln(Me)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

34. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDEARAKSFVEWLEKT-OH
or a pharmaceutically acceptable salt or solvate thereof.

35. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLDEARAKSFVEWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

36. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAKSFVEWLEKT-OH

or a pharmaceutically acceptable salt or solvate thereof.

37. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLESA-OH
or a pharmaceutically acceptable salt or solvate thereof.

38. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

39. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

40. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVSWLEKT-OH
or a pharmaceutically acceptable salt or solvate thereof.

41. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAEKFVEWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

42. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVAWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

43. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEET-OH
or a pharmaceutically acceptable salt or solvate thereof.

44. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLE-Aib-ARAEEFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

45. The compound according to any one of claims 1, 3, 4 or 8 which is:

Hy-HSHGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

46. A nucleic acid construct encoding a peptide Z according to any one of claims 1 to 7 wherein said peptide is composed entirely of naturally occurring amino acids.

47. An expression vector comprising a nucleic acid construct according to claim 46.

48. A host cell comprising a nucleic acid construct according to claim 46 or an expression vector according to claim 47.

49. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1-45 and a pharmaceutically acceptable carrier.

50. A method of treating a disease or condition in a subject in need thereof, comprising administering a therapeutically effective amount of a compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-45, or a pharmaceutical composition according to claim 49, to the subject.

51. The method of claim 50, wherein the disease is selected from the group consisting of: hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease.

52. The method of claim 51, wherein the disease or condition is hypoglycaemia.

53. The method of claim 52, wherein the hypoglycaemia is selected from the group consisting of: diabetic hypoglycaemia, acute insulin-induced hypoglycaemia, non-diabetic hypoglycaemia, reactive hypoglycaemia, fasting hypoglycaemia, drug-induced hypoglycaemia, alcohol-induced hypoglycaemia, gastric bypass-induced hypoglycaemia, and hypoglycaemia occurring during pregnancy.

54. A compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-45 for use in a method of medical treatment.

55. A compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-45 for the treatment of hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease.

56. A compound or pharmaceutically acceptable salt or solvate thereof for use according to claim 55 wherein the hypoglycaemia is selected from the group consisting of: diabetic hypoglycaemia, acute insulin-induced hypoglycaemia, non-diabetic hypoglycaemia, reactive hypoglycaemia, fasting hypoglycaemia, drug-induced hypoglycaemia, alcohol-induced hypoglycaemia, gastric bypass-induced hypoglycaemia, and hypoglycaemia occurring during pregnancy.

57. Use of a compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-45 in the preparation of a medicament for the treatment of hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease.

58. Use according to claim 57 wherein the hypoglycaemia is selected from the group consisting of: diabetic hypoglycaemia, acute insulin-induced hypoglycaemia, non-diabetic hypoglycaemia, reactive hypoglycaemia, fasting hypoglycaemia, drug-induced hypoglycaemia, alcohol-induced hypoglycaemia, gastric bypass-induced hypoglycaemia, and hypoglycaemia occurring during pregnancy.

CLAIMS

1. A compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;

R^2 is OH or NH_2; and

Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at sequence positions selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;

X3 is selected from His, Pro, Dab(Ac), Dap(Ac) and Gln(Me);

X4 is DAla;

X9 is Glu;

X10 is selected from Val, Leu, N-Me-Tyr and N-Me-DTyr;

X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;

X17 is selected from Ala and Ser;

X20 is selected from Glu and Lys;

X21 is selected from Glu, Lys and Ser;

X24 is selected from Lys, Ser, Glu and Ala;

X28 is selected from Ser and Lys, and Glu, or is absent;

X29 is selected from Ser and Ala, or is absent;with the proviso that Z is not selected from: HSQGTFTSDYSKYLDSARAEDFVKWLEST; and

HSQGTFTSDYSKYLESRRAKEFVEWLEST;

wherein the compound has glucagon agonist activity and improved solubility and/or stability as compared to native human glucagon.

2. A compound having the formula I:

R^1-Z-R^2 (I)

or a pharmaceutically acceptable salt or solvate thereof;
wherein

R^1 is hydrogen, C_{1-4} alkyl, acetyl, formyl, benzoyl or trifluoroacetyl;
R^2 is OH or NH_2; and
Z is an amino acid sequence deriving from the sequence of formula Ia:

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-
Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Glu-Asn-Thr (Ia)

and further comprising at least four amino acid substitutions or deletions that are only at sequence positions (designated as X) selected from 2, 3, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29, as follows:

X2 is selected from Aib and Ala;
X3 is selected from His and Pro;
X9 is Glu;
X10 is selected from N-Me-Tyr and N-Me-DTyr;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, Val, DVal, Phe, His, Arg, Pro, DPro, N-Me-Ser and N-Me-DSer;
X17 is selected from Ala and Ser;
X20 is selected from Glu and Lys;
X21 is selected from Glu, Lys and Ser;
X24 is selected from Lys, Ser, Glu and Ala;
X28 is selected from Ser and Lys, or is absent;

X29 is selected from Ser and Ala, or is absent;

with the proviso that Z is not selected from:
HSQGTFTSDYSKYLDSARAEDFVKWLEST; and
HSQGTFTSDYSKYLESRRAKEFVEWLEST;

wherein the compound has glucagon agonist activity and improved solubility and/or stability as compared to native human glucagon.

3. The compound or pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein said at least four amino acid substitutions or deletions at amino acid sequence positions (designated as X) selected from 2, 3, 4, 9, 10, 15, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I are as follows:

X2 is selected from Aib and Ala;
X3 is selected from His and Pro;
X4 is DAla;
X9 is Glu;
X10 is selected from N-Me-Tyr and N-Me-DTyr;
X15 is Glu;
X16 is selected from Aib, Lys, Glu, Leu, Val, Phe, His and Arg;
X17 is selected from Ala and Ser;
X20 is selected from Glu and Lys;
X21 is selected from Glu, Lys and Ser;
X24 is selected from Lys, Ser, Glu and Ala;
X28 is selected from Ser, Glu, and Lys, or is absent;
X29 is selected from Ser and Ala, or is absent.

4. The compound or pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein the at least four amino acid substitutions or deletions are at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 10, 15, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I, and are as follows:

X2 is Ala;

X3 is Dab(Ac), Dap(Ac) and Gln(Me);

X4 is DAla;

X10 is selected from Leu and Val;

X15 is Glu;

X16 is selected from Aib, Lys, Glu, Leu, and Val;

X17 is Ala;

X20 is selected from Glu and Lys;

X21 is selected from Glu and Ser;

X24 is selected from Lys, Ser and Glu;

X28 is selected from Ser, Glu and Lys;

X29 is Ala, or is absent.

5. The compound or pharmaceutically acceptable salt or solvate thereof according to claim 1, wherein the at least four amino acid substitutions or deletions are at amino acid sequence positions (designated by an X) selected from 2, 3, 4, 16, 17, 20, 21, 24, 28 and 29 of the compound of formula I, and are as follows:

X2 is Ala;

X3 is Dab(Ac), Dap(Ac), Gln(Me) or His;

X4 is DAla;

X16 is selected from Aib, Lys, Glu;

X17 is Ala;

X20 is selected from Glu and Lys;

X21 is selected from Glu and Ser;

X24 is selected from Lys, Ser and Glu;

X28 is selected from Ser, Glu and Lys;

X29 is Ala, or is absent.

6. The compound according to any one of claims 1 to 5, wherein X17 is Ala.

7. The compound according to any one of claims 1 to 5, wherein Z is selected from the group consisting of:

HSQGTFTSDYSKYLDSARAESFVKWLEST	(SEQ ID NO: 2)
HSQGTFTSDYSKYLDSARAEDFVKWLEET	(SEQ ID NO: 3)
HSQGTFTSDYSKYLDKARAEDFVKWLEST	(SEQ ID NO: 4)
HSQGTFTSDYSKYLDSARAEDFVAWLEST	(SEQ ID NO: 5)
HSQGTFTSDYSKYLDEARAKDFVEWLEKT	(SEQ ID NO: 6)
HSQGTFTSDYSKYLDSARAEDFVEWLEST	(SEQ ID NO: 7)
HSQGTFTSDYSKYLESARAEDFVKWLEST	(SEQ ID NO: 9)
HSQGTFTSDYSKYLDSARAEEFVKWLEST	(SEQ ID NO: 10)
HSQGTFTSDYSKYLDSARAEDFVSWLEST	(SEQ ID NO: 11)
HSQGTFTSDLSKYLDSARAEDFVKWLEST	(SEQ ID NO: 12)
HSQGTFTSDYSKYLD-Aib-ARAEDFVKWLEST	(SEQ ID NO: 13)
HSQGTFTSDYSKYLDSARAEDFVKWLES	(SEQ ID NO: 14)
HSQGTFTSDYSKYLDEARAEDFVKWLEST	(SEQ ID NO: 15)
HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 16)
HSQGTFTSDYSKYLESARAESFVKWLEST	(SEQ ID NO: 17)
HSQGTFTSDYSKYLDLARAEDFVKWLEST	(SEQ ID NO: 18)
HSQGTFTSDYSKYLDKRRAEDFVSWLEST	(SEQ ID NO: 19)
HSQGTFTSDYSKYLDVARAESFVKWLEST	(SEQ ID NO: 20)
HAQGTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 21)
HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEST	(SEQ ID NO: 22)
HSQ-DAla-TFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 23)
HSQGTFTSDVSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 24)
HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 25)
HSQGTFTSDYSKYLD-Aib-RRAESFVKWLEST	(SEQ ID NO: 26)
HS-[Gln(Me)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST	(SEQ ID NO: 27)
HSQGTFTSDYSKYLDEARAKSFVEWLEKT	(SEQ ID NO: 28)
HSQGTFTSDYSKYLDEARAKSFVEWLEST	(SEQ ID NO: 29)
HSQGTFTSDYSKYLD-Aib-ARAKSFVEWLEKT	(SEQ ID NO: 30)
HSQGTFTSDYSKYLD-Aib-ARAESFVKWLESA	(SEQ ID NO: 31)

HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST (SEQ ID NO: 32)

HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST (SEQ ID NO: 33)

HSQGTFTSDYSKYLD-Aib-ARAEEFVSWLEKT (SEQ ID NO: 34)

HSQGTFTSDYSKYLD-Aib-ARAEKFVEWLEST (SEQ ID NO: 35)

HSQGTFTSDYSKYLD-Aib-ARAEEFVAWLEST (SEQ ID NO: 36)

HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEET (SEQ ID NO: 37)

HSQGTFTSDYSKYLE-Aib-ARAEEFVKWLEST (SEQ ID NO: 38)

HSHGTFTSDYSKYLD-Aib-ARAEEFVKWLEST (SEQ ID NO: 39)

HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST (SEQ ID NO: 40)

and

HS-[Dap(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST (SEQ ID NO: 41).

8. The compound according to any one of claims 1 to 5, selected from the group consisting of:

Hy-HSQGTFTSDYSKYLDSARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVKWLEET-OH

Hy-HSQGTFTSDYSKYLDKARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVAWLEST-OH

Hy-HSQGTFTSDYSKYLDEARAKDFVEWLEKT-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVEWLEST-OH

Hy-HSQGTFTSDYSKYLESARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEEFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVSWLEST-OH

Hy-HSQGTFTSDLSKYLDSARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDSARAEDFVKWLES-OH

Hy-HSQGTFTSDYSKYLDEARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLESARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDLARAEDFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDKRRAEDFVSWLEST-OH

Hy-HSQGTFTSDYSKYLDVARAESFVKWLEST-OH

Hy-HAQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-OH

Hy-HSQ-DAla-TFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HSQGTFTSDVSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2

Hy-HSQGTFTSDYSKYLD-Aib-RRAESFVKWLEST-OH

Hy-HS-[Gln(Me)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLDEARAKSFVEWLEKT-OH

Hy-HSQGTFTSDYSKYLDEARAKSFVEWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAKSFVEWLEKT-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLESA-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2

Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVSWLEKT-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEKFVEWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVAWLEST-OH

Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEET-OH

Hy-HSQGTFTSDYSKYLE-Aib-ARAEEFVKWLEST-OH

Hy-HSHGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2

Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST-OH

Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2

Hy-HS-[Dap(Ac)]-GTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2

and pharmaceutically acceptable salts and solvates thereof.

9. The compound according to any one of claims 1, 3, 4 or 8 which is:

Hy-HSQGTFTSDYSKYLDSARAEEFVKWLEST-OH

or a pharmaceutically acceptable salt or solvate thereof.

10. The compound according to any one of claims 1, 3, 4 or 8 which is:

Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH

or a pharmaceutically acceptable salt or solvate thereof.

11. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

12. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HS-[Dab(Ac)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

13. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-RRAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

14. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HS-[Gln(Me)]-GTFTSDYSKYLD-Aib-ARAESFVKWLEST-OH
or a pharmaceutically acceptable salt or solvate thereof.

15. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSQGTFTSDYSKYLD-Aib-ARAESFVKWLEST-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

16. The compound according to any one of claims 1, 3, 4 or 8 which is:
Hy-HSHGTFTSDYSKYLD-Aib-ARAEEFVKWLEST-NH_2
or a pharmaceutically acceptable salt or solvate thereof.

17. A nucleic acid construct encoding a peptide Z according to any one of claims 1 to 7 wherein said peptide is composed entirely of naturally occurring amino acids.

18. An expression vector comprising a nucleic acid construct according to claim 17.

19. A host cell comprising a nucleic acid construct according to claim 17 or an expression vector according to claim 18.

20. A pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt or solvate thereof, according to any one of claims 1-16 and a pharmaceutically acceptable carrier.

21. A compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-16 for use in a method of medical treatment.

22. A compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-16 for use in the treatment of hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease.

23. A compound or pharmaceutically acceptable salt or solvate thereof for use according to claim 22 wherein the hypoglycaemia is selected from the group consisting of: diabetic hypoglycaemia, acute insulin-induced hypoglycaemia, non-diabetic hypoglycaemia, reactive hypoglycaemia, fasting hypoglycaemia, drug-induced hypoglycaemia, alcohol-induced hypoglycaemia, gastric bypass-induced hypoglycaemia, and hypoglycaemia occurring during pregnancy.

24. Use of a compound or pharmaceutically acceptable salt or solvate thereof according to any one of claims 1-16 in the preparation of a medicament for the treatment of hypoglycaemia, acute hypoglycaemia, chronic hypoglycaemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity, coronary heart disease, atherosclerosis, hypertension, dyslipidemia, hepatic steatosis, β-blocker poisoning, insulinoma, and Von Gierkes disease.

25. Use according to claim 24 wherein the hypoglycaemia is selected from the group consisting of: diabetic hypoglycaemia, acute insulin-induced hypoglycaemia, non-diabetic hypoglycaemia, reactive hypoglycaemia, fasting hypoglycaemia, drug-induced hypoglycaemia, alcohol-induced hypoglycaemia, gastric bypass-induced hypoglycaemia, and hypoglycaemia occurring during pregnancy.