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(54) Title: GIP-GLP-1 DUAL AGONIST COMPOUNDS AND METHODS

(57) Abstract: The present invention relates to truncated GIP analogues which comprise one or more substitutions as compared to wiid-type GIP and which may have the property of an altered, preferably increased GLP-1 activity, e.g. as assessed in *in vitro* efficacy assays. The invention provides GIP-GLP-1 dual agonist compounds and associated methods.

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GIP-GLP-1 DUAL AGONIST COMPOUNDS AND METHODS

Background of the Invention

[0001] Diabetes and obesity are increasing health problems globally and are associated with various other diseases, particularly cardiovascular diseases (CVD), obstructive sleep apnea, stroke, peripheral artery disease, microvascular complications and osteoarthritis. There are 246 million people worldwide with diabetes, and by 2025 it is estimated that 380 million will have diabetes. Many have additional cardiovascular risk factors including high/aberrant LDL and triglycerides and low HDL. Cardiovascular diseases account for about 50% of the mortality in people with diabetes, and the morbidity and mortality rates relating to obesity and diabetes underscore the medical need for efficacious treatment options.

[0002] Incretins are gastrointestinal hormones that regulate blood glucose by enhancing glucose-stimulated insulin secretion (Drucker, DJ and Nauck, MA, Lancet 368: 1696–705 (2006)). To date there are two known incretins: glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). The incretin GLP-1 is derived from the pre-proglucagon gene. Pre-proglucagon is a 158-amino acid precursor polypeptide that is processed in different tissues to form a number of different proglucagon-derived peptides, including glucagon, GLP-1, glucagon-like peptide-2 (GLP-2) and oxyntomodulin (OXM). Glucagon is a 29-amino acid peptide that corresponds to amino acids 33 through 61 of pre-proglucagon, while GLP-1 is produced as a 37-amino acid peptide that corresponds to amino acids 72 through 108 of pre-proglucagon. GIP is a 42-amino acid peptide derived by proteolytic processing from a 133-amino acid precursor, pre-pro-GIP. All the peptides are involved in a wide variety of physiological functions, including glucose homeostasis, insulin secretion, gastric emptying, and intestinal growth, as well as the regulation of food intake.

[0003] The discovery of the incretins has led to the development of two new classes of drugs for the treatment of diabetes mellitus. Thus, injectable GLP-1 receptor agonists, and small molecule compounds (oral DPP-4 inhibitors) that inhibit enzymatic inactivation of both endogenous GLP-1 and GIP, are now on the market (GLP-1 receptor agonists: Byetta™, Bydureon™ and Victoza™; and DPP-4 inhibitors: Januvia™, Galvus™, Onglyza™ and Trajenta™). Apart from the

acute effects of GLP-1 and GIP on insulin secretion, the incretins have some long-term effects. Evidence from several laboratories shows that GLP-1 receptor agonists protect pancreatic β-cells by inhibiting apoptosis and enhancing proliferation. For instance, a study by Farilla *et al.* showed that GLP-1 has anti-apoptotic effects in human islets (Farilla, L, Endocrinology 144: 5149-58 (2003)). Such effects have not been reported for GIP until recently. Weidenmaier *et al.* reported that a DPP-4 resistant GIP analogue had anti-apoptotic effects (Weidenmaier, SD, PLOS One 5(3): e9590 (2010)). Interestingly, in mouse models of diabetes and obesity, the combination of the GLP-1 receptor agonist Liraglutide and GIP showed superior glucose-lowering and insulinotropic effects compared to treatment with Liraglutide and GIP alone (Gault, VA, Clinical Science 121: 107–117 (2011)).

[0004] Chronic treatment with GLP-1 receptor agonists causes significant weight loss in diabetic humans. Interestingly, extended use of DPP-4 inhibitors in similar patients does not consistently change body weight. Evidence suggests (Matthias Tschöp oral presentation at ADA (American Diabetes Association), 2011) that body weight loss associated with GLP-1 agonist treatment is enhanced when GLP-1 and GIP are co-administered. In rodents, co-administration of GLP-1 and GIP results in greater body weight loss than GLP-1 treatment alone. Thus, in addition to improving blood glucose control, GIP may also enhance GLP-1-mediated body weight loss.

Summary of the Invention

[0005] Broadly, the present invention concerns truncated GIP analogues which comprise one or more substitutions as compared to wild-type GIP and which may have the property of an altered, preferably increased GLP-1 activity, e.g., as assessed in *in vitro* efficacy assays. In the present invention it has been found that GIP-GLP1 dual acting receptor agonists are superior to existing and marketed GLP-1 analogues because the dual agonists offer improved glycemic control,and enhanced body weight loss. The GIP-GLP1 dual agonists (also known as GIP analogues) may thus be used as therapeutics for type 2 diabetes mellitus, obesity and related disorders.

[0006] More particularly, preferred GIP analogues of the present invention comprise non-conservative substitutions at one or more of amino acid positions 1, 2, 3, 7, 9, 13, 14, 15, 17, 19, 20, 21, 22, 23, 24, 27, 28, 29, and 30 of the wild-type

GIP sequence in combination with Ile,Gln, Lys, Arg or Glu in position 17, optionally in combination with further conservative or non-conservative substitutions at one or more of amino acid positions 10,11, and 16; and acylation of one or more of amino acid positions 15, 16, 17, 19, 20, 24, 27, 28 and 30 and/or a substitution or deletion of one or more of amino acids corresponding to positions 30 to 42 of the wild-type GIP sequence.

[0007] In some embodiments, a GIP analogue of the invention is represented by the general Formula I:

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I) (SEQ ID NO 59)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is: His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp, Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Lys, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys or Arg;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Glu, Lys, Gly or Tyr;

X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0008] In some embodiments, a GIP analogue of the invention is represented by the general Formula I':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I') (SEQ ID NO 61)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr, Ser or Ile;
X9 is Asp or Glu;
X10 is Tyr, Leu or Ser;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;
X22 is Phe or 1Nal;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Val, Ile, Lys, Glu or Ser;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Aib, Lys, Gly or Ala;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0009] In other embodiments, a GIP analogue of the invention is represented by the general Formula I(a):

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(a)) (SEQ ID NO 33)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X1 is His or Tyr;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr, Ser or Ile;
X9 is Asp or Glu;
X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X17 is Ile, Lys, Gln, Arg or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys or Arg;
X21 is Asp, Ala or Glu;
X22 is Phe or 1Nal;
X23 is Val, Ile or Leu ;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Val, Ile, Lys, Glu or Ser;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Aib, Glu, Lys or Tyr;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0010] In other embodiments, a GIP analogue of the invention is represented by the general Formula I(a)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(a)') (SEQ ID NO 62)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X14 is Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu ;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Lys, Gly or Ala;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;

X36 is Trp, Pro, Lys or absent;

X37 is Lys, Pro, Glu or absent;

X38 is His, Pro, Ser, Lys or absent;

X39 is Asn, Ser or absent;

X40 is Ile or absent;

X41 is Thr or absent;

X42 is Gln or absent; and

R^2 is $-NH_2$ or -OH.

[0011] In other embodiments, a GIP analogue of the invention is represented by the general Formula I(b):

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)) (SEQ ID NO 1)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr or Ser;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Lys, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys or Arg;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu ;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys or Ser;

X28 is Ala or Aib;

X29 is Gln, Gly, Aib or Tyr;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0012] In other embodiments, a GIP analogue of the invention is represented by the general Formula I(b)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)') (SEQ ID NO 63)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr or Ser;
X9 is Asp or Glu;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;
X21 is Asp, Ala or Glu;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Glu, Val or Ile;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Gly, Aib or Ala;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

[0013] In some embodiments, a GIP analogue of the invention is represented by the general Formula II:

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II)
(SEQ ID NO 60)
wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr, Leu or Ser
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X14 is Leu;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;

X19 is Gln, Lys, Ala or Glu;
X20 is Lys or Arg;
X21 is Ala or Glu;
X23 is Val or Ile;
X24 is Asn or Glu;
X27 is Leu, Glu, Ser, Lys or Val;
X28 is Aib, Ala, Ser or Arg;
X29 is Aib, Glu, Gly or Lys;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

[0014] In some embodiments, a GIP analogue of the invention is represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X19 is Gln or Ala;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;
X27 is Leu, Glu, Val or Ile;

X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala, Gly or Lys;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

[0015] In other embodiments, a GIP analogue of the invention is represented by the general Formula II(a):
R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a))
(SEQ ID NO 34)
wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr, Leu or Ser
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X14 is Leu;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;
X19 is Gln, Lys, Ala or Glu;
X20 is Lys or Arg;
X21 is Ala or Glu;
X23 is Val or Ile;
X24 is Asn or Glu;
X27 is Leu, Glu, Ser, Lys or Val;
X28 is Aib, Ala, Ser or Arg;
X29 is Aib, Glu or Lys;
X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0016] In other embodiments, a GIP analogue of the invention is represented by the general Formula II(a)':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a)')

(SEQ ID NO 65)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr or Leu;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;

X28 is Aib, Ala, Ser or Arg;

X29 is Gln, Aib, Ala, or Gly;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0017] In other embodiments, a GIP analogue of the invention is represented by the general Formula II(b):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-X14-X15-Lys-X17-Ala-Gln-X20-X21-Phe-X23-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(b))
(SEQ ID NO 2)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Ala, Tyr or Aib;
X14 is Leu;
X15 is Asp or Glu;
X17 is Ile or Lys;
X20 is Lys or Arg;
X21 is Ala or Glu;
X23 is Val or Ile;
X24 is Asn or Glu;
X27 is Leu or Val;
X29 is Aib or Gly;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is -NH_2 or -OH.

[0018] In other embodiments, a GIP analogue of the invention is represented by the general Formula II(b)':

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-X23-Glu-Trp-Leu-X27-X28- Ala-X30-Y1-R^2 (II(b)')
(SEQ ID NO: 66)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Ala or Tyr;
X15 is Asp or Glu;
X16 is Lys or Ser;

X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X27 is Leu, Glu or Val;
X28 is Arg or Ser;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

[0019] In other embodiments, a GIP analogue of the invention is represented by the general Formula II(c):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-Val-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(c))
(SEQ ID NO: 67)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Aib or Tyr ;
X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X24 is Glu or Asn
X27 is Leu, Glu or Val;
X29 is Gln or Aib;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

[0020] In other embodiments, a GIP analogue of the invention is represented by the general Formula II(d):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-Ala-Phe-Val-Glu-Trp-Leu-X27-Ala-Gln-X30-Y1-R^2 (II(d))

(SEQ ID NO: 68)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Aib or Tyr;

X15 is Asp or Glu;

X16 is Glu, Lys or Ser;

X20 is Lys, His or Arg;

X27 is Leu, Glu or Val;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

[0021] Without wishing to be bound by any particular theory, the Isoleucine at position 7 of native GIP appears to provide significant selectivity for the GIP receptor. A small polar residue (e.g. Thr or Ser) at position 7 may increase potency and/or selectivity at the GLP-1 receptor.

[0022] Without wishing to be bound by any particular theory, it is believed that substitution of Met found in position 14 of native GIP with a hydrophobic residue like leucine is important for enhancing GLP-1 receptor activity and so increase potency and/or selectivity at the GLP-1 receptor. The substitution of Met at position 14 with leucine also reduces the potential for oxidation, so increasing the chemical stability of the compounds. The non-conservative and non-obvious substitution of Ile for Lys in position 17 may enhance GLP-1 receptor activity and in addition provide a handle for acylation to prolong half life of the peptide.

[0023] Without wishing to be bound by any particular theory, the histidine at position 18 of native GIP appears to provide significant selectivity for the GIP receptor. A non-conservative substitution of histidine in position 18 with a small

hydrophobic residue (e.g. Ala) may increase potency and/or selectivity at the GLP-1 receptor.

[0024] Without wishing to be bound by any particular theory, it is believed that a truncation of the C-terminal of native GIP may be performed without affecting the GIP receptor activity. The truncation can be of any length (1-13 amino acids) down to a 29 amino acid GIP peptide.

[0025] Without wishing to be bound by any particular theory, the addition of Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser or Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser at or after position 29 or at or after position 30 of a native GIP or a GIP analogue may increase GLP1 receptor activity.

[0026] Aib in amino acid position 2 may render GIP peptide having from 42 amino acids down to 29 amino acids resistant to DPP-IV cleavage.

[0027] Aib in amino acid position 13 and/or 29 will enhance the stability of the peptide towards enzymatic degradation. In addition, without wishing to be bound by any particular theory, the Aib mayenhance the helicity of the peptide and hence enhance the GLP-1 receptor activity. Furthermore, Nal1 in position 22 may also render the peptide stable to enzymatic degradation.

[0028] In a preferred embodiment, the GIP analogue of the invention comprises:

Glu at position 24 and/or Ala at position 21, truncated or full length, which may be combined with any of the following:

Thr at position 7, Leu at position 14, truncated or full length;

Thr at position 7, Leu at position 14, Ala at position 18, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, (Aib at position 13 and/or 29), truncated or full length;

Thr at position 7, Leu at position 14, Ala at position 19, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, (Aib at position 13 and/or 29), truncated or full length;

Thr at position 7, Leu at position 14, Gln at position 19, truncated or full length;

Thr at position 7, Leu at position 14, Lys at position 17, Gln at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Gln at position 19, truncated or full length; or

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Gln at position 19, (Aib at position 13 and/or 29), truncated or full length.

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, truncated or full length;

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, Leu at position 27, Ser at position 28 and Ala at position 29, truncated or full length; or

Aib at position 2, Thr at position 7, Leu at position 14, Lys at position 17, Ala at position 18, Ala at position 19, Glu at position 27, Ser at position 28 and Ala at position 29, truncated or full length.

[0029] Some embodiments of the invention are:

1. A GIP analogue represented by the general Formula I:

R^1-X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42-R^2 (I) (SEQ ID NO 59)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X17 is Ile, Lys, Gln, Arg or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys or Arg;
X21 is Asp, Ala or Glu;
X22 is Phe or 1Nal;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Val, Ile, Lys, Glu or Ser;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Aib, Glu, Lys, Gly or Tyr;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

2. The GIP analogue of embodiment 1, wherein the GIP analogue is represented by the general Formula I(a):

R^1- X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42-R^2 (I(a)) (SEQ ID NO 33)

or a pharmaceutically acceptable salt or solvate thereof,
wherein

R^1 is Hy-, Ac or pGlu;
X1 is His or Tyr;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr, Ser or Ile;
X9 is Asp or Glu;
X10 is Tyr, Leu or Ser;
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X17 is Ile, Lys, Gln, Arg or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys or Arg;
X21 is Asp, Ala or Glu;
X22 is Phe or 1Nal;
X23 is Val, Ile or Leu ;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Val, Ile, Lys, Glu or Ser;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Aib, Glu, Lys or Tyr;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and

R^2 is -NH_2 or -OH.

3. The GIP analogue of embodiment 1, wherein the GIP analogue is represented by the general Formula I(b):

R^1-X1-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42-R^2 (I(b)) (SEQ ID NO 1)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X1 is His or Tyr;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr or Ser;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X17 is Ile, Lys, Gln, Arg or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys or Arg;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys or Ser;

X28 is Ala or Aib;

X29 is Gln, Gly, Aib or Tyr;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

4. A GIP analogue represented by the general Formula II:

R^1-Tyr-X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II)

(SEQ ID NO 60)

wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr, Leu or Ser
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X14 is Leu;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;
X19 is Gln, Lys, Ala or Glu;
X20 is Lys or Arg;
X21 is Ala or Glu;
X23 is Val or Ile;
X24 is Asn or Glu;
X27 is Leu, Glu, Ser, Lys or Val;
X28 is Aib, Ala, Ser or Arg;
X29 is Aib, Glu, Gly or Lys;
X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

5. The GIP analogue of embodiment 4, wherein the GIP analogue is represented by the general Formula II(a):

R^1-Tyr-X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-X14-X15-X16-X17-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a))

(SEQ ID NO 34)

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Aib or Gly;

X7 is Thr, Ile or Ser;

X10 is Tyr, Leu or Ser

X11 is Ser or Leu;

X13 is Ala, Tyr or Aib;

X14 is Leu;

X15 is Asp or Glu;

X16 is Ser, Glu or Lys;

X17 is Ile or Lys;

X19 is Gln, Lys, Ala or Glu;

X20 is Lys or Arg;

X21 is Ala or Glu;

X23 is Val or Ile;

X24 is Asn or Glu;

X27 is Leu, Glu, Ser, Lys or Val;

X28 is Aib, Ala, Ser or Arg;

X29 is Aib, Glu or Lys;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

6. The GIP analogue of embodiment 4, wherein the GIP analogue is represented by the general Formula II(b):

R^1-Tyr-Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-X14-X15-Lys-X17-Ala-Gln-X20-X21-Phe-X23-X24-Trp-Leu-X27-Ala-X29-X30-Y1-R^2 (II(b))

(SEQ ID NO 2)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala, Tyr or Aib;

X14 is Leu;

X15 is Asp or Glu;

X17 is Ile or Lys;

X20 is Lys or Arg;

X21 is Ala or Glu;

X23 is Val or Ile;

X24 is Asn or Glu;

X27 is Leu or Val;

X29 is Aib or Gly;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

7. A GIP analogue represented by the general Formula I':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I') (SEQ ID NO 61)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;
X10 is Tyr, Leu or Ser;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Met, Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Gly, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;
X21 is Asp, Ala or Glu;
X22 is Phe or 1Nal;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Val, Ile, Lys, Glu or Ser;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Aib, Lys, Gly or Ala;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

8. The GIP analogue of embodiment 7, wherein the GIP analogue is represented by the general Formula I(a)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(a)') (SEQ ID NO 62)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X14 is Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu ;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Lys, Gly or Ala;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;

X36 is Trp, Pro, Lys or absent;

X37 is Lys, Pro, Glu or absent;

X38 is His, Pro, Ser, Lys or absent;

X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

9. The GIP analogue of embodiment 7, wherein the GIP analogue is represented by the general Formula I(b)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)') (SEQ ID NO 63)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr or Ser;
X9 is Asp or Glu;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;
X21 is Asp, Ala or Glu;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Glu, Val or Ile;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Gly, Aib or Ala;
X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

10. A GIP analogue represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X19 is Gln or Ala;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;
X27 is Leu, Glu, Val or Ile;
X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala, Gly or Lys;

X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

11. The GIP analogue of embodiment 10, wherein the GIP analogue is represented by the general Formula II(a)':
R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a)')
(SEQ ID NO 65)
wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X19 is Gln, Lys, Ala or Glu;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;
X27 is Leu, Glu, Val or Ile;
X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala, or Gly;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

12. The GIP analogue of embodiment 10, wherein the GIP analogue is represented by the general Formula II(b)':

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-X23-Glu-Trp-Leu-X27-X28- Ala-X30-Y1-R^2 (II(b)')

(SEQ ID NO: 66)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala, Tyr or Aib;

X15 is Asp or Glu;

X16 is Lys, Glu or Ser;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X27 is Leu, Glu or Val;

X28 is Arg or Ser;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

13. The GIP analogue of embodiment 10, wherein the GIP analogue is represented by the general Formula II(c):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-Val-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(c))

(SEQ ID NO: 67)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala, Aib or Tyr;

X15 is Asp or Glu;

X16 is Glu, Lys or Ser;

X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X24 is Glu or Asn
X27 is Leu, Glu or Val;
X29 is Gln or Aib;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

14. The GIP analogue of embodiment 13, wherein the GIP analogue is represented by the general Formula II(d):
R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-Ala-Phe-Val-Glu-Trp-Leu-X27-Ala-Gln-X30-Y1-R^2 (II(d))
(SEQ ID NO: 68)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Ala, Aib or Tyr;
X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X27 is Leu, Glu or Val;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

15. A GIP analogue compound according to any one of embodiments 1 to 14 wherein X24 is Glu and/or X21 is Ala.

16. A GIP analogue compound according to any one of embodiments 1 to 15, wherein X7 is Thr and X14 is Leu.

17. A GIP analogue according to any one of embodiments 1 to 15, wherein X7 is Thr, X14 is Leu and X18 is Ala.

18. A GIP analogue according to any one of embodiments 1 to 15, wherein X7 is Thr, X14 is Leu and X17 is Lys.

19. A GIP analogue according to any one of embodiments 1 to 15, wherein X7 is Thr, X14 is Leu, X17 is Lys and X18 is Ala.

20. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu and X17 is Lys.

21. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, and X13 and/or X29 is Aib.

22. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, X27 is Leu or Glu and X28 is Ser.

23. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys and X24 is Glu.

24. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, X24 is Glu and X29 is Gln.

25. A GIP analogue according to any one of claims 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, X21 is Ala, X24 is Glu and X29 is Gln

26. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, X24 is Glu, X27 is Leu and X28 is Ser.

27. A GIP analogue according to any one of embodiments 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, X24 is Glu, X27 is Glu and X28 is Ser.

28. A GIP analogue according to any one of claims 1 to 15, wherein X2 is Aib, X7 is Thr, X14 is Leu, X17 is Lys, X20 is His, X24 is Glu, X27 is Leu and X28 is Ser.

29. A GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-KYG-1Nal-LDF-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLAYG-1Nal-LDF-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2;
Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;
Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2;
Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2; and
Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;
or a pharmaceutically acceptable salt or solvate thereof.

30. A GIP analogue according to any one of the preceding embodiments with a lipophilic substituent conjugated to one or more of positions 15, 16, 17, 19, 20, 24, 27, 28 and 30.

31. A GIP analogue according to any one of the preceding embodiments for use in a therapeutic method.

32. A pharmaceutical composition comprising a GIP analogue of any one of the preceding embodiments, or a salt, solvate or derivative thereof, in admixture with a carrier.

33. The pharmaceutical composition of embodiment 32, wherein the GIP analogue is a pharmaceutically acceptable acid addition salt.

34. The pharmaceutical composition of embodiment 32 or embodiment 33, which is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of said GIP analogue.

35. Use of a GIP analogue of any one of embodiments 1 to 30 for the preparation of a medicament for the treatment and/or prevention of metabolic diseases.

36. Use of a GIP analogue of any one of embodiments 1 to 30 for the preparation of a medicament for the treatment and/or prevention of diabetes or a diabetes related disorder.

37. Use of a GIP analogue of any one of embodiments 1 to 30 for the preparation of a medicament for the treatment and/or prevention of obesity or an obesity related disorder.

38. The use of embodiment 37, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

39. The use of embodiment 37, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and proinflammatory state, or a combination thereof.

40. The use of embodiment 39, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, and plaque buildup in artery walls, or a combination thereof.

41. The use of embodiment 39, wherein the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood.

42. The use of embodiment 39, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

43. The use of embodiment 37, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea, or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

44. A nucleic acid molecule comprising a nucleic acid sequence encoding a GIP analogue of any one of embodiments 1 to 30.

45. An expression vector comprising the nucleic acid sequence of embodiment 44, in combination with control sequences to direct its expression.

46. A host cell transformed with the expression vector of embodiment 45.

47. A method of producing the GIP analogue of any one of embodiments 1 to 30, the method comprising culturing the host cells of embodiment 46 under

conditions suitable for expressing the GIP analogue and purifying the GIP analogue thus produced.

48. A nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46 for use in therapy.

49. Use of a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45 or a host cell according to embodiment 46, in the preparation of a medicament for the treatment and/or prevention of a metabolic disorder.

50. The use of embodiment 49, wherein the metabolic disorder is selected from diabetes and obesity.

51. A method of treating a stomach and/or bowel-related disorder in a patient in need thereof by administering an effective amount a GIP analogue of any one of embodiments 1 to 30, a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46.

52. A method of treatment and/or prevention of a metabolic disease or disorder in a patient in need thereof comprising administering to said patient an effective amount of the GIP analogue of any one of embodiments 1 to 30, a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46.

53. The method of embodiment 52, wherein the metabolic disease or disorder is selected from diabetes and obesity.

54. A method of treatment and/or prevention of a diabetes related disorder in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of embodiments 1 to 30, a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46.

55. A method of treatment and/or prevention of an obesity related disorder in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of embodiments 1 to 30, a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46.

56. The method of embodiment 54, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

57. The method of embodiment 54, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

58. The method of embodiment 57, wherein the blood fat disorder is selected from high triglyceride level, low HDL cholesterol level, high LDL cholesterol level, plaque buildup in artery walls, or a combination thereof.

59. The method of embodiment 57, wherein the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood.

60. The method of embodiment 57, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

61. The method of embodiment 55, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

62. A therapeutic kit comprising a GIP analogue according to any one of embodiments 1 to 30, a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46, each optionally in combination with a pharmaceutically acceptable carrier.

63. A device comprising a GIP analogue according to any one of embodiments 1 to 30, a nucleic acid molecule according to embodiment 44, an expression vector according to embodiment 45, or a host cell according to embodiment 46, for delivery of the GIP analogue to a subject.

64. A pharmaceutical composition comprising the GIP analogue of any one of embodiments 1 to 30 for use in treating a stomach and bowel-related disorder in a patient in need thereof.

65. A pharmaceutical composition comprising the GIP analogue of any one of embodiments 1 to 30 for use in treatment and/or prevention of a metabolic disease or disorder in a patient in need thereof.

66. The pharmaceutical composition of embodiment 65, wherein the metabolic disorder is selected from diabetes and obesity.

67. A pharmaceutical composition comprising the GIP analogue of any one of embodiments 1 to 30 for use in treatment and/or prevention of a diabetes related disorder in a patient in need thereof.

68. A pharmaceutical composition comprising the GIP analogue of any one of embodiments 1 to 30 for use in treatment and/or prevention of an obesity related disorder in a patient in need thereof.

69. The pharmaceutical composition of embodiment 67, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension and dyslipidemia, or a combination thereof.

70. The pharmaceutical composition of embodiment 67, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

71. The pharmaceutical composition of embodiment 70, wherein the blood fat disorder is selected from high triglyceride level, low HDL cholesterol level, high LDL cholesterol level, plaque buildup in artery walls, or a combination thereof.

72. The pharmaceutical composition of embodiment 70, wherein the prothrombotic state is selected from high fibrinogen levels in the blood, and high plasminogen activator inhibitor-1 levels in the blood.

73. The pharmaceutical composition of embodiment 70, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

74. The pharmaceutical composition of embodiment 68, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease, and obesity induced sleep apnea.

In Formulae I, Ia, Ib, I', Ia' and Ib', residues X30 to X42 may be present or absent. They are not present or absent independently of one another. If any one of these residues is absent, then all residues C-terminus of that residue are also absent. Thus, the only combinations of residues which can be absent are X42; X41-X42; X40-X41-X42; X39-X40-X41-X42; X38-X39-X40-X41-X42; X37-X38-X39-X40-X41-X42; X36-X37-X38-X39-X40-X41-X42; X35-X36-X37-X38-X39-X40-X41-X42; X34-X35-X36-X37-X38-X39-X40-X41-X42; X33-X34-X35-X36-X37-X38-X39-X40-X41-X42; X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42; X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42; X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42. To put it another way, if residue XN is present (where N is an integer between 30 and 42) then residue X(N-1) is also present.

For all of the embodiments described above, it may be desirable that the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDKKAQRAFVEWLLAQ (SEQ ID NO: 70). The amino acid sequence X1-X29 may, for example, have no more than 5, 4, 3, 2 or 1 amino acid differences from that sequence.

For all of the embodiments described above, it may be desirable that the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA (SEQ ID NO: 71). The amino acid sequence X1-X29 may, for example, have no more than 5, 4, 3, 2 or 1 amino acid differences from that sequence.

For all of the embodiments described above, it may be desirable that the amino acid sequence X1-X29 has no more than 5 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDEKAAKEFIEWLESA (SEQ ID NO: 72). The amino acid sequence X1-X29 may, for example, have no more than 4, 3, 2 or 1 amino acid differences from that sequence.

Brief Description of the Drawings

[0030] Figure 1: Effect of Compounds 32 and 33 on glucose tolerance. Compound 32, Compound 33 and liraglutide significantly improved glucose tolerance as compared to vehicle at all time points ($p < 0.05$). At time t = 60 min, Compound 33 caused a statistically significant greater reduction ($p < 0.05$) in blood glucose than liraglutide. *, $p < 0.05$ vs. vehicle; #, $p < 0.05$ vs. liraglutide. Two-way ANOVA followed by Bonferroni post-tests were used for the statistical analysis. Data are mean ± SEM; n = 2-6.

[0031] Figure 2: Body weight during the 21-days treatment period (**A**) and absolute body weight changes (delta Δ = body weight at day 21 – body weight at day 0) (**B**). Data are means ± SEM; n = 7-10.

[0032] **Figure 3:** Percent body fat mass (delta Δ = fat mass at day 19 – fat mass before treatment) (**A**) and percent body lean mass (delta Δ = lean mass at day 19 – lean mass before treatment) (**B**) on day 19. Data are means ± SEM; n = 7-10.

[0033] **Figure 4:** Accumulated food intake. Food intake was not measured on day 14. Data are means ± SEM; n = 7-10.

[0034] **Figure 5:** Blood glucose (**A**) and plasma insulin (**B**) on day 13. The blood samples were taken from 4-hour fasted mice. The mice were not dosed in the morning prior to the blood sampling. Data are means ± SEM; n = 7-10.

[0035] **Figure 6:** Blood glucose (**A**) and plasma insulin (**B**) on day 21. The mice were injected with vehicle, liraglutide or test substance 2 hours prior to the blood sampling. Data are means ± SEM; n = 7-10.

[0036] **Figure 7:** Plasma total cholesterol (**A**), plasma LDL cholesterol (**B**), plasma HDL cholesterol (**C**), and plasma triglycerides (**D**) on day 21. Data are means ± SEM; n = 7-10.

Detailed Description of the Invention

[0037] 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.

[0038] All publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

[0039] Each embodiment of the invention described herein may be taken alone or in combination with one or more other embodiments of the invention.

Definitions

[0040] Unless specified otherwise, the following definitions are provided for specific terms, which are used in the above written description.

[0041] Throughout this specification, the word "comprise" or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

[0042] The singular forms "a," "an," and "the" include the plurals unless the context clearly dictates otherwise.

[0043] The term "including" is used to mean "including but not limited to." "Including" and "including but not limited to" are used interchangeably.

[0044] The terms "patient," "subject," and "individual" may be used interchangeably and refer to either a human or a non-human animal. These terms include mammals such as humans, primates, livestock animals (e.g., bovines, porcines), companion animals (e.g., canines, felines) and rodents (e.g., mice and rats).

[0045] The term "solvate" in the context of the present invention refers to a complex of defined stoichiometry formed between a solute (*in casu*, a peptide conjugate or pharmaceutically acceptable salt thereof according to the invention) and a solvent. The solvent in this connection may, for example, be water, ethanol or another pharmaceutically acceptable, typically small-molecular organic species, such as, but not limited to, acetic acid or lactic acid. When the solvent in question is water, such a solvate is normally referred to as a hydrate.

[0046] The term "agonist" as employed in the context of the invention refers to a substance (ligand) that activates the receptor type in question.

[0047] Throughout the description and claims the conventional one-letter and three-letter codes for natural amino acids are used as well as generally accepted three letter codes for other α-amino acids, such as sarcosine (Sar), norleucine (Nle), α-aminoisobutyric acid (Aib) and β-(1-naphthyl)-alanine (1Nal). All amino acid residues in peptides of the invention are preferably of the L-configuration. However, D-configuration amino acids may also be present.

[0048] Among sequences disclosed herein are sequences incorporating an "Hy-" moiety at the amino terminus (N-terminus) of the sequence, and either an "-OH" moiety or an "$-NH_2$" moiety at the carboxy terminus (C-terminus) of the sequence. In such cases, and unless otherwise indicated, an "Hy-" moiety at the N-terminus of the sequence in question indicates a hydrogen atom [e.g., R^1 = Hy- in formulas I I(a), I(b), II, II(a) or II(b); corresponding to the presence of a free

primary or secondary amino group at the N-terminus], while an "-OH" or an "–NH_2" moiety at the C-terminus of the sequence indicates a hydroxy group [e.g., R^2 = OH in formulas I I(a), I(b), II, II(a) or II(b); corresponding to the presence of a carboxy (COOH) group at the C-terminus] or an amino group [e.g., R^2 = NH_2 in formulas I I(a), I(b), II, II(a) or II(b); corresponding to the presence of an amido ($CONH_2$) group at the C-terminus], respectively. In each sequence of the invention, a C-terminal "–OH" moiety may be substituted for a C-terminal "–NH_2" moiety, and vice-versa.

[0049] As used herein "conservative substitution" means that an amino acid residue belonging to a certain position of the native human GIP peptide sequence has been exchanged with an amino acid residue belonging to the same group (I, II, III, IV, V, 1, 2, 3) as defined in the following table:

I	II	III	IV	V
A	N	H	M	F
S	D	R	L	Y
T	E	K	I	W
P	Q		V	
G			C	

[0050] In the scheme below, conservative substitutions of amino acids are grouped by physicochemical properties. I: neutral or hydrophobic, II: acidic, III: basic, IV: polar, V: aromatic.

I	II	III	IV	V
A	E	H	M	F

L	D	R	S	Y
I		K	T	W
P			C	
G			N	
V			Q	

[0051] A "non-conservative" substitution as used herein means any other substitution of an amino acid residue of the native human GIP sequence, e.g. such as substituting with a non-protein amino acid (Sar, Nle, Aib, 1Nal) or substituting with an amino acid which does not belong to the same group.
In some embodiments, the peptide conjugate of the invention may comprise functional fragments or variants thereof that have at most 34, 33, 32, 31 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions compared to one or more of the specific sequences recited below.

[0052] Preferred compounds of the present invention have at least one GIP and one GLP-1 biological activity, in particular in treatment of metabolic diseases such as diabetes and obesity. This can be assessed, e.g., in *in vivo* assays, for example as described in the examples, in which the blood glucose level or another biological activity is determined after a test animal has been treated or exposed to a GIP analogue. In particular, compounds of the invention may be capable of improving glycaemic control when adminstered to a diabetic subject. Additionally or alternatively, they may be capable of reducing body weight when administered to an overweight or obese subject. In either case, the effect may be superior to that obtained with an equivalent quantity (by mass, or molar ratio) of wild type human GIP or GLP-1 in comparable subjects when given according to a comparable dosing regime.

[0053] Activity in *in vitro* assays may also be used as a measure of the compounds' activity. Typically the compounds have activity at both the GLP-1 and GIP receptors. EC_{50} values may be used as a numerical measure of agonist potency at a given receptor. An EC_{50} value is a measure of the concentration of a compound required to achieve half of that compound's maximal activity in a particular assay. Thus, for example, a compound having EC_{50} [GLP-1R] lower

than the EC_{50} [GLP-1R] of native glucagon in a particular assay may be considered to have higher potency at the GLP-1R than glucagon. In some embodiments of the present invention, the EC_{50} GLP-1-R and/or EC_{50} GIP-R is below 1.0 nM, below 0.9 nM, below 0.8 nM, below 0.7 nM, below 0.6 nM, below 0.5 nM, below 0.4 nM, below 0.3 nM, below 0.2 nM, below 0.1 nM, below 0.09 nM, below 0.08 nM, below 0.07 nM, below 0.06 nM, below 0.05 nM, below 0.04 nM, below 0.03 nM, below 0.02 nM, below 0.01 nM, below 0.009 nM, below 0.008 nM, below 0.007 nM, below 0.006 nM, or below 0.005 nM, e.g. when assessed using the assay described in Example 2. In any given assay, the EC_{50} value of a compound in a given assay may be assessed relative to the EC_{50} of human GIP. Thus, the ratio of the EC_{50} value of the test compound to the EC_{50} value of wild type human GIP (EC_{50}[test compound] / EC_{50}[GIP]) at the human GIP receptor may be less than 10, less than 5, less than 1, less than 0.1, less than 0.05 or less than 0.01. The ratio of the EC_{50} value of the test compound to the EC_{50} value of wild type human GIP (EC_{50}[test compound] / EC_{50}[GIP]) at the GLP-1 receptor may be less than 10, less than 5, less than 1, less than 0.1, less than 0.05 or less than 0.01. It may also be desirable to compare the ratio of EC_{50} values at the two receptors for the test compound and for human GIP. Preferably the test compound has an EC_{50}[GIP] / EC_{50}[GLP-1] which is greater than the equivalent ratio for GIP in the same assays.

[0054] The GIP analogue compounds of the present invention have one or more amino acid substitutions, deletions, inversions, or additions compared with native GIP and as defined above. This definition also includes the synonym terms GIP mimetics and/or GIP-GLP1 agonists. Further, the analogue of the present invention may additionally have chemical modification of one or more of its amino acid side groups, α-carbon atoms, terminal amino group, or terminal carboxylic acid group. A chemical modification includes, but is not limited to, adding chemical moieties, creating new bonds, and removing chemical moieties. Modifications at amino acid side groups include, without limitation, acylation of lysine ε-amino groups, N-alkylation of arginine, histidine, or lysine, alkylation of glutamic or aspartic carboxylic acid groups, and deamidation of glutamine or asparagine. Modifications of the terminal amino include, without limitation, the des-amino, N-lower alkyl, N-di-lower alkyl, and N-acyl modifications. Modifications of the terminal carboxy group include, without limitation, the amide, lower alkyl amide, dialkyl amide, and lower alkyl ester modifications. Preferably herein lower alkyl is

C_1-C_4 alkyl. Furthermore, one or more side groups, or terminal groups, may be protected by protective groups known to the ordinarily-skilled peptide chemist. The α-carbon of an amino acid may be mono- or di-methylated.

[0055] Exemplary GIP analogue compounds of the present invention (formulae I, II, III or IV) are described below, where said compounds may be modified at the N-terminus and C-terminus as described for R1 and R2, and include a pharmaceutically acceptable salt, solvate or derivative thereof:

Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK	SEQ ID NO. 3
Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS	SEQ ID NO. 4
Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K	SEQ ID NO. 5
Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK	SEQ ID NO. 6
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 7
YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 8
YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 9
Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 10
Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 11
Y-Aib-EGTFTSDSSIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 12
Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 13
Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 14
Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 15
Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 16
Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K	SEQ ID NO. 17
Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K	SEQ ID NO. 18
Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K	SEQ ID NO. 19
Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K	SEQ ID NO. 20
Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K	SEQ ID NO. 21
Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K	SEQ ID NO. 22

Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K	SEQ ID NO. 23
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLSA-Aib-K	SEQ ID NO. 24
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K	SEQ ID NO. 25
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K	SEQ ID NO. 26
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-KYG-1Nal-LDF	SEQ ID NO. 27
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLAYG-1Nal-LDF	SEQ ID NO. 28
Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K	SEQ ID NO. 29
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS	SEQ ID NO. 30
Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS	SEQ ID NO. 31
Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK	SEQ ID NO. 32
Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K	SEQ ID NO. 35
Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS	SEQ ID NO. 36
Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS	SEQ ID NO. 37
Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA	SEQ ID NO. 38
Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS	SEQ ID NO. 39
Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS	SEQ ID NO. 40
Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA	SEQ ID NO. 41
Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA	
Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA	SEQ ID NO. 42
Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA	SEQ ID NO. 43
Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA	SEQ ID NO. 44

Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA	SEQ ID NO. 45
Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA	SEQ ID NO. 46
Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA	SEQ ID NO. 47
Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA	SEQ ID NO. 48
Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA	SEQ ID NO. 49
Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA	SEQ ID NO. 50
Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA	SEQ ID NO. 51
Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA	SEQ ID NO. 52
Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA	SEQ ID NO. 53
Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA	SEQ ID NO. 54
Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA	SEQ ID NO. 55
Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS	SEQ ID NO. 56
Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS	SEQ ID NO. 57
Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS	SEQ ID NO. 58
Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA	SEQ ID NO: 69

Lipophilic substituents

[0056] One or more of the amino acid side chains in a compound employed in the context of the invention may be conjugated to a lipophilic substituent Z^1. Without wishing to be bound by theory, it is thought that the lipophilic substituent binds albumin in the blood stream, thus shielding the compounds employed in the context of the invention from enzymatic degradation which can enhance the half-

life of the compounds. The lipophilic substituent may also modulate the potency of the compound, *e.g.*, with respect to the GIP receptor and/or the GLP-1 receptor.

[0057] In certain embodiments, only one amino acid side chain is conjugated to a lipophilic substituent. In other embodiments, two amino acid side chains are each conjugated to a lipophilic substituent. In yet further embodiments, three or even more amino acid side chains are each conjugated to a lipophilic substituent. When a compound contains two or more lipophilic substituents, they may be the same or different.

[0058] The lipophilic substituent Z^1 may be covalently bonded to an atom in the amino acid side chain, or alternatively may be conjugated to the amino acid side chain by one or more spacers Z^2.

[0059] The term "conjugated" is used here to describe the covalent attachment of one identifiable chemical moiety to another, and the structural relationship between such moieties. It should not be taken to imply any particular method of synthesis. The spacer Z^2, when present, is used to provide a spacing between the compound and the lipophilic moiety.

[0060] The lipophilic substituent may be attached to the amino acid side chain or to the spacer via an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. Accordingly it will be understood that preferably the lipophilic substituent includes an acyl group, a sulphonyl group, an N atom, an O atom or an S atom which forms part of the ester, sulphonyl ester, thioester, amide or sulphonamide. Preferably, an acyl group in the lipophilic substituent forms part of an amide or ester with the amino acid side chain or the spacer.

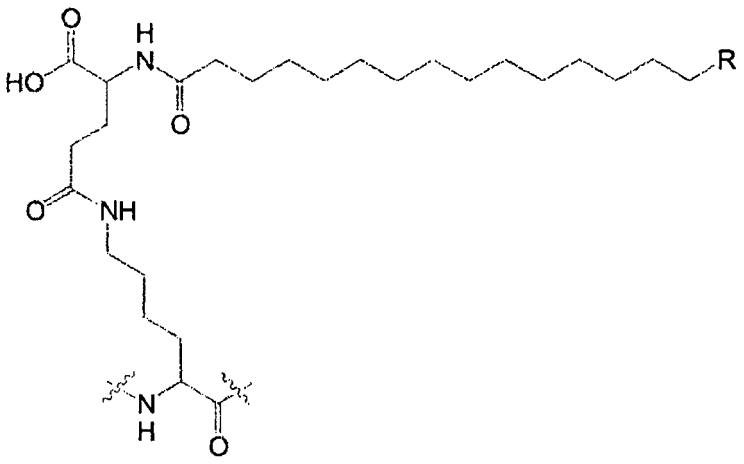
[0061] The lipophilic substituent may include a hydrocarbon chain having 10 to 24 carbon (C) atoms, e.g. 10 to 22 C atoms, e.g. 10 to 20 C atoms. Preferably it has at least 11 C atoms, and preferably it has 18 C atoms or fewer. For example, the hydrocarbon chain may contain 12, 13, 14, 15, 16, 17 or 18 carbon atoms. The hydrocarbon chain may be linear or branched and may be saturated or unsaturated. Furthermore, it can include a functional group in the end of the lipophilic chain, e.g., carboxylic acid which may or may not be protected during synthesis. From the discussion above it will be understood that the hydrocarbon chain is preferably substituted with a moiety which forms part of the attachment to the amino acid side chain or the spacer, for example an acyl group, a sulphonyl group, an N atom, an O atom or an S atom.

[0062] Most preferably, the hydrocarbon chain is substituted with acyl, and accordingly the hydrocarbon chain may be part of an alkanoyl group, for example a dodecanoyl, 2-butyloctanoyl, tetradecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl or eicosanoyl group. An example of a functionalized hydrocarbon chain is the 15-carboxy-pentadecanoyl.

[0063] As mentioned above, the lipophilic substituent Z^1 may be conjugated to the amino acid side chain by one or more spacers Z^2. When present, the spacer is attached to the lipophilic substituent and to the amino acid side chain. The spacer may be attached to the lipophilic substituent and to the amino acid side chain independently by an ester, a sulphonyl ester, a thioester, an amide or a sulphonamide. Accordingly, it may include two moieties independently selected from acyl, sulphonyl, an N atom, an O atom or an S atom. The spacer may consist of a linear C1-10 hydrocarbon chain or more preferably a linear C1-5 hydrocarbon chain. Furthermore, the spacer may be substituted with one or more substituents selected from C1-6 alkyl, C1-6 alkyl amine, C1-6 alkyl hydroxy and C1-6 alkyl carboxy.

[0064] The spacer may be, for example, a residue of any naturally occurring or unnatural amino acid. For example, the spacer may be a residue of Gly, Pro, Ala, Val, Leu, Ile, Met, Cys, Phe, Tyr, Trp, His, Lys, Arg, Gln, Asn, α-Glu, γ-Glu, ε-Lys, Asp, Ser, Thr, Gaba, Aib, β-Ala (i.e. 3-aminopropanoyl), 4-aminobutanoyl, 5-aminopentanoyl, 6-aminohexanoyl, 7-aminoheptanoyl, 8-aminooctanoyl, 9-aminononanoyl, 10-aminodecanoyl or 8-amino-3,6-dioxaoctanoyl. In certain embodiments, the spacer is a residue of Glu, γ-Glu, ε -Lys, β-Ala (i.e. 3-aminopropanoyl), 4-aminobutanoyl, 8- aminooctanoyl or 8-amino-3,6-dioxaoctanoyl. In the present context, γ-Glu and isoGlu are used interchangeably. The amino acid side chain to which the lipophilic substituent is conjugated is a side chain, e.g., of a Glu, Lys, Ser, Cys, Dbu, Dpr or Orn residue. For example, it may be a side chain of a Lys, Glu or Cys residue. Where two or more side chains carry a lipophilic substituent, they may be independently selected from these residues. Thus the amino acid side chain includes a carboxy, hydroxyl, thiol, amide or amine group, for forming an ester, a sulphonyl ester, a thioester, an amide, or a sulphonamide with the spacer or lipophilic substituent.

[0065] An example of a lipophilic substituent comprising a lipophilic moiety Z^1 and spacer Z^2 is shown in the formula below:



[0066] Here, the side chain of a Lys residue is covalently attached to a γ-Glu spacer (Z^2) via an amide linkage. A hexadecanoyl group (Z^1, R=CH_3) is covalently attached to the γ-Glu spacer via an amide linkage. This combination of lipophilic moiety and spacer, conjugated to a Lys residue, may be referred to by the short-hand notation K(Hexadecanoyl-γ-Glu), *e.g.*, when shown in formulae of specific compounds. γ-Glu can also be referred to as isoGlu, and a hexadecanoyl group as a palmitoyl group. Thus it will be apparent that the notation (Hexadecanoyl-γ-Glu) is equivalent to the notations (isoGlu(Palm)) or (isoGlu(Palmitoyl)) as used for example in PCT/GB2008/004121. In different embodiments, the 15-carboxy-pentadecanoyl group (Z^2, R=COOH) is covalently attached to the γ-Glu spacer via an amide linkage. The combination of lipophilic moiety with a functional group like COOH and a spacer, conjugated to a Lys residue may be referred to as K(15-carboxy-pentadecanoyl-γ–Glu) or K(15-carboxy-pentadecanoyl- isoGlu).

[0067] In certain embodiments, a GIP analogue of the invention is conjugated with a lipophilic substituent to one or more of amino acid positions 16, 17,19, 20, 24, 27, 28, 30 and 32.

[0068] The skilled person will be well aware of suitable techniques for preparing the compounds employed in the context of the invention. For examples of suitable chemistry, see, e.g., WO98/08871, WO00/55184, WO00/55119, Madsen et al. (*J. Med. Chem.* 2007, 50, 6126-32), and Knudsen et al. 2000 (*J. Med Chem.* 43, 1664-1669).

Non-proteinogenic amino acids

[0069] One or more of the amino acids of a GIP analogue compound may be a non-proteinogenic (non-naturally occurring) amino acid. Non-proteinogenic amino acids may include those amino acids not encompassed by the 20 "standard"

amino acids used in protein synthesis, *e.g.*, alanine, arginine, aspartate, asparagine, cysteine, glutamate, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. Examples of non-proteinogenic amino acids include, but are not limited to, para amino benzoic acid (PABA), 2-amino benzoic acid, anthranilic acid, p-hydroxybenzoic acid (PHBA), 3-amino benzoic acid, 4-aminomethyl benzoic acid, 4-amino salicylic acid (PAS), 4-amino cyclohexanoic acid 4-amino-phenyl acetic acid, 4-amino-hippuric acid, 4-amino-2-chlorobenzoic acid, 6-aminonicotinic acid, methyl-6-aminonicotinate, 4-amino methyl salicylate, 2-amino thiazole-4-acetic acid, 2-amino-4-(2-aminophenyl)-4-oxobutanoic acid (L-kynurenine), O-methyl serine, acetylamino alanine, β-alanine, β -(acetylamino)alanine, β-aminoalanine, β-chloroalanine, citrulline, homocitrulline, hydroxyproline, homoarginine, homoserine, homotyrosine, homoproline, ornithine, 4-amino-phenylalanine, sarcosine, biphenylalanine, homophenylalanine, 4-nitro-phenylalanine, 4-fluoro-phenylalanine, 2,3,4,5,6-pentafluoro-phenylalanine, norleucine, cyclohexylalanine, *N*-methyl-alanine, *N*-methyl-glycine, *N*-methyl-glutamic acid, tert-butylglycine, α-aminobutyric acid, α-aminoisobutyric acid (AIB), 2-aminoisobutyric acid, 2-aminoindane-2-carboxylic acid, selenomethionine, lanthionine, dehydroalanine, γ-aminobutyric acid, naphthylalanine, aminohexanoic acid, phenylglycine, pipecolic acid, 2,3-diaminoproprionic acid, tetrahydroisoquinoline-3-carboxylic acid, taurine, tert-leucine, tert-butylalanine, cyclohexylglycine, diethylglycine, and dipropylglycine.

C-terminal amidation

[0070] The major biologically active fragment of a GIP analogue is produced as a 42-amino acid peptide with a free carboxylic acid at the C-terminal. In some embodiments, a compound employed in the context of the invention may also comprise a truncated or full length analogue of naturally occurring GIP and further comprise a C-terminal modification, e.g., amidation.

Clinical utility

[0071] The GIP analogue compounds employed in the context of the invention may provide an attractive treatment option for metabolic diseases including obesity, diabetes mellitus (diabetes), obesity-related disorders, and diabetes-related disorders. Diabetes comprises a group of metabolic diseases

characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes is classified into type 1 diabetes, type 2 diabetes and gestational diabetes on the basis on pathogenic characteristics. Type 1 diabetes accounts for 5-10% of all diabetes cases and is caused by auto-immune destruction of insulin-secreting pancreatic β-cells. Acute signs of diabetes include excessive urine production, resulting compensatory thirst and increased fluid intake, blurred vision, unexplained weight loss, lethargy, and changes in energy metabolism. However, in type 2 diabetes symptoms are often not severe or may be absent. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, notably the eyes, kidneys, nerves, heart and blood vessels.

[0072] Type 2 diabetes accounts for 90-95% of diabetes cases and is a result of a complex set of metabolic disorders. However, symptoms are often not severe or may be absent. Type 2 diabetes is the consequence of endogenous insulin production becoming insufficient to maintain plasma glucose levels below diagnostic thresholds.

[0073] Gestational diabetes refers to any degree of glucose intolerance identified during pregnancy.

[0074] Pre-diabetes includes impaired fasting glucose and impaired glucose tolerance and refers to those states that occur when blood glucose levels are elevated but below the levels that are established for the clinical diagnosis for diabetes.

[0075] A large proportion of people with type 2 diabetes and pre-diabetes are at increased risk of morbidity and mortality due to the high prevalence of additional metabolic risk factors, including abdominal obesity (excessive fat tissue around the abdominal internal organs), atherogenic dyslipidemia (blood fat disorders including high triglycerides, low HDL cholesterol and/or high LDL cholesterol, which foster plaque buildup in artery walls), elevated blood pressure (hypertension) a prothrombotic state (e.g. high fibrinogen or plasminogen activator inhibitor- 1 in the blood), and/or a proinflammatory state (e.g., elevated C-reactive protein in the blood).

[0076] Conversely, obesity confers an increased risk of developing pre-diabetes, type 2 diabetes as well as, e.g., certain types of cancer, obstructive sleep apnea and gall-bladder disease. Dyslipidemia is associated with increased risk of cardiovascular disease. High Density Lipoprotein (HDL) is of clinical

importance since an inverse correlation exists between plasma HDL concentrations and risk of atherosclerotic disease. The majority of cholesterol stored in atherosclerotic plaques originates from LDL and hence an elevated concentration of Low Density Lipoproteins (LDL) is closely associated with atherosclerosis. The HDL/LDL ratio is a clinical risk indictor for atherosclerosis and coronary atherosclerosis in particular.

[0077] Compounds employed in the context of the invention act as GIP-GLP1 dual agonists. The dual agonist may combine the effect of GIP, *e.g.*, on fat metabolism and weight loss, and blood glucose, with the effect of GLP-1, *e.g.*, on blood glucose levels and food intake. They may therefore act to accelerate elimination of excessive adipose tissue, induce sustainable weight loss, and improve glycemic control. Dual GIP-GLP1 agonists may also act to reduce cardiovascular risk factors such as high cholesterol, such as high LDL-cholesterol.

[0078] The GIP-GLP1 dual agonist compounds of the present invention may therefore be used as pharmaceutical agents for preventing weight gain, promoting weight loss, reducing excess body weight or treating obesity (e.g., by control of appetite, feeding, food intake, calorie intake, and/or energy expenditure and lipolysis), including morbid obesity, as well as associated diseases and health conditions including but not limited to obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea. The GIP-GLP1 dual agonist compounds employed in the context of the invention may also be used for treatment of insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose, type 2 diabetes, hypertension, dyslipidemia (or a combination of these metabolic risk factors), atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke. These are all conditions which may be associated with obesity. However, the effects of the compounds employed in the context of the invention on these conditions may be mediated in whole or in part via an effect on body weight, or may be independent thereof. The GIP-GLP1 dual agonist compounds employed in the context of the invention may also be used for treating a stomach and/or bowel-related disorder.

[0079] The GIP-GLP1 dual agonist compounds, nucleic acids, vectors, host cells, and pharmaceutical compositions thereof, also may be used for the treatment and/or prevention of any of the diseases, disorders, or conditions described herein, including metabolic diseases, diabetes or diabetes related disorders, stomach and/or bowel related disorder, and/or obesity or obesity

related disorders. In some embodiments, the GIP-GLP1 dual agonist compounds, nucleic acids, vectors, host cells, also may be used for the preparation of a medicament for the treatment and/or prevention of any of the diseases, disorders, or conditions described herein, including metabolic diseases, diabetes or diabetes related disorders, and/or obesity or obesity related disorders. In certain embodiments, the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof. In certain embodiments, the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and proinflammatory state, or a combination thereof. In certain embodiments, the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, plaque buildup in artery walls, or a combination thereof. In certain embodiments, the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood. In certain embodiments, the proinflammatory state is an elevated C-reactive protein level in the blood. In certain embodiments, the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

[0080] In some embodiments, the invention also provides a therapeutic kit comprising a GIP analogue of the invention, a nucleic acid molecule of the invention, an expression vector of the invention, or a host cell of the invention, each optionally in combination with a pharmaceutically acceptable carrier. In some embodiments, the invention provides a device comprising a GIP analogue of the invention, a nucleic acid molecule of the invention, an expression vector of the invention, or a host cell of the invention for delivery of the GIP analogue to a subject.

Pharmaceutical compositions

[0081] The GIP-GLP1 dual agonist compounds of the present invention, or salts or solvates thereof, may be formulated as pharmaceutical compositions prepared for storage or administration, which typically comprise a therapeutically effective amount of a compound employed in the context of the invention, or a salt or

solvate thereof, in a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of the GIP-GLP1 dual agonist compound

[0082] The therapeutically effective amount of a compound of the present invention will depend, e.g., on the route of administration, the type of mammal being treated, and the physical characteristics of the specific mammal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy, and may depend on such factors as weight, diet, concurrent medication and other factors, well known to those skilled in the medical arts. The dosage sizes and dosing regimen most appropriate for human use may be guided by the results obtained by the present invention, and may be confirmed in properly designed clinical trials.

[0083] An effective dosage and treatment protocol may be determined by conventional means, starting with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well. Numerous factors may be taken into consideration by a clinician when determining an optimal dosage for a given subject. Such considerations are known to the skilled person. The term "pharmaceutically acceptable carrier" includes any of the standard pharmaceutical carriers. Pharmaceutically acceptable carriers for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). For example, sterile saline and phosphate- buffered saline at slightly acidic or physiological pH may be used. Suitable pH buffering agents may be, e.g., phosphate, citrate, acetate, lactate, maleate, tris/hydroxymethyl)aminomethane (TRIS), *N*-Tris(hydroxymethyl)methyl-3-aminopropanesulphonic acid (TAPS), ammonium bicarbonate, diethanolamine, histidine, which in certain embodiments is a preferred buffer, arginine, lysine, or acetate or mixtures thereof. The term further encompasses any agents listed in the US Pharmacopeia for use in animals, including humans.

[0084] The term "pharmaceutically acceptable salt" refers to a salt of the compound. Salts include pharmaceutically acceptable salts, such as, e.g., acid addition salts and basic salts. Examples of acid addition salts include

hydrochloride salts, citrate salts and acetate salts. Examples of basic salts include salts where the cation is selected from alkali metals, such as sodium and potassium, alkaline earth metals such as calcium, and ammonium ions $^{+}N(R^3)_3(R^4)$, where R^3 and R^4 independently designate optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl. Other examples of pharmaceutically acceptable salts are described in "Remington's Pharmaceutical Sciences" ,17th edition. Ed. Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, U.S.A., 1985 and more recent editions, and in the Encyclopaedia of Pharmaceutical Technology.

[0085] "Treatment" is an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" may also mean prolonging survival as compared to expected survival if not receiving treatment. "Treatment" is an intervention performed with the intention of preventing the development or altering the pathology of a disorder. Accordingly, "treatment" refers to both therapeutic treatment and prophylactic or preventative measures in certain embodiments. Those in need of treatment include those already with the disorder as well as those in which the disorder is to be prevented. By treatment is meant inhibiting or reducing an increase in pathology or symptoms (e.g. weight gain, hyperglycemia) when compared to the absence of treatment, and is not necessarily meant to imply complete cessation of the relevant condition.

[0086] The pharmaceutical compositions of the invention may be in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms. It may be provided in single dose injectable form, for example in the form of an injection pen. Compositions may be formulated for any suitable route and means of administration. Pharmaceutically acceptable carriers or diluents include those used in formulations suitable for oral, rectal, nasal or parenteral (including

subcutaneous, intramuscular, intravenous, intradermal, and transdermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Subcutaneous or transdermal modes of administration may be particularly suitable for certain of the compounds described herein.

Combination therapy

[0087] In certain embodiments, a GIP-GLP-1 dual agonist compound employed in the context of the invention may be administered as part of a combination therapy with at least one other agent for treatment of diabetes, obesity, dyslipidemia, or hypertension.

[0088] In such cases, the at least two active agents may be given together or separately, and as part of the same pharmaceutical formulation or as separate formulations. Thus, the GIP-GLP-1 dual agonist compound employed in the context of the invention (or the salt or solvate thereof) may be used in combination with an antidiabetic agent including but not limited to metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, or insulin. In certain embodiments, the compound or salt or solvate thereof is used in combination with insulin, DPP-IV inhibitor, sulfonylurea or metformin, particularly sulfonylurea or metformin, for achieving adequate glycemic control. In certain preferred embodiments, the compound or salt or solvate thereof is used in combination with insulin or an insulin analogue for achieving adequate glycemic control. Examples of insulin analogues include but are not limited to Lantus®, NovoRapid®, Humalog®, NovoMix®, Actraphane HM®, Levemir® and Apidra®.

[0089] In certain embodiments, the GIP-GLP-1 dual agonist compound or salt or solvate thereof may further be used in combination with one or more of an anti-obesity agent, including but not limited to a glucagon-like peptide receptor 1 agonist, peptide YY or analogue thereof, cannabinoid receptor 1 antagonist, lipase inhibitor, melanocortin receptor 4 agonist, or melanin concentrating hormone receptor 1 antagonist.

[0090] In certain embodiments, the GIP-GLP-1 dual agonist compound or salt or solvate thereof may be used in combination with an anti-hypertension agent, including but not limited to an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretics, beta-blocker, or calcium channel blocker.

[0091] In certain embodiments, the GIP-GLP-1 dual agonist compound or salt thereof may be used in combination with an anti-dyslipidemia agent, including but not limited to a statin, a fibrate, a niacin and/or a cholesterol absorption inhibitor.

Nucleic acids, vectors, and host cells

[0092] In some embodiments, the invention provides a nucleic acid molecule comprising a nucleic acid sequence encoding a GIP analogue of the invention. In some embodiments, the invention provides an expression vector comprising a nucleic acid sequence encoding a GIP analogue of the invention, in combination with control sequences to direct its expression. In some embodiments, the invention provides a host cell transformed with such an expression vector. In some embodiments, the invention provides a method of producing a GIP analogue of the invention, the method comprising culturing the host cells described above under conditions suitable for expressing the GIP analogue and purifying the GIP analogue thus produced. In some embodiments, the invention provides a nucleic acid molecule, an expression vector, or a host cell, as described above, for use in therapy. In some embodiments, the invention provides the use of a nucleic acid molecule according, an expression vector, or a host cell, as described above, in the preparation of a medicament for the treatment and/or prevention of a metabolic disorder.

[0093] It will be understood that a nucleic acid will typically only be capable of encoding a polypeptide of the invention when the polypeptide sequence consists entirely of the 20 naturally occurring (proteinogenic) amino acids. However, nucleic acids may be employed which encode a fragment or precursor of the compound of the invention.

[0094] The peptide compounds of the invention may be manufactured by standard peptide synthetic methods, by use of recombinant expression systems, or by any other suitable method. Thus, the compounds may be synthesized in a number of ways, including, e.g., methods comprising:

(a) synthesizing the peptide compound by standard solid-phase or liquid-phase methodology, either stepwise or by fragment assembly, and isolating and purifying the final peptide compound product;

(b) expressing a nucleic acid construct that encodes the peptide compound or a fragment or precursor thereof in a host cell and recovering the expression product from the host cell culture; or

(c) effecting cell-free in vitro expression of a nucleic acid construct encoding the peptide compound or a fragment or precursor thereof, and recovering the expression product;

or by any combination of the methods of (a), (b) or (c) to obtain fragments of the peptide compound, subsequently joining (e.g., ligating) the fragments to obtain the peptide compound, and recovering the peptide compound.

[0095] The method of synthesis may comprise the step of chemically modifying one of more amino acid side chains in a precursor peptide to yield a compound of the invention. Such modification may, for example, introduce a non-naturally occurring amino acid, convert one or more amino acids into non-naturally occurring amino acids, introduce an intramolecular bridge between two amino acid side chains, e.g. by forming a lactam ring between a Glu and a Lys residue, or introduce a lipophilic substituent at a lysine residue.

[0096] It may be preferable to synthesize the peptide compounds of the invention by means of solid-phase or liquid-phase peptide synthesis. In this context, reference may be made to WO 98/11125 or, *inter alia*, Fields, G.B. et al., "Principles and Practice of Solid-Phase Peptide Synthesis"; in: Synthetic Peptides, Gregory A. Grant (ed.), Oxford University Press (2nd edition, 2002) and the synthesis examples herein.

[0097] Accordingly, the present invention also provides methods for producing a polypeptide of the invention according to above recited methods; a nucleic acid molecule encoding part or all of a polypeptide of the invention or a precursor thereof, a vector comprising at least one nucleic acid of the invention, expression vectors comprising at least one nucleic acid of the invention capable of producing a polypeptide of the invention when introduced into a host cell, and a host cell comprising a nucleic acid molecule, vector or expression vector of the invention.

Examples

[0098] The following examples demonstrate certain embodiments of the present invention. However, it is to be understood that these examples neither purport nor are they intended to be wholly definitive as to conditions and scope of this invention. The examples were carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. The following examples are presented for illustrative purposes only, and should not be construed in any way as limiting the scope of this invention.

[0099] Disclosed are GIP-GLP1 dual agonist compounds that exhibit signaling selectivity, and methods for screening these compounds. Signaling selectivity may be, for example, preferential pathway activation or preferential pathway inhibition, or both. The GIP-GLP1 dual agonist compounds may be useful for the treatment and/or prevention of diseases or conditions caused or characterized by excess body weight, including, but not limited to, obesity, morbid obesity, obesity linked inflammation, obesity linked gallbladder disease, obesity induced sleep apnea, metabolic syndrome, pre-diabetes, insulin resistance, glucose intolerance, type 2 diabetes, type I diabetes, hypertension, atherogenic dyslipidaemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease, and stroke or microvascular disease.

[0100] While some embodiments of the invention have been described by way of illustration, it will be apparent that the invention can be put into practice with many different modifications, variations and adaptations, and with the use of numerous equivalents or alternative solutions that are within the scope of persons skilled in the art, without departing from the spirit of the invention or exceeding the scope of the claims.

[0101] All publications, patents, and patent applications referred to herein are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

Example 1

[0102] The methods used in the instant invention are described below, except where expressly indicated otherwise.

General synthesis of acylated GIP analogues

[0103] Solid phase peptide synthesis was performed on a CEM Liberty Peptide Synthesizer using standard Fmoc chemistry. TentaGel S Ram resin (1 g; 0.25 mmol/g) was swelled in NMP (10 ml) prior to use and transferred between tube and reaction vessel using DCM and NMP.

Coupling

[0104] An Fmoc-amino acid in NMP/DMF/DCM (1:1:1 ; 0.2 M; 5 ml) was added to the resin in a CEM Discover microwave unit together with HATU/DMF or COMU/DMF (0.5 M; 2 ml) and DIPEA/NMP (2.0 M; 1 ml). The coupling mixture was heated to 75°C for 5 min while nitrogen was bubbled through the mixture. The resin was then washed with NMP (4 x 10 ml).

Deprotection

[0105] Piperidine/DMF (20%; 10 ml) was added to the resin for initial deprotection and the mixture was heated by microwaves (30 sec; 40°C). The reaction vessel was drained and a second portion of piperidine/NMP (20%; 10 ml) was added and heated (75°C; 3 min.) again. The resin was then washed with DMF (6 x 10 ml).

Side chain acylation

[0106] Fmoc-Lys(ivDde)-OH or alternatively another amino acid with an orthogonal side chain protective group was introduced at the position of the acylation. The N-terminal of the peptide backbone was then Boc-protected using Boc2O or alternatively by using a Boc-protected amino acid in the last coupling. While the peptide was still attached to the resin, the orthogonal side chain protective group was selectively cleaved using freshly prepared hydrazine hydrate (2-4%) in NMP for 2 x 15 min. The unprotected lysine side chain was first coupled with Fmoc-Glu-OtBu or another spacer amino acid, which was deprotected with piperidine and acylated with a lipophilic moiety using the peptide coupling methodology as described above. Alternatively, the acylation moiety was introduced as a premade building block e.g. Fmoc-Lys(hexadecanoyl-gamma-Glu)-OH where gamm-Glu is the coupling of Glutamic acid through the side-chain. Abbreviations employed are as follows:

COMU: 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)-dimethylamino-morpholinomethylene)]methanaminium hexaflourophosphate

ivDde: 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)3-methyl-butyl
Dde: 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)-ethyl
DCM: dichloromethane
DMF: *N*,*N*-dimethylformamide
DIPEA: diisopropylethylamine
EtOH: ethanol
Et_2O: diethyl ether
HATU: *N*-[(dimethylamino)-1H-1,2,3-triazol[4,5-b]pyridine-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide
MeCN: acetonitrile
NMP: *N*-methylpyrrolidone
TFA: trifluoroacetic acid
TIS: triisopropylsilane

Cleavage

[0107] The resin was washed with EtOH (3 x 10 ml) and Et_2O (3 x 10 ml) and dried to constant weight at room temperature (r.t.). The crude peptide was cleaved from the resin by treatment with TFA/TIS/water (95/2.5/2.5; 40 ml, 2 h; r.t.). Most of the TFA was removed at reduced pressure and the crude peptide was precipitated and washed three times with diethylether and dried to constant weight at room temperature.

HPLC purification of the crude peptide

[0108] The crude peptide was purified to greater than 90% by preparative reverse phase HPLC using a PerSeptive Biosystems VISION Workstation equipped with a C-18 column (5 cm; 10 µm) and a fraction collector and run at 35 ml/min with a gradient of buffer A (0.1% TFA, aq.) and buffer B (0.1% TFA, 90% MeCN, aq.). Fractions were analyzed by analytical HPLC and MS and relevant fractions were pooled and lyophilized. The final product was characterized by HPLC and MS.

[0109] The synthesized compounds are shown in Table 1 and Table 2.

Table 1.

Compound No.	Sequence
1	Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2
2	Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2
3	Hy-Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K-NH_2
4	Hy-Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH_2
5	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2

Table 2.

Compound No.	Sequence
6	pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2
7	Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2
8	Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2
9	Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2
10	Hy-Y-Aib-EGTFTSDSSIYLDKKAQRAFVNWLLA-Aib-K-NH_2
11	Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2
12	Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2
13	Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2
14	Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2
15	Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2
16	Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2
17	Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2
18	Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2
19	Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2
20	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2
21	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2
22	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLSA-Aib-K-NH_2

23	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2
24	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2
25	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-KYG-1Nal-LDF-NH_2
26	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLAYG-1Nal-LDF-NH_2
27	Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2
28	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2
29	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2
30	Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2
31	Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2
32	Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2
33	Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2
34	Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2
35	Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2
36	Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2
37	Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2
38	Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2
39	Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2
40	Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2
41	Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2
42	Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2
43	Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2
44	Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2

45	Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2
46	Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2
47	Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2
48	Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2
49	Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2
50	Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2
51	Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2
52	Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2
53	Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2
54	Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2
55	Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2
56	Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA

Synthesis of compound no. 36

[0110] Solid phase peptide synthesis was performed on a CEM Liberty Peptide Synthesizer using standard Fmoc chemistry. TentaGel S Ram S resin (1,05 g; 0.25 mmol/g) was swelled in DMF (10 ml) prior to use and transferred between tube and reaction vessel using DCM and DMF.

Coupling

[0111] An Fmoc-amino acid in DMF/DCM (2:1 ; 0.2 M; 5 ml) was added to the resin in a CEM Discover microwave unit together with COMU/DMF (0.5 M; 2 ml) and DIPEA&DMF (2.0 M; 1 ml). The coupling mixture was heated to 75°C for 5 min while nitrogen was bubbled through the mixture. The resin was then washed with DMF (4 x 10 ml). Fmoc-Tyr(OtBu)-Ser(Psi Me,Me)-OH pseudoproline was used for amino acid number 29 and 30 counting from the C-terminal. Fmoc-Lys(hexadecanoyl-gamma-Glu)-OH (2:1 ; 0.2 M; 5 ml) was incorporated as a premade building block using standard Fmoc coupling chemistry. The first 9 amino acids and amino acid number 24 (counting from the C-terminal) was double couple meaning the building block was coupled twice before deprotection.

Deprotection

[0112] Piperidine/DMF (20%; 10 ml) was added to the resin for initial deprotection and the mixture was heated by microwaves (30 sec; 40°C). The reaction vessel was drained and a second portion of piperidine/DMF (20%; 10 ml) was added and heated (75°C; 3 min.) again. The resin was then washed with DMF (6 x 10 ml).

[0113] The resin was washed with EtOH (3 x 10 ml) and Et2O (3 x 10 ml) and dried to constant weight at room temperature (r.t.). The crude peptide was cleaved from the resin by treatment with TFA/TIS/H_2O (95/2.5/2.5; 60 ml, 2 h; r.t.). Most of the TFA was removed at reduced pressure and the crude peptide was precipitated and washed three times with diethylether and dried to constant weight at room temperature.

HPLC purification of the crude peptide

[0114] The crude peptide was first purified to 45% by preparative reverse phase HPLC using a PerSeptive Biosystems VISION Workstation equipped with a Gemini NX 5µ C-18 110A, 10x250 mm column and a fraction collector and run at 35 ml/min with a gradient of buffer A (0.1% TFA, aq.) and buffer B (0.1% TFA, 90% MeCN, aq.). Fractions were analyzed by analytical HPLC and MS and relevant fractions were pooled and lyophilized. The product (138 mg) was analysed to give a purity of 96% as characterized by HPLC and MS. Calculated monoisotopic mass = 4534,42, found 4534,43.

Example 2

Human GIP receptor (GIP R) and GLP-1 receptor (GLP-1 R) activity assay

[0115] *In vitro* effects of peptide conjugates of the invention were assessed by measuring the induction of cAMP following stimulation of the respective receptor by GIP, GLP1 or analogues of these, as outlined in the invention, using the AlphaSceen® cAMP kit from Perkin-Elmer according to instructions. Briefly, HEK293 cells expressing the human GIP R or GLP-1 R (stable cell lines generated through transfection of the cDNA for human GIP R or GLP-1 and selection of stable clones) were seeded at 30,000 cells/well in 96-well microtiter plates coated with 0.01 % poly-L-lysine, and grown for 1 day in culture in 200 µl growth medium (DMEM, 10% FCS, Penicillin (100 IU/ml), Streptomycin (100 µg/ml)). On the day of analysis, growth medium was removed and the cells were washed once with 150 ml Tyrode's buffer (Tyrode's Salts (9.6 g/l), 10 mM HEPES, pH 7.4). Cells were then incubated in 100 ml Assay buffer (0.1% W/V Alkali-treated Casein and 100 µM IBMX in Tyrode's Buffer) containing increasing concentrations of control and test compounds for 15 min at 37° C. The Assay buffer was removed and cells are lysed in 80 µl Lysis buffer (0.1 % w/v BSA, 5 mM HEPES, 0.3 % v/v Tween-20) per well. From each well 10 µl lysed cells was transferred to a 384-well plate and mixed with 15 µl bead-mix (1 Unit/15 µl anti-cAMP Acceptor Beads, 1 Unit/15 µl Donor Beads, and 1 Unit/15 µl Biotinylated cAMP in Assay Buffer). The plates were mixed and incubated in the dark for an hour at room temperature before measuring using an Envision™ plate reader (Perkin-Elmer). The results are summarized in Table 3.

Table 3: EC_{50} average values of the compounds on the GIP-R and GLP1-R compared to control peptides.

Compound No		GIP R (EC_{50} in nM)	GLP1 R (EC_{50} in nM)
hGIP		0.0038	
Exendin-4			0.0043
2		0.0068	0.015
3		0.015	0.022
4		0.022*	2.6
5		0.031	0.023
6		0.27	0.97
7		0.21	0.024
8		0.10	0.029

9		0.091	0.014
11		0.76	0.47
12		0.050	0.010
13		0.14	0.032
14		0.036	0.0087
15		0.060	0.010
16		0.053	0.012
17		0.021	0.0074
18		0.36	0.015
19		0.015	0.0073
20		0.049	0.0090
21		0.080	0.0090
23		0.42	0.012
24		0.096	0.0085
25		0.12	0.041
26		0.80	0.39
27		0.30	0.074
28		0.020	0.0051
29		0.024	0.0088
30		0.054	0.0093
31		0.022	0.020
32		0.012	0.018
33		0.035	0.031
34		0.045	0.031
35		0.028	0.022
36		0.0099	0.015
37		0.0097	0.018
38		0.0070	0.018
39		0.0083	0.011
40		0.011	0.022
41		0.013	0.011
42		0.0070	0.012
43		0.0091	0.017
44		0.016	0.013
45		0.32	0.11
46		0.088	0.048
47		0.096	0.14
48		0.061	0.041
49		0.092	0.049
50		0.053	0.090
51		0.24	0.11
52		0.087	0.18
53		0.062	0.092
54		0.037	0.033
55		0.0071	0.0087
56		0.14	0.13

* Value is slightly adjusted from that in U.S. Application No. 61/642,439 due to additional determinations. All values are based on multiple determinations.

Example 3

Pharmacokinetics of Compounds 32 and 33 in mice

Method

[0116] C57BL/6J mice were given a single subcutaneous dose of 200 nmol/kg body weight of each peptide to be tested. Blood samples were drawn 0.5, 2, 4, 6, 8, 16, 24 and 36 hours post-dose by sublingual bleeding. At each time point, samples from two mice were taken, *i.e.* 16 mice per compound. The mice were euthanized immediately after blood sampling by cervical dislocation. Plasma samples were analyzed after solid phase extraction (SPE) by liquid chromatography mass spectrometry (LC-MS/MS). The pharmacokinetic analyses were performed by using the non-compartmental approach (see Table 4).

Table 4. Terminal elimination half-life (h) in mice following subcutaneous administration of 200 nmol/kg body weight.

Compound	$T_{½}$ (h)
32	3.4
33	3.7

Example 4

[0117] IPGTT (Intraperitoneal Glucose Tolerance Test) in mice.

Male C57BL/6J mice (Charles River, Germany) were maintained on normal chow (Altromin 1324, Brogaarden A/S, Gentofte, Denmark) and domestic quality water with added citric acid to pH ~ 3.6. The animals were housed pair-wise in a light-, temperature-, and humidity-controlled room (12:12 h light-dark cycle, with lights on at 06.00-18.00 hr; 20-22 °C; 50-80% relative humidity). Mice were fasted for 5 hr before the IPGTT. Peptides and vehicle were administered subcutaneously before the intraperitoneal injection of glucose (t = 0 min; 2 g/kg; 5 ml/kg). Tail vein blood was sampled at time t = 0 (before glucose administration), 15, 30, 45, 60, 90, and 120 min for measurements of blood glucose. Results are shown in Figure 1.

Example 5

Sub-chronic effects of GIP-GLP-1 receptor dual acting agonist on body weight, body composition, food intake, blood glucose, plasma insulin, cholesterol and triglycerides in diet-induced obese C57BL/6J mice

[0118] Male C57BL/6J mice (obtained from Jackson Labs, USA) fed high-fat diet (60% of total energy from fat, D12492, Research Diet Inc.) for approximately 6 months were used. The mice were housed individually, and they were maintained on a 12:12 hour light-dark cycle (lights on at 05.00-17.00). All mice were mock-treated (once daily s.c. injection of vehicle) for a week to acclimatize the animals to handling and injections. Subsequently, the mice were stratified according to body fat mass (measured by magnetic resonance technique) and body weight into five groups (n = 10). Animals were thereafter treated twice daily with s.c. injections (5 ml/kg) of vehicle (group 1: 50 mM phosphate buffer, pH 7.5), the GLP-1 analogue liraglutide (group 2: 2*25 nmol/kg), or test substance (group 3, 2*5 nmol/kg; group 4, 2*25 nmol/kg, or group 5, 2*100 nmol/kg) for a total of 21 days. The daily injections were given in the morning (at 8.00-9.00) and in the afternoon (15.00-16.00 hr). Body weight, food and water intake were determined daily throughout the study. On day 8 of treatment, the 2*100 nmol/kg dose of test substance was halved due to profound body weight loss. This dose (2*50 nmol/kg) was used throughout the remaining treatment period. On day 13, animals were fasted for 4 hours, and blood samples were taken for measurements of blood glucose and plasma insulin. The animals were not dosed in the morning before the blood sampling. On day 19, body composition was measured using a MR scanner. On day 21, blood was sampled for measurements of blood glucose, plasma insulin, plasma cholesterol, and plasma triglycerides. Animals were injected with vehicle, liraglutide or test substance 2 hours before blood sampling. After the final blood sampling, the mice were euthanized.

[0119] Statistical analyses were performed using Graph Pad Prism version 5. The measured parameters were compared using one-way or two-way ANOVAs followed by Tukey's multiple comparison tests or Bonferroni post tests. Student's two-tailed, unpaired t-test was used to compare the means of two independent groups. Differences were considered statistically significant at $p < 0.05$.

Claims:

1. A GIP analogue represented by the general Formula I':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-X22-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I') (SEQ ID NO 61)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X2 is Ala, Aib or Gly;

X3 is Glu or Asp;

X7 is Thr, Ser or Ile;

X9 is Asp or Glu;

X10 is Tyr, Leu or Ser;

X11 is Ser or Leu;

X12 is Ile or Lys;

X13 is Ala, Tyr or Aib;

X14 is Met, Leu or Ser;

X15 is Asp or Glu;

X16 is Lys, Gly, Ser or Glu;

X19 is Gln, Ala, Glu or Lys;

X20 is Gln, Lys, Arg or His;

X21 is Asp, Ala or Glu;

X22 is Phe or 1Nal;

X23 is Val, Ile or Leu;

X24 is Asn, Glu, Arg or Lys;

X27 is Leu, Val, Ile, Lys, Glu or Ser;

X28 is Ala, Ser, Arg or Aib;

X29 is Gln, Aib, Lys, Gly or Ala;

X30 is Lys, Gly, Pro or absent;

X31 is Gly, Pro, Ser, Glu or absent;

X32 is Lys, Ser or absent;

X33 is Lys, Ser, Glu or absent;

X34 is Asn, Gly, Ala, Lys or absent;

X35 is Asp, Ala, Pro, Glu or absent;

X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

2. The GIP analogue of claim 1, wherein the GIP analogue is represented by the general Formula I(b)':

R^1- Tyr-X2-X3-Gly-Thr-Phe-X7-Ser-X9-X10-X11-X12-X13-X14-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28-X29-X30-X31-X32-X33-X34-X35-X36-X37-X38-X39-X40-X41-X42- R^2 (I(b)') (SEQ ID NO 63)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;
X2 is Ala, Aib or Gly;
X3 is Glu or Asp;
X7 is Thr or Ser;
X9 is Asp or Glu;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X14 is Leu or Ser;
X15 is Asp or Glu;
X16 is Lys, Ser or Glu;
X19 is Gln, Ala, Glu or Lys;
X20 is Gln, Lys, Arg or His;
X21 is Asp, Ala or Glu;
X23 is Val, Ile or Leu;
X24 is Asn, Glu, Arg or Lys;
X27 is Leu, Glu, Val or Ile;
X28 is Ala, Ser, Arg or Aib;
X29 is Gln, Gly, Aib or Ala;

X30 is Lys, Gly, Pro or absent;
X31 is Gly, Pro, Ser, Glu or absent;
X32 is Lys, Ser or absent;
X33 is Lys, Ser, Glu or absent;
X34 is Asn, Gly, Ala, Lys or absent;
X35 is Asp, Ala, Pro, Glu or absent;
X36 is Trp, Pro, Lys or absent;
X37 is Lys, Pro, Glu or absent;
X38 is His, Pro, Ser, Lys or absent;
X39 is Asn, Ser or absent;
X40 is Ile or absent;
X41 is Thr or absent;
X42 is Gln or absent; and
R^2 is $-NH_2$ or -OH.

3. A GIP analogue represented by the general Formula II':

R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-X12-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II')

(SEQ ID NO 64)

wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X12 is Ile or Lys;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X17 is Ile or Lys;
X19 is Gln or Ala;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;

X27 is Leu, Glu, Val or Ile;
X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala, Gly or Lys;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

4. The GIP analogue of claim 4, wherein the GIP analogue is represented by the general Formula II(a)':
R^1- Tyr- X2-Glu-Gly-Thr-Phe-X7-Ser-Asp-X10-X11-Ile-X13-Leu-X15-X16-Lys-Ala-X19-X20-X21-Phe-X23-X24-Trp-Leu-X27-X28- X29-X30-Y1-R^2 (II(a)')
(SEQ ID NO 65)
wherein
R^1 is Hy-, Ac or pGlu;
X2 is Aib or Gly;
X7 is Thr, Ile or Ser;
X10 is Tyr or Leu;
X11 is Ser or Leu;
X13 is Ala, Tyr or Aib;
X15 is Asp or Glu;
X16 is Ser, Glu or Lys;
X19 is Gln, Lys, Ala or Glu;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X23 is Val or Ile;
X24 is Asn, Lys or Glu;
X27 is Leu, Glu, Val or Ile;
X28 is Aib, Ala, Ser or Arg;
X29 is Gln, Aib, Ala or Gly;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

5. The GIP analogue of claim 4, wherein the GIP analogue is represented by the general Formula II(b)':

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-X23-Glu-Trp-Leu-X27-X28-Ala-X30-Y1-R^2 (II(b)')

(SEQ ID NO: 66)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala or Tyr;

X15 is Asp or Glu;

X16 is Lys, Glu or Ser;

X20 is Lys, His or Arg;

X21 is Ala, Asp or Glu;

X23 is Val or Ile;

X27 is Leu, Glu or Val;

X28 is Arg or Ser;

X30 is Lys, Gly or absent;

Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and

R^2 is $-NH_2$ or -OH.

6. The GIP analogue of claim 4, wherein the GIP analogue is represented by the general Formula II(c):

R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-X21-Phe-Val-X24-Trp-Leu-X27-Ala- X29-X30-Y1-R^2 (II(c))

(SEQ ID NO: 67)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is Hy-, Ac or pGlu;

X7 is Thr or Ser;

X13 is Ala, Aib or Tyr ;

X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X21 is Ala, Asp or Glu;
X24 is Glu or Asn
X27 is Leu, Glu or Val;
X29 is Gln or Aib;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

7. The GIP analogue of claim 5, wherein the GIP analogue is represented by the general Formula II(d):
R^1- Tyr- Aib-Glu-Gly-Thr-Phe-X7-Ser-Asp-Tyr-Ser-Ile-X13-Leu-X15-X16-Lys-Ala-Gln-X20-Ala-Phe-Val-Glu-Trp-Leu-X27-Ala-Gln-X30-Y1-R^2 (II(d))
(SEQ ID NO: 68)
or a pharmaceutically acceptable salt or solvate thereof,
wherein
R^1 is Hy-, Ac or pGlu;
X7 is Thr or Ser;
X13 is Ala, Aib or Tyr;
X15 is Asp or Glu;
X16 is Glu, Lys or Ser;
X20 is Lys, His or Arg;
X27 is Leu, Glu or Val;
X30 is Lys, Gly or absent;
Y1 is Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser or absent; and
R^2 is $-NH_2$ or -OH.

8. A GIP analogue of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDKKAQRAFVEWLLAQ (SEQ ID NO: 70).

9. A GIP analogue of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 6 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA (SEQ ID NO: 71).

10. A GIP analogue of any one of claims 1 to 7 wherein the amino acid sequence X1-X29 has no more than 5 amino acid differences from the sequence Y-Aib-EGTFTSDYSIYLDEKAAKEFIEWLESA (SEQ ID NO: 72).

11. A GIP analogue compound according to any one of claims 1 to 7 wherein X24 is Glu and/or X21 is Ala.

12. A GIP analogue compound according to any one of claims 1-11, wherein X7 is Thr and X14 is Leu.

13. A GIP analogue according to any one of claims 1-11, wherein X7 is Thr, X14 is Leu and X18 is Ala.

14. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr and X14 is Leu.

15. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu and X13 and/or X29 is Aib.

16. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu and X24 is Glu,

17. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu and X29 is Gln.

18. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X21 is Ala, X24 is Glu and X29 is Gln.

19. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu, X27 is Leu and X28 is Ser.

20. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X24 is Glu, X27 is Glu and X28 is Ser.

21. A GIP analogue according to any one of claims 1-11, wherein X2 is Aib, X7 is Thr, X14 is Leu, X20 is His, X24 is Glu, X27 is Leu and X28 is Ser.

22. A GIP analogue selected from:

Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2,

pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLKA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLL-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAEKAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-GPSSGAPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVNWLLAQK-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(15-carboxy-pentadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-K-NH_2;

Hy-Y-Aib-EGTFTSDYSI-Aib-LDK-K(Hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVEWLLAQGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(hexadecanoyl-isoGlu)-AAKEFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLLA-Aib-KPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIALDK-K(hexadecanoyl-isoGlu)-AQRAFVNWLVA-Aib-KPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLE-KKAAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLE-KKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAQKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDEKAAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLESKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDKKAAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEKKAAKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEK-K(Hexadecanoyl-isoGlu)-AAKEFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFIEWLESA-NH_2;

Hy-Y-Aib-EGTFTSDYSKYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLRA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAKDFVEWLLSA-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLDS-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSAGPSSGAPPPS-NH_2;

Hy-Y-Aib-EGTFTSDYSIYLEK-K-(Hexadecanoyl-isoGlu)-AAKEFVEWLLSAGPSSGAPPPS-NH_2; and

Hy-Y-Aib-EGTFTSDYSIYLDSKAAHDFVEWLLSAGPSSGAPPPS-NH_2; and

Hy-Y-Aib-EGTFTSDYSIYLDE-K(Hexadecanoyl-isoGlu)-AAHDFVEWLLSA-NH_2

or a pharmaceutically acceptable salt or solvate thereof.

23. A GIP analogue according to any one of the preceding claims with a lipophilic substituent conjugated to one or more of positions 15, 16, 17, 19, 20, 24, 27, 28 and 30.

24. A GIP analogue according to any one of the preceding claims for use in a therapeutic method.

25. A pharmaceutical composition comprising a GIP analogue of any one of the preceding claims, or a salt, solvate or derivative thereof, in admixture with a carrier.

26. The pharmaceutical composition of claim 25, wherein the GIP analogue is a pharmaceutically acceptable acid addition salt.

27. The pharmaceutical composition of claim 25 or claim 26, which is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of said GIP analogue.

28. Use of a GIP analogue of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of metabolic diseases.

29. Use of a GIP analogue of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of diabetes or a diabetes related disorder.

30. Use of a GIP analogue of any one of claims 1 to 23 for the preparation of a medicament for the treatment and/or prevention of obesity or an obesity related disorder.

31. The use of claim 30, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

32. The use of claim 30, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and proinflammatory state, or a combination thereof.

33. The use of claim 32, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, and plaque buildup in artery walls, or a combination thereof.

34. The use of claim 32, wherein the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood.

35. The use of claim 32, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

36. The use of claim 30, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea, or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

37. A nucleic acid molecule comprising a nucleic acid sequence encoding a GIP analogue of any one of claims 1 to 23.

38. An expression vector comprising the nucleic acid sequence of claim 37, in combination with control sequences to direct its expression.

39. A host cell transformed with the expression vector of claim 38.

40. A method of producing the GIP analogue of any one of claims 1 to 23, the method comprising culturing the host cells of claim 39 under conditions suitable for expressing the GIP analogue and purifying the GIP analogue thus produced.

41. A nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39 for use in therapy.

42. Use of a nucleic acid molecule according to claim 37, an expression vector according to claim 38 or a host cell according to claim 39, in the preparation of a medicament for the treatment and/or prevention of a metabolic disorder.

43. The use of claim 42, wherein the metabolic disorder is selected from diabetes and obesity.

44. A method of treating a stomach and/or bowel-related disorder in a patient in need thereof by administering an effective amount a GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39.

45. A method of treatment and/or prevention of a metabolic disease or disorder in a patient in need thereof comprising administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39.

46. The method of claim 45, wherein the metabolic disease or disorder is selected from diabetes and obesity.

47. A method of treatment and/or prevention of a diabetes related disorder in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39.

48. A method of treatment and/or prevention of an obesity related disorder in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39.

49. The method of claim 47, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

50. The method of claim 47, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

51. The method of claim 50, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, plaque buildup in artery walls, or a combination thereof.

52. The method of claim 50, wherein the prothrombotic state is selected from high fibrinogen levels in the blood and high plasminogen activator inhibitor-1 levels in the blood.

53. The method of claim 50, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

54. The method of claim 48, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease and obesity induced sleep apnea.

55. A therapeutic kit comprising a GIP analogue according to any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according to claim 38, or a host cell according to claim 39, each optionally in combination with a pharmaceutically acceptable carrier.

56. A device comprising a GIP analogue according to any one of claims 1 to 23, a nucleic acid molecule according to claim 37, an expression vector according

to claim 38, or a host cell according to claim 39, for delivery of the GIP analogue to a subject.

57. A pharmaceutical composition comprising the GIP analogue of any one of claims 1 to 23 for use in treating a stomach and bowel-related disorder in a patient in need thereof.

58. A pharmaceutical composition comprising the GIP analogue of any one of claims 1 to 23 for use in treatment and/or prevention of a metabolic disease or disorder in a patient in need thereof.

59. The pharmaceutical composition of claim 58, wherein the metabolic disorder is selected from diabetes and obesity.

60. A pharmaceutical composition comprising the GIP analogue of any one of claims 1 to 23 for use in treatment and/or prevention of a diabetes related disorder in a patient in need thereof.

61. A pharmaceutical composition comprising the GIP analogue of any one of claims 1 to 23 for use in treatment and/or prevention of an obesity related disorder in a patient in need thereof.

62. The pharmaceutical composition of claim 60, wherein the diabetes related disorder is selected from insulin resistance, glucose intolerance, increased fasting glucose, pre-diabetes, type 1 diabetes, type 2 diabetes, gestational diabetes hypertension, dyslipidemia, or a combination thereof.

63. The pharmaceutical composition of claim 60, wherein the diabetes related disorder is selected from atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke; or is associated with a condition selected from atherogenic dyslipidemia, blood fat disorders, elevated blood pressure, hypertension, a prothrombotic state, and a proinflammatory state, or a combination thereof.

64. The pharmaceutical composition of claim 63, wherein the blood fat disorder is selected from high triglycerides, low HDL cholesterol, high LDL cholesterol, plaque buildup in artery walls, or a combination thereof.

65. The pharmaceutical composition of claim 63, wherein the prothrombotic state is selected from high fibrinogen levels in the blood, and high plasminogen activator inhibitor-1 levels in the blood.

66. The pharmaceutical composition of claim 63, wherein the proinflammatory state is an elevated C-reactive protein level in the blood.

67. The pharmaceutical composition of claim 61, wherein the obesity related disorder is selected from obesity linked inflammation, obesity linked gallbladder disease, and obesity induced sleep apnea.

Figure 1

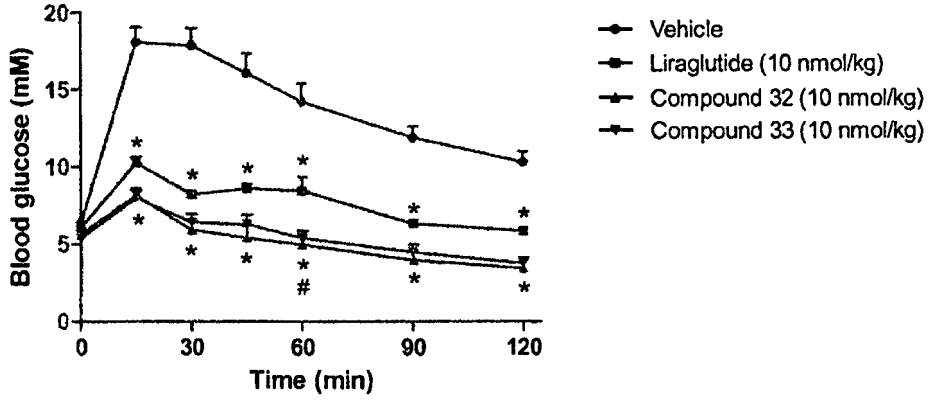
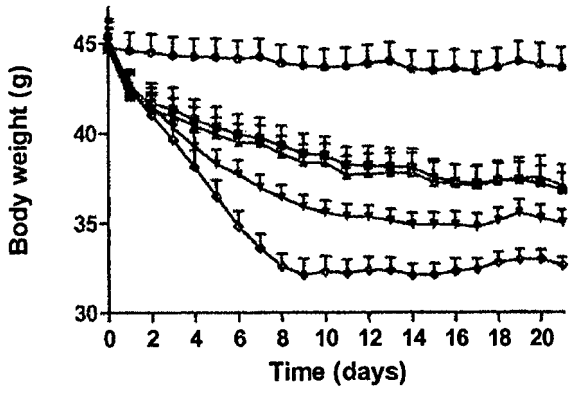

Blood glucose (mM)
20
15
10
5
0
0
30
60
90
120
Time (min)
Vehicle
Liraglutide (10 nmol/kg)
Compound 32 (10 nmol/kg)
Compound 33 (10 nmol/kg)

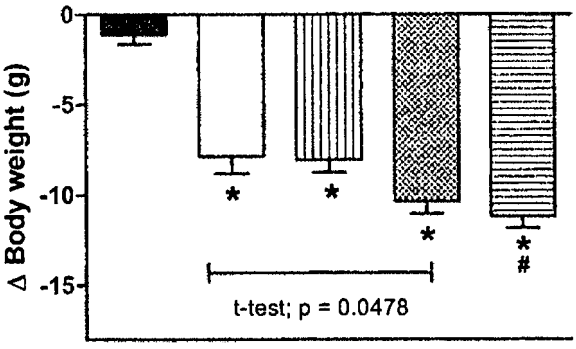
Figure 2:

A



- Vehicle
- Liraglutide (2*25 nmol/kg)
- Compound 33 (2*5 nmol/kg)
- Compound 33 (2*25 nmol/kg)
- Compound 33 (2*100 nmol/kg) - dose was halved on day 8

B

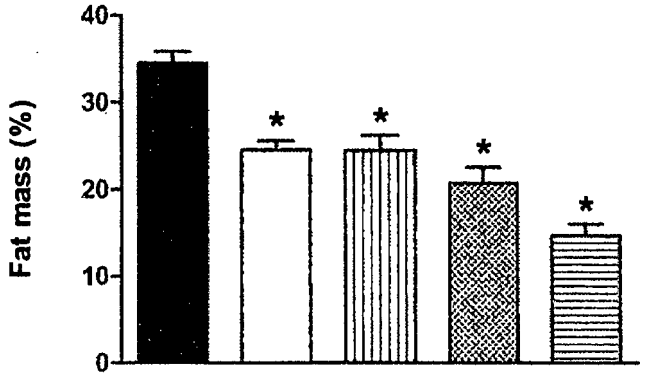


- Vehicle
- Liraglutide (2*25 nmol/kg)
- Compound 33 (2*5 nmol/kg)
- Compound 33 (2*25 nmol/kg)
- Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
#, $p < 0.05$ vs Liraglutide (2*25 nmol/kg)
One-way ANOVA followed by Tukey's multiple comparison tests

Figure 3:

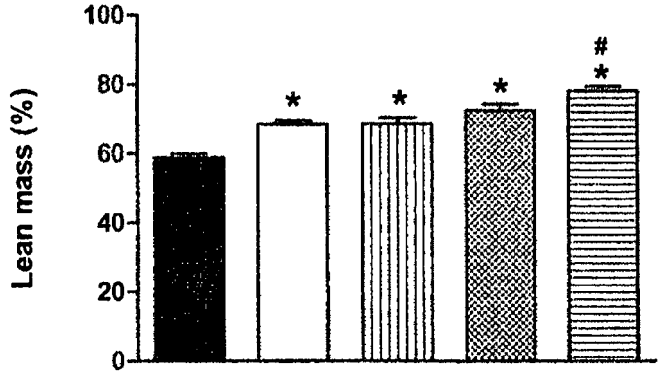
A



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
One-way ANOVA; Tukey's multiple comparison tests

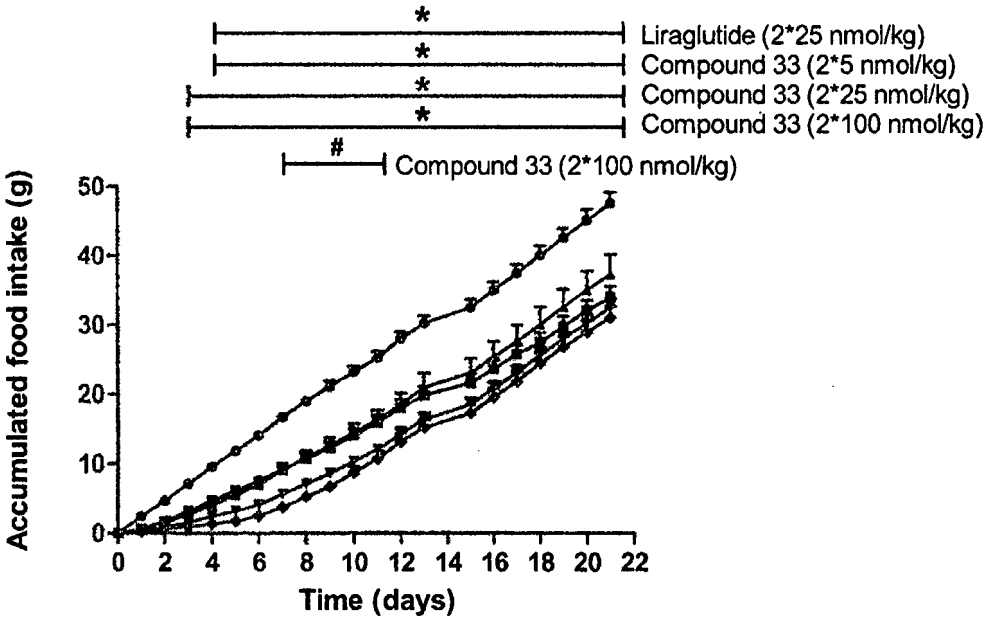
B



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose halved on day 8

*, $p < 0.05$ vs Vehicle
#, $p < 0.05$ vs Liraglutide (2*25 nmol/kg)
One-way ANOVA; Tukey's multiple comparison tests

Figure 4:

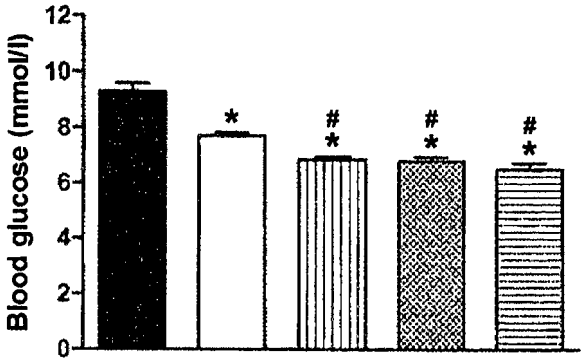


- Vehicle
- Liraglutide (2*25 nmol/kg)
- Compound 33 (2*5 nmol/kg)
- Compound 33 (2*25 nmol/kg)
- Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
#, $p < 0.05$ vs Liraglutide (2*25 nmol/kg)
Two-way ANOVA; Bonferroni post tests

Figure 5:

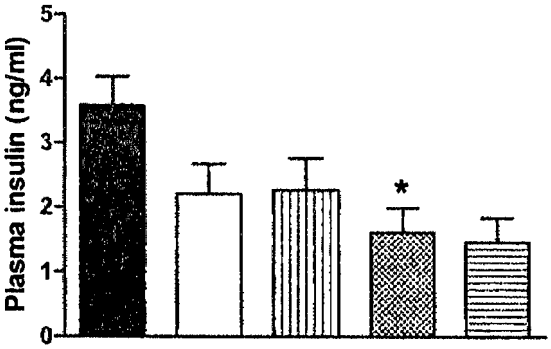
A



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
#, $p < 0.05$ vs Liraglutide (2*25 nmol/kg)
One-way ANOVA; Tukey's multiple comparison tests

B

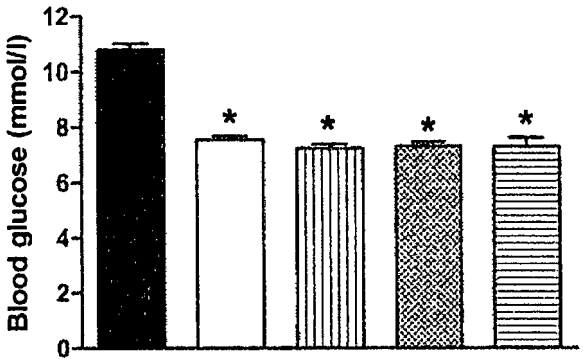


Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
One-way ANOVA; Tukey's multiple comparison tests

Figure 6:

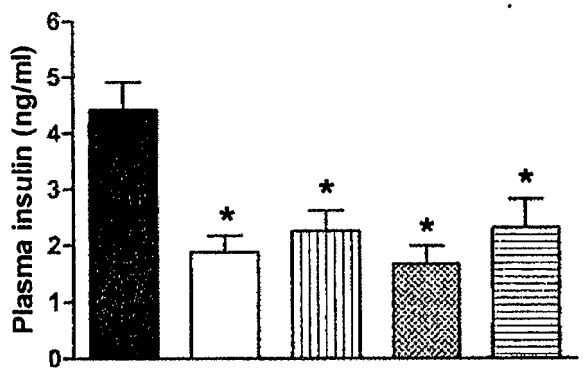
A



- Vehicle
- Liraglutide (2*25 nmol/kg)
- Compound 33 (2*5 nmol/kg)
- Compound 33 (2*25 nmol/kg)
- Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
One-way ANOVA; Tukey's multiple comparison tests

B

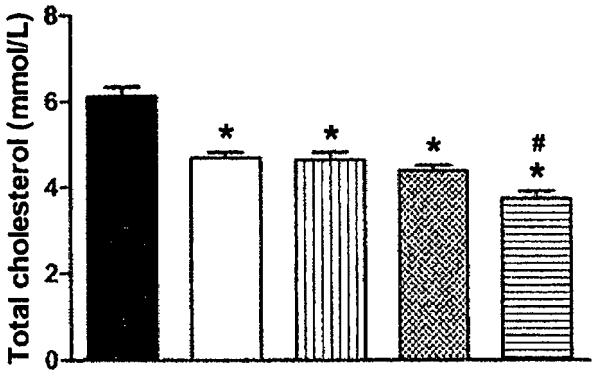


- Vehicle
- Liraglutide (2*25 nmol/kg)
- Compound 33 (2*5 nmol/kg)
- Compound 33 (2*25 nmol/kg)
- Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
One-way ANOVA; Tukey's multiple comparison tests

Figure 7

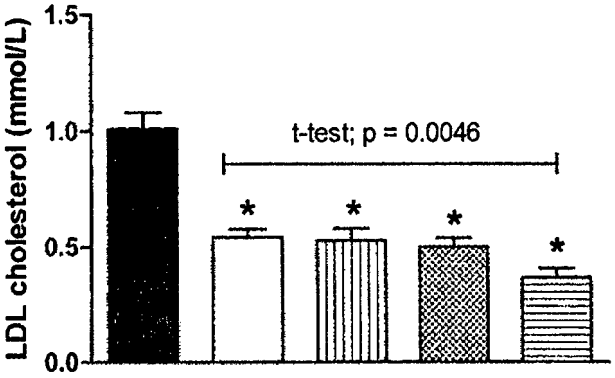
A



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
#, $p < 0.05$ vs Liraglutide (2*25 nmol/kg)
One way ANOVA; Tukey's multiple comparison tests

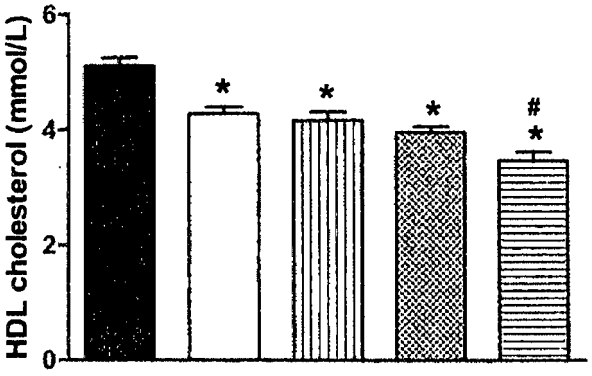
B



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
One way ANOVA; Tukey's multiple comparison tests

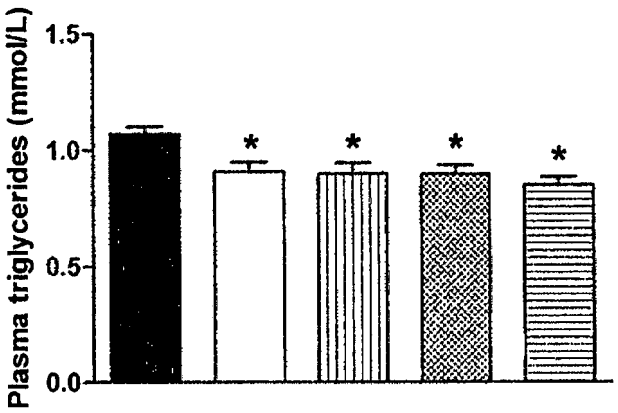
C



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
#, $p < 0.05$ vs Liraglutide (2*25 nmol/kg)
One way ANOVA; Tukey's multiple comparison tests

D



Vehicle
Liraglutide (2*25 nmol/kg)
Compound 33 (2*5 nmol/kg)
Compound 33 (2*25 nmol/kg)
Compound 33 (2*100 nmol/kg) - dose was halved on day 8

*, $p < 0.05$ vs Vehicle
One way ANOVA; Tukey's multiple comparison tests

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/059319

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K14/605 A61K38/26 C12N1/15 C12N1/21
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/016940 A2 (IPSEN PHARMA SAS [FR]; DONG ZHENG XIN [US]) 11 February 2010 (2010-02-11) the whole document	1-67
A	GREEN B D ET AL: "STRUCTURALLY MODIFIED ANALOGUES OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) AS FUTURE ANTIDIABETIC AGENTS", CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, NL, vol. 10, no. 29, 1 January 2004 (2004-01-01), pages 3651-3662, XP009068381, ISSN: 1381-6128, DOI: 10.2174/1381612043382774 the whole document	1-67

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 September 2013	12/09/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kools, Patrick

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALPESHKUMAR K. MALDE ET AL: "Understanding interactions of gastric inhibitory polypeptide (GIP) with its G-protein coupled receptor through NMR and molecular modeling", JOURNAL OF PEPTIDE SCIENCE, vol. 13, no. 5, 1 May 2007 (2007-05-01), pages 287-300, XP055077705, ISSN: 1075-2617, DOI: 10.1002/psc.839 the whole document	1-67
A	VICTOR A. GAULT ET AL: "Administration of an acylated GLP-1 and GIP preparation provides added beneficial glucose-lowering and insulinotropic actions over single incretins in mice with Type 2 diabetes and obesity", CLINICAL SCIENCE, vol. 84, no. 3, 1 August 2011 (2011-08-01) , pages 331-117, XP055077821, ISSN: 0143-5221, DOI: 10.1016/j.mce.2008.08.012 cited in the application the whole document	1-67
A	IRWIN NIGEL ET AL: "Antidiabetic potential of two novel fatty acid derivatised, N-terminally modified analogues of glucose-dependent insulinotropic polypeptide (GIP): N-AcGIP(LysPAL(16)) and N-AcGIP(LysPAL(37))", BIOLOGICAL CHEMISTRY, WALTER DE GRUYTER GMBH & CO, BERLIN, DE, vol. 386, no. 7, 1 July 2005 (2005-07-01), pages 679-687, XP002428433, ISSN: 1431-6730, DOI: 10.1515/BC.2005.079 the whole document	1-67
A	SUSANNE MANHART ET AL: "Structure-function analysis of a series of novel GIP analogues containing different helical length linkers", BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 42, no. 10, 18 March 2003 (2003-03-18), pages 3081-3088, XP002661510, ISSN: 0006-2960, DOI: 10.1021/BI026868E [retrieved on 2003-02-20] the whole document	1-67

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1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	RUNGE STEFFEN ET AL: "Differential structural properties of GLP-1 and exendin-4 determine their relative affinity for the GLP-1 receptor N-terminal extracellular domain", BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 46, no. 19, 15 May 2007 (2007-05-15), pages 5830-5840, XP009095139, ISSN: 0006-2960, DOI: 10.1021/BI062309M abstract	1-67

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/059319

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010016940 A2	11-02-2010	AU 2009280017 A1	11-02-2010
		CA 2732949 A1	11-02-2010
		CN 102171244 A	31-08-2011
		EA 201170304 A1	31-10-2011
		EP 2328922 A2	08-06-2011
		JP 2011530508 A	22-12-2011
		KR 20110043686 A	27-04-2011
		US 2011136733 A1	09-06-2011
		WO 2010016940 A2	11-02-2010

GIP-GLP-1 雙激動劑化合物及方法

本發明涉及截短的 GIP 類似物，與野生型 GIP 相比，其包括一個或更多個替換，並且其可具有改變的(優選提高)的 GLP-1 活性，例如，如在體外效力測定中所評估的。本發明提供了 GIP-GLP-1 雙激動劑化合物及相關方法。