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(54) USE OF EXENDINS AND AGONISTS THEREOF FOR THE TREATMENT OF GESTATIONAL DIABETES MELLITUS

VERWENDUNG VON EXENDINS UND DEREN AGONISTEN ZUR BEHANDLUNG VON SCHWANGERSCHAFTSDIABETES

UTILISATION D'EXENDINES ET DE LEURS AGONISTES POUR LE TRAITEMENT DU DIABETE SUCRE GESTATIONNEL

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- **GREIG N H ET AL: "Once daily injection of exendin-4 to diabetic mice achieves long-term beneficial effects on blood glucose concentrations." DIABETOLOGIA, vol. 42, no. 1, 1 January 1999 (1999-01-01), pages 45-50, XP000971927 ISSN: 0012-186X**

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Description

Field Of The Invention

[0001] The present invention relates to a use in the manufacture of a medicament for treating gestational diabetes mellitus.

Background

[0002] The following description summarizes information relevant to the present invention. It is not an admission that any of the information provided herein is prior art to the presently claimed invention, nor that any of the publications specifically or implicitly referenced are prior art to that invention.

Gestational Diabetes Mellitus

[0003] Gestational diabetes mellitus ("GDM") is a disorder associated with elevated circulating plasma glucose. Although the diagnostic criteria for GDM have been the subject of controversy for decades, it was defined by the Third Workshop Conference on Gestational Diabetes Mellitus as carbohydrate intolerance of varying severity with onset or first recognition during pregnancy, irrespective of the glycemic status after delivery. Metzger (ed.) Proceedings of the Third International Workshop Conference on Gestational Diabetes Mellitus, Diabetes 40(Suppl. 2), 1991. Despite advances in clinical management of GDM, there are problems associated with GDM which persist, including elevated rate of perinatal morbidity and elevated rate of malformations in newborns. Persson et al., Diabetes and Pregnancy, In International Textbook of Diabetes Mellitus, Second Edition, John Wiley & Sons 1997 (Alberti et al. Eds.). For example, it has been reported that, when the mean blood glucose level is greater than 105 mg/dl, there is a greater risk for the development of large-for-gestational age ("LGA") infants when compared with a control population. Id. Additional reported consequences of untreated GDM include an increased incidence of macrosomia, respiratory distress syndrome, and other abnormalities of fetal metabolism. Langer, Am. J. Obstet Gynecol. 176:S186, 1997; American Diabetes Association: Self-Monitoring of Blood Glucose Consensus Statement, Diabetes Care 17:81-82, 1994("ABA Consensus Statement"); Coetzee & Jackson, S. Afr. Med. J. 56:467-475, 1979. It has been clearly established by those in the field that tight glycemic control can serve as the primary prevention of fetal disease relating to GDM. Drexel et al., Diabetes Care 11: 761-768, 1988; Roversi et al., Diabetes Care 3:489-494, 1980; Langer & Mazze, Am. J. Obstet Gynecol. 159:1478-1483, 1988; Langer et al., Am. J. Obstet Gynecol. 161:646-653, 1989). GDM results in a greater incidence of intrauterine death or neonatal mortality. Position Statement American Diabetes Association: Gestational Diabetes Mellitus, Diabetes Care 21 (Suppl. 1):S60-61, 1998. GDM pregnancies are at an increased risk for fetal macrosomia and neonatal morbidities including neural tube defects, hypoglycemia, hypocalcemiea, hypomagnsemia, polycythemia and hyperbilirubinemia and subsequent childhood and adolescent obesity. Siccardi, Gestational Diabetes. Other complications to the woman include increased rates of cesarean delivery, hypertensive disorders including preeclamsia and urinary tract infections.

[0004] It has been reported that approximately 4% of all pregnancies (135,000 cases annually) are complicated by GDM, however, it has been estimated that the incidence may range from 1% to 14% of all pregnancies, depending on the population and diagnostic tests employed. ADA Consensus Statement, supra.

[0005] Normally during pregnancy, fasting plasma levels of insulin gradually increase to reach concentrations that are approximately twice as high in the third trimester as they were outside of pregnancy. Women with gestational diabetes mellitus ("GDM") have fasting insulin levels comparable to or higher than those of normal pregnant women with the highest levels seen in women with GDM who are obese. Insulin secretion also increases gradually in pregnancy and also reaches a maximum during the third trimester. However, the relative increase in secretion is significantly smaller in women with GDM than in normal glucose tolerant ("NGT") women. The first-phase insulin response in NGT women is significantly higher than in GDM women; second phase insulin response was similarly increased during pregnancy in both groups. This finding is consistent with the finding that GDM women have a later time of peak insulin concentration during an oral glucose tolerance test than do NGT women. Consistent with this observation, the insulin response per unit of glycemic stimulus is significantly higher in NGT women than in GDM women (90% and 40%, respectively). The fact that glucose tolerance deteriorates in both normal and GDM pregnancies while at the same time, insulin secretion increases indicates a decrease in insulin sensitivity. Comparative results from an intravenous glucose tolerance test and a hyperinsulinemic, euglycemic clamp showed a sensitivity decrease during pregnancy in both groups of 50-60%, but GDM women had a slightly lower sensitivity. In another study using radioactive glucose, turnover of glucose and amino acids in GDM women was comparable to NGT women only when insulin concentrations 3-5 fold higher in the GDM group were used. Thus, it appears that GDM is due to a combination of diminished insulin sensitivity and an impaired ability to increase insulin secretion and has, in fact, many features in common with type 2 diabetes. Normal or near normal glycemic control returns upon parturition.

Clinical Diagnosis:

[0006] It is common clinical practice to screen women for elevated glucose and glucose intolerance between weeks 24 and 28 of gestation, especially women with any one the following four characteristics: age ≥25; race/ethnicity of Hispanic, Native American, Asian, African-American or Pacific Islander origin; obese or a family history of diabetes. In addition, women with previous pregnancies with complications due to a large weight fetus/neonate are usually tested. In some medical centers all pregnant women are tested. Indeed, certain investigators have found that historical risk factors account for only roughly half of the women known to have GDM. Carr, Diabetes Care 21(Suppl. 2):B14-B18, 1998. Additionally, there is some reported evidence that advancing maternal age is associated with increased incidence of GDM. Id.

[0007] The clinical diagnosis is generally based on a multistep process. The evaluation is most typically performed by measuring plasma glucose 1 hour after a 50-gram oral glucose challenge test in either the fasted or the unfasted state. If the value in the glucose challenge test is ≥ 140 mg/dl, a 3-hr 100 g oral glucose tolerance test is done. If two or more of the following criteria are met, the patient is considered in need of glycemic control: fasted venous plasma ≥ 105 mg/dl, venous plasma ≥ 190 mg/dl at 1 hr, venous plasma ≥ 165 mg/dl at 2 hr or venous plasma ≥ 145 mg/dl at 3 hr. Williams et al., Diabetes Care 22: 418 - 421, 1999. Variations of this test are also used by some. See, e.g., Coustan, Gestational Diabetes In Diabetes in America, 2d ed. National Institutes of Health Publication No. 95-1468, 1995.

Current Clinical Therapy:

[0008] The current therapeutic approach for GDM is to control plasma glucose for the remainder of the gestation (i.e., the third trimester through parturition). GDM has many features in common with type 2 diabetes. The endocrine (impaired insulin secretion) and metabolic (insulin resistance) abnormalities that characterize both forms of diabetes are similar. In general, pregnancy is characterized by increases in both insulin resistance and insulin secretion. Women with GDM fail to respond with increased insulin to the decrease in insulin sensitivity.

[0009] A significant correlation has been shown to exist between late-stage gestational maternal glucose levels and preeclamsia, macrosomia, Cesarean section delivery and phototherapy for hyperbilirubinemia. Sermer et al., Diabetic Care 21 (Suppl. 2):B33-B42, 1998. It has also been determined that the length of hospitalization of the new mother and the length of time the neonate spent in the nursery could be correlated to the degree of elevation of plasma glucose in the pregnant woman. Id. Tallarigo, et al. reported a striking rise in the risk of fetal macrosomia (9.9 vs. 27.5%) and preeclamsia/Cesarean sections (19.9 vs. 40.0%) in women with abnormal glucose tolerance when compared to NGT women. Tallarigo et al., N. Engl. J. Med. 315:989-992, 1986.

[0010] Thus, the goals for therapy of GDM are to achieve and maintain as near normal glycemia as feasible with a special emphasis to keep postprandial glucose concentrations within the normal range. Optimal therapeutic strategies are safe and efficacious in achieving a metabolic balancing without creating complications, which may include ketosis and/or hypoglycemia. Jovanovic, Diabetes Care 21(Suppl. 2):B131-B137, 1998. The initial therapeutic approach is through diet. Jovanovic-Peterson & Peterson, J. Am. Coll. Nutr. 9:320-325, 1990.

[0011] If diet or diet and exercise are not effective (i.e., failure is fasting glucose ≥ 105 mg/dl and/or a 2-hr postprandial plasma glucose of ≥ 120 mg/dl on 2 or more occasions within a 1- to 2-week period), then insulin therapy (preferably, human insulin) is considered appropriate. ADA Position Statement, supra.

[0012] Oral glucose-lowering agents are not recommended during pregnancy. Kuhl et al., Diabetic Care 21 (Suppl. 2): B19-B26, 1998. Although sulfonylureas are used in the treatment of type 2 diabetes due to their activity in increasing insulin sensitivity, these agents are contraindicated for use in GDM. Jovanovic, Diabetes Care 21 (Suppl. 2):B131-B137, 1998. See also Kahn & Shechter, Insulin, Oral Hypoglycemic Agents, and the Pharmacology of the Endocrine Pancreas, In Goodman & Gilman's The Pharmacological Basis of Therapeutics (8th ed. 1993 Goodman Gilman et al. eds.). Oral hypoglycemic drugs traverse the placenta, and may cause prolonged severe hypoglycemia in the newborn. Persson et al., supra.

[0013] The difficulties with, and the highly variable approaches to insulin therapy in GDM have been reviewed, for example, by Langer, et al. Langer, Diabetes Care 21(Suppl.2):B91-B98, 1998. The problems commonly associated with insulin therapy in a non-pregnant population remain when used in the treatment of GDM. They are determination of the proper dose, maintenance of good glucose control through each 24-hr period, possible hypoglycemia and weight gain. Hypoglycemia can result when insulin is administered to control postprandial plasma glucose, but the fetus demands for energy in the presence of excess insulin later causes the glucose level to drop to a hypoglycemic level. This physiological state can be dangerous to both the mother and the fetus. Excess weight gain is undesirable in any pregnancy. Another problem with insulin therapy is the day-to-day and week-to-week variability in glucose control vs.insulin dose.

[0014] Thus, it can be appreciated that an effective means to treat gestational diabetes remains a major challenge and a superior method of treatment would be of great utility. Such a method, and compounds and compositions which are useful therefor, have been invented and are described and claimed herein.

Exendins and Exendin Agonists

[0015] Exendins are peptides that were first isolated form the salivary secretions of the Gila-monster, a lizard found in Arizona, and the Mexican Beaded Lizard. Exendin-3 is present in the salivary secretions of Heloderma horridum, and exendin-4 is present in the salivary secretions of Heloderma suspectum (Eng, J., et al., J. Biol. Chem., 265:20259-62, 1990; Eng., J., et al., J. Biol. Chem., 267:7402-05, 1992). The exendins have some sequence similarity to several members of the glucagon-like peptide family, with the highest homology, 53%, being to GLP-1[7-36]NH_2 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993). GLP-1[7-36]NH_2, also known as proglucagon[78-107] and most commonly as "GLP-1," has an insulinotropic effect, stimulating insulin secretion from pancreatic β-cells; GLP-1 also inhibits glucagon secretion from pancreatic α-cells (Orskov, et al., Diabetes, 42:658-61, 1993; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). GLP-1 is reported to inhibit gastric emptying (Williams B, et al., J Clin Endocrinol Metab 81 (1): 327-32, 1996; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993), and gastric acid secretion. (Schjoldager BT, et al., Dig Dis Sci 34 (5): 703-8, 1989; O'Halloran DJ, et al., J Endocrinol 126 (1): 169-73, 1990; Wettergren A, et al., Dig Dis Sci 38 (4): 665-73, 1993). GLP-1[7-37], which has an additional glycine residue at its carboxy terminus, also stimulates insulin secretion in humans (Orskov, et al., Diabetes, 42:658-61, 1993). A transmembrane G-protein adenylate-cyclase-coupled receptor believed to be responsible for the insulinotropic effect of GLP-1 is reported to have been cloned from a β-cell line (Thorens, Proc. Natl. Acad. Sci. USA 89:8641-45 (1992)).

[0016] Exendin-4 potently binds at GLP-1 receptors on insulin-secreting βTC1 cells, at dispersed acinar cells from guinea pig pancreas, and at parietal cells from stomach; the peptide is also said to stimulate somatostatin release and inhibit gastrin release in isolated stomachs (Goke, et al., J. Biol. Chem. 268:19650-55, 1993; Schepp, et al., Eur. J. Pharmacol., 69:183-91, 1994; Eissele, et al., Life Sci., 55:629-34, 1994). Exendin-3 and exendin-4 were reported to stimulate cAMP production in, and amylase release from, pancreatic acinar cells (Malhotra, R., et al., Regulatory Peptides, 41:149-56, 1992; Raufman, et al., J. Biol. Chem. 267:21432-37, 1992; Singh, et al., Regul. Pept. 53:47-59, 1994). The use of exendin-3 and exendin-4 as insulinotrophic agents for the treatment of diabetes mellitus and the prevention of hyperglycemia has been proposed (Eng, U.S. Patent No. 5,424,286).

[0017] C-terminally truncated exendin peptides such as exendin-4[9-39], a carboxyamidated molecule, and fragments 3-39 through 9-39 have been reported to be potent and selective antagonists of GLP-1 (Goke, et al., J. Biol. Chem., 268:19650-55, 1993; Raufman, J.P., et al., J. Biol. Chem. 266:2897-902, 1991; Schepp, W., et al., Eur. J. Pharm. 269: 183-91, 1994; Montrose-Rafizadeh, et al., Diabetes, 45(Suppl. 2) :152A, 1996). Exendin-4 [9-39] is said to block endogenous GLP-1 in vivo, resulting in reduced insulin secretion. Wang, et al., J. Clin. Invest., 95:417-21, 1995; D'Alessio, et al., J. Clin. Invest., 97:133-38, 1996). The receptor apparently responsible for the insulinotropic effect of GLP-1 has reportedly been cloned from rat pancreatic islet cell (Thorens, B., Proc. Natl. Acad. Sci. USA 89:8641-8645, 1992). Exendins and exendin-4 [9-39] are said to bind to the cloned GLP 1 receptor (rat pancreatic β-cell GLP-1 receptor (Fehmann HC, et al., Peptides 15 (3): 453-6, 1994) and human GLP-1 receptor (Thorens B, et al., Diabetes 42 (11): 1678-82, 1993). In cells transfected with the cloned GLP-1 receptor, exendin-4 is reportedly an agonist, i.e., it increases cAMP, while exendin [9-39] is identified as an antagonist, i.e., it blocks the stimulatory actions of exendin-4 and GLP-1. Id.

[0018] Exendin-4[9-39] is also reported to act as an antagonist of the full length exendins, inhibiting stimulation of pancreatic acinar cells by exendin-3 and exendin-4 (Raufman, et al., J. Biol. Chem. 266:2897-902, 1991; Raufman, et al., J. Biol. Chem , 266:21432-37, 1992). It is also reported that exendin[9-39] inhibits the stimulation of plasma insulin levels by exendin-4, and inhibits the somatostatin release-stimulating and gastrin release-inhibiting activities of exendin-4 and GLP-1 (Kolligs, F., et al., Diabetes, 44:16-19, 1995; Eissele, et al., Life Sciences, 55:629-34, 1994).

[0019] Methods for regulating gastrointestinal motility using exendin agonists are described and claimed PCT/US97/14199 entitled, "Methods for Regulating Gastrointestinal Motility," which enjoys common ownership with the present invention.

[0020] Methods of reducing food intake using exendin agonists are described and claimed PCT/US 98/00449, entitled, "Use of Exendin and Agonists Thereof for the Reduction of Food Intake," claiming the benefit of Provisional Application Nos. 60/034,905, filed January 7, 1997, 60/055,404, filed August 7, 1997, 60/065,442 filed November 14, 1997, and 60/066,029 filed November 14, 1997. These applications also enjoy common ownership with the present invention.

[0021] Exendins have also been found to have inotropic and diuretic effects. International Application No. PCT/US99/02554, filed February 5, 1999, 1998, claiming the benefit of Provisional Application No. 60/075,122, filed February 13, 1998. These applications also enjoy common ownership with the present invention.

[0022] Additionally, exendins have been found to suppress glucagon secretion PCT/US00/009920 entitled "Methods for Glucagon Suppression," which enjoys common ownership with the present invention.

[0023] Exendin [9-39] has been used to investigate the physiological relevance of central GLP-1 in control of food intake (Turton, M.D. et al. Nature 379:69-72, 1996). GLP-1 administered by intracerebroventricular injection inhibits food intake in rats. This satiety-inducing effect of GLP-1 delivered ICV is reported to be inhibited by ICV injection of exendin [9-39] (Turton, supra). However, it has been reported that GLP-1 does not inhibit food intake in mice when administered by peripheral injection (Turton, M.D., Nature 379:69-72, 1996; Bhavsar, S.P., Soc. Neurosci. Abstr. 21:460 (188.8), 1995).

Summary Of The Invention

[0024] The present invention concerns the surprising discovery that exendins and exendin agonists do not cross the placenta, and yet have a profound and prolonged effect on blood glucose, rendering them ideal agents for the treatment of gestational diabetes mellitus.

[0025] The present invention may be used for treating gestational diabetes mellitus by the administration of an exendin, for example, exendin-3 [SEQ ID NO. 1: His Ser Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser], or exendin-4 [SEQ ID NO. 2: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Ser], or other compounds which effectively bind to the receptor at which exendin exerts its actions which are beneficial in treatment of gestational diabetes mellitus.

[0026] In a first aspect, the invention provides use of an exendin or exendin agonist peptide for the manufacture of a medicament for treating gestational diabetes in a subject, said medicament comprising a therapeutically effective amount of an exendin or an exendin agonist peptide wherein said exendin or exendin agonist peptide binds to a receptor that binds exendin-3 or exendin-4 wherein said exendin or exendin agonist peptide comprises the sequence of formula (I) [SEQ ID NO 3], formula (II) [SEQ ID NO. 4] or formula (III) [SEQ ID NO.5], set forth herein.

[0027] By an "exendin agonist" is meant a compound that mimics the effects of exendin in the treatment of gestational diabetes mellitus by binding to the receptor or receptors where exendin causes one or more of these effects. Exendins and exendin agonists should be especially beneficially in the treatment of GDM because, due to their actions to inhibit gastric emptying, administration of such compounds should not result in increased weight gain. Additionally, in animal and human studies to date, administration of exendins and exendin agonists have not resulted in an increased incidence of hypoglycemia.

[0028] Exendin agonist peptide compounds include exendin acids, for example exendin-3 acid and exendin-4 acid. Exendin agonist peptide compounds include those described in International Application No. PCT/US98/16387, entitled, "Novel Exendin Agonist Compounds," filed August 6, 1998, claiming the benefit of United States Provisional Patent Application Serial No. 60/055,404, entitled, filed August 8, 1997; International Application No. PCT/US98/24220 entitled, "Novel Exendin Agonist Compounds," filed November 13, 1998, claiming priority on United States Provisional Patent Application Serial No. 60/065,442, filed November 14, 1997; and International Application No. PCT/US98/24273 entitled, "Novel Exendin Agonist Compounds," filed November 13, 1998, claiming priority on United States United States Provisional Patent Application Serial No. 60/066,029, filed November 14, 1997; all of which enjoy common ownership with the present application. Additional preferred exendin agonist compounds are those described and claimed in PCT/US00/11814, entitled, "Modified Exendins and Exendin Agonists," which enjoys common ownership with the present application.

[0029] By "gestational diabetes mellitus" or "GDM" is meant any degree of glucose intolerance with onset or first recognition during pregnancy.

[0030] Preferably, the subject is a vertebrate, more preferably a mammal, and most preferably a human woman. In preferred aspects, the exendin or exendin agonist is administered parenterally, more preferably by injection. In a most preferred aspect, the injection is a peripheral injection. Preferably, about 1 μg-30 μg to about 1 mg of the exendin or exendin agonist is administered per day. More preferably, about 1-30 μg to about 500 μg, or about 1-30 μg to about 50 μg of the exendin or exendin agonist is administered per day. Most preferably, about 3 μg to about 50 μg of the exendin or exendin agonist is administered per day.

[0031] In one preferred aspect, the exendin or exendin agonist peptide used in the present invention is exendin-3. In another preferred aspect, said exendin is exendin-4. Other preferred exendin agonist peptides include exendin-4 (1-30) [SEQ ID NO 6: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly], exendin-4 (1-30) amide [SEQ ID NO 7: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly-NH2], exendin-4 (1-28) amide [SEQ ID NO 40: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2], ^{14}Leu, ^{25}Phe exendin-4 amide [SEQ ID NO 9: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu,Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH_2], ^{14}Leu, ^{25}Phe exendin-4 (1-28) amide [SEQ ID NO 41: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2], and ^{14}Leu, ^{22}Ala, ^{25}Phe exendin-4 (1-28) amide [SEQ ID NO 8: His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Ala Ile Glu Phe Leu Lys Asn-NH_2].

[0032] The exendins and exendin agonist peptides may be administered separately or together with one or more other compounds and compositions that exhibit a long term or short-term blood glucose control action, including, but not limited to other compounds and compositions that comprise an insulin or an amylin agonist. Suitable amylin agonists include, for example, [^{25,28,29}Pro-]-human amylin (also known as "pramlintide," previously referred to as "AC-137," and , referred to in its acetate salt form by its trademark SYMLIN™ (pramlintide acetate), as described in "Amylin Agonist Peptides and Uses Therefor," U.S. Patent No. 5,686,511, issued November 11, 1997, and salmon calcitonin.

Brief Description Of The Drawings

[0033]

Figure 1 depicts the amino acid sequences for certain exendin agonist compounds useful in the present invention [SEQ ID NOS 9-39].
Figure 2 depicts concentrations of exendin-4 (AC2993) in plasma and amniotic fluid of rats after 21 μg subcutaneous injection.
Figure 3 depicts concentrations of exendin-4 (AC2993) in plasma and amniotic fluid of rats after 210 μg subcutaneous injection.

Detailed Description Of The Invention

[0034] Exendins and exendin agonist peptides are useful as described herein in view of their pharmacological properties. Activity as exendin agonists can be indicated by activity in the assays described below. Effects of exendins or exendin agonists in treating gestational diabetes can be identified, evaluated, or screened for, using the methods described in the Examples below, or other methods known in the art for determining effects on blood glucose control.

Exendin Agonist compounds

[0035] Exendins or exending agonist peptide compounds include those described in International Application No. PCT/US98/16387, filed August 6, 1998, entitled, "Novel Exendin Agonist Compounds," which claims the benefit of United States Provisional Application No. 60/055,404, filed August 8, 1997, including compounds of the formula (I) [SEQ ID NO. 3]:

$Xaa_1\ Xaa_2\ Xaa_3$ Gly Thr $Xaa_4\ Xaa_5\ Xaa_6\ Xaa_7\ Xaa_8$
Ser Lys Gln Xaa_9 Glu Glu Glu Ala Val Arg Leu
$Xaa_{10}\ Xaa_{11}\ Xaa_{12}\ Xaa_{13}$ Leu Lys Asn Gly Gly Xaa_{14}
Ser Ser Gly Ala $Xaa_{15}\ Xaa_{16}\ Xaa_{17}\ Xaa_{18}$-Z

wherein Xaa_1 is His, Arg or Tyr; Xaa_2 is Ser, Gly, Ala or Thr; Xaa_3 is Asp or Glu; Xaa_4 is Phe, Tyr or naphthylalanine; Xaa_5 is Thr or Ser; Xaa_6 is Ser or Thr; Xaa_7 is Asp or Glu; Xaa_8 is Leu, Ile, Val, pentylglycine or Met; Xaa_9 is Leu, Ile, pentylglycine, Val or Met; Xaa_{10} is Phe, Tyr or naphthylalanine; Xaa_{11} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met; Xaa_{12} is Glu or Asp; Xaa_{13} is Trp, Phe, Tyr, or naphthylalanine; Xaa_{14}, Xaa_{15}, Xaa_{16} and Xaa_{17} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; Xaa_{18} is Ser, Thr or Tyr; and Z is -OH or $-NH_2$.

[0036] Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms. Suitable compounds include those listed in Figure 10 having amino acid sequences of SEQ. ID. NOS. 9 to 39.

[0037] Preferred exendin agonist compounds include those wherein Xaa_1 is His or Tyr. More preferably Xaa_1 is His.

[0038] Preferred are those compounds wherein Xaa_2 is Gly.

[0039] Preferred are those compounds wherein Xaa_9 is Leu, pentylglycine or Met.

[0040] Preferred compounds include those wherein Xaa_{13} is Trp or Phe.

[0041] Also preferred are compounds where Xaa_4 is Phe or naphthylalanine; Xaa_{11} is Ile or Val and Xaa_{14}, Xaa_{15}, Xaa_{16} and Xaa_{17} are independently selected from Pro, homoproline, thioproline or N-alkylalanine. Preferably N-alkylalanine has a N-alkyl group of 1 to about 6 carbon atoms.

[0042] According to an especially preferred aspect, Xaa_{15}, Xaa_{16} and Xaa_{17} are the same amino acid reside.

[0043] Preferred are compounds wherein Xaa_{18} is Ser or Tyr, more preferably Ser.

[0044] Preferably Z is $-NH_2$.

[0045] According to one aspect, preferred are compounds of formula (I) wherein Xaa_1 is His or Tyr, more preferably His; Xaa_2 is Gly; Xaa_4 is Phe or naphthylalanine; Xaa_9 is Leu, pentylglycine or Met; Xaa_{10}, is Phe or naphthylalanine; Xaa_{11} is Ile or Val; Xaa_{14}, Xaa_{15}, Xaa_{16} and Xaa_{17} are independently selected from Pro, homoproline, thioproline or N-alkylalanine; and Xaa_{18} is Ser or Tyr, more preferably Ser. More preferably Z is $-NH_2$.

[0046] According to an especially preferred aspect, especially preferred compounds include those of formula (I) wherein: Xaa_1 is His or Arg; Xaa_2 is Gly; Xaa_3 is Asp or Glu; Xaa_4 is Phe or napthylalanine; Xaa_5 is Thr or Ser; Xaa_6 is Ser or Thr; Xaa_7 is Asp or Glu; Xaa_8 is Leu or pentylglycine; Xaa_9 is Leu or pentylglycine; Xaa_{10} is Phe or naphthylalanine; Xaa_{11} is Ile, Val or t-butyltylglycine; Xaa_{12} is Glu or Asp; Xaa_{13} is Trp or Phe; Xaa_{14}, Xaa_{15}, Xaa_{16}, and Xaa_{17} are independently Pro, homoproline, thioproline, or N-methylalanine; Xaa_{18} is Ser or Tyr: and Z is -OH or $-NH_2$; with the

proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2. More preferably Z is $-NH_2$. Especially preferred compounds include those having the amino acid sequence of SEQ. ID. NOS. 9, 10, 21, 22, 23, 26, 28, 34, 35 and 39.

[0047] According to an especially preferred aspect, provided are compounds where Xaa_9 is Leu, Ile, Val or pentylglycine, more preferably Leu or pentylglycine, and Xaa_{13} is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will exhibit advantageous duration of action and be less subject to oxidative degradation, both in vitro and in vivo, as well as during synthesis of the compound.

[0048] Exendins or exendin agonist peptide compounds also include those described in International Application No. PCT/US98/24210, filed November 13, 1998, entitled, "Novel Exendin Agonist compounds," which claims the benefit of United States Provisional Application No. 60/065,442, filed November 14, 1997, including compounds of the formula (II) [SEQ ID NO. 4]:

$Xaa_1\ Xaa_2\ Xaa_3\ Gly\ Xaa_5\ Xaa_6\ Xaa_7\ Xaa_8\ Xaa_9\ Xaa_{10}$
$Xaa_{11}\ Xaa_{12}\ Xaa_{13}\ Xaa_{14}\ Xaa_{15}\ Xaa_{16}\ Xaa_{17}\ Ala\ Xaa_{19},\ Xaa_{20}$
$Xaa_{21}\ Xaa_{22}\ Xaa_{23}\ Xaa_{24}\ Xaa_{25}\ Xaa_{26}\ Xaa_{27}\ Xaa_{28}$-$Z_1$; wherein
Xaa_1 is His, Arg or Tyr;
Xaa_2 is Ser, Gly, Ala or Thr;
Xaa_3 is Asp or Glu;
Xaa_5 is Ala or Thr;
Xaa_6 is Ala, Phe, Tyr or naphthylalanine;
Xaa_7 is Thr or Ser;
Xaa_8 is Ala, Ser or Thr;
Xaa_9 is Asp or Glu;
Xaa_{10} is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa_{11} is Ala or Ser;
Xaa_{12} is Ala or Lys;
Xaa_{13} is Ala or Gln;
Xaa_{14} is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa_{15} is Ala or Glu;
Xaa_{16} is Ala or Glu;
Xaa_{17} is Ala or Glu;
Xaa_{19} is Ala or Val;
Xaa_{20} is Ala or Arg;
Xaa_{21} is Ala or Leu;
Xaa_{22} is Ala, Phe, Tyr or naphthylalanine;
Xaa_{23} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa_{24} is Ala, Glu or Asp;
Xaa_{25} is Ala, Trp, Phe, Tyr or naphthylalanine;
Xaa_{26} is Ala or Leu;
Xaa_{27} is Ala or Lys;
Xaa_{28} is Ala or Asn;
Z_1 is-OH,
$-NH_2$
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2 or
Gly ,Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2;
Xaa_{31}, Xaa_{36}, Xaa_{37} and Xaa_{39} are independently Pro, homoproline; 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; and

Z_2 is -OH or -NH_2;

provided that no more than three of Xaa_5, Xaa_6, Xaa_8, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala. Preferred N-alkyl groups for N-alkylglycine, N-alkylpentylglycine and N-alkylalanine include lower alkyl groups preferably of 1 to about 6 carbon atoms, more preferably of 1 to 4 carbon atoms.

[0049] Preferred exendin agonist compounds include those wherein Xaa_1 is His or Tyr. More preferably Xaa_1 is His.

[0050] Preferred are those compounds wherein Xaa_2 is Gly.

[0051] Preferred are those compounds wherein Xaa_{14} is Leu, pentylglycine or Met.

[0052] Preferred compounds are those wherein Xaa_{25} is Trp or Phe.

[0053] Preferred compounds are those where Xaa_6 is Phe or naphthylalanine; Xaa_{22} is Phe or naphthylalanine and

[0054] Xaa_{23} is Ile or Val.

[0055] Preferred are compounds wherein Xaa_{31}, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from Pro, homoproline, thioproline and N-alkylalanine.

[0056] Preferably Z_1 is -NH_2.

[0057] Preferable Z_2 is -NH_2.

[0058] According to one aspect, preferred are compounds of formula (II) wherein Xaa_1 is His or Tyr, more preferably His; Xaa_2 is Gly; Xaa_6 is Phe or naphthylalanine; Xaa_{14} is Leu, pentylglycine or Met; Xaa_{22} is Phe or naphthylalanine; Xaa_{23} is Ile or Val; Xaa_{31}, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently selected from Pro, homoproline, thioproline or N-alkylalanine. More preferably Z_1 is -NH_2.

[0059] According to an especially preferred aspect, especially preferred compounds include those of formula (II) wherein: Xaa_1 is His or Arg; Xaa_2 is Gly or Ala; Xaa_3 is Asp or Glu; Xaa_5 is Ala or Thr; Xaa_6 is Ala, Phe or nephthylalaine; Xaa_7 is Thr or Ser; Xaa_8 is Ala, Ser or Thr; Xaa_9 is Asp or Glu; Xaa_{10} is Ala, Leu or pentylglycine; Xaa_{11} is Ala or Ser; Xaa_{12} is Ala or Lys; Xaa_{13} is Ala or Gln; Xaa_{14} is Ala, Leu or pentylglycine; Xaa_{15} is Ala or Glu; Xaa_{16} is Ala or Glu; Xaa_{17} is Ala or Glu; Xaa_{19} is Ala or Val; Xaa_{20} is Ala or Arg; Xaa_{21} is Ala or Leu; Xaa_{22} is Phe or naphthylalanine; Xaa_{23} is Ile, Val or tert-butylglycine; Xaa_{24} is Ala, Glu or Asp; Xaa_{25} is Ala; Trp or Phe; Xaa_{26} is Ala or Leu; Xaa_{27} is Ala or Lys; Xaa_{28} is Ala or Asn; Z_1 is -OH, -NH_2, Gly-Z_2, Gly Gly-Z_2, Gly Gly Xaa_{31}-Z_2, Gly Gly Xaa_{31} Ser-Z_2, Gly Gly Xaa_{31} Ser Ser-Z_2, Gly Gly Xaa_{31} Ser Ser Gly-Z_2, Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2, Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2, Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2; Xaa_{31}, Xaa_{36}, Xaa_{37} and Xaa_{38} being independently Pro homoproline, thioproline or N-methylalanine; and Z_2 being -OH or -NH_2; provided that no more than three of Xaa_3, Xaa_5, Xaa_6, Xaa_8, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala. Especially preferred compounds include those having the amino acid sequence of SEQ. ID. NOS. 40-61.

[0060] According to an especially preferred aspect, provided are compounds where Xaa_{14} is Leu, Ile, Val or pentylglycine, more preferably Leu or pentylglycine, and Xaa_{25} is Phe, Tyr or naphthylalanine, more preferably Phe or naphthylalanine. These compounds will be less susceptive to oxidative degration, both in vitro and in vivo, as well as during

Synthesis of the Compound.

[0061] Exendins or exendin agonist peptide compounds also include those described in International Patent Application No. PCT/US98/24273, filed November 13, 1998, entitled, "Novel Exendin Agonist compounds," which claims the benefit of United States Provisional Application No. 60/066,029, filed November 14,1997, including compounds of the formula (III)[SEQ ID NO. 5]:

Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10}
Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17}, Ala Xaa_{19} Xaa_{20}
Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Z_1; wherein

Xaa_1 is His, Arg, Tyr, Ala, Norval, Val or Norleu;
Xaa_2 is Ser, Gly, Ala or Thr;
Xaa_3 is Ala, Asp or Glu;
Xaa_4 is Ala, Norval, Val, Norleu or Gly;
Xaa_5 is Ala or Thr;
Xaa_6 is Phe, Tyr or naphthylalanine;
Xaa_7 is Thr or Ser;
Xaa_8 is Ala, Ser or Thr;
Xaa_9 is Ala, Norval, Val, Norleu, Asp or Glu;

Xaa_{10} is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa_{11} is Ala or Ser;
Xaa_{12} is Ala or Lys;
Xaa_{13} is Ala or Gln ;
Xaa_{14} is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa_{15} is Ala or Glu ;
Xaa_{16} is Ala or Glu ;
Xaa_{17} is Ala or Glu ;
Xaa_{19} is Ala or val ;
Xaa_{20} is Ala or Arg ;
Xaa_{21} is Ala or Leu ;
Xaa_{22} is Phe, Tyr or naphthylalanine;
Xaa_{23} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa_{24} is Ala, Glu or Asp;
Xaa_{25} is Ala, Trp, Phe, Tyr or naphthylalanine;
Xaa_{26} is Ala or Leu;
Xaa_{27} is Ala or Lys;
Xaa_{28} is Ala or Asn;
Z_1 is -OH,
$-NH_2$,
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2;
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2;

wherein

Xaa_{31}, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine ; and

Z_2 is -OH or $-NH_2$;

provided that no more than three of Xaa_3, Xaa_4, Xaa_5, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala; and provided also that, if Xaa_1 is His, Arg or Tyr, then at least one of Xaa_3, Xaa_4 and Xaa_9 is Ala.

Definitions

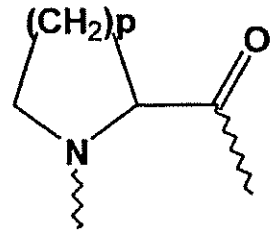
[0062] In accordance with the present invention and as used herein, the, following terms are defined to have the following meanings, unless explicitly stated otherwise.

[0063] The term "amino acid" refers to natural amino acids, unnatural amino acids, and amino acid analogs, all in their D and L stereoisomers if their structure allow such stereoisomeric forms. Natural amino acids include alanine (Ala), arginine (Arg), asparagine (Asn), aspartic acid (Asp), cysteine (Cys), glutamine (Gln), glutamic acid (Glu), glycine (Gly), histidine (His), isoleucine (Ile), leucine (Leu), Lysine (Lys), methionine (Met), phenylalanine (Phe), proline (Pro), serine (Ser), threonine (Thr), typtophan (Trp), tyrosine (Tyr) and valine (Val) Unnatural amino acids include, but are not limited to azetidinecarboxylic acid, 2-aminoadipic acid, 3-aminoadipic acid, beta-alanine, aminopropionic acid, 2-aminobutyric acid, 4-aminobutyric acid, 6-aminocaproic acid, 2-aminoheptanoic acid, 2-aminoisobutyric acid, 3-aminoisbutyric acid, 2-aminopimelic acid, tertiary-butylglycine, 2,4-diaminoisobutyric acid, desmosine, 2,2'-diaminopimelic acid, 2,3-diaminopropionic acid, N-ethylglycine, N-ethylasparagine, homoproline, hydroxylysine, allo-hydroxylysine, 3-hydroxyproline, 4-hydroxyproline, isodesmosine, allo-isoleucine, N-methylalanine, N-methylglycine, N-methylisoleucine, N-methylpentylglycine, N-methylvaline, naphthalanine, norvaline, norleucine, ornithine, pentylglycine, pipecolic acid and thiopro-

line. Amino acid analogs include the natural and unnatural amino acids which are chemically blocked, reversibly or irreversibly, or modified on their N-terminal amino group or their side-chain groups, as for example, methionine sulfoxide, methionine sulfone, S-(carboxymethyl)-cysteine, S-(carboxymethyl)-cysteine sulfoxide and S-(carboxymethyl)-cysteine sulfone.

[0064] The term "amino acid analog" refers to an amino acid wherein either the C-terminal carboxy group, the N-terminal amino group or side-chain functional group has been chemically codified to another functional group. For example, aspartic acid-(beta-methyl ester) is an amino acid analog of aspartic acid; N-ethylglycine is an amino acid analog of glycine; or alanine carboxamide is an amino acid analog of alanine.

[0065] The term "amino acid residue" refers to radicals having the structure: (1) -C(O)-R-NH-, wherein R typically is - CH(R')-, wherein R' is an amino acid side chain, typically H or a carbon containing substitutent; or (2)



wherein p is 1, 2 or 3 representing the azetidinecarboxylic acid, proline or pipecolic acid residues, respectively.

[0066] The term "lower" referred to herein in connection with organic radicals such as alkyl groups defines such groups with up to and including about 6, preferably up to and including 4 and advantageously one or two carbon atoms. Such groups may be straight chain or branched chain.

[0067] "Pharmaceutically acceptable salt" includes salts of the compounds described herein derived from the combination of such compounds and an organic or inorganic acid. In practice the use of the salt form amounts to use of the base form. The compounds are useful in both free base and salt form.

[0068] In addition, the following abbreviations stand for the following:

"ACN" or "CH_3CN" refers to acetonitrile.
"Boc", "tBoc" or "Tboc" refers to t-butoxy carbonyl.
"DCC" refers to N,N'-dicyclohexylcarbodiimide.
"Fmoc" refers to fluorenylmethoxycarbonyl.
"HBTU" refers to 2-(1H-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexaflurophosphate.
"HOBt" refers to 1-hydroxybenzotriazole monohydrate.
"homoP" or hPro" refers to homoproline.
"MeAla" or "Nme" refers to N-methylalanine.
"naph" refers to naphthylalanine.
"pG" or pGly" refers to pentylglycine.
"tBuG" refers to tertiary-butylglycine.
"ThioP" or tPro" refers to thioproline.
"3Hyp" refers to 3-hydroxyproline
"4Hyp" refers to 4-hydroxyproline
"NAG" refers to N-alkylglycine
"NAPG" refers to N-alkylpentylglycine
"Norval" refers to norvaline
"Norleu" refers to norleucine

Preparation of Compounds

[0069] The exendins and exendin agonist peptides described herein may be prepared using standard solid-phase peptide synthesis techniques and preferably an automated or semiautomated peptide synthesizer. Typically, using such techniques, an α-N-carbamoyl protected amino acid and an amino acid attached to the growing peptide chain on a resin are coupled at room temperature in an inert solvent such as dimethylformamide, N-methylpyrrolidinone or methylene chloride in the presence of coupling agents such as dicyclohexylcarbodiimide and 1-hydroxybenzotriazole in the presence of a base such as diisopropylethylamine. The α-N-carbamoyl protecting group is removed from the resulting peptide-

resin using a reagent such as trifluoroacetic acid or piperidine, and the coupling reaction repeated with the next desired N-protected amino acid to be added to the peptide chain. Suitable N-protecting groups are well known in the art, with t-butyloxycarbonyl (tBoc) and fluorenylmethoxycarbonyl (Fmoc) being preferred herein.

[0070] The solvents, amino acid derivatives and 4-methylbenzhydryl-amine resin used in the peptide synthesizer may be purchased from Applied Biosystems Inc. (Foster City, CA). The following side-chain protected amino acids may be purchased from Applied Biosystems, Inc : Boc-Arg(Mts), Fmoc-Arg(Pmc), Boc-Thr(Bzl), Fmoc-Thr(t-Bu), Boc-Ser(Bzl), Fmoc-Ser(t-Bu), Boc-Tyr(BrZ), Fmoc-Tyr(t-Bu), Boc-Lys(Cl-Z), Fmoc-Lys(Boc), Boc-Glu(Bzl), Fmoc-Glu(t-Bu), Fmoc-His(Trt), Fmoc-Asn(Trt), and Fmoc-Gln(Trt). Boc-His(BOM) may be purchased from Applied Biosystems, Inc. or Bachem Inc. (Torrance, CA). Anisole, dimethylsulfide, phenol, ethanedithiol, and thioanisole may be obtained from Aldrich Chemical Company (Milwaukee, WI). Air Products and Chemicals (Allentown, PA) supplies HF. Ethyl ether, acetic acid and methanol may be purchased from Fisher Scientific (Pittsburgh, PA).

[0071] Solid phase peptide synthesis may be carried out with an automatic peptide synthesizer (Model 430A, Applied Biosystems Inc., Foster City, CA) using the NMP/HOBt (Option 1) system and tBoc or Fmoc chemistry (see, Applied Biosystems User's Manual for the ABI 430A Peptide Synthesizer, Version 1.3B July 1, 1988, section 6, pp. 49-70, Applied Biosystems, Inc., Foster City, CA) with capping. Boc-peptide-resins may be cleaved with HF (-5° C to 0° C, 1 hour). The peptide may be extracted from the resin with alternating water and acetic acid, and the filtrates lyophilized. The Fmoc-peptide resins may be cleaved according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc., 1990, pp. 6-12). Peptides may be also be assembled using an Advanced Chem Tech Synthesizer (Model MPS 350, Louisville, Kentucky).

[0072] Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters Delta Prep 3000 system. A C4, C8 or C18 preparative column (10μ , 2.2 x 25 cm; Vydac, Hesperia, CA) may be used to isolate peptides, and purity may be determined using a C4, C8 or C18 analytical column (5μ, 0.46 x 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH_3CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the Waters Pico Tag system and processed using the Maxima program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115° C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems Bio-Ion 20 mass spectrometer. Electrospray mass spectroscopy may be carried out on a VG-Trio machine.

[0073] Peptide compounds useful in the invention may also be prepared using recombinant DNA techniques, using methods now known in the art. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2d Ed., Cold Spring Harbor (1989). Non-peptide compounds useful in the present invention may be prepared by art-known methods. For example, phosphate-containing amino acids and peptides containing such amino acids, may be prepared using methods known in the art. See, e.g., Bartlett and Landen, Biorg. Chem. 14:356-377 (1986).

[0074] Compositions useful in the invention may conveniently be provided in the form of formulations suitable for parenteral (including intravenous, intramuscular and subcutaneous) or nasal or oral administration. In some cases, it will be convenient to provide an exendin or exendin agonist and another blood glucose-controlling, plasma glucose-lowering agent, such as an insulin, an amylin, an amylin agonist, in a single composition or solution for administration together. In other cases, it may be more advantageous to administer the additional agent separately from said exendin or exendin agonist. A suitable administration format may best be determined by a medical practitioner for each patient individually. Suitable pharmaceutically acceptable carriers and their formulation are described in standard formulation treatises, e.g., Remington's Pharmaceutical Sciences by E. W. Martin. See also Wang, Y. J. and Hanson, M. A. "Parenteral Formulations of Proteins and Peptides: Stability and Stabilizers," Journal of Parenteral Science and Technology, Technical Report No. 10, Supp. 42:2S (1988).

[0075] Compounds useful in the invention can be provided as parenteral compositions for injection or infusion. Preferred formulations are those described and claimed in PCT/US 00/00902, entitled, "Novel Exendin Agonist Formulations and Methods of Administration Thereof," which enjoys common ownership with the present application. They can, for example, be suspended in an inert oil, suitably a vegetable oil such as sesame, peanut, olive oil, or other acceptable carrier. Preferably, they are suspended in an aqueous carrier, for example, in an isotonic buffer solution at a pH of about 3.0 to 8.0, preferably at a pH of about 3.5 to 5.0. These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH buffering agents. Useful buffers include for example, sodium acetate/acetic acid buffers. A form of repository or "depot" slow release preparation may be used so that therapeutically effective amounts of the preparation are delivered into the bloodstream over many hours or days following transdermal injection or delivery.

[0076] The desired isotonicity may be accomplished using sodium chloride or other pharmaceutically acceptable

agents such as dextrose, boric acid, sodium tartrate, propylene glycol, polyols (such as mannitol and sorbitol), or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions.

[0077] The claimed compositions can also be formulated as pharmaceutically acceptable salts (*e.g.*, acid addition salts) and/or complexes thereof. Pharmaceutically acceptable salts are non-toxic salts at the concentration at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical-chemical characteristics of the composition without preventing the composition from exerting its physiological effect. Examples of useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate the administration of higher concentrations of the drug.

[0078] Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, and quinic acid. Such salts may be prepared by, for example, reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another ion on a suitable ion exchange resin.

[0079] Carriers or excipients can also be used to facilitate administration of the compound. Examples of carriers and excipients include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. The compositions or pharmaceutical composition can be administered by different routes including intravenously, intraperitoneal, subcutaneous, and intramuscular, orally, topically, transmucosally, or by pulmonary inhalation.

[0080] If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose. They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be employed including, for example, acacia powder, a non-ionic surfactant (such as a Tween), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a Triton).

[0081] Compositions useful in the invention are prepared by mixing the ingredients following generally accepted procedures. For example, the selected components may be simply mixed in a blender or other standard device to produce a concentrated mixture which may then be adjusted to the final concentration and viscosity by the addition of water or thickening agent and possibly a buffer to control pH or an additional solute to control tonicity.

[0082] For use by the physician, the compositions will be provided in dosage unit form containing an amount of an exendin or exendin agonist, for example, exendin-3, and/or exendin-4, with or without another glucosed-lowering agent. Therapeutically effective amounts of an exendin or exendin agonist for use treating a subject with gestational diabetes mellitus are those that lower blood glucose to a desired level. As will be recognized by those in the field, an effective amount of therapeutic agent will vary with many factors including the age and weight of the patient, the patient's physical condition, the blood glucose level and other factors.

[0083] The effective daily blood glucose controlling dose of the compounds will typically be in the range of about 3 to 30 μg to about 1 mg/day, preferably about 1 to 30 μg to about 500 μg/day and more preferably about 1 to 30 μg to about 100 μg/day, most preferably about 3 μg to about 50 μg/day, for a 70 kg patient, administered in a single or divided doses. Preferred dosages are described in PCT/US00/00902 entitled, "Novel Exendin Agonist Formulations and Methods of Administration Thereof," A preferred dose for twice daily administration is about 0.05 to about 0.3 μg per kilogram. The exact dose to be administered is determined by the attending clinician and is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual, and the mode of adminstration. Administration should begin shortly after diagnosis of GDM and continue for the remainder of the gestation (i.e., the third trimester through parturition). Administration may be by injection, preferably subcutaneous or intramuscular. Administration may also be by non-injectable routes, for example, via the respiratory tract, the mouth and the gut. Orally active compounds may be taken orally, however dosages should be increased 5-10 fold. Preferred methods of administration are described in PCT/US 00/00902 entitled, "Novel Exendin Agonist Formulations and Methods of Administration Thereof," filed January 14, 1999. Solid dosage forms, such as those useful for oral, buccal, sublingual, intra-tracheal, nasal or pulmonary delivery may be used. Additionally, preserved or unpreserved liquid formulations or dry powder may be used

[0084] The optimal formulation and mode of administration of compounds of the present application to a patient depend on factors known in the art such as the particular disease or disorder, the desired effect, and the type of patient. While the compounds will typically be used to treat human subjects they may also be used to treat similar or identical diseases in other vertebrates such as other primates, farm animals such as swine, cattle and poultry, and sports animals and pets such as horses, dogs and cats.

[0085] To assist in understanding the present invention, the following Examples are included. The experiments relating to this invention should not, of course, be construed as specifically limiting the invention and such variations of the

invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the invention as described herein and hereinafter claimed.

Example 1

Preparation of amidated peptide having SEQ. ID. NO. 9

[0086] The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. However, at some positions coupling was less efficient than expected and double couplings were required. In particular, residues Asp_9, Thr_7 and Phe_6 all required double coupling. Deprotection (Fmoc group removal)of the growing peptide chain using piperidine was not always efficient. Double deprotection was required at positions Arg_{20}, Val_{19} and Leu_{14}. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 55%.

[0087] Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

[0088] The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M): calculated 4131.7; found 4129.3.

Example 2

Preparation of Peptide having SEQ. ID. NO. 10

[0089] The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 5. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 25% to 75% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 21.5 minutes. Electrospray Mass Spectrometry (M): calculated 4168.6; found 4171.2.

Example 3

Preparation of Peptide having SEQ. ID. NO. 11

[0090] The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.9 minutes. Electrospray Mass Spectrometry (M): calculated 4147.6; found 4150.2.

Example 3

Preparation of Peptide having SEQ. ID. NO. 12

[0091] The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 65% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.7 minutes. Electrospray Mass Spectrometry (M): calculated 4212.6; found 4213.2.

Example 4

Preparation of Peptide having SEQ. ID. NO. 13

[0092] The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 50% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 16.3 minutes. Electrospray Mass Spectrometry (M): calculated 4262.7; found 4262.4.

Example 5

Preparation of Peptide having SEQ. ID. NO. 14

[0093] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6

Example 6

Preparation of Peptide having SEQ. ID. NO. 15

[0094] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4224.7.

Example 7

Preparation of Peptide having SEQ. ID. NO. 16

[0095] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6

Example 8

Preparation of Peptide having SEQ. ID. NO. 17

[0096] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4186.6

Example 9

Preparation of Peptide having SEQ. ID. NO. 18

[0097] The above-identified peptide is assembled on 4- (2' -4' - dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4200.7

EXAMPLE 10

Preparation of Peptide having SEQ. ID. NO. 19

[0098] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4200.7

Example 11

Preparation of Peptide having SEQ. ID. NO. 20

[0099] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4202.7.

Example 12

Preparation of Peptide having SEQ. ID. NO. 21

[0100] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4145.6.

Example 13

Preparation of Peptide having SEQ. ID. NO. 22

[0101] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4184.6.

Example 14

Preparation of Peptide having SEQ. ID. NO. 23

[0102] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4145.6.

Example 15

Preparation of Peptide having SEQ. ID. NO. 24

[0103] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4224.7.

Example 16

Preparation of Peptide having SEQ. ID. NO. 25

[0104] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6.

Example 17

Preparation of Peptide having SEQ. ID. NO. 26

[0105] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4115.5.

Example 18

Preparation of Peptide having SEQ. ID. NO. 27

[0106] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4188.6.

Example 19

Preparation of Peptide having SEQ. ID. NO. 28

[0107] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4131.6.

Example 20

Preparation of Peptide having SEQ. ID. NO. 29

[0108] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4172.6.

Example 21

Preparation of Peptide having SEQ. ID. NO. 30

[0109] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4145.6.

Example 22

Preparation of Peptide having SEQ. ID. NO. 31

[0110] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the thioproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4266.8.

Example 23

Preparation of Peptide having SEQ. ID. NO. 32

[0111] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the thioproline positions 38, 37 and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4246.8.

Example 24

Preparation of Peptide having SEQ. ID. NO. 33

[0112] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4250.8.

Example 25

Preparation of Peptide having SEQ. ID. NO. 34

[0113] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the homoproline positions 38, 37, and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4234.8.

Example 26

Preparation of Peptide having SEQ. ID. NO. 35

[0114] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the thioproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4209.8.

Example 27

Preparation of Peptide having SEQ. ID. NO. 36

[0115] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the homoproline positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4193.7.

Example 28

Preparation of Peptide having SEQ. ID. NO. 37

[0116] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the N-methylalanine positions 38, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass

Spectrometry (M): calculated 3858.2.

Example 29

Preparation of Peptide having SEQ. ID. NO. 38

[0117] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the N-methylalanine positions 38, 37 and 36. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3940.3.

Example 30

Preparation of Peptide having SEQ. ID. NO. 39

[0118] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Additional double couplings are required at the N-methylalanine positions 30, 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3801.1.

Example 31

Preparation of C-terminal carboxylic acid Peptides corresponding to the above C-terminal amide sequences.

[0119] The above peptides of Examples 1-5 to 30 are assembled on the so called Wang resin (p-alkoxybenzylalacohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 1. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

Example 32

Preparation of Peptide having SEQ ID NO.7

[0120]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly-NH_2 [SEQ. ID. NO. 7]

[0121] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. Deprotection (Fmoc group removal)of the growing peptide chain was achieved using piperidine. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 75%.

[0122] Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

[0123] The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 50% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 18.9 minutes. Electrospray Mass Spectrometry (M): calculated 3408.0; found 3408.9.

Example 33

Preparation of Peptide having SEQ ID NO. 40

[0124]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 40]

[0125] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 40% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.9 minutes. Electrospray Mass Spectrometry (M): calculated 3294.7; found 3294.8.

Example 34

Preparation of Peptide having SEQ ID NO. 41

[0126]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 41]

[0127] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 29% to 36% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 20.7 minutes. Electrospray Mass Spectrometry (M): calculated 3237.6; found 3240.

Example 35

Preparation of Peptide having SEQ ID NO. 42

[0128]

His Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 42]

[0129] The above amidated peptide was assembled on 9-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy aceta-

mide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 15.2 minutes. Electrospray Mass Spectrometry (M): calculated 3251.6; found 3251.5.

Example 36

Preparation of Peptide having SEQ ID NO. 43

[0130]

His Gly Glu Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 43]

[0131] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 13.1 minutes. Electrospray Mass Spectrometry (M): calculated 3207.6; found 3208.3.

Example 37

Preparation of Peptide having SEQ ID NO. 44

[0132]

His Gly Glu Gly Thr Ala Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 44]

[0133] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 12.8 minutes. Electrospray Mass Spectrometry (M): calculated 3161.5; found 3163.

Example 38

Preparation of Peptide having SEQ ID NO. 45

[0134]

His Gly Glu Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 45]

[0135] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied

Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 15.2 minutes. Electrospray Mass Spectrometry (M): calculated 3221.6; found 3222.7.

Example 39

Preparation of Peptide having SEQ ID NO. 46

[0136]

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 46]

[0137] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 34% to 44% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3199.4.

Example 40

Preparation of Peptide having SEQ ID NO. 47

[0138]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 47]

[0139] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 15.7 minutes. Electrospray Mass Spectrometry (M): calculated 3221.6; found 3221.6.

Example 41

Preparation of Peptide having SEQ ID NO. 48

[0140]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 48]

[0141] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis

were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 18.1 minutes. Electrospray Mass Spectrometry (M): calculated 3180.5; found 3180.9.

Example 42

Preparation of Peptide having SEQ ID NO. 49

[0142]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 49]

[0143] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.0 minutes. Electrospray Mass Spectrometry (M): calculated 3180.6; found 3182.8.

Example 43

Preparation of Peptide having SEQ ID NO. 50

[0144]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 50]

[0145] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 32% to 42% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.9 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3195.9.

Example 44

Preparation of Peptide having SEQ ID NO. 51

[0146]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 51]

[0147] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 37% to 47%

Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.9 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3179.0.

Example 45

Preparation of Peptide having SEQ ID NO. 52

[0148]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Ala Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 52]

[0149] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3180.0.

Example 46

Preparation of Peptide having SEQ ID NO. 53

[0150]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 53]

[0151] The above-identified peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 13.7 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3179.0.

Example 47

Preparation of Peptide having SEQ ID NO. 54

[0152]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 54]

[0153] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention

time of 14.0 minutes. Electrospray Mass Spectrometry (M): calculated 3209.6; found 3212.8.

Example 48

Preparation of Peptide having SEQ ID NO. 55

[0154]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 55]

[0155] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.3 minutes. Electrospray Mass Spectrometry (M): calculated 3152.5; found 3153.5.

Example 49

Preparation of Peptide having SEQ ID NO. 56

[0156]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 56]

[0157] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 12.1 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3197.7.

Example 50

Preparation of Peptide having SEQ ID NO. 57

[0158]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Ala Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 57]

[0159] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 10.9 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3180.5.

Example 51

Preparation of Peptide having SEQ ID NO. 58

[0160]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH_2 [SEQ. ID. NO. 58]

[0161] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 32% to 42% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 17.5 minutes. Electrospray Mass Spectrometry (M): calculated 3161.5; found 3163.0.

Example 52

Preparation of Peptide having SEQ ID NO. 59

[0162]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn-NH_2 [SEQ. ID. NO. 59]

[0163] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 32% to 42% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19.5 minutes. Electrospray Mass Spectrometry (M): calculated 3195.5; found 3199.

Example 53

Preparation of Peptide having SEQ ID NO. 60

[0164]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn-NH_2 [SEQ. ID. NO. 60]

[0165] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 38% to 48% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.5 minutes. Electrospray Mass Spectrometry (M): calculated 3180.5; found 3183.7.

Example 54

Preparation of Peptide having SEQ ID NO. 61

[0166]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala-NH_2 [SEQ. ID. NO. 61]

[0167] The above-identified amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 34% to 44% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 22.8 minutes. Electrospray Mass Spectrometry (M): calculated 3194.6; found 3197.6.

Example 55

Preparation of Peptide having SEQ ID NO. 62

[0168]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH_2 [SEQ. ID. NO. 62]

[0169] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4099.6.

Example 56

Preparation of Peptide having SEQ ID NO. 63

[0170]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH_2 [SEQ. ID. NO. 63]

[0171] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4042.5.

Example 57

Preparation of Peptide having SEQ ID NO. 64

[0172]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro-NH_2 [SEQ. ID. NO. 64]

[0173] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30-minutes) of the lyophilized peptide is then carried out to determine the retention tire of the product peptide. Electrospray Mass Spectrometry (M): calculated 4002.4

Example 58

Preparation of Peptide having SEQ ID NO. 65

[0174]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro-NH_2 [SEQ. ID. NO. 65]

[0175] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3945.4.

Example 59

Preparation of Peptide having SEQ ID NO. 66

[0176]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro-NH_2 [SEQ. ID. NO. 66]

[0177] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g), using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3905.3.

Example 60

Preparation of Peptide having SEQ ID NO. 67

[0178]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro-NH_2 [SEQ. ID. NO. 67]

[0179] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3848.2.

Example 61

Preparation of Peptide having SEQ ID NO. 68

[0180]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala-NH_2 [SEQ. ID. NO. 68]

[0181] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3808.2.

Example 62

Preparation of Peptide having SEQ ID NO. 69

[0182]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala-NH_2 [SEQ. ID. NO. 69]

[0183] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3751.1.

Example 63

Preparation of Peptide having SEQ ID NO. 70

[0184]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly-NH_2 [SEQ. ID. NO. 70]

[0185] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3737.1.

Example 64

Preparation of Peptide having SEQ ID NO. 71

[0186]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly-NH_2 [SEQ. ID. NO. 71]

[0187] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3680.1.

Example 65

Preparation of Peptide having SEQ ID NO. 72

[0188]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser-NH_2 [SEQ. ID. NO. 72]

[0189] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3680.1

Example 66

Preparation of Peptide having SEQ ID NO. 73

[0190]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser-NH_2 [SEQ. ID. NO. 73]

[0191] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3623.0.

Example 67

Preparation of Peptide having SEQ ID NO. 74

[0192]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser-NH_2 [SEQ. ID. NO. 74]

[0193] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3593.0

Example 68

Preparation of Peptide having SEQ ID NO. 75

[0194]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser-NH_2 [SEQ. ID. NO. 75]

[0195] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3535.9

Example 69

Preparation of Peptide having SEQ ID NO. 76

[0196]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro-NH_2 [SEQ. ID. NO. 76]

Example 70

Preparation of Peptide having SEQ ID NO. 77

[0197]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro-NH_2 [SEQ. ID. NO. 77]

[0198] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3448.8.

Example 71

Preparation of Peptide having SEQ ID NO. 78

[0199]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly-NH_2 [SEQ. ID. NO. 78]

[0200] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide Electrospray Mass Spectrometry (M): calculated 3351.7.

Example 72

Preparation of Peptide having SEQ ID NO. 79

[0201]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly-NH_2 [SEQ. ID. NO. 79]

[0202] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3351.8

Example 73

Preparation of Peptide having SEQ ID NO. 80

[0203]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly-NH_2 [SEQ. ID. NO. 80]

[0204] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3294.7

Example 74

Preparation of Peptide having SEQ ID NO. 81

[0205]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly tPro Ser Ser Gly Ala tPro tPro tPro-NH_2 [SEQ. ID. NO. 81]

[0206] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 32. Double couplings are required at residues 37,36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4197.1.

Example 75

Preparation of Peptide having SEQ ID NO. 82

[0207]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala tPro tPro tPro-NH_2 [SEQ. ID. NO. 82]

[0208] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Double couplings are required at residues 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4179.1.

Example 76

Preparation of Peptide having SEQ ID NO. 83

[0209]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly NMeala Ser Ser Gly Ala Pro Pro-NH_2 [SEQ. ID. NO. 83]

[0210] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3948.3.

Example 77

Preparation of Peptide having SEQ ID NO. 84

[0211]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly NMeala Ser Ser Gly Ala NMeala Nmeala-NH_2 [SEQ. ID. NO. 84]

[0212] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3840.1.

Example 78

Preparation of Peptide having SEQ ID NO. 85

[0213]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly hPro Ser Ser Gly Ala hPro hPro-NH_2 [SEQ. ID. NO. 85]

[0214] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4050.1.

Example 79

Preparation of Peptide having SEQ ID NO. 86

[0215]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly hPro Ser Ser Gly Ala hPro-NH_2 [SEQ. ID. NO. 86]

[0216] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. A double coupling is required at residue 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3937.1

Example 80

Preparation of Peptide having SEQ ID NO. 87

[0217]

Arg Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala-NH_2 [SEQ. ID. NO. 87]

[0218] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3827.2.

Example 81

Preparation of Peptide having SEQ ID NO. 88

[0219]

His Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly-NH_2 [SEQ. ID. NO. 88]

[0220] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3394.8.

Example 82

Preparation of Peptide having SEQ ID NO. 89

[0221]

His Gly Glu Gly Thr Naphthylala Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 89]

[0222] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3289.5.

Example 83

Preparation of Peptide having SEQ ID NO. 90

[0223]

His Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 90]

[0224] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3280.7.

Example 84

Preparation of Peptide having SEQ ID NO. 91

[0225]

His Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 91]

[0226] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3294.7.

Example 85

Preparation of Peptide having SEQ ID NO. 92

[0227]

His Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 92]

[0228] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3250.7.

Example 86

Preparation of Peptide having SEQ ID NO. 93

[0229]

His Gly Glu Gly Thr Phe Thr Ser Asp pentylgly Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 93]

[0230] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3253.5.

Example 87

Preparation of Peptide having SEQ ID NO. 94

[0231]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 94]

[0232] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3289.5.

Example 88

Preparation of Peptide having SEQ ID NO. 95

[0233]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe tButylgly Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 95]

[0234] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3183.4.

Example 89

Preparation of Peptide having SEQ ID NO. 96

[0235]

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 96]

[0236] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3237.6.

Example 90

Preparation of Peptide having SEQ ID NO. 97

[0237]

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser-NH_2 [SEQ. ID. NO. 97]

[0238] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3637.9.

Example 91

Preparation of Peptide having SEQ ID NO. 98

[0239]

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly-NH_2 [SEQ. ID. NO. 98]

[0240] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3309.7.

Example 92

Preparation of Peptide having SEQ ID NO. 99

[0241]

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly hPro Ser Ser Gly Ala hPro hPro-NH_2 [SEQ. ID. NO. 99]

[0242] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 37. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3711.1.

Example 93

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for SEQ ID NOS. 7, 40-61, 68-75, 78-80 and 87-96

[0243] Peptides having the sequences of SEQ ID NOS. 7, 40-61, 68-75, 78-80 and 87-96 are assembled on the so called Wang resin (p-alkoxybenzylalacohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied

Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

Example 94

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for SEQ ID NOS. 62-67, 76, 77 and 81-86

[0244] Peptides having the sequences of SEQ ID NOS. 62-67, 76, 77 and 81-86 are assembled on the 2-chlorotritylchloride resin (200-400 mesh), 2% DVB (Novabiochem, 0.4-1.0 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 32. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

Example 95

Preparation of Peptide having SEQ ID NO. 100

[0245]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 100]

[0246] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.). In general, single-coupling cycles were used throughout the synthesis and Fast Moc (HBTU activation) chemistry was employed. Deprotection (Fmoc group removal)of the growing peptide chain was achieved using piperidine. Final deprotection of the completed peptide resin was achieved using a mixture of triethylsilane (0.2 mL), ethanedithiol (0.2 mL), anisole (0.2 mL), water (0.2 mL) and trifluoroacetic acid (15 mL) according to standard methods (Introduction to Cleavage Techniques, Applied Biosystems, Inc.) The peptide was precipitated in ether/water (50 mL) and centrifuged. The precipitate was reconstituted in glacial acetic acid and lyophilized. The lyophilized peptide was dissolved in water). Crude purity was about 75%.

[0247] Used in purification steps and analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN).

[0248] The solution containing peptide was applied to a preparative C-18 column and purified (10% to 40% Solvent B in Solvent A over 40 minutes). Purity of fractions was determined isocratically using a C-18 analytical column. Pure fractions were pooled furnishing the above-identified peptide. Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 19 2 minutes. Electrospray Mass Spectrometry (M): calculated 3171.6; found 3172.

Example 96

Preparation of Peptide having SEQ ID NO. 101

[0249]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 101]

[0250] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy aceta-

mide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 36% to 46% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 14.9 minutes. Electrospray Mass Spectrometry (M): calculated 3179.6; found 3180.

Example 97

Preparation of Peptide having SEQ ID NO. 102

[0251]

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 102]

[0252] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 37% to 47% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 12.2 minutes. Electrospray Mass Spectrometry (M): calculated 3251.6; found 3253.3.

Example 98

Preparation of Peptide having SEQ ID NO. 103

[0253]

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 103]

[0254] The above amidated peptide was assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis were Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 35% to 45% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide gave product peptide having an observed retention time of 16.3 minutes. Electrospray Mass Spectrometry (M): calculated 3193.6; found 3197.

Example 99

Preparation of Peptide having SEQ ID NO. 104

[0255]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 104]

[0256] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosys-

tems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3228.6.

Example 100

Preparation of Peptide having SEQ ID NO. 105

[0257]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 105]

[0258] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3234.7.

Example 101

Preparation of Peptide having SEQ ID NO. 106

[0259]

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 106]

[0260] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3308.7.

Example 102

Preparation of Peptide having SEQ ID NO. 107

[0261]

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 107]

[0262] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent

A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3250.7

Example 103

Preparation of Peptide having SEQ ID NO. 108

[0263]

His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 108]

[0264] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3252.6.

Example 104

Preparation of Peptide having SEQ ID NO. 109

[0265]

Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 109]

[0266] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3200.6.

Example 105

Preparation of Peptide having SEQ ID NO. 110

[0267]

Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 110]

[0268] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent

A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

Example 106

Preparation of Peptide having SEQ ID NO. 111

[0269]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 111]

[0270] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3214.6.

Example 107

Preparation of Peptide having SEQ ID NO. 112

[0271]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 112]

[0272] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.5.

Example 108

Preparation of Peptide having SEQ ID NO. 113

[0273]

Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 113]

[0274] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide.

Electrospray Mass Spectrometry (M): calculated 3184.6.

Example 109

Preparation of Peptide having SEQ ID NO. 114

[0275]

Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 114]

[0276] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3127.5.

Example 110

Preparation of Peptide having SEQ ID NO. 115

[0277]

Ala Gly Asp Gly Thr NaphthylAla Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 115]

[0278] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3266.4.

EXAMPLE 111

Preparation of Peptide having SEQ ID NO. 116

[0279]

Ala Gly Asp Gly Thr Naphthylala Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 116]

[0280] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3209.4.

Example 112

Preparation of Peptide having SEQ ID NO. 117

[0281]

Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 117]

[0282] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3200.6.

Example 113

Preparation of Peptide having SEQ ID NO. 118

[0283]

Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 118]

[0284] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

Example 114

Preparation of Peptide having SEQ ID NO. 119

[0285]

Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 119]

[0286] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3198.6.

Example 115

Preparation of Peptide having SEQ ID NO. 120

[0287]

Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 120]

[0288] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3141.5.

Example 116

Preparation of Peptide having SEQ ID NO. 121

[0289]

Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 121]

[0290] The above-identified peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3170.6.

Example 117

Preparation of Peptide having SEQ ID NO. 122

[0291]

Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 122]

[0292] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3113.5.

Example 118

Preparation of Peptide having SEQ ID NO. 123

[0293]

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 123]

[0294] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3228.6.

Example 119

Preparation of Peptide having SEQ ID NO. 124

[0295]

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 124]

[0296] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3171.6.

Example 120

Preparation of Peptide having SEQ ID NO. 125

[0297]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 125]

[0298] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

Example 121

Preparation of Peptide having SEQ ID NO. 126

[0299]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 126]

[0300] The above-identified amidated peptiden is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.4.

Example 122

Preparation of Peptide having SEQ ID NO. 127

[0301]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Pentylgly Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 127]

[0302] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3230.4.

Example 123

Preparation of Peptide having SEQ ID NO. 128

[0303]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Pentylgly Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 128]

[0304] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3198.6.

Example 124

Preparation of Peptide having SEQ ID NO. 129

[0305]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 129]

[0306] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3141.5.

Example 125

Preparation of Peptide having SEQ ID NO. 130

[0307]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 130]

[0308] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.5.

Example 126

Preparation of Peptide having SEQ ID NO. 131

[0309]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 131]

[0310] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3100.4.

Example 127

Preparation of Peptide having SEQ ID NO. 132

[0311]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 132]

[0312] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.6.

Example 128

Preparation of Peptide having SEQ ID NO. 133

[0313]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 133]

[0314] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3100.5.

Example 129

Preparation of Peptide having SEQ ID NO. 134

[0315]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 134]

[0316] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3100.5.

Example 130

Preparation of Peptide having SEQ ID NO. 135

[0317]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 135]

[0318] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3154.5.

Example 131

Preparation of Peptide having SEQ ID NO. 136

[0319]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 136]

[0320] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.5.

Example 132

Preparation of Peptide having SEQ ID NO. 137

[0321]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Pentylgly Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 137]

[0322] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3212.4.

Example 133

Preparation of Peptide having SEQ ID NO. 138

[0323]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Pentylgly Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 138]

[0324] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3173.4.

Example 134

Preparation of Peptide having SEQ ID NO. 139

[0325]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 139]

[0326] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3156.6.

Example 135

Preparation of Peptide having SEQ ID NO. 140

[0327]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 140]

[0328] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

Example 136

Preparation of Peptide having SEQ ID NO. 141

[0329]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Ala Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 141]

[0330] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3156.6.

Example 137

Preparation of Peptide having SEQ ID NO. 142

[0331]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Ala Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 142]

[0332] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

Example 138

Preparation of Peptide having SEQ ID NO. 143

[0333]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 143]

[0334] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3156.6.

Example 139

Preparation of Peptide having SEQ ID NO. 144

[0335]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 144]

[0336] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

Example 140

Preparation of Peptide having SEQ ID NO. 145

[0337]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Ala Arg Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 145]

[0338] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3186.6.

Example 141

Preparation of Peptide having SEQ ID NO. 146

[0339]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 146]

[0340] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used_in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3129.5.

Example 142

Preparation of Peptide having SEQ ID NO. 147

[0341]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Ala Leu Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 147]

[0342] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3129.5.

Example 143

Preparation of Peptide having SEQ ID NO. 148

[0343]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 148]

[0344] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3072.4.

Example 144

Preparation of Peptide having SEQ ID NO. 149

[0345]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Ala Phe Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 149]

[0346] The above-identified amidated peptide is assembled on 4-(2' 4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

Example 145

Preparation of Peptide having SEQ ID NO. 150

[0347]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 150]

[0348] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.5.

Example 146

Preparation of Peptide having SEQ ID NO. 151

[0349]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 151]

[0350] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3266.4.

Example 147

Preparation of Peptide having SEQ ID NO. 152

[0351]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Naphthylala Ile Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 152]

[0352] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3209.4.

Example 148

Preparation of Peptide having SEQ ID NO. 153

[0353]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Val Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 153]

[0354] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3200.6.

Example 149

Preparation of Peptide having SEQ ID NO. 154

[0355]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Val Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 154]

[0356] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

Example 150

Preparation of Peptide having SEQ ID NO. 155

[0357]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe tButylgly Glu Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 155]

[0358] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3216.5.

Example 151

Preparation of Peptide having SEQ ID NO. 156

[0359]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe tButylgly Glu Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 156]

[0360] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3159.4.

Example 152

Preparation of Peptide having SEQ ID NO. 157

[0361]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Asp Trp Leu Lys Asn-NH_2 [SEQ. ID. NO. 157]

[0362] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3200.6.

Example 153

Preparation of Peptide having SEQ ID NO. 158

[0363]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn-NH_2 [SEQ. ID. NO. 158]

[0364] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3143.5.

Example 154

Preparation of Peptide having SEQ ID NO. 159

[0365]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH_2 [SEQ. ID. NO. 159]

[0366] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3099.5.

Example 155

Preparation of Peptide having SEQ ID NO. 160

[0367]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn-NH_2 [SEQ. ID. NO. 160]

[0368] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used_in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1° TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3081.4.

Example 156

Preparation of Peptide having SEQ ID NO. 161

[0369]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Ala Lys Asn-NH_2 [SEQ. ID. NO. 161]

[0370] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3172.5.

Example 157

Preparation of Peptide having SEQ ID NO. 162

[0371]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn-NH_2 [SEQ. ID. NO. 162]

[0372] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3115.5.

Example 158

Preparation of Peptide having SEQ ID NO. 163

[0373]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Ala Asn-NH_2 [SEQ. ID. NO. 163]

[0374] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3157.5.

Example 159

Preparation of Peptide having SEQ ID NO. 164

[0375]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn-NH_2 [SEQ. ID. NO. 164]

[0376] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3100.4.

Example 160

Preparation of Peptide having SEQ ID NO. 165

[0377]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Ala-NH_2 [SEQ. ID. NO. 165]

[0378] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3171.6.

Example 161

Preparation of Peptide having SEQ ID NO. 166

[0379]

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala-NH_2 [SEQ. ID. NO. 166]

[0380] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3114.5.

Example 162

Preparation of Peptide having SEQ ID NO. 167

[0381]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH_2 [SEQ. ID. NO. 167]

[0382] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4033.5.

Example 163

Preparation of Peptide having SEQ ID NO. 168

[0383]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro-NH_2 [SEQ. ID. NO. 168]

[0384] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3984.4.

Example 164

Preparation of Peptide having SEQ ID NO. 169

[0385]

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro-NH_2 [SEQ. ID. NO. 169]

[0386] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4016.5.

Example 165

Preparation of Peptide having SEQ ID NO. 170

[0387]

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro-NH_2 [SEQ. ID. NO. 170]

[0388] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3861.3.

Example 166

Preparation of Peptide having SEQ ID NO. 171

[0389]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro-NH_2 [SEQ. ID. NO. 171]

[0390] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3746.1.

Example 167

Preparation of Peptide having SEQ ID NO. 172

[0391]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala-NH_2 [SEQ. ID. NO. 172]

[0392] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3742.1.

Example 168

Preparation of Peptide having SEQ ID NO. 173

[0393]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala-NH_2 [SEQ. ID. NO. 173]

[0394] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3693.1.

Example 169

Preparation of Peptide having SEQ ID NO. 174

[0395]

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly-NH_2 [SEQ. ID. NO. 174]

[0396] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3751.2.

Example 170

Preparation of Peptide having SEQ ID NO. 175

[0397]

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser-NH_2 [SEQ. ID. NO. 175]

[0398] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3634.1.

Example 171

Preparation of Peptide having SEQ ID NO. 176

[0399]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser-NH_2 [SEQ. ID. NO. 176]

[0400] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3526.9.

Example 172

Preparation of Peptide having SEQ ID NO. 177

[0401]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser-NH_2 [SEQ. ID. NO. 177]

[0402] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3477.9.

Example 173

Preparation of Peptide having SEQ ID NO. 178

[0403]

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro-NH_2 [SEQ. ID. NO. 178]

[0404] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3519.9.

Example 174

Preparation of Peptide having SEQ ID NO. 179

[0405]

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly-NH_2 [SEQ. ID. NO. 179]

[0406] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3307.7.

Example 175

Preparation of Peptide having SEQ ID NO. 180

[0407]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly-NH_2 [SEQ. ID. NO. 180]

[0408] The above-identified amidated peptide is assembled on 4-(2'-9'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3186.5.

Example 176

Preparation of Peptide having SEQ ID NO. 181

[0409]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly tPro Ser Ser Gly Ala tPro tPro tPro-NH_2 [SEQ. ID. NO. 181]

[0410] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Double couplings are required at residues 37,36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4121.1.

Example 177

Preparation of Peptide having SEQ ID NO. 182

[0411]

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala tPro tPro tPro-NH_2 [SEQ. ID. NO. 182].

[0412] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Double couplings are required at residues 37, 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4173.2.

Example 178

Preparation of Peptide having SEQ ID NO. 183

[0413]

His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly NMeala Ser Ser Gly Ala NMeala NMeala-NH_2 [SEQ. ID. NO. 183]

[0414] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Compound 1. Double couplings are required at residues 36 and 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3796.1.

Example 179

Preparation of Peptide having SEQ ID NO. 184

[0415]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly hPro Ser Ser Gly Ala hPro-NH_2 [SEQ. ID. NO. 184]

[0416] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. A double coupling is required at residue 31. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3871.1.

Example 180

Preparation of Peptide having SEQ ID NO. 185

[0417]

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala-NH_2 [SEQ. ID. NO. 185]

[0418] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3750.2.

Example 181

Preparation of Peptide having SEQ ID NO. 186

[0419]

His Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly-NH_2 [SEQ. ID. NO. 186]

[0420] The above-identified amdiated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 3408.8.

Example 182

Preparation of Peptide having SEQ ID NO. 187

[0421]

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH_2 [SEQ. ID. NO. 187]

[0422] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4120.6.

Example 183

Preparation of Peptide having SEQ ID NO. 188

[0423]

Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser-NH_2 [SEQ. ID. NO. 188]

[0424] The above-identified amidated peptide is assembled on 4-(2'-4'-dimethoxyphenyl)-Fmoc aminomethyl phenoxy acetamide norleucine MBHA resin (Novabiochem, 0.55 mmole/g) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry (M): calculated 4005.5.

Example 184

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for Peptides having SEQ ID NOS. 100-166, 172-177, 179-180 and 185-188.

[0425] C-terminal carboxylic acid peptides corresponding to amidated having SEQ ID NOS. 100-166, 172-177, 179-180 and 185-188 are assembled on the so called Wang resin (p-alkoxybenzylalacohol resin (Bachem, 0.54 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to that described in Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

EXAMPLE 185

Preparation of C-terminal carboxylic acid peptides corresponding to the above C-terminal amide sequences for Peptides having SEQ ID NOS. 167-171, 178 and 181-184.

[0426] C-terminal carboxylic acid peptides corresponding to amidated SEQ ID NOS. 167-171, 178 and 181-184 are assembled on the 2-chlorotritylchloride resin (200-400 mesh), 2% DVB (Novabiochem, 0.4-1.0 mmole/g)) using Fmoc-protected amino acids (Applied Biosystems, Inc.), cleaved from the resin, deprotected and purified in a similar way to that described in Example 95. Used in analysis are Solvent A (0.1% TFA in water) and Solvent B (0.1% TFA in ACN). Analytical RP-HPLC (gradient 30% to 60% Solvent B in Solvent A over 30 minutes) of the lyophilized peptide is then carried out to determine the retention time of the product peptide. Electrospray Mass Spectrometry provides an experimentally determined (M).

Example 186

Evaluation of Ability to Cross Placenta

I. Introduction

[0427] The purpose of this experiment was to determine whether this exendin-4, when delivered to the maternal circulation, is transported across the placenta and is detectable in amniotic fluid or fetal blood.

II. Materials and Methods

Animals:

[0428] Female Harlan Sprague Dawley rats (age 12 weeks, 17-21 days pregnant, approximately 300 grams) were housed at 22.8 +/- 0.8 °C in a 12:12 hour light : dark cycle. All experiments were performed during the light cycle. Animals were given free access to food and water until the start of the experiment.

Sample collection:

[0429] Rats were anesthetized with 5% halothane and then maintained with 2% halothane during the surgical procedures. Body temperature was measured and controlled using a thermistor probe/controller (Model 73A, YSI, Yellow Springs, OH) and a heated operating table. Blood was collected from the tail vein immediately prior to a subcutaneous injection of exendin-4 (AC2993 Amylin Pharmaceuticals, Inc.) or vehicle (100µl 0.15M NaCl) at t = 0. At t = 30 minutes, when plasma concentrations following a subcutaneous injection have been found to be maximal, another blood sample was taken. Immediately thereafter, a midline laparotomy was made to expose the uterine horns. Fluid was collected from the individual amniotic sacs by aspiration through a 16g needle into a syringe. The amniotic fluids from individual fetuses were pooled from a given rat, but fluids from each rat were kept separate. Fetal blood was collected by heart puncture with a 28g microfine needle and aspirated into a syringe. Amniotic fluid and fetal blood samples were collected within 10 minutes of when the laparotomy was made (t = 30-40 min.). All blood and fluid samples were centrifuged. The plasma or supernatant was stored at -70°C until assayed.

Treatment groups:

[0430] There were 2 treatment groups:

Group A: Rats receiving exendin-4 dissolved at 21μg/100μl in 0.15M NaCl n=4.
Group B: Rats receiving exendin-4 dissolved at 210μg/100μl in 0.15M NaCl n=5.

III. Results

[0431] Exendin-4 was not detected in any of the baseline samples, taken at t = 0, when measured by a specific IRMA (immuno-radio-metric-assay) which has a LLQ (low limit of quantitation) of 15pM. At t = 30 plasma levels of exendin-4 in the mother rats that received 21μg exendin-4 were 16.47nM ± 2.45. Values obtained from amniotic fluid (6.1±5.3pM) and fetal blood (12.7±6.5pM) were 2700-fold and 1300-fold less than those in plasma and were generally below the lower limit of quantitation of the assay (Figure 2). Similar results were obtained with the rats receiving 210μg exendin-4 where plasma levels in the mother rats at t = 30 were 232.16nM ± 63.45 (Figure 3). Values obtained from amniotic fluid (18.3±9.3pM) and fetal blood (16.9±13.8pM) were 12,680-fold and 13,750-fold less than those in plasma and were undetectable in over half of the samples.

IV. Discussion

[0432] The placenta is the organ responsible for nutrient and waste exchange between the fetus and the mother. Maternal and fetal circulations are separated by an epithelial layer that allows or denies diffusion or carrier mediated transport of substances across the interface. The risk of adverse effects on the fetus can be related to the extent to which the drug enters the fetal circulation. The data obtained here indicate that, even with high injected doses, which may exceed the per-kilogram doses administered to humans by up to 3000-fold, little or no exendin-4 appeared in the fetal circulation or amniotic fluid. Six out of 15 measurements were above the lower limit of quantitation, and in 9 of 15, exendin-4 was undetectable. In those samples in which exendin-4 was measurable, its presence may have been due to contamination from maternal blood (which need be present only at 1:1,000-1:10,000 to be measurable). Such contamination is possible following laparotomy of the dam and puncture of the fetus.

[0433] Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the following claims.

SEQUENCE LISTING

[0434]

<110> Amylin Pharmaceuticals, Inc.
Hiles, Richard and Prickett, Kathryn, S.

<120> USE OF EXENDINS AND AGONISTS THEREOF FOR THE TREATMENT OF GESTATIONAL DIABETES MELLITUS

<130> 243/131 WO

<140> PCT/US00/14231
<141> 2000-05-23

<150> 09/323,867
<151> 1999-06-01

<160> 188

<170> Patent In Ver. 2.1 and Microsoft Word

<210> 1
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<212> PRT
<213> Heloderma horridum

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 1

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            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
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<210> 2
<211> 39
<212> PRT
<213> Heloderma suspectum

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 2

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 3
<211> 40
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (1)
<223> His, Arg or Thr

<220>
<221> VARIANT
<222> (2)
<223> Ser, Gly, Ala or Thr

<220>
<221> VARIANT

<222> (3)
<223> Asp or Glu

<220>
<221> VARIANT
<222> (6)
<223> Phe, Tyr or naphthalanine

<220>
<221> VARIANT
<222> (7)
<223> Thr or Ser

<220>
<221> VARIANT
<222> (8)
<223> Ser or Thr

<220>
<221> VARIANT
<222> (9)
<223> Asp or Glu

<220>
<221> VARIANT
<222> (10)
<223> Leu, Ile, Val, pentylglycine or Met

<220>
<221> VARIANT
<222> (14)
<223> Leu, Ile, pentylglycine, Val or Met

<220>
<221> VARIANT
<222> (22)
<223> Phe, Tyr or naphthalanine

<220>
<221> VARIANT
<222> (23)
<223> Ile, Val, Leu, pentylglycine, tert-butylglycine or Met

<220>
<221> VARIANT
<222> (24)
<223> Glu or Asp

<220>
<221> VARIANT
<222> (25)
<223> Trp, Phe, Tyr or naphthylalanine

<220>
<221> VARIANT
<222> (31)
<223> independently Pro, homoproline, 3-hydroxyproline, 4-hydroxyproline, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine

<220>
<221> VARIANT
<222> (36)..(38)
<223> independently Pro, homoproline, 3-hydroxyproline, 4-hydroxyproline, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine

<220>
<221> VARIANT
<222> (39)
<223> Ser, Thr or Tyr

<220>
<221> VARIANT
<222> (40)
<223> -OH or NH2, with the proviso that the compound does not have the formula of either SEQ. ID. NOS. 1 or 2.

<400> 3

```
Xaa Xaa Xaa Gly Thr Xaa Xaa Xaa Xaa Xaa Ser Lys Gln Xaa Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Xaa Xaa Xaa Xaa Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Xaa Xaa
        35                  40
```

<210> 4
<211> 29
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (1)
<223> His, Arg, or Tyr

<220>
<221> VARIANT
<222> (2)
<223> Ser, Gly, Ala or Thr

<220>
<221> VARIANT
<222> (3)
<223> Asp or Glu

<220>
<221> VARIANT
<222> (5)
<223> Ala or Thr

<220>
<221> VARIANT
<222> (6)
<223> Ala, Phe, Tyr or napthylalanine

<220>
<221> VARIANT
<222> (7)
<223> Thr or Ser

<220>
<221> VARIANT
<222> (8)
<223> Ala, Ser or Thr

<220>
<221> VARIANT
<222> (9)
<223> Asp or Glu

<220>
<221> VARIANT
<222> (10)
<223> Ala, Leu, Ile, Val, pentylglycine or Met

<220>
<221> VARIANT
<222> (11)
<223> Ala or Ser

<220>
<221> VARIANT
<222> (12)
<223> Ala or Lys

<220>
<221> VARIANT
<222> (13)
<223> Ala or Gln

<220>
<221> VARIANT
<222> (14)
<223> Ala, Leu, Ile, pentylglycine, Val or Met

<220>
<221> VARIANT
<222> (15)..(17)
<223> Ala or Glu

<220>
<221> VARIANT
<222> (19)
<223> Ala or Val

<220>
<221> VARIANT
<222> (20)
<223> Ala or Arg

<220>
<221> VARIANT
<222> (21)

<223> Ala or Leu

<220>
<221> VARIANT
<222> (22)
<223> Ala, Phe, Tyr or naphthylalanine

<220>
<221> VARIANT
<222> (23)
<223> Ile, Val, Leu, pentylglycine, tert-butylglycine or Met

<220>
<221> VARIANT
<222> (24)
<223> Ala, Glu or Asp

<220>
<221> VARIANT
<222> (25)
<223> Ala, Trp, Phe, Tyr or naphthylalanine

<220>
<221> VARIANT
<222> (26)
<223> Ala or Leu

<220>
<221> VARIANT
<222> (27)
<223> Ala or Lys

<220>
<221> VARIANT
<222> (28)
<223> Ala or Asn

<220>
<221> VARIANT
<222> (29)
<223> OH, NH2, Gly-OH, Gly-NH2, Gly-Gly-OH, Gly-Gly-NH2 and further as indicated in specification

<400> 4

```
Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
  1               5                  10                  15

Xaa Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25
```

<210> 5
<211> 29
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT

<222> (1)
<223> His, Arg, Tyr, Ala, norvaline, Val, or norleucine

<220>
<221> VARIANT
<222> (2)
<223> Ser, Gly, Ala, or Thr

<220>
<221> VARIANT
<222> (3)
<223> Ala, Asp, or Glu

<220>
<221> VARIANT
<222> (4)
<223> Ala, norvaline, Val, norleucine or Gly

<220>
<221> VARIANT
<222> (5)
<223> Ala or Thr

<220>
<221> VARIANT
<222> (6)
<223> Phe, Tyr or napthylalanine

<220>
<221> VARIANT
<222> (7)
<223> Thr or Ser

<220>
<221> VARIANT
<222> (8)
<223> Ala, Ser or Thr

<220>
<221> VARIANT
<222> (9)
<223> Ala, Norvaline, Val, Norleucine, Asp or Glu

<220>
<221> VARIANT
<222> (10)
<223> Ala, Leu, Ile, Val, pentylglycine or Met

<220>
<221> VARIANT
<222> (11)
<223> Ala or Ser

<220>
<221> VARIANT
<222> (12)
<223> Ala or Lys

<220>
<221> VARIANT
<222> (13)
<223> Ala or Gln

<220>
<221> VARIANT
<222> (14)
<223> Ala, Leu, Ile, pentylglycine, Val or Met

<220>
<221> VARIANT
<222> (15)..(17)
<223> Ala or Glu

<220>
<221> VARIANT
<222> (19)
<223> Ala or Val

<220>
<221> VARIANT
<222> (20)
<223> Ala or Arg

<220>
<221> VARIANT
<222> (21)
<223> Ala or Leu

<220>
<221> VARIANT
<222> (22)
<223> Phe, Tyr or naphthylalanine

<220>
<221> VARIANT
<222> (23)
<223> Ile, Val, Leu, pentylglycine, tert-butylglycine or Met

<220>
<221> VARIANT
<222> (24)
<223> Ala, Glu or Asp

<220>
<221> VARIANT
<222> (25)
<223> Ala, Trp, Phe, Tyr or napthylalanine

<220>
<221> VARIANT
<222> (26)
<223> Ala or Leu

<220>
<221> VARIANT
<222> (27)

<223> Ala or Lys

<220>
<221> VARIANT
<222> (28)
<223> Ala or Asn

<220>
<221> VARIANT
<222> (29)
<223> OH, NH2, Gly-OH, Gly-NH2, Gly-Gly-OH, Gly-Gly-NH2 and further as indicated in the specification

<400> 5

```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
  1               5                  10                  15

Xaa Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
            20                  25
```

<210> 6
<211> 30
<212> PRT
<213> synthetic construct

<400> 6

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly
            20                  25                  30
```

<210> 7
<211> 30
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (30)
<223> AMIDATION, Position 30 is Gly-NH2

<400> 7

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly
            20                  25                  30
```

<210> 8
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 8

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Ala Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 9
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 9

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 10
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 10

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 11
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 11

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 12
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 12

```
Tyr Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 13
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Tyr-NH2

<400> 13

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Tyr
        35
```

<210> 14
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 14

```
His Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 15
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<220>
<221> VARIANT
<222> (6)
<223> Xaa is napthylalanine

<400> 15

```
His Gly Glu Gly Thr Xaa Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 16
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 16

```
His Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 17
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 17

```
His Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 18
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 18

```
His Gly Glu Gly Thr Phe Thr Thr Asp Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
          35
```

<210> 19
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 19

```
His Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
          35
```

<210> 20
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<220>
<221> VARIANT
<222> (10)
<223> Xaa is pentylglycine

<400> 20

```
His Gly Glu Gly Thr Phe Thr Ser Asp Xaa Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
         35
```

<210> 21
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<220>
<221> VARIANT
<222> (10)
<223> Xaa is pentylglycine

<400> 21

```
His Gly Glu Gly Thr Phe Thr Ser Asp Xaa Ser Lys Gln Leu Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
         35
```

<210> 22
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<220>
<221> VARIANT
<222> (14)
<223> Xaa is pentylglycine

<400> 22

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Xaa Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 23
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<220>
<221> VARIANT
<222> (14)
<223> Xaa is pentylglycine

<400> 23

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Xaa Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 24
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<220>
<221> VARIANT
<222> (22)
<223> Xaa is napthylalanine

<400> 24

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Xaa Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 25
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 25

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

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

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 26
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 26

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Val Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 27
<211> 39
<212> PRT

<213> synthetic construct

<220>
<221> VARIANT
<222> (23)
<223> Xaa at Position 23 is tertiary-butylglycine

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 27

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Xaa Glu Trp Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
         35
```

<210> 28
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (23)
<223> Xaa at position 23 is tertiary-butylglycine

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 28

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Xaa Glu Phe Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
         35
```

<210> 29
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES

<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 29

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Asp Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 30
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, position 39 is Ser-NH2

<400> 30

```
His Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 31
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa at position 31 is thioproline

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa at positions 36, 36, and 38 is thioproline

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 31

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu

1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
20 25 30

Ser Gly Ala Xaa Xaa Xaa Ser
35

<210> 32
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (36).. (38)
<223> Xaa at positions 36, 37, and 38 is thioproline

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 32

His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Xaa Xaa Xaa Ser
35

<210> 33
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa at position 31 is homoproline

<220>
<221> VARIANT
<222> (36) .. (38)
<223> Xaa at positions 36, 37, and 38 is homoproline

<220>
<221> MOD_RES

<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 33

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu

 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
        35
```

<210> 34
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa at positions 36, 37, and 38 is homoproline

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 34

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
        35
```

<210> 35
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa at position 31 is thioproline

<220>
<221> VARIANT

<222> (36)..(38)
<223> Xaa at positions 36, 37, and 38 is thioproline

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 35

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu

 1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
        35
```

<210> 36
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa at position 31 is homoproline

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa at positions 36,37, and 38 is homoproline

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 36

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
        35
```

<210> 37
<211> 39
<212> PRT

<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa at position 31 is N-methylalanine

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa at positions 36, 37, and 38 is N-methylalanine

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 37

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
             20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
         35
```

<210> 38
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa at positions 36, 37, and 38 is N-methylalanine

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 38

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
             20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
         35
```

<210> 39
<211> 39

<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa at position 31 is N-methylalanine

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa at positions 36, 37, and 38 is N-methylalanine

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 39

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
  1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Xaa Ser
             20                  25                  30

Ser Gly Ala Xaa Xaa Xaa Ser
         35
```

<210> 40
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 40

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
             20                  25
```

<210> 41
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 41

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 42
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 42

```
His Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 43
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 43

```
His Gly Glu Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 44
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 44

```
His Gly Glu Gly Thr Ala Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 45
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 45

```
His Gly Glu Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 46
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 46

```
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 47
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 47

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 48
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 48

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 49
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 49

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 50
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 50

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Ala Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 51
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 51

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 52
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 52

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Ala
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 53
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 53

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 54
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 54

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 55
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 55

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 56
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 56

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 57
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 57

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Ala Phe Leu Lys Asn
            20                  25
```

<210> 58
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 58

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn
            20                  25
```

<210> 59
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 59

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn
            20                  25
```

<210> 60
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 60

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn
            20                  25
```

<210> 61
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Ala-NH2

<400> 61

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala
            20                  25
```

<210> 62
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is Pro-NH2

<400> 62

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro
        35
```

<210> 63
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is Pro-NH2

<400> 63

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro
        35
```

<210> 64
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is Pro-NH2

<400> 64

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro
        35
```

<210> 65
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is Pro-NH2

<400> 65

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro
        35
```

<210> 66
<211> 36
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (36)
<223> AMIDATION, Position 36 is Pro-NH2

<400> 66

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro
        35
```

<210> 67
<211> 36
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (36)
<223> AMIDATION, Position 36 is Pro-NH2

<400> 67

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro
        35
```

<210> 68
<211> 35
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (35)
<223> AMIDATION, Position 35 is Ala-NH2

<400> 68

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala
        35
```

<210> 69
<211> 35
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (35)
<223> AMIDATION, Position 35 is Ala-NH2

<400> 69

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala
        35
```

<210> 70
<211> 34

<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (34)
<223> AMIDATION, Position 34 is Gly-NH2

<400> 70

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly
```

<210> 71
<211> 34
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (34)
<223> AMIDATION, Position 34 is Gly-NH2

<400> 71

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly
```

<210> 72
<211> 33
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (33)
<223> AMIDATION, Position 33 is Ser-NH2

<400> 72

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser
```

<210> 73
<211> 33
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (33)
<223> AMIDATION, Position 33 is Ser-NH2

<400> 73

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser
```

<210> 74
<211> 32
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (32)
<223> AMIDATION, Position 32 is Ser-NH2

<400> 74

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30
```

<210> 75
<211> 32
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (32)
<223> AMIDATION, Position 32 is Ser-NH2

<400> 75

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30
```

<210> 76
<211> 31
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (31)
<223> AMIDATION, Position 31 is Pro-NH2

<400> 76

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro
            20                  25                  30
```

<210> 77
<211> 31
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (31)
<223> AMIDATION, Position 31 is Pro-NH2

<400> 77

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro
            20                  25                  30
```

<210> 78
<211> 30
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (30)
<223> AMIDATION, Position 30 is Gly-NH2

<400> 78

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly
            20                  25                  30
```

<210> 79
<211> 29
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (29)
<223> AMIDATION, Position 29 is Gly-NH2

<400> 79

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly
            20                  25
```

<210> 80
<211> 29
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (29)
<223> AMIDATION, Position 29 is Gly-NH2

<400> 80

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly
            20                  25
```

<210> 81
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is thioproline

<220>

<221> VARIANT
<222> (36)..(38)
<223> Xaa is thioproline

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is thioproline-NH2

<400> 81

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa
        35
```

<210> 82
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa is thioproline

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is thioproline-NH2

<400> 82

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa Xaa
        35
```

<210> 83
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is N-methylalanine

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is Pro-NH2

<400> 83

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Pro Pro
        35
```

<210> 84
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is N-methylalanine

<220>
<221> VARIANT
<222> (36)..(37)
<223> Xaa is N-methylalanine

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is N-methylalanine-NH2

<400> 84

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa
        35
```

<210> 85
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is homoproline

<220>
<221> VARIANT
<222> (36) .. (37)
<223> Xaa is homoproline

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is homoproline-NH2

<400> 85

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa
        35
```

<210> 86
<211> 36
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is homoproline

<220>
<221> VARIANT
<222> (36)
<223> Xaa is homoproline

<220>
<221> MOD_RES
<222> (36)
<223> AMIDATION, Position 36 is homoproline-NH2

<400> 86

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa
        35
```

<210> 87
<211> 35
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (35)
<223> AMIDATION, Position 35 is Ala-NH2

<400> 87

```
Arg Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala
        35
```

<210> 88
<211> 30
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (30)
<223> AMIDATION, Position 30 is Gly-NH2

<400> 88

```
His Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly
            20                  25                  30
```

<210> 89
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (6)
<223> Xaa is napthylalanine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 89

His Gly Glu Gly Thr Xaa Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 90
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 90

His Gly Glu Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 91
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 91

His Gly Glu Gly Thr Phe Ser Thr Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 92
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 92

```
His Gly Glu Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Ala Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 93
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (10)
<223> Xaa is pentylglycine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 93

```
His Gly Glu Gly Thr Phe Thr Ser Asp Xaa Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 94
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (22)
<223> Xaa is napthylalanine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 94

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Xaa Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 95
<211> 28

<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (23)
<223> Xaa is tertiary-butylglycine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 95

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Xaa Glu Trp Leu Lys Asn
            20                  25
```

<210> 96
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 96

```
His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn
            20                  25
```

<210> 97
<211> 33
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (33)
<223> AMIDATION, Position 33 is Ser-NH2
/

<400> 97

```
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser
```

<210> 98
<211> 29
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (29)
<223> AMIDATION, Position 29 is Gly-NH2

<400> 98

```
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly
            20                  25
```

<210> 99
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is homoproline

<220>
<221> VARIANT
<222> (36)..(37)
<223> Xaa is homoproline

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is homoproline-NH2

<400> 99

```
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa
        35
```

<210> 100
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 100

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 101
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 101

```
His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 102
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 102

```
His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 103
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 103

```
His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 104
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 104

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 105
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 105

```
His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 106
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 106

```
His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 107
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 107

```
His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 108
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 108

```
His Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 109
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 109

```
Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 110
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 110

```
Ala Ala Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 111
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 111

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 112
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 112

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 113
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 113

```
Ala Gly Asp Gly Ala Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 114
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 114

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 115
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (6)
<223> Xaa is napthylalanine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 115

Ala Gly Asp Gly Thr Xaa Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 116
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (6)
<223> Xaa is napthylalanine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 116

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 117
<211> 28
<212> PRT

<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 117

```
Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 118
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 118

```
Ala Gly Asp Gly Thr Phe Ser Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 119
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 119

```
Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 120
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 120

```
Ala Gly Asp Gly Thr Phe Thr Ala Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 121
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 121

```
Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 122
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 122

```
Ala Gly Asp Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 123
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 123

Ala Gly Asp Gly Thr Phe Thr Ser Glu Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 124
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 124

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 125
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 125

Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 126
<211> 28
<212> PRT

<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 126

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 127
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (10)
<223> Xaa is pentylgylcine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 127

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Xaa Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 128
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (10)
<223> Xaa is pentylgylcine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 128

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 129
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 129

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ala Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 130
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 130

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 131
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 131

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 132
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 132

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Ala Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 133
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 133

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 134
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 134

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Ala Leu Glu Glu

1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 135
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 135

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

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
20 25

<210> 136
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 136

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
20 25

<210> 137
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (14)
<223> Xaa is pentylglycine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 137

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

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 138
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (14)
<223> Xaa is pentylglycine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 138

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 139
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 139

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Ala Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 140

<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 140

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Ala Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 141
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 141

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Ala
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 142
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 142

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Ala
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 143
<211> 28

<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 143

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Ala Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 144
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 144

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Ala Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 145
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 145

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Ala Arg Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 146

<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 146

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Ala Arg Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 147
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 147

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Ala Leu Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 148
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 148

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Ala Leu Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 149
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 149

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Ala Phe Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 150
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 150

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Ala Phe Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 151
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (22)
<223> Xaa is napthylalanine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 151

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Xaa Ile Glu Trp Leu Lys Asn
            20                  25
```

<210> 152
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (22)
<223> Xaa is napthylalanine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 152

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Xaa Ile Glu Phe Leu Lys Asn
            20                  25
```

<210> 153
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 153

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Val Glu Trp Leu Lys Asn
            20                  25
```

<210> 154
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)

<223> AMIDATION, Position 28 is Asn-NH2

<400> 154

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Val Glu Phe Leu Lys Asn
            20                  25
```

<210> 155
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (23)
<223> Xaa is tertiary-butylglycine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 155

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Xaa Glu Trp Leu Lys Asn
            20                  25
```

<210> 156
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (23)
<223> Xaa is tertiary-butylglycine

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 156

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Xaa Glu Phe Leu Lys Asn
            20                  25
```

<210> 157
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 157

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Asp Trp Leu Lys Asn
            20                  25
```

<210> 158
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 158

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Asp Phe Leu Lys Asn
            20                  25
```

<210> 159
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 159

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn
            20                  25
```

<210> 160

<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 160

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Ala Leu Lys Asn
            20                  25
```

<210> 161
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 161

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Ala Lys Asn
            20                  25
```

<210> 162
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 162

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Ala Lys Asn
            20                  25
```

<210> 163

<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 163

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Ala Asn
            20                  25
```

<210> 164
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Asn-NH2

<400> 164

```
Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu

1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Ala Asn
            20                  25
```

<210> 165
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Ala-NH2

<400> 165

Ala Gly Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Ala
20 25

<210> 166
<211> 28
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (28)
<223> AMIDATION, Position 28 is Ala-NH2

<400> 166

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

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Ala
20 25

<210> 167
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is Pro-NH2

<400> 167

Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala Pro Pro Pro
35

<210> 168
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (38)

<223> AMIDATION, Position 38 is Pro-NH2

<400> 168

```
His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro
        35
```

<210> 169
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (37)
<223> AMIDATION, Position 37 is Pro-NH2

<400> 169

```
His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro
        35
```

<210> 170
<211> 36
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (36)
<223> AMIDATION, Position 36 is Pro-NH2

<400> 170

```
His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro
        35
```

<210> 171
<211> 36
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (36)
<223> AMIDATION, Position 36 is Pro-NH2

<400> 171

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Ala Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro
        35
```

<210> 172
<211> 35
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (35)
<223> AMIDATION, Position 35 is Ala-NH2

<400> 172

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala
        35
```

<210> 173
<211> 35
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (35)
<223> AMIDATION, Position 35 is Ala-NH2

<400> 173

```
His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala
        35
```

<210> 174
<211> 34
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (34)
<223> AMIDATION, Position 34 is Gly-NH2

<400> 174

```
His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly
```

<210> 175
<211> 33
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (33)
<223> AMIDATION, Position 33 is Ser-NH2

<400> 175

```
His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser
```

<210> 176
<211> 32
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (32)
<223> AMIDATION, Position 32 is Ser-NH2

<400> 176

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30
```

<210> 177
<211> 32
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (32)
<223> AMIDATION, Position 32 is Ser-NH2

<400> 177

```
His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30
```

<210> 178
<211> 31
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (31)
<223> AMIDATION, Position 31 is Pro-NH2

<400> 178

```
His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro
            20                  25                  30
```

<210> 179
<211> 30
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (30)
<223> AMIDATION, Position 30 is Gly-NH2

<400> 179

```
His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly
            20                  25                  30
```

<210> 180
<211> 29
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (29)
<223> AMIDATION, Position 29 is Gly-NH2

<400> 180

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly
            20                  25
```

<210> 181
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is thioproline

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa is thioproline

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is thioproline-NH2

<400> 181

His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
20 25 30

Ser Gly Ala Xaa Xaa Xaa
35

<210> 182
<211> 38
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (36)..(38)
<223> Xaa is thioproline

<220>
<221> MOD_RES
<222> (38)
<223> AMIDATION, Position 38 is thioproline-NH2

<400> 182

His Gly Glu Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1 5 10 15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
20 25 30

Ser Gly Ala tPro tPro tPro
35

<210> 183
<211> 37
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is N-methylalanine

<220>
<221> VARIANT
<222> (36)..(37)
<223> Xaa is N-methylalanine

<220>
<221> MOD_RES
<222> (37)

<223> AMIDATION, Position 37 is N-methylalanine-NH2

<400> 183

```
His Gly Glu Gly Thr Phe Thr Ser Ala Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa Xaa
        35
```

<210> 184
<211> 36
<212> PRT
<213> synthetic construct

<220>
<221> VARIANT
<222> (31)
<223> Xaa is homoproline

<220>
<221> VARIANT
<222> (36)
<223> Xaa is homoproline

<220>
<221> MOD_RES
<222> (36)
<223> AMIDATION, Position 36 is homoproline-NH2

<400> 184

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Xaa Ser
            20                  25                  30

Ser Gly Ala Xaa
        35
```

<210> 185
<211> 35
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (35)
<223> AMIDATION, Position 35 is Ala-NH2

<400> 185

```
His Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala
        35
```

<210> 186
<211> 30
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (30)
<223> AMIDATION, Position 30 is Gly-NH2

<400> 186

```
His Gly Asp Ala Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly
            20                  25                  30
```

<210> 187
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 187

```
Ala Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

<210> 188
<211> 39
<212> PRT
<213> synthetic construct

<220>
<221> MOD_RES
<222> (39)
<223> AMIDATION, Position 39 is Ser-NH2

<400> 188

```
Ala Gly Ala Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Leu Glu Glu
1               5                  10                  15

Glu Ala Val Arg Leu Phe Ile Glu Phe Leu Lys Asn Gly Gly Pro Ser
            20                  25                  30

Ser Gly Ala Pro Pro Pro Ser
        35
```

Claims

1. Use of an exendin or an exendin agonist peptide for the manufacture of a medicament for treating gestational diabetes in a subject, said medicament comprising a therapeutically effective amount of an exendin or an exendin agonist peptide wherein said exendin or exendin agonist peptide binds to a receptor that binds exendin-3 or exendin-4, and
wherein said exendin or exendin agonist peptide comprises the sequence Xaa_1 Xaa_2 Xaa_3 Gly Thr Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Ser Lys Gln Xaa_9 Glu Glu Glu Ala Val Arg Leu Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Leu Lys Asn Gly Gly Xaa_{14} Ser Ser Gly Ala Xaa_{15} Xaa_{16} Xaa_{17} Xaa_{18}-Z; wherein

   Xaa_1 is His, Arg or Tyr;
   Xaa_2 is Ser, Gly, Ala or Thr;
   Xaa_3 is Asp or Glu;
   Xaa_4 is Phe, Tyr or naphthylalanine;
   Xaa_5 is Thr or Ser;
   Xaa_6 is Ser or Thr;
   Xaa_7 is Asp or Glu;
   Xaa_8 is Leu, Ile, Val, pentylglycine or Met;
   Xaa_9 is Leu, Ile, pentylglycine, Val or Met;
   Xaa_{10} is Phe, Tyr or naphthylalanine;
   Xaa_{11} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
   Xaa_{12} is Glu or Asp;
   Xaa_{13} is Trp, Phe, Tyr, or naphthylalanine ;
   Xaa_{14}, Xaa_{15}, Xaa_{16} and Xaa_{17} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N- alkylglycine, N-alkylpentylglycine or N-alkylalanine ;
   Xaa_{18} is Ser, Thr or Tyr; and
   Z is-OH or-NH2.

2. Use of an exendin or an exendin agonist peptide for the manufacture of a medicament for treating gestational diabetes in a subject, said medicament comprising a therapeutically effective amount of an exendin or an exendin agonist peptide wherein said exendin or exendin agonist peptide binds to a receptor that binds exendin-3 or exendin-4, and
wherein said exendin or exendin agonist peptide comprises the sequence Xaa_1 Xaa_2 Xaa_3 Gly Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{19} Xaa_{20}, Xaa_{21}, Xaa_{22} Xaa_{23} Xaa_{24}, Xaa_{25}, Xaa_{26} Xaa_{27}, Xaa_{28}-Z_1; wherein

   Xaa_1 is His, Arg or Tyr;
   Xaa_2 is Ser, Gly, Ala or Thr;

Xaa_3 is Asp or Glu;
Xaa_5 is Ala or Thr;
Xaa_6 is Ala, Phe, Tyr or naphthylalanine;
Xaa_7 is Thr or Ser;
Xaa_8 is Ala, Ser or Thr;
Xaa_9 is Asp or Glu;
Xaa_{10} is Ala, Leu, Ile, Val, pentylglycine or Met;
Xaa_{11} is Ala or Ser;
Xaa_{12} is Ala or Lys;
Xaa_{13} is Ala or Gln;
Xaa_{14} is Ala, Leu, Ile, pentylglycine, Val or Met;
Xaa_{15} is Ala or Glu;
Xaa_{16} is Ala or Glu;
Xaa_{17} is Ala or Glu;
Xaa_{19} is Ala or Val;
Xaa_{20} is Ala or Arg;
Xaa_{21} is Ala or Leu;
Xaa_{22} is Ala, Phe, Tyr or naphthylalanine;
Xaa_{23} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa_{24} is Ala, Glu or Asp;
Xaa_{25} is Ala, Trp, Phe, Tyr or naphthylalanine;
Xaa_{26} is Ala or Leu;
Xaa_{27} is Ala or Lys;
Xaa_{28} is Ala or Asn;
Z_1 is -OH,
$-NH_2$,
Gly-Z_2,
Gly Gly-Z_2,,
Gly Gly Xaa_{31}-Z_2
Gly Gly Xaa_{31} Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, or
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2;
Xaa_{31} Xaa_{36}, Xaa_{37} and Xaa_{38} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycirle or N-alkylalanine; and
Z_2 is-OH or-NH_2;
provided that no more than three of Xaa_5, Xaa_6, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27}, and Xaa_{28} are Ala.

3. Use of an exendin or an exendin agonist peptide for the manufacture of a medicament for treating gestational diabetes in a subject, said medicament comprising a therapeutically effective amount of an exendin or an exendin agonist peptide wherein said exendin or exendin agonist peptide binds to a receptor that binds exendin-3 or exendin-4, and
wherein said exendin or exendin agonist peptide comprises the sequence Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Z_1; wherein

Xaa_1 is His, Arg, Tyr, Ala, Norval, Val or Norleu;
Xaa_2 is Ser, Gly, Ala or Thr ;
Xaa_3 is Ala, Asp or Glu;
Xaa_4 is Ala, Norval, Val, Norleu or Gly;
Xaa_5 is Ala or Thr ;
Xaa_6 is Phe, Tyr or naphthylalanine ;
Xaa_7 is Thr or Ser ;
Xaa_8 is Ala, Ser or Thr ;

Xaa_9 is Ala, Norval, Val, Norleu, Asp or Glu ;
Xaa_{10} is Ala, Leu, Ile, Val, pentylglycine or Met;
$Xaa_{11}$is Ala or Ser ;
Xaa_{12} is Ala or Lys ;
Xaa_{13} is Ala or Gln;
Xaa_{14} is Ala, Leu, Ile, pentylglycine, Val or Met ;
Xaa_{15} is Ala or Glu ;
Xaa_{16} is Ala or Glu ;
Xaa_{17} is Ala or Glu ;
Xaa_{19} is Ala or Val ;
Xaa_{20} is Ala or Arg ;
Xaa_{21} is Ala or Leu ;
Xaa_{22} is Phe, Tyr or naphthylalanine ;
Xaa_{23} is Ile, Val, Leu, pentylglycine, tert-butylglycine or Met;
Xaa_{24} is Ala, Glu or Asp;
Xaa_{25} is Ala, Trp, Phe, Tyr or naphthylalanine;
Xaa_{26} is Ala or Leu;
Xaa_{27} is Ala or Lys ;
Xaa_{28} is Ala or Asn;
Z1 is -OH,
$-NH_2$
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, or
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2; wherein
Xaa_{31}, Xaa_{36}, Xaa_{37} and Xaa_{38} are independently Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine or N-alkylalanine; and
Z_2 is -OH or-NH2;
provided that no more than three of Xaa_3, Xaa_4, Xaa_5, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} and Xaa_{28} are Ala; and provided also that, if Xaa_1 is His, Arg or Tyr, then at least one of Xaa_3, Xaa_4 and Xaa_9 is Ala.

4. The use according to any one of claims 1 to 3, wherein said exendin or exendin agonist peptide is selected from the group consisting of SEQ ID NO. 1, 2 and 6-188.

5. Use according to claim 1, when said exendin or exendin or exendin agonist peptide is selected from the group consisting of exendin-4-acid and ^{14}Leu, ^{25}Phe exendin-4 amide.

6. The use according to claim 2 or 3, wherein said exendin or exendin agonist peptide is selected from the group consisting of exendin-4 (1-30), exendin-4 (1-30) amide, exendin-4 (1-28) amide and ^{14}Leu, ^{25}Phe exendin-4 (1-28) amide.

7. The use according to claim 1, wherein said exendin or exendin agonist peptide is exendin-3.

8. The use according to claim 1, wherein said exendin or exendin agonist peptide is exendin-4.

9. The use according to any one of claims 1-8, where said therapeutically effective amount reduces blood glucose.

10. The use according to any one of claims 1-9, wherein said medicament is in a form suitable for being administered continuously.

11. The use according to any one of claims 1-9, wherein said medicament is in a form suitable for administration by

injection.

12. The use according to claim 11, wherein said medicament is in a form suitable for being administered by subcutaneous injection.

13. The use according to any one of claims 1-12, wherein said medicament is in a form to be administered in a single dose or divided doses to contain a daily dose of 1 μg to 1 mg of said exendin or exendin agonist peptide.

14. The use according to any one of claims 1-12, wherein said medicament is in a form to be administered in a single dose or divided doses to contain a daily dose of 1 μg to 30 μg of said exendin or exendin agonist peptide.

15. The use according to any one of claims 1-12, wherein said medicament is in a form to be administered in a single dose or divided doses to contain a daily dose of about 3 μg to about 50 μg of said exendin or exendin agonist peptide.

16. The use according to any one of claims 1-15, wherein said subject is a human.

17. The use according to any one of claims 1-16, wherein said medicament further comprises a therapeutically effective amount of one or more compounds selected from the group consisting of insulin and an amylin agonist.

Patentansprüche

1. Verwendung eines Exendin- oder eines Exendin-Agonist-Peptids für die Herstellung eines Medikaments für die Behandlung von Gestationsdiabetes bei einem Patienten, welches Medikament eine therapeutisch wirksame Menge eines Exendin- oder eines Exendin-Agonist-Peptids umfasst, wobei das Exendin- oder Exendin-Agonist-Peptid an einen Rezeptor bindet, der Exendin-3 oder Exendin-4 bindet, und
wobei das Exendin- oder Exendin-Agonist-Peptid die Sequenz Xaa_1 Xaa_2 Xaa_3 Gly Thr Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Ser Lys Gin Xaa_9 Glu Glu Glu Ala Val Arg Leu Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Leu Lys Asn Gly Gly Xaa_{14} Ser Ser Gly Ala Xaa_{15} Xaa_{16} Xaa_{17} Xaa_{18}-Z umfasst; worin

   Xaa_1 His, Arg oder Tyr ist;
   Xaa_2 Ser, Gly, Ala oder Thr ist;
   Xaa_3 Asp oder Glu ist;
   Xaa_4 Phe, Tyr oder Naphthylalanin ist;
   Xaa_5Thr oder Ser ist;
   Xaa_6 Ser oder Thr ist;
   Xaa_7 Asp oder Glu ist;
   Xaa_8 Leu, Ile, Val, Pentylglycin oder Met ist;
   Xaa_9 Leu, Ile, Pentylglycin, Val oder Met ist;
   Xaa_{10} Phe, Tyr oder Naphthylalanin ist;
   Xaa_{11} Ile, Val, Leu, Pentylglycin, tert-Butylglycin oder Met ist;
   Xaa_{12} Glu oder Asp ist;
   Xaa_{13}Trp, Phe, Tyr oder Naphthylalanin ist;
   Xaa_{14}, Xaa_{15}, Xaa_{16} und Xaa_{17} unabhängig Pro, Homoprolin, 3Hyp, 4Hyp, Thioprolin, N-Alkylglycin, N-Alkylpentylglycin oder N-Alkylalanin sind;
   Xaa_{18} Ser, Thr oder Tyr ist; und
   Z -OH oder -NH_2 ist.

2. Verwendung eines Exendin- oder eines Exendin-Agonist-Peptids für die Herstellung eines Medikaments für die Behandlung von Gestationsdiabetes bei einem Patienten, welches Medikament eine therapeutisch wirksame Menge eines Exendin- oder eines Exendin-Agonist-Peptids umfasst, wobei das Exendin- oder Exendin-Agonist-Peptid an einen Rezeptor bindet, der Exendin-3 oder Exendin-4 bindet, und
wobei das Exendin- oder Exendin-Agonist-Peptid die Sequenz Xaa_1 Xaa_2 Xaa_3 Gly Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Z_1 umfasst; worin

   Xaa_1 His, Arg oder Tyr ist;
   Xaa_2 Ser, Gly, Ala oder Thr ist;

Xaa_3 Asp oder Glu ist;
Xaa_5 Ala oder Thr ist;
Xaa_6 Ala, Phe, Tyr oder Naphthylalanin ist;
Xaa_7 Thr oder Ser ist;
Xaa_8 Ala, Ser oder Thr ist;
Xaa_9 Asp oder Glu ist;
Xaa_{10} Ala, Leu, Ile, Val, Pentylglycin oder Met ist;
Xaa_{11} Ala oder Ser ist;
Xaa_{12} Ala oder Lys ist;
Xaa_{13} Ala oder Gln ist;
Xaa_{14} Ala, Leu, Ile, Pentylglycin, Val oder Met ist;
Xaa_{15} Ala oder Glu ist;
Xaa_{16} Ala oder Glu ist;
Xaa_{17} Ala oder Glu ist;
Xaa_{19} Ala oder Val ist;
Xaa_{20} Ala oder Arg ist;
Xaa_{21} Ala oder Leu ist;
Xaa_{22} Ala, Phe, Tyr oder Naphthylalanin ist;
Xaa_{23} Ile, Val, Leu, Pentylglycin, tert-Butylglycin oder Met ist;
Xaa_{24} Ala, Glu oder Asp ist;
Xaa_{25} Ala, Trp, Phe, Tyr oder Naphthylalanin ist;
Xaa_{26} Ala oder Leu ist;
Xaa_{27} Ala oder Lys ist;
Xaa_{28} Ala oder Asn ist;
Z_1 ist -OH,
$-NH_2$,
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, oder
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2; Xaa_{31}, Xaa_{36}, Xaa_{37} und Xaa_{38} unabhängig Pro, Homoprolin, 3 Hyp, 4Hyp, Thioprolin, N-Alkylglycin, N-Alkylpentylglycin oder N-Alkylalanin sind; und Z_2 -OH oder-NH_2 ist;

vorausgesetzt, dass nicht mehr als drei von Xaa_5, Xaa_6, Xaa_9; Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} und Xaa_{28} Ala sind.

3. Verwendung eines Exendin- oder eines Exendin-Agonist-Peptids für die Herstellung eines Medikaments für die Behandlung von Gestationsdiabetes bei einem Patienten, welches Medikament eine therapeutisch wirksame Menge eines Exendin- oder eines Exendin-Agonist-Peptids umfasst, wobei das Exendin- oder Exendin-Agonist-Peptid an einen Rezeptor bindet, der Exendin-3 oder Exendin-4 bindet, und
wobei das Exendin- oder Exendin-Agonist-Peptid die Sequenz Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Z_1 umfasst; worin

Xaa_1 His, Arg, Tyr, Ala, Norval, Val oder Norleu ist;
Xaa_2 Ser, Gly, Ala oder Thr ist;
Xaa_3 Ala, Asp oder Glu ist;
Xaa_4 Ala, Norval, Val, Norleu oder Gly ist;
Xaa_5 Ala oder Thr ist;
Xaa_6 Ala, Phe, Tyr oder Naphthylalanin ist;
Xaa_7 Thr oder Ser ist;
Xaa_8 Ala, Ser oder Thr ist;

Xaa_9 Ala, Noral, Val, Norleu, Asp oder Glu ist;
Xaa_{10} Ala, Leu, Ile, Val, Pentylglycin oder Met ist;
Xaa_{11} Ala oder Ser ist;
Xaa_{12} Ala oder Lys ist;
Xaa_{13} Ala oder Gln ist;
Xaa_{14} Ala, Leu, Ile, Pentylglycin, Val oder Met ist;
Xaa_{15} Ala oder Glu ist;
Xaa_{16} Ala oder Glu ist;
Xaa_{17} Ala oder Glu ist;
Xaa_{19} Ala oder Val ist;
Xaa_{20} Ala oder Arg ist;
Xaa_{21} Ala oder Leu ist;
Xaa_{22} Phe, Tyr oder Naphthylalanin ist;
Xaa_{23} Ile, Val, Leu, Pentylglycin, tert-Butylglycin oder Met ist;
Xaa_{24} Ala, Glu oder Asp ist;
Xaa_{25} Ala, Trp, Phe, Tyr oder Naphthylalanin ist;
Xaa_{26} Ala oder Leu ist;
Xaa_{27} Ala oder Lys ist;
Xaa_{28} Ala oder Asn ist;
Z_1 ist -OH,
$-NH_2$,
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, oder
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2; worin Xaa_{31}, Xaa_{36}, Xaa_{37} und Xaa_{38} unabhängig Pro, Homoprolin, 3 Hyp, 4Hyp, Thioprolin, N-Alkylglycin, N-Alkylpentylglycin oder N-Alkylalanin sind; und Z_2 -OH oder $-NH_2$ ist,

vorausgesetzt, dass nicht mehr als drei von Xaa_3, Xaa_4, Xaa_5, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} und Xaa_{28} Ala sind;
und außerdem vorausgesetzt, dass, wenn Xaa_1 His, Arg oder Tyr ist, dann wenigstens eines von Xaa_3, Xaa_4 und Xaa_9 Ala ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, wobei das Exendin- oder Exendin-Agonist-Peptid ausgewählt ist aus der Gruppe, bestehend aus SEQ ID NR. 1, 2 und 6-188.

5. Verwendung nach Anspruch 1, wobei das Exendin- oder Exendin-Agonist-Peptid ausgewählt ist aus der Gruppe, bestehend aus Exendin-4-säure und ^{14}Leu, ^{25}Phe-Exendin-4-amid.

6. Verwendung nach Anspruch 2 oder 3, wobei Exendin- oder Exendin-Agonist-Peptid ausgewählt ist aus der Gruppe, bestehend aus Exendin-4 (1-30), Exendin-4-(1-30)-amid, Exendin-4-(1-28)-amid und ^{14}Leu,^{25}Phe-Exendin-4-(1-28)-amid.

7. Verwendung nach Anspruch 1, wobei das Exendin- oder Exendin-Agonist-Peptid Exendin-3 ist.

8. Verwendung nach Anspruch 1, wobei das Exendin- oder Exendin-Agonist-Peptid Exendin-4 ist.

9. Verwendung nach einem der Ansprüche 1-8, wobei die therapeutisch wirksame Menge die Blutglucose reduziert.

10. Verwendung nach einem der Ansprüche 1-9, wobei das Medikament in einer Form vorliegt, die für die fortgesetzte Verabreichung geeignet ist.

11. Verwendung nach einem der Ansprüche 1-9, wobei das Medikament in einer Form vorliegt, die für die Verabreichung durch Injektion geeignet ist.

12. Verwendung nach Anspruch 11, wobei das Medikament in einer Form vorliegt, die für die Verabreichung durch subkutane Injektion geeignet ist.

13. Verwendung nach einem der Ansprüche 1-12, wobei das Medikament in einer Form vorliegt, die in einer einzelnen Dosis oder aufgeteilten Dosen verabreicht wird, wobei diese eine tägliche Dosis von 1 μg bis 1 mg des Exendin- oder Exendin-Agonist-Peptids enthält.

14. Verwendung nach einem der Ansprüche 1-12, wobei das Medikament in einer Form vorliegt, die in einer einzelnen Dosis oder aufgeteilten Dosen verabreicht wird, wobei diese eine tägliche Dosis von 1 μg bis 30 μg des Exendin- oder Exendin-Agonist-Peptids enthält.

15. Verwendung nach einem der Ansprüche 1-12, wobei das Medikament in einer Form vorliegt, die in einer einzelnen Dosis oder aufgeteilten Dosen verabreicht wird, wobei diese eine tägliche Dosis von 3 μg bis etwa 50 μg des Exendin- oder Exendin-Agonist-Peptids enthält.

16. Verwendung nach einem der Ansprüche 1-15, wobei der Patient ein Mensch ist.

17. Verwendung nach einem der Ansprüche 1-16, wobei das Medikament außerdem eine therapeutisch wirksame Menge einer oder mehrerer Verbindungen umfasst, ausgewählt aus der Gruppe, bestehend aus Insulin und einem Amylin-Agonisten.

Revendications

1. Utilisation d'une exendine ou d'un peptide agoniste d'exendine pour la préparation d'un médicament destiné au traitement du diabète gestationnel chez un sujet, ledit médicament comprenant une quantité thérapeutiquement efficace d'exendine ou d'un peptide agoniste d'exendine dans laquelle ladite exendine ou ledit peptide agoniste d'exendine se lie à un récepteur qui se lie à l'exendine-3 ou à l'exendine-4, et
dans laquelle ladite exendine ou ledit peptide agoniste d'exendine comprend la séquence Xaa_1 Xaa_2 Xaa_3 Gly Thr Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Ser Lys Gln Xaa_9 Glu Glu Glu Ala Val Arg Leu Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Leu Lys Asn Gly Gly Xaa_{14} Ser Ser Gly Ala Xaa_{15} Xaa_{16} Xaa_{17} Xaa_{18}-Z ; dans laquelle

   Xaa_1 est His, Arg ou Tyr ;
   Xaa_2 est Ser, Gly, Ala ou Thr ;
   Xaa_3 est Asp ou Glu ;
   Xaa_4 est Phe, Tyr ou naphtylalanine ;
   Xaa_5 est Thr ou Ser ;
   Xaa_6 est Ser ou Thr ;
   Xaa_7 est Asp ou Glu ;
   Xaa_8 est Leu, Ile, Val, pentylglycine ou Met ;
   Xaa_9 est Leu, Ile, pentylglycine, Val ou Met ;
   Xaa_{10} est Phe, Tyr ou naphtylalanine ;
   Xaa_{11} est Ile, Val, Leu, pentylglycine,
   tert-butylglycine ou Met ;
   Xaa_{12} est Glu ou Asp ;
   Xaa_{13} est Trp, Phe, Tyr, ou naphtylalanine ;
   Xaa_{14}, Xaa_{15}, Xaa_{16} et Xaa_{17} sont indépendamment Pro, homoproline, 3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine ou N-alkylalanine ;
   Xaa_{18} est Ser, Thr ou Tyr ; et
   Z est -OH ou $-NH_2$.

2. Utilisation d'une exendine ou d'un peptide agoniste d'exendine pour la préparation d'un médicament destiné au traitement du diabète gestationnel chez un sujet, ledit médicament comprenant une quantité thérapeutiquement efficace d'une exendine ou d'un peptide agoniste d'exendine dans laquelle ladite exendine ou ledit peptide agoniste d'exendine se lie à un récepteur qui se lie à l'exendine-3 ou à l'exendine-4, et

dans laquelle ladite exendine ou ledit peptide agoniste d'exendine comprend la séquence Xaa_1 Xaa_2 Xaa_3 Gly Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{26} Xaa_{27} Xaa_{28}-Z_1 ; dans laquelle

Xaa_1 est His, Arg ou Tyr ;
Xaa_2 est Ser, Gly, Ala ou Thr ;
Xaa_3 est Asp ou Glu ;
Xaa_5 est Ala ou Thr ;
Xaa_6 est Ala, Phe, Tyr ou naphthylalanine ;
Xaa_7 est Thr ou Ser ;
Xaa_8 est Ala, Ser ou Thr ;
Xaa_9 est Asp ou Glu ;
Xaa_{10} est Ala, Leu, Ile, Val, pentylglycine ou Met ;
Xaa_{11} est Ala ou Ser ;
Xaa_{12} est Ala ou Lys ;
Xaa_{13} est Ala ou Gln ;
Xaa_{14} est Ala, Leu, Ile, pentylglycine, Val ou Met;
Xaa_{15} est Ala ou Glu ;
Xaa_{16} est Ala ou Glu ;
Xaa_{17} est Ala ou Glu ;
Xaa_{19} est Ala ou Val;
Xaa_{20} est Ala ou Arg ;
Xaa_{21} est Ala ou Leu ;
Xaa_{22} est Ala, Phe, Tyr ou naphtylananine;
Xaa_{23} est Ile, Val, Leu, pentylglycine,
tert-butylglycine ou Met;
Xaa_{24} est Ala, Glu ou Asp ;
Xaa_{25} est Ala, Trp, Phe, Tyr ou naphtylananine ;
Xaa_{26}est Ala ou Leu:
Xaa_{27} est Ala ou Lys;
Xaa_{28} est Ala ou Asn;
Z_1 est -OH,
$-NH_2$,
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser -Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, ou
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2 ;
Xaa_{31} Xaa_{36} Xaa_{37} et Xaa_{38} sont indépendamment Pro, homopropline

3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine ou N-alkylalanine ; et Z_2 est -OH ou $-NH_2$;

à condition que pas plus de trois des Xaa_5, Xaa_6, Xaa_8, Xaa_{10}, Xaa_{11}, Xaa_{12} , Xaa_{13} , Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20} , Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} et Xaa_{28} ne soient Ala.

3. Utilisation d'une exendine ou d'un peptide agoniste d'exendine pour la préparation d'un médicament destiné au traitement du diabète gestationnel chez un sujet, ledit médicament comprenant une quantité thérapeutiquement efficace d'une exendine ou d'un peptide agoniste d'exendine dans laquelle ladite exendine ou ledit peptide agoniste d'exendine se lie à un récepteur se lie à l'exendine-3 ou à l'exendine-4, et
dans laquelle ladite exendine ou ledit peptide agoniste d'exendine comprend la séquence Xaa_1 Xaa_2 Xaa_3 Xaa_4 Xaa_5 Xaa_6 Xaa_7 Xaa_8 Xaa_9 Xaa_{10} Xaa_{11} Xaa_{12} Xaa_{13} Xaa_{14} Xaa_{15} Xaa_{16} Xaa_{17} Ala Xaa_{19} Xaa_{20} Xaa_{21} Xaa_{22} Xaa_{23} Xaa_{24} Xaa_{25} Xaa_{27} Xaa_{28}-Z_1 ; dans laquelle

Xaa_1 est His, Arg, Tyr, Ala, Norval, Val ou Norleu ;
Xaa_2 est Ser, Gly, Ala ou Thr ;
Xaa_3 est Ala, Asp ou Glu ;
Xaa_4 est Ala, Norval, Val, Norleu ou Gly ;
Xaa_5 est Ala ou Thr ;
Xaa_6 est Phe, Tyr ou naphtylalanine ;
Xaa_7 est Thr ou Ser ;
Xaa_8 est Ala, Ser ou Thr ;
Xaa_9 est Ala, Norval, Val, Norleu, Asp ou Glu ;
Xaa_{10} est Ala, Leu, Ile, Val, pentylglycine ou Met ;
Xaa_{11} est Ala ou Ser ;
Xaa_{12} est Ala ou Lys ;
Xaa_{13} est Ala ou Gln ;
Xaa_{14} est Ala, Leu, Ile, pentylglycine, Val ou Met ;
Xaa_{15} est Ala ou Glu ;
Xaa_{16} est Ala ou Glu ;
Xaa_{17} est Ala ou Glu ;
Xaa_{19} est Ala ou Val ;
Xaa_{20} est Ala ou Arg ;
Xaa_{21} est Ala ou Leu ;
Xaa_{22} est Phe, Tyr ou naphtylalanine ;
Xaa_{23} est Ile, Val, Leu, pentylglycine, tert-butylglycine ou Met ;
Xaa_{24} est Ala, Glu ou Asp ;
Xaa_{25} est Ala, Trp, Phe, Tyr ou naphtylalanine;
Xaa_{26} est Ala ou Leu;
Xaa_{27} est Ala ou Lys;
Xaa_{28} est Ala ou Asn ;
Z est -OH
$-NH_2$,
Gly-Z_2,
Gly Gly-Z_2,
Gly Gly Xaa_{31}-Z_2,
Gly Gly Xaa_{31} Ser -Z_2,
Gly Gly Xaa_{31} Ser Ser-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36}-Z_2,
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37}-Z_2, ou
Gly Gly Xaa_{31} Ser Ser Gly Ala Xaa_{36} Xaa_{37} Xaa_{38}-Z_2 ; dans laquelle

Xaa_{31} Xaa_{36} Xaa_{37} et Xaa_{38} sont indépendamment Pro, homopropline

3Hyp, 4Hyp, thioproline, N-alkylglycine, N-alkylpentylglycine ou N-alkylalanine ; et Z_2 est -OH ou $-NH_2$;
à condition que pas plus de trois des Xaa_3, Xaa_4, Xaa_5, Xaa_8, Xaa_9, Xaa_{10}, Xaa_{11}, Xaa_{12}, Xaa_{13}, Xaa_{14}, Xaa_{15}, Xaa_{16}, Xaa_{17}, Xaa_{19}, Xaa_{20}, Xaa_{21}, Xaa_{24}, Xaa_{25}, Xaa_{26}, Xaa_{27} et Xaa_{28} ne soient Ala.

et à condition que, si Xaa_1 est His, Arg ou Tyr, alors au moins un parmi Xaa_3, Xaa_4 et Xaa_9 est Ala.

4. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle ladite exendine ou ledit peptide agoniste d'exendine est choisi dans le groupe constitué de SEQ ID NO 1, 2 et 6-188.

5. Utilisation selon la revendication 1, dans laquelle ladite exendine ou ledit peptide agoniste d'exendine est choisi dans le groupe constitué d'un acide d'exendine-4 et d'un amide de ^{14}Leu, ^{25}Phe exendine-4.

6. Utilisation selon la revendication 2 ou 3, dans laquelle ladite exendine ou ledit peptide agoniste d'exendine est choisi dans le groupe constitué de l'exendine-4 (1-30), d'un amide d'exendine-4 (1-30), d'un amide d'exendine-4 (1-28) et d'un amide de ^{14}Leu, ^{25}Phe exendine (1-28).

7. Utilisation selon la revendication 1, dans laquelle ladite exendine ou ledit peptide agoniste d'exendine est l'exendine-3.

8. Utilisation selon la revendication 1, dans laquelle ladite exendine ou ledit peptide agoniste d'exendine est l'exendine-4.

9. Utilisation selon l'une quelconque des revendications 1 à 8, dans laquelle ladite quantité thérapeutiquement efficace réduit le glucose dans le sang.

10. Utilisation selon l'une quelconque des revendications 1 à 9, dans laquelle ledit médicament est sous une forme appropriée pour être administrée de manière continue.

11. Utilisation selon l'une quelconque des revendications 1 à 9, dans laquelle ledit médicament est sous une forme appropriée pour être administrée par injection.

12. Utilisation selon la revendication 11, dans laquelle ledit médicament est sous une forme appropriée pour être administrée par injection sous-cutanée.

13. Utilisation selon l'une quelconque des revendications 1 à 12, dans laquelle ledit médicament est sous une forme destinée à être administrée en une dose unique ou en doses fractionnées pour contenir une dose quotidienne de 1 μg à 1 mg de ladite exendine ou dudit peptide agoniste d'exendine.

14. Utilisation selon l'une quelconque des revendications 1 à 12, dans laquelle ledit médicament est sous une forme destinée à être administrée en une dose unique ou en doses fractionnées pour contenir une dose quotidienne de 1 μg à 30 μg de ladite exendine ou dudit peptide agoniste d'exendine.

15. Utilisation selon l'une quelconque des revendications 1 à 12, dans laquelle ledit médicament est sous une forme destinée à être administrée en une dose unique ou en doses fractionnées pour contenir une dose quotidienne d'environ 3 μg à environ 50 μg de ladite exendine ou dudit peptide agoniste d'exendine.

16. Utilisation selon l'une quelconque des revendications 1 à 15, dans laquelle ledit sujet est un humain.

17. Utilisation selon l'une quelconque des revendications 1 à 16, dans laquelle ledit médicament comprend en outre une quantité thérapeutiquement efficace d'un ou plusieurs composés choisis dans le groupe constitué de l'insuline et d'un agoniste d'amyline.

1 5 10 15 20

$Xaa_1\ Xaa_2\ Xaa_3$ Gly Thr $Xaa_4\ Xaa_5\ Xaa_6\ Xaa_7\ Xaa_8$ Ser Lys Gln Xaa_9 Glu Glu Glu Ala Val Arg Leu

25 30 35

$Xaa_{10}\ Xaa_{11}\ Xaa_{12}\ Xaa_{13}$ Leu Lys Asn Gly Gly Xaa_{14} Ser Ser Gly Ala $Xaa_{15}\ Xaa_{16}\ Xaa_{17}\ Xaa_{18}$-Z

[SEQ.ID.NO.]	Xaa_1	Xaa_2	Xaa_3	Xaa_4	Xaa_5	Xaa_6	Xaa_7	Xaa_8	Xaa_9	Xaa_{10}	Xaa_{11}	Xaa_{12}	Xaa_{13}	Xaa_{14}	Xaa_{15}	Xaa_{16}	Xaa_{17}	Xaa_{18}	Z
9	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
10	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
11	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
12	Tyr	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
13	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Tyr	NH_2
14	His	Gly	Asp	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
15	His	Gly	Glu	naph	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
16	His	Gly	Glu	Phe	Ser	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
17	His	Gly	Glu	Phe	Ser	Thr	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
18	His	Gly	Glu	Phe	Thr	Thr	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
19	His	Gly	Glu	Phe	Thr	Ser	Glu	Leu	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
20	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Met	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
21	His	Gly	Glu	Phe	Thr	Ser	Asp	pGly	Leu	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
22	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2

Fig. 1A

[SEQ.ID.NO.]	Xaa_1	Xaa_2	Xaa_3	Xaa_4	Xaa_5	Xaa_6	Xaa_7	Xaa_8	Xaa_9	Xaa_{10}	Xaa_{11}	Xaa_{12}	Xaa_{13}	Xaa_{14}	Xaa_{15}	Xaa_{16}	Xaa_{17}	Xaa_{18}	Z
23	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	pGly	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
24	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	naph	Ile	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
25	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Val	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
26	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Val	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
27	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	tBuG	Glu	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
28	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	tBuG	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
29	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Asp	Trp	Pro	Pro	Pro	Pro	Ser	NH_2
30	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Phe	Pro	Pro	Pro	Pro	Ser	NH_2
31	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	tPro	tPro	tPro	tPro	Ser	NH_2
32	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	tPro	tPro	tPro	Ser	NH_2
33	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	hPro	hPro	hPro	hPro	Ser	NH_2
34	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	hPro	hPro	hPro	Ser	NH_2
35	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	tPro	tPro	tPro	tPro	Ser	NH_2
36	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Ile	Glu	Phe	hPro	hPro	hPro	hPro	Ser	NH_2
37	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	MeAla	MeAla	MeAla	MeAla	Ser	NH_2
38	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Met	Phe	Ile	Glu	Trp	Pro	MeAla	MeAla	MeAla	Ser	NH_2
39	His	Gly	Glu	Phe	Thr	Ser	Asp	Leu	Leu	Phe	Val	Glu	Phe	MeAla	MeAla	MeAla	MeAla	Ser	NH_2

Fig. 1B

Fig. 2

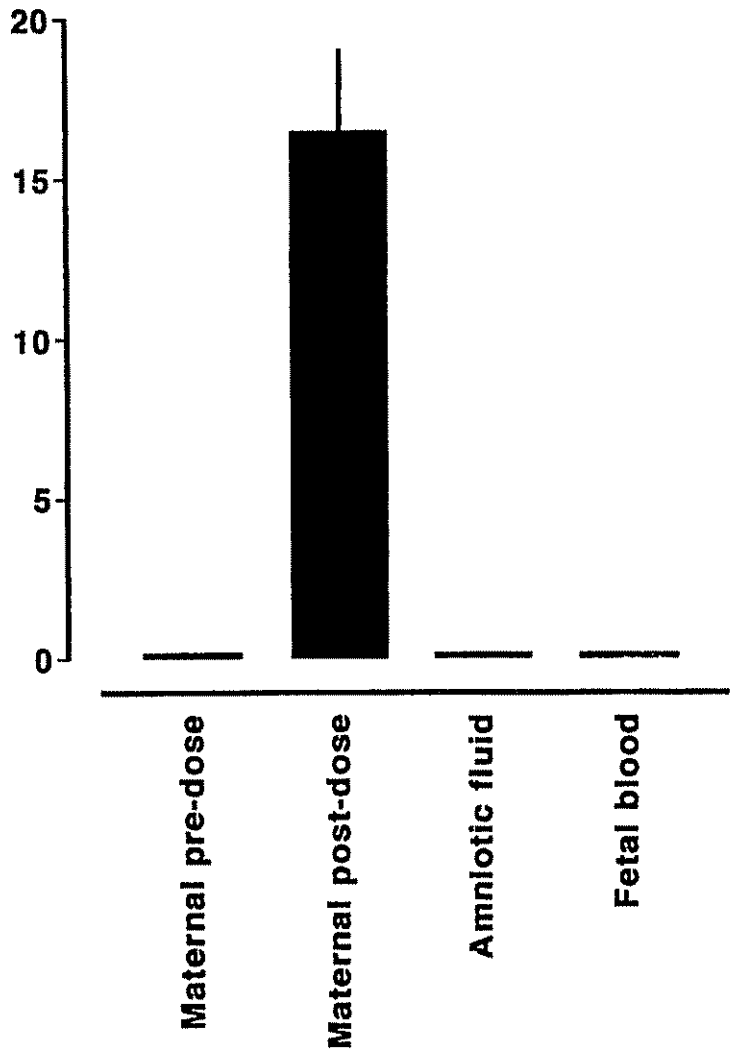
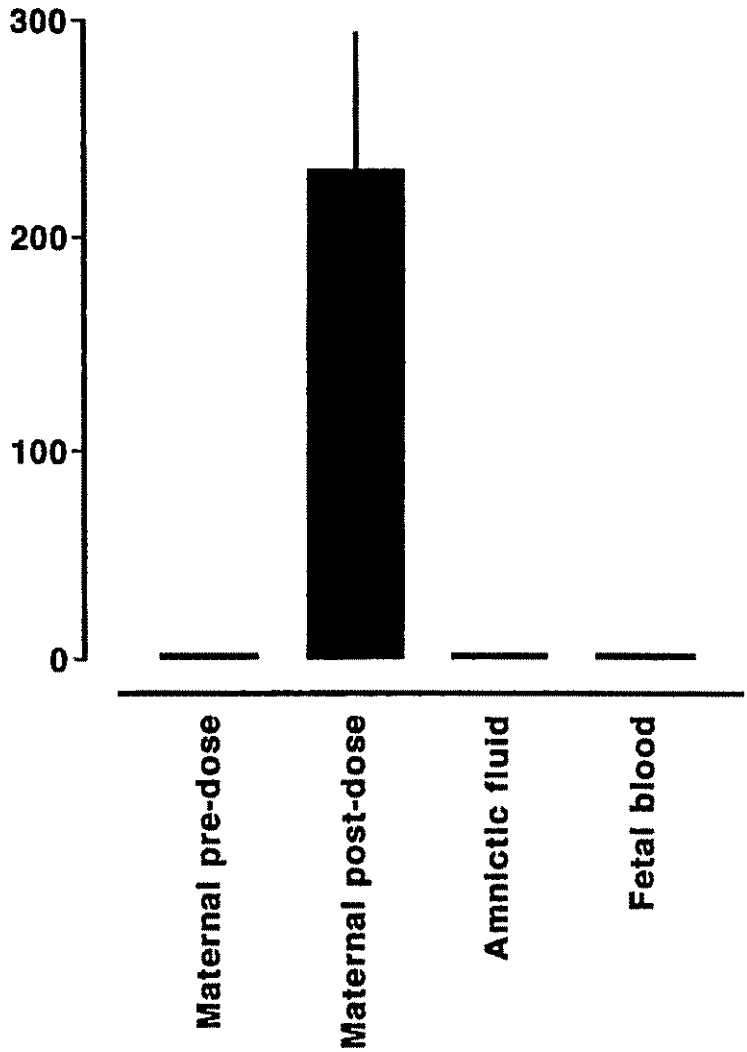

20
15
10
5
0
Maternal pre-dose
Maternal post-dose
Amniotic fluid
Fetal blood

Fig. 3


300
200
100
0
Maternal pre-dose
Maternal post-dose
Amniotic fluid
Fetal blood

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