

(19) **DANMARK**



Patent- og
Varemærkestyrelsen

(12)

Oversættelse af europæisk patentskrift

(10) **DK/EP 3004155 T3**

-
- (51) Int.Cl.: **A 61 P 3/04 (2006.01)** **A 61 K 38/00 (2006.01)** **A 61 P 3/10 (2006.01)**
A 61 P 43/00 (2006.01) **C 07 K 14/605 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2022-01-03**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2021-11-24**
- (86) Europæisk ansøgning nr.: **14729976.2**
- (86) Europæisk indleveringsdag: **2014-05-27**
- (87) Den europæiske ansøgnings publiceringsdag: **2016-04-13**
- (86) International ansøgning nr.: **JP2014002772**
- (87) Internationalt publikationsnr.: **WO2014192284**
- (30) Prioritet: **2013-05-28 JP 2013111893**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Takeda Pharmaceutical Company Limited, 1-1 Doshomachi 4-chome Chuo-ku, Osaka-shi, Osaka 541-0045, Japan**
- (72) Opfinder: **ASAMI, Taiji, , Fujisawa, Kanagawa 251-0012, Japan**
NIIDA, Ayumu, , Fujisawa, Kanagawa 251-0012, Japan
- (74) Fuldmægtig i Danmark: **Budde Schou A/S, Dronningens Tværgade 30, 1302 København K, Danmark**
- (54) Benævnelse: **PEPTIDFORBINDELSE**
- (56) Fremdragne publikationer:
WO-A2-2010/011439
WO-A2-2012/088379
STEFFEN RUNGE 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, vol. 46, no. 19, 1 May 2007 (2007-05-01), pages 5830-5840, XP055138608, ISSN: 0006-2960, DOI: 10.1021/bi062309m
AL-SABAH SULEIMAN ET AL: "A model for receptor-peptide binding at the glucagon-like peptide-1 (GLP-1) receptor through the analysis of truncated ligands and receptors", BRITISH JOURNAL OF PHARMACOLOGY, NATURE PUBLISHING GROUP, BASINGSTOKE, HANTS; GB, vol. 140, no. 2, 1 September 2003 (2003-09-01), pages 339-346, XP002437826, ISSN: 0007-1188, DOI: 10.1038/SJ.BJP.0705453
None

DESCRIPTION

[Technical Field]

[0001] The present invention relates to a novel peptide compound having an activating action on GLP-1 receptors and GIP receptors and use of the peptide compound as a medicament.

[Background of the Invention]

[0002] Both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) are peptides called incretin. GLP-1 and GIP are secreted from small intestinal L cells and K cells, respectively.

[0003] GLP-1 acts via GLP-1 receptors and is known to have a glucose-dependent insulintropic action and a feeding suppressive action. On the other hand, GIP is known to have a glucose-dependent insulintropic action via GIP receptors, though its influence on feeding is not clear.

[0004] The co-administration of a GLP-1 receptor agonist liraglutide and a GIP receptor agonist N-Ac-GIP has been reported to more promote a glucose tolerance-improving action and a body weight-lowering action than the administration of liraglutide alone (Non Patent Literature 1). Also, a GLP-1 receptor/GIP receptor coagonist peptide has been reported to show a stronger hypoglycemic action and body weight-lowering action than those of a GLP-1 receptor agonist alone (Patent Literature 1).

[0005] Attempts have also been made to search for peptides having GLP-1 receptor/GIP receptor coagonist or glucagon/GLP-1 receptor/GIP receptor triagonist activity and develop these peptides as anti-obesity drugs or therapeutic drugs for diabetes, on the basis of the structure of natural glucagon, GIP, or GLP-1 (Patent Literatures 1 to 8). None of the literatures, however, disclose the peptide compound of the present invention.

[Citation List]

[Patent Literature]

[0006]

[Patent Literature 1] WO2010/011439

[Patent Literature 2] WO2010/148089

[Patent Literature 3] WO2011/119657

[Patent Literature 4] WO2012/088379

[Patent Literature 5] WO2012/167744

[Patent Literature 6] WO2013/164483

[Patent Literature 7] WO2013/192129

[Patent Literature 8] WO2013/192130

[Non Patent Literature]

[0007] [Non Patent Literature 1] Clinical Science 121, 107-117 (2011)

[Summary of Invention]

[Technical Problem]

[0008] The present invention aims to provide a novel peptide compound having high GLP-1 receptor/GIP receptor coagonist activity, and useful as an agent for the prophylaxis or treatment of obesity or diabetes.

[Solution to Problem]

[0009] The present inventors have conducted intensive studies about a novel peptide compound having superior GLP-1 receptor/GIP receptor coagonist activity, and useful as an agent for the prophylaxis or treatment of obesity or diabetes, and consequently found that a peptide as defined in claim 1 has superior GLP-1 receptor/GIP receptor coagonist activity, which resulted in the completion of the present invention.

[0010] Accordingly, the present invention relates to [1] a peptide selected from H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ or a salt thereof, H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Ile-Aib-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ or a salt

thereof, H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ or a salt thereof, and H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂ or a salt thereof (hereinafter sometimes to be abbreviated as compound (I)), medicaments or compositions comprising compound (I), and uses of compound (I), as defined in the appended claims.

[Advantageous Effects of Invention]

[0011] Compound (I) has superior GLP-1 receptor/GIP receptor coagonist activity, and shows significant feeding suppressive and body weight-lowering effects *in vivo*. In addition, compound (I) has a low risk of hyperglycemic action, and is also useful in the treatment of obesity associated with diabetes, because of its low glucagon receptor agonist activity. Moreover, compound (I) is excellent in solubility, and also has the advantage that the compound can be easily formulated as a medicament.

[Detailed Description of the Invention]

[0012] Compound (I) can be produced according to a peptide synthesis method known per se.

[0013] When the compound (I) is present as a configurational isomer such as enantiomer, diastereomer etc., or a conformer, they are also encompassed in compound (I) and each can be isolated by a means known per se. In addition, when the compound (I) is in the form of a racemate, it can be separated into S- and R-forms by conventional optical resolution.

[0014] When the compound (I) includes stereoisomers, both the isomers alone and mixtures of each isomers are also encompassed in compound (I).

[0015] Compound (I) can be chemically modified according to a method known per se and using polyethylene glycol. For example, chemically modified compound (I) can be produced by conjugatedly binding polyethylene glycol to Cys residue, Asp residue, Glu residue, or Lys residue of compound (I).

[0016] Compound (I) modified by polyethylene glycol (PEG) produces, for example, the effects of promoting the biological activity, prolonging the blood circulation time, reducing the immunogenicity, enhancing the solubility, and enhancing the resistance to metabolism, of a therapeutically and diagnostically important peptide.

[0017] In addition, the compound (I) may be a solvate (e.g., hydrate) or a non-solvate (e.g., non-hydrate).

[0018] The compound (I) may be labeled with an isotope (e.g., ^3H , ^{14}C , ^{35}S , ^{125}I).

[0019] Furthermore, compound (I) may be a deuterium conversion form wherein ^1H is converted to $^2\text{H}(\text{D})$.

[0020] Compound (I) labeled or substituted with an isotope can be used as, for example, a tracer (PET tracer) for use in Positron Emission Tomography (PET), and is useful in the fields of medical diagnosis.

[0021] For the peptides mentioned herein, the left end is the N-terminal (amino terminal) and the right end is the C-terminal (carboxyl terminal) in accordance with the conventional peptide marking. The C-terminal of peptide may be any of an amide ($-\text{CONH}_2$), a carboxyl group ($-\text{COOH}$), a carboxylate ($-\text{COO}^-$), an alkylamide ($-\text{CONHR}^a$), and an ester ($-\text{COOR}^a$). Particularly, amide ($-\text{CONH}_2$) is preferable.

[0022] Compound (I) may be in a salt form. Examples of such salt include metal salts, ammonium salts, salts with organic base, salts with inorganic acid, salts with organic acid, and salts with basic or acidic amino acid.

[0023] Among the above-mentioned salts, a pharmaceutically acceptable salt is preferable. For example, when a compound has an acidic functional group, an inorganic salt such as alkali metal salt (e.g., sodium salt, potassium salt etc.), alkaline earth metal salt (e.g., calcium salt, magnesium salt, barium salt etc.), ammonium salt etc., and when a compound has a basic functional group, for example, a salt with inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, or a salt with organic acid such as acetic acid, phthalic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, methanesulfonic acid, or p-toluenesulfonic acid are preferable.

[0024] Compound (I) may be used as a prodrug form.

[0025] A prodrug means a compound which is converted to compound (I) with a reaction due to an enzyme, gastric acid, etc. under the physiological condition in the living body, that is, a compound which is converted to compound (I) with oxidation, reduction, hydrolysis, etc. according to an enzyme; a compound which is converted to compound (I) by hydrolysis etc. due to gastric acid, etc.

[0026] Compound (I) may be a crystal. Crystals having a singular crystal form or a mixture of plural crystal forms are also included in compound (I). Crystals can be produced by crystallizing compound (I) according to a crystallization method known per se.

[0027] Compound (I) and a prodrug thereof (hereinafter to be sometimes abbreviated as the compound of the present invention) have an activating action on GLP-1 receptors and GIP

receptors.

[0028] The compound of the present invention has a high activating action on GLP-1 receptors and GIP receptors, particularly, *in vivo*.

[0029] GLP-1 and GIP are gut hormones called incretin, and have the action of promoting insulin secretion from the pancreas. Since incretin is closely related to glucose metabolism, the compound having an activating action on GLP-1 receptors and GIP receptors is useful in the prophylaxis or treatment of symptoms associated with glucose metabolism disorder, including obesity.

[0030] Thus, the compound of the present invention has a feeding suppressive action and a weight increase inhibitory action.

[0031] In addition, the compound of the present invention has superior solubility. The solubility of the compound of the present invention in water is preferably 1 mg/mL or higher, more preferably 10 mg/mL or higher.

[0032] The compound of the present invention can be used as an activator of a GLP-1 receptor and a GIP receptor (GLP-1 receptor/GIP receptor coagonist).

[0033] In the present invention, the activator of a GLP-1 receptor and a GIP receptor (GLP-1 receptor/GIP receptor coagonist) means an agent having both of a GLP-1 receptor-activating action (GLP-1 receptor agonist action) and a GIP receptor-activating action (GIP receptor agonist action). Specifically, the activator of a GLP-1 receptor and a GIP receptor (GLP-1 receptor/GIP receptor coagonist) means an agent wherein EC_{50} against the GLP-1 receptor and EC_{50} against the GIP receptor are 1:20 to 20:1, preferably 1:5 to 5:1.

[0034] The compound of the present invention has a low glucagon receptor-activating action (glucagon receptor agonist), and therefore has a low hyperglycemic action attributed thereto. EC_{50} of the compound of the present invention against the glucagon receptor is 1/1000 or lower, preferably 1/10000 or lower, compared with EC_{50} of the compound of the present invention against the GLP-1 receptor or the GIP receptor.

[0035] The compound of the present invention is low in its toxicity (e.g., acute toxicity, chronic toxicity, genetic toxicity, reproductive toxicity, cardiac toxicity, carcinogenicity), shows a few side effects, and can be safely administered to a mammal (e.g., human, bovine, horse, dog, cat, monkey, mouse, rat) as an agent for the prophylaxis or treatment of various diseases mentioned below.

[0036] The compound of the present invention can be used as an agent for the treatment or prophylaxis of various diseases including obesity, by virtue of the above-mentioned activating action on GLP-1 receptors and GIP receptors. The compound of the present invention can be

used as an agent for the prophylaxis or treatment of, for example, symptomatic obesity, obesity based on simple obesity, disease state or disease associated with obesity, eating disorder, diabetes (e.g., type 1 diabetes, type 2 diabetes, gestational diabetes, obese diabetes), hyperlipidemia (e.g., hypertriglyceridemia, hypercholesterolemia, high LDL-cholesterolemia, low HDL-cholesterolemia, postprandial hyperlipemia), hypertension, cardiac failure, diabetic complications [e.g., neuropathy, nephropathy, retinopathy, diabetic cardiomyopathy, cataract, macroangiopathy, osteopenia, hyperosmolar diabetic coma, infectious disease (e.g., respiratory infection, urinary tract infection, gastrointestinal infection, dermal soft tissue infections, inferior limb infection), diabetic gangrene, xerostomia, hypacusis, cerebrovascular disorder, peripheral blood circulation disorder], metabolic syndrome (disease states having 3 or more selected from hypertriglycerid(TG)emia, low HDL cholesterol(HDL-C)emia, hypertension, abdominal obesity and impaired glucose tolerance), or sarcopenia.

[0037] Examples of the symptomatic obesity include endocrine obesity (e.g., Cushing syndrome, hypothyroidism, insulinoma, obese type II diabetes, pseudohypoparathyroidism, hypogonadism), central obesity (e.g., hypothalamic obesity, frontal lobe syndrome, Kleine-Levin syndrome), hereditary obesity (e.g., Prader-Willi syndrome, Laurence-Moon-Biedl syndrome), and drug-induced obesity (e.g., steroid, phenothiazine, insulin, sulfonylurea (SU) agent, β -blocker-induced obesity).

[0038] Examples of the disease state or disease associated with obesity include glucose tolerance disorders, diabetes (particularly type 2 diabetes, obese diabetes), lipid metabolism abnormality (synonymous with the above-mentioned hyperlipidemia), hypertension, cardiac failure, hyperuricemia.gout, fatty liver (including non-alcoholic steato-hepatitis), coronary heart disease (myocardial infarction, angina pectoris), cerebral infarction (brain thrombosis, transient cerebral ischemic attack), bone/ articular disease (knee osteoarthritis, hip osteoarthritis, spondylitis deformans, lumbago), sleep apnea syndrome/Pickwick syndrome, menstrual disorder (abnormal menstrual cycle, abnormality of menstrual flow and cycle, amenorrhea, abnormal catamenial symptom), and metabolic syndrome.

[0039] New diagnostic criteria were reported by The Japan Diabetes Society in 1999 about the diagnostic criteria of diabetes.

[0040] According to this report, diabetes refers to a state that meets any of a fasting blood glucose level (glucose concentration in venous plasma) of 126 mg/dl or more, a 2-hr value (glucose concentration in venous plasma) of 200 mg/dl or more in the 75 g oral glucose tolerance test (75 g OGTT), and a casual blood glucose level (glucose concentration in venous plasma) of 200 mg/dl or more. Also, a state that does not apply to the above-mentioned diabetes, and is not a state exhibiting "a fasting blood glucose level (glucose concentration in venous plasma) less than 110 mg/dl or a 2-hr value (glucose concentration in venous plasma) less than 140 mg/dl in the 75 g oral glucose tolerance test (75 g OGTT) " (normal type) is called "borderline type" .

[0041] Moreover, new diagnostic criteria were reported by American Diabetes Association

(ADA) in 1997 and by World Health Organization (WHO) in 1998 about the diagnostic criteria of diabetes.

[0042] According to these reports, diabetes refers to a state that meets a fasting blood glucose level (glucose concentration in venous plasma) of 126 mg/dl or more and a 2-hr value (glucose concentration in venous plasma) of 200 mg/dl or more in the 75 g oral glucose tolerance test.

[0043] According to the above-mentioned reports, impaired glucose tolerance refers to a state that meets a fasting blood glucose level (glucose concentration in venous plasma) less than 126 mg/dl and a 2-hr value (glucose concentration in venous plasma) of 140 mg/dl or more and less than 200 mg/dl in the 75 g oral glucose tolerance test. According to the report of ADA, a state exhibiting a fasting blood glucose level (glucose concentration in venous plasma) of 110 mg/dl or more and less than 126 mg/dl is called IFG (Impaired Fasting Glucose). On the other hand, according to the report of WHO, a state of the IFG (Impaired Fasting Glucose) exhibiting a 2-hr value (glucose concentration in venous plasma) less than 140 mg/dl in the 75 g oral glucose tolerance test is called IFG (Impaired Fasting Glycemia).

[0044] The compound of the present invention is also used as an agent for the prophylaxis or treatment of diabetes determined according to the above-mentioned new diagnostic criteria, borderline type diabetes, impaired glucose tolerance, IFG (Impaired Fasting Glucose) and IFG (Impaired Fasting Glycemia). Moreover, the compound of the present invention can prevent progress of borderline type, impaired glucose tolerance, IFG (Impaired Fasting Glucose) or IFG (Impaired Fasting Glycemia) into diabetes.

[0045] The compound of the present invention has the action of inhibiting weight increase, and as such, can be used as a weight increase inhibitor for mammals. A mammal that is subject to the application of the compound of the present invention can be a mammal desired to avoid weight increase. The mammal may be a mammal having a genetic risk of weight increase, or may be a mammal affected by lifestyle-related disease such as diabetes, hypertension and/or hyperlipidemia. The weight increase may be attributed to excessive ingestion of food or unbalanced diets, or may be weight increase derived from a concomitant drug (e.g., insulin sensitizers having a PPAR γ agonist-like action, such as troglitazone, rosiglitazone, englitazone, ciglitazone, or pioglitazone). Alternatively, the weight increase may be weight increase before reaching obesity, or may be weight increase in obesity patients. Here, obesity is defined as a body mass index (BMI: $\text{body weight (kg)} \div [\text{height (m)}]^2$) of 25 or more (according to the criteria of Japan Society for the Study of Obesity) for Japanese and as BMI of 30 or more (according to the criteria of WHO) for Western people.

[0046] The compound of the present invention can also be used for secondary prevention or suppression of progression of the above-mentioned various diseases (e.g., cardiovascular events such as myocardial infarction). In addition, the compound of the present invention is also useful as a feeding suppressant and a weight increase inhibitor. The compound of the present invention can also be used in combination with a diet therapy (e.g., diet therapy for diabetes), and an exercise therapy.

[0047] A medicament containing the compound of the present invention shows low toxicity and is obtained using the compound of the present invention alone or in admixture with a pharmacologically acceptable carrier according to a method known per se (e.g., the method described in the Japanese Pharmacopoeia) generally used as production methods of pharmaceutical preparations, and safely administered orally or parenterally (e.g., topically, rectally, intravenously administered) as a pharmaceutical preparation, for example, tablets (inclusive of sugar-coated tablets, film-coated tablets, sublingual tablets, orally disintegrating tablets), powders, granules, capsules (inclusive of soft capsules, microcapsules), liquids, troches, syrups, emulsions, suspensions, injections (e.g., subcutaneous injections, intravenous injections, intramuscular injections, intraperitoneal injections etc.), external preparations (e.g., transnasal preparations, dermal preparations, ointments), suppository (e.g., rectal suppositories, vaginal suppositories), pellets, nasal preparations, pulmonary preparations (inhalants), or transfusions.

[0048] These preparations may be controlled release preparations such as a rapid release preparation, or a sustained release preparation (e.g., a sustained release microcapsule).

[0049] The content of the compound of the present invention in a pharmaceutical preparation is about 0.01 - about 100 wt% of the whole preparation.

[0050] The above-mentioned pharmaceutically acceptable carrier may be exemplified by various organic or inorganic carrier materials that are conventionally used as preparation materials, for example, excipient, lubricant, binding agent and disintegrant for solid preparations; or solvent, solubilizing agent, suspending agent, isotonic agent, buffering agent, or soothing agent for liquid preparations. Further, if necessary, general additives such as preservative, antioxidant, colorant, sweetening agent, adsorbing agent, or wetting agent can be also used appropriately in a suitable amount.

[0051] During production of an oral preparation, coating may be applied as necessary for the purpose of masking of taste, enteric property or durability.

[0052] The dosage of the compound of the present invention is appropriately determined according to the subject of administration, symptom, or administration method. For example, when the compound of the present invention is administered orally to an obesity or diabetes patient (body weight 60 kg), the daily dose of the compound of the present invention is about 0.1 to 100 mg, preferably about 1.0 to 50 mg, more preferably about 1.0 to 20 mg. When the compound of the present invention is administered parenterally to an obesity or diabetes patient (body weight 60 kg), the daily dose of the compound of the present invention is about 0.01 to 30 mg, preferably about 0.1 to 20 mg, more preferably about 0.5 to 10 mg. These amounts can be administered in about 1 to several portions a day.

[0053] The compound of the present invention can be administered, for example, every day (once per day, twice per day, 3 times per day, 4 times per day, 5 times per day, 6 times per

day), every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, every week, twice per week, every other week, every 3 weeks, every month, every 2 months, every 3 months, every 4 months, every 5 months or every 6 months.

[0054] The compound of the present invention can be used in combination with other drug that does not adversely influence the compound of the present invention, for the purpose of, for example, promoting the action (treatment of effect for obesity or diabetes) of the compound of the present invention, or reducing the dose of the compound of the present invention.

[0055] Examples of a drug that can be used in combination with the compound of the present invention (hereinafter sometimes to be abbreviated as a concomitant drug) include anti-obesity agents, therapeutic agents for diabetes, therapeutic agents for diabetic complications, therapeutic agents for hyperlipidemia, antihypertensive agents, diuretics, chemotherapeutics, immunotherapeutics, anti-inflammatory drugs, antithrombotic agents, therapeutic agents for osteoporosis, vitamins, antidementia drugs, erectile dysfunction drugs, therapeutic drugs for urinary frequency or urinary incontinence, and therapeutic agents for dysuria. Specific examples of the concomitant drug include those mentioned below.

[0056] Examples of the anti-obesity agent include monoamine uptake inhibitors (e.g., phentermine, sibutramine, mazindol, fluoxetine, tesofensine), serotonin 2C receptor agonists (e.g., lorcaserin), serotonin 6 receptor antagonists, histamine H3 receptor modulator, GABA modulator (e.g., topiramate), neuropeptide Y antagonists (e.g., velneperit), cannabinoid receptor antagonists (e.g., rimonabant, taranabant), ghrelin antagonists, ghrelin receptor antagonists, ghrelinacylation enzyme inhibitors, opioid receptor antagonists (e.g., GSK-1521498), orexin receptor antagonists, melanocortin 4 receptor agonists, 11 β -hydroxysteroid dehydrogenase inhibitors (e.g., AZD-4017), pancreatic lipase inhibitors (e.g., orlistat, cetilistat), β 3 agonists (e.g., N-5984), diacylglycerol acyltransferase 1 (DGAT1) inhibitors, acetylCoA carboxylase (ACC) inhibitors, stearoyl-CoA desaturated enzyme inhibitors, microsomal triglyceride transfer protein inhibitors (e.g., R-256918), Na-glucose cotransporter inhibitors (e.g., JNJ-28431754, remogliflozin), NFK inhibitory (e.g., HE-3286), PPAR agonists (e.g., GFT-505, DRF-11605), phosphotyrosine phosphatase inhibitors (e.g., sodium vanadate, Trodusquemine), GPR119 agonists (e.g., PSN-821, MBX-2982, APD597), glucokinase activators (e.g., AZD-1656), leptin, leptin derivatives (e.g., metreleptin), CNTF (ciliary neurotrophic factor), BDNF (brain-derived neurotrophic factor), cholecystokinin agonists, amylin preparations (e.g., pramlintide, AC-2307), neuropeptide Y agonists (e.g., PYY3-36, derivatives of PYY3-36, obineptide, TM-30339, TM-30335), oxyntomodulin preparations: FGF21 preparations (e.g., animal FGF21 preparations extracted from the pancreas of bovine or swine; human FGF21 preparations genetically synthesized using *Escherichia coli* or yeast; fragments or derivatives of FGF21), and anorexigenic agents (e.g., P-57).

[0057] Here, as the therapeutic agent for diabetes, for example, insulin preparations (e.g., animal insulin preparations extracted from the pancreas of bovine or swine; human insulin preparations genetically synthesized using *Escherichia coli* or yeast; zinc insulin; protamine zinc insulin; fragment or derivative of insulin (e.g., INS-1), oral insulin preparation), insulin

sensitizers (e.g., pioglitazone or a salt thereof (preferably, hydrochloride), rosiglitazone or a salt thereof (preferably, maleate), Metaglidasen, AMG-131, Balaglitazone, MBX-2044, Rivoglitazone, Aleglitazar, Chiglitazar, Lobeglitazone, PLX-204, PN-2034, GFT-505, THR-0921, compound described in WO007/013694, WO2007/018314, WO2008/093639 or WO2008/099794), α -glucosidase inhibitors (e.g., voglibose, acarbose, miglitol, emiglitate), biguanides (e.g., metformin, buformin or a salt thereof (e.g., hydrochloride, fumarate, succinate)), insulin secretagogues (e.g., sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glycopyramide, glimepiride, glipizide, glybuzole), repaglinide, nateglinide, mitiglinide or calcium salt hydrate thereof), dipeptidyl peptidase IV inhibitors (e.g., Alogliptin or a salt thereof (preferably, benzoate), Vildagliptin, Sitagliptin, Saxagliptin, BI1356, GRC8200, MP-513, PF-00734200, PHX1149, SK-0403, ALS2-0426, TA-6666, TS-021, KRP-104, Trelagliptin or a salt thereof (preferably succinate)), β 3 agonists (e.g., N-5984), GPR40 agonists (e.g., Fasiglifam or a hydrate thereof, compound described in WO2004/041266, WO2004/106276, WO2005/063729, WO2005/063725, WO2005/087710, WO2005/095338, WO2007/013689 or WO2008/001931), SGLT2 (sodium-glucose cotransporter 2) inhibitors (e.g., Depagliflozin, AVE2268, TS-033, YM543, TA-7284, Remogliflozin, ASP1941), SGLT1 inhibitors, 11β -hydroxysteroid dehydrogenase inhibitors (e.g., BVT-3498, INCB-13739), adiponectin or agonist thereof, IKK inhibitors (e.g., AS-2868), leptin resistance improving drugs, somatostatin receptor agonists, glucokinase activators (e.g., Piragliatin, AZD1656, AZD6370, TTP-355, compound described in WO006/112549, WO007/028135, WO008/047821, WO008/050821, WO008/136428 or WO008/156757), GPR119 agonists (e.g., PSN821, MBX-2982, APD597), FGF21, FGF analogue, and ACC2 inhibitors can be mentioned.

[0058] As the therapeutic agent for diabetic complications, aldose reductase inhibitors (e.g., tolrestat, epalrestat, zopolrestat, fidarestat, CT-112, ranirestat (AS-3201), lidorestat), neurotrophic factor and increasing agents thereof (e.g., NGF, NT-3, BDNF, neurotrophic production/secretion promoting agent described in WO01/14372 (e.g., 4-(4-chlorophenyl)-2-(2-methyl-1-imidazolyl)-5-[3-(2-methylphenoxy)propyl]oxazole), compound described in WO2004/039365), PKC inhibitors (e.g., ruboxistaurin mesylate), AGE inhibitors (e.g., ALT946, N-phenacylthiazolium bromide (ALT766), EXO-226, Pyridorin, pyridoxamine), GABA receptor agonists (e.g., gabapentin, pregabalin), serotonin and noradrenalin reuptake inhibitors (e.g., duloxetine), sodium channel inhibitors (e.g., lacosamide), active oxygen scavengers (e.g., thiocetic acid), cerebral vasodilators (e.g., tiapuride, mexiletine), somatostatin receptor agonists (e.g., BIM23190), and apoptosis signal regulating kinase-1 (ASK-1) inhibitors can be mentioned.

[0059] As the therapeutic agent for hyperlipidemia, HMG-CoA reductase inhibitors (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, rosuvastatin, pitavastatin or a salt thereof (e.g., sodium salt, calcium salt)), squalene synthase inhibitors (e.g., compound described in WO97/10224, for example, N-[[[(3R,5S)-1-(3-acetoxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl]piperidin-4-acetic acid), fibrate compounds (e.g., bezafibrate, clofibrate, simfibrate, ciprofibrate), anion exchange resin (e.g., colestyramine), probucol, nicotinic acid drugs (e.g.,

nicomol, niceritrol, niaspan), ethyl icosapentate, phytosterol (e.g., soysterol, gamma oryzanol (γ -oryzanol)), cholesterol absorption inhibitors (e.g., zechia), CETP inhibitors (e.g., dalcetrapib, anacetrapib), and ω -3 fatty acid preparations (e.g., ω -3-fatty acid ethyl esters 90 (ω -3-acid ethyl esters 90)) can be mentioned.

[0060] Examples of the antihypertensive agent include angiotensin converting enzyme inhibitors (e.g., captopril, enalapril, delapril, etc.), angiotensin II antagonists (e.g., candesartan cilexetil, candesartan, losartan, losartan potassium, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, olmesartan, olmesartan medoxomil, azilsartan, azilsartan medoxomil, etc.), calcium antagonists (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine, cilnidipine, etc.), β blockers (e.g., metoprolol, atenolol, propranolol, carvedilol, pindolol, etc.), and clonidine.

[0061] As the diuretic, for example, xanthine derivatives (e.g., theobromine sodium salicylate, theobromine calcium salicylate), thiazide preparations (e.g., ethiazide, cyclopenthiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penfluthiazide, polythiazide, methyclothiazide), antialdosterone preparations (e.g., spironolactone, triamterene), carbonic anhydrase inhibitors (e.g., acetazolamide), chlorobenzenesulfonamide agents (e.g., chlortalidone, mefruside, indapamide), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide, and furosemide can be mentioned.

[0062] Examples of the chemotherapeutic include alkylating agents (e.g., cyclophosphamide, ifosfamide), antimetabolites (e.g., methotrexate, 5-fluorouracil), anticancer antibiotics (e.g., mitomycin, adriamycin), plant-derived anticancer agents (e.g., vincristine, vindesine, Taxol), cisplatin, carboplatin, and etoposide. Among others, a 5-fluorouracil derivative Furtulon or Neofurtulon is preferable.

[0063] Examples of the immunotherapeutic include microbial or bacterial components (e.g., muramyl dipeptide derivative, Picibanil), polysaccharides having immunoenhancing activity (e.g., lentinan, sizofiran, Krestin), cytokines obtained by genetic engineering approaches (e.g., interferon, interleukin (IL)), and colony-stimulating factors (e.g., granulocyte colony-stimulating factor, erythropoietin). Among others, interleukins such as IL-1, IL-2, or IL-12 are preferable.

[0064] Examples of the anti-inflammatory drug include nonsteroidal anti-inflammatory drugs such as aspirin, acetaminophen, or indomethacin.

[0065] As the antithrombotic agent, for example, heparin (e.g., heparin sodium, heparin calcium, enoxaparin sodium, dalteparin sodium), warfarin (e.g., warfarin potassium), anti-thrombin drugs (e.g., aragatroban, dabigatran), FXa inhibitors (e.g., rivaroxaban, apixaban, edoxaban, YM150, compound described in WO02/06234, WO2004/048363, WO2005/030740, WO2005/058823 or WO2005/113504), thrombolytic agents (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), and platelet aggregation inhibitors (e.g., ticlopidine hydrochloride, clopidogrel, prasugrel, E5555, SHC530348, cilostazol, ethyl icosapentate, beraprost sodium, sarpogrelate hydrochloride) can be mentioned.

[0066] Examples of the therapeutic agent for osteoporosis include alfacalcidol, calcitriol, elcatonin, calcitonin salmon, estriol, ipriflavone, pamidronate disodium, alendronate sodium hydrate, incadronate disodium, and risedronate disodium.

[0067] Examples of the vitamin include vitamin B₁ and vitamin B₁₂.

[0068] Examples of the antidementia drug include tacrine, donepezil, rivastigmine, and galanthamine.

[0069] Examples of the erectile dysfunction drug include apomorphine and sildenafil citrate.

[0070] Examples of the therapeutic drug for urinary frequency or urinary incontinence include flavoxate hydrochloride, oxybutynin hydrochloride, and propiverine hydrochloride.

[0071] Examples of the therapeutic agent for dysuria include acetylcholine esterase inhibitors (e.g., distigmine).

[0072] Moreover, a drug confirmed to have a cachexiaameliorating action either in animal models or clinically, i.e., a cyclooxygenase inhibitor (e.g., indomethacin), a progesterone derivative (e.g., megestrol acetate), glucocorticoid (e.g., dexamethasone), a metoclopramide drug, a tetrahydrocannabinol drug, an agent for improving fat metabolism (e.g., eicosapentaenoic acid), growth hormone, IGF-1, or an antibody against a cachexia-inducing factor TNF- α , LIF, IL-6 or oncostatin M can also be used in combination with the compound of the present invention.

[0073] Alternatively, a glycation inhibitor (e.g., ALT-711), a nerve regeneration-promoting drug (e.g., Y-128, VX853, prosaptide), an antidepressant (e.g., desipramine, amitriptyline, imipramine), an antiepileptic drug (e.g., lamotrigine, Trileptal, Keppra, Zonegran, Pregabalin, Harkoseride, carbamazepine), an antiarrhythmic drug (e.g., mexiletine), an acetylcholine receptor ligand (e.g., ABT-594), an endothelin receptor antagonist (e.g., ABT-627), a monoamine uptake inhibitor (e.g., tramadol), a narcotic analgesic (e.g., morphine), a GABA receptor agonist (e.g., gabapentin, MR preparation of gabapentin), an α 2 receptor agonist (e.g., clonidine), a local analgesic (e.g., capsaicin), an antianxiety drug (e.g., benzothiazepine), a phosphodiesterase inhibitor (e.g., sildenafil), a dopamine receptor agonist (e.g., apomorphine), midazolam, or ketoconazole may be used in combination with the compound of the present invention.

[0074] The time of administration of the compound of the present invention and that of the concomitant drug are not limited, and they may be administered simultaneously or in a staggered manner to the administration subject.

[0075] By combining the compound of the present invention and concomitant drug:

1. (1) the dose of the compound of the present invention or a concomitant drug can be

reduced as compared to single administration of the compound of the present invention or a concomitant drug,

2. (2) the drug to be used in combination with the compound of the present invention can be selected depending on the condition of patients (mild, severe),
3. (3) the period of treatment can be set longer by selecting a concomitant drug having different action and mechanism from those of the compound of the present invention,
4. (4) a sustained treatment effect can be designed by selecting a concomitant drug having different action and mechanism from those of the compound of the present invention,
5. (5) a synergistic effect can be afforded by a combined use of the compound of the present invention and a concomitant drug, can be achieved.

[Examples]

[0076] The abbreviations used in the present specification mean the following (Table 1-1 and Table 1-2). A hyphen in terms such as α -MePhe and the like as described herein may be omitted, and in the event of omission also represents the same meaning.

[Table 1-1]

Ac	acetyl
Aib	α -aminoisobutyric acid
GABA	γ -aminobutyric acid

[Table 1-2]

α -MePhe	α -methylphenylalanine
-----------------	-------------------------------

[0077] In the specification, where bases, amino acids, etc. are denoted by their codes, they are based on conventional codes in accordance with the IUPAC-IUB Commission on Biochemical Nomenclature or by the common codes in the art, examples of which are shown below. For amino acids that may have an optical isomer, L-form is presented unless otherwise indicated (e.g., "Ala" is L-form of Ala). In addition, "D-" means a D-form (e.g., "D-Ala" is D-form of Ala), and "DL-" means a racemate of a D-form and an L-form (e.g., "DL-Ala" is DL racemate of Ala).

TFA : : trifluoroacetic acid

Gly or G : : glycine

Ala or A : : alanine

Val or V : : valine

Leu or L : : leucine

Ile or I : : isoleucine

Ser or S : : serine

Thr or T : : threonine

Cys or C : : cysteine

Met or M : : methionine

Glu or E : : glutamic acid

Asp or D : : aspartic acid

Lys or K : : lysine

Phe or F : : phenylalanine

Tyr or Y : : tyrosine

Trp or W : : tryptophan

Pro or P : : proline

Gln or Q : : glutamine

[0078] The present invention is explained in detail in the following by referring to the following Reference Examples, Examples and Test Examples, which are mere embodiments and not to be construed as limitative. In addition, the present invention may be modified without departing from the scope of invention.

[0079] The term "room temperature" in the following Examples indicates the range of generally from about 10°C to about 35°C. As for " % " , the yield is in mol/mol%, the solvent used for chromatography is in % by volume and other " %" is in % by weight.

[0080]

DMF: N,N-dimethylformamide

HOBt: 1-hydroxybenzotriazole monohydrate

Reference Example 1

Synthesis of H-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-

Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin (SEQ ID NO: 10)

[0081] Sieber amide resin (0.69 meq/g, 362 mg) was added to a reaction tube, which was then loaded in a peptide synthesizer. Amino acids were successively condensed according to the Fmoc/DCC/HOBt protocol. In the final step, the N-terminal Fmoc group was removed. After the termination of condensation, the resin was washed with MeOH, and dried under reduced pressure. As a result, 1025 mg (0.244 meq/g) of the protected peptide resin of interest was obtained.

Reference Example 2

Synthesis of H- Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)- Sieber amide resin (SEQ ID NO: 11)

[0082] Sieber amide resin (0.69 meq/g, 362 mg) was added to a reaction tube, which was then loaded in a peptide synthesizer. Amino acids were successively condensed according to the Fmoc/DCC/HOBt protocol. In the final step, the N-terminal Fmoc group was removed. After the termination of condensation, the resin was washed with MeOH, and dried under reduced pressure. As a result, 1331 mg (0.188 meq/g) of the protected peptide resin of interest was obtained.

Example 2

Synthesis of H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Ile-Aib-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ (SEQ ID NO: 14)

[0083] H-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin (0.244 meq/g, 41.0 mg) prepared in Reference Example 1 was weighed into a reaction tube, and swollen with DMF. After removal of DMF by filtration, Fmoc-Ala-OH (31.1 mg), 0.5 M Oxymapure in DMF (200 μ L) and diisopropylcarbodiimide (15.9 μ L) were successively added to the resin, and then the mixture was shaken for 1.5 hours. The reaction solution was filtered off, and the resin was then washed with DMF 6 times. After confirmation of negativity in the Kaiser test, a DMF solution of 20% piperidine was added thereto, and the mixture was shaken for 1 minute. The solution was filtered off, and a DMF solution of 20% piperidine was then added thereto again, and the

mixture was shaken for 20 minutes. The solution was filtered off, and the resin was then washed with DMF 10 times. This Fmoc amino acid condensation-Fmoc deprotection cycle was repeated to successively condense Gln(Trt), Ala, Gln(Trt), Lys(Boc), Asp(OtBu), Leu, Aib, Ile*, Aib, Tyr(tBu), Asp(OtBu), Ser(tBu), Thr(tBu), α MePhe, Thr(tBu)*, Gly, Glu(OtBu), Aib and Tyr(tBu) (*: overnight reaction). The resin was washed with MeOH, and then dried under reduced pressure to give 84.5 mg of H-Tyr(tBu)-Aib-Glu(OtBu)-Gly-Thr(tBu)- α MePhe-Thr(tBu)-Ser(tBu)-Asp(OtBu)-Tyr(tBu)-Aib-Ile-Aib-Leu-Asp(OtBu)-Lys(Boc)-Gln(Trt)-Ala-Gln(Trt)-Ala-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin.

[0084] To 84.5 mg of the obtained resin was added 1 mL of TFA: m-cresol: thioanisole: ethanedithiol: H₂O: triisopropylsilane (80:5:5:5:2.5:2.5), and the mixture was stirred for 1.5 hours. Diethyl ether was added to the reaction solution to obtain precipitation, and the precipitation was washed by repeating three times an operation to remove the supernatant after centrifugation. The residue was extracted with 50% aqueous acetic acid solution, and the resin was removed by filtration, followed by preparative HPLC using Daisopak SP-100-5-ODS-P column (250 × 20 mm I.D.) [Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, flow rate 8 mL/min, A/B: 65/35-55/45 linear concentration gradient elution (60 min)]. The fractions containing the object product were collected and freeze-dried to give 21.5 mg of a white powder.

[0085] Mass spectrometry, (M+H)⁺ 4281.5 (Calculated: 4281.2)

HPLC elution time: 7.2 min

elution condition: column: Merck Chromolith Performance RP-18e (100 × 4.6 mm I.D.)

eluent: using Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, A/B: 95/5 - 35/65 linear concentration gradient elution (10 min)

flow rate: 3.0 mL/min

Example 24

Synthesis of H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ (SEQ ID NO: 36)

[0086] The H-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin (0.244 meq/g, 41.0 mg) prepared in Reference Example 1 was weighed into a reaction tube, and swollen with DMF.

After removal of DMF by filtration, Fmoc-Ala-OH (31.1 mg), 0.5 M Oxymapure in DMF (200 μ L) and diisopropylcarbodiimide (15.9 μ L) were successively added to the resin, and then the mixture was shaken for 1.5 hours. The reaction solution was filtered off, and the resin was then washed with DMF 6 times. After confirmation of negativity in the Kaiser test, a DMF solution of 20% piperidine was added thereto, and the mixture was shaken for 1 minute. The solution was filtered off, and a DMF solution of 20% piperidine was then added thereto again, and the mixture was shaken for 20 minutes. The solution was filtered off, and the resin was then washed with DMF 10 times. This Fmoc amino acid condensation-Fmoc deprotection cycle was repeated to successively condense Gln(Trt), Ala, Gln(Trt), Lys(Boc), Asp(OtBu), Leu, Tyr(tBu), Lys(Boc)*, Aib, Tyr(tBu), Asp(OtBu), Ser(tBu), Thr(tBu), α MePhe, Thr(tBu)*, Gly, Glu(OtBu), Aib and Tyr(tBu) (*: overnight reaction). The resin was washed with MeOH, and then dried under reduced pressure to give 66.8 mg of H-Tyr(tBu)-Aib-Glu(OtBu)-Gly-Thr(tBu)- α MePhe-Thr(tBu)-Ser(tBu)-Asp(OtBu)-Tyr(tBu)-Aib-Lys(Boc)-Tyr(tBu)-Leu-Asp(OtBu)-Lys(Boc)-Gln(Trt)-Ala-Gln(Trt)-Ala-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin.

[0087] To 66.8 mg of the obtained resin was added 1 mL of TF A:m-cresol:thioanisole:ethanedithiol:H₂O:triisopropylsilane (80:5:5:5:2.5:2.5), and the mixture was stirred for 1.5 hours. Diethyl ether was added to the reaction solution to obtain precipitate, and the precipitate was washed by repeating three times an operation to remove the supernatant after centrifugation. The residue was extracted with 50% aqueous acetic acid solution, and the resin was removed by filtration, followed by preparative HPLC using Daisopak SP-100-5-ODS-P column (250 $\times$ 20 mm I.D.) [Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, flow rate 8 mL/min, A/B: 66/34-56/44 linear concentration gradient elution (60 min)]. The fractions containing the object product were collected and freeze-dried to give 16.1 mg of a white powder.

[0088] Mass spectrometry, (M+H)⁺ 4374.6 (Calculated: 4374.2)

HPLC elution time: 6.9 min

elution condition:

column: Merck Chromolith Performance RP-18e (100 $\times$ 4.6 mm I.D.)

eluent: using Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, A/B: 95/5 - 35/65 linear concentration gradient elution (10 min)

flow rate: 3.0 mL/min

Example 25

Synthesis of H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ (SEQ ID NO: 37)

[0089] The H-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin (0.244 meq/g, 41.0 mg) prepared in Reference Example 1 was weighed into a reaction tube, and swollen with DMF. After removal of DMF by filtration, Fmoc-Gln(Trt)-OH (61.1 mg), 0.5 M Oxymapure in DMF (200 μ L) and diisopropylcarbodiimide (15.9 μ L) were successively added to the resin, and then the mixture was shaken for 1.5 hours. The reaction solution was filtered off, and the resin was then washed with DMF 6 times. After confirmation of negativity in the Kaiser test, a DMF solution of 20% piperidine was added thereto, and the mixture was shaken for 1 minute. The solution was filtered off, and a DMF solution of 20% piperidine was then added thereto again, and the mixture was shaken for 20 minutes. The solution was filtered off, and the resin was then washed with DMF 10 times. This Fmoc amino acid condensation-Fmoc deprotection cycle was repeated to successively condense Gln(Trt), Ala, Gln(Trt), Lys(Boc), Asp(OtBu), Leu, Tyr(tBu), Lys(Boc)*, Aib, Tyr(tBu), Asp(OtBu), Ser(tBu), Thr(tBu), α MePhe, Thr(tBu)*, Gly, Glu(OtBu), Aib and Tyr(tBu) (*: overnight reaction). The resin was washed with MeOH, and then dried under reduced pressure to give 55.0 mg of H-Tyr(tBu)-Aib-Glu(OtBu)-Gly-Thr(tBu)- α MePhe-Thr(tBu)-Ser(tBu)-Asp(OtBu)-Tyr(tBu)-Aib-Lys(Boc)-Tyr(tBu)-Leu-Asp(OtBu)-Lys(Boc)-Gln(Trt)-Ala-Gln(Trt)-Gln(Trt)-Glu(OtBu)-Phe-Val-Lys (Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Lys(Boc)-Sieber amide resin.

[0090] To 55.0 mg of the obtained resin was added 1 mL of TF A:m-cresol:thioanisole:ethanedithiol:H₂O:triisopropylsilane (80:5:5:5:2.5:2.5), and the mixture was stirred for 1.5 hours. Diethyl ether was added to the reaction solution to obtain precipitate, and the precipitate was washed by repeating three times an operation to remove the supernatant after centrifugation. The residue was extracted with 50% aqueous acetic acid solution, and the resin was removed by filtration, followed by preparative HPLC using Daisopak SP-100-5-ODS-P column (250 $\times$ 20 mm I.D.) [Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, flow rate 8 mL/min, A/B: 66/34-56/44 linear concentration gradient elution (60 min)]. The fractions containing the object product were collected and freeze-dried to give 13.7 mg of a white powder.

[0091] Mass spectrometry, (M+H)⁺ 4431.5 (Calculated: 4431.3)

HPLC elution time: 6.9 min

elution condition:

column: Merck Chromolith Performance RP-18e (100 $\times$ 4.6 mm I.D.)

eluent: using Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, A/B: 95/5 - 35/65 linear concentration gradient elution (10 min)

flow rate: 3.0 mL/min

Example 26

Synthesis of H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂ (SEQ ID NO: 38)

[0092] The H-Glu(OtBu)-Phe-Val-Lys(Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Sieber amide resin (0.188 meq/g, 53.2 mg) prepared in Reference Example 2 was weighed into a reaction tube, and swollen with DMF. After removal of DMF by filtration, Fmoc-Gln(Trt)-OH (61.1 mg), 0.5 M Oxymapure in DMF (200 μ L) and diisopropylcarbodiimide (15.9 μ L) were successively added to the resin, and then the mixture was shaken for 1.5 hours. The reaction solution was filtered off, and the resin was then washed with DMF 6 times. After confirmation of negativity in the Kaiser test, a DMF solution of 20% piperidine was added thereto, and the mixture was shaken for 1 minute. The solution was filtered off, and a DMF solution of 20% piperidine was then added thereto again, and the mixture was shaken for 20 minutes. The solution was filtered off, and the resin was then washed with DMF 10 times. This Fmoc amino acid condensation-Fmoc deprotection cycle was repeated to successively condense Gln(Trt), Ala, Gln(Trt), Lys(Boc), Asp(OtBu), Leu, Tyr(tBu), Lys(Boc)*, Aib, Tyr(tBu), Asp (OtBu), Ser(tBu), Thr(tBu), α MePhe, Thr(tBu)*, Gly, Glu(OtBu), Aib and Tyr(tBu) (*: overnight reaction). The resin was washed with MeOH, and then dried under reduced pressure to give 95.4 mg of H-Tyr(tBu)-Aib-Glu(OtBu)-Gly-Thr(tBu)- α MePhe-Thr(tBu)-Ser(tBu)-Asp(OtBu)-Tyr(tBu)-Aib-Lys(Boc)-Tyr(tBu)-Leu-Asp(OtBu)-Lys(Boc)-Gln(Trt)-Ala-Gln(Trt)-Gln(Trt)-Glu(OtBu)-Phe-Val-Lys (Boc)-Trp(Boc)-Leu-Leu-Lys(Boc)-Gly-Gly-Pro-Ser(tBu)-Ser(tBu)-Gly-Ala-Pro-Pro-Pro-Ser(tBu)-Sieber amide resin.

[0093] To 95.4 mg of the obtained resin was added 1 mL of TF A:m-cresol:thioanisole:ethanedithiol:H₂O:triisopropylsilane (80:5:5:5:2.5:2.5), and the mixture was stirred for 1.5 hours. Diethyl ether was added to the reaction solution to obtain precipitate, and the precipitate was washed by repeating three times an operation to remove the supernatant after centrifugation. The residue was extracted with 50% aqueous acetic acid solution, and the resin was removed by filtration, followed by preparative HPLC using Daisopak SP-100-5-ODS-P column (250 $\times$ 20 mm I.D.) [Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, flow rate 8 mL/min, A/B: 61/39-51/49 linear concentration gradient elution (60 min)]. The fractions containing the object product were collected and freeze-dried to give 20.0 mg of a white powder.

[0094] Mass spectrometry, (M+H)⁺ 4303.0 (Calculated: 4303.2)

HPLC elution time: 7.1 min

elution condition:

column: Merck Chromolith Performance RP-18e (100 × 4.6 mm I.D.)

eluent: using Solution A: 0.1% TFA-water, Solution B: 0.1% TFA-containing acetonitrile, A/B: 95/5 - 35/65 linear concentration gradient elution (10 min)

flow rate: 3.0 mL/min

Test Example 1

[0095] Evaluation of agonist activity against human GIPR, human GLP-1R and human glucagon R using rise in intracellular cAMP concentration as index

(1) Construction of expression plasmid for the human GIPR gene

[0096] The human GIPR gene having a sequence identical to the sequence of GenBank Accession No. U39231 was cloned into pMSRα-neo vector to prepare hGIPR/pMSRα-neo.

(2) Construction of reporter plasmid-expressing cell

[0097] The luciferase reporter gene having an upstream cAMP response sequence was introduced to CHO-K1 cells to construct CRE-LUC/CHO-K1 cells.

(3) Construction of reporter plasmid

[0098] Four copies of the cAMP response sequence and the Zeocin resistance gene were introduced to pGL3(R2.2)-Basic Vector (Promega) to construct Cre-luc(Zeo) reporter plasmid.

(4) Introduction of the human GIPR gene into CRE-LUC/CHO-K1 cell and obtainment of expressing cell

[0099] The plasmid hGIPR/pMSR α -neo obtained in (1) was introduced to the CRE-LUC/CHO-K1 cells obtained in (2) to obtain transformants. Next, a cell line induced to express luciferase, i.e., hGIPR/CRE-LUC/CHO-K1 cells, were selected from the obtained transformants by the addition of GIP.

(5) Construction of expression plasmid for the human GLP-1R gene

[0100] The human GLP-1R gene having a sequence identical to the sequence of GenBank Accession No. NM_002062 was cloned into pIRESneo3 vector to prepare hGLP-1/pIRESneo3.

(6) Introduction of the human GLP-1R gene and the reporter plasmid into CHO-K1 cell and obtainment of expressing cell

[0101] The Cre-luc(Zeo) obtained in (3) and the plasmid hGLP-1/pIRESneo3 obtained in (5) were introduced to CHO-K1 cells to obtain transformants. Next, a cell line induced to express luciferase, i.e., hGLP-1R/CRE-luc/CHO-K1 cells, were selected from the obtained transformants by the addition of GLP-1.

(7) Construction of expression plasmid for the human Glucagon R gene

[0102] The human glucagon R gene having a sequence identical to the sequence of GenBank Accession No. NM_000160 was cloned into pMSR α -neo vector to prepare hGlucagonR/pMSR α -neo.

(8) Introduction of the human glucagon R gene into CRE-LUC/CHO-K1 cell and obtainment of expressing cell

[0103] The plasmid hGlucagonR/pMSR α -neo obtained in (7) was introduced to the CRE-LUC/CHO-K1 cells obtained in (2) to obtain transformants. Next, a cell line induced to express luciferase, i.e., hGlucagonR/CRE-LUC/CHO-K1 cells, were selected from the obtained transformants by the addition of glucagon.

(9) Reporter assay

[0104] The hGIPR/CRE-LUC/CHO-K1 cells were inoculated at a cell density of 25 μ L/well (5×10^4 cells/well) to a 384-well white plate (Corning), and cultured overnight in Ham F12 medium containing 10% fetal bovine serum, 100 U/mL penicillin and 100 μ g/mL streptomycin in a CO₂

incubator of 37°C. A medium containing a test compound was added at a concentration of 5 µL/well to the cells, and the resultant cells were incubated for 4 hours in a CO₂ incubator of 37°C to give the final concentration of 1 µM. PicaGene LT7.5 (Toyo Ink Co., Ltd.) was added thereto at a concentration of 30 µL/well, and the mixture was shaken with light shielded. After 30 minutes, the luciferase activity was measured using a plate reader Envision (PerkinElmer). The luciferase activity in the presence of 10 nM GIP was defined as 100%, and the luciferase activity from the addition of DMSO instead of the test compound was defined as 0%. The GIPR agonist activity was calculated with a rise in intracellular cAMP concentration as an index. The results are shown in Table 2.

[0105] The GLP-1R agonist activity was assayed in the same way as above using the hGLP-1R/CRE-luc/CHO-K1 cells. The luciferase activity in the presence of 10 nM GLP-1 was defined as 100%, and the luciferase activity from the addition of DMSO instead of the test compound was defined as 0%. The GLP-1R agonist activity was calculated with a rise in intracellular cAMP concentration as an index.

The results are shown in Table 2.

[0106] The glucagon R agonist activity was assayed in the same way as above using the hGlucagonR/CRE-LUC/CHO-K1 cells. The luciferase activity in the presence of 10 nM glucagon was defined as 100%, and the luciferase activity from the addition of DMSO instead of the test compound was defined as 0%. The glucagon agonist activity was calculated with a rise in intracellular cAMP concentration as an index. The results are shown in Table 2.

[0107] As shown in Table 2, the compound of the present invention has a superior activating action on GLP-1 receptors and GIP receptors. In addition, the compound of the present invention has a low glucagon receptor-activating action.

[Table 2]

Example	Agonist activity (EC ₅₀)		
	hGIPR	hGLP-1R	hGCGR
2	6.8E-12	1.6E-11	>1.0E-06
24	9.9E-12	1.1E-11	>1.0E-06
25	1.3E-11	1.4E-11	>1.0E-06
26	1.3E-11	1.5E-11	>1.0E-06

Test Example 2

2-days continuous subcutaneous administration test

[0108] The feeding suppressive activity of a test compound was examined by the method described below.

[0109] The test compound was dissolved in a solvent (50% DMSO) so that sustained release would occur at 10 nmol/kg/day, and the solution was filled in the Alzet Pump (DURECT Corporation, model: 1003D). The pump thus filled with the solution to be administered was immersed in physiological saline for priming, and then used. The pump was embedded by the following method. Each male C57BL/6J mouse at 8-9 weeks of age (20-26°C, allowed to take food and water ad libitum; 12-hour bright-12-hour dark cycle) was anesthetized; the skin in the upper back thereof was incised, and the above-mentioned pump was embedded subcutaneously; the incision was sutured. After weighing, this mouse was returned to the rearing cage (reared alone), and given previously weighed food; food consumption as of 2 days after the start of administration was measured. The food consumption was calculated by subtracting the amount of remaining food from the weight of the food given on the day of the start of administration. When the food consumption of a control group receiving administration of the solvent alone was regarded as a suppression rate of 0%, the feeding suppressive activity of each test compound was evaluated on the basis of 2-days cumulative food consumption after the start of administration. The food intake suppression rate (%) of the test compound was defined as $(\text{Food consumption of the control group} - \text{Food consumption of the test compound-administered group}) / \text{Food consumption of the control group} \times 100$.

[0110] As shown in Table 3, the compound of the present invention has a superior food intake suppressive action.

[Table 3]

Example	Food intake suppression (%)
2	64.80
24	54.18
25	53.12
26	53.06

Test Example 3

2-weeks continuous subcutaneous administration study in DIO mice

[0111] The anti-obesity activity of a test compound was examined by the method described below.

[0112] Diet-induced obesity (DIO) mice were prepared by feeding male C57BL/6J mice with

high-fat diet (D12451: Research Diets, Inc.). The test compound was dissolved in a solvent (50% DMSO) so that sustained release would occur at 1 nmol/kg/day, and the solution was filled in the Alzet Pump (DURECT Corporation, model: 1002). The pump thus filled with the solution to be administered was immersed in physiological saline for priming, and then used. The pump was embedded by the following method. Each male DIO-C57BL/6J mouse at 35-37 weeks of age (20-26°C, allowed to take food and water ad libitum; 12-hour bright-12-hour dark cycle) was anesthetized; the skin in the upper back thereof was incised, and the above-mentioned pump was embedded subcutaneously; the incision was sutured. After weighing, this mouse was returned to the rearing cage (reared alone), and given previously weighed food; the body weight was measured every 1 to 3 days after the start of administration. The anti-obesity activity of each test compound was evaluated on the basis of the rate of weight loss 2 weeks after the start of administration, with the rate of weight loss in a control group receiving administration of the solvent alone regarded as 0%.

[0113] As shown in Table 4, the compound of the present invention has a superior anti-obesity activity.

[Table 4]

Example	Change in body weight
2	-16.3
24	-11.1
25	-11.2
26	-16.2

Test Example 4

Solubility Test

[0114] The solubility of a test compound was examined by the method described below.

[0115] The test compound of approximately 2 mg was measured precisely. Solvents (10 μ L, 20 μ L or 40 μ L) with different pH (Britton-Robinson buffer (pH 3, 5, 7, 9)) were added to each test compound at 25 °C, and the solubility was observed visually.

[0116] As shown in Table 5, all the test compounds showed good solubility at each pH.

[Table 5]

Example	Solubility (mg/mL)			
	pH 3	pH 5	pH 7	pH 9
2	> 100	> 100	> 50	> 50

Example	Solubility (mg/mL)			
	pH 3	pH 5	pH 7	pH 9
24	> 200	> 200	> 200	> 200
25	> 200	> 200	> 200	> 200
26	> 200	> 200	> 200	> 200

[Industrial Applicability]

[0117] The compound of the present invention has superior GLP-1 receptor/GIP receptor coagonist activity, and is useful as a drug for the prophylaxis or treatment of various diseases associated with GLP-1 receptor/GIP receptor, for example, obesity.

[Free Text for Sequence Listing]**[0118]**

SEQ ID NO: 10: Artificial sequence (Synthetic peptide (Reference Example 1))

SEQ ID NO: 11: Artificial sequence (Synthetic peptide (Reference Example 2))

SEQ ID NO: 14: Artificial sequence (Synthetic peptide (Example 2))

SEQ ID NO: 36: Artificial sequence (Synthetic peptide (Example 24))

SEQ ID NO: 37: Artificial sequence (Synthetic peptide (Example 25))

SEQ ID NO: 38: Artificial sequence (Synthetic peptide (Example 26))

SEQUENCE LISTING**[0119]**

<110> Takeda Pharmaceutical Company Limited

<120> Peptide Compound

<130> PT38-9002WO

<150> JP2013-111893

<151> 2013-05-28

<160> 38

<170> PatentIn version 3.5

<210> 1

<211> 29

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Formula (I))

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib or Ala

<220>

<221> misc_feature

<222> (12)..(12)

<223> Xaa stands for Ala, Ile, Lys, Phe or Pya(4)

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib, Cha, Leu, alpha-MePhe, or alpha-MeTyr

<220>

<221> misc_feature

<222> (16)..(16)

<223> Xaa stands for Lys or Ser

<220>

<221> misc_feature

<222> (17)..(17)

<223> Xaa stands for Gln or Ile

<220>

<221> misc_feature

<222> (20)..(20)

<223> Xaa stands for Ala or Ser

<220>

<221> misc_feature

<222> (29).. (29)

<223> Xaa stands for Gln or Gly

<220>

<221> NON_TER

<222> (29).. (29)

<400> 1

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Xaa	Xaa	Leu	Asp	Xaa
1				5					10					15	

Xaa	Ala	Gln	Xaa	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Xaa
		20					25					

<210> 2

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 2

Gly	Pro	Ser	Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
1				5					10	

<210> 3

<211> 4

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 3

Gly Pro Ser Ser

Gly Pro Ser Ser
1

<210> 4

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 4

Gly Pro Ser Ser Gly
1 5

<210> 5

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 5

Gly Pro Ser Ser Gly Ala
1 5

<210> 6

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 6

Gly Pro Ser Ser Gly Ala Pro
1 5

<210> 7

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 7

Gly	Pro	Ser	Ser	Gly	Ala	Pro	Pro
1				5			

<210> 8

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 8

Gly	Pro	Ser	Ser	Gly	Ala	Pro	Pro	Pro
1				5				

<210> 9

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (C-terminal sequence)

<220>

<221> NON_TER

<222> (1)..(1)

<400> 9

Gly	Pro	Ser	Ser	Gly	Ala	Pro	Pro	Pro	Ser
1				5					10

<210> 10

<211> 20

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Reference Example 1)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> OtBu protection

<220>

<221> MOD_RES

<222> (4, 5, 8, 20)..(4, 5, 8, 20)

<223> Boc protection

<220>

<221> MOD_RES

<222> (12, 13, 19)..(12, 13, 19)

<223> tBu protection

<400> 10

Gln	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro
1				5					10					15	

Pro	Pro	Ser	Lys
			20

<210> 11

<211> 19

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Reference Example 2)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> OtBu protection

<220>

<221> MOD_RES

<222> (4, 5, 8)..(4, 5, 8)

<223> Boc protection

<220>

<221> MOD_RES

<222> (12, 13, 19)..(12, 13, 19)

<223> tBu protection

<400> 11

Gln	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser	Ser	Gly	Ala	Pro
1				5					10					15	

Pro Pro Ser

<210> 12

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Reference Example 3)

<220>

<221> MOD_RES

<222> (2)..(2)

<223> Trt protection

<220>

<221> MOD_RES

<222> (4)..(4)

<223> OtBu protection

<220>

<221> MOD_RES

<222> (7, 8, 11, 23)..(7, 8, 11, 23)

<223> Boc protection

<220>

<221> MOD_RES

<222> (15, 16, 22)..(15, 16, 22)

<223> tBu protection

<400> 12

Ala	Gln	Ala	Gln	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser	Ser
1				5					10					15	

Gly	Ala	Pro	Pro	Pro	Ser	Lys
			20			

<210> 13

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 1)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 13

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ala	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

20

25

30

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 14

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 2)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 14

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20						25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
		35					40

<210> 15

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 3)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 15

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ala	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ser	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
			20					25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
			35				40

<210> 16

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 4)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 16

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln Ala Gln Ser Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser Lys
 35 40

<210> 17

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 5)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (39)..(39)

<223> C terminal amidation

<400> 17

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Ala Ile Xaa Leu Asp Lys
 1 5 10 15

Gln Ala Gln Ala Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser
 35

<210> 18

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 6)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (39)..(39)

<223> C terminal amidation

<400> 18

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20						25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser
		35				

<210> 19

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 7)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (39)..(39)

<223> C terminal amidation

<400> 19

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Ala	Ile	Xaa	Leu	Asp	Lys
1				5				10					15		

Gln	Ala	Gln	Ser	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser
		35				

<210> 20

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 8)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (39)..(39)

<223> C terminal amidation

<400> 20

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ser	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
			20					25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser
			35			

<210> 21

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 9)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 21

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Lys	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25						30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 22

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 10)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 22

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ala	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln Ala Gln Ala Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser Lys
 35 40

<210> 23

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 11)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 23

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Xaa Phe Xaa Leu Asp Lys
 1 5 10 15

Gln Ala Gln Ala Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
 20 25 30

Ser Gly Ala Pro Pro Pro Ser Lys
 35 40

<210> 24
 <211> 40
 <212> PRT
 <213> Artificial Sequence
 <220>
 <223> Synthetic Peptide (Example 12)

<220>
 <221> misc_feature
 <222> (2)..(2)
 <223> Xaa stands for Aib

<220>
 <221> MOD_RES
 <222> (6)..(6)
 <223> alpha-METHYLATION

<220>
 <221> misc_feature
 <222> (11)..(11)
 <223> Xaa stands for Aib

<220>
 <221> misc_feature
 <222> (12)..(12)
 <223> Xaa stands for Pya(4)

<220>
 <221> misc_feature
 <222> (13)..(13)
 <223> Xaa stands for Aib

<220>
 <221> MOD_RES
 <222> (40)..(40)
 <223> C terminal amidation

<400> 24
 Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Xaa Xaa Xaa Leu Asp Lys
 1 5 10 15
 Gln Ala Gln Ala Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
 20 25 30
 Ser Gly Ala Pro Pro Pro Ser Lys
 35 40

<210> 25

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 13)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (13)..(13)

<223> alpha-METHYLATION

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 25

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Phe	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 26

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 14)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Cha

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 26

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
			20					25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
			35				40

<210> 27

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 15)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (13)..(13)

<223> alpha-METHYLATION

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 27

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Lys	Phe	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
		35					40

<210> 28

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 16)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Cha

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 28

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Lys	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
		35					40

<210> 29

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 17)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (13)..(13)

<223> alpha-METHYLATION

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 29

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Xaa Ile Tyr Leu Asp Lys
1 5 10 15

Gln Ala Gln Ala Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser Lys
35 40

<210> 30

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 18)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N terminal (acetyl)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 30

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20						25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
		35					40

<210> 31

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 19)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N terminal (benzoyl)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 31

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Xaa Ile Xaa Leu Asp Lys
1 5 10 15

Gln Ala Gln Ala Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser Lys
35 40

<210> 32

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 20)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N terminal (4-PyCO (4-pyridylcarbonyl))

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N terminal (4-PyCO (4-pyridylcarbonyl))

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 32

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5				10					15		

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 33

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 21)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N terminal (cPrCO (Cyclopropanecarbonyl))

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 33

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20						25					30		

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
		35					40

<210> 34

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 22)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N terminal (amidino)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 34

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
		35					40

<210> 35

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 23)

<220>

<221> MOD_RES

<222> (1)..(1)

<223> N-METHYLATION

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<220>

<221> misc_feature

<222> (13)..(13)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (40)..(40)

<223> C terminal amidation

<400> 35

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Ile	Xaa	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 36

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 24)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<400> 36

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Lys	Tyr	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Ala	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 37

<211> 40

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 25)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<400> 37

Tyr	Xaa	Glu	Gly	Thr	Phe	Thr	Ser	Asp	Tyr	Xaa	Lys	Tyr	Leu	Asp	Lys
1				5					10					15	

Gln	Ala	Gln	Gln	Glu	Phe	Val	Lys	Trp	Leu	Leu	Lys	Gly	Gly	Pro	Ser
		20					25					30			

Ser	Gly	Ala	Pro	Pro	Pro	Ser	Lys
	35					40	

<210> 38

<211> 39

<212> PRT

<213> Artificial Sequence

<220>

<223> Synthetic Peptide (Example 26)

<220>

<221> misc_feature

<222> (2)..(2)

<223> Xaa stands for Aib

<220>

<221> MOD_RES

<222> (6)..(6)

<223> alpha-METHYLATION

<220>

<221> misc_feature

<222> (11)..(11)

<223> Xaa stands for Aib

<400> 38

Tyr Xaa Glu Gly Thr Phe Thr Ser Asp Tyr Xaa Lys Tyr Leu Asp Lys
1 5 10 15

Gln Ala Gln Gln Glu Phe Val Lys Trp Leu Leu Lys Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro Ser
35

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- [WO2010011439A \[0006\]](#)
- [WO2010148089A \[0006\]](#)
- [WO2011119657A \[0006\]](#)
- [WO2012088379A \[0006\]](#)
- [WO2012167744A \[0006\]](#)
- [WO2013164483A \[0006\]](#)
- [WO2013192129A \[0006\]](#)
- [WO2013192130A \[0006\]](#)
- [WO007013694A \[0057\]](#)
- [WO2007018314A \[0057\]](#)
- [WO2008093639A \[0057\]](#)
- [WO2008099794A \[0057\]](#)
- [WO2004041266A \[0057\]](#)

- [WO2004106276A](#) [0057]
- [WO2005063729A](#) [0057]
- [WO2005063725A](#) [0057]
- [WO2005087710A](#) [0057]
- [WO2005095338A](#) [0057]
- [WO2007013689A](#) [0057]
- [WO2008001931A](#) [0057]
- [WO006112549A](#) [0057]
- [WO007028135A](#) [0057]
- [WO008047821A](#) [0057]
- [WO008050821A](#) [0057]
- [WO008136428A](#) [0057]
- [WO008156757A](#) [0057]
- [WO0114372A](#) [0058]
- [WO2004039365A](#) [0058]
- [WO9710224A](#) [0059]
- [WO0206234A](#) [0065]
- [WO2004048363A](#) [0065]
- [WO2005030740A](#) [0065]
- [WO2005058823A](#) [0065]
- [WO2005113504A](#) [0065]
- [JP2013111893A](#) [0119]

Non-patent literature cited in the description

- Clinical Science, 2011, vol. 121, 107-117 [0007]

Patentkrav**1.** Peptid, der er valgt blandt

H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ eller et salt deraf,

H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Ile-Aib-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ eller et salt deraf,

H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ eller et salt deraf og

H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂ eller et salt deraf.

2. Peptid eller salt ifølge krav 1, der er H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ eller et salt deraf.

3. Peptid eller salt ifølge krav 1, der er H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Ile-Aib-Leu-Asp-Lys-Gln-Ala-Gln-Ala-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ eller et salt deraf.

4. Peptid eller salt ifølge krav 1, der er H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-NH₂ eller et salt deraf.

5. Peptid eller salt ifølge krav 1, der er H-Tyr-Aib-Glu-Gly-Thr- α MePhe-Thr-Ser-Asp-Tyr-Aib-Lys-Tyr-Leu-Asp-Lys-Gln-Ala-Gln-Gln-Glu-Phe-Val-Lys-Trp-Leu-Leu-Lys-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH₂ eller et salt deraf.

6. Medikament, der omfatter peptidet ifølge krav 1 eller et salt deraf.

7. Medikament ifølge krav 6 til anvendelse ved profylakse eller behandling af adipositas eller diabetes.

8. Peptid ifølge krav 1 eller et salt deraf til anvendelse ved profylakse eller behandling af adipositas eller diabetes.

9. Sammensætning, der omfatter peptidet ifølge krav 1 eller et salt deraf og et ledsagende lægemiddel.