Claims

1. A prodrug or a pharmaceutically acceptable salt thereof comprising a drug linker conjugate of formula (I)

$Z - L^1 - L^2 - L - Y - R^{20}$ (I)

wherein Y is a peptide moiety having the formula (II)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-Asp-Glu-Gln-X18-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-X28-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (II)

X2 represents an amino acid residue selected from Ser, D-Ser and Aib,

X3 represents an amino acid residue selected from Gln and His,
X18 represents an amino acid residue selected from Arg and Lys
X20 represents an amino acid residue selected from Lys, Gln and His,
X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Ser and Ala,
X32 represents an amino acid residue selected from Ser and Val,

or wherein Y is a peptide moiety having the formula (III)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-Asp-Glu-Gln-X18-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-X28-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (III)

X2 represents an amino acid residue selected from Ser, D-Ser and Aib,

X3 represents an amino acid residue selected from Gln and His,
X18 represents an amino acid residue selected from Leu and His
X20 represents an amino acid residue selected from His, Arg, Lys, and Gln,

X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Lys, Ser and Ala,
X32 represents an amino acid residue selected from Ser and Val,

or

wherein Y is a peptide moiety having the formula (IV)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Leu-Leu-Asp-Glu-Gln-X18-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Ile-Ala-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (IV)

X2 represents an amino acid residue selected from Ser, D-Ser and Aib,

X3 represents an amino acid residue selected from Gln and His,
X18 represents an amino acid residue selected from Arg and Leu,
X32 represents an amino acid residue selected from Ser and Val,

or

wherein Y is a peptide moiety having the formula (IVa)

H_2N-His-Aib-His-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-X15-Glu-Gln-Leu-Ala-Arg-Asp-Phe-Ile-Glu-Trp-Leu-Ile-Bal-X29-Gly-X31-X32-Ser-X34-X35-Pro-Pro-Pro-X39-R^{20} (V)

X15 represents an amino acid residue selected from Asp and Glu, (pref. Asp)
X29 represents an amino acid residue selected from Gly, D-Ala and Pro, (pref) Gly, D-Ala
X31 represents an amino acid residue selected from Pro, His and Trp, (pref. Pro)
X32 represents an amino acid residue selected from Ser, His, Pro and Arg, (pref. Ser, His, Pro),
X34 represents an amino acid residue selected from Gly and D-Ala,
X35 represents an amino acid residue selected from Ala, Pro and Lys, (pref. Ala, Pro)
X39 represents Ser or Pro-Pro-Pro,

or

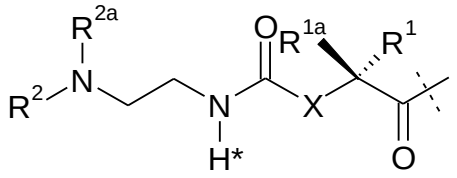
wherein Y is a peptide moiety having the formula (IVb)

H_2N-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Leu-Leu-Glu-Glu-Gln-Arg-Ala-Arg-Glu-Phe-Ile-Glu-Trp-Leu-Ile-Bal-D-Ala-Gly-Pro-Pro-Ser-D-Ala -Ala-Pro-Pro-Pro-Ser-R^{20};

or a salt or solvate thereof;

R^{20} is OH or NH_2;

L is a linker of formula (Ia),



Ia

wherein the dashed line indicates the attachment to the N-Terminus of Y by forming an amide bond;

X is $C(R^4R^{4a})$; $N(R^4)$;

R^1, R^{1a}, are independently selected from the group consisting of H; and C_{1-4} alkyl;

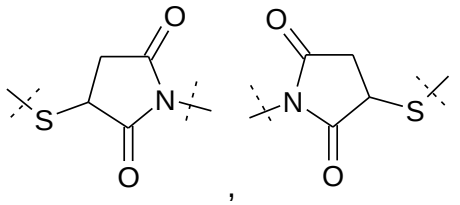
R^2, R^{2a}, are independently selected from the group consisting of H; and C_{1-4} alkyl;

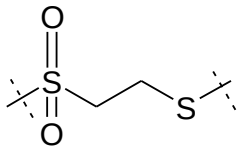
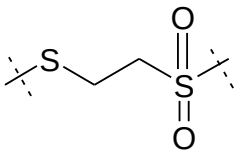
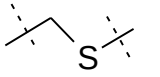
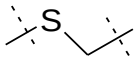
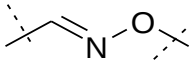
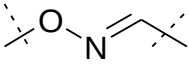
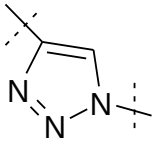
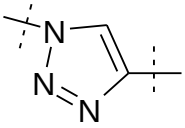
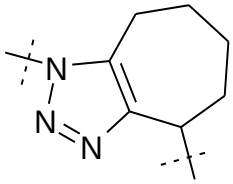
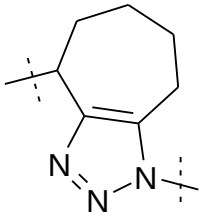
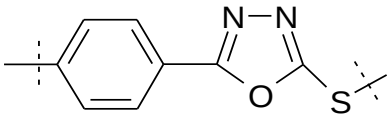
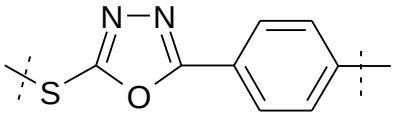
R^4, R^{4a}, are independently selected from the group consisting of H; and C_{1-4} alkyl;

wherein R^2 , R^{2a}, R^4 or R^{4a} is substituted with one group L^2-L^1-Z; wherein

L^2 is a single chemical bond or is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O- and $C(O)N(R^{3aa})$ and is optionally substituted with one or more groups independently selected from OH and $C(O)N(R^{3aa}R^{3aaa})$, wherein R^{3aa} and R^{3aaa} are independently selected from the group consisting of H and C_{1-4} alkyl; and

L^2 is attached to L^1 via a terminal group selected from the group consisting of


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and

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wherein L^2 is attached to the one position indicated with the dashed line and and L^1 is attached to the position indicated with the other dashed line; and

L^1 is a $C_{1\text{-}20}$ alkyl chain, which is optionally interrupted by one or more groups independently selected from -O- and C(O)N(R^{5aa}) and is optionally substituted with one or more groups independently selected from OH and C(O)N($R^{5aa}R^{5aaa}$), wherein R^{5aa} and R^{5aaa} are independently selected from the group consisting of H and $C_{1\text{-}4}$ alkyl; and

L^1 is attached to Z via a terminal amino group forming an amide bond with the carboxy group of the beta-1,3-D-glucuronic acid of the hyaluronic acid of Z;

Z is a crosslinked hyaluronic acid hydrogel, in which

0.05 to 20 % of the monomeric disaccharide units are crosslinked by a crosslinker; and
0.2 to 8.5 % of the monomeric disaccharide units bear L^1-L^2 -L-Y-R^{20}.groups.

2. A prodrug or a pharmaceutically acceptable salt thereof comprising a drug linker conjugate of formula (I) as claimed in claim 1

$Z - L^1 - L^2 - L - Y - R^{20}$ (I)

wherein Y is a peptide moiety having the formula (II)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-Asp-Glu-Gln-X18-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-X28-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (II)

X2 represents an amino acid residue selected from Ser, D-Ser and Aib,
X3 represents an amino acid residue selected from Gln and His,
X18 represents an amino acid residue selected from Arg and Lys
X20 represents an amino acid residue selected from Lys, Gln and His,
X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Ser and Ala,
X32 represents an amino acid residue selected from Ser and Val,

or wherein Y is a peptide moiety having the formula (III)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-Asp-Glu-Gln-X18-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-X28-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (III)

X2 represents an amino acid residue selected from Ser, D-Ser and Aib,
X3 represents an amino acid residue selected from Gln and His,
X18 represents an amino acid residue selected from Leu and His
X20 represents an amino acid residue selected from His, Arg, Lys, and Gln,
X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Lys, Ser and Ala,
X32 represents an amino acid residue selected from Ser and Val,

or

wherein Y is a peptide moiety having the formula (IV)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Leu-Leu-Asp-Glu-Gln-X18-Ala-Lys-Asp-Phe-Ile-Glu-Trp-Leu-Ile-Ala-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (IV)

X2 represents an amino acid residue selected from Ser, D-Ser and Aib,

X3 represents an amino acid residue selected from Gln and His,

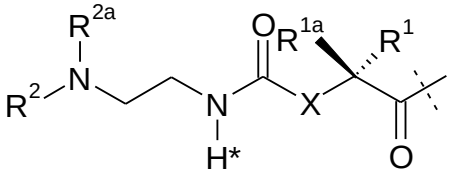
X18 represents an amino acid residue selected from Arg and Leu,

X32 represents an amino acid residue selected from Ser and Val,

or a salt or solvate thereof;

R^{20} is OH or NH_2;

L is a linker of formula (Ia),



Ia

wherein the dashed line indicates the attachment to the N-Terminus of Y by forming an amide bond;

X is $C(R^4R^{4a})$; $N(R^4)$;

R^1, R^{1a}, are independently selected from the group consisting of H; and C_{1-4} alkyl;

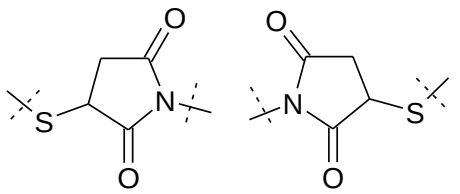
R^2, R^{2a}, are independently selected from the group consisting of H; and C_{1-4} alkyl;

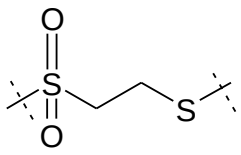
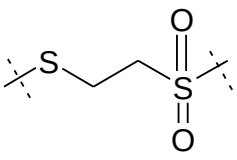
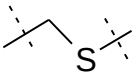
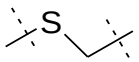
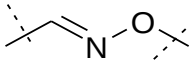
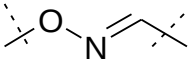
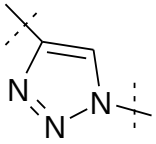
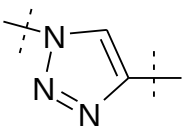
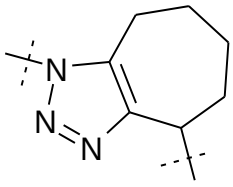
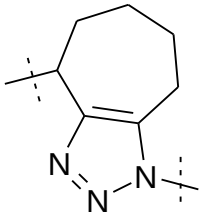
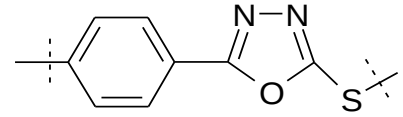
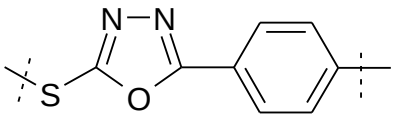
R^4, R^{4a}, are independently selected from the group consisting of H; and C_{1-4} alkyl;

wherein R^2 , R^{2a}, R^4 or R^{4a} is substituted with one group L^2-L^1-Z; wherein

L^2 is a single chemical bond or is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O- and C(O)N(R^{3aa}) and is optionally substituted with one or more groups independently selected from OH and C(O)N($R^{3aa}R^{3aaa}$), wherein R^{3aa} and R^{3aaa} are independently selected from the group consisting of H and C_{1-4} alkyl; and

L^2 is attached to L^1 via a terminal group selected from the group consisting of














and ;

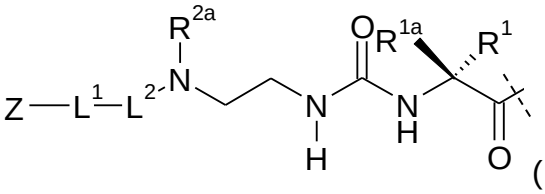
wherein L^2 is attached to the one position indicated with the dashed line and and L^1 is attached to the position indicated with the other dashed line; and

L^1 is a C_{1-20} alkyl chain, which is optionally interrupted by one or more groups independently selected from -O- and C(O)N(R^{5aa}) and is optionally substituted with one or more groups independently selected from OH and C(O)N($R^{5aa}R^{5aaa}$), wherein R^{5aa} and R^{5aaa} are independently selected from the group consisting of H and C_{1-4} alkyl; and

L^1 is attached to Z via a terminal amino group forming an amide bond with the carboxy group of the beta-1,3-D-glucuronic acid of the hyaluronic acid of Z;

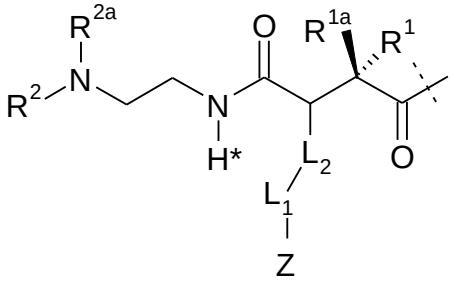
Z is a crosslinked hyaluronic acid hydrogel, in which
0.05 to 20 % of the monomeric disaccharide units are crosslinked by a crosslinker; and
0.2 to 8.5 % of the monomeric disaccharide units bear L^1-L^2 -L-Y-R^{20}.groups.

3. The prodrug of claim 1, wherein
L is a linker moiety of formula (Ib),


(Ib),

wherein the dashed line indicates attachment to Y by forming an amide bond;
R^1, R^{1a}, R^{2a} are selected independently from the group consisting of H and C_{1-4} alkyl;
L^2-L^1-Z is defined as in claim 1.

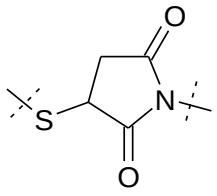
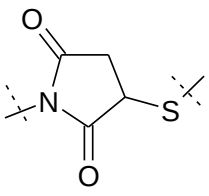
4. The prodrug of claim 1, wherein
L is a linker moiety -L of formula (Ic),


(Ic)

wherein the dashed line indicates attachment to Y by forming an amide bond;
R^1 and R^{1a} are H;
R^2, R^{2a} are independently selected from the group consisting of H and CH_3;
wherein L^2-L^1-Z is defined as in claim 1.

5. The prodrug of any of claims 1 to 4, wherein
L^2 is a C_{1-6} alkyl chain, which is optionally interrupted by one group selected from -O- and C(O)N(R^{3aa}) and, wherein R^{3aa} is independently selected from the group consisting of H and C_{1-4} alkyl; and

L^2 is attached to L^1 via a terminal group selected from the group consisting of


and

;

wherein L^2 is attached to the one position indicated with the dashed line and and L^1 is attached to the position indicated with the other dashed line.

6. The prodrug of any of claims 1 to 5, wherein

wherein Y is a peptide moiety having the formula (II)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-Asp-Glu-Gln-X18-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-X28-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (II)

wherein

X2 represents an D-Ser
X3 represents His,
X18 represents Arg
X20 represents Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Ser and Ala,
X32 represents an amino acid residue selected from Ser and Val;

or wherein Y is a peptide moiety having the formula (III)

His-X2-X3-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-Asp-Glu-Gln-X18-Ala-X20-X21-Phe-Ile-Glu-Trp-Leu-Ile-X28-Gly-Gly-Pro-X32-Ser-Gly-Ala-Pro-Pro-Pro-Ser (III)

wherein

X2 represents Aib,
X3 represents His,
X18 represents Leu,
X20 represents Lys,
X21 represents an amino acid residue selected from Asp and Glu,
X28 represents an amino acid residue selected from Ser and Ala,
X32 represents an amino acid residue selected from Ser and Val.

7. The prodrug of any of claims 1 to 5, wherein Y is a peptide moiety having the formula (IVa)

H_2N-His-Aib-His-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Leu-X15-Glu-Gln-Leu-Ala-Arg-Asp-Phe-Ile-Glu-Trp-Leu-Ile-Bal-X29-Gly-X31-X32-Ser-X34-X35-Pro-Pro-Pro-X39-R^{20} (IVa)

X15 represents an amino acid residue selected from Asp and Glu, (pref. Asp)
X29 represents an amino acid residue selected from Gly, D-Ala and Pro, (pref) Gly, D-Ala
X31 represents an amino acid residue selected from Pro, His and Trp, (pref. Pro)
X32 represents an amino acid residue selected from Ser, His, Pro and Arg, (pref. Ser, His, Pro),
X34 represents an amino acid residue selected from Gly and D-Ala,
X35 represents an amino acid residue selected from Ala, Pro and Lys, (pref. Ala, Pro)
X39 represents Ser or Pro-Pro-Pro.

8. The prodrug of any of claims 1 to 5, wherein Y is a peptide moiety having the formula (IVb)

H_2N-His-Aib-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Leu-Leu-Glu-Glu-Gln-Arg-Ala-Arg-Glu-Phe-Ile-Glu-Trp-Leu-Ile-Bal-D-Ala-Gly-Pro-Pro-Ser-D-Ala -Ala-Pro-Pro-Pro-Ser-R^{20}.

9. The prodrug of any of claims 1 to 8, wherein

Y is GLP-1/Glucagon agonist selected from sequences Seq. ID No 4 to 60.

10. A pharmaceutical composition comprising a prodrug of any of claims 1 to 9 or a pharmaceutical salt thereof together with at least one pharmaceutically acceptable excipient.

11. A pharmaceutical composition comprising a prodrug of any of claims 1 to 9 or a pharmaceutical salt thereof together with at least one pharmaceutically acceptable excipient and a viscosity modifier.

12. A pharmaceutical composition as claimed in claim 11, wherein the viscosity modifier is hyaluronic acid.

13. A pharmaceutical composition as claimed in claims 10 to 12 in form of an injectable formulation.

14. A pharmaceutical composition as claimed in claims 10 to 13 in form of a suspension.

15. A pharmaceutical composition as claimed in claims 10 to 14 in form of a suspension, wherein a prodrug of any of claims 1 to 6 has a concentration of 0.5 to 8 weight/volume percent.

16. A pharmaceutical composition as claimed in claims 10 to 14 in form of a suspension, wherein a prodrug of any of claims 1 to 6 has a concentration of 1.5 to 3 weight/volume percent.

17. A composition according to any of claims 10 to 16, wherein the prodrug is sufficiently dosed in the composition to provide a therapeutically effective amount of GLP1/Glucagon agonist for at least 6 days in one application.

18. A composition according to any of claims 10 to 17, wherein it is a single dose composition.

19. The prodrug of any of claims 1 to 9 or the pharmaceutical composition of claims 10 to 18 for use as a medicament.

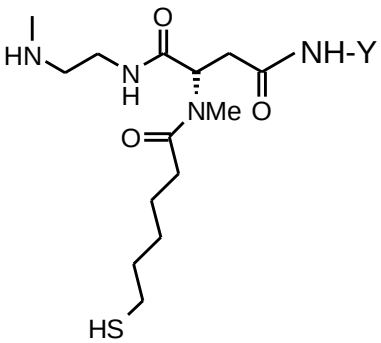
20. The prodrug of any of claims 1 to 9 or the pharmaceutical composition of claims 10 to 18 for use in a method of treating or preventing diabetes.

21. The prodrug of any of claims 1 to 7 or the pharmaceutical composition of claims 10 to 18 for use in a method of treating or preventing dyslipemia.

22. The prodrug of any of claims 1 to 9 or the pharmaceutical composition of claims 10 to 16 for use in a method of treating or preventing metabolic syndrom.

23. The prodrug of any of claims 1 to 9 or the pharmaceutical composition of claims 10 to 18 for use in a method of treating or preventing of hepatosteatosis, preferably non-alcoholic liver-disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

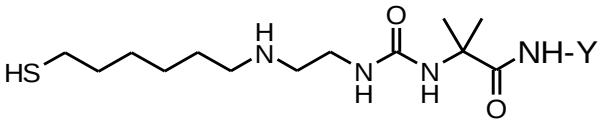
24. A GLP-1/Glucagon agonist-linker conjugate intermediate L^{2*}-L-Y of formula (VIII)



(VIII),

wherein Y is a peptide of Seq ID 4 to 60.

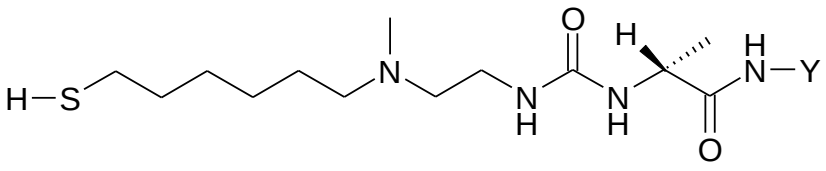
25. GLP-1/Glucagon agonist-linker conjugate intermediate L^{2*}-L-Y of formula (IX)



(IX)

wherein Y is a peptide of Seq ID 4 to 60.

26. An GLP-1/Glucagon agonist-linker conjugate intermediate L^{2*}-L-Y of formula (X)



(X),

wherein Y is a peptide of Seq ID 4 to 60.

27. The composition of claim 18, wherein the prodrug suspension can be administered by injection through a needle smaller than 0.26 mm inner diameter.